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Preface

In recent decades, better understanding of tumor biology enabled us to replace some of the previously used extensive and mutilating surgical procedures by minor surgical interventions combined with irradiation and systemic therapy. Thus organ preservation associated with better quality of life is possible in substantial number of cancer patients without jeopardising their survival.

Despite the great advances in the field of combined cancer treatment using organ-sparing approach, a number of questions remain unresolved, such as those related to the optimal combination and sequence of individual treatment modalities, immediate and late sequelae of treatment, spared organ function, and many others.

Considering the great interest of medical profession in combined, organ-sparing oriented treatment, we have decided to organize an international symposium of the Alps-Adriatic community on organ sparing treatment in oncology. The contributions presented at this meeting, prove that this kind of treatment approach has also found its place in this part of the world.

Our first idea was to have the contributions published in a "Book of Proceedings". Later on, however, we accepted the kind offer of the editors of "Radiology and Oncology" journal to have the materials published in one of their regular issues. Due to the time pressure we took the liberty of making some editorial changes on the manuscripts in order to adjust them as closely as possible to the journal's requirements. The authors have been consulted personally only in the cases when the occasional error in the original was of such nature that only the author himself could correct it. However, in spite of all our efforts, the journal's requirements often could not be met, but the Editorial Board of Radiology and Oncology kindly decided to overlook those inconsistencies, for which we feel very obliged.

We wish to thank the authors for their interesting papers and ideas contributed to the topic discussed. We should also appreciate their consent to the editorial changes that had to be made in their manuscripts. Thanks are due to all the invited speakers for their valuable papers. And last but not least, we want to thank our two language proof-readers and to the staff of our special library for their editorial work.

Tanja Čufer, Marjan Budihna

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Conservative treatment evolution in breast cancer

Umberto Veronesi

European Institute of Oncology, Milan, Italy

In the late 1960s, we became interested in the possibility of preserving the breast in patients with small breast carcinomas for a number of reasons: new information on the natural course of this disease, tendency that smaller tumors are being detected on diagnosis, and the fact that aggressive local-regional treatments have failed to improve prognosis. For example, at the end of the 1960s an international randomised trial, comparing traditional Halsted mastectomy with Halsted mastectomy plus dissection of the internal mammary nodes, showed that the more aggressive approach had no advantage over the traditional surgery.

The objectives in conserving the breast are to achieve effective local control and at the same time produce a good cosmetic result. To this end we developed an extensive surgical excision called "quadrantectomy", whose main characteristic was a radially directed incision by which the resection encompassed the whole ductal tree from the retro-areolar region downwards and to the periphery. We were convinced that intraductal permeation was an important mechanism of tumor spread, and that therefore all branches to the involved duct had to be removed. The main duct and its associated tree is often referred to as a breast lobe and the operation could have been designated "lobectomy"; however we chose the name quadrantectomy since the quadrant concept was simpler to explain. After quadrantectomy we planned radiotherapeutic treatment consisting of 50 Gy delivered to two tangentially opposed fields, using high energy equipment, plus a boost of 10 Gy on the scar with orthovoltage equipment. The procedure was completed by total axillary lymph node dissection (all three levels). We considered that this intervention, which we called QUART, was radical, although at the beginning we applied it only to T1 tumors (less than 2 cm).

In 1973 we began a randomized trial (the *Milan I Trial*) to compare small size breast cancer patients treated by Halsted mastectomy with those receiving QUART. The trial was concluded by the beginning of 1980, after 701 cases had been recruited: 349 underwent mutilating surgical intervention while in 352 the breast was conserved. The preliminary results[1] indicated similar survival in both groups. After 20 years this trend was confirmed,[2] and also demonstrated that local recurrences treated by salvage mastectomy did not affect the prognosis. The thirteen year survival data showed that QUART gave identical results as Halsted mastectomy, and that subdivision of patients by tumor size, site and age still did not reveal any difference between the treatments. Subdivision by lymph node involvement showed that QUART was superior to Halsted, although the difference was not statistically significant. Furthermore, the fear that radiotherapy might entail a late oncogenic effect was not confirmed. There were nine new ipsilateral cancers in patients with heavily irradiated breasts, and 19 new cases in the contralateral breasts, the same number that occurred in the contralateral non-irradiated breasts of Halsted patients. It appeared therefore that breast irradiation, at the doses we used, might protect the breast, either by destroying occult foci of *in situ* lesions or by inactivating any proliferative precancerous lesions.

The conclusion that breast conservation is as safe a procedure as traditional mastectomy in small breast carcinoma was confirmed in subsequent publications.[3-6]

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Key words: breast neoplasms; mastectomy, segmental resection

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The question arose, however, as to whether better cosmetic results could be achieved by an even less aggressive surgical approach. Following a number of second generation trials implemented in various centers,[7-9] studying different surgical approaches and types of radiotherapy, we initiated a new trial which compared classic quadrantectomy, axillary dissection and radiotherapy with a more limited surgical treatment consisting of a lumpectomy ("tumorectomy") plus axillary dissection, followed by external radiotherapy and a boost with ^{192}Ir implantation (TART). Lumpectomy consisted of excision of the primary tumor with a 1 cm margin of normal breast tissue, without including the overlying skin except for a very small portion for histologic confirmation. Axillary dissection was always total, and was performed by separate incision, as defined. Radiotherapy was both external and interstitial. External irradiation began four weeks after surgery and the technique was the same as that used after quadrantectomy, with the difference that the total dose (45 Gy) was given over five weeks. After 2-3 weeks ^{192}Ir wires were implanted interstitially to give a boost of 15 Gy directly to the tumor bed. A total of 60 Gy was thus given to both groups of patients. Radiation was never applied to the axillary or supraclavicular regions. Seven hundred five patients were admitted, 360 received QUART and 345 received TART, the groups being comparable clinically and in terms of the adjuvant treatment received. Local failures in the area of the previous surgery (i.e. cutaneous, subcutaneous and parenchymal lesions) appearing three to five cm from the quadrantectomy/lumpectomy scar were considered true local recurrences. At the time of last review there were 15 local recurrences in the QUART group and 34 in the TART group. Survival was the same in both groups.

The results of this trial will pose a very delicate dilemma to the surgeon as he has to decide whether the better cosmetic result obtained by tumerectomy and radiotherapy could counterbalance the greater incidence of local recurrences taking into account the fact that recurrences are traumatic for patients, in whom intense anxiety often appears or reappears. Since local recurrences are in some cases treated by mastectomy, an excessive number of salvage operations would compromise the original objectives of the procedure.

In more recent years new trials have been undertaken in an attempt to verify whether radiotherapy is necessary after breast conservative procedures. In Sweden, the Uppsala-Örebro Breast Cancer Study Group[10] showed that women who underwent conservative surgery without radiotherapy had a significantly higher rate of local recurrences than those in whom radiotherapy was used.

Between 1987 and 1989 in Milan we randomly assigned 567 women with small breast cancers to quadrantectomy followed by radiotherapy or to quadrantectomy without radiotherapy.[11] As usual, all patients underwent total axillary dissection and regular follow-up (for a mean period of 39 months). Two hundred ninety nine patients received QUART and 280 received quadrantectomy plus axillary dissection without radiotherapy (QUAD). There was no significant difference between the two groups with respect to age, site and size of the primary, histological characteristics, or level of axillary invasion; neither was there any difference with regard to level of nodular involvement broken down by adjuvant treatment administered. We did, however, observe a marked difference between the two groups with respect to recurrences. Only three of the 294 QUART patients (1%) developed a local recurrence, compared with 28 local recurrences among the 280 patients (10%) of the QUAD group.

This trial clearly showed that postoperative radiotherapy administered directly after quadrantectomy has a protective effect against local recurrences and new primary carcinomas. That there was a difference between the two groups did not surprise us; what was a surprise was the magnitude of the difference between them: 28 local recurrences and four new carcinomas after quadrantectomy alone, compared with three recurrences and no new tumors when quadrantectomy was combined with radiotherapy. In the QUAD group local recurrences occurred mainly in patients under 55 years of age, but rarely in patients older than that. The presence of an extensive intraductal component was also confirmed as an important predictor of local recurrences. This trial definitively established quadrantectomy plus axillary dissection and radiotherapy as an effective conservative treatment that does not expose patients to increased risk of local recurrence, notwithstanding the fact that in older women conservative surgery without radiotherapy may result in a low rate of local recurrences, provided that the surgery is an extensive one, removing two to three cm of normal tissue around the primary carcinoma.

In a more recent analysis of breast cancer patients uniformly treated by quadrantectomy, axillary dissection and subsequent radiotherapy, we evaluated local and distant recurrences according to

demographic, biological and pathological variables in 2233 women.[12] Young age was an important risk factor for recurrence, with peritumoral lymphatic invasion also predictive for local and distant events. Tumor size and axillary lymphnode involvement were not related to local recurrences but were important predictors of distant metastases. Extensive intraductal component was only a risk factor for local recurrence. Finally, women up to the age of 35 at first diagnosis, who had initial peritumoral lymphatic invasion and local recurrence within two years of surgery, were at high risk for distant spread.

More recent developments of the conservative approach to breast cancer are directed to the avoidance of the axillary dissection in cases with clinically negative nodes.[13] In fact, the axillary dissection is presently performed for staging purposes and any method that would identify the presence of occult metastases without the need of such an extensive total axillary dissection, would greatly improve the quality of life of breast cancer patients. Following this line of thought we developed the "sentinel node" technique, consisting in an injection of a minimal quantity of colloid albumin labelled with ^{99}Tc around the primary carcinoma which would be captured via the lymphatic route by the first axillary node (sentinel node) which would drain the lymph from that area. In a series of 163 patients we discovered that the predictive value of the sentinel node histology is very high, superior to 95%. When the sentinel node is negative for metastases the chances that other axillary lymph nodes are involved by metastatic cancer cells are very low. We hope that if the data will be confirmed by larger case-series, the axillary dissection would be avoided in all cases without clinical nodal involvement.

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Conservative surgery of the breast: Ten years of experience at the University Hospital for Tumours, Zagreb, Croatia

Vladimir Orešić, Zrinko Petrinec, Mladen Stanec and Danko Velemir Vrdoljak

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In this presentation we tried to show the evolution of breast conserving surgery in our Department. The first breast conserving operations were done in 1982. In 1986 the number of patients undergoing these procedures started to increase. The break point was the year 1993 when we started our breast cancer screening program, and since then the number has been increasing rapidly.

Key words: breast neoplasms; mastectomy-methods; treatment outcome

Introduction

This survey of ten-year experience is aimed at pointing out the number of changes that breast cancer surgery has undergone and is still going through. Over 35% of all breast carcinomas registered in Croatia are treated at the University Hospital for Tumors in Zagreb. The first conservative surgical procedure for breast cancer was performed in 1981, and up to 1987, a modest number of segmentectomies was registered at our Hospital, starting to increase thereafter. An actual increase was achieved only by 1993.

Patients and methods

In the period between 1986 to March 1997, 7875 patients underwent surgery for breast tumors, of which 4627 were diagnosed as carcinoma of the breast. Other types of breast surgery were applied for various breast diseases (Figure 1). From the total number of breast carcinoma registered in that period, there were 4133 modified radical mastectomies and 494 segmentectomies including dissection of the axilla. Conservative surgery for breast cancer accounted for 10% (Figure 2).

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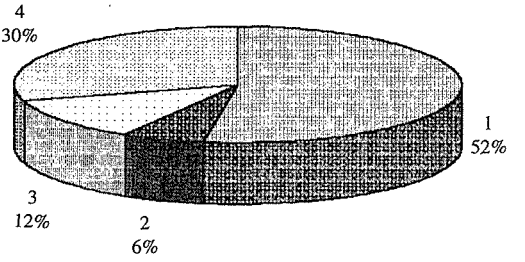

Figure 1. Breast surgery in total performed from 1986 to March 1997 (total 7805). 1. MRM; 2. segmant.; 3. fibroaden.; 4. negative biop.

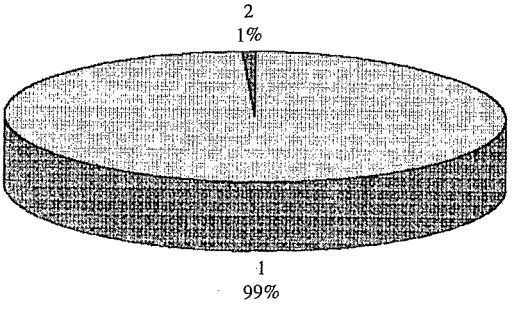

Figure 2. MRM and segmentectomies ratio in 1986. 1. MRM; 2. segment.

Following the protocol of the University Hospital for Tumors in Zagreb, all patients were submitted to postoperative irradiation and, if necessary, adjuvant chemotherapy or hormone therapy, which depended on the axillary status.[1-4]

There are several reasons for the small number of conservative operations performed at our Hospital.

Although some authors allow for up to 70% of negative breast tumor biopsies, we are of the opinion that the indications should be reexamined and reviewed in the case when negative biopsies exceed 30%.

Our criteria for conservative surgery, which some still consider rather rigorous, are based upon experience gained with numerous breast cancer patients and the results achieved. As regards the above, conservative surgery in breast cancer patients often happens to be the method of choice. At our Hospital, the indications for breast cancer conservative surgery are as follows:[5]

1. cancer size less than 3(4) cm;
2. no multicentricity on mammography or / and ultrasound examination;
3. clinically negative axilla;
4. adequate volume of the breast which allows uniform dosage of irradiation;
5. patient's decision.

In 1993, the University Hospital for Tumors along with the Croatian League against Cancer outlined a program for early detection of breast cancer, and some results have already been obtained. It is considered that the number of patients with smaller breast tumors has increased and that there is a growing number of breast cancer patients detected by screening.

The comparison of the numbers of patients operated on in 1986 with that in 1993, and after the introduction of the screening program in the same year, reveals three key turning points and some changes that have occurred since.[6] Until 1986, only twelve conservative operations had been performed in total. By 1993, the number reached the modest 33, accounting for 8% of all surgically treated carcinomas. After 1993, it started to increase significantly, and in 1996, the number of conservative operations accounted for 24% of all surgically treated breast carcinomas. In the first three months of 1997, 35/114 patients were submitted to conservative surgery (Figures 2, 3, 4, 5).

Conclusion

In conclusion, there is an explanation for such a relatively small number of conservative surgeries for breast carcinoma performed at our Hospital. First, all screening that was carried out before 1993 lacked planning. After the program for early detection was launched, the statistical records have greatly improved, but that does not necessarily mean that we consider the present numbers satisfactory. Being aware that further imporvement can only be achieved by as early as possible diagnosis of breast cancer, and by public education, we do hope that the total number of breast conservative surgeries will account for approx. 40% by the end of 1997.

The increased rate of conservative surgery registered at our Hospital could be considered satisfactory in the last four years alone (Figure 6).

As regards the screening program and its effects on the population, the response is huge. With quality and prompt outpatient treatment (surgical examination, mammography, US and cytological test) we are able to ensure the expeditious flow of patients that further results in a rather large number of patients operated on at our Hospital. In the end, the number of negative biopsies should also be taken into consideration. Our attempt to improve early diagnosis has resulted in a somewhat larger number of negative breast tumor biopsies that could also be justified by a wider indication field involved (Figure 6).

Table 1. Types of surgery performed at different periods

	Carcinoma			
year	radical	segment.	fibroaden.	other
1986	273	2	38	113
1987	322	15	51	128
1988	344	13	99	203
1989	376	18	82	250
1990	352	39	105	172
1991	317	41	73	145
1992	413	33	46	243
1993	407	33	92	281
1994	412	64	106	290
1995	411	76	90	241
1996	347	100	120	192
1997	114	35	27	61
	4088	469	929	2319
		4557	929	2319
			5486	2319
				7805

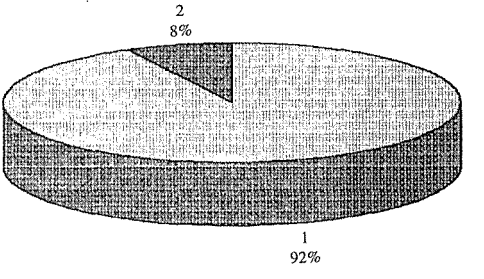

Figure 3. MRM and segmentectomies ratio in 1993. 1. MRM; 2. segment.

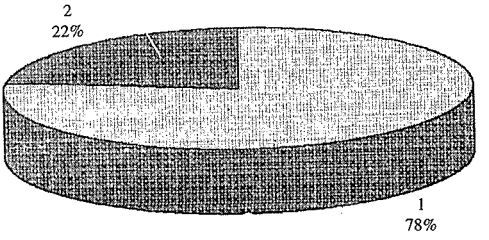

Figure 4. MRM and segmentectomies ratio in 1996. 1. MRM; 2. segment.

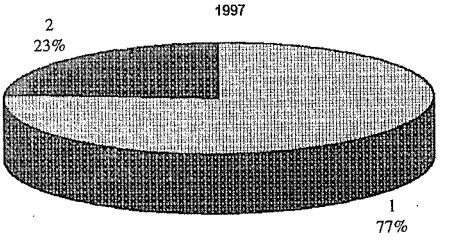

Figure 5. MRM and segmentectomies ratio in the first three months of 1997. 1. MRM; 2. segment.

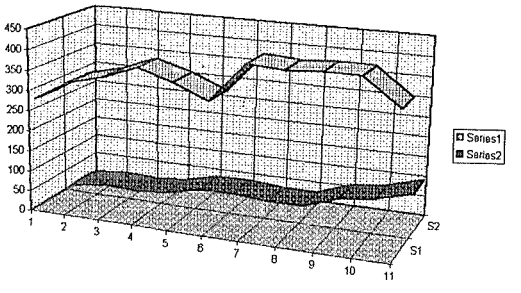

Figure 6. MRM and segmentectomies ratio from 1986 to 1997. 1. MRM; 2. segment.

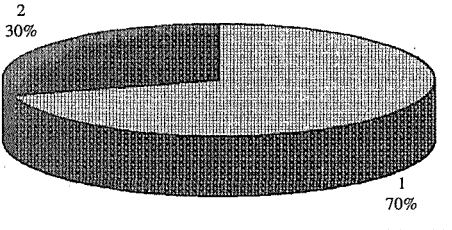

Figure 7. The ratio of negative biopsies. 1. positive biop.; 2. negative biop.

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Breast conserving operations, prognostic factors and life quality

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The incidence of breast cancer in Latvia has increased. Early breast cancer ($T_1N_0M_0$) makes only 18% of all cases. The study comprised 247 patients treated at the Latvia Center of Oncology in the period 1990 - 1992. We analyzed the correlation between 5-year survival, risk factors, histology, age, and type of surgical treatment; 118 patients were treated postoperatively by adjuvant chemotherapy and radiotherapy. Data on life quality are shown in the study.

Key words: breast neoplasms; mastectomy-methods; prognosis

Introduction

The incidence of breast cancer in Latvia has increased. In 1996 it was 63.7 per 100000. During the last 10 years the incidence has been increasing approx. by 2% per year. Early breast cancer ($T_1N_0M_0$) makes only 18% of all cases. The role of adjuvant therapy in node-positive breast cancer patients is more or less clear. Such factors as pathology, number and localization of lymph nodes are considered.[1-4] Yet the use of systemic adjuvant therapy in patients with small tumors and negative lymph nodes is still unclear. For the last 10-15 years, breast cancer prognostic factors have been intensively investigated. Several new prognostic factors are being studied, which can play an important role in the selection of systemic adjuvant therapy, but often they are not available in the clinical practice.

More and more surgeons prefer breast conserving surgery, especially in small breast cancers. Yet, concerning prognosis, we must take into account several factors - tumor localization, incision margins, tumor histology, differentiation grade and others.[5] Node negative breast cancer is a heterogeneous disease because of its varying tumor growth rate, invasiveness potential and generalization rate (metastasizing potential). We must admit that no relapse was observed in 70% of cases after surgical treatment and radiation, and therefore the use of systemic adjuvant therapy in all breast cancer patients is questionable. Side-effects and costs of chemotherapy must also be considered. Yet the use of systemic therapy in high risk patients after surgical treatment is still to be decided. Low-risk patients can be treated by surgery alone.

Type of surgical treatment plays an important role in the quality of patients' life. Psychological aspects, as well as mobility of the arm, should be considered.

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Patients and methods

From 1990 - 1993, 247 patients with breast cancer ($T_1N_0M_0$) were treated at Latvia Center of Oncology. The date of the patient's admission to the hospital was taken as the beginning of treatment. Disease-free survival was assessed till the onset of relapse or diagnosis of distant metastases. Overall survival was assessed till exitus letalis, when the file was removed from the registry. Survival rate was calculated till January 1, 1997. The prognostic factors were analyzed using univariate and multivariate methods, with the aim to assess simultaneous effect of different prognostic factors on the overall survival, as well as to determine the impor-

tance of different prognostic factors, and evaluate the differences and similarity of information acquired from the prognostic factors.

Radical mastectomy after Halsted was performed in 106 patients, amputation - in 24, breast conserving operation after Patey - in 78, and quadrantectomy with axillary clearance - in 39 patients. Tumor localization was as follows: medial - in 41 patient, lateral - in 128, central - in 25, and areolar - in 53 patients. The distribution by histological finding was as follows: intraductal cancer - 99 patients, lobular - 66, and other - 82 patients. Distribution by age: under 41 years - 31 patient, 41 - 50 years - 59 patients, 51 - 60 years - 64 patients, and above 61 years - 93 patients.

Positive familial history was observed in 8 patients only. Relapse and metastases were observed in 0.4%. During treatment, 101 patient received postoperative radiation, but 17 patients were treated by chemotherapy due to poor prognosis.

Besides, the edema in the arm 10 cm above the medial epicondyle of the humerus was estimated. If the circumference of the affected arm was 2.5-3 cm bigger than that of the healthy one, it was considered as a complication. The amplitude of movements was assessed by lifting the arm (abduction and adduction) from 0-180°; if it was limited by 10°, it was considered as a complication. On check-ups the patients were inquired about pain and paresthesia in the site of operation.

Results

The size of tumor in all patients was up to 2 cm, which corresponds to T_1. We analyzed the correlation between tumor localization and survival (Figure 1).

The cumulative rate of 5-year survival was the lowest in the case of tumor localization in the areolar area – 0.827 ± 0.22 ($p < 0.05$). Survival rate in the case of tumor localization in the medial quadrant was 0.861 ± 0.019; in the case of central localization - 0.931 ± 0.015. Patients with tumor localization in the lateral part of the breast were clinically healthy and alive throughout the follow-up period.

The correlation between the histological type and 5-year survival is shown in Figure 2. No significant difference was observed between ductal cancer and cancers of other types: 0.917 ± 0.017 and 0.912 ± 0.017. Slightly higher survival rate was observed in patients with lobular cancer - 0.930 ± 0.019.

Figure 3 shows the survival of patients in different age groups. The highest survival rate was in the age group below 40 years - 0.964 ± 0.008, and in the age group 41 - 50 years - 0.909 ± 0.013; 5-year survival in the age group above 60 years was 0.843 ± 0.016, but in the age group 51 - 60 years it was the lowest - 0.880 ± 0.028 ($p < 0.05$).

In the study we analyzed the correlation between the survival and type of surgical treatment (Figure 4). No significant difference in survival rates was observed in groups with quadrantectomy and mastectomy: 0.874 ± 0.021 and 0.878 ± 0.012, respectively. The results differed in the group after breast amputation - 0.818 ± 0.022.

In patients with poor prognosis, radiation to the breast or regional lymph nodes was suggested. Figure 5 shows 5-year survival in a group of 101 patient: 0.854 ± 0.017 patients were treated by adjuvant chemotherapy after surgery; 5-year survival was 0.816 ± 0.024 (Figure 6).

Evaluating the quality of patients' life, we found that 60% complained about loss of sensation and paresthesia in the operation site. Edema was observed in 7.8% after breast conserving surgery - quadrantectomy, in 15% after modified radical mastectomy, and in 18% after mastectomy.

Impaired shoulder mobility was observed in 11% of patients after mastectomy or modified radical mastectomy modus Patey. Impaired arm mobility was observed in 24% of patients treated by postoperative radiation therapy. In the group with systemic adjuvant chemotherapy, restriction of movement was observed in 1 patient only.

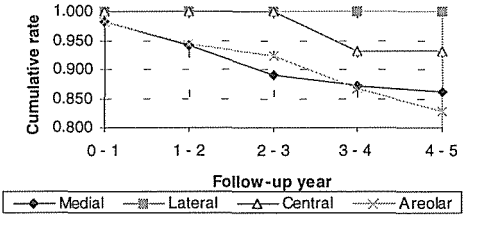

Figure 1. Correlation between tumor localization and survival.

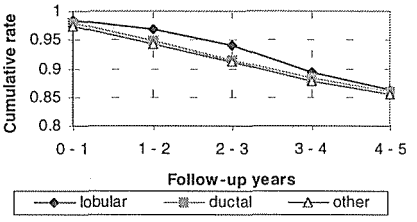

Figure 2. Correlation between histological type and survival.

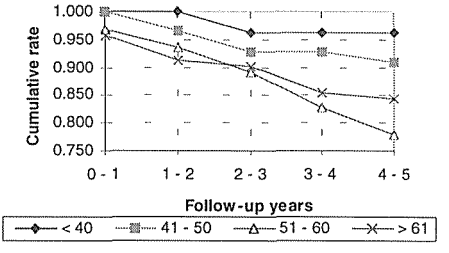

Figure 3. Survival in different age groups.

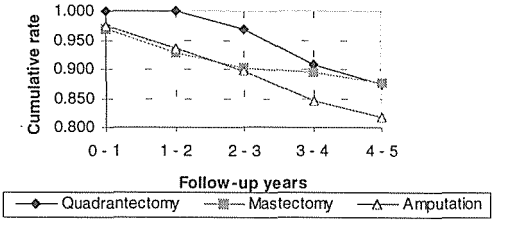

Figure 4. Correlation between the type of surgical treatment and survival.

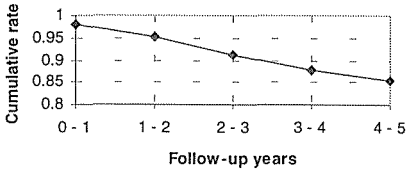

Figure 5. Survival rate in patients with radiotherapy.

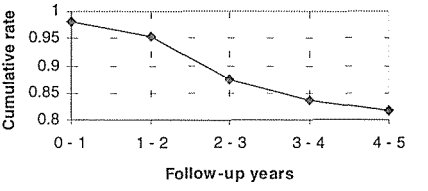

Figure 6. Survival rate in patients with adjuvant chemotherapy.

Discussion and conclusions

Tumor localization plays a role in the choice of surgical treatment, i.e. the extent of surgery. At present there is a tendency to use breast conserving operations in the case of a small tumor. Around 1990, the attitude of oncologists in Latvia towards this tendency was very cautious. There was an opinion that only classical mastectomy after Halsted can give good results. Little by little, the attitude has changed. Local recurrences in the scar after breast conserving operations were observed in 0.4% of cases only, but we must admit that the number of patients was small. Veronesi *et al.*[6] found 2.8% local recurrences after quadrantectomy. In large retrospective studies the rate of local recurrence was even higher - 7% in 5 years of follow up.[7] In our study the patients, who died within 5-year follow-up period had distant metastases, mainly pleural and pulmonal.

Tumor localization also plays an important prognostic role. According to our data, long-term results are worse in patients with tumor localization in the areolar area, central part and medial quadrant. With respect to the histological form, better survival was observed in the case of lobular cancer in the 2nd and 3rd year, but no difference was observed in the 5th year. In choosing the type of surgery according to tumor localization, histological form and the patient's age, we must take into account that small tumors tend to spread through the ductal system. Santini *et al.*[5] describe the growth type of such tumors and their presence in the areolar complex. Comparing different types of surgical treatments, according to our data there is no difference between quadrantectomy and mastectomy. Five-year survival rate was practically the same.

Therefore, conserving operations (such as quadrantectomy) in the case of small tumors are reasonable. But the surgeon must be very cautious to perform an adequate operation. In the case of central localization or localization in the areolar area, we perform histological examination of the incision margin to ensure that no tumor cells have remained around the incision. completeness of surgery. According to our data, the worst results were observed in postmenopausal women in the age group 51 - 60 years and older.

The use of additional radiotherapy in patients without metastases in lymph nodes is questionable. In our center radiation therapy was performed in 101 cases - in patients with tumor localization in the central part and in the areola or in the medial quadrant. After surgery, patients received radiotherapy with 45 Gy to infra and supra clavicular regions and parasternal area, 50 Gy to the breast, and additional 10 Gy as a boost. After consultation and individual assessment, chemotherapy was performed in 17 patients according to CMF regimen.

Data from large randomized trials suggest that adjuvant chemotherapy increases disease-free survival, as well as overall survival in node-negative breast cancer patients.[8, 9,10] Yet, the question about the need of adjuvant chemotherapy or radiotherapy in high-risk patients remains to be solved.

Breast conserving operations have clear advantages in terms of the quality of life, at least with respect to psychological factors. There were no complications observed after breast conserving operations and chemotherapy. Edema of the arm and movement restriction occurred mainly after classical mastectomy and after radiation following radical mastectomy. Radiation therapy in high-risk patients increased the possibility of late complications which affected the quality of life. Several other studies have given similar data.[12,13]

Results of our study suggest that in the case of early breast cancer (T_1) breast conserving surgery - quadrantectomy should be performed. Additional therapy is required in high risk patients. Taking into account the quality of life, adjuvant chemotherapy is the method of choice. Yet more investigations are necessary to evaluate additional risk factors that could be easily applied in the practical work, as well as to increase the number of patients under study.

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Ductal carcinoma in situ of the breast: Evaluation of the treatment options

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From January 1978 to December 1994, 87 patients with ductal carcinoma in situ (DCIS) of the breast were observed at the Centro Oncologico of Trieste. 43/87 (49.5%) patients underwent mastectomy; 42/87 (48.2%) quadrantectomy and radiation therapy and 2/87 (2.3%) lumpectomy alone. The local recurrence rate was 3.4% (3/87 cases), with a median follow-up of 69 months. The 3 patients who relapsed had been treated by conservative surgery and radiation therapy; they had a salvage mastectomy and are alive and free of disease. The 15-year actuarial overall and disease-free survivals are 100% and 89.9% respectively. In our retrospective study the conservative treatment proved to be a good alternative to mastectomy in patients with DCIS.

Key words: breast neoplasms; ductal carcinoma in situ; treatment options; treatment outcome

Introduction

Ductal carcinoma in situ represents almost 15% of all breast cancer in the United States and almost 40% of those screening detected.[1]

Historically, mastectomy has been the traditional treatment for DCIS.

Based on the success of conserving surgery in patients with early invasive breast cancer, this approach would appear to be a logical choice for treating DCIS. During the last decade, patients with DCIS have been accepted for conservative surgery with or without radiation therapy, and the results of several studies have already been published.[2-5]

In this study we have evaluated the results of treatment in patients with DCIS observed at the Centro Oncologico of Trieste from January 1978 to December 1994.

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Patients and methods

From January 1978 to December 1994, 87 patients with DCIS of the breast were observed at the Centro Oncologico of Trieste; patients with synchronous or metachronous invasive carcinoma of the breast were excluded from analysis. The median age was 57 years (range: 31-84 years). All patients underwent preoperative mammography: 5/87 cases (5.8%) were detected only clinically; 51/87 (58.6%) clinically and by mammography, and 31/87 (35.6%) by mammography alone.

Mastectomy was performed in 43/87 (49.5%) patients; quadrantectomy and radiation therapy in 42/87 (48.2%) and lumpectomy alone in 2/87 (2.3%). All cases treated by conservative surgery had negative resection margins. All patients, except those treated by lumpectomy, underwent axillary dissection; in all cases lymph nodes were negative for metastatic involvement.

Patients who underwent quadrantectomy received postoperative radiation therapy at the Istituto di Radioterapia Oncologica of Trieste. They were treated with tangential fields delivered by a Cobalt Unit; the prescribed dose was 50 Gy in 25 fractions,

followed by a boost of 10 Gy to the primary tumour bed with electrons from a Linear Accelerator. Since 1984, the treatment planning was performed on CT scans using a 2-D planning system.

Twelve patients were receiving hormonal therapy with tamoxifen for 5 years after surgery.

The follow-up schedule included clinical examination every 3 months for 3 years, every 6 months for the following 3 years, and later on once yearly; mammography was carried out once a year while other radiological and laboratory examinations were done only in specific cases.

Actuarial survival curves were calculated using the Kaplan-Meier method.

Results

The median follow up was 69 months (range 16-227 months).

Local failure occurred in 3/87 patients (3.4%) in the group treated with quadrantectomy and radiotherapy. Time from surgical treatment to relapse ranged from 9 to 85 months. These patients underwent salvage mastectomy and adjuvant therapy with tamoxifen (estrogen receptors were positive at the time of recurrence). They are alive and free of any distant failure or further local recurrence.

In our series, 15-year actuarial disease-free survival was 89.9%, and the overall survival was 100%.

Cosmetic results in patients treated by conservative surgery and radiotherapy were satisfactory.

Discussion and conclusions

The optimal management for the patients with DCIS remains controversial. Mastectomy cures almost all patients and is the standard by which other therapeutic options are measured.[6]

Recurrence rate after conservative surgery without irradiation is high: 23-75%,[3] whereas in series using radiotherapy after conservative approach, local failure rates range from 4% to 10% at 3-5 year follow up.[7]

In the randomized study published by Fisher et al.[8] the local control following lumpectomy with irradiation is higher in comparison with lumpectomy alone.

The majority of breast recurrences after conservative treatment occur near the original tumor and approximately 50% are invasive.[3] The outcome of salvage treatment must be regarded as an important issue in the treatment of DCIS because of the risk of local relapse. Virtually all patients who develop a non-invasive recurrence and almost 75% of those with an invasive recurrence are salvaged.[3]

The risk of axillary nodal metastases is very low[4] and therefore axillary dissection is no longer recommended. In our series there were no nodal metastases in the patients who underwent axillary dissection.

The results of our retrospective study showed an incidence of relapse at 3.4% (3/87 cases) after quadrantectomy and radiotherapy; while there were no recurrences in the group treated with mastectomy. There was no difference, however, in the survival rate after salvage treatment. The conservative approach proved to be a good alternative to mastectomy in patients with DCIS. Ongoing randomized clinical trials comparing conservative surgery versus conservative surgery and radiation therapy are expected to add more information on the therapeutic approach and will clarify the optimal management for the patients with DCIS.

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Treatment of intraductal carcinoma of the breast with conservative surgery and radiotherapy: An Italian multicenter retrospective study

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A collaborative multi-institutional study on intraductal carcinoma (IDC) of the breast in twelve Radiation Oncology Departments of the north Italy was conducted. The study population comprised 206 women with IDC of the breast treated between 1982 and 1992. Surgical procedures were as follows: quadrantectomy in 158, lumpectomy in 34, and wide excision in 14 cases. The axilla was surgically staged in 141 cases: all the patients were node negative. Radiation therapy was delivered with ^{60}Co units (73%) or 6 MV linear accelerators (27%) for a median total dose to the entire breast of 50 Gy (mean, 49.52 Gy). The tumour bed was boosted in 137 cases at a median dose of 10 Gy. Median follow-up is 72 months. Nineteen local recurrences were recorded. All recurrent patients had a salvage mastectomy and are alive and free of disease. Actuarial overall-, cause-specific-, and recurrence-free survivals at 10 years were 93.5%, 100%, and 84%, respectively. The results of this retrospective multicentric study confirm the favourable data reported in the literature about the efficacy of breast conserving treatment of IDC with conservative surgery and adjuvant radiation therapy.

Key words: breast neoplasms; intraductal carcinoma; treatment options; treatment outcome; multicenter studies

Introduction

After its recognition in 1907, intraductal carcinoma (IDC) of the breast was rarely diagnosed, except as an incidental finding or as a palpable mass, until the 80's.[1] During the past decade, the diffusion of mammographic screening increased the frequency of the diagnosis of IDC in a preclinical stage.[2] Currently, IDC represents about 10% of all newly diagnosed breast cancers.[3]

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The treatment employed for DCIS of the breast varies widely, and the best treatment option has not yet been clearly defined. Experience with conservative management of IDC with surgery and radiotherapy (XRT) is limited in terms of both patients number reported from single Institution series and the duration of follow-up.

In this study, an analysis of 206 women with IDC of the breast treated with this conservative approach in twelve Italian institutions, is reported.

Patients and methods

A collaborative, multi-institutional retrospective study of patients affected by IDC of the breast

treated with breast-conserving therapy (excision and radiation therapy) was performed, analyzing data from 12 Institutions of the north Italy for the period 1982 to 1992.

A total of 206 sequential evaluable cases were collected. Their median age was 49 years (range 23-88 years), 92 patients had post-menopausal status; twenty-nine patients had a family history of breast cancer. Of the 126 patients with known clinical status, 103 (54%) had a palpable lump. Preoperative mammography was performed in 177 patients: 77 (43.5% of the total) were due to microcalcifications alone, 60 (34%) to mass effect alone, and 18 (10.2%) to mass plus calcification. In 112 patients a measurement of the extent of the disease in the surgical specimen was available: the median pathologic tumor size was 1.2 cm (range 0.2-5.5 cm).

The surgical treatment consisted of quadrantectomy in 158 cases, wide excision in 14, and tumourectomy in 34. An axillary dissection was performed in 141 out of 206 cases with a median of 15 lymph nodes dissected (mean 14, range 3 - 36): all the cases were pathologically negative for metastatic disease.

The tumor diagnoses were reviewed and confirmed as IDC by institutional pathologists, central pathology review being unfeasible.

The cases were classified according to the established histological criteria with respect to the dominant growth pattern; the structural features were categorized as follows: comedo (61), solid (8), cribriform (42), papillary and micropapillary (29), and cases associated with lobular carcinoma in situ (13). Irradiation with curative intent was delivered with cobalt-60 (151 cases; 73%) or 6-MV photons (55 cases; 27%), by tangential fields, encompassing the entire breast, up to doses of 45-60 Gy (mean, 49.52 Gy; median, 50 Gy) delivered in 2 Gy dose fractions in all but 2 patients. A boost consisting of an additional median dose of 10 Gy to the primary site was delivered after treatment of the whole breast in 137 cases. Neither regional nodal irradiation nor adjuvant systemic treatments were used.

Overall survival, cause-specific survival and relapse-free survival were calculated using the Kaplan-Meier method,[4] starting from the time of surgery.

Results

The median follow-up for the group was 72 months from the date of surgery, with a range of 31-167 months. Local failure was recorded in 19 patients, at an interval of 7-109 months after surgical treatment. Ten cases were invasive carcinoma and 9 intraductal carcinoma. One patient developed an axillary nodal relapse after invasive local recurrence. No distant metastases were observed. In 12 women, both the first and the second tumors were true recurrences, occurring either at the site of previous excision or on the border of the same quadrant. Eight of the 19 patients with relapse had received a tumor-bed dose of 50 Gy, and 11 had had a supplemental external boost of 10 Gy. The initial surgical intervention had been quadrantectomy in 14 cases, tumourectomy in 4 and wide excision in one. Salvage mastectomy was performed in all the patients. One patient was also treated with adjuvant tamoxifen at the time of recurrence. All the patients with breast failure are alive without evidence of disease. None of them has subsequently failed with distant metastases.

Five- and ten-year actuarial breast recurrence-free rate is 93.5% and 84% respectively, overall survival is 98% and 93% respectively; while cause-specific survival and freedom from distant metastases is 100% at five and ten years. Subsequently, 7 patients developed a contralateral carcinoma of the breast, of these 3 intraductal and 4 infiltrating.

The cosmetic outcome was separately assessed at the last follow-up in 175 cases: 87% of them had an excellent or good result.

Discussion

The surgical approach to IDC of the breast changed during the second half of the eighties by increasing use of breast conserving treatments with or without radiotherapy; thus, better cosmesis can be achieved than with mastectomy.

The results of limited surgery alone are rather unsatisfactory: local recurrence has been reported at a cumulative average rate of 19.7%, ranging from 0% to 66%, calculated from about a thousand cases reported in the literature. A comparison of these data with the reported results of conservative surgery plus definitive irradiation suggests that radiotherapy can reduce the breast cancer recurrence rate to an acceptable level but does not eliminate it. This suggests that a combination of excision and radiotherapy provides acceptable local control while ensuring excellent survival and cosmetic results.[5-10]

The only published randomized study is the NSABP B-17 trial[11] comparing limited excision fol-

lowed by irradiation or observation. There were 790 women evaluable for analysis; the addition of radiation decreased the risk of breast cancer recurrence and subsequently, the development of invasive breast cancer. The current study is the largest series of IDC treated by conservative surgery and irradiation reported in Italy. Our results are closely comparable with those reported for a series with a similar follow-up,[12-16] according to which the probability of breast preservation at 10 years was 84%. In our series cause-specific survival was 100% at 10 years, all the 19 patients with local recurrence being salvaged by mastectomy. The majority of breast recurrences in our study were observed at or near the site of primary IDC suggesting a persistence rather than a new second tumor: 12/15 known sites of recurrence were in the same quadrant as the first lesion. From these data it can be concluded that multicentric cancers rarely evolve into clinical cancer. The clinical size of the measurable palpable primary tumours in our series was relatively small, with about 80% of lesions smaller than 2 cm, and 65 patients in our study had non-palpable, mammographically discovered lesions. Recently, White et al. reported a low rate of local recurrences in patients treated by surgery and irradiation for mammographically detected lesions.[8]

An axillary dissection was performed in 141 patients: all the cases were pathologically negative. In the literature on conservatively treated and irradiated patients, axillary invasion was reported in 2 cases only, confirming the results reported in patients treated with mastectomy.[17] Our study, although involving numerous Institutions, indicates that clinically or mammographically detected IDC can be succesfully treated by conservative surgery and definitive irradiation.

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Pathological examination for quality assurance in breast conserving therapy for breast cancer

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Long-term survival in patients after breast conserving therapy (BCT) is similar to that after mastectomy. Nevertheless, there is a significant risk of local recurrence. Although local recurrence does not appear to affect the survival, there certainly is associated morbidity and attendant emotional trauma present. The margin status was shown to be a risk factor for local recurrence. Microscopic evaluation of the margins of lumpectomy specimens is the only way to define the extent of the tumour, especially of its intraductal component, and the adequacy of resection. We intended to check the influence of a standardised protocol for pathological examination on the results of histological margin assessment. Moreover, we wanted to investigate the effects of margin status and size of the area of the DCIS-component on the choice of treatment. Between February 1994 and February 1996, 582 women had an unilateral breast excision at the Berlin-Buch Medical Centre. In 233 patients (71.8%) there were no clinical or mammographic contraindications for BCT and their carcinomas were treated by conservative surgery and irradiation. The aim of all tumour excisions was the complete removal of the tumour. As a result of our standardised margin investigation, in 28% of cases there was microscopic evidence of tumour tissue in the margins of 100 consecutive BCT specimens although the margins looked clear macroscopically. In two periods when histological investigations were not carried out on non suspicious-looking margins and the margin assessment was non-standardised, the evidence of tumour could be found in only 2% and 12% of the patients respectively. In each case with invasive carcinoma or DCIS detected in paraffin slides of the margins, either directly at the resection line or within a distance of 5 mm from it, a second operation followed. Finally, 100 women out of the primary BCT group of 323 patients were advised to undergo mastectomy, and thus 132 / 323 (40.8%) patients with malignancies were treated by definitive BCT. The importance of standardised evaluation of BCT specimens is to select patients for re-excision or for treatment with conversion to mastectomy, and thus reduce local recurrence.

Key words: breast cancer; breast conserving therapy; margin investigation; treatment outcome

Introduction

The efficacy of breast conserving therapy (BCT) and mastectomy in breast cancer has been compared in several randomised clinical trials. The long-term disease free survival in patients treated by BCT is similar to that of patients treated by mastectomy.[1-7] Nevertheless, long-term survival should not be the only gauge of treatment efficacy. There is a significant risk of local recurrence.[8-11] Although local recurrence does not appear to affect the survival, it is certainly associated with morbidity and attendant emotional trauma.

Ductal carcinoma in situ (DCIS) has implications for breast conserving therapy regardless whether it

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is associated with invasive carcinoma or not. DCIS significantly affects local control rates.[12-15] Microscopic evaluation of the margins of lumpectomy specimens is the only way to define the extent of the tumour, especially of its intraductal component, and the adequacy of resection.[11,16-20] We intended to check the influence of a standardised protocol for pathological examination on the results of histological margin assessment. Moreover, we wanted to investigate the effects of margin status and the size of DCIS-component area on the choice of treatment.

Materials and methods

Patients

Between February 1994 and February 1996, 582 women had an unilateral breast excision parformed at the Berlin-Buch Medical Centre. The malignancy yield in our centre was 55.5% (327/582). In 4 of these 327 malignancies lobular carcinoma *in situ* was diagnosed. Out of the remaining 323 women, 91 (28.2%) underwent primary mastectomy for various reasons. In 233 patients (71.8%) there were no clinical or mammographic contraindications for BCT and their pT i.s.; pT1, and pT2 carcinomas were treated by conservative surgery and irradiation. They had been evaluated by a team of breast surgeons, radiologists and pathologists before they were given the option of breast conserving therapy. 205 (88.0%) of the tumours treated by BCT were invasive (all but 6 invasive lobular carcinomas had an invasive ductal histology). Except for two tumours with diameters of 22 and 24 mm respectively, all the invasive carcinomas were in stage pT1 (mean diameter 13 mm); 28 (12.0%) of the 233 tumours treated by BCT were "pure" DCIS without invasion (pTi.s.).

Surgery

All tumour excisions were performed by the same team of gynaecologists under supervision of an experienced breast surgeon. The aim was complete tumour removal by wide excision with an attempted margin of 10 mm, which would ensure at least 5 mm of macroscopically healthy tissue. In the cases of positive margins on gross inspection or a macroscopic distance less than 5 mm between the tumour and excision margin, the site of the margin involved was re-excised unless an indication for mastectomy was given. The data for this study have been derived from the primary excision specimens. In every case with invasive carcinoma or DCIS detected in paraffin slides of the margins, either directly at the resection line or within a distance of 5 mm to it, a second operation followed. Taking into consideration the surgical possibilities, re-resection was performed always when the diameter of the DCIS ("pure" or as an component of invasive carcinoma) was less than 40 mm; in all other cases, especially such with DCIS diameters exceeding 40 mm, the patients are advised to undergo mastectomy. In all patients with invasive tumours axillary dissection was performed, which was not done for DCIS.

Pathology protocol

In order to ensure standardization, we base our histopathological investigations of BCT specimens on a practice protocol.[21] This protocol includes eight steps:

1. Review of the preoperative clinical checklist.
2. Preoperative interdisciplinary consultation with gynaecologists, radiologists and pathologists.
3. Wide excision of the lesion (see above), after mammographic hook wire localisation if necessary.
4. Orientation of the BCT specimen on a drawn form showing the nipple - by the surgeon (additionally, the margins are marked with sutures).
5. Review of the intraoperative clinical checklist.
6. Conducting a gross examination and selecting the tissue for microscopic examination, after specimen radiography with needle localisation, if necessary.
7. Review of the pathological checklist comprising gross examination, microscopic evaluation and diagnoses.
8. Postoperative interdisciplinary consultation.

Handling instructions for gross examination and tissue sampling

1. Determination of specimen dimensions.
2. Marking of the margins with Latex.
3. Serial slicing of the specimen at 4 mm intervals in a plane perpendicular to the mammillar-peripheral axis and, of course, perpendicular to the ductal system.
4. Determination of location, dimension, and configuration of the tumour, and measuring its distance to the margins, determination of location and dis-

tance of the radiographic needle, marking as appropriate.

5. Blocking of any suspicious area of the inner part.

6. Blocking of margins: As the slices are made perpendicular to the mammillar-peripheral axis, it is clear that the mammillar and peripheral slices contain margins which can be seen as a plane and can be submitted *in toto* for blocking. The other four margins are sampled from the edges of the tumour-bearing slices and the neighbouring ones (so-called radial sampling).

Definition of positive margins and measuring of macroscopically invisible tumour

Any tumour in mammillary and peripheral tissue blocks is considered as evidence of positive margin. In radial tissue blocks only the presence of tumour in the definitive margins themselves is taken as evidence of positive margin. The distance to the margins of invasive carcinoma as well as of DCIS were determined by ocular micrometry from the slides for measuring smaller spaces. For larger distances, a combination of direct measuring and estimation by reconstruction, based on the standardised handling protocol, was used.

Evaluation of the sensitivity of the standardised procedure

We compared the results of our standardised margin investigation of 100 cases with the analysis of the margin status of 100 BCT specimens, each from two different time periods with different handling. Before 1989 only margins where tumour tissue was suspected on macroscopic examination were investigated microscopically. From 1989 to 1991, margins were evaluated more systematically, but the evaluations were not standardised and did not consider the orientation of the ductal system.

Results

Margin status

In 28% of cases, tumour tissue was found upon the investigation under the microscope, in the margins of 100 consecutive BCT specimens where the margins looked clear macroscopically. In the periods when histological investigations were not carried out on non suspicious-looking margins and when margin assessment was non-standardised, tumour could be found in only 2% and 12% respectively. Based on our standardised practice protocol we discovered invasive carcinoma in 8% of cases investigated under the microscope exclusively as invasive carcinoma, 14% of the tumours discovered were only carcinomas *in situ*, and in 5% were combined invasive and intraductal carcinomas.

Therapeutic consequences

Primary in 233 (71.8%) of 323 women with malignancies there were neither clinical nor mammographic contraindications for BCT. DCIS was found much more frequently than invasive carcinoma within a 5 mm distance to the surgical margin or transsected at the resection line. There were 144 secondary operations (re-excisions or secondary mastectomies) performed because of the positive margin status or because the extent of the DCIS-area was more than 40 mm. Finally, 100 women out of the primary BCT group of 323 patients were advised to undergo mastectomy, and thus 132/323 (40.8%) patients with malignancies were treated by definitive BCT.

Discussion and conclusions

Initial studies on recurrence rates following wide local excision used a margin of excision of 5 cm, but the cosmetic results were poor.[22] Subsequently, the trend has been towards taking less and less tissue. Better cosmetic results has been achieved, but a lumpectomy alone is associated with a high incidence of local recurrence.[23] The hypothesis that recurrence is due to residual tumour is supported by patterns of failure studies.[10, 24] The margin status is shown to be a risk factor for local recurrence.[14,25] Though excision may be clinically adequate, microscopic examination may reveal tumour at the specimen edge,[1,25-27] and therefore confirmation of clearance by pathological examination must be sought.

Our results verify a strong influence of our practice protocol on the results of the examination of BCT specimens: Firstly, there is a higher sensitivity for tumour bearing margins compared with random sampling of margin tissue. Moreover, based on the consideration of the ductal orientation, our protocol offers a better chance to detect *in situ* components of tumour in the margins. With our method we are able to define exactly the tumour

bearing margin and thus also the site of re-excision, if necessary.

Finally, based on our protocol, it is possible to determine the size of the area involved by DCIS. The proximity of DCIS to a marked margin is determined by direct measuring and ocular micrometry. Based on the standardised sampling, we estimated the diameter of DCIS by combining direct measuring and reconstruction in a manner similar to that of the Van Nuys group.[28] This has got very strong implications for BCT: Recent results by the group of Schnitt et al. have shown that an extensive intraductal component (EIC) as defined by Conolly and Schnitt[29] significantly affects local control rates only when the non invasive component contributes to the residual tumour load in the breast.[14] With complete excision for EIC-positive invasive breast carcinomas, irradiation provides a local control rate equal to that of EIC-negative lesions. Therefore EIC *per se* should not be considered a contraindication to BCT unless substantial DCIS remains in the breast.[26]

The standardised practice protocol for the handling of BCT specimens provides the clinical team with more detailed information about margin status and the size of DCIS component of the tumour than was available before.

The aim of standardised evaluation of BCT specimens is to select patients for a re-excision, or for treatment with conversion to mastectomy. We think that such careful planning of treatment assures better tumour control rates and cosmetic outcome than more aggressive surgery.

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Selection of impalpable breast cancer for conservative surgery

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Breast sparing surgical interventions have been accepted worldwide in early symptomatic cancer cases. They should be applied especially in the case of mammographically screened impalpable, invasive or noninvasive cancer. The dilemma is as follows: (1.) total axillary block-dissection or lower dissection or sampling of lymph nodes, (2.) how wide the tumor "ball" should be removed, and (3.) which types of ductal carcinoma in-situ (DCIS) should be handled with special attention, and when total mastectomy should be carried out. Thanks to the efficient mammographic screening, in most of our patients breast conserving operations can be carried out. We are planning to introduce the Van Nuys classification for ductal carcinoma in-situ (DCIS).

Key words: breast neoplasms; conservative surgery; impalpable lessions

Introduction

Comparing the axillary lymph node status of symptomatic and screened small breast tumors, it seems to be evident that the size of the tumor is not the most important factor of aggressiveness.[1]

Many of the impalpable, non-screened cancers are detected by palpation of the enlarged axillary lymph nodes (i.e. occult breast cancer).[3]

Better awareness of the population through media, leaflets, lectures etc. has helped the early detection of breast cancer in many countries. With earlier detection conservative breast surgery can be applied in more and more cases. This is particularly true of screen-detected invasive or noninvasive cancers.[4,5]

Patients and methods

Due to the newly established mammographic screening at the MaMMa Clinic in Budapest, with their referred breast cancer patients the rate of conservative surgery at our Surgical Department reached 85%. During a 21-month period between March 1995 - December 1996, there were 8 impalpable tumors and 40 microcalcifications found among 210 breast cases.

On surgery, 8 impalpable tumors could be found by the help of accurate radiological description. The diameter of the tumors ranged from 6 to 15 mm, and all of them were ductal invasive cancers.

The microcalcifications were marked by wire localisation, and the histological findings were as follow:

ductal invasive cancer	15
lobular invasive cancer	3
DCIS comedo type	5
DCIS non-comedo type	8
fibrocystic disease	4
radial scar	2
fibroadenoma	2
adenomyoepithelioma	1

Discussion and conclusions

As frozen section histology is not always able to determine the real features of the lesion, in certain

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cases a second intervention is necessary for the definitive treatment.[6,7] This was the case in two large comedo type DCIS. Adenectomy or mastectomy and immediate reconstruction should be considered as a second intervention.

Table 1. Axillary lymph node positivity in screened and symptomatic breast cancer patients according to tumor size

	[1]Silverstein et al.		[2]Natl. Oncol. Inst.
	screening	symptomatic	symptomatic
T =< 1 cm	7 %	15 %	55 %
T = 1–2 cm	15 %	32 %	47 %
T > 2 cm		44 %	52 %

[1]Silverstein et al.[2]
[2]Unpublished data of a larger series of the National Oncological Institute, Budapest, Hungary

The relatively high number of impalpable, T_{1a}, T_{1b} tumors provides the reason for decreasing the radicality of axillary lymph node dissection. Only 13 % of screen-detected ≤ 1 cm tumors were found to develop axillary metastases, and 71 % of these had only 1-2 positive nodes.[8] The rate reported by Silverstein et al.[7] was even lower, i.e. 7%. Furthermore, it was stated, that in T1a tumors the frequency of axillary metastases did not exceed 3 %, thus the axillary lymph node dissection should be eliminated. The value of total axillary dissection was discredited by the NSABP B-04 trial. Looking at the increasing number of postoperative morbidity (shoulder-arm impairment, lymphedema, paresthesia, discomfort etc.) many surgeons try to decide the extent of the dissecton intraoperatively. At our surgical departement if there are no macroscopically positive nodes, total blockdissection is not suggested.

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Radiation therapy after conservative surgery in the treatment of early breast cancer

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It is now generally accepted that conservative surgery combined with radiation therapy (RT) represents an appropriate alternative to mastectomy in the treatment of stages I and II breast cancer. In accordance with the development of this knowledge, an increasing number of patients have undergone breast conserving therapy (BCT). Between February 1983 and February 1995, 392 patients were treated by RT at the Dept. of Radiation Therapy in Klagenfurt, Austria. 6 MeV photon beams were applied for homogenous radiation of the entire breast, while electrons were used as standard boost technique for tumor site; 126 patients also received adjuvant chemotherapy (CMF standard) , 92 Tamoxifen and 11 both. In February 1995, 316 persons (81%) were alive without evidence of disease, 39 (10%) developed distant metastases and 18 (4.6%) local recurrences. The latter were salvaged by mastectomy, and 13 are still in a complete remission, while 5 have died of progressive tumor disease. By our preliminary estimation, no significant correlation between the proposed risk factors and the local recurrence rate could be detected. Furthermore, a slight decrease in the single daily dose seemed to have no negative impact on the local tumor control. At least the investigating surgeons have not reported any sequel caused by this boost technique up to now.

Key words: breast neoplasms; breast conserving therapy; radiotherapy; treatment outcome

Introduction

Since the opening of the Dept. of Radiation Oncology in Klagenfurt, Austria, 392 patients were treated with RT after conservative surgery up to February 1995. Thirteen departments of surgery all over Carinthia and Styria have referred their women to our institute after BCT. 69% of the patients have been treated with tumorectomy, 31% with quadrantectomy (or extended resection), both including dissection of the axillary lymph nodes. The follow-up examinations after RT are performed by the attending surgeons.

Since 5 to 6 years ago, the radiation oncologists have partly succeeded in emphasizing the importance of clip marks around the tumor bed. Today about 43% of the tumor sites are determined by clips. Altough we are aware of the possibility of geographical miss of the clips we consider this device useful for indicating the extent of the tumor bed. Nevertheless, the duration of follow-up has been too short to allow a comparison.

Up to 1990, we calculated a single dose of 2 Gy at the surrounding isodose of the breast; a maximum of 2.2 Gy was tolerated. In order to reduce acute side effects we reduced the dose per fraction to 1.8 Gy; a maximum of 2 Gy in the cross-point of the central axis (ICRU) should not be exceeded. Three years later the dose/fraction of the e-boost was decreased to 1.7 Gy.

The aim of this retrospective analysis was to prove the results in relation to international data presented. Moreover, we wanted to evaluate the influence of the changes of dose per fraction on the outcome of the patients.

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Methods

Commonly, the radiation treatment starts 3-5 weeks after surgery. In the case of combined adjuvant radio-chemotherapy the RT follows 2-3 weeks after the third cycle of chemotherapy (sandwich-regimen). 6 MeV photon beams have been generated by the same linear accelerator all over the years. From the beginning, dose calculation was done by computer, based on handgraphs and CT-scans.

Up to 1990, 50 Gy - conventionally split into 2 Gy fractions - were applied 5 days per week. This course was followed by 10 Gy e-boost. Afterwards, we introduced the ICRU-guidelines for dose-prescription and limited single dose at a maximum level of 1.8 Gy (surrounding isodose). Later the boost concept has changed too. Dose per fraction is now 1.7 Gy (85% isodose approximately 1 cm deeper than the bottom of the tumor bed). Risk factors that have been identified by other authors are associated with a significantly higher rate of local recurrences (tumor diameter, grading, extensive intraductal component, hormone receptor status, lymphangio-invasion, positive lymphnodes, resection margin). Patients with high risk parameters were treated with 14 Gy, others with 10 Gy. The boost volume plan and the choice of energy depended on clinical (scar, surgeon's report) and radiological findings. In recent years, more and more surgeons use clip marks (MRT-compatible).

Patients and results

The characteristics of our 392 patients are not different from the comparable cohorts. The distribution by histological pattern is as expected: invasive ductal carcinoma prevails with 83%, while invasive lobular breast cancer represents 7% and other subtypes 10%. Eight women (2%) were treated because of *in-situ* carcinomas; Conservative surgery was performed even in stages T3 (1) and T4 (6) disease. In the case of T4 tumors the diameter was small but infiltration of the dermis had been described. Chemotherapy according to the CMF protocol was used in 126 patients while 92 were receiving Tamoxifen 30 mg for at least 3 years.

The examinations after treatment are performed by the attending surgeons, who send their reports frequently. The median follow-up duration was 36 months (range 5 - 184 months) by February 1995. At that time 316 patients (80%) had been alive with no evidence of disease, whereas 10 (2.5%) still suffered from distant metastases; 28 (7%) had died of the disease and 4 of other causes - 34 are lost to follow-up.

Thirty-eight (10%) patients developed distant metastases and 18 (4.6%) local recurrences; 5 of these patients developed both and died of the disease in the meantime. The remaining 13 patients were in complete remission after having been salvaged with mastectomy.

A recurrence in the pre-treated breast was established in 3.7% of women with positive lymph nodes (n=135) and in 5% of those with negative lymph nodes (n=259). Fifteen patients had T1 tumors at the time of diagnosis. Almost all (17) of the local recurrences were invasive ductal carcinomas, 12 were sub-classified as grade 1 or 2. In only 1 case of relapse, tumor cells were found in the post-resection specimen. Hormone receptor status was generally not determined before 1990.

Concerning the cosmetic outcome, 2 cases of complication were reported to and investigated by us. Both patients developed a painful induration of the whole breast after RT - we were unable to detect an association with autoimmunological disorder, diabetes mellitus or others.

Conclusions

1. Referring to our results and experience, there seems to be no need to change our electron boost concept or to introduce another technique. Still, indications for and the value of the boost are uncertain. Perhaps, the on-going prospective randomized trails will be able to provide answers to some of the questions in near future.

2. Surprisingly, our findings do not sustain the conviction, that certain risk factors imply a higher rate of local recurrences.

3. A decrease of the dose per fraction appeared to improve the acute toxicity (less interruptions of the radiation course) and seems to have no influence on th patients' outcome.

4. The results of radiation therapy after breast conserving surgery at the Dept. of Radiation Oncology in Klagenfurt are similiar to those reported in the literature.

5. To-date, we have not been able to obtain all the recent data from the cooperating surgeons in time. A detailed analysis of the data will be presented at the Symposium in Ljubljana in June 1997.

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Long term local control and survival in breast cancer patients stage I and II after breast conserving treatment

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Purpose: *1. To present 9 years survival and local control rates in our patients*
2. To establish the eventual impact of our management strategies and some patients' characteristics on the treatment results

Patients and methods: *From January 1980 till December 1991 579 breast cancer patients were treated with conservation surgery and radiotherapy at the Institute of Oncology in Ljubljana. There were 274 patients with a T1 tumor and 305 with a T2 tumor. Quadrantectomy was performed in 332 patients and tumorectomy in 247 patients, an axillary dissection in 508 patients. Histologically, 309 patients had negative axillary dissection while 199 had histologically confirmed axillary metastases. Postoperatively all patients were irradiated with 50 Gy to the whole breast in 5 weeks, followed by a boost of 6-20 Gy in 504 cases. Radiotherapy to regional nodes (axilla and supraclavicular), TD 50 Gy was given to 58 patients who had no axillary dissection performed. Adjuvant chemotherapy was given to 197 patients and hormonal therapy to 91 patients.*

Results: *With a minimum follow-up of 5 years and a median follow-up of 9.2 years, the 9 year actuarial local recurrence free rate in our patients is 93.8% and the 9 year actuarial survival rate is 80%.*
Statistically significant prognostic factors for survival were as follows: axillary nodes status ($p < 0.001$), tumor size ($p < 0.001$), hormonal receptor status ($p < 0.001$), tumor grade ($p < 0.005$), local recurrence ($p < 0.005$). There was no impact of age, the extent of surgery, RT dose, adjuvant chemotherapy or hormonal therapy on survival.
Statistically significant prognostic factors for local control were as follows: age ($p < 0.001$), extensive intraductal component ($p < 0.001$), RT dose ($p < 0.005$), the extent of surgery ($p < 0.05$). RT dose higher than 50 Gy (boost) was significant only in the group of patients treated by tumorectomy, while the extent of surgery was important only in the group of patients who received TD 50 Gy (no boost).
There were 3 axillary failures noted, 1/58 irradiated without axillary dissection, 1/13 patients without axillary dissection and no radiotherapy and 1/508 dissected but not irradiated axilla (199 patients in this group had histologically confirmed metastases).

Conclusion: *Treatment by means of conservation surgery and radiotherapy is associated with low breast cancer recurrence. As the extent of surgery and radiotherapy dose are inversely related in our patients, we conclude that tumorectomy with a boost to the tumor bed is probably cosmetically preferable to quadrantectomy. Omission of axillary irradiation after axillary dissection even in patients with axillary metastases appears appropriate.*

Key words: breast neoplasms; conservation surgery; radiotherapy; survival rate; local control; prognostic factors

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Factors of local recurrence rate after whole breast irradiation with and without boost radiotherapy after breast conserving surgery

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The authors analysed and evaluated 111 records of patients after breast conserving surgery (BCS) followed by radiotherapy. They found 6 factors that could be examined on a routine basis, which were grouped as "high" and "medium" risk factors. The authors consider the boost technique necessary in the presence of 1 "high" or 2 "medium" risk factors.

Key words: breast neoplasms; breast conserving surgery; radiotherapy; local recurrence; risk factors

Introduction

Breast conserving therapy (BCT) is a success story in clinical oncology, particularly with reference to radiation oncology. The idea behind BCT was to combine limited surgery for the removal of gross disease and moderate-dose radiation therapy for the eradication of residual microscopic disease. Previously, local therapy consisted of either deforming surgical resection or high-dose radiotherapy. This new concept employed surgery and radiotherapy in a way that limited the toxicities of each, but optimized local tumor control while retaining the function and cosmetic appearance of the breast. The technology behind BCT involved the use of supervoltage equipment, simulation, different boost techniques (interstitial, electron) and the beginnings of computer-based treatment planning.[1] The number of BCS is growing continuously (replacing mastectomy) and is common in most surgical wards in our country. After BCS, percutaneous irradiation of the whole breast is definitely indicated since BCS involves some risk of recurrence in the remaining tissue. However, no significant differences in overall survival at 10 years were found in patients with mastectomy vs. those with BCS plus radiotherapy (4891 women), with more extensive surgery vs. less-extensive surgery (4818 women), or with axillary clearance vs. radiotherapy as adjuncts to mastectomy (4370 women).[2] The authors are seeking answers to the following questions:

- which are the risk factors that increase the frequency of local failure, and
- in which cases and whether it is necessary to perform the "boost" supplementary irradiation to the original tumor bed?

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Patients and methods

111 BCS plus radiotherapy patient records were suitable for evaluation from Jan. 1986. till Dec. 1990. The radiotherapy consisted of 50 Gy to the whole breast tissue in 56 cases (Telecobalt or 6 MeV photon) and whole breast photon plus 12-20 Gy boost (RadioCobalt needles or HDR-Iridium-AL) in 55 cases. The patients' median age was 55.6 years vs. 48.8 years respectively, with 61.8 vs. 62.5 month median follow up. In the case of involved axillary nodes (19 pts, 1-3 lymph nodes) percutaneous photon irradiation with 46-50 Gy/5 weeks was delivered to the axillary region. All the patients had tumors which measured less than 2 cm in diameter (T1).

Results

We detected only 9 local recurrences: 6 patients received external radiotherapy alone (median time to local recurrence: 11.6 mo.), the other 3 patients received external plus interstitial boost radiotherapy (median time to local recurrence: 23.0 mo.). There was no significant difference between the median age of groups with and without recurrence (50.1 vs. 52.5 years respectively).

The local recurrence appeared in the expected percentage independently of the primary tumor size (in 7-9 %). In stage pT1a (pN0) local recurrence did not occur. We also did not find any significant difference between the premenopausal and postmenopausal groups. But: lobular and lobular plus ductal histological types of tumors were encountered with a substantially higher frequency.

In the case of endolymphatic spread of tumor cells, the occurrence of local recurrences was also higher. Of 20 patients with endolymphatic spread 19 had positive axillary nodes (see above).

Among 12 patients with histologically proven extensive intraductal component (EIC) 3 presented with recurrences (10 patients had microcalcifications on mammogram).[3]

In 6 cases the excised margins were infiltrated; despite 5 re-excisions, local recurrence occurred in half of the cases (3 patients). In one case, re-excision was not performed and the patient developed a big, infiltrating local recurrence.

In most cases (85 patients) the resection margins were free of tumor, there was only 1 local recurrence. If the excised tissue had a free margin of 5 mm or less, the local rec. occurred at 20%.

Discussion and conclusions

We examined the role of possible risk factors after BCS for T1 breast tumors treated by radiotherapy (with vs. without boost). The overall tumor recurrence rates were 6/56 (10.7 %) in the external beam group and 3/55 (5.4 %) in the external beam plus boost group. There was no significant difference in the breast relapse rate in patients receiving either interstital 192 Ir boost or 60 Co manual interstitial boost. The frequency of breast failure was not influenced by age, tumor size (all patients had less than 2 cm tumors) and menopausal stage. Local recurrences developed 2.5-3.0 times more often in the case of histologically proven endolymphatic spread, EIC positivity and close resection margins (less than 5 mm). These 3 factors were referred to as "medium risk" factors.

The recurrence became more frequent (4.0-4.5 times) if the histological report described invasive lobular or invasive ductal-lobular carcinoma. If the excised tissue margins were infiltrated, local failure occurred 8 times more often, despite of re-excision. Therefore, the latter 3 factors were referred to as "high risk" factors (Table 1)

Table 1. Probability of local failure after BCS plus radiotherapy

Tumor size	1 x
Menopausal status	1 x
Endolymphatic spread	2.5 x
EIC positivity	3 x
Histology: cc. lobulare invasivum	4 x
cc. lobulare et ductale	4.5 x
Excision margin: free margin	1 x
less than 5 mm	2.5 x
infiltrated margin	8 x

The boost therapy reduces the local failure rate, regardless whether the patients. have risk factors or not, by about 50 %. (Table 2)

Table 2. Local failure rate in patients with and without risk factors according to the type of radiotherapy

Pts. no.	Whole breast radioth.	Whole breast plus boost radioth.
Total 111 pts	6/56 (10.7 %)	3/55 (5.4 %)
Pts. with 2 moderate or 1 high risk factor (n : 29)	6/14 (42.8 %)	3/15 (20.2 %)

The effect of boost radiotherapy on the survival is under analysis now.

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Limb sparing in osteosarcoma of the extremity treated by neoadjuvant chemotherapy. Fifteen-year experience at the Rizzoli Institute

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In recent years the number of patients with osteosarcoma of the extremity treated by limb salvage (LS) has been constantly increasing. For instance, in five neoadjuvant studies carried out at our Institute between the years 1983 and 1995, the rate of limb salvage increased from the 72% in the first study (1983-1986) to 95% in the last study (1993-1995).

This increased number of LS is necessarily associated with an increased risk of inadequate surgical margins, and we know that in the cases when osteosarcoma has been treated by surgery alone, inadequate surgical margins have been followed by local recurrences in more than 50% of patients. Therefore, the main question remains whether limb salvage procedures are really safe. Or, in other words, are we entitled to reduce surgical margins, relying on adjuvant chemotherapy for local control?

To answer these questions, we evaluated 533 patients primary high grade central osteosarcoma of the extremity, up to 40 years of age, without evidence of metastases on diagnosis, treated at our Institute by neoadjuvant chemotherapy between the years 1983 and 1994. Chemotherapy was performed according to five different protocols used successively. Surgery was a limb salvage procedure in 83%, an amputation in 12%, and a rotation-plasty in 5% of patients.

At a median follow-up of 7.5 years (2.5-13), 322 patients (61%) remained continuously free of disease, 205 relapsed, and 5 died for chemotherapy related toxicity.

The results achieved in these five studies were quite different, with a 3-year disease free survival (DFS) ranging between 50% and 80%, according to the chemotherapy protocol used.

Thirty-one (15%) of patients who relapsed had a local recurrence (LR). The rate of LR in all the 527 evaluable patients was 5.9%. The median time to local recurrence was 21 months (5-76 mos), and in 3 patients (10%) LR appeared more than 4.5 years after surgery.

The rate of LR were found to be unrelated to site, volume, and histotype of the tumor, hospital of biopsy performance, route of cisplatin (CDP) infusion (i.v. or i.a.), and the presence/absence of pathological fractures. According to the type of surgery, in patients treated by LS, the rate of LR was twice that seen in patients treated by amputation or rotation-plasty (28/438 - 6.3% vs. 3/89 - 3.3%). This difference, however, is not statistically significant, probably due to the small number of amputated patients.

The rate of LR was found to be related to:

a) surgical margins;

b) histologic response to chemotherapy.

According to the surgical margins, the rate of LR was found to be higher in patients with inadequate surgical margins (marginal, intralesional or contaminated) than in patients with adequate surgical margins (radical or wide): 14/467 - 3% vs. 17/60 - 28%. This difference is highly significant ($p<0.0001$).

According to the histologic response to chemotherapy, the percentage of LR was significantly higher in poor responders (necrosis less than 90%) than in good responders (90% or more tumor necro-

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sis): 18/185 (9.7%) vs. 13/342 (3.8%). However, no differences were found between patients with total necrosis and those with necrosis between 90-99%. It is important to stress that LRs were also observed in 4 patients with total necrosis.

Even though both, surgical margins and necrosis, are important factors influencing the LR, surgical margins seem to be more important. In fact, as regards patients with inadequate surgical margins, the rate of LR was also very high in those who had a good histologic response to chemotherapy (7/34 - 20.5%) while for patients with adequate surgical margins the rate of local recurrence was relatively low (8/159 - 5%), also in those with a poor response.

According to different studies, the highest rate of LR was registered in the last one, reporting the highest number of LS (96%) performed, while the lowest rate of LR was observed in the second study also using the protocol that gave the highest rate of 3-year disease-free survival (80%). It is interesting to note that that the second study was the only one in which no local recurrences were observed in patients with adequate surgical margins. This data could mean that a more effective chemotherapy - besides reducing the rate of systemic relapse - probably also improves local control.

In all but one case, local recurrences were associated with metastases. In 19 cases metastases followed LR; in 6 cases the two events were concurrent, and in 5 cases LR followed the appearance of metastases.

Bone metastases as the first site of systemic recurrence we found to be significantly more frequent in patients with LR than in those without LR: 10/30 (33.3%) vs. 17/176 (6.9%); $p< 0.0003$. Such different behaviour of metastatic spread could indicate a different biology of the tumours which recur locally.

The outcome after relapse in those patients who experienced LR was as follows: one patient is alive and free of disease 15 months after the treatment for LR; 30 patients are dead or alive with uncontrolled disease. This postrelapse outcome is significantly worse than the one in patients who relapsed with metastases only. In fact, the rate of patients who are free of disease 1-5 years after the last treatment is 28% for the 174 patients who relapsed with metastases alone, and only 3% for the 30 patients who also had local recurrence ($p = 0.006$). In other words, the probability of cure after relapse is only 3% for patients with local recurrence vs. more than 25% for patients who relapse only with metastases.

We conclude that in osteosarcoma of the extremity treated by neoadjuvant chemotherapy, it is possible to avoid amputation in a majority of patients, and limb-salvage procedures are relatively safe. However, when such a procedure results in inadequate surgical margins, the risk of LR is high - especially if coupled with a poor response, in spite of the adjuvant chemotherapy used. Therefore, performing a limb-salvage procedure, the evaluation of surgical margins is mandatory, because the outcome in patients who relapse with local recurrence is very poor, significantly worse than the outcome in those who relapse with metastases only.

For these reasons we believe that a LS should be planned only when the preoperative staging seems to assure the possibility of achieving adequate surgical margins. However, if at the pathologic examination of the surgical specimen, surgical margins are found to be inadequate, and immediate amputation should always be considered, especially if the histologically confirmed response to chemotherapy has been poor.

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Organ and function sparing treatment for soft tissue sarcomas: The Memorial Sloan-Kettering experience

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Introduction

The primary treatment for soft tissue sarcomas of the extremity or superficial trunk has evolved significantly over the last 25 years. Conservative, limb-sparing procedures have now replaced amputation as a primary surgical modality and is now considered standard of care. The efficacy of limb-sparing surgery was demonstrated in a randomized trial reported by Rosenberg, *et al*[1] comparing amputation with conservative surgery and adjuvant radiotherapy. This landmark study demonstrated equivalent survival rates. The reported local control rates with limb-sparing surgery and EBRT have been reported to be in the range of 80-96%.[2,3] More recently, investigations have centered around attempting to identify which patients benefit from this treatment, and which patients may be treated with conservative surgery alone. In addition, considerable debate continues to exist regarding the impact of local control on the development of distant metastasis and disease-specific survival for patients with soft tissue sarcomas. These issues have been addressed at MSKCC through a prospective randomized trial initiated in 1982. Patients with soft tissue sarcomas were randomized to receive either surgery alone or surgery plus adjuvant radiation therapy. RT has been the preferred delivery method of adjuvant radiation therapy at our institution. Both preliminary and long-term data have been reported.[4] Based on our accumulative experience, we are able to make long-term observations and conclusions regarding several issues including:(1) appropriate selection for BRT, (2) appropriate selection of BRT combined with EBRT for patients with positive surgical margins, (3) the functional preservation of limb mobility and strength testing, as well as (4) the ability of neurovascular structures to tolerate BRT in the recurrent setting.

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Rationale of BRT

This section deals with the evolving interest of using BRT as an alternative to EBRT in the adjuvant setting as a means of delivering high doses of radiation to the tumor bed with maximal sparing of normal tissues. The advantages of BRT include shorter overall time duration of therapy, convenience and comfort for selected patients, potential cost advantages of shorter treatment, after-loading computerized dose optimization, and minimization of dose to normal tissues while maximizing dose of radiation to the tumor bed. In addition, BRT can be used with or without external beam in combination or as an adjuvant modality in the recurrent setting where external beam radiation can no longer be performed. Finally, the ability of BRT to begin within one week of surgery allows optimal treatment during a time when a lower tumor burden exists with less hypoxia.

BRT technique

BRT consists of an interstitial implant via after-loading catheters using Iridium-192 sources. Typically the tumor bed is jointly evaluated by both the surgeon and a radiation oncologist after removal of the primary tumor. The target area is defined by

adding a 2 cm margin in the superior and inferior dimension, as well a 1.5 to 2.0 cm margin in the medial and lateral dimension. The radiation oncologist then implants the target area with after-loading catheters, placed percutaneously, and spaced usually in 1 cm increments. The catheters are sutured in place in the target region with chromic cat gut sutures, then fixed to the skin with buttons and silk sutures. A drain is placed by the surgeon to the tumor bed and the wound is closed at the skin surface. Generally on postoperative day 2 or 3, the patient is brought to the simulation suite where localization films are taken and computerized dosimetry is then performed. A loading plan is then created to deliver a minimum dose of 40-45 Gy over 4-6 days with Iridium-192. The patient is typically loaded on postoperative day 5 or 6.[5]

For patients receiving BRT as a boost in conjunction with EBRT, we typically deliver a dose of 20-25 Gy followed by an external beam dose in the range of 45-50 Gy. EBRT is usually delivered 2-3 weeks after the completion of the BRT treatment. The optimal dose of BRT in the combined setting is not known.

Early experience

Hilaris *et al*, reported an initial experience at MSKCC in 1985.[6] 17 patients with soft tissue sarcoma of the extremities were treated with a conservative limb-sparing operation followed by BRT to the tumor bed. 13 patients had high-grade histology, and 15 had involved resection margins. 6 of the 17 patients would have required amputation to resect all disease. Despite what was considered an unfavorable group, implants were performed using Iridium-192 with after-loading catheters, to a median dose of 40 Gy in 4 to 5 days. Similar margins as described were used. With minimum follow-up of 34 months there were local recurrences. These remarkable results led to the conclusion that adjuvant BRT could be effective in eradicating residual sarcoma.

Similarly, Roy *et al* reported the results of adjuvant BRT for liposarcomas of the extremity. 33 patients were treated with limb-sparing surgery followed by BRT.[7] Although treatment consisted of complete gross resection, no effort was made to resect either nerve or blood vessel, and tumor was dissected off the neurovascular bundle. 45% of patients had high-grade histology and 18% had involved surgical margins. Patients received a mean dose 41.8 Gy with Iridium-192. The median follow-up was 2 years, and only 1 patient developed local recurrence yielding an overall local control rate of 97%. The one patient who failed was actually salvaged with wide excision plus further BRT. The overall survival at 5 years was 80%, and the disease-free survival was 66%. 16% of patients developed distant metastasis within 1 year of treatment. Complications occurred in 27% of cases due to either delayed wound healing or wound ulceration. 3 patients required surgical wound debridement.

Prospective data

This initial favorable experience led to the desire to test the role of adjuvant radiation therapy in a prospective setting. Specifically, the issue of the need for adjuvant radiation therapy after complete resection was addressed as well as whether the BRT technique was adequate. In addition, a prospective trial was needed to determine selection criteria for adjuvant therapy. For these reasons, a prospective randomized trial was designed and performed to explore the following questions: (1) Which patients, if any, benefit from adjuvant irradiation after complete resection? and (2) Is adjuvant BRT alone, with minimal margins an effective adjuvant therapy? Since that time, additional questions that have been answered based on our prospective data include the role of combined BRT and EBRT for patients with positive margins and the maximal functional outcome of this limb-sparing approach.

Between July of 1982 and July 1987, 126 patients were randomized to receive either surgical resection alone or surgical resection and adjuvant BRT. Inclusion into the trial included soft tissue sarcoma involving the extremity or superficial trunk with all patients undergoing a complete, limb-sparing resection. Patients were randomized at the time of surgery to receive or not receive adjuvant BRT. The range of dose delivered was 42 to 45 Gy over a 4 to 6 day period. Minimum follow-up was 4 years, with a median follow-up of 63 months for all living patients in the most recent update.

Results of the MSKCC randomized trial: Local control was significantly improved with BRT. When analyzed by grade, the local control advantage was limited only to patients with high-grade lesions. Local control for BRT was 90% vs. 69% for no BRT for high-grade patients (P=.013) he local con-

trol for the BRT group compared favorably with other series reporting treatment with adjuvant radiation therapy. This data challenged the concept of wide-field treatment as necessary as a routine procedure.8 Despite excellent local control, this did not translate into an improvement in survival as well as impacting on incidence of distant metastasis. This suggests that distant metastasis may already be present at the time presentation and are too small to detect. However, this does not deemphasize the importance of obtaining local control with this approach to maximize quality of life despite the fact that survival may not be affected.

This trial aided in selecting out patients for adjuvant BRT. There was a clear benefit for high-grade lesions but no benefit for low-grade tumors. The selection of patients for adjuvant EBRT for low-grade sarcomas has been previously addressed in other series.[3,8] Local failure in the patients in our trial who had low-grade lesion was in the range of 20 to 30% and was not affected by an adjuvant implant. This suggests the need for adjuvant irradiation. The inability of BRT to impact on local control may a function of tumor biology and kinetics. Specifically, this may be a result of the small dwell-time of the implant and thus the inability to catch cells in a radio-sensitive phase of the cell cycle. This may be an advantage for EBRT.

BRT alone vs. BRT boost plus external beam irradiation

At MSKCC the predominant form of adjuvant therapy has been in the form of BRT alone. However, the vast majority of cases in which BRT is used in the community setting has been in conjunction with EBRT. The prospective experience at MSKCC challenges the concepts by Suit and Lindberg in earlier experiences.[3,8] This specifically deals with the need for wide margins (Greater than or equal to 5 cm) as well inclusion of the scar and drain sites. Our randomized data for BRT alone in the setting of negative margins disputes this concept.[9] However, at our institution, combined BRT and EBRT have been used in the presence of positive surgical margins. Alekhteyar *et al* have reviewed this issue.[10] They found that for patients with positive resection margins, the use of BRT plus EBRT produce better local control that BRT alone (9 out of 10 [90%] vs. 10 out of 17 [59%]). This showed a trend toward statistical significance (p=0.08). No difference however was seen in patients treated with either BRT or BRT plus EBRT with negative margins. No significant differences in overall wound complication rates or in the combined major and moderate wound complication rates were seen. Based on this retrospective analysis, it has been the policy since 1992 to combine BRT as a boost followed by EBRT as optimal treatment for patients with positive surgical margins. This study however was unable to determine the clinical relevance of recurrent tumor vs. primary tumor on local control and patients with positive margins who were treated with combined treatment. The advantage of combined BRT plus EBRT over BRT alone in patients with positive margins is most likely a reflection of higher doses of radiation to a larger volume of tissue.3 This observation has been substantiated by Gemer *et al* from the University of Kansas experience. The author has evaluated local control in conjunction with a number potential prognostic factors in patients receiving combined BRT and EBRT for soft tissue sarcomas. The only variable impacting on local failure was a ratio of tumor volume that received 65 Gy to the tumor volume (TV_{65}/TV). All but one of the local failures had a ratio less than 1, signifying that tumor dose of 65 Gy was important in obtaining local control.[11] What is unknown is the optimal dose of BRT in conjunction with EBRT. Another unknown is the optimum dose of BRT used alone. In general, we have used 40-45 Gy prescribed to the defined volumes as outlined at the time of localization. There is no significant data on prescription doses of BRT alone in the 65 Gy dose range.

Special situations: Sarcomas involving neurovascular structures

A challenging and not uncommon problem is to treat sarcomas that involve major neurovascular structures.[12] As is often the case, they are considered unresectable and generally receive preoperative radiotherapy or require amputation. Zelefsky *et al.* reported on a series of 45 patients with locally advanced soft tissue sarcomas that either involved or extended to major neurovascular structures. A limb-sparing approach was utilized despite that the local disease was extensive. An en-bloc resection was done with sharp dissection of tumor off major nerve and vascular structures. In nearly 70% of cases, gross disease was left behind or microscopic

tumor was at or close to the surgical margin. 64% of the patients had tumors greater that 10cm and 68% of the patients had high-grade histology with and additional 28% with pathological evidence of invasion of neurovascular structures. Treatment consisted of BRT. A median dose 44 Gy was delivered with Iridium-192. Some patients had supplemental external beam radiation and/or chemotherapy. The 5 year actuarial local control was 70%. Several patients failed at the periphery of the implant volume, suggesting that for this subset margins wider that 1.5 to 2.0 cm may be optimal. he 5 year actuarial "in-field" local control rate 79%. The 5 year distant metastasis-free survival rate was 69%. These numbers, despite this unfavorable group of patients compare favorably with the Massachusetts General Hospital experience for patients with large high-grade sarcomas.[2] Local control with postoperative EBRT was 68% and with preoperative EBRT 83%. The 5 year actuarial disease-free survival rate with preoperative EBRT was approximately 50%.

A concern of radiation neuropathy arises when the neurovascular bundle is implanted. The incidence of neuropathy in the Memorial series was 9%. All 4 patients who experienced this morbidity received a total cumulative dose to the peripheral nerve of greater than 90 Gy when prior external beam irradiation (3 patients) is added to the implant dose. Although there is no biologically proven way to summate the dose, it shows that the peripheral nerve was actually tolerant to BRT. No patients who received doses less than 90 Gy developed radiation neuropathy.

Conclusions and future directions

We continue to use BRT alone for high-grade sarcomas with negative surgical margins in less than 10cm. For larger tumors or with positive surgical margins we generally combine BRT as a boost followed by EBRT. We are currently exploring the use of fractionated high dose rate BRT as an alternative to low dose rate BRT as a means of further reducing hospital stay and costs to the patient. Data from Raben *et al.* from the University of Alabama, Birmingham experience (personal communication) appear to suggest that high dose rate fractionated BRT as a boost treatment is feasible and cost-effective.13 Also, recent data from the Massachusetts General Hospital suggesting an improvement in disease survival and distant metastasis-free survival for Stage IIIB extremity sarcomas with the use of preoperative MAID chemotherapy further emphasizes the importance of limb-sparing and functional outcome.

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Malignant bone tumours of the extremities: The role of limb sparing surgery

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The aim of our retrospective analysis was to evaluate the treatment outcome in 88 patients with malignant bone tumours of extremities treated in Ljubljana between 1980 and 1995. The histologic type of tumours were: osteogenic sarcoma 61, chondrosarcoma 12, Ewing sarcoma 4, PNET 2, malignant gigantocellular tumour 2 and unclassified malignant tumour in 7. Of these 40 were resected and 48 amputated. The percentage of amputations is decreasing by time (first 5 year period 74%, second 46% and third 42%). The overall survival at ten years for the resected patients is 60% and for the amputated 50%, while these figures for patients with osteosarcoma are 52% and 34% respectively. We could achieve an improvement of our results with strict use of core needle biopsies, application of more effective chemotherapy preoperatively and multidisciplinary surgical approach.

Key words: bone neoplasms; amputation; extremities; survival rate

Introduction

With the development of effective preoperative chemotherapy for malignant bone tumours limb sparing procedures replaced amputations in an important percentage of patients.[1]

The aim of our retrospective analysis was to evaluate the treatment outcome in patients with malignant bone tumours of extremities treated in Ljubljana between 1980 and 1995.

Patients and methods

During this period 88 patients with malignant bone tumours of extremities underwent treatment. Chemotherapy was administered at the University Paediatric Hospital or Institute of Oncology, Ljubljana. Surgery was performed at the University Orthopaedic Hospital with a combined team consisting of an oncological surgeon who performed the resection of the tumour, and orthopaedic surgeon for reconstruction. Of the 88 patients treated 40 had a limb sparing procedure (15 males, 25 females, age 9 to 64 years, median 21 years), and 48 were amputated (32 males, 15 females, age 6 to 68 years, median 25 years). Tables 1, 2 and 3 show the distribution of TNM Stage,[2] site and histology between the resected and amputated patients. Table 4 shows the distribution of TNM Stage in osteogenic sarcoma patients for whom follow-up data are available. In the resected patients the preoperative diagnosis was obtained by open biopsy in 20 and by core needle biopsy in 20 patients. In the amputated patients the preoperative diagnosis was obtained by open biopsy in 33 and by core needle biopsy in 15. Preoperative histology erroneously classified 3 cases of classical osteogenic sarcomas as paraosteal osteogenic sarcomas. Preoperative chemotherapy was administered in 26/40 resected patients and in 29/48 amputated patients.

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Table 1. Distribution of all patients by TNM Stage and type of surgery

	Ia	Ib	IIa	IIb	IVa	IVb	All
Resections	2	5	12	19	0	2	40
Amputations	1	6	1	36	1	3	48
All	3	11	13	55	1	5	88

Table 2. All patients by site of primary tumour and type of surgery

	Resections	Amputations	All
Distal femur	21	23	44
Proximal femur	2	1	3
Distal tibia	2	5	7
Proximal tibia	6	15	21
Humerus	8	4	12
Other	1	0	1
All	40	48	88

Table 3. All patients by histology and type of surgery

	Resections	Amputations	All
Osteogenic sarcoma	22	31	53
Paraosteal osteogenic sarcoma	6	2	8
Chondrosarcoma	7	5	12
Ewing sarcoma	2	2	4
PNET	1	1	2
Gigantocellular tumour	1	1	2
Unclassified malignant tumour	1	6	7
All	40	48	88

Table 4. Distribution of osteogenic sarcoma patients with available follow-up information by TNM Stage and type of surgery

	Ia	Ib	IIa	IIb	IVa	IVb	All
Resections	1	2	5	15	0	2	25
Amputations	0	2	1	22	1	3	29
All	1	4	6	37	1	5	54

Surgery in resected patients

After resection of the tumour the reconstruction was performed with endoprothesis in 24, in 3 with rotation plasty tibia pro femur, in 3 with autograft fibula pro humerus (two of them with vascularized graft and microsurgery) in 7 patients with a combination of auto and homografts. In 3 patients expendable bones (2 fibulas, 1 clavicle) were resected.

Surgery in amputated patients.

5/48 patients had pathologic fractures at the site of the tumour, in 13/48 patients an inadequate surgical procedure was performed previously (excochleation of the tumour) elsewhere, and in 3 patients there was a rapid progression despite chemotherapy. All others had large advanced tumours and a resection was not feasible.

Results

Table 5 shows the grade of necrosis after preoperative chemotherapy (almost all osteogenic sarcoma patients) in resected and amputated patients.

Table 5. Effect of preoperative chemotherapy and type of surgery performed

	Grade I	Grade II	Grade III	Grade IV	All
Resection	5	9	5	7	26
Amputation	14	8	3	1	29
All	19	17	8	8	53

Out of the 40 resected patients 26 are alive, one of these with pulmonary metastases, 10 patients died and 4 are lost to follow-up. Causes of death were local recurrence and generalised disease in 5 and generalised disease in 5 patients. In the group of 26 survivors there were 10 patients with grade III and IV response to preoperative chemotherapy whereas in 10 patients who died only one had grade IV response. Complications after surgery occurred altogether in 12/40 patients and were as follows: local infection requiring amputation in 2 patients, 3 loosening of the prosthesis requiring replacement and fracture of the prosthesis in 1 patient. There were 7 local recurrences. In 4 of these amputations were performed, 2 patients refused further treatment.

Out of the 48 amputated patients 20 are alive without evidence of disease, 4 are alive with metastatic disease, 17 patients died and 7 are lost to follow up. Causes of death were local recurrence and generalised disease in 2 patients, and generalised disease in 14, one patient died in the postoperative period due to heart failure.

In Figure 1 overall survival of all patients by type of surgical procedure is shown (Kaplan-Meyer method). In Figure 2 the same plot is shown for the patients with osteogenic sarcoma with available follow up information.

Discussion and conclusions

In our series of 88 patients with malignant bone tumours we performed limb sparing surgery only in 40 but in Figure 3 we can see that the proportion of

amputations is decreasing substantially by time. This rather low percentage of resections can be attributed to the advanced stage of tumours in our series as well as previous inadequate surgical interventions. Even in the group of patients with resections 50% had IIb or IVa stage of disease according to TNM classification.

The overall incidence of local recurrence 7/40 (17.5%) in the resected patients and 2/48 (4%) in the amputated patients is high in comparison with many similar reported series[3,4] and could be connected either with advanced stage or poor effect of preoperative chemotherapy or high incidence of previous inadequate surgery in our series.

We could achieve an improvement of our results with strict use of core needle biopsies, application of more effective chemotherapy preoperatively and multidisciplinary surgical approach.

Resection of tumours should be performed by an oncologic surgeon and reconstruction by an ortopeadic and plastic surgeon.

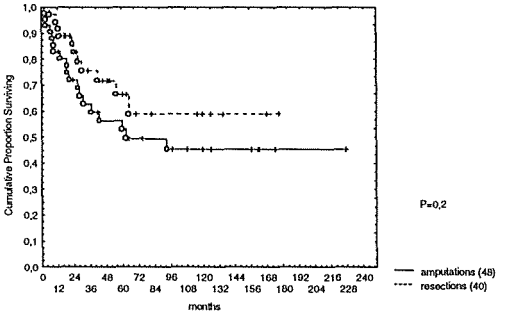

Figure 1. Overall survival of resected and amputated patients for bone sarcomas of the extremities.

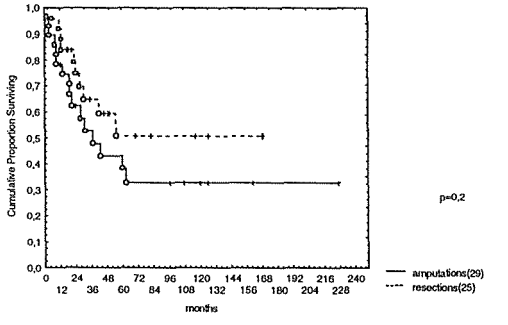

Figure 2. Overall survival of resected and amputated osteosarcoma patients.

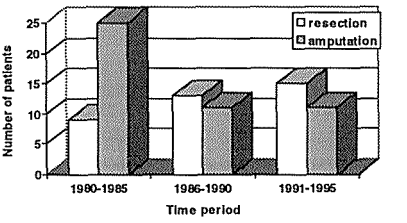

Figure 3. Proportion of amputations Vs resections in three 5-year periods from 1980 to 1995.

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Resections of pelvic bone and sacrum, Ljubljana experience

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From 1976-1996, 85 patients with tumors in the pelvic region were operated on, of these 70 were pelvic bone resections and 15 hemipelvectomies. Of the 70 patients who underwent a pelvic bone resection there were 45 primary malignant bone tumors, 11 locally advanced soft-tissue sarcomas, 3 locally advanced primary carcinomas and 11 benign locally aggressive bone lesions. Of the 15 patients who underwent a hemipelvectomy 11 had primary bone sarcomas and 3 soft tissue sarcomas. The overall survival of patients with malignant tumors who were resected and those who underwent a hemipelvectomy was similar (at 5 years 50% for resected, 60% for those with hemipelvectomy; p=0.27). The quality of life after anterior and posterior resections is from good to excellent, when no major nerves have been sacrificed.

Key words: bone neoplasms; pelvic bones resection; hemipelvectomy

Introduction

The Institute of Oncology Ljubljana is the oldest institution of this sort in the territory of the former Yugoslavia. Until the late 1960's, it was mainly a radiotherapeutic institution, later to become a comprehensive cancer center with a fairly strong surgical oncology unit. Twenty years ago a multidisciplinary team for bone and soft-tissue sarcoma treatment was formed. The first hind-quarter amputation in the institute was performed in 1976 and the first pelvic resection in 1979. This report presents the experience of the very same surgical team in treating tumors of the pelvic region.

Patients and methods

From 1976-1996, 85 patients with tumors in the pelvic region were operated on, of these 70 had pelvic bone resection and 15 hemipelvectomy. The resection itself was accomplished by an oncologic surgeon and the reconstruction by an orthopedic one.

A quarter of the patients had already undergone a previous surgery elsewhere, while many of the remaining ones had been referred to us as unresectable. Of the 70 patients who underwent a pelvic bone resection there were 45 with primary malignant bone tumors (17 chondrosarcomas, 7 osteosarcomas, 7 chordomas, 6 Ewings and 8 tumors of other type), 11 with locally advanced soft-tissue sarcomas, 3 with locally advanced primary carcinomas and 11 with benign locally aggressive bone lesions (prevailing osteoblastomas). Of the 15 patients who underwent a hemipelvectomy 11 had primary bone sarcomas and 3 soft tissue sarcomas.

The resected patients (70) were 1 - 77 years old (mean 38 yrs); of these, 33 were females and 37 males. Almost all of them had large tumors (only one was T_1). At the time of surgery 2/70 patients had metastatic spread in the lymph nodes and 5/70 distant metastases. In the pathologist's report 13/70 had satellite nodules around the tumor and 4/70 blastomatous venous thrombi. In slightly more than half of the cases the malignancy grade was high; 32/70 tumors were growing over the midline. Half of the patients had been treated by chemotherapy and/or radiotherapy prior to resection.

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The time needed for resection was 2-18 hours (mean 7.6 hours). Blood replacement during the procedure was 350-27.300 ml (mean 4600 ml).

In order to classify our procedures we added another two segments to the frontal, acetabular and posterior pelvic segments as classified by Enneking,[1,2] i.e., the sacral and lumbar. Because of the tumor's extent a partial resection of the lumbar vertebrae was required in 14/70 cases, together with the resection of other parts of the pelvis. In 30/70 cases the resection affected only one segment (sacrum in 12/30), in 21/70 two segments, in 17/70 three, in 1/70 four, while in 1/70 cases all five segments were affected.

In some cases, besides bone resections, a resection of visceral organs (large bowel 6/70, urinary bladder 2/70), thigh muscle groups (7/70) and/or nerve roots was necessary.

Due to the usually enormous deficits of soft tissues after tumor resections, the reconstructions were as simple as possible. In our opinion, there is no need for bone reconstruction of the frontal part of the ring and after posterior resections, with a narrow bone-bridge remaining. After complete dorsal resections, simple autotransplants were used, while after incomplete acetabular and lumbo-sacral resections, homotransplants were occasionally used. After real "inner hemipelvectomies" the femur was attached to the bone remnants by simple means.

Results

There were 3 serious intraoperative complications encountered: a complete rupture of the external iliac artery - successfully taken care of, a massive bleeding causing postoperative ARDS and death, and an unsuccessful vessel reconstruction resulting in immediate hemipelvectomy.

Postoperative bleeding and deep infections requiring reoperation, sepsis, ARDS and multiorgan failure were among the most common severe postoperative complications, which affected one third of the patients (23/70). They ended with death within the first month after the resection in 3/70 patients (4.3 %), including the patient with intraoperative massive bleeding and 2 other patients who died within the following two months. A definite hemipelvectomy was the final outcome of postoperative complication in 2/70 patients.

Late complications consisted of deep infections, usually osteitis, requiring reoperation in five patients.

The group of 11 patients with benign lesions were excluded from the survival analysis. There were no serious postoperative complications encountered, and all the patients are alive without local recurrence.

Of the 59 patients resected for malignant tumors, 2 had R_2, 13 R_1 and 44 R_0 resections.

The median follow up is 62 months (2-174 mos). Figure 1. shows the overall survival of all 59 resected patients, Figure 2. the overall survival of the patients with R_0 and R_1 resections, and Figure 3. the overall survival of patients with resection vs. those with hemipelvectomy (n=15). Table 1 shows the recurrence rate (local, local and distant, distant) in the resected patients with N_0 M_0 disease (n=50) with respect to R_0 or R_1 operation. Overall survival was calculated using the Kaplan-Meyer method. The differences are not statistically significant.

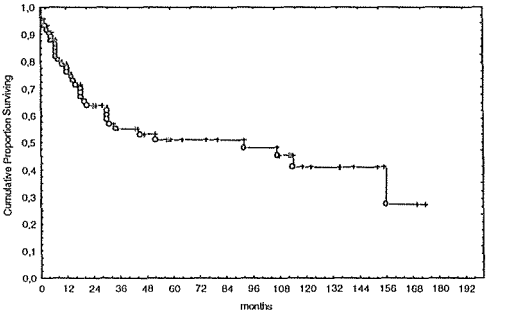

Figure 1. Overall survival of all patients with malignant tumors of the pelvic region treated by resection (n=59)

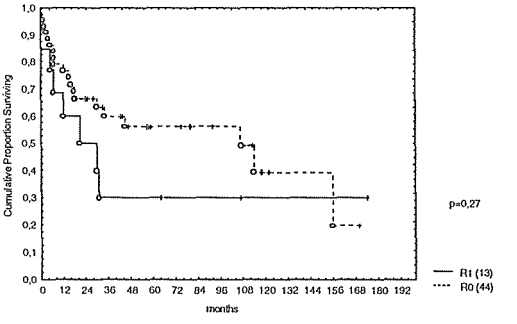

Figure 2. Overall survival of patients with malignant tumors of the pelvic region treated by resection according to the type of surgery (R_0=44, R_1=13)

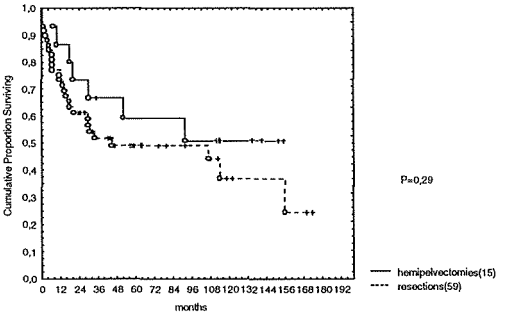

Figure 3. Overall survival of all patients with malignant tumors of the pelvic region treated by resection (n=59) and those treated by hemipelvectomy (n=15)

Conclusion

The quality of life after anterior and posterior resections is from good to excellent, when no major nerves have been sacrificed. The functioning of the limb after real inner hemipelvectomy is worse, but the majority of the patients gain some active mobility of the newly formed fibrous joint as well as full weight bearing. Even after a resection of one major nerve these patients live better than after a hemipelvectomy. Patients with high bilateral sacrum resections have problems with micturition and rarely with defecation. In terms of survival, the results of resections are not considerably worse than those after a mutilating procedure. Many of the medially lying tumors can not be treated by the latter. No matter how demanding resection procedures can be for all members of the surgical team, the effort seems to be justified by the results obtained.

Table 1. Recurrence rate in 50 M_0 patients resected for tumors in the pelvic region (NED=no evidence of disease, LR=local recurrence, M= metastases)

	NED	LR	LR+M	M	All
R0 resection	20 (51%)	2 (5%)	8 (21%)	9 (23%)	39 (100%)
R1 resection	6 (55%)	0 (0%)	3 (27%)	2 (18%)	11 (100%)
All	26 (52%)	2 (4%)	12 (24%)	11 (22%)	50 (100%)

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Tumour surgery in the pelvic region

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During the past ten years the authors operated on 27 tumours of the pelvic region, 12 of them involving the pelvic blade, 6 the periacetabular region, further 9 the os pubis and ischii, respectively. Most of the cases (16) were chondrosarcomas. The mean age of the patients - 13 male and 14 female - was 41 years. As to surgical radicality, 11 wide, 10 marginal and 6 intralesional resections were performed. After a mean follow-up period of 3 years (0.5-11 years) 19 patients are alive and tumour-free, 2 with tumour, 4 have died and 2 have been lost to follow-up. As postsurgical complication a wound-healing disorder and inguinal hernia occurred in 5 cases, surgical field thrombosis with secondary compartment syndrome and renal insufficiency developed in one case. The authors draw attention to the difficulties and indications for pelvic resections (internal hemipelvectomies).

Key words: bone neoplasms; pelvic bones-surgery; hemipelvectomy

Introduction

One of the greatest challenges for tumour surgeons is to operate osseal tumours originating from the pelvic region or soft tissue tumours destructing pelvic bones. The reconstruction following "internal hemipelvectomy", i.e. partial pelvic resection, may be particularly difficult for restoring the walking ability of the patient and for achieving an adequate quality of life.[1]

Methods

Between 1986 and 1995 we performed "internal hemipelvectomy" thus saving the extremity in a total of 27 cases. In our series we had 13 male and 14 female patients; their mean age was 41 years, ranging from 18 to 78 years. In our material an overwhelming majority of tumours was represented by chondrosarcoma (16 patients). In other 4 patients we were compelled to perform a partial pelvic resection due to a giant cell bone tumour. As to surgical radicality, the intervention was wide in 11 cases, in 8 cases at least one surface of the resection was marginal, while in other 2 cases the tumour could only be extirpated in two parts due to its large size, which meant that contaminated marginal resection took place. Intralesional intervention was performed in 6 patients. Reconstruction was done in 3 patients: one patient had pelvic endoprosthesis implanted, while in the other 2 patients we fixed the femoral head to the ileal stump of the acetabular defect by cerclage, and then secured the site with a pelvic plaster.

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Results

Local recurrence was observed in 6 patients. Complications occurred in 8 cases. After a mean follow-up of 3 years, 18 (66%) of our 27 patients are alive and tumour-free; in 6 patients the follow-up period has exceeded 5 years.

Discussion

While one should attempt a complete tumour removal, we should not commence on an operation if the prerequisites are not present. For a proper judgement the up-to-date imaging techniques should be used. In our opinion, hemipelvectomy is indicated in the following cases: 1) if the tumour has invaded along the ischiadic nerve into the gluteal muscles, or the posterior surface of the thigh; 2) if the tumour involves the iliac externa, or the femoral artery and vein and if it extended to the adductors via the adductal canal; 3) if the tumour equally infiltrates the E/I, E/II and E/III regions. Although in this case internal hemipelvectomy can be carried out, there is no possibility of a reconstruction, and the flail hip offers an extremely poor rehabilitation outcome; 4) the age and general condition of the patient should be considered individually.

Opinions in the literature are controversial as regards the reconstruction of the defects. The defect need not be reconstructed if the pelvic arc remains intact, i.e. the 2-finger-thick osseal arc above the ischiadic incision and the acetabulum are not damaged.[2,3]

Conclusion

Among our 27 patients operated on during 10 years, 20 are alive, 18 without a tumour at present. This is an encouraging figure! The prerequisite for the favourable results is to perform surgery for pelvic tumours in well-equipped centres, with experienced multidisciplinary surgical teams including orthopedic, abdominal surgeons, possibly gynecologists and/or urologists as well.

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Preoperative intraarterial chemotherapy with cisplatin for locally advanced high grade soft tissues sarcomas of the extremities

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The aim of our study was to determine the activity and feasibility of CDP IA given preoperatively at higher dose intensity in locally advanced high grade non-metastatic soft tissue sarcomas of the extremities in adults. From 1986 to 1996 we treated 16 patients with locally advanced high grade STS of the extremities, with a diameter of 10 cm or more. Clinical remission of tumor after IA CDP was observed in 9 out of 16 patients. After IA CDP, 90 % or more necrosis of the tumor was achieved in 5 patients, between 75% and 90% in 4, and less than 75% in 7 patients. The disease-free survival at a median follow up of 52 months (range 5-122) was 62 % (95% CI 37 to 87%) and the overall survival 64 % (95% CI 37 to 91%). The functionality of the limb after treatment was excellent in 4, good in 7, fair in 4, and poor in 1 patient. We can conclude that limb sparing treatment with excellent or good limb functionality is possible in patients with locally advanced STS, without causing major local toxicity and without jeopardizing the patients' survival

Key words: soft tissue sarcomas; preoperative chemotherapy; cisplatin; extremities; treatment outcome

Introduction

Soft tissue sarcomas (STS) present about 1% of all malignant tumors, and in Slovenia about 60 new cases are diagnosed each year.[1] The treatment of choice for these types of tumors is surgery, which must be properly planned and the tumor must be removed in one block with an adequate margin of healthy tissue.[2] Local recurrence and lung metastases are the usual sites of relapse in these patients. The main factors that predict relapse are stage and grade of tumor and, extent of surgery performed (radical vs. non-radical). In the case of locally advanced tumors the radicality of surgery can often be ensured only by a mutilating procedure. Some trials have already tried to clarify whether it is possible to downstage these tumors by preoperative intraarterial (IA) chemotherapy, mainly adriamycin[3] without jeopardizing the patient's survival. The main drawback of adriamycin, although this being the most effective drug in soft tissue sarcomas, is its local toxicity to healthy tissues. On the other hand, experience with IA cisplatin (CDP) in osteosarcoma[4,5] and few reports in STS[6] show very low local toxicity and a promising activity. Low activity of CDP in the treatment of STS, when used as a systemic treatment in standard doses, renders the use of cisplatin in these tumors questionable. However, some reports indicate that this relative inactivity of cisplatin in STS could be overcome with a greater dose intensity and greater exposure of the tumor to higher concentrations of the drug, which is the case when the drug is given IA.[7]

The aim of our study was to determine the activity and feasibility of CDP IA given preoperatively at a higher dose intensity in locally advanced high-grade non-metastatic soft tissue sarcomas of the extremities in adults. The endpoints were: local recurrence rate after limb sparing surgery, tumor remission rate after CDP IA, necrosis (%) found by the pathologist, toxicity of the IA CDP, functionality of the limb after surgery, and survival.

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UDC: 616.747/.748-006.3.04-085

Patients and methods

From April 1986 to April 1996, we treated 16 patients with locally advanced non- metastatic high grade STS of the extremities, with a diameter of 10 cm or more; there were 10 males and 6 females, 18 to 73 years old (median 48 yrs). According to their histological type, STS were distributed as follows: 9 malignant fibrous histiocytomas, 3 synovial sarcomas and 1 liposarcoma, leiomyosarcoma, rhabdomyosarcoma and neuroepithelioma. All were grade 3 tumors, except for the leiomyosarcoma, which was grade 1. The sites were as follows: 12 thighs, 3 shank and 1 in the popliteal region. Preoperative evaluation consisted of clinical evaluation, measurement of the tumor, fine needle aspiration biopsy, chest X-ray and skeletal X-ray, CT-scan when feasible, followed by arteriography where a catheter was placed in one or two main arteries vascularizing the tumor. The chemotherapy schedule consisted of CDP 120 mg/m^2 IA in 6 hour intraarterial infusion given with a pump. The cycle was repeated every 14 days. Eight patients received 3, and other eight patients 2 consecutive cycles of IA CDP. The median interval between cycles was 15 days (range 13-17 days) and the median calculated dose intensity delivered was 47 mg/m^2/week (range 37 to 56) of CDP IA. After IA CDP the patients were submitted to surgery. After surgery, the oriented resected specimen was analyzed by the pathologist. Tumor margins and the percentage of tumor necrosis were reported. All patients with G3 tumors received additional postoperative anthracycline-based chemotherapy. When the surgical resection was not wide or radical they were also irradiated.

The criteria for clinical response evaluation were as follows: size, consistency, mobility, definition of margins, and reduction of possible direct or indirect symptoms such as pain, edema, malfunction.[3] Disease-free survival and overall survival curves with 95% confidence intervals (CI) were calculated using the Kaplan-Meier method.

Results

The median follow-up of our patients is 52 months (range 5-122). The following remission rates were achieved after IA CDP: complete remission in 2 patients, partial in 7, no change in 5 and progression in 2 patients. After IA CDP, 90% or more tumor necrosis was observed in 5 patients, between 75% and 90% in 4, and less than 75% in 7 patients. As to the type of surgery performed, 3 patients had marginal resection, 10 wide resection, while 3/16 patients had radical resection. There were no local recurrences. The site of recurrence was always in the lung (one patient who has not been included in this study because of lung metastases at the beginning of treatment was also treated with the same regimen and achieved a complete remission of lung metastases after IA CDP; later he relapsed in the lung and died without local recurrence), which was also the cause of death in 5/16 patients that died within the follow-up period The disease-free survival at the median follow up is 62 % (95% CI 37 to 87%) (Figure 1)and the overall survival 64 % (95% CI 37 to 91%) (Figure 2). The functionality of the limb after treatment was excellent in 4, good in 7, fair in 4 and poor in 1 patient.

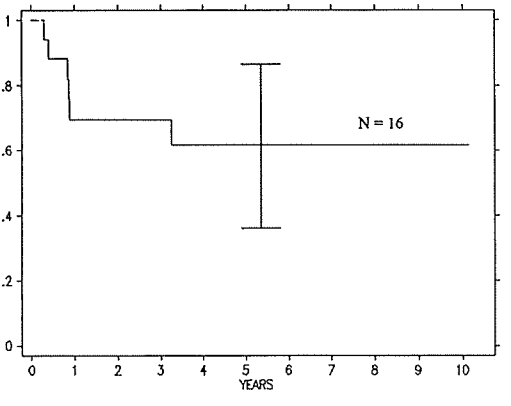

Figure 1. Disease free survival and 95% confidence intervals.

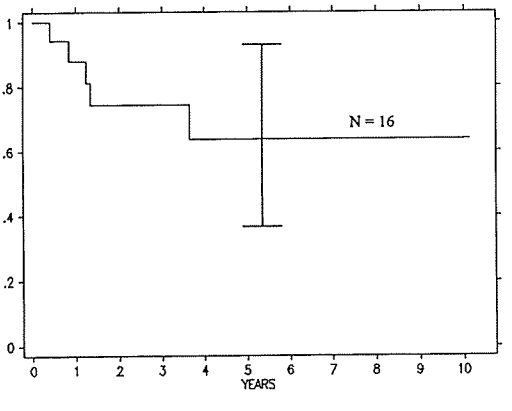

Figure 2. Overall survival and 95% confidence intervals.

Discussion

Although STS are a highly curable disease if the patient presents at an early stage, frequently - at least in our country - we see tumors in very advanced stages when the only possible local treatment is a mutilating procedure. Even after an amputation the prognosis of these patients is dismal, with survival rates at five years around 30%.[8,9]

The question that all clinicians who have to convince patients to undergo an amputation ask themselves is whether it is possible to spare a patients limb with the same or even better chances of survival, using a different treatment approach. In our study we selected IA CDP preoperatively instead of adriamycin which has been used by other authors with reported high local toxicity.[10] Another possible solution is preoperative radiotherapy with considerable radiation sequelae,[11] or maybe even a combination of both.

In view of the results of our study, we are most surprised by the fact that in all 16 patients we have had not a single case of local recurrence, even though the effect of IA CDP (either clinical or % of tumor necrosis) was not always present. It is presumed that some other mechanisms may play a role in the process, e.g. the effect of IA CDP on microscopic satellite nests of tumor cells in the surrounding tissue, or an effect on neoangiogenesis (tumors on surgery appear more demarcated, and there is usually less bleeding than in patients who have not received IA CDP).

All the patients who failed to survive died due to distant metastases with the evidence of lung involvement. Obviously, CDP given IA has a systemic effect (as it was seen in the patient with lung metastases, who was not included in the study), and maybe the surprisingly high survival rate seen in our patients could be attributed to the systemic effect of IA CDP given at a higher dose intensity. Of course, due to the small number of patients included in our study, these results should be confirmed on a larger number of patients.

We can conclude that limb sparing treatment with excellent or good limb functionality is possible in selected patients with locally advanced high grade STS without causing major local toxicity and without jeopardising the patients' survival (this may even be improved).

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Update on use of expandable prostheses in limb salvage surgery for children's bone sarcomas of lower limb

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Introduction: *New techniques in the care of children with malignant bone sarcomas have contributed to the prolonged duration of survival. Attempts to improve the quality of life have become a priority, leading us to improve the techniques of limb sparing reconstructive surgery. Growing children, especially those under 10 years of age have until recently fared better with an amputation than with a limb saving reconstruction because of the unavoidable limb length discrepancy. We used expandable prostheses after Sneath, and later on after Lewis. The present report is a review of our 12-year experience with tibial and femoral prostheses and our successive models., the last two grow without open surgery.*

Methods: *Prostheses are made of titanium, which has been chosen for its better mechanical properties, being twice as elastic and light as stainless steel. The prosthesis is manufactured following the recommendations of the surgeon, with individualised size for each patient. The size of the epiphyseal part is small enough to be used in patients from 5 years of age on, and its smooth edges minimize the soft tissue damage. There is no limit to the extendibility of the prosthesis; can be more than 15 cms, even for resection of 10 cms.*

Patients: *From 1984 to 1996, we used 32 growing prostheses for children aged 4.5 - 17 years: 5 tibial growing prostheses, 3 superior femoral prostheses, 5 total femur replacements, and 19 inferior femur prostheses. The patients had Ewing's sarcoma (8), osteosarcomas (23) or other (1).*

Results: *Five patients died from the disease. Prosthesis was extended in 28 patients. The mean lengthening was 6 cm (min. 2 mm, max. 120 mm). The function of the limb was much improved by lengthening. Following EMSOS criteria, functional results on the last examination are rated as follows: excellent or very good (18), fair (9), bad (5). Two patients suffered of aseptic loosening and 4 of infection following open surgery to increase the limb, requiring removal of the prosthesis to treat the infection. One of those patients had a subsequent amputation. Three had a new growing prosthesis.*

Conclusions: *The expandable prosthesis provides an excellent alternative to amputation in young children. Nevertheless, the infection risk associated with multiple surgical procedures in the 1st generation of growing prostheses, challenges us to develop new generations of growing prostheses which do not need open surgery for lengthening.*

Key words: children; bone sarcomas; prosthesis; function of the limb

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"Hand on" prosthesis reconstruction after peri-acetabular resection for malignant bone tumors. Our experience

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Introduction: *After peri-acetabular resection for bone malignancies, a reconstructive procedure is necessary to stabilise the hip, avoid limb discrepancy, and to permit full weight bearing. But as resection of this area is time and blood consuming, this procedure should be easy to perform. In this case, we use a "hand on" prosthesis.*

Methods: *Our reconstructive prosthesis uses a titanium cup with a long screw in the remaining bone (sacrum or spine). Once the cup is firmly fixed to the bone, the gap between the cup and the bone is filled with cement loaded with antibiotics and the polyethylene component, cemented on the cup. Then, the femoral component of a standard total hip prosthesis is implanted.*

Patients: *Since 1990, we have used such a reconstructive procedure in 27 patients with bone sarcoma involving the acetabulum (7 chondrosarcomas, 6 osteosarcomas, 5 bone metastases, 6 Ewing's sarcomas and 3 other sarcomas). The average duration of the reconstructive procedure was 45 minutes. Walking started 4 to 10 days after surgery, but full weight bearing was usually authorised after 6 weeks.*

Results: *Postoperative complications were frequent: in five cases deep infections required ablation of the prosthesis (one of those got a secondary saddle prosthesis). Nine patients experienced postoperative luxation requiring orthopaedic reduction and plaster with no further complications.*
Oncologic results: Within a median follow up of 5 years, 7 patients died of the disease and 1 from an unrelated cause. The others are disease-free survivors.
Orthopaedic results: According to the criteria set by the Society for Musculo-Skeletal Oncology, the results were graded as excellent in 4, good in 13, fair in 5, and bad in 5. Only two cases of loosening have been observed till now.
Best functional results are observed after resection of the acetabular and the anterior ring.

Comments: *Its rapidity (average duration: 45 minutes) and efficacy render this procedure the reconstruction method of choice. The use of cement to fill the iliac gap permits the adjunction of antimycotics or antibiotics often needed in these complicated cases.*

Conclusion: *"Hand on" acetabular prosthesis seems to be very promising for reconstruction after* en bloc *resection for primary bone sarcoma. A longer follow up and more cases are necessary for a more reliable conclusion.*

Key words: malignant bone tumors; pelvic bones surgery; prosthesis reconstruction

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Place of bank allograft with patellar tendon in prosthetic reconstructions of the upper tibia after en bloc resection and gastrocnemius flap

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Introduction: *After en bloc resection of the upper tibia for bone sarcomas, the functional results depend mostly on the strength of patellar tendon reattachment and the quality of skin healing.*

Patients and methods: *From years 1982 to 1995, 50 upper tibial reconstructions were made by authors after en bloc resection for primary bone tumors (osteosarcoma 35, Ewing 5, chondrosarcoma 3, fibrosarcoma 2, MFH 2, osteoclastoma 2, chondroblastoma 1). 13 patients had a direct skin closure, while 37 others benefited from gastrocnemius flap. In 5 cases, reconstruction procedures used long, stainless steel prostheses coated with stem polyethylene. In others, we used a long stem custom made titanium prosthesis coated with massive bank allograft. In 8 cases, we used only bone graft ; the patellar tendon was reinserted either directly through bone or with patient tibial tuberosity. In other cases, bank allograft was harvested with the patellar tendon and patella, and patient's patellar tendon was reattached to the patella and the graft. Weight bearing was immediate in all cases but active motion was restricted during 45 days to help muscle's reattachment. All patients have been followed by authors. Median follow up is 72 months (min 18 - max 144).*

Results: *Complications are frequent: 10 cases of loosening and 12 infections required reoperation in 18 patients, leading to 8 secondary amputations. The gastrocnemius flap is the best prevention of infection: we had 9/13 infections without flap, versus 3/37 with flap. A massive stainless steel prosthesis coated with polyethylene does not provide a reliable reattachment of the patellar tendon: extension lag appears in all 5 cases after 6 to 10 months. Bone allograft permits a real reinsertion of the patellar tendon, but is exposed to shortening of the tendon (which limits flexion) and is at risk of a secondary fracture. Best results were obtained with grafts of the tibia, tendon and patella. Such aprocedure provides an adequate length of the patellar tendon and permits suture through the patella.*

Conclusions: *1) Upper tibia allograft should be harvested with the patella and patellar tendon. Such allograft permits a much more reliable reconstruction of the patellar tendon avoiding extensor lag while allowing acceptable knee flexion. 2) Gastrocnemius flap is the best prevention of deep infection after upper tibial reconstruction using prostheses.*

Key words: bone neoplasms-surgery; tibia-surgery; prosthetic reconstruction

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Combined chemo-radiotherapy with organ preservation for invasive bladder cancer

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In North America, radical cystectomy remains the standard treatment for patients with muscle-invading bladder cancer. However, despite radical surgery and resulting loss of normal urinary function, the expected 5 year survival is less than 50%. Radiation therapy has long been recognized a standard treatment option, capable of preserving organ function. However local control with radiotherapy is only 30-50%. Incorporation of systemic chemotherapy into the primary management of invasive bladder cancer is an attractive strategy for several reasons. The risk of distant metastases is high and local treatment modalities cannot reduce that risk and preclinical studies have demonstrated synergistic cytotoxicity when cisplatin is combined with concurrent radiotherapy. Phase II clinical trials have established chemo-radiotherapy with selective bladder preservation as an reasonable option for patients with muscle-invading bladder cancer. However, we still need to further improve local control rates, decrease the risk of non-invasive recurrences, decrease the risk of distant metastases and optimize quality of life of patients with muscle-invading bladder cancer.

Key words: bladder neoplasms; combined modality therapy; treatment outcome

In North America, radical cystectomy remains the standard treatment for patients with muscle-invading bladder cancer. However, despite radical surgery and resulting loss of normal urinary function, the expected 5 year survival is less than 50%. The majority of deaths are related to the development of distant metastases. Also, many patients are poor surgical risks or will not agree to radical surgery. Radiation therapy has long been recognized a standard treatment option, capable of preserving organ function. However local control with radiotherapy is only 30-50%. Five year survivals of 20-40% are typically observed for patients selected for radiotherapy.[1,2]

Clinical "radio-responsiveness" has been employed by some to determine which patients are best candidates for definitive radiotherapy and bladder preservation. At some centers, patients are treated with definitive radiotherapy while "salvage cystectomy" is being employed for those with local failure.[3,4] This treatment strategy has allowed bladder preservation for selected patients who achieve a complete response with radical radiotherapy. It also results in long-term survival for approximately 30-40% of patients able to undergo cystectomy at the time of recurrence. In a Danish randomized trial the use of preoperative radiation and cystectomy was compared to radical irradiation and early salvage cystectomy for local recurrence. In that study this delayed use of cystectomy did not seem to impact negatively upon survival.[4]

Incorporation of systemic chemotherapy into the primary management of invasive bladder cancer is an attractive strategy for several reasons. The risk of distant metastases is high and local treatment modalities cannot reduce that risk. Preclinical studies have demonstrated synergistic cytotoxicity when cisplatin is combined with concurrent radiotherapy.[5,6] Combination chemotherapy has also been reported to result in significant responses in both the

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primary tumor as well as distant metastases.[7,8] Therefore its incorporation into the primary management of invasive bladder cancer could potentially have positive effects on both local control and distant failure. Cisplatin-based combination chemotherapy regimens are now considered standard for patients with metastatic disease.

The National Bladder Group treated patients not considered suitable for cystectomy with radiotherapy and concurrent cisplatin.[9] This study demonstrated the safety of such a combined modality treatment approach. The complete response rate of 70% also suggested a therapeutic gain with the addition of cisplatin to radiotherapy. The National Cancer Institute of Canada conducted the only randomized phase III study comparing radiotherapy with concurrent cisplatin-radiotherapy for patients with invasive bladder cancer. Although the use of cisplatin had no effect upon the risk of distant metastases, it did significantly reduce the risk of pelvic failure.[10]

Encouraging results from initial phase II studies have led investigators to further explore the role of transurethral resection followed by chemo-radiotherapy. Goals of this combined modality therapy include the eradication of local tumor, maintenance of normal organ function, improvement in the quality of life, and prevention of distant metastases. Salvage cystectomy has been reserved for isolated bladder recurrence following chemo-radiotherapy. Proponents have assumed that the quality of life of patients treated with organ sparing approaches is better than that of patients treated with radical surgery.

The Radiation Therapy Oncology Group (RTOG) and others have utilized selective bladder preservation for those patients who respond well to initial chemotherapy-radiotherapy. The RTOG initially reported results of its pilot study of cisplatin and concurrent radiotherapy. In this initial trial, 48 patients were treated with cisplatin-radiotherapy and selective bladder preservation for those patients with cystoscopic complete response. The complete response rate was 66%, bladder preservation was 52%, and 4-year overall survival was 52%.[11]

The second RTOG trial employed the addition of two cycles of "neoadjuvant" methotrexate, cisplatin and vinblastine (MCV) prior to cisplatin and concurrent radiotherapy. Results were similar, with complete response rate 75%, bladder preservation 60%, and 4-year overall survival being 62%.[12] The third RTOG trial was a prospective randomized comparison of cisplatin-radiotherapy with and without neoadjuvant MCV chemotherapy. Preliminary results of this third study show increased toxicity, with six deaths occurring during treatment. Unfortunately, no improvement in response nor survival was observed with the addition of MCV prior to cisplatin-radiotherapy.[13]

These combined modality studies confirm the effectiveness of combined chemo-radiotherapy when combined with selective bladder preservation reported by others. In two trials employing MCV chemotherapy and cisplatin-radiotherapy, similar rates of complete response (66% and 66%), survival with bladder preservation (55% vs 43%) and overall survival (62% vs 52%) are reported.[12,15] An additional problem observed in these organ preservation treatments has been the development of superficial non-invasive cancers during follow-up. These are generally managed with transurethral resection and intravesical treatment.

Other phase II trials of cisplatin-based chemotherapy plus radiotherapy have confirmed similar rates of complete response, bladder preservation, and overall survival.[14-17] A summary of these phase II chemo-radiotherapy trials employing selective bladder preservation are summarized in the Table 1. Although similar in design, the results of these trials cannot be directly compared because of differences in patient populations and response criteria. However, these studies show consistent rates of tumor clearance of 57-75% and 3-5 year overall survival of 47-62%. Because of study design and short follow-up, the long term survival is not known exactly, but it appears similar to survival of patients treated with radical cystectomy.

Recognizing the difference between clinical and surgical staging, it is difficult to compare exactly the survival results from these bladder preservation series with those from surgical series. However, for muscle-invading bladder cancers, survival results are similar to those reported in radical cystectomy series where patient eligibility is based upon clinical stage.[18,19] An important component of the success of these organ preserving studies is close follow-up and the incorporation of salvage cystectomy early if local failure occurs.

The toxicity of combined chemotherapy-radiotherapy is substantial. In the above cited phase II trials, 10-38% of patients enrolled were unable to complete the treatment as planned. Grade 3-4 reversible toxicities were fairly common, but treatment-related deaths were uncommon in these early trials. It is of great concern that in the most recent

Table 1. Chemo-radiotherapy and bladder preservation

Reference	Pts	Drugs	CR	Actuarial	
				Survival with Bladder Preserved	Survival
Tester[11]	42	C	66%	52%	52% (5-yr)
Tester[12]	91	MCV-C	75%	55%	62% (4-yr)
Shipley[13]	126	C/MCV-C	57%	36%	47% (5-yr)
Dunst[14]	139	C/P	80%	40%	47% (5-yr)
Kachnic[15]	106	MCV-C	66%	43%	52% (5-yr)
Cervek[16]	105	MCV	62%	49%	62% (3-yr)
Housset[17]	54	FC	74%	-	59% (3-yr)

M = methotrexate; C = cisplatin; V = vinblastine; F = fluorouracil; P = carboplatin; Pts = patients; CR = complete response

RTOG study 6 of 126 patients enrolled died during treatment, 5 on the MCV chemotherapy arm.[13] These deaths were related to either neutropenic sepsis or surgical complications.

In general, bladder function following this treatment has been acceptable. Rare patients will require cystectomy for treatment complications; 2 of 259 in the three RTOG series [11-13] and 3 of 192 patients in the Erlangen series [14] required cystectomy for complications of treatment.

Phase II clinical trials have established chemo-radiotherapy with selective bladder preservation as an reasonable option for patients with muscle-invading bladder cancer. Implicit in this approach has been the assumption that the quality of life of patients treated with bladder preservation strategies is better than that of patients treated with radical cystectomy. However, very little published data is available to support this contention today. Future organ preservation studies should include monitoring of standard quality of life assessments. As surgical techniques improve, and the use of continent reservoirs becomes more available, the negative effects of radical surgery may well decrease.[20]

We still need to further improve local control rates, decrease the risk of non-invasive recurrences, decrease the risk of distant metastases, and optimize quality of life. Also, the development of biologic measures with predictive value for chemo-radiotherapy responsiveness might be extremely useful in the selection of patients for bladder preservation programs. Effective chemotherapy-radiotherapy regimens are needed that will be better tolerated by an elderly population of patients who often have other medical problems. Other active chemotherapy agents that have also demonstrated evidence of radiation enhancement in early preclinical studies include paclitaxel, ifosfamide, gallium nitrate, and gemcitabine. The role of these agents and their effects when combined with radiotherapy remain to be studied.

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Bladder preservation after radiochemotherapy for muscle invasive bladder cancer

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To determine efficacy of radio-chemo-therapy (RCT) with platin-derivatives compared to radiotherapy (RT) alone in patients with bladder cancer. From May '82 to May '96, 333 patients with bladder cancer were treated at the University Hospital of Erlangen. 282 of them, who presented with muscle-invasive or high risk T1 (e.g. G3/4, R1/2, N+) bladder cancer, were treated either by radiotherapy (RT) or concomitant radiochemotherapy with platinum derivatives (RCT-Cis or RCT-Carbo) after preceding transurethral resection of bladder (TUR), with curative intent. Median doses of 50.4 Gy and 41.4 Gy in fractions of 1.8 Gy (once a day, 5 times per week) were applied to the bladder and pelvic lymphnodes. 54 patients recieved 45 Gy to the paraaortal lymphnodes. 128 patients received irradiation alone, while 205 patients received it simultaneously with either cisplatin or carboplatin in the 1st and 5th treatment weeks. Uni- and multivariate analyses were performed in order to assess the impact of age, sex, grading, T-category, R-status, and treatment modality on patients' survival and bladder preservation. Complete remissions were noted in 57%, 70% and 85% of patients after RT, RCT-Carbo or RCT-Cis, respectively ($p<0.05$). The strongest impact on CR was exerted by R-status ($p<0.0003$) and T-category ($p<0.0001$). 79% of survivors have a functional bladder. Concerning survival, RT, and RCT differed significantly only after univariate analysis. For survival with preserved bladder, only initial R-status was significant in multivariate analysis ($p<0.04$). Bladder cancer can be effectively treated by RT/RCT following TURB.

Key words: bladder neoplasms-radiotherapy-chemotherapy; treatment outcome.

Introduction

Until now, radical cystectomy has been the standard treatment for muscle-invasive bladder cancer. This procedure involves removal of the bladder, uterus, upper vagina and adnexa in women, or the bladder, prostate and seminal vesicles in men. Though perioperative mortality seems to be low, an artificial bladder can never replace the original organ in view of its functionality. For this reasons, we tried to establish a method which would avoid primary cystectomy and result in bladder conservation.

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Patients and methods

From May '82 to May '96, 333 patients suffering from bladder cancer were treated either by radiotherapy (RT) alone or by concomitant radiochemotherapy (RCT) after preceding TUR-bladder (TURB). For a detailed description of our treatment schedule see Dunst *et al.* 1994.[1] Only patients with muscle invasive bladder cancer or high-risk T1 bladder cancer were analyzed. Patients with a total dose of less than 40 Gy and histology other than urothelial carcinoma (e.g. squamous cell carcinoma) were excluded from the analysis. So 282 patients were eligible for evaluation.

In conventional fractions median doses of 51.4 Gy (40.0 - 69.4 Gy) and 45.0 Gy (40 - 59.4) were applied to the bladder and pelvic lymphnodes, respectively (10 MV photons, 4-field-box); 54 patients received 45 Gy to paraaortal lymphnodes. After TURB

98 patients received irradiation alone and 184 patients simultaneously with either cisplatin (RCT-CIS, 115 patients) or carboplatin (RCT-CARBO, 69 patients) in the first and fifth treatment weeks. 64/92 patients received more than 200 mg/m² cisplatin, 40/69 patients more than 535 mg/m² carboplatin, which was more than 80% of the dose prescribed. Within 8 weeks after RT/RCT a second TURB was performed. In the case of a persistent tumor or invasive relapse cystectomy was recommended.

Results

Initial complete remission rates (CR) were 57%, 70% and 85% after RT, RCT-Carbo or RCT-Cis. This difference was significant in multivariate analysis. The strongest impact was exerted by R-status and pT-category (Table 1).

Five-year-survival rates were 88%, 58% and 24% for R0, R1 and R2-status, respectively. This difference was significant again ($p<0.001$). In univariate analysis a significant advantage for those patients who had been treated by RCT could be shown ($p<0.05$). After five years, 47%, 69% and 57% of patients survived after RT alone or RCT-Cis and RCT-Carbo, respectively.

Discussion

Recently, Jung and Jakse reported on five year survival rates of 56-75% for T2, 26-78% for T3a and 11-29% for pT3b tumors.[2] For our population the corresponding rates are 55%, 50% and 41%. Considering the T2 and T3a category, our data are within the same range, while for T3b and T4 tumors they are even better. A 79% rate of preserved bladder needs no further comment. The strongest prognostic factor for all endpoints was R-status after initial TURB. This emphasizes the importance of as radical as possible TURB before the start of RCT. Though chemotherapy seemed to have a positive influence on survival in univariate analysis its impact on survival was not significant in multivariate analysis due to worse prognosis of patients who did not receive chemotherapy. Nevertheless, the advantage for those patients who received chemotherapy has been proven with respect to initial response. Therefore we recommend RCT to be performed instead of RT alone if the patient's general condition allows this procedure.

Table 1. Univariate and multivariate analysis of factors related to complete response after transurethral resection and survival

	CR after 1st TURB		Survival	
	univ. p	multiv. p	univ. p	multiv. p
Age	<0.01	n.s.	0.001	0.005
pT-category	<0.0001	<0.0001	0.005	0.033
Grading	0.03	n.s.	n.s.	–
R-Status	<0.0001	0.0003	<0.001	0.002
RT vs. RCT-Cis	0.0002	0.003	0.04	n.s.
RCT-Cis vs. RCT-Carbo	0.025	0.02	0.045	n.s.

R = resection; RT = radiotherapy; RCT = radio-chemotherapy; Cis = Cisplatin; Carbo = Carboplatin; CR = complete response; TURB = transurethral resection of bladder

Conclusion

Organ sparing treatment of bladder cancer is effective. Survival is as good as after radical cystectomy, but 80% of survivors have a functional bladder. The strongest impact on response and survival was exerted by R-status after the first TURB. Consequently, R0 resection is recommended before starting RT/RCT. Major prognostic factors for initial response are age, R-status and pT-category. Concurrent cisplatin (carboplatin) improves the CR rate by 1/3. Cisplatin is superior to carboplatin with respect to CR rate and survival.

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Bladder perservation by combined modality treatment in invasive bladder cancer

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105 patients with biopsy-proven invasive bladder cancer were entered into the study of combined modality treatment with bladder sparing approach. After a maximal transurethral resection of the tumor, the patients were treated with 2 - 4 cycles of MCV (methotrexate, cisplatinum, vinblastine) polychemotherapy. Re-evaluation including cystoscopy with tumor-site biopsy and urine cytology was performed thereafter. In patients with a complete response (CR), the treatment was continued by radiotherapy, whereas in all other patients cystectomy was performed whenever feasible. The CR after TUR and chemotherapy was achieved in 52% of patients. After a median follow-up of 42 months, 52 out of 75 (69%) patients selected for bladder preservation were without evidence of disease in the bladder. The 3.5-year actuarial survival in the entire group of 105 patients was 62%, whereas the survival with the bladder intact was 49%. The survival was significantly better in patients who responded to chemotherapy than in nonresponders. The actuarial survival of complete responders was 82%, whereas their survival with the bladder intact was 78%. In non-responders there was no significant difference in survival between patients who underwent cystectomy and those who completed treatment with radiotherapy. We found that the bladder sparing approach is safe and does not compromise the survivall in patients with invasive bladder cancer.

Key words: bladder neoplasms; combined modality therapy; treatment outcome; survival rate

Introduction

Radical cystectomy still represents the standard treatment for muscle invasive bladder carcinoma. This procedure provides good local control but is associated with a high probability, approaching 50 %, of subsequent distant metastases.[1] The other drawback of this treatment approach lies in the fact that neovesica can never substitute the patients original bladder.

In view of the above problems, in the 80's several clinical studies were initiated using bladder sparing approach to the treatment of this disease.[2-10] In the last decade, the most promising advance has been achieved using transurethral surgery (TUR) and combined chemo-radiotherapy regimens.[2-6,8] This treatment approach takes the advantages of favorable effects of cis-platinum based chemotherapy as well as the synergistic effects of chemotherapy and radiotherapy.[11] The results of these combined chemo-radiotherapy programs showed the overall survival rates of 47-62% at 4-5 years and these results are similar to that obtained by radical cystectomy.[1] Moreever, bladder preservation was possible in 58-79% of patients entered into these studies.[2,4,6,8]

Our study, which was started in 1989, represents one of the first attempts to introduce such an organ sparing program. The preliminary results were published in 1993.[8] The high response rate and the number of preserved bladders, as well as the overall survival rates justified the continuation of our study.

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Our therapeutic approach remained basically unchanged. However, the greater number of patients and the longer duration of follow-up in the present study render the obtained results more reliable.

Materials and methods

Between December 1988 and June 1995, 105 patients with biopsy-proven invasive bladder cancer were entered into the study. There were 83 males and 22 females with the age range of 34 to 77 years (median, 62). The distribution of patients by clinical stage was as follows: cT1 in 7, cT2-3 in 78 and cT4 in 20 patients. All patients with T1 stage had grade 3 tumor, nonresectable by transurethral surgery. Of the 105 patients, 84 had pure transitional cell carcinoma, of these 25 were grade 2, and 59 grade 3. The remaining 21 patients had either transitional cell carcinoma with metaplasia, or anaplastic carcinoma. Transurethral resection of the tumor was judged to be complete by the urological surgeon in 27 patients.

After maximal transurethral resection of the tumor, the patients were treated with 2 - 4 cycles of polychemotherapy according to MCV schedule (methotrexate (M) 30 mg/m^2 i.v. on days 1, 14; cisplatinum (C) 100 mg/m^2 i.v. on day 2 and vinblastine (V) 3 mg/m^2 i.v. on days 1, 14). The cycles were repeated after 21 days. Cystoscopic evaluation was performed after 3 - 4 cycles of MCV. Restaging included examination under anesthesia, cystoscopy with tumor-site biopsy, and urine cytology. Patients were considered to have complete response if there was no evidence of tumor on all of the above investigations. In patients with a complete response, the treatment was continued by radiotherapy, whereas in all other patients cystectomy was performed whenever feasible.

Radiotherapy was started within 2-3 weeks after completed chemotherapy. Patients were treated in a supine position, using 8 or 10 MV linear accelerator, and the following technique: a four-field arrangement to the pelvis and a three-field arrangement coned down on the urinary bladder. Total dose to the urinary bladder was 50 Gy and to the regional lymph nodes 40 Gy, given in five 2 Gy fractions per week.

Three months after completed chemotherapy and radiotherapy, cystoscopic re-evaluation, chest X-ray and CT-scan were done. Thereafter, follow-up examinations (clinical and laboratory diagnostic studies, cystoscopy, urine cytology, chest X-ray, CT-scan) were performed every 3 months for 2 years and every 6 months thereafter.

Actuarial survival was calculated according to the method of Kaplan and Meier.[12] For comparison of survival curves, the log- rank test was used. Survival was measured from the date of diagnosis. The comparison of survival of complete responders vs. non-complete responders was calculated using the land mark method as proposed by Anderson.[13,14]

Results

The present report includes 105 patients with a median follow-up of 42 months (range, 4 - 96). The complete response after TUR and chemotherapy was achieved in 52% of patients and it was higher in those with lower T stage (Table 1). All patients with complete response after TUR and chemotherapy were irradiated. Four patients, who were not completely evaluated for response after chemotherapy, were treated with radiotherapy and complete response was obtained in three of them; 46 patients with the residual disease at restaging were assigned to cystectomy and 30 of them underwent recommended cystectomy while 16 did not owing to medical or other reasons.

Table 1. Patients with complete response (CR)

Tumor stage	Number of patients CR/total	%
All patients	55/105	52
Stage cT1	5/7	71
Stages cT2T3	43/78	55
Stage cT4	7/20	35

TUR = transurethral resection; ChT = chemotherapy; RT = radiotherapy

After a median follow-up of 42 months, 52 out of 75 (69%) patients selected for bladder preservation were without evidence of disease in the bladder. Freedom from local failure in complete responders to chemotherapy was 80% (95% CI, 69% to 91%) at 3.5 years (Figure 1). Eleven out of 55 complete responders to TUR and chemotheray developed bladder recurrences which were found to be invasive in 7 patients and non invasive in 4 patients. Additional three patients, complete responders to chemotherapy and radiotherapy, developed bladder recurrences, which were found to be invasive in two and non invasive in one patient. Non invasive recurrences were managed by

transurethral resection, which had to be repeated in two patients, in one patient invasive cancer occurred subsequently. Salvage cystectomy was performed in 7 patients with invasive recurrences.

The 3.5-year actuarial survival in the entire group of 105 patients was 62% (95% CI, 51% - 72%), whereas the survival with the bladder intact was 49% (95% CI, 38%-60%) (Figure 2). As shown in Figure 3, the 3.5-year actuarial survival was significantly better in patients who responded to chemotherapy (82%) than in nonresponders (35%, $p < 0.0001$). The 3.5-year actuarial survival of complete responders was 82%, whereas their survival with the bladder intact was 78% (Figure 4). In nonresponders there was no significant difference in survival between patients who underwent cystectomy and those who completed treatment with radiotherapy (approx. 30% at 3-year) (Figure 5).

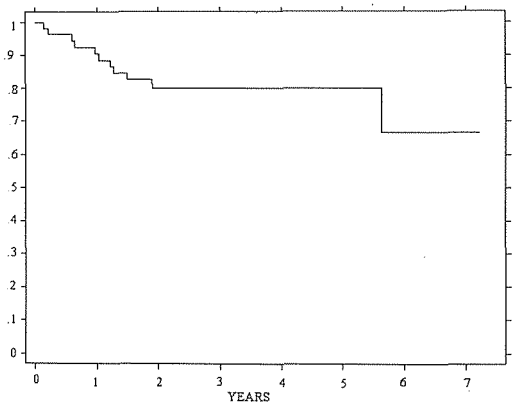

Figure 1. Freedom from local failure in 55 patients with complete response.

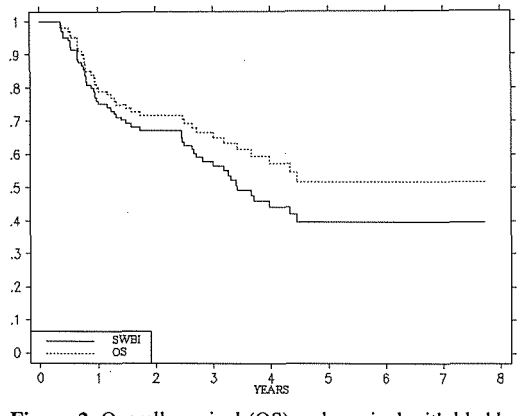

Figure 2. Overall survival (OS) and survival with bladder intact (SWBI) (all patients).

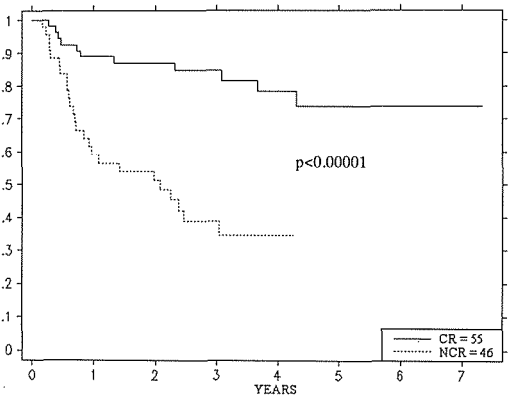

Figure 3. Overall survival according to response to transurethral resection and chemotherapy (CR = complete responders, NCR = non-responders).

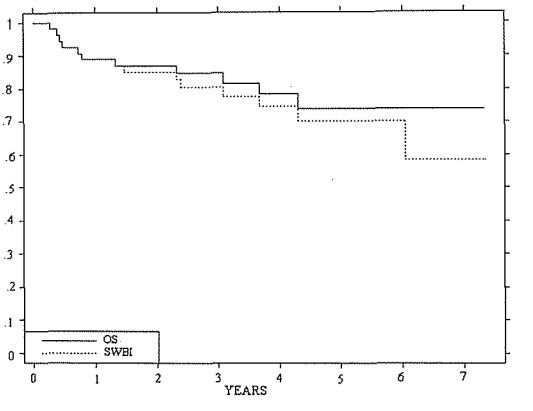

Figure 4. Overall survival (OS) and survival with bladder intact (SWBI) (55 patients with complete response).

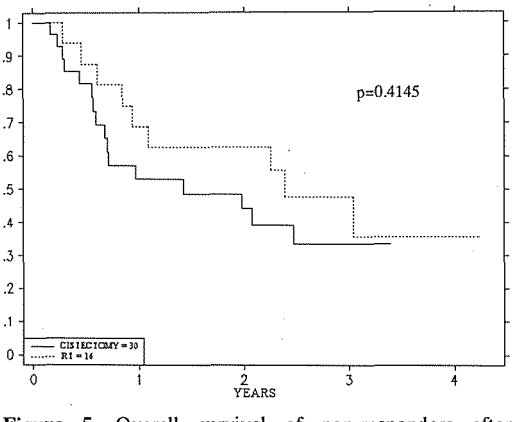

Figure 5. Overall survival of non-responders after transurethral resection and chemotherapy according to local therapy (RT = radiotherapy).

Discussion

Our results obtained by combined modality treatment in invasive bladder cancer patients are encouraging. Out of 105 patients entered into the study, 75 (71%) had their bladder preserved; after a median follow-up of 3.5 years, 69% (52/75) of them have an intact functioning bladder. The 3.5-year survival of the entire group is 62% whereas the survival with the bladder intact is 49%. The 3.5-year survival of complete responders is 82% and the survival with the intact functioning bladder in these patients is almost the same.

Survival and bladder preservation rates in our patients are similar to the results obtained in other studies with combined chemo-radiotherapy, either concomitant[2,4-6] or sequential.[3] They report the bladder preservation in 58-79% of patients, in our case 71%, with an overall survival rates of 47-62% at 4-5 years, in our case 62% at 3.5 years. The same authors report a freedom from local failure from 73-89% at 4-5 years,whereas in our study it was 80% at 3.5 years. In contrast, we had a higher proportion of invasive bladder recurrences compared to non-invasive ones, which was not the case in other studies.[6,15] The reason for this could be in that not always biopsies were performed on follow-up cystoscopies.

Consistently with other authors,[4,5] we found that the patients with complete response to chemotherapy have a better prognosis than the patients who do not respond to chemotherapy. Their survival with intact functioning bladder was found to be 78% at 3.5-year. Moreever, we have found that non-responders have a dismal prognosis, regardlass what treatment they receive afterwards. Complete response after TUR and chemotherapy seems to be a very important prognostic factor for the further course of disease.

In conclusion, we found that invasive bladder cancer is a heterogeneous disease. Among the patients affected, there are more than a half in whom the bladder sparing approach is safe and does not compromise the survival outcome. However, there are some patients with biologically more aggressive tumors that are not manageable either by cystectomy or other combined modality treatment Apparently, the development of biologic markers which could predict chemoradiotherapy responsiveness might be extremely useful in the selection of patients for bladder preservation by combined modality treatment.

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Cytomorphology and flow cytometry in monitoring patients treated for bladder cancer; preliminary results

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The sensitivity of voided urine and urine flow cytometry in detecting bladder cancer recurrence after combined modality treatement was studied in 106 patients. Two different techniques were used for preparation of the urine: conventional centrifugation which has been later replaced by milipore filter imprint technique. The cytologic diagnoses of patients without local recurrence were as follows: 1 (2%) positive, 6 (13 %) suspicious, 9 (19 %) atypical , 26 (56 %) negative , and 4 (9%) inadequate material for diagnosis. In 21 patients with local recurrence urinary cytology was positive or suspicious in 10 (47%), atypical in 6(28 %) and negative in 5 (23%) patients. DNA aneuploid stemline was seen in 2 patients with histologically confirmed recurrent in situ carcinoma and 6 patients without recurrent disease. Among them, there were 3 patients with positive cytology, 4 with suspicious and 1 patient with atypical cells in the urine.

Key words: bladder neoplasms-pathology; flow cytometry; urine-cytology

Introduction

The follow up of patients with bladder cancer is performed by cytology and cystoscopy with biopsy. Urinary cytology and bladder washing have distinct advantages over random or selected biopsies of bladder mucosa because they provide a wider sampling[1,2] and can identify flat carcinoma *in situ*, which is not recognized by cystoscopy. The sensitivity of cytologic examination partially depends on specimen collection and partially on the experience of the cytopathologists evaluating reactive cellular changes and changes after radio and chemo therapy. The accuracy of urinary cytology is lower in initial low-grade than in high grade tumors, therefore flow cytometry (FCM) analysis of exfoliated cells as a complementary test to urinary cytology was introduced.[3]

The aim of our study was to analyse results of urinary cytology and FCM measurements in monitoring the patients with bladder cancer treated with sequential transurethral surgery, multiple drug chemotherapy and radiation therapy.

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Material and methods

One thousand thirty seven urinary samples were collected from 106 patients, treated for bladder cancer with combined modality.[4] In 67 patients cytopathologic analysis of the urine was performed while in 39 patients DNA analysis was done as well. Two different techniques were used for urinary sample preparation: conventional centrifugation, and later miliporefilter imprint technique (filter device, Costar, Italy). All slides were immediately fixed in Delaunay and stained by Papanicolaou method. Cytologic reports were categorized as negative, atypical, suspicious, and positive.

The samples for DNA measurements were prepared by filtration of the urine through a miliporefilter, and by washing the filter in the mixture of 0.2 M citric acid and Tween 20-CA. The suspension was centrifuged at 400 g and the sediment fixed in 70% ethanol. Before staining, the samples

were centrifuged again, and the sediment was treated with 0.5% pepsin for 5 minutes. The nuclei were stained with 4-6-diamidino-2-phenilyndole (DAPI) and sulphorhodamine 101 (SR 101). Measurements were performed on a PARTEC PAS II (Munster, Germany) flow cytometer equipped with a 100W arc mercury high pressure lamp.

Classification of histograms

DNA histograms were classified into two categories: diploid and aneuploid. The histograms were classified as diploid if there was a single peak in the diploid channel position, while aneuploid histograms exhibited two or more G0 /G1 peaks. DNA index (DI) was calculated as the ratio of the modal chanel numbers of the aneuploid and diploid peaks.

Results

Cytopathologic analysis

Recurrent tumors were confirmed by histology in 21/67 patients; cytologic diagnoses in these patients were as follows: 10 patients (47%) had positive or suspicious cytopatologic diagnosis, 6 (28 %) atypical, and 5 patients (23 %) had negative diagnosis. The cytologic diagnoses in patients without local recurrence were as follows: 1 positive (2 %), 6 suspicious (13 %), 9 atypical (19 %), 26 negative (56 %), and 4 (9 %) material inadequate for diagnosis.

FCM analysis

In 39 patients there were 95 FCM measurements performed (1-8 measurements per patient). In 4 patients (13.6%) samples were inadequate for FCM analysis because of scarcity of the cells. From samples 8200-40000 signals were analysed at a flow rate of about 60/sec. CV ranged from 0.95-8, with the mean value of 2.6. DNA aneuploid stem lines were found in 8 patients, DI varied from 1.35-1.64.

Among aneuploid samples, there were 3 patients with positive cytology, 4 with suspicious and 1 patient with atypical cells in the urine. In only 2/8 patients recurrent carcinoma *in situ* was histologically confirmed. Aneuploidy antedated histologic diagnosis of recurrence by 11 and 20 months. Five patients were followed-up from 6 to 12 months, only one patient was followed-up for 3 years. The comparison of FCM data with cytopathologic diagnosis is shown in Table 1.

Table1. Comparison of FCM and cytopathologic analysis in 39 patients

	Cytologic diagnosis				
FCM analysis	neg	atyp	susp	pos	Total
diploid	14	7	3	3	27
aneuploid	–	1	4	3	8
inadequate	1	1	1	1	4
Total	15	9	8	7	39

neg = negative; atyp = atypical; susp = suspicious; pos = positive

Discussion

Since Papanicolaou and Marshal in 1945[5] described malignant cells in the sediment of the urine, cytology has become an important factor in the diagnosis and follow-up of patients with bladder carcinoma.Voided urine and irrigation specimen samples the entire bladder mucosa, and therefore the probability to identify recurrence is greater then in random biopsies. The sensitivity of the conventional urinary cytology is 50-75% and depends on several factors: on the number of specimens and the specimen collection technique, the histologic grade of the tumor, and on experience of the cytopathologist. The interpretation of cytopathologic findings in patients treated by chemo-, radio- and BCG therapy is difficult and demanding.

The sesitivity of urinary cytology in our study was 75 %, which corresponds to the data reported for Grade II and Grade III transitiocellular carcinoma. The comparison of cytologic diagnosis and ploidy analysis showed an excelent correlation: 7/8 patients with aneuploid stem lines had malignant or supicious cells in the urine. Originally, 7/8 patients had G3 transitiocellular carcinoma and 1 patient G2 tumor. Comparing cytopathologic diagnosis and DNA analysis with histology revealed some discrepancies. Of the 8 patients with aneuploid DNA histograms and suspicious or malignant cells in the urine, only 2 had recurrent cancer *in situ* documented histologically, while the remaining 6 patients had urothelial displasia. The duration of follow-up was 6 to 12 months in 5/6 patients, and 3 years in 1 patient. Now the question arises whether in these 6 patients endoscopically undetectable carcinoma *in situ* is present, or, perhaps, their cytologic and flow cytometric findings are false positive. We know that chemo- and radio-therapy may produce rather severe cellular changes[6] including enlargement of the cells, vacuolisation of the cytoplasm, enlarge-

ment of the nucleus, multinucleation of the cells, degeneration and necrosis of the superficial urothelial cells. These changes may be identified correctly with the knowledge of the patient's history.[7] Aneuploidy remains a strong marker of malignancy after treatement and is not influenced by prior intravesical chemotherapy or radition therapy.[8]

According to our experience and the data from literature, bladder washing is superior to voided urine technique regarding the preservation as well as the number of cells. In addition, the new milipore filter imprint technique collects a higher number of cells on slides. With new technique the procentage of inadequate samples was reduced to 2 % . Our experience with FCM analysis is still limited, but on the basis of this study, we consider FCM measurements very usefull and complementary to cytomorphology in monitoring patients with bladder carcinoma. To assess the definitive value of these two techniques a longer follow-up of at least two years or more is needed.[9]

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Conservative treatment in head and neck cancer

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The incidence of head and neck cancer in Slovenia is increasing, especially in male population. Late diagnosis, in advanced stages of disease, influences not only the treatment results but also the treatment strategies and modalities: aggressive surgery combined with radiotherapy and reconstructive procedures and chemotherapy in inoperable tumors is therefore indicated too frequently instead of organ sparing treatment. Early detection should be improved, especially in the target population, and all up-to-date diagnostic technology should be employed in centralized multidisciplinary pre-treatment assessment. Good co-operation between surgeons, radio and chemotherapists in planning, performing as well as in evaluating the treatment is also a basic condition for better implementation of organ sparing approaches in head and neck cancer.

Key words: head and neck neoplasms; combined modality therapy

Epidemiological data as introduction

According to data from the Cancer Registry of Slovenia, the incidence of cancer of the mouth, oropharynx, hypopharynx, and throat (besides colon) was increasing most steeply among all types of male cancer during the period 1978-1987.[1] In the year 1991 head and neck cancer (including lip and regional skin carcinoma) comprised 19% of all cancer localizations in male and 9% in female population.[2] The incidence and its increasing rate are among the highest in Europe in the male population, comparing the data from 22 European states.[2]

The result of five-year survival rate for the patients with the oral, oropharyngeal and hypopharyngeal cancer has not improved; for patients from the period 1973-1976 it was 13% and for those diagnosed in 1981-1984 period it was 14%. The proportion of localized stage even decreased in the last mentioned period (20% in the period 1973-1976, 14% in the years 1981-1984).[1]

Incidence of laryngeal carcinoma is increasing more moderately as it was established for previously mentioned localizations. The extent of disease at the time of diagnosis was more favorable in the last time period (about 50% of localized stages). The relative one- and three- year survival rates increased in the last periods while the five-year rates dropped in the last observed period after previous significant increase.[3]

In Slovenia, 102 patients with malignant tumors of the nasal cavity and paranasal sinuses were treated from 1985 to 1993. Overall projected survival rate at 9 years was 29% (44% in patients treated with surgery and 12% in non-surgical group). Among 46 patients with carcinoma of the maxillary sinus 30 were in T4 stage at the time of diagnosis and 19 of 20 patients with carcinoma of ethmoid.[4]

In the context of these epidemiological data, comparable to those reported from other countries, the problems of early diagnosis and the place and role of organ sparing treatment (and its modalities) of cancer in head and neck region should be discussed.

Problems of early detection and staging

Early diagnosis is only possible if the patient seeks advice immediately on noticing symptoms. According to our data[5] and to other reports[6] the delay in diagnosis is still often very long also in patients

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with evident symptoms as in vocal cord carcinoma, where the late diagnosis results in one of the most mutilating surgical procedures - laryngectomy. The factors, defining the population at risk for oral cavity, pharyngeal and laryngeal cancer are well known: male sex, increasing incidence with age, alcohol consumption and cigarette smoking, either alone or even more in combination. Consequently, the ideal target group is well defined but the screening in this population is connected with several difficulties:

- the target population consists of subjects who are not health conscious and do not seek preventive care;
- acceptance of primary preventive behavior such as smoking cessation is generally low;
- acceptance of secondary preventive behavior (willingness to undergo examinations) is not so infrequently missing.

Much more should be done in the field of a public health education, using all modern methods of propaganda. The role of general practitioners is crucial.

Early diagnosis is also possible only if the physician thinks of a possibility of tumor, if he performs basic investigation, or, at least, if he immediately sends the patient to otorhinolaryngologist. Due to improved medical education the situation has been improved in this field in the last decade.

The third level, crucial for improvement of recruiting of candidates for organ sparing treatment in carcinoma of the head and neck is the level of specialist. On this level, the employment of all up to date examinations is mandatory to discover precancerous lesions and early cancers and to delineate their localization and extent.

Besides laryngomicroscopy, endoscopies using various types of rigid telescopes and flexible fiberoptic endoscopes, fluorescence pharyngo-laryngoscopy was developed at the University Department of Otorhinolaryngology and Cervicofacial Surgery in Ljubljana. It is based on the detection of fluorescence induced by helium-cadmium laser, without photodynamic drugs, where the reduction or even absence of fluorescence reveals the cancerous tissue. The experience from our work shows that autofluorescence endoscopy is a useful complementary method in detecting laryngeal and pharyngeal malignancies.[7,8]

The current role of diagnostic imaging is to offer more accurate information on the standard clinical and endoscopic staging of the primary tumor, its regional lymph node spread and distant metastases.

Computer tomography is indispensable in choosing the treatment modalities and planning the extent of surgery in cancer of the nose and paranasal cavities, and it is useful in selected cases of laryngeal carcinoma, determining the possible invasion of laryngeal cartilage which can divert the therapeutical strategy from conservation treatment towards radical surgery.

Magnetic resonance has proved to be sometimes of decisive importance in tongue and floor of the mouth carcinoma.

Ultrasound scanning is used in our department in the first place for detecting lymph node metastases and estimating the operability of nodal disease. Ultrasound guided fine needle biopsy is not used routinely but in selected cases, for instance, in diagnosis of possible contralateral neck metastasis and in local and regional recurrences.[9]

We are starting with video-laryngostroboscopy for detecting early glottic cancer, estimating the extent of subepithelial cancer invasion, evaluating the treatment results and detecting early reccurrences following radiotherapy.

No technology can replace experiences in diagnostics, especially when decision upon conservation treatment is made. Therefore it is crucial that patients with head and neck carcinomas are centralized in institutions where besides technology a high experienced and specialized team is available.

Standard and the changing role of conservation surgery in head and neck region

Standard in the head and neck conservation surgery is without doubt conservation surgery of the larynx. It has developed for more than hundred years and appeared almost simultaneously with laryngectomy. The reason is obvious: the voice is the most cherished possession and despite its replacement by artificial means there is no substitute for the natural voice - even one which is impaired. Nothing especially revolutionary has happened in this surgical field in the last decades: basic goal (to preserve voice and natural way of breathing) and basic oncologic principles (radical excision) have remained unchanged. Frozen-section diagnosis in the operating room is the basic condition for this surgery. Our results showed that the reliability of this histologic method was very high in comparison with the diagnosis from specimens embedded in paraffin but it depends mainly upon the thorough knowledge and

experience of the pathologist, upon the experience and also the professional integrity of surgeon, good cooperation between the surgeon and pathologist as well as upon the adequate organisation of work.[10]

The conservation principle in surgery of some oral cavity, especially tongue tumors, is the same. The surgeon should excise just "enough" and verify the excisional margins of properly orientated specimens by frozen section technique. Some recipes and sketches in surgical atlases are sometimes misleading or, better, leading to unnecessary extent of excision, but, on the other hand, basic principles of frozen section technique are sometimes not strictly applied. The conservation of function in T1 and T2 lesions is usually not a problem and depends mainly on surgeon's skill and experience in using local recontructional techniques.

Besides the larynx, the mandible is perhaps the second most important site of conservation treatment attempts. In recent decades the opinion has begun to dominate, as regards planning surgeries for floor of the mouth cancer, that it is safe enough to excise tumor as local treatment so long as the tumor does not directly involve the periosteum. Our study, comparing the 3-year survival rate of patients with floor of the mouth cancer in terms of spread of the disease and form of treatment showed us that survival after segmental intervention or hemimandibulectomy, despite the late stage of the disease (III. and IV.), was 50%, whereas the overall survival was only 21%, primarily because of local tumor recurrence, in patients with limited tumors (stage II.) where only excision was performed as local surgical treatment. Other therapeutic parameters were the same in both groups. Lightmicroscopic and immunohistochemical methods were used to prove the link between the lymphatic vessels of the floor of the mouth and the mandibular periosteum as well as the lymphatic tumour embolization of the periosteum of the lower jaw. More aggressive surgical treatment has been adopted in the last years at our department in spite of cosmetic and functional sequelae following partial mandibulectomies.[11]

It is well known that the histopathological presence and the extent of lymph node metastasis in the neck is the most important prognostic factor, not only in terms of loco-regional reccurence, but also of distant metastases. The chance of survival in patients with regional metastases is half of those with tumors confined to the primary site. Elective neck dissection and elective radiation give comparable results for the N0 neck. The problem is that despite a thorough pre-treatment assessment staging errors are not infrequent. "Wait and see" policy is therefore too hazardous in our opinion, but the same is true for elective radiotherapy as "probabilistic" approach. Modified neck dissections have been used at our department in the last 15 years (supraomohyoid, anterolateral - depending on the site of primary tumor) as staging surgical procedures. This type of surgery should not be rigid, and staging operation should be continued as classical functional dissection if positive nodes are found and verified during surgery. The similar principle is applied to patients with smaller and mobile palpable nodes. Despite controversial opinions we believe that funcional neck dissection is a safe procedure and follows the idea of organ sparing surgery of Suarez. The Argentinian Suarez, who in 1962 introduced this operation, stated that "the extent of a radical approach should be conceived against cancer, not against neck". In the case of positive nodes at the periphery of dissection or extracapsular spread established on histopathologic study of in paraffin embedded surgical specimens, postoperative radiation therapy is used as well as in doubtful cases. We must admit with humility that the principle "the more the better", despite its questionableness, is applied in these cases.[12,13]

On the other hand, the surgeon should respect the classical radical neck dissection and perform it is cases of larger metastases or evident regionally disseminated disease despite its mutilating consequences.

Radiation therapy as organ sparing treatment

Knowing the basic principles of radiotherapy, the radiation therapy with curative intent is used in early and superficial head and neck cancer where no evidence of nodal disease exists or its probability is very low. The organs and their function are spared, but we are facing the constant problem of the possibility of understaging. Surgical approach in the cases where the extent of disease could be questionable and where surgery does not leave any relevant sequels is in our opinion a better choice.

The role of definitive radiation therapy for laryngeal cancer in the context of organ sparing treatment is specific. The principle is that initial radiotherapy of laryngeal carcinoma has the capability of being curative or final treatment, and can be

followed, if necessary, by salvage surgery. On the occasion of every meeting when surgeons and radiotherapists are brought together, the same statement, that radiotherapy and surgery must not be considered as competitive methods but rather as partners is repeated. In reality, as usual, the situation is different and the philosophy of initial approach is varying from one to another institution, country or region. It is known that radiotherapy is preferred as initial treatment in Scandinavia, United Kingdom, Canada, and surgery in Germany, Latin countries.

The rationale for the definitive radiation therapy are the reported treatment results which demonstrate an overall five-year cure rate for glottic cancer from 87% to 98% in T1, from 80% to92% in T2 and from 57% to 75 % in T3 stage and also larynx preservation in about 50% of cases of T3 glottic carcinoma.[14]

While T1 supraglottic tumors are uncommon and could be suitable for radiotherapy in T2 N0 category the success rate lies between 51% and 77%. In spite of these results, mainly because of the unpredictable nodal disease and well established surgical techniques, the surgical management is generally preferred.[15]

Comparison of treatment results of the two therapeutic modalities in early laryngeal cancer usually shows very similar results. The problem is that the studies are retrospective, nonrandomized, and that factors influencing treatment outcome are very numerous. Reports are based on TNM system, which unfortunately carries a high proportion of incorrectly classified cases and even each T category represents a wide spectrum of cancers ranging from those that are so small that they can be removed by biopsy to others large enough to be almost the next T stage. A deficiency of radiotherapy is that it consists of more or less standard schemes and dosage regimens which are not adapted to the volume of tumor. On the other side surgical procedures are tailored. The problem is that the exact limits of the tumor cannot be always defined prior the surgery and being aware of the fact that radiation therapy is not a substitute for free margins a planned and attempted conservation procedure may be finished as laryngectomy.

Obviously, in many cases, there is no treatment of choice but choice of treatment. The initial treatment of patients with head and neck carcinoma in Slovenia is therefore always planned by a standard team of surgeons and radiotherapist from the University Department of Otorhinolaryngology and Cervicofacial Surgery and from the Institute of Oncology in Ljubljana. Our treatment results show that in T1 and T2 glottic carcinomas, suitable for voice preservation surgery, no significant difference between the groups of primarily irradiated and primarily operated patients exists. The patient should be therefore fully informed of the advantages and disadvantages of each treatment and must take his part in decision making.[16]

We hope that improved therapeutic schemes using chemotherapy in combination with radiotherapy will improve organ sparing treatment of the head and neck, especially of laryngeal carcinoma. While our approach to inoperable head and neck cancer showed significantly better results in patients, where radiotherapy was combined with concomittant chemotherapy[17] and was introduced as standard therapy we still watch with guarded optimism the results of studies using neoadjuvant chemotherapy combined with radiotherapy in responders with T3 laryngeal carcinoma.[18] The goal of these clinical trials - larynx preservation, could be evidently applied also to organ sparing treatment in the head and neck cancer in general.

Organ reconstruction

Due to the high percentage of advanced tumors in head and neck carcinomas at the time of diagnosis the treatment success is greatly dependent on the extent of surgical excision with convincing safety margins. Therefore, the operability of these patients is primarily influenced by the possibility of related defect reconstruction. The microvascular free tissue transfer most closely complies with the basic requirements of reconstruction: the method should be a reliable and final one and it should offer a wide range of possibilities to achieve the optimum functional and cosmetic results, so very important in our specific anatomical region.

In the last two decades, several different microvascular flaps have been introduced at our institution, selected with respect to the tissue to be substituted (e.g. the skin or mucosa alone, or deeper defects including a missing bone). This technique has shown so many advantages over pedicled flaps that it is now regarded as the method of choice particularly in recurrences after previous unsuccessful treatment, where an extremely well vascularized flap is needed. Double-team approach using

highly qualified head and neck surgeon and a micro-vascular surgeon who handles free-flap transfers routinely, has minimized the rate of complications and shortened the duration of surgery.[19]

In 1991, free jejunum flap was introduced at our department, mainly for reconstruction of defects after total pharyngolaryngectomies. 20 reconstructions have been performed with an overall technical success rate of 90%. Three patients also required additional reconstruction of soft tissues of the neck by free radial forearm flaps and in last cases a voice prosthesis was implanted additionally to improve the functional success. The functional results and low complication rate of the free vascularized jejunum transfer has led to abandoning of classical techniques of reconstruction.[20]

Conclusions

Some guidelines should be drawn from this discussion regarding the place and role of organ sparing treatment in head and neck carcinoma.

Early detection is generally inadequate and should be improved as basic condition for conservation surgery and definitive radiation therapy.

Multidisciplinary pre-treatment assessment, selectively including all up-to-date technology, is mandatory for proper selection of conservation treatment modalities.

Choice of treatment modalities must be performed by a standard and highly qualified team, including surgeons of different specialities, radiotherapists, chemotherapists, pathologists and radiologists. In cases in which there is no "treatment of choice" available, a fully informed patient must take his part in deciding upon the treatment modality.

The role of chemotherapy, not only in patients with advanced or progressive locoregional disease but also in the frame of organ sparing treatment should be defined.

For the time when we are dealing with aggressive surgery in combination with radiotherapy, in advanced tumors the term "organ sparing" could be replaced with the term "organ reconstructing".

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Combined chemotherapy and radiotherapy in head and neck cancer: Hopes and facts

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Squamous cell carcinoma of the head and neck is one of the most common malignancies world-wide with more than 500,000 new cases projected annually.[1] Overall, only one-third of patients present with early local disease which may be successfully managed with either surgery or radiotherapy. The remaining two-thirds of patients already have locally advanced (T_3 or T_4) lesions and/or regional lymph node involvement (N_1 - N_3) at diagnosis.

Most of the patients with locally advanced tumor are treated with external beam irradiation with or without surgery. Despite the continued refinement of radiotherapy techniques, local tumor control remains a significant problem, with a recurrence rate of up to 60%. The majority of deaths from this malignancy are attributable to progressive locoregional disease. Many patients suffer significant morbidity from both, the therapy and cancer itself.

In an attempt to improve the outcome, many alternative strategies were tested within the last decades of which particularly common was adding chemotherapy to standard local treatment. Chemotherapy was applied before definitive local therapy (induction, neoadjuvant), after local treatment (adjuvant) or concomitantly with radiotherapy. The major expectation from the addition of chemotherapy is increasing the overall cure rate by either improved locoregional tumor control or by early elimination of micrometastases.

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Key words: head and neck neoplasms-drug therapy-radiotherapy; treatment outcome

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Many phase II or pilot clinical trials, combining chemotherapy and radiation in a great variety of schedules, suggested a substantial benefit from the addition of chemotherapy. These claims, based on historical experiences, were usually subjected to various biases in favor of the new treatment and in general were not confirmed in randomized studies.[2] Of the three most common combined chemotherapy-radiotherapy approaches (induction, adjuvant, concomitant chemotherapy), a benefit in favor of chemotherapy, in terms of better local control and - to a lesser degree - prolonged survival was noted only with the last.[2,3] This improvement, however, was in most instances achieved at the expense of significantly increased toxicity of treatment. Chemotherapy usually enhanced acute local reactions (particularly mucositis), which led to a compromise in the dose of irradiation, interruption of treatment and increased number of treatment refusals. It is therefore possible that improved local control and survival might have been achieved at a similar, or even at lower level of toxicity, by simply increasing the total radiation dose or by employing altered fractionation regimens.

The lack of therapeutic gain from the addition of chemotherapy to radiation may be due to a number of reasons, including biological factors, increased rate of side effects and suboptimal methodology of clinical investigations. Head and neck cancers are a heterogeneous group of malignant tumors that differ considerably in their clinical manifestations, prognosis and therapeutic approaches. They are usually grouped together in clinical studies due to the small number of patients with individual tumor locations. This heterogeneity makes it difficult to evaluate chemotherapy as an independent variable. The most important factor, however, that influenced the outcome was insufficient patient number in

particular trials.[4] For this reason, most of the trials performed so far should be considered inconclusive rather than "negative", as usually claimed. Other components which might have influenced the reliability of published clinical reports are short duration of follow up and a large proportion of patients excluded from the analysis.

In spite of the disappointment with the current use of chemotherapy, there are still areas that deserve further investigation. One of them is the possibility of decreasing treatment morbidity by replacing mutilating surgery with organ-sparing procedures. This idea was tested in a few recent trials of which two attracted most interest,[5,6] addressing of the possibility to preserve the larynx. In both studies, patients with locally advanced laryngeal[5] or hypopharyngeal[6] cancers were randomized to either standard immediate surgery and postoperative radiotherapy or to induction chemotherapy followed by radiotherapy, which was applied only to responders to chemotherapy. Both studies demonstrated that the larynx preservation without compromising survival was possible in a proportion of patients. These studies, however, did not include a radiotherapy-only treatment arm and the extent to which induction chemotherapy contributed to organ preservation could not be therefore clearly defined. There are clinical data suggesting that larynx preservation could be achieved in a similar proportion of patients with the use of radiotherapy alone.[7] Further progress may also be expected from the application of newer radiotherapy techniques. e.g. hyperfractionation.[8,9] Anyway, the results of these studies may represent a major therapeutic achievement but warrant confirmation. Further exploration of this strategy may therefore be considered in patients with locally advanced laryngeal or hypopharyngeal cancer. It would be desirable to address the potential of organ preservation in concomitant chemoradiation protocols which have been proved to be more efficacious than induction chemotherapy.[10-12] It is also strongly advised to use, in the future studies, radiotherapy alone as a control arm, like in a currently running RTOG study.[13] Not only would such a design allow an assessment of the impact of chemotherapy, but it would also allow a comparative analysis of late side effects of radiation alone or combined with chemotherapy.

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Minimally invasive therapy in carcinomas of the head and neck - an updated overview

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In this up-to-date review the current role of minimally invasive procedures in head and neck oncology is defined. Endoscopic laser surgery in comparison with commando procedures is discussed as well as other non-operative treatment modalities, such as simultaneous chemo-radiotherapy. Special reference is given to the question if functional or radical neck dissection are of the same oncological value.

Key words: head and neck neoplasms-therapy

Treatment of carcinomas of the oral cavity and the oropharynx

In the surgical treatment of tumors of the oral cavity and oropharynx, the removal of carcinomas by radical surgery - implying a monobloc resection of primary tumor in continuity with radical neck dissection and splitting or resection of the mandible - has been in the foreground of discussion since the end of the last century. These radical surgical strategies, advocated mainly by Martin and Sugarbaker[1] and Conley and von Fraenkel[2] require extensive use of flaps to reconstruct the defects and are frequently associated with mutilation of the patient, prominent dysphagia and impaired speech. A theoretical basis for these extensive operations is provided by the investigations of Ward and Robben[3] and Larsson *et al.*[4], who demonstrated a lateral drainage from the floor of the mouth towards the periosteal lymph vessels of the mandible and from there into the deep cervical lymph nodes. There is concern that malignant cells will remain in the region of the lymphatic drainage system and, above all, in the lymph vessels of the periosteum of the mandible if the primary tumor and the neck receive discontinuous treatment and if mandibular resection is neglected.

In 1971, Marchetta[5] used histological analysis to show that even with extensive carcinomas in the oral cavity associated with regional lymph node metastases involvement of the periosteum occurred only via a direct infiltration. Whenever macroscopically visible healthy tissue was found between the tumor and the mandible, no metastatic involvement of the periosteum was detectable in the course of these investigations. Weidenbecher and Pesch[6] were unable to identify either tumor cells in lymphatic vessels of the periosteum or tumor extension into the Haversian channels, or intraosseus formation of metastases. In a recent study, no difference in disease free survival of patients with oral cancer between "radical" and "functional" regimens could be found.[7]

On the basis of the various studies, one can conclude that, even if infiltration of the mandibular periosteum has occurred, a partial resection which does not disrupt the continuity of the mandible could be sufficient for the cure of the tumor. In terms of disappointing treatment results, the demand for gen-

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eral monobloc resections of the primary tumor in continuity with the region of the lymphatic drainage system appears out of date. Within the last two decades, various research groups have published reports on transoral resections which were performed in cases of advanced malignancies in regions of the oral cavity and oropharynx.[8,9] The treatment results reported are comparable to those achieved by en bloc resection and reconstruction of defects by pedicled or microvascular anastomosed flaps. Panje *et al.*[10] as well as Steiner[11], in particular, have emphasized the substantially lower degree of impairment of important functions and disfiguring of the patient caused by transoral resections, thus rendering measures to reconstruct defects unnecessary. By spontaneous epithelization of the operated sites, good preservation of the function and little cosmetic impairment can be obtained. Nonetheless, the principles of curative therapy of the tumor in both, enoral and transoral, minimally invasive and function-conserving operative techniques must be strictly observed.

Treatment of laryngeal carcinomas

After the introduction of microlaryngoscopy, the transoral endolaryngeal resections of carcinomas of the vocal cord were soon widely accepted. In 1972, Strong and Jako[12] introduced the carbon dioxide laser - coupled to the microscope - into clinical practice. In the years to follow, various research groups reported on a successful therapy of small vocal cord cancer.[8] The laser, however, also allows the transoral endolaryngeal resection of larger glottic tumors as well as supraglottic carcinoma. Notably, Steiner *et al.*[13] pointed out that the application of CO_2 lasers has substantially expanded the range of indications for minimally invasive, organ-sparing and function-maintaining endolaryngeal surgery also on advanced laryngeal carcinomas.

Endolaryngeal laser surgery seems to be especially suitable for the treatment of superficially spreading T2 carcinomas which are not easily accessible to conventional external partial resections. The treatment results after endolaryngeal laser resections of T2 laryngeal carcinomas - which had been partly achieved by additional postoperative radiation therapy - are comparable to the results of conventional surgical methods (Figure 1). Endolaryngeal surgery also allows the larynx to be preserved with a lower degree of functional impairment and tracheotomy to be avoided.

Deep infiltration of the anterior commissure is considered to be a contraindication to endolaryngeal surgery. While Steiner *et al.*[13] also treat T3 laryngeal cancer by means of endolaryngeal laser surgery, Eckel and Thumfart[14] among others reject an endolaryngeal therapeutic approach for these advanced types of laryngeal carcinomas.

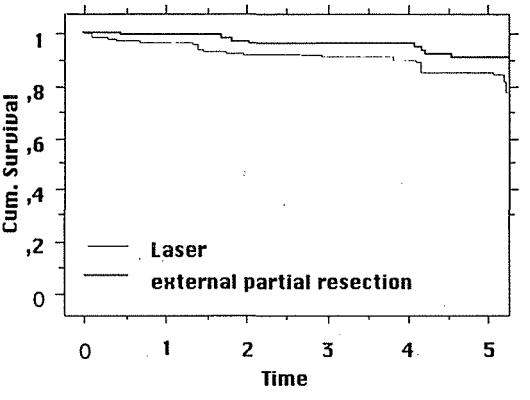

Figure 1. Comparison in survival (years) of endolaryngeal laser surgery and conventional external partial resection of T2 glottic carcinoma (N=128, Department of Otorhinlaryngology, Head & Neck Surgery, Erlangen, Germany).

Treatment of the neck in cancer of the upper respiratory tract

Whereas in 1906, Crile[15] described radical neck dissection as the treatment of choice for lymph node metastases in the neck, only 16 years later Truffert[16] laid the anatomical-pathological foundations for functional lymph node surgery of the neck. In 1963, Suarez[17] and in 1967 Bocca and Pignatoro[18] developed the fundamental concepts of "conservative" neck dissection with the preservation of sternocleidomastoid muscle, accessory nerve and internal jugular vein. Conservative or "functional" neck dissection proved itself to reduce distinctly the morbidity rate while maintaining a comparable degree of treatment effectiveness. In Figure 2, a comparison of disease free survival rates is drawn between functional and radical neck dissections in an unselected group of patients with head and neck squamous cell carcinoma (unreleased data, Department of Otorhinolaryngology, Head and Neck Surgery, University Erlangen, 1970-1990). The distribution of stages was approximately equal in both groups.

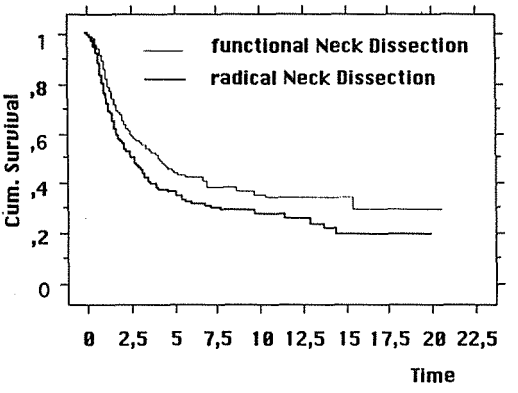

Figure 2. Comparison of disease free survival (years) in cancer of the oral cavity, pharynx and larynx in accordance to neck dissection mode (N = 840, Department of Otorhinplarygology, Head & Neck Surgery, Erlangen, Germany).

Non-surgical therapy of head and neck cancer

Nowadays, simultaneous chemo-radiotherapy must be - in accordance to several publications (overview at [19] considered as the treatment of choice in primary unresectable cancer of the upper respiratory tract with "unresectable" also meaning "unresectable" from a functional point of view). CDDP and 5-fluorouracil are the most often used chemotherapeutic agents for this purpose. In addition, hyperfractionated radiotherapy seems to be superior to conventional radiation. Simultaneous chemoradiotherapy has become feasible by application of supportive measures such as nutrition via percutaneous endoscopically guided gastrostomy, hemopoietic growth factors and adequate pain management.

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Chemo-radiotherapy in the elderly and /or poor performance status patients with advanced head and neck cancer

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The aim of this study was to evaluate the toxicity and response rate, as well as to assess the impact of chemo-radiotherapy on local control and survival in the elderly and/or patients in poor performance status with head and neck squamous cell cancer (HNSCC). The treatment consisted of four cycles of induction chemotherapy with Carboplatin, Fluouracil and Leucovorin, followed by continuous infusion of Carboplatin combined with radiotherapy. Up to now, nine patients entered this study, all evaluable for toxicity and treatment response. Six patients completed the planned treatment, obtaining 2 complete responses and 2 partial responses, the other two patients remained stable during the therapy. No patient stopped the treatment due to toxicity, which was mild and limited to mucositis during radiotherapy. Due to a small number of patients and the fact that the study is still in progress we are unable to draw any definitive conclusions.

Key words: head and neck neoplasms-drug therapy-radiotherapy; aged

Introduction

In Italy, rapid aging of population is one of the most important and serious demographic phenomenon in recent years. In 1990, the average life expectancy was 73.6 years for males and 80.2 for females which is among the highest in the world.[1] In 1996, in Italy, the proportion of elderly population (over 65 years) was higher than that of young population (under 20 years). Approximately 50% of neoplastic diseases affect patients over 65 years.[1]

In elderly patients with cancer, there are often concomitant diseases that need to be considered and which limit the choice of the most appropriate cancer therapy.[2] Locoregionally advanced stage III and IV head and neck cancer has been usually treated with combined surgery and post-operative radiotherapy. Inoperable patients and those with advanced unresectable disease have been irradiated only, although the cure was achieved only in a minority of patients.[3]

Based on recent data, chemotherapy should at least be considered as an integral part of the therapy for many stage III and locally advanced stage IV patients.[4] Anticancer agents usually exhibit a relatively narrow therapeutic index leading to significant toxicity to normal tissue even at standard doses used in routine chemotherapy regimens.

Only 50% of elderly cancer patients succeed in completing the scheduled chemotherapy program at full dosage and without significant delay between courses.[5] Accurate measures of renal, liver and marrow function indexes should be considered as more important guides for the use of chemotherapy in the elderly rather than an arbitrary age limit.[5]

Carboplatin has been used in metastatic or recurrent head and neck tumors with approximately the same response rate but with less gastrointestinal and no significant chemotoxicity-ototoxicity or re-

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nal toxicity as compared with Cisplatin and has also been successfully combined with Fluouracil.[6] The interaction of Carboplatin with radiation seems more advantageous than radiation alone in lung cancer cell lines and patients.[7,8]

The present study was undertaken to establish the activity and toxicity of Carboplatin 5-fluorouracil (5FU) and Leucovorin for 4 cycles followed by Carboplatin i.v. combined with radiotherapy in elderly, inoperable HNSCC patients.

Materials and methods

From March 1996 to February 1997, 9 patients, (8 male and 1 female), of median age of 71 years (range 58-81) and a median Karnofsky Performance Status of 70 (range 60-90), with advanced, non resectable, histologically proved squamous cell carcinoma of the head and neck region, or with recurrent disease after previous primary surgery and/or radiotherapy, were recruited in the study. Three patients had stage III and 6 stage IV tumors. The primary lesion was located in the oropharynx in 6 patients, in the larynx in 1 and in the hypopharynx in 2. Informed consent was obtained from all patients.

Patients were considered eligible if they fulfilled the following criteria: inoperable disease; age over 70 and/or performance status, according to Karnofsky over 40 and under 70; a life expectancy of at least 12 weeks; absence of metastases; informed consent to treatment and follow-up; WBC count > 4,000/mm^3, PLT count > 100,000/mm^3, Hb >10 g/dl; patients with good liver function with AST, ALT, LDH, gamma-GT <2.5 times the upper limit of normal values; creatinine level < 1,2 mg/dl or creatinine clearance > 60 ml/min.

Staging was performed according to the American Joint Committee on Cancer Staging (AJCC) 1989 classification. Before entering the study, all patients underwent physical examination, and a laryngoscopy under local anesthesia. General check-up included lung and esophageal endoscopy, chest x-ray, liver echography, complete blood count and blood chemistry.

All patients received Carboplatin (AUC 3 mg/ml/min) i.v. over 1 hour, 5FU 375 mg/mq i.v. bolus, Leucovorin 100 mg/mq i.v. over 30 minutes, on day one, for a total of 4 courses, each course was repeat every two weeks.

During radiotherapy Carboplatin was adminstered at 20 mg/m^2/day, 5 days/week with a portable battery pump (Pharmacia Deltec CADD-1) connected to venous access port, recharged every week till the end of the radiotherapy treatment.

In the case of severe toxicity (> grade 2), lasting until the scheduled treatment day the course was postponed for one week. If recovery of the toxicity was still incomplete, dose modification was performed. In the case of hematologic toxicity, both drugs were reduced to 50% in granulocyte count between 1,000/μL and 2,000/μL or platelet count between 50,000/μL and 100,000/μL; in renal toxicity, the dose of Carboplatin was reduced to 75%; in mucosal toxicity, the dose of 5FU was reduced to 50% for grade > 2.

A first clinical evaluation of response was performed after the fourth chemotherapy cycle. The final evaluation was assessed by a clinical examination and a laryngoscopy under local anesthesia with biopsies for primary tumor, and by echography for neck nodes. The response was defined as progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR), according to World Health Organization (WHO) guidelines. The pathologic complete response (PCR) for primary tumor was defined as macroscopic disappearance of the lesion with negative biopsy. The response was scored separately for primary tumor and lymph nodes.

Standard external beam radiotherapy program consisted of 1.8-2.0 Gy daily fractions and a total dose of 70 Gy in seven weeks for primary lesion (T) (a 1 to 2 week split was performed when necessary) and 60 Gy to regional lymph nodes. Radiotherapy was delivered by a LINAC 6 MeV. The target volume varied according to tumor localization and stage. Whenever possible, the therapy was planned from CT scan images at several different levels. In the case of retreatment, the dose was 60 Gy (1.8 Gy/fraction) with weekly control of toxicity. Treatment fields of photons were combined with electron fields (6-15 MeV) and/or brachytherapy treatment with Ir 192 as boost.

Results

All 9 patients who entered the study, were evaluable for response to induction chemotherapy, local treatment toxicity and survival. Three patients stopped the treatment after the fourth cycle of in-

duction chemotherapy due to disease progression with worsening of the clinical condition. Six patients completed the planned treatment obtaining 2 CRs, 2 PRs and 2 SDs.

In responding patients the shrinkage of the tumor started after the second cycle of induction chemotherapy in 3, and after the first cycle in 1. All the responding patients had the primary lesion located in the oropharynx. Lymph node response was obtained only in 1 case; another patient with CR of the primary lesion is now disease free, after a neck dissection.

The toxicity of induction chemotherapy was mild without renal or liver damage, only 3 cycles were delayed by seven days to allow platelet recovery, and vomiting was observed only in 7 out of 35 cycles. During radiochemotherapy 4 patients experienced grade III mucositis and 2 grade II. The median dose of radiotherapy delivered was 61 Gy (range 60-70) in 8 weeks (range 6-10) with a median split of one week (range 0-3). One patient experienced a central catheter line thrombosis.

Up to now, 8 patients are alive, 2 without disease and 6 with persistent disease. One died two months from the start of induction chemotherapy due to neoplastic cachexia.

Discussion

With Cisplatin and 5FU infusions (PF) given for four cycles before definitive local therapy a significant survival advantage in a large subgroup of inoperable stage III and IV patients was found.[9]

More than 35% of the patients with advanced head and neck tumor, seen at our department could not be treated with PF since they did not fulfill the inclusion criteria. It is important to stress that there is no known way how to modify a curative treatment for the elderly to be associated with fewer side effects without compromising the chance for cure.

Nevertheless, renal, gastrointestinal and neural toxicities of Cisplatin limit its dosage, especially in old or debilitated head and neck cancer patients.[4] Induction chemotherapy decreases distant metastases but does not improve local disease control.[9,10] Carboplatin, besides being less toxic than Cisplatin with similar activity in head and neck patients,[6] induces potentiation of moderate-dose radiation cytotoxicity in human lung cancer cell lines.[7] It could be safely administered by continuous infusion over 6 weeks at 20 mg/m^2/day in combination with loco-regional fractionated radiation therapy 30 x 2 Gy, with mild toxicity.[8]

However, due to the small number of patients in our study, it is difficult to draw any definitive conclusion. Nevertheless, we can say that 4 cycles of Carboplatin-5-fluorouracil and Leucovorin even at low, well tolerated doses, seem to have some effect upon the tumor in elderly patients and could be followed without additional toxicity by radiotherapy with combined systemic Carboplatin infusion. The overall response in 4 out of 9 patients, with only 2 CRs is not significant. This protocol needs further evaluation, and if efficacious, it has to be compared with radiotherapy alone in a randomized study.

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Combined application of cisplatin, vindesine, hyaluronidase and radiation for treatment of advanced squamous cell carcinoma of the head and neck

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Forty eight patients with advanced head and neck tumours were treated with irradiation and concomitant chemotherapy with cisplatin, vindesine and hyaluronidase. The disease-free survival rate at 5 years was 47%. The toxic effects were mucositis (48 patients), nausea (25 patients - in 6 patients vomiting), bone marrow depression (15 patients), and peripheral neuropathy (14 patients). The results warrant a randomised trial.

Key words: head and neck neoplasms-therapy; radiotherapy; cisplatin; vindesine; hyaluronidase; treatment outcome

Introduction

Advanced, unresectable epithelial cancer of the head and neck is a challenging problem in oncology. Standard radiation therapy is suboptimal because of a comparatively high risk of recurrence and long term survival is only achieved in less than 10% of the cases. Recent studies have shown that simultaneous radiochemotheray can prolong the recurrence-free interval as well as the patient's survival time.[1] Also, the radiosensitizing effect of Cisplatin has been observed.[2,3,4] The tumor-cell synchronizing effect of vinca alcaloids is well known.[5] The combination of Vindesine and Cisplatin was tested in several clinical studies.[6,7] The sensitizing effect of Hyaluronidase on polychemotherapy has already been demonstrated in separate studies, also as additive to the regimen with Cisplatin and Vindesine.[8,9]

The purpose of the present study is to evaluate the effect of radiation therapy in combination with chemotherapy consisting of Vindesine, Cisplatin and additional Hyaluronidase.

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Material and methods

The chemotherapy scheme was as follows: on day 1 (5 mg Vindesine) and day 2 (80 mg/sqm Cisplatin), with 200.000 IU Hyaluronidase administered i.v. over 20 min. on each of these two days before initiation of chemotherapy, and on 12 radiation days 3 - 5, 8 - 12 and 15 - 18. Renal function was protected by infusions before and after chemotherapy. This therapy regimen was repeated twice starting with chemotherapy on days 22 and 43.

The irradiation treatment was given by 6 MeV photon beam unit, 5 x 2 Gy per week, to the mid-plane tumour dose 72 Gy with shrinking field technique. If the radiomucositis was severe, the irradiation treatment was interrupted for a week.

The response to the treatment was evaluated after each cycle and after every month and finally three months after completion of treatment (according to WHO-guidelines). Mean observation time was 62 months (range: 32 - 85 months).

Results

To date, 48 patients were treated. No one was lost to follow-up. The survival of patients at 5 years was 47%. Sixteen patients are still in complete remission without relapse. The complete and partial remission was achieved in 40/48 patients and 3/48, respectively; in 1 patient, the condition remained unchanged. In 4 patients, tumor progression was evident under therapy and they died 3, 5, 6 and 8 months after therapy. In 12 cases relapses occurred after complete remission and all died because of cancer. Those who did not achieve complete remission died as well. Nine patients with stage T4 N2 and T4 N3 tumor died from tumor progression or recurrent disease. One patient died of pneumonia 5 months after achieving complete remission; another died of sudden heart failure 25 months after achieving complete remission. One patient died from secondary liver carcinoma.

Toxic effects: nausea occurred in 25 cases (WHO-grade 1 - 2); only 6 patients suffered from vomiting (WHO-grade 1 - 2). In 15 patients, signs of myelotoxicity (in 13 patients with WHO-grade 1, and in 2 patients with WHO-grade 2) and in 14 cases peripheral neuropathy (WHO-grade 1) developed. Twenty seven patients suffered from moderate/severe mucositis (WHO-grade 1 - 2) caused by radiation, and 12 patients experienced mucositis WHO-grade 3. Nine patients developed mucositis WHO-grade 4 and at this point radiation therapy was stopped for about a week. However, chemotherapy was administered according to the protocol in these patients as well.

Conclusion

Encouraged by the promising results of the presented trial, a randomized trial is being made with unchanged combined radiochemotherapy plus or minus additional hyaluronidase to evaluate the impact of this enzyme on the effectiveness of the therapy.

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Concomitant radiotherapy and mitomycin C with bleomycin in inoperable head and neck cancer

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In a prospective randomized study the efficacy of simultaneous irradiation with Mitomycin C and Bleomycin in patients with inoperable head and neck carcinoma was assessed. Between March 1991 and December 1994, 64 patients with inoperable head and neck carcinoma were randomly assigned to receive either radiation therapy alone (group A) or radiotherapy combined with simultaneous Mitomycin C and Bleomycin (group B). The disease-free survival (DFS) at 4 years for group B was 37%, and for group A 8%. (P=0.016), and the overall survival (OS) was 26% for group B and 7% for group A (p=0.09). The DFS for patients with oropharyngeal carcinoma in group B was 48% and in Group A 10% (p=0.0009) and the OS was 38% in group B and 10% in group A (p=0.024). In patients with nonoropharyngeal carcinoma, there were practically no differences in DFS and OS between groups B and A.The concomitant treatment (radiotherapy, Mitomycin C, Bleomycin) significantly improved DFS and OS in patients with oropharyngeal carcinoma.

Key words: head and neck neoplasms-therapy; radiotherapy; bleomycin; mitomycin C; treatment outcome

Introduction

During the past 20 years, the incidence of carcinoma of the oral cavity and pharynx has been increasing considerably in our country.[1] At diagnosis, more than half of the tumors are in advanced, inoperable stage. Various combinations of treatment modalities tested so far have failed to provide significant improvement of survival. Chemotherapy, applied as induction treatment has not yielded significant survival benefit.[2] In contrast to this, simultaneous application of combined radio- and chemotherapy has proved to be more effective in the treatment of advanced head and neck carcinomas.[3-6] Yet, the question of the most suitable chemotherapeutic combination still remains to be solved.[7]

The aim of our prospective randomized clinical study was to compare radiotherapy (arm A) and radiotherapy combined with simultaneous application of Mitomycin C, Bleomycin, Nicotinamid, Chlorpromazine, and Dicoumarol (arm B).

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Rationale for selection of chemotherapeutic scheme

According to some basic experimental studies that bioreductive alkylating agent Mitomycin C is selectively toxic to radioresistant hypoxic cells[8,9] and considering clinical studies of Weisberg[6] and Dobrowsky,[10] it appears that its use in patients with advanced head and neck carcinoma is justified. Namely, in a majority of these patients, a high percentage of hypoxic cells due to large tumor mass can be expected. Since more than only additive effect of combination of Mitomycin C and irradiation was speculated,[11,12] we decided to apply Mitomycin C and two irradiation fractions (2 Gy each) in the same day, after patients had received a dose of 10 Gy. Some studies[6,13] indicate that the repeated application of Mitomycin C improves the treatment effect. In accordance with this observation, a re-

peated dose of Mitomycin C before the end of therapy was planned.

It seems that Dicoumarol significantly enhances the effect of Mitomycin C on hypoxic tumor cells.[14] Therefore, the application of Mitomycin C was combined with Dicoumarol. In contrast to Mitomycin C, Bleomycin prevailingly acts on oxygenated cells. Due to its radiosensitizing effect, Bleomycin has been tested in several clinical studies.[2,4,5,15] In the treatment of carcinoma of the oral cavity, a simultaneous combination of irradiation and Bleomycin-based chemotherapy improved survival in some randomized studies.[4,5]

Some studies *in vitro* have confirmed the resistance of certain tumor cell lines to Bleomycin.[16] It seems possible that this resistance could be further enhanced by mutagens such as ionizing irradiation and Mitomycin C. In attempt to avoid the appearance of resistant cell lines, our patients received Bleomycin in combination with Nicotinamid, as suggested by the results of a corresponding basic study.[16]

According to the findings of Hait and coworkers[17] that simultaneous application of Bleomycin and Chlorpromazine significantly enhances the effect of Bleomycin on tumor cells and, at the same time, reduces the appearance of pulmonary fibrosis, Chlorpromazine was also incorporated in our chemotherapeutic scheme.

Combination of both, Mitomycin C and Bleomycin proved to be effective in the treatment of advanced squamous cell carcinoma of the cervix uteri.[13] The same cytotoxic drugs were used by Andreasson et al. in the treatment of advanced head and neck carcinomas. In this study, severe local adverse reactions due to intraarterial application of Mitomycin C were reported. Considering this, our patients were treated by intravenous application of Mitomycin C, while Bleomycin was given intramusculary.

Patients and methods

Between March 1991 and December 1994, 64 patients with previously untreated, histologically confirmed inoperable squamous cell carcinoma of the head and neck entered the study. The median age of patients was 51 years (range 37-68). Pretreatment assessment consisted of physical examination, endoscopy with biopsy, radiography of the head and neck with or without computerized tomography, and ultrasonography of the neck and abdomen, complete blood count and blood biochemistry, diffusion for CO. For staging, the UICC staging criteria were used. Criteria for inoperability were technical unresectability and/or selection based on low surgical curability.[4] Eligibility criteria, determined by the multidisciplinary team of radiation oncologist, head and neck surgeon, and medical oncologist included performance status < 3 (WHO), Hb > 100 g/l, L > 3.5 x 10^9/l, Tr > 100 x 10^9/l, normal bilirubin, creatinin, prothrombine time, and diffusion for CO. Informed consent was obtained from all patients. Patients with distant metastases, previous or simultaneous other malignancy except cured skin carcinoma, psychotic and senile patients, and those refusing the proposed treatment were excluded from the study. Eligible patients were randomly assigned to one of the two treatment groups using randomization with permuted blocks and stratified according to primary tumor site (Table 1). Sixty patients had Stage IV and four Stage III of disease.

Table 1. Treatment by site (RT=radiotherapy, ChT=chemotherapy)

Site	RT	RT + ChT	All
paranasal sinuses	2	4	6
oral cavity	6	4	10
oropharynx	21	20	41
hypopharynx	3	4	7
All	32	32	64

All patients in both groups received fractionated irradiation five times weekly with 2 Gy to the total dose of 66-70 Gy to the gross disease and 50 Gy to the clinically negative regions of the neck and supraclavicular lymph-node areas. On the day of the first application of Mitomycin C, patients in group B were treated with two fractions of 2 Gy with an interval of at least 6 h in between. The radiation dose to the spinal cord was 40 Gy.

Chemotherapy regimen included intramuscular application of Bleomycin 5 units twice a week with the planned total dose being 70 units and Mitomycin C 15 mg/m^2 given intravenously after delivery of 10 - 12 Gy of irradiation. The application of Mitomycin C was planned to be repeated on the last day of radiotherapy in a dose of 10 mg/m^2. Throughout the therapy, patients in group B received Nicotinamid (650 mg/day) and Chlorpromazine (200 mg with Bleomycin). Dicoumarol (300 mg) was applied in the evening and morning before Mitomycin C.

The main endpoints of the trial were tumor response, toxicity, disease-free survival (DSF), and overall survival (OS). The response rate was estimated 2 months after therapy. The difference in response rates was tested with X^2 test. If the number of patients was less then 5 in any cell of the table, a Fischer exact test was used. The survival was calculated after the completed treatment using the method of Kaplan - Meier and a logrank test was used to test the differences between groups.

Results and conclusions

All 64 patients who had entered the study, were evaluable for tumor response, toxicity, DFS and OS. Median follow-up was 42 months (range 21 - 63 months). Table 2 shows tumor response 2 months after treatment.

Table 2. Response rates in all, oropharyngeal and nonoropharygeal carcinoma patients (RT=radiotherapy, ChT=chemotherapy, CR=complete remission)

All patients	RT	RT + ChT	p
CR	10 (31%)	19 (59%)	
not CR	22 (69%)	13 (41%)	0,04
Oropharynx			
CR	6 (29%)	15 (75%)	
not CR	15 (71%)	5 (25%)	0,007
Others			
CR	4 (36%)	4 (33%)	
not CR	7 (64%)	8 (67%)	0,33

There was no treatment related death. The frequency and severity of early toxic effects due to therapy were more pronounced in patients in treatment group B (Table 3) and sometimes the dose reduction of Bleomycin and/or Mitomycin C was necessary, while there was no reduction of the total irradiation dose.

Table 3. Incidence of toxic side-effects by WHO toxicity grade (RT=radiotherapy, ChT=chemotherapy)

Grade		0	1	2	3	4
mukositis	RT	0	2	11	17	2
	RT+ChT	0	1	3	13	15
infection	RT	30	1	0	1	0
	RT+ChT	19	5	4	4	0
leucopenia	RT	31	1	0	0	0
	RT+ChT	18	8	5	1	0

Eight patients underwent salvage surgery, 2 from group A and 6 from group B. Surgery was successful in two group B patients only.

The DFS for group B was 37%, and for group A 8%. (P=0.01) (Figure 1), and the OS was 26% for group B and 7% for group A (p=0.08)(Figure 2). The DFS in patients with oropharyngeal carcinoma in group B was 48% and in Group A 10% (p=0.001) (Figure 3) and the OS was 38% in group B and 10% in group A (p=0.019) (Figure 4). In patients with nonoropharyngeal carcinoma, there were practically no differences in DFS and OS between groups B and A.

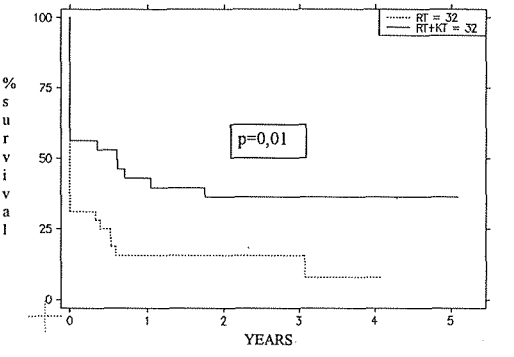

Figure 1. Disease free survival in all patients (RT=radiotherapy, KT=chemotherapy).

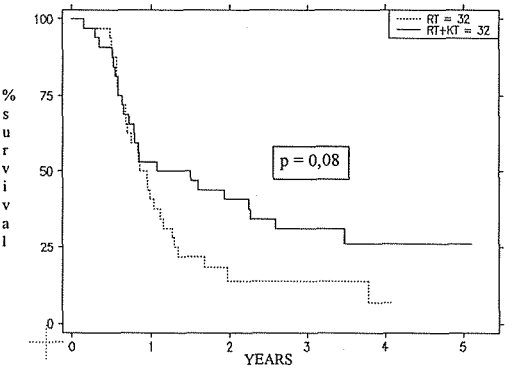

Figure 2. Overall survival in all patients (RT=radiotherapy, KT=chemotherapy).

From our study it seems that concomitant radiochemotherapy improves survival significantly in patients with inoperable oropharyngeal squamous cell carcinoma. Although the number of patients with nonoropharyngeal carcinoma is rather small, it

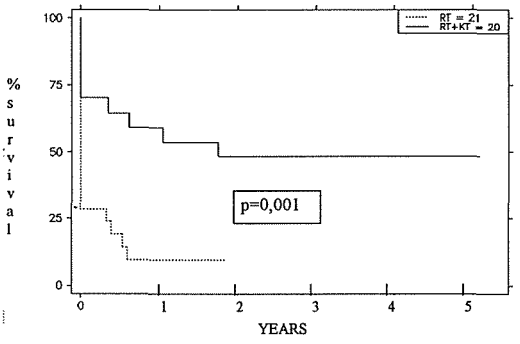

Figure 3. Disease free survival of patients with oropharyngeal carcinoma (RT=radiotherapy, KT=chemotherapy).

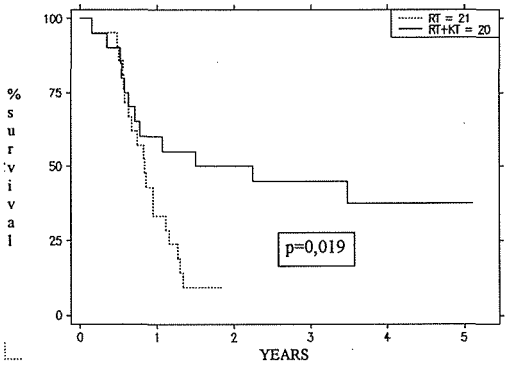

Figure 4. Overall survival of patients with oropharyngeal carcinoma (RT=radiotherapy, KT=chemotherapy).

seems that this concomitant treatment modality is not profitable for these patients.

The intent of our concomitant treatment was to achieve a higher percentage of complete response rates and better survival by enhancing the effect of radiotherapy with several additional drugs. The prevalence of complete responders and improved survival in the combined therapy group is therefore not the consequence of only one, but probably of several coexisting factors.

The choice of chemotherapeutic agents used in our trial was done on the basis of their effectiveness on hypoxic tumor cells, as well as their radiosensitizing effect. The latter is believed to be responsible for marked acute mucositis in patients treated by combined therapy.

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Treatment of malignant tumors of the oral cavity - state of the art

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In the past decades minimally invasive surgery and multimodal treatment strategies have gained in importance in the treatment of oral cancer as well as elsewhere. Within this concept, the primary tumor is resected enorally whenever possible, especially by carbon dioxide laser. The regional lymphatics are treated preferentially with functional neck dissection, preserving the sternocleido-mastoid muscle, accessory nerve and internal jugular vein. As a part of this multimodal treatment concept, percutaneous and interstitial radiotherapy was of great significance. Interstitial radiotherapy with iridium-seeds in the region of the (removed) primary tumor allows, on the one hand, local application of a high radiation dose and, on the other, protection of the surrounding tissues. The neck may be irradiated percutaneously, if necessary. By using this concept, extensive surgery with disfiguring defects, impaired swallowing, speech and chewing, and the necessity of reconstruction measures can be avoided in many cases with equally good treatment results and even improved quality of life. Tumours which cannot be resected by organ sparing surgery, will be treated by simultaneous radiochemotherapy. This report discusses the results of treating of 614 patients with oral cancer admitted to the Department of Otolaryngology, Head and Neck Surgery, University Erlangen-Nüremberg, during the period of 1970 to 1994.

Key words: mouth neoplasms-therapy; combined modality therapy

Introduction

Most common etiologic factors for oral cancer are abuse of alcohol and nicotine; recent epidemiologic data have demonstrated an increase in incidence in the last decades.

The progress in oncology all in all has failed to demonstrate a significant improvement on survival of patients with oral cancer, since most patients ask for medical help only just in advanced stages of the disease.

In the past, a typical treatment of oral cancer was transcutaneous surgery with the resection of the primary tumour and the lymphatics of the neck "en bloc" (commando procedure,[1]). Therefore, often the continuity of the mandible had to be interrupted. The neck dissection was performed as a radical surgery method with resection of the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve.[1] These jaw-neck procedures either required mandibular reconstructions with extensive flaps for covering the defects or resulted in disfiguring defects with severe functional impairment and loss of quality of life.

The concept of organ sparing treatment with minimally invasive surgery tries to avoid percutaneous or transmandibular surgical access to the primary site and instead makes use of the natural "entrance" through the oral cavity. The primary tumour is resected with high-frequency diathermic knives and needles and carbon dioxide laser.[2-4] The neck is treated discontinously and, if possible, using functional, nerve and muscle sparing surgical techniques.[3]

Postoperative radiotherapy proved to be especially beneficial in stages III and IV of the disease. If tumour resection seems unfeasible from the func-

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tional point of view, simultaneous chemoradiotherapy must nowadays be considered as the treatment policy of choice. We discuss the results in oral cancer treatment obtained in the last two decades, especially by comparing "functional" vs. "radical" therapy.

Materials and methods

Within a retrospective analysis, the records of all 506 patients, treated for oral cancer at the Department of Otorhinolaryngology, Head and Neck Surgery, University Erlangen, between 1970 and 1990, were reviewed. TNM classification was updated in accordance with the 4th edition. Follow-up data were obtained from cooperating hospitals (especially radiation oncology departments), the resident doctors, the registration offices and the relatives of the patients.

Data were analyzed by using the statistic software Stat View for Macintosh.

The mean age of the 423 men and 83 women was 56 years (range: 29 - 93 years). Patients of group 1 (242) were treated by enoral surgery and the patients of group 2 (143) by percutaneous surgery. T-, N- and stage distributions are shown in Figure 1. In group 1, 43% received postoperative radiotherapy, in group 2, 28%.

Results

The 5-year and 10-year disease free survival rates for the whole group were 57% and 51%, respectively. The 5-year and 10-year disease-free survival rates were 61% and 58% resp. for group 1 and 62% and 53% resp. for group 2 (Figure 2). The difference in disease-free survival between the two groups was not statistically significant. The stage dependent survival rates are summarized in Table 1.

Table 1. Percentage of the disease free survival in both treatment groups according to stage

Stage	Group 1 enoral			Group 2 percutaneous		
	n	5 years	10 years	n	5 years	10 years
I	59	61,7	61,7	9	(87,5)	(87,5)
II	43	70,7	55,0	22	62,8	52,9
III	76	67,8	67,8	53	65,8	59,2
IV	66	43,2	43,2	59	53,9	46,0

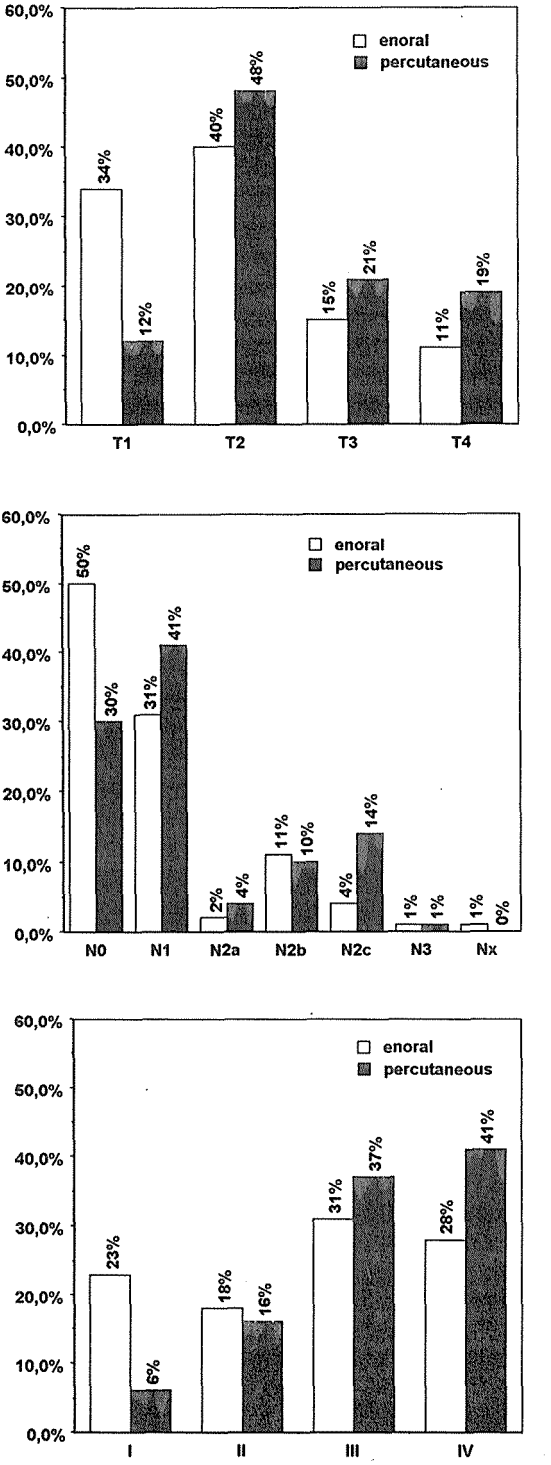

Figure 1. Distribution of T-, N-categories and stage in both treatment groups.

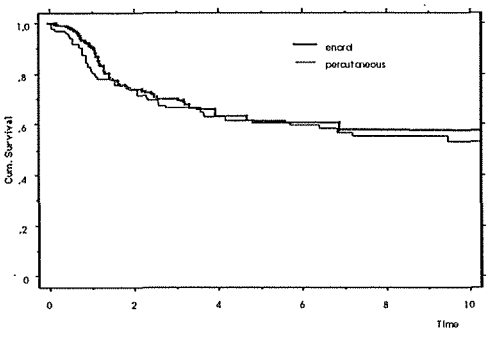

Figure 2. Disease free survival by method of surgery.

Discussion and conclusions

Figure 2. shows that in oral cancer enoral surgery and percutaneous surgery, such as commando operation, jaw-neck procedure or mandibular split procedure seem to be equal from the viewpoint of prognosis. However, when comparing T, N and stage distributions, some minor heterogeneities were obvious, but also stage dependent survival rates as demonstrated in Table 1. failed to demonstrate any significant difference in survival between the two groups for stages II to IV. In stage I the numbers are too small for valid statements.

Within the last two decades, various authors have published reports on enoral resections of oral cancer.[2,4,5] The treatment results reported are comparable to those achieved by en bloc resections and reconstruction of the resulting defects by peddled or microvascular anastomosed flaps.[6]

We conclude with reference to our analysis, that organ sparing or "functional" surgery (in combination with postoperative radiotherapy) in comparison with classic "radical" surgery can be performed without any decrease in survival rate. Considering the lesser impairment of swallowing and speech in particular and of function in general,[7] "functional" treatment of cancer of the oral cavity should be emphasized as the treatment option of choice.

Acknowledgment

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Combined therapy of undifferentiated carcinoma of nasopharyngeal type

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From November 1989 to October 1993, 339 patients with stage IV undifferentiated carcinoma of nasopharyngeal type (UCNT) were enrolled in a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin - BEC) plus radiotherapy (171 patients) vs. radiotherapy alone (168 patients). All patient characteristics were well-balanced in both arms. The overall response rate assessed clinically by the investigator at the end of chemotherapy was 91% (WHO) with 47% CR and 44% PR. Three months after the completion of radiotherapy, a CR (clinical + CT scan) was observed in 55% of the combined treatment group, compared to 34% in the radiotherapy-alone group ($p<0.01$). Tumor recurrence or progression was observed in 55/171 patients in the chemotherapy arm (32.7%), compared to 92/168 patients in the radiotherapy-alone arm (54.7%) ($p<0.01$). In conclusion, the addition of BEC type chemotherapy, preceding radiotherapy, has changed the proportion of UCNT patients continuously disease free but the overall survival data are not yet mature.

Key words: nasopharyngeal neoplasms-drug therapy-radiotherapy; treatment outcome

Introduction

As high as 85% of all nasopharyngeal tumors are carcinomas. The incidence of undifferentiated and poorly differentiated tumors is the highest, especially in endemic regions (over 90%). Undifferentiated carcinoma of the nasopharynx is an Epstein-Barr virus-related carcinoma of epidermoid origin different in its carcinogenesis, epidemiology and behaviour patterns from other squamous cell carcinomas of the head and neck.[1,2,3]

Carcinoma of the nasopharynx is a relatively rare tumor. In the United States and Western Europe, it accounts for only 0.2-0.3% of all malignant tumors,[4] or 1-3% of all carcinomas of the upper respiratory and digestive tract.[5] Its incidence is much higher in the Mediterranean countries (5-7 newly detected cases per 100,000 inhabitants a year).[6,7,8] In Southeast Asia, this number reaches 15-30 cases per 100,000 inhabitants and accounts for even 60-75% of upper respiratory and digestive tract carcinomas, or 20% of all malignant tumors.[9,10] Of all head and neck tumors, nasopharyngeal carcinomas are the fastest to metastasize.

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Treatment

Nowadays, radical surgery of nasopharyngeal carcinoma, has been almost completely abandoned. Treatment of nasopharyngeal carcinoma is primarily the concern of radiotherapy. The radiotherapy response in early-stage disease is usually successful, but the response of locally advanced disease is relatively poor, with local nodal failure reported in up to 40% of cases.[11-14]

Nasopharyngeal carcinoma, in particular that of poorly differentiated cells, is a chemosensitive tumor in which anticancer drugs figure prominently for years.[15-18] Formerly, chemotherapy was applied only in disseminated disease, while in the last ten years it is applied in early locally advanced cases.

Chemotherapy is sometimes applied alone or combined with radiotherapy as part of a multimodal therapy approach.

Results of numerous nonrandomized clinical trials have confirmed the advantage of polychemotherapy, and with the combination of cytostatic agents bleomycin, cyclophosphamid, methotrexate, and fluorouracil (BCMF) the therapy response is reported in 50-80% of patients.[19-29] Clinical trials on the efficiency of cisplatin (CDDP) based polychemotherapeutic protocols show the best results (86%).[30-34] Despite the well-known chemosensitivity of nasopharyngeal carcinoma, randomized prospective clinical trials on chemotherapy efficiency in metastatic disease have started only recently. In 1991, a clinical trial aiming at comparing the antitumor efficiency of cisplatin, bleomycin and fluorouracil (PBF) combination with the combination in which fluorouracil is replaced with epirubicin (BEP) was carried out at the Institute Gustave Roussy. The response rate assessed in both groups was 80%, but complete remission was observed only in 20% of patients of the first group and 13% of patients of the second group.[16]

Despite such promising results, no randomized trial testing the value of the added neoadjuvant chemotherapy has yet been reported, and it remains to be shown in a randomized trial whether the addition of neoadjuvant chemotherapy to conventional radiotherapy could improve the treatment outcome.

Phase II trial of bleomycin-epirubicin-CDDP regimen (BEC) in N2c-N3 patients showed a 98% objective response rate, including a high proportion of complete clinical responses (66%).[35] This high complete response rate contrasted with the lower complete response rate (10%) obtained in a comparable group of patients from the same institution related with CDDP-bleomycin-5FU,[15] suggests that BEC fulfilled the activity required for a prospectively controlled trial testing the value neoadjuvant chemotherapy in this type of tumor. With that aim, a large-scale randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV undifferentiated nasopharyngeal carcinoma was initiated in 1989, by the International Nasopharynx Cancer Study Group with the participation of Algeria, Croatia, Greece, France, Malaysia, Morocco, Portugal, Saudi Arabia, Spain and Turkey.

Material and methods

From November 1989 to October 1993, 339 patients were enrolled in this study. The eligibility criteria were as follows: biopsy-proven UCNT (World Health Organization type 2-3), age between 15-70, any T, N $\geq$ 2, M0 (UICC 1987), performance status 0-2 (WHO). Prerandomization work-up required CT scan of the nasopharynx, base of the skull, and cervical nodes, adequate ($\geq$ 75 ml/min creatinin clearance) renal function, normal cardiac and hematological functions, and chest x-ray, bone scintigraphy, bone marrow biopsy, liver ultrasound and/or CT scan showing no evidence of distant metastases. The patients were randomized, after giving informed consent, to receive radiotherapy alone consisting of 70 Gy in 7 weeks or 3 cycles of BEC (days 1, 21, and 42) followed 3 weeks after chemotherapy by the same radiotherapy schedule.

The BEC protocol consisted of bleomycin 15 mg IV push day 1 followed by 12 mg/m^2/day slow IV bolus day 1, cisplatinum 100 mg/m^2 over 1 h on day 1 with pre- and posthydration manitol induced diuresis, to be given every 3 weeks. A delay of 1 week was added between cycles if neutrophile counts or platelets toxicity was grade > 2 (WHO) on day 20, and CDDP was decreased to 75 mg/m^2 if calculated creatinin clearance was between 50 and 75 ml/min. Chemotherapy was discontinued if clearance was lower than 50 ml/min or if hematological toxicity was Grade 3 or more by day 35.

In both arms, the radiotherapy protocol planned to deliver 65-70 Gy in 6.5-7.5 weeks to the primary tumor, 65 Gy to clinically involved nodes, and 50 Gy to the remaining cervical and supraclavicular nodal area. The fractionation schedule used was five daily fractions of 2 Gy per week. The treatment was performed using photon beam of a ^{60}Co unit or a 4-5 MeV linear accelerator. The guidelines for irradiation of the primary site and upper cervical chain were as follows: two lateral opposed fields were used up to 42 Gy with an anterior limit of 2-3 cm in front of the pterygoid plane for T2 tumors and, depending on spread, for T3-T4; the inferior limit was above the margin of the hyoid bone; the posterior limit was generally a plane running behind the spinal apophysis; the upper limit for T2-T3 was the upper third of sphenoid sinus and above tumor spread to the base of the skull or intracranial for T4 tumors. After 42 Gy, the posterior limit was modified to exclude the spinal cord, and 28 Gy added using a reduced lateral photon fields. The

posterior fields were treated with 8 Gy if N0, and 23 Gy if palpable nodes were initially present, using 8-10 MeV electron beams.

The middle and inferior cervical nodes were treated by an anterior cervical field using photon beams of ^{60}Co or 4-5 MeV unit and the dose was specified at a depth of 3 cm. The upper limit was separated from the lower limits of the lateral fields if running through involved lymph node. The inferior limit was the upper margin of the sternum and the lateral limits were middle third of the clavicle. A systemic midline protection was used as well as subclavicular protection for the lung. In case of spinal involvement of posterior cervical nodes, two equally weighted anterior and posterior fields were used. Median follow-up was 49 months (range 23-79).

Follow-up examinations

Three months after the completion of radiotherapy, a clinical endoscopic examination, a chest x-ray and a CT scan were performed. Six months after the completion of radiotherapy, the same procedures were repeated plus a bone scan examination and a liver echography. The same procedure was then repeated in one of the two yearly follow-up visits.

Evaluation of response

Response to chemotherapy assessed at the end of every cycle and before radiotherapy were defined under WHO response criteria.[36] Response after the radiation therapy course was defined as complete if all clinically and scintigraphically detectable malignant disease had completely disappeared 3 months after the end of treatment.

Statistical analysis

The primary objective of the study was to compare overall survival at 5 years in the two treatment groups. Its secondary goal was to assess and compare the objective response rate, toxicity, and survival free of disease progression in both groups.

Results

Out of the 339 patients randomized, 171 were assigned to chemotherapy plus radiotherapy and 168 to radiotherapy only. There was no difference between the two treatment arms in the distribution of patients by tumor types. Most of the patients had T3-T4 primary tumor and N2c-N3 nodal status. The distribution of the main clinical and histological characteristics of the patients were well balanced between the two treatment groups.

Response to treatment

The response rate assessed clinically by the investigator at the completion of chemotherapy was 91% (WHO) with 47% CR and 44% PR. Three months after the completion of radiotherapy, a CR (clinical + CT scan) was observed in 55% of the combined treatment group, compared to 34% in the radiotherapy-alone group ($p<0.01$).

Tumor recurrence or progression at 4 years was observed in 55/171 (32.7%) patients in the chemotherapy arm, compared to 92/168 (54.7%) patients in the radiotherapy-alone arm ($p<0.01$).

The incidence of both, relapse and distant metastases, was reduced in the combined treatment arm. The progression-free survival at 4 years shows a statistically significant difference in favor of the chemotherapy arm. The current overall survival data are not statistically different between the two treatment modalities, but the number of events to determine its final significance has not yet been reached.

Discussion and conclusion

The most important finding of this study was the increase in progression-free survival in the combined therapy arm and the dramatic decrease in the incidence of relapse both at the primary site and at distant metastatic site.

Despite the advantage in progression-free survival, there is no survival benefit in favor of the chemotherapy arm. It is too early to report on a lack in survival difference because the initially planned number of events to show a statistically significant difference has not yet been reached.

Based on the present positive preliminary results, the International Nasopharynx Cancer Study Group has started a new trial in February 1995. With a slightly modified BEC protocol given to all patients, the patients are randomized to standard radiotherapy or to the same plus daily oral Hydroxiurea in order to reach a better local control of disease.

In conclusion, the addition of BEC type chemotherapy preceding radiotherapy has changed the proportion of UCNT patients continuously disease free. Overall survival data are not yet mature. Morbidity

and mortality are relevant problems which, when combined with radiotherapy compliance issues, make the need for close collaboration of multidisciplinary teams mandatory.

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Surgical treatment of advanced oropharyngeal cancer by preservation of the larynx

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This retrospective study evaluates the treatment and functional results obtained in 61 patients with advanced oropharyngeal cancer who underwent extended tumor resection as a primary treatment procedure or as salvage surgery. Although the oropharyngeal cancers involved the base of the tongue, and some of them extended to the lateral hypopharyngeal wall, the surgery was performed without total laryngectomy. In 5 cases, the tumor extended to the vallecula and/or to the pharyngo-epiglottic fold, which required supraglottic laryngectomy. In all patients, the closure of tissue defects after extended tumor resection was done with flap reconstruction. The most preferred method was the pectoralis major myocutaneous flap. The survival rates were 75% at 1 year, 31% at 2 years, and 25% from 2 to 5 years. In this series, satisfactory functional results were obtained. Most of our patients had their larynx and voice preserved. In one of our patient, the nasogastric tube could not be removed and, in another, decanulation was not possible because of persistent oedema after postoperative radiation.

Key words: oropharyngeal neoplasms-surgery; treatment outcome

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Early pyriform sinus cancers removed by vertical partial pharyngectomy with preservation of the larynx

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Hypopharyngeal carcinomas belong to the most aggressive tumors. The anatomical and functional features of the region as well as high grade of malignancy contribute considerably to the invasion and spread of cancer cells and to its unfavourable prognosis. Most of the hypopharyngeal tumors are - due to their hidden location and lack of early symptoms - so advanced at the time of diagnosis and therapy that it is impossible to preserve the larynx or a part of it. In spite of these facts, in a smaller part of careful selected patients - 15-20 percent -can be treated by conservation surgery.

Between 1986 and 1995, at our department, vertical partial pharyngectomy was performed in 35 patients with carcinoma of the pyriform sinus. The tumors involved the upper part of the pyriform sinus - its lateral wall and/or the pharyngoepiglottic fold. After ipsilateral neck dissection, cancers were eradicated either by extended horisontal or in 13 cases vertical partial resection. In these cases, the access to the primary tumors was carried out through lateral pharyngotomy.

It must be emphasized the careful TNM classification of tumors, the rigorous keeping of oncological principles and importance of one stage reconstruction. Good functional and survival results show that conservation surgery of early hypopharyngeal cancer is a reasonable approach.

Key words: hypopharyngeal neoplasms-surgery; pharyngectomy-methods; survival rate

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Comparison of sequential and simultaneous chemo-radiotherapy for advanced hypopharyngeal carcinoma - Results of a randomized study

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In prospective randomized study, a comparison was drawn between intensified sequential chemo-therapy (arm A) and simultaneous chemo-radiotherapy (arm B) in stage IV hypopharyngeal cancer. G-CSF support was given in both arms; chemotherapy consisted of 2 courses of CDDP (25 mg/m²/d for 5 days) and 5-FU (750 mg/m²/d for 5 days continuously). Radiotherapy dosages were 70 Gy on the primary lesion and 60 Gy on the neck. Ninety eight patients were randomized; 60 patients (28 arm A, 32 arm B) finally fulfilled inclusion criteria. Complete remission could be observed in 49% in arm A and in 57% in arm B (p=0.07) and the two-year survival was 27% and 47%, respectively.

Key words: hypopharyngeal neoplasms-drug therapy; radiotherapy; treatment outcome

Material and methods

In this single center study, 98 subsequent unselected patients with advanced, non-resectable squamous cell carcinomas of the hypopharynx (UICC stage IV) were randomized to two different therapeutic regimes: sequential chemo-radiotherapy (arm A) or simultaneous chemo-radiotherapy (arm B).

The patients in arm A received two courses of CDDP (dosage 25 mg/m²/d for 5 days) and 5-Fluorouracil (dosage 750 mg/m²/d for 5 days as continuous infusion), followed by the application of G-CSF for 6 days. Course 2 was started already at day 14 to intensify chemotherapy and was followed by external beam radiotherapy (70 Gy on primary lesion, 60 Gy on neck).

Arm B consisted of concomitant chemo-radiotherapy with identical dosages of chemotherapeutic agents, but with 3-week interval between the 2 courses.

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Results

After a thorough examination, approximately one third of the patients were not eligible or could not be enrolled mainly because of medical problems, such as renal failure or liver cirrhosis. Finally, 28 patients were treated in arm A and 32 patients in arm B.

Sequential treatment was better tolerated due to less mucositis (WHO grade 3 mucositis 4% in arm A, versus 32% in arm B and 73% of the patients could receive the second course in time. Neutropenia was more often and more distinctive in arm B. Three therapy-related deaths occurred.

Complete remissions (according to the WHO definition) could be achieved in 49 % in arm A and in 57 % in arm B (Logrank-Test: p = 0,07). Long lasting complete remissions were seen in both arms. The two-year overall survival was 27% in arm A and 47 % in arm B (Figure 1).

Discussion and conclusions

Escalation of chemotherapy with G-CSF support demonstrated to be feasible in both groups. As expected, acute toxicity in arm B was pronounced.

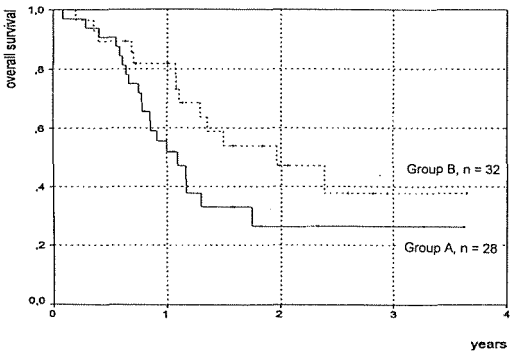

Figure 1. Overall survival of patients treated by sequential (Group A) and simulateous chemoradiotherapy (Group B).

This study suggests that concomitant chemo-radiotherapy in comparison with intensified sequential chemo-radiotherapy is even more beneficial.

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Carcinoma of the posterior pharyngeal wall - larynx preservation with the radial forearm flap or transoral resection

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In a series of 15 patients with advanced (T2 and T4) tumors of the posterior hypopharyngeal wall, we tried to preserve the larynx during surgical therapy. Four patients with T2 tumors and with limited invasion of the lateral pharyngeal wall were resected transorally under microscopic control. In 9 cases, the access to the pharynx was done with lateral pharyngotomy and the pharynx was reconstructed in 8 cases with a radial forearm flap and in one case with a jejunal transplant. Two patients preferred radiotherapy or combined chemo-radiotherapy. One patient died after transoral tumor resection due to osteomyelitis of the cervical vertebral spine. The other three patients of this group learned to swallow within the period of four months. Three months after the reconstruction of the posterior pharyngeal wall with free flaps, 7 patients were able to swallow without aspiration. One patient needed 4 month to swallow without aspiration. One year after the reconstruction, one patient still needs tracheotomy because of aspiration problems. Surgical resection of advanced tumors of the posterior pharyngeal wall is possible without laryngectomy. The reconstruction with the radial forearm flap is preferred for T4 tumors with extension to the lateral pharyngeal areas and transoral resection under microscopic control is useful for T2 tumors.

Key words: hypopharyngeal neoplasms; pharyngectomy

Introduction

Surgical treatment of T1 and T2 tumors of the posterior pharyngeal wall is usually possible with transoral microscopic resection.[1] Advanced tumors show involvement of the oesophagus and extension to the lateral parts of the pharynx. So, due to functional problems, laryngectomy was usual after surgical therapy.[2] We tried to evaluate surgical therapy (transoral microscopic resection or reconstruction with radial forearm flap) in a series of 15 patients with advanced carcinoma of the posterior pharyngeal wall with the intention to combine radical tumor resection with larynx preservation.

Material and methods

Between 1993 and 1997, 15 patients with T2 (N=8) and T4 (N=7) carcinoma of the posterior hypopharyngeal wall were treated at our institution. Tumor staging was done according to the TNM classification, 1987.

Two different surgical treatment options were used; the decision depended on the extension of the carcinomas. In cases where lateral pharyngeal walls or the oesophagus were involved by tumorous growth, reconstruction with free flaps was performed, and in cases of smaller tumors without extension in the above mentioned structures, transoral resection was used.

1. Transoral microscopically controlled resection (4 patients, all with T2 tumors and with limited invasion of the posterior pharyngeal wall):
   - transoral resection
   - percutaneous endoscopic gastrotomy (PEG)
   - bilateral neck dissection 3 weeks after transoral resection
   - postoperative radiotherapy.

2. Free flap reconstruction of the posterior pharyngeal wall after lateral pharyngotomy (9 patients):
   - lateral pharyngotomy; bilateral neck dissection and tracheotomy

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- reconstruction with microvascular reanastomosized free flap (radial forearm flap or jejunal flap)
- postoperative radiotherapy
- PEG, if swallowing function is not restored over a longer period.

Two out of 15 patients preferred ratiotherapy or combined chemo-radiotherapy.

Results

Complications

One patient with transoral tumor resection developed an osteomyelitis of the cervical vertebral spine during postoperative radiotherapy and died a few days later. During lateral pharyngotomy, the superior laryngeal nerve on the tumor side could not be preserved in one case.

Functional outcome

Three weeks after transoral tumor resection, two patients showed sufficient swallowing function. In one patient, pharyngeal stenosis developed and, 5 months postoperatively, he is still unable to swallow satisfactorily.

In the group of patients with free flap reconstruction, 7 patients were able to swallow sufficiently three months after the operation. One patient needed a percutaneous endoscopic gastrostomy over a period of four months before he could swallow without aspiration, and one patient still has a tracheostoma for mild aspiration 12 months after operation.

Discussion and conclusions

There are a few reports on larynx preservation after surgical therapy of advanced carcinoma of the posterior pharyngeal wall.[3-6] We tried to combine surgical treatment of these carcinomas with optimal functional rehabilitation. The most important factors in this regard are the preservation of the larynx and the ability to swallow without aspiration. Transoral resection is preferred for smaller tumors without extension to the lateral parts of the pharynx and without involvement of the oesophagus. The reconstruction of the posterior pharyngeal wall with the radial forearm flap allows the resection of advanced carcinomas with acceptable functional outcome. For carcinomas extending from the nasopharynx to the oesophagus, the jejunal flap is a further option to reconstruct the resection defect.

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Organ-sparing surgery in supraglottic cancer: Functional results and survival in 25 year period

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This study is to analyse my personal experience in organ-sparing surgery which was done for 348 patients between 1966 and 1990. Simplified (standard) supraglottic laryngectomy was used for T1 and T2 lesions in 245 patients. One hundred and three patients were operated on with extended supraglottic laryngectomy: 61 of those were treated by supraglottic subtotal laryngectomy and 42 patients by supraglottic laryngectomy extended to the base of the tongue. Significant problems with aspiration occurred in 26 patients (7.5%). In four of those, total laryngectomy was required. In three patients, tracheostomy was necessary. Local recurrence was recorded in 23 (6.6%) patients. Overall survival at 5 years was 74% in the first group, 69% in the second group, and 62% in the third group. The survival of patients without metastases in the neck was 84%, and in those with the metastases in the neck nodes was 50%. These results showed that, in supraglottic cancer, a good local control can be achieved by organ preserving surgery.

Key words: laryngeal neoplasms-surgery; laryngectomy-methods; treatment outcome

Introduction

The treatment for supraglottic cancer of the larynx has changed over the years. In Great Britain and North-West Europe, the majority of patients are treated with radiotherapy (RT).[1,2,3] If primary surgery was advocated[4,5,6], mostly total laryngectomy was performed. In the series of 401 patients reported by Meyer *et al.*,[7] supraglottic laryngectomy was performed in less than 10% and total laryngectomy in over 90% of patients.

On the other hand, supraglottic laryngectomy – with or without RT – was advocated by others[8,9] with superior results when compared with RT alone, especially for T2 and T3 lesions.[10]

The purpose of this study was to assess the efficiency of organ-sparing surgery in supraglottic carcinoma (over 50% of all laryngeal cancer) in 25 years and to analyse other prognostic factors on all patients who underwent supraglottic partial laryngectomies (at three centres in Hungary) under my auspices between the years from 1966 to 1990 with a minimum follow-up of 5 years.

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Material and methods

A retrospective review of 648 patients with squamous cell carcinoma of the supraglottic larynx diagnosed and treated from 1966 to 1990 was done. Of the 648 patients, 131 (20%) were treated primarily with RT. Total laryngectomy was required in 169 patients (26%). Organ-sparing surgery was the primary treatment modality in 348 patients (54%). In total, surgery as a primary treatment for supraglottic cancer was used in 517 patients (80%).

The organ-sparing supraglottic surgery techniques reported earlier,[11] were used as follows:

1. Simplified (standard) supraglottic laryngectomy was used for T1 and T2 lesions in 245 patients (38%).

2. One hundred and three patients were operated on by extended supraglottic laryngectomy:

2.1. Supraglottic subtotal laryngectomy was designed for the resection of the entire supraglottic larynx and one true vocal cord with the arytenoid and ipsilateral wing of the thyroid cartilage below the thyro-arytenoid muscles - 61 patients (9%) were treated with this techniques.

2.2. Supraglottic laryngectomy extended to the base of the tongue - 42 patients (7%) were operated on by this method.

Combined surgery and RT were occasionally indicated. I am very cautious to decide to perform these operations after a complete course of RT; in fact, only 3 patients belonged to this group.

The reconstruction was performed carefully in all techniques:

1. The base of the tongue was transversely dissected, producing two layers to cover the cut thyroid cartilage by using two heavy U-shape sutures;
2. Appropriate suturing of the new laryngeal vestibulum;
3. Attention had to be paid that the residual larynx was sinking down and to the reconstruction of a functioning larynx; an important factor was a secure elevation and fixation of the rest-larynx up to the base of the tongue.

Results

Aspiration occurred practically in all patients, but it improved in the first month after surgery in most of them. Aspiration pneumonia occurred in 7.5%, and 3 of them died. Wound break-down and fistula formation were recorded in 4 and 7 patients, respectively. In 7 patients, swallowing could not be restored satisfactorily and a tube for drinking was necessary. In 4 patients, total laryngectomy was required. Prolonged decanulation was more frequent earlier, but only 3 surviving patients had permanent tracheostomy.

Voice was preserved in 326 out of 517 surgically treated patients (63%): both vocal cords were preserved in 269 (52%) and one vocal cord in 57 (11%) of patients. Only 191 (37%) patients lost their larynx.

Five-year actuarial survival rates were as follows:

- Simplified (standard) supraglottic laryngectomy - 74%;
- Supraglottic subtotal laryngectomy - 69%;
- Supraglottic laryngectomy extended to the base of the tongue - 62%.

Of 348 patients, 236 (68%) were alive over five years without evidence of disease. The local recurrence rate was acceptable - 23/348 (6.6%).

Loco-regional failure occurred in 79 (22.7%) patients. The most common site was the cervical lymph nodes. Of the 79 patients with recurrent disease, 56 (71%) developed cervical metastases, and 48 (61%) of them died of carcinoma. Patients with metastases in the neck had lower survival rates (49% - 71/143) than those with N0 disease (80% -165/205).

Conclusions

Organ-sparing surgery for supraglottic cancer provides an effective therapeutic modality. Technically, most of the supraglottic lesions of intermediate size can be resected with preservation of the voice. Primary RT is an effective alternative for many of these lesions. The problems still exist in the control of lymphatic metastases.

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Supraglottic laringectomy: Treatament results of two different operation methods

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Treatment results of two different kinds of supraglottic laryngectomies were compared.
Material and methods: Treatment results of all patients treated at our department between 1st January 1990 and 31st December 1994 with partial supraglottic laryngectomy were analyzed. Patients were treated with two different methods of operation - in 29 patients, the defect was reconstructed with simple suspension of the rest of larynx to the base of the tongue and, in 23 patients, the defect was covered with the sternohyoid fascia. The majority of patients were postoperatively irradiated (42/52). Patients were followed for at least two years.
Results: An overall 79% (41/52) local and regional control of disease was achieved. Decanulation was possible in 66% (34/52) of patients and in 85% (44/52) of patients peroral intake was achieved. Locoregional control was comparable to that published in the literature, but the percentage of decanulated patients was lower. There was no statistically significant difference in survival and function between the two methods compared.
Conclusion: Since with both methods comparable results were obtained, we think that the simpler method without the use of fascia, is a more appropriate one.

Key words: laryngectomy-methods; laryngeal neoplasms-surgery; treatment outcome

Introduction

Supraglottic laryngectomy is very often initial treatment of supraglottic tumors.[1-3] In classic supraglottic laryngectomy, embryologic unit of the larynx with the tumor is removed.[4] With some extension, this operation can be applied in some hypopharyngeal and oropharyngeal carcinomas.[5-7]

A tissue defect between the base of the tongue and the remaining part of the larynx appears after tumor removal. In our patients, we used two methods of reconstruction; the defect was either bridged with the sternohyoid fascia[8] or the larynx was suspended on the base of the tongue with the sutures.

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The aim of this retrospective study was to assess with which of the two methods used better functional and survival results were achieved.

Material and methods

From 1st January 1990 to 31st December 1994, supraglottic laryngectomy was performed on 59 patients at our department. The patients previously treated for the same or another malignant disease in the head and neck region were excluded from the study. Thus, treatment results of 52 patients were evaluated.

Patients were divided into two groups. In the first group, there were 23 patients operated on using the sternohyoid fascia for reconstruction and, in the second group, there were 29 patients operated on with the suspension method.

The majority of our patients (42/52) was postoperatively irradiated. Indications for irradiation were:

positive or insecure margins of excision, stage III and IV of disease, perineural spread, more than one positive neck node or positive node low in the neck,and extracapsular spread of tumor.

Irradiated patients received tumor doses of 50-70 Gy. Irradiation was applied in daily fractions of 2 Gy, 5 fractions per week.

All patients included in the study were followed for at least two years. Data of all patients were put in the computer and analyzed with Msaccess and Statistica for Windows software. Disease specific survival rate was computed with Kaplan-Meier method. Two-tailed t-test for independent samples was used for evaluation of differences between the groups.

Results

In the period under study, partial supraglottic laryngectomy was performed on 13 patients with carcinoma of the hypopharynx, 36 patients with carcinoma of the supraglottis and 3 patients with disease in the oropharynx. There were 7 women and 45 men, aged 32 - 82 years (median, 56 years). Distribution of our patients according to the TNM Classification of Malignant diseases[9] is presented in Tables 1, 2 and 3:

Table 1. Distribution of patients with hypopharyngeal carcinoma (n=13)

	N0	N1	N2a	N2b	N2c	N3	
T1	0	0	0	1	0	0	1
T2	2	2	2	0	1	1	8
T3	1	0	0	1	0	1	3
T4	0	0	0	1	0	0	1
	3	2	2	3	1	2	13

Table 2. Distribution of patients with supraglottic carcinoma (n=36)

	N0	N1	N2a	N2b	N2c	N3	
T1	0	0	0	0	0	0	0
T2	12	2	2	5	3	0	24
T3	4	1	0	2	1	0	8
T4	0	0	1	0	3	0	4
	16	3	3	7	7	0	36

Table 3. Distribution of patients with oropharyngeal carcinoma (n=3)

	N0	N1	N2a	N2b	N2c	N3	
T1	0	0	0	0	0	0	0
T2	0	0	0	2	0	0	2
T3	0	0	0	1	0	0	1
T4	0	0	0	0	0	0	0
	0	0	0	3	0	0	3

In total, 42 patients were postoperatively irradiated, out of whom 27 were decanulated (64%). Seven patients out of 10 without irradiation were decanulated (70%). Postoperatively, decanulation was possible in 34 (66%) patients. In 18 of them, suspension was used for reconstruction, and in 16, the fascia was used (Figure 1). In supraglottic tumors decanulation was possible in 27 out of 36 patients (75%). The reconstruction method with the fascia was applied to 16 patients out of whom 14 (88%) were decanulated. Suspension method was used in 20 patients out of whom 13 (65%) were decanulated. Tumor size did not influence significantly the proportion of decanulated patients. In all three patients with the tumor in the oropharynx, the suspension method of operation was performed. In spite of a very extensive excision of the base of the tongue, we managed to decanulate two of them (66%). Five out of 13 (38%) patients with hypopharyngeal carcinoma were decanulated postoperatively. Reconstruction with the fascia was used in 7 patients of whom 2(29%) were decanulated. Suspension was used in 5 patients of whom 3 (60%) were decanulated. Tumor size did not influence significantly the proportion of decanulated patients. The peroral feeding after treatment was achieved in 85% (44/52) of patients (Figure 2). Regarding the method of operation, peroral intake was possible in 18/23 patients (78%) operated with fascia method and in 26/29 (89%) with suspension method. Regarding the localization of the tumor, peroral intake was possible in 9/13 (69%) patients with hypopharyngeal tumors, in 32/36 (89%) patients with supraglottic tumors and in all three patients with the tumor of the oropharynx. Age did not influence the proportion of decanulated patients. A two year disease specific survival of patients with supraglottic and hypopharyngeal tu-

mors was 89% and 44% respectively (Figure 3). There was no statistically significant difference in disease specific survival of patients with supratlottic carcinoma whether the reconstruction with suspension or fascia method was done (Figure 4). There was a slightly better disease specific survival in patients with hypopharyngeal carcinomas when the method with fascia was applied, but the difference was not statistically significant (Figure 5).

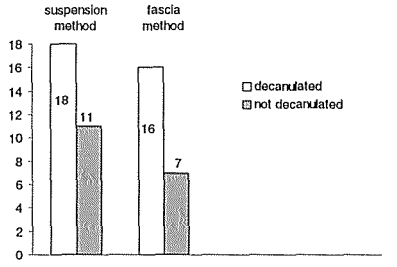

Figure 1. Decanulation rate according to the method of operation (n=52).

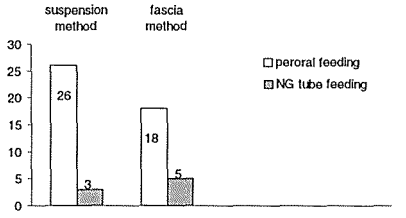

Figure 2. Posttreatment feeding according to the method of operation (n=52); NG tube = naso-gastric tube.

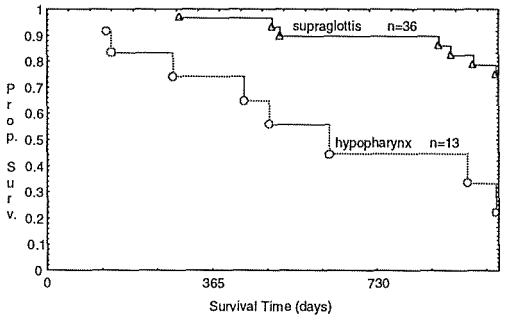

Figure 3. Disease specific survival of patients with the supraglottic and hypopharyngeal carcinomas of all stages (n=49, p=0.07).

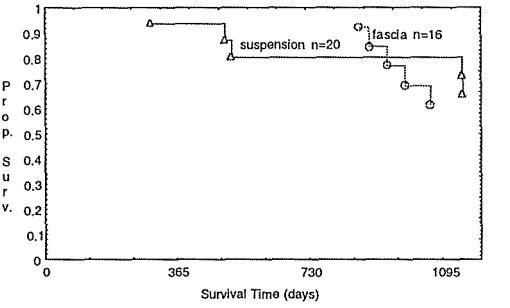

Figure 4. Disease specific survival of patients with the supraglottic carcinoma operated on with the suspension and reconstruction with the fascia method (n=36, p=0.26).

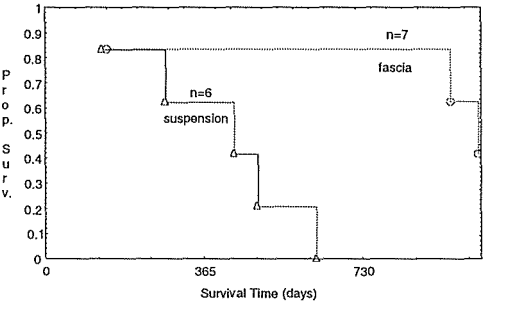

Figure 5. Disease specific survival of patients with the hypopharyngeal carcinoma operated on with the suspension and reconstruction with the fascia method (n=13, p=0.13).

Discussion

The comparison of survival according to localizations of the tumor showed worse survival in patients with hypopharyngeal than with the supraglottic carcinomas. The percentage of patients who were decanulated and were able to swallow satisfactorily was lower in the group with hypopharyngeal carcinoma compared to the patients with other two localizations of carcinoma. In our series, the method of operation had little influence on survival and functional results and extension of resection did not influence the postoperative function. The age of patients did not influence functional results which, in our opinion, makes supraglottic laryngectomy acceptable treatment option also in older patients. Due to the small number of unirradiated patients, it was impossible to compare the influence of irradiation on functional rehabilitation of our patients. We managed to decanulate 66% (34/52) of patients, which is less than described in the literature (7,10). However, we had a larger proportion of postopera-

tively irradiated patients and tumors not localized to the supraglottis only, thus more extensive excisions were necessary.

Conclusions

In both methods of partial supraglottic laryngectomy, functional and oncological results are comparable. Since the method with suspension is simpler and quicker than the method with fascia, it is in our opinion a more appropriate one.

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Laser surgery as the organ sparing treatment for vocal cord carcinoma. Cost benefit relation in 100 cases

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Nowadays, there are three internationally accepted, almost equally effective treatment options for the early vocal cord cancer: radiotherapy, cordectomy via thyrotomy or partial vertical laryngectomy and endolaryngeal cordectomy commonly performed with laser. The latter method was applied on 100 patients between May 1987 and May 1994. The cost of the laser cordectomies was analysed by the authors. Local control rate after single laser cordectomy alone was 87% and together with salvage therapy the success rate was 98%. The voice preservation was 97%, and one patient remained canulated following a salvage partial laryngectomy. The average cost of one patient's treatment - taking into consideration the salvage interventions as well - was about 66 thousand HUF (appr. 390 $) per patient, according to the actual prices of the Hungarian Health Care Insurance. In case of radiotherapy or vertical partial laryngectomy as primary treatment the estimated costs were much higher: approximately 143 thousand and 210 thousand HUF (appr. 800 $ and 1400 $). These facts suggest that the endolaryngeal laser chordectomy is an effective and cost-conscious management option for primary treatment of T1 and selected cases of T2 glottic cancer.

Key words: laryngeal neoplasms-surgery; vocal cords; laser surgery

Introduction

Nowadays, there are three internationally accepted, almost equally effective treatment options for the early vocal chord cancer: radiotherapy, cordectomy via thyrotomy or partial vertical laryngectomy and endolaryngeal cordectomy commonly performed with laser. However, with the increased insurance constraints, physicians must now consider treatment costs along with medical decision-making to provide cost-effective treatment. The costs of laser cordectomies were analysed by the authors, taking into consideration also the costs of the necessary salvage therapy and compared to the estimated costs of other treatment modalities.

Patients and procedure

At the ENT Clinic of Szent-Györgyi Albert University (Hungary) 100 laser cordectomies were performed between May of 1987 and May of 1994 as a primary treatment for T1 and selected cases of T2 glottic cancer. The average follow-up period was 75 months (31 - 116 months). There were 93 male and 7 female patients with an average age of 62 (range 35 to 90 years) at the time of the first operation. Vocal cord lesions were staged by the TNM classification as follows: 8 carcinomas *in situ*, 65 T1a, 23 T1b, and 4 T2 carcinomas. All patients were treated under intratracheal anesthesia through laryngomicroscopic approach with TUNGSRAM TLS-61 type CO_2 laser device. The average hospitalisation period was 4 days, and the average total recovery time (the complete reepithelisation) was considered to be at least 6 weeks. All patients, except one (T1b), had a close follow-up.

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Cost analysis

To determine the total cost of the treatment in this group of patients, the costs of all the procedures were added together. The costs for each type of procedure were calculated by the actual prices of

Hungarian Health Care Insurance Office (based on the all-patient DRG-10 system of USA). Prices of these single procedures were the following: laryngomicroscopy, laser cordectomy (LC) and endolaryngeal laser excision (LE) were approximately 33 900 HUF (200 $), partial laryngeal surgery (PL), laryngectomy (L) as a salvage therapy, and neck dissection (ND) were approximately 205 000 HUF (1200 $). Radiotherapy (RT) treatment per admitted patient was approximately 68 600 HUF (400 $). The expected cost of the PL and RT were extrapolated to a theoretic group of 100 patients according to the expected primary cure rate and further necessary salvage therapy on the basis of the data presented in the literature. In order to simplify the calculation L was mentioned under the salvage therapy in the study.

Results

Primary LC: 87 patients demonstrated a successful local control following the primary laser cordectomy, but one contralateral vocal cord carcinoma and one late regional metastasis occurred. These failures were treated by LC and ND.

The histological examination revealed 2 incomplete resections. The first patient underwent a RT and later on a L. The second one was salvaged by PL.

Local recurrence occurred in 10 cases. Four of them were salvaged by RT and two of these patients were laryngectomized later, whereas in one case the histological examination didn't prove malignancy. Another 4 patients had a repeated endolaryngeal LE. In one of them further LE was made and later on PL. Two patients were salvaged by primary PL, and one was laryngectomized later.

Up to the time of the study, we have lost 8 patients altogether. Two of them died because of cancer, and 6 died of intercurrent disease. The voice presevation was 97% and among these patients only one – who underwent PL earlier – remained canulated. One patient (T1b) was lost from the follow up, however, at the last control, he was found to be tumor-free for one year following the surgery.

In short, the treatment modalities used in 100 patients, were: 100 LC, 7 LE, 4 PL, 3 L, 1 ND, 5 RT. The average treatment costs of all therapeutic interventions per patient was estimated at about 66 000 HUF (appr. 390 $).

Discussion

Following primary PL for T1 glottic lesions, the highest primary cure rates mentioned in the literature - with a minimum follow-up of 2-3 years - are as follows: Rothfield *et al.* 94%,[1] Lacourrey *et al.*[2] 93%. According to these data, the average cure rate was found to be approximately 94%. Extrapolating to a theoretic group of 100 patients, there would be 100 partial laryngeal resections and further 6 „salvage" laryngectomies (the diagnostic laryngomicroscopy is covered by the price of PL). The average treatment cost per patient was approximately 210 000 HUF (appr. 1240 $).

Following primary RT, 67% and 93% primary cure rates were achieved by Davis *et al.*[3] and Mendenhall *et al.*[4], respectively. Hence, the average cure rate would be expected 80%. Extrapolating to 100 patients we would count with 100 diagnostic laryngomicroscopies, 100 primary RT and a further 20 salvage L. One patient's average total cost would be approximately 143 000 HUF (840 $).

In our 15 year series, the glottic cancer was found in 48% of all laryngeal tumors and was, in 90%, diagnosed as T1-T2 lesion. Early glottic lesions are one of the main groups of the laryngeal cancer. This ratio could be increased by improving early diagnosis, which gives importance to the „cost-benefit" analysis of the treatment of early glottic cancers.

In general practice, better quality of voice could be retained after RT than following LC. According to our experience, a very good quality of voice could be expected especially after LC for T1 glottic lesions. The objective voice analysis, carried out by Cragle and Brandenburg,[5] showed no significant differences between the voice qualities after laser chordectomy and irradiation. Among all three treatment options, L is the most commonly used salvage intervention for recurrence following RT. Therefore, one must be very careful when choosing RT as primary treatment of the vocal cord carcinoma. We agree with the opinion of Saphsay *et al.*,[6] that irradiation as a primary treatment should be used only in patients with high risk factors.

PL as a primary treatment was found to be very inconvenient in early vocal cord lesions in spite of the good cure rate, because of the external approach, and with decanulation- and aspiration-related difficulties, long admission time, and last but not least, because of the worst voice condition.

We conclude that the primary cure rate of LC was found to be more than 85% and, with the secondary salvage attempts, the cure rate could be higher than 95%.[6-8] According to our calculations LC was the cheapest treatment option of all. Similar cost rates were arrived at by Myers *at al*[9] in the USA in 1994.

In the hand of a skilled surgeon the most recommended treatment for glottic T1 lesions would be the LC, which is supported also from the financial point of view.

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Concomitant radio-chemotherapy for larynx preservation

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Background: A pilot multicentric study of concomitant radio-chemotherapy was performed to evaluate the feasibility, the toxicity and larynx preservation rate in patients with previously untreated, resectable laryngo-pharyngeal squamous cell carcinoma, otherwise requiring laryngectomy ± pharyngectomy.
Materials and methods. Forty-two patients entered the study: radiotherapy was planned to a tumour dose of 70 Gy and chemotherapy was applied concomitantly, consisting of Cisplatinum and 5-Fluorouracil (bolus) or Carboplatinum and 5-Fluorouracil (continuous infusion) combination repeated every 3 weeks. In all but complete responders laryngectomy ± pharyngectomy and/or neck dissection was performed for residual disease.
Results: Toxicity was mild and no drug related deaths occurred. Complete response rate was 81% and, after salvage surgery, 93% of patients were considered disease free. After a median follow-up of 38 months, 53% of patients were alive and of these 88% with larynx preserved.
Conclusion: Concomitant radiochemotherapy seems to be a feasible strategy with acceptable toxicity for patients with laryngo-pharyngeal squamous cell carcinoma, otherwise eligible for total laryngectomy.

Key words: laryngeal neoplasms-drug therapy; laryngectomy

Introduction

During the last 20 years, chemotherapy has been used in the treatment of the larynx cancer, with various objectives and strategies. Pilot and multicentric randomized studies have been published on larynx preservation. Neoadjuvant chemotherapy has been the treatment of choice for the majority of these studies.[1-4] The use of concomitant radio-chemotherapy has been very limited. In September 1989, we started a pilot multicentric study of concomitant radio-chemotherapy in an integrated program of larynx preservation. The aim of this study was to evaluate the feasibility, the toxicity and the larynx preservation rate.

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Materials and methods

Patients

From September 1989 to December 1994, 42 patients with biopsy proven, previously untreated laryngo-pharyngeal squamous cell carcinoma entered the study. All had tumors that were resectable and would require total laryngectomy +/- pharyngectomy according to the assessment of the attending surgeon. Thirty-two patients, with a minimum follow-up of 24 months, have been evaluated. The median age was 54 years (range 39-67), and the median Karnofsky performance status was 90 (range 70-100). All patients had adequate hematopoietic, hepatic and renal functions, and no coexisting medical problems to prevent full compliance with the study. The site of primary tumor and stage was as follows:

– larynx 16/32: (supraglottic: T3 N1-2 = 4; T4 N2-3 = 6; glottic: T3 N0-2 = 3; T2 N0 = 1; transglottic: T3 N0-1 = 2);

– hypopharynx +/- oropharynx 16/32 (T2 N0-2 = 3; T3 N0-1 = 6 ; T3 N2 = 5; T4 N1 = 2).

Treatment program

Radiotherapy was administered as standard treatment: 2 Gy daily 5 fractions per week up to a total dose of 70 Gy.

Concomitant chemotherapy:

– from 1989 to 1991: PF regimen = Cisplatinum 20 mg/m^2 IV days 1-4 and 5-Fluorouracil 200 mg/m^2 IV bolus days 1-4 ; cycles repeated every 3 weeks.

– from 1991 to 1995: CF regimen = Carboplatinum 75 mg/m^2 IV days 1-4 and 5-Fluorouracil 1000 mg/m^2 IV continuous infusion days 1-4 (96 hrs c.i.).

Clinical evaluation

Clinical evaluation was planned to be carried out 1 month after the completion of concomitant radio-chemotherapy. Patients in complete remission (CR) were followed-up, while patients with residual lesion on the primary tumor were candidates for a total laryngectomy +/- pharyngectomy. Patients with residual nodal lesions were eligible for neck dissection.

Results

The median dose of radiotherapy was 64 Gy and the median number of administered cycles of chemotherapy was 3.

Toxicity (RTOG-WHO): Grade 1-2 nausea and vomiting occurred in about 20% of patients, grade 2 anemia in 20%, grade 3 thrombocytopenia in 25%, grade 2 neuro-ototoxicity 25%, grade 1 nephrotoxicity 10%, aspirational bronchopneumonia 5%, neuro-nephro-ototoxicity occurred only in patients treated with the PF regimen. One patient had a miocardial infarction before the second cycle of CF. No drug-related deaths occurred.

Clinical results

After concomitant radio-chemotherapy 26/32 (81%) patients achieved CR. Three patients with residual disease of the primary tumor underwent total laryngectomy: microscopic disease was present in 2/3 of these patients, while only necrosis and fibrosis was evident in 1/3. One patient with residual nodal lesion underwent neck dissection and the histology showed only necrosis and fibrosis; one patient refused total laryngectomy, and one developed distant metastases before salvage surgery. At the end of the integrated program (concomitant radio-chemotherapy and salvage surgery), 30/32 (93%) patients were disease-free.

After a median follow-up of 38 months (24-68+ months), 17/32 (53%) patients were alive and disease-free. The larynx preservation rate was as follows: alive, disease-free with larynx/total: 15/32 (47%) patients; alive, disease-free with larynx/alive, disease-free: 15/17 patients (88%). Two patients out of 17 are alive, disease free without larynx. Fifteen patients out of 32 are dead: 6 with local or regional disease, 9 with distant metastases or a second primary cancer but with the larynx preserved and without evidence of locoregional disease; so the local and regional control were possible in 26/32 (81%) patients.

Conclusions

The use of radiotherapy and concomitant PF or CF chemotherapy, in patients with laryngo-pharyngeal cancer, eligible for a total laryngectomy, can be considered a feasible strategy and its toxicity seems acceptable. Both PF and CF regimens were used without major complications. Obviously, the administration of 5-Fluorouracil as IV continuous infusion was more complicated than 5-Fluorouracil IV bolus injection. In this study, the clinical advantage of the first modality of administration of 5-Fluorouracil compared to the second one remains to be established. Furthermore, also the clinical benefit of Carboplatinum *vs.* Cisplatinum in terms of toxicity, remains to be defined. Anyway, in both regimens a very high percentage of CR (81%) was obtained. The larynx preservation rate was very high.

Of the whole group of patients, 17/32 (47%) were cured of cancer and 15/17 (88%) had their larynx preserved. These results are highly competitive with those achieved with neoadjuvant chemotherapy.[1-4] Although concomitant radio-chemotherapy seems the best strategy to improve the locoregional control,[5,6] we think that only randomized studies can better define whether it is superior to neoadjuvant chemotherapy followed by radiotherapy or to radiotherapy alone in terms of toxicity, larynx preservation rate, survival and quality of life. Both, the appearance of distant metastases and second primary tumors, remain important problems to resolve, also with a concomitant treatment.

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Early glottic cancer: The influence of primary therapy on ultimate organ preservation

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With the aim to achieve better comparison of final treatment results between 44 primarily operated and 219 primarily irradiated patients with early glottic cancer, a retrospective identification of patients based on criteria of suitability for voice-sparing surgery was made. In patients, found to be suitable for organ preservation surgery, 10-years disease specific survival (DSS) of 94% vs. 92% in T1 and 94% vs. 87% in T2 tumors was estimated for primarily operated and irradiated patients respectively (p=0.1). If the overall treatment time in primary irradiated patients was shorter than 48 days, final preservation of the larynx was achieved in 97% and was identical with the primary surgery group. In patients with T2 tumors unsuitable for voice-sparing operation a significantly lower 10-years DSS, namely 71% vs. 65%, for primary surgery and radiotherapy respectively was found. If treated by primary surgery, all those patients would have needed total laryngectomy, however, with primary radiotherapy with an over-all treatment time < 48 days, the final preservation of voice succeeded in 87% of patients.

Key words: laryngeal neoplasms-surgery-radiotherapy; glottis

Introduction

Analyzing the results of two basic approaches to the treatment of early glottic cancer, i.e., primary radiotherapy and conservative surgery, patients treated with organ preservation surgery are generally compared with radiation therapy series in total.[1-4] The fact that certain proportion of primarily irradiated patients had lesions unsuitable for voice-sparing surgery has been usually disregarded.[5,6] Recently, the significance of over-all treatment time in radiotherapy of laryngeal cancer was also recognized as an important factor influencing the final local control.[7,8] Considering the above statements, the most reasonable analysis of ultimate therapeutic effect of both treatment modalities should be based on the evaluation of specific survival and the estimation of. the proportion of total laryngectomies needed, in really comparable groups of patients, regarding the eligibility for voice sparing surgery and taking into account the important prognostic factors in radiotherapy.

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Materials and methods

Patients characteristics

Between 1976 and 1990, 263 previously untreated patients with T1N0 and T2N0 squamous-cell carcinomas of the glottis were treated. There were 248 men and 15 women, their median age being 59 years (range 23-86 years). Tumors were staged according to TNM classification (UICC, 1987): 187 (71%) were classified as stage I, and 80 (29%) as stage II. Laryngoscopy and biopsy were performed in all patients to evaluate tumor extent and histology. Out of 199 cases with histological grading assessed, there were 85 (43%) well differentiated, 95 (47%) moderately, and 19 (10%) poorly differentiated squamous cell carcinomas.

To enable a better comparison between primarily operated and primarily irradiated patients, with respect to final voice preservation, a retrospective selection of patients as suggested by Dickens *et al.*[5] was made. Using the criteria of suitability for a primary voice-sparing operation, among 219 patients treated by primary radiotherapy, 168 (143 T1 and 34 T2) were retrospectively found suitable, and 51 (25 T1 and 26 T2) unsuitable for chordectomy or hemilaryngectomy. The treatment outcome in these two groups was compared with corresponding groups of those patients who underwent primary surgical therapy.

The duration of follow-up ranged from 25-175 months (median 71 months).

Treatment

From a total of 263 patients studied, the primary treatment was radiotherapy in 219 cases (159 T1 and 60 T2), and surgery in 44 (28 T1 and 16 T2) patients.

1. Radiotherapy – during the observed period the radiotherapy technique remained unaltered. The patients were treated in supine position in most cases for immobilization plastic cast was used. All patients were irradiated on ^{60}Co megavoltage units using wedge filters, with continuous-course irradiation at 2 Gy per fraction, five fractions per week. The prescribed tumor dose was 60-74 Gy (median 65 Gy). Average total tumor doses received by T2 tumors were somewhat higher than those received by T1 tumors. In all patients the dose was prescribed to a 100% isodose line, using computer-generated dosimetry. The field size ranged between 5 x 5 cm and 11 x 6 cm (median 6 x 6 cm), being slightly larger for T2 than for T1 tumors. All the treatment fields included at least 1 cm flash-off of the anterior neck. Treatment duration ranged from 32 - 68 days (median 48 days).

2. Surgery – Among primarily operated T1 patients, 23 underwent chordectomy and five partial vertical laryngectomy. In the T2 group, five patients underwent chordectomy, while four patients had partial vertical laryngectomy, and seven total laryngectomy.

3. Salvage surgery – among 26 recurrences in T1 patients treated by primary radiotherapy, there were 8 chordectomies, 3 partial vertical laryngectomies, and 13 total laryngectomies performed. Surgical procedures for 32 recurrences in T2 primarily irradiated patients involved chordectomy in four and total laryngectomy in 20 cases. Altogether, 10 out of 58 recurrent patients received no further surgical treatment. Two out of seven recurrences in primarily operated patients were treated by total laryngectomies.

Statistical analysis

Recurrence-free survival and disease specific survival were calculated using Kaplan-Meier method, and the differences between groups were tested by log-rank test.

Results and conclusions

Using salvage surgery for treatment failures the disease specific survival (DSS) was 96% vs. 92% in T1 and 78% vs. 78% in T2 tumors for primarily operated and primarily irradiated patients respectively (Figure 1).

Figure 2 shows recurrence-free survival (RFS) for 219 primarily irradiated patients according to treatment duration. Significantly better RFS was achieved for patients in whom overall treatment time did not exceed 48 days.

Figure 3. shows different types of surgical procedures needed for ultimate local control (ULC) in patients retrospectively selected to be suitable for primary voice-sparing surgery. Patients are divided according the stage, type of primary treatment and overall treatment time in primary irradiated patients. In T1 patients no laryngectomies were required in 28 primary operated patients and in 74 irradiated patients in whom overall treatment time did not exceed 48 days. In T2 patients the same proportion of LE was required in 9 primary operated and 11 primary irradiated patients with shorter overall treatment time in order to achieve the same ULC. In primary irradiated patients with a longer overall treatment time a substantially higher proportion of LE was required in both stage groups.

Figure 4 shows proportion of LE necessary in ULC in patients found to be unsuitable for primary voice-sparing surgery. All patients treated by radiotherapy should need LE if operated, however in 31/41 finally cured patients the larynx was preserved. Again, an important influence of overall treatment time was observed.

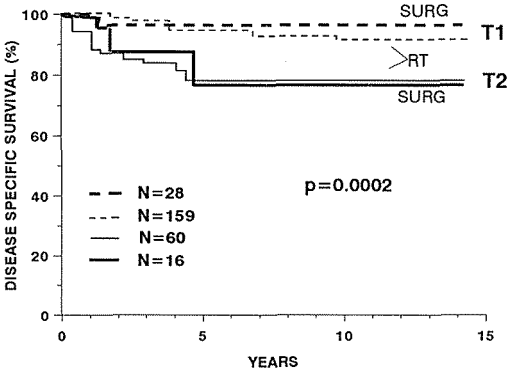

Figure 1. Recurrence-free survival in all 263 treated patients regarding the stage of disease and type of primary treatment.

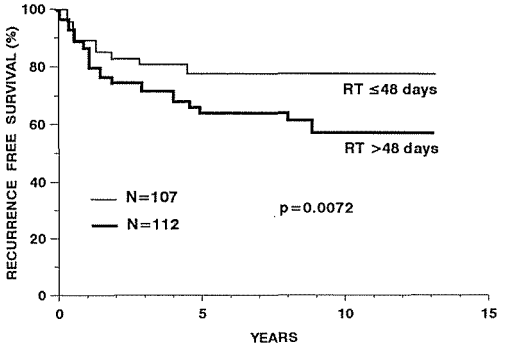

Figure 2. Recurrence-free survival in 219 patients treated with primary irradiation according to treatment duration.

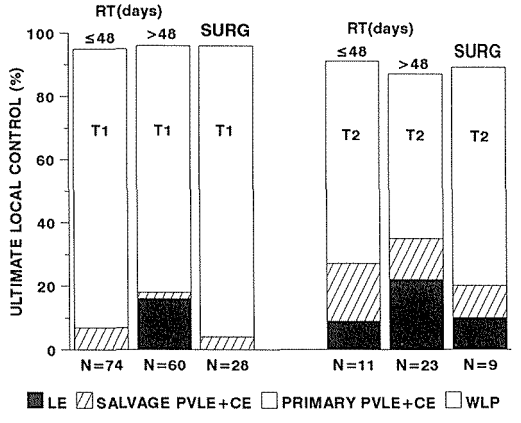

Figure 3. Ultimate local control achieved in patients retrospectively selected to be suitable for voice-sparing operation according to stage, primary treatment modality, duration of treatment time in irradiated patients and type of salvage surgery. LE = laryngectomy, PVLE = partial vertical laryngectomy, CE = cordectomy, WLP = whole larynx preserved.

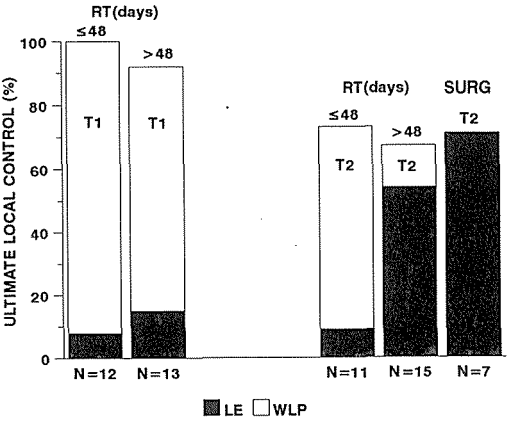

Figure 4. Proportion of laryngectomies needed for ultimate local control in patients unsuitable for voice-sparing operation according to stage, primary treatment modality and duration of radiation therapy. LE = laryngectomy, WLP = whole larynx preserved.

Regarding the final cure rate, the stage of the disease in patients with early glottic cancer is still the most important prognostic factor. In our study, the type of primary treatment modality (surgery or radiotherapy) did not interfere with the final treatment outcome within each particular stage. On the other hand, the pretreatment estimation of the suitability of tumor lesions for conservation surgery should be of crucial importance for the final quality of life (i.e., voice-preservation) of treated patients. In smaller lesions, preservation of normal voice in irradiated patients was dependent on the over-all treatment time, while in bigger tumors (unsuitable for conservation surgery) radiotherapy offered better final preservation of the larynx. If radiotherapy should become the preferential treatment modality in early glottic cancer, the problem remains how to assure an optimum treatment outcome. Shorter overall treatment time and higher dose per fraction offer some improvement.[7-11] Using predictive assays for investigation of intrinsic radiosensitivity[12,13] in future will probably enable an easier solution in choosing optimum primary treatment for early glottic cancer.

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Treatment of early epilaryngeal tumours by CO_2 laser with preservation of laryngeal function

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Introduction: *Our 20 years' experience with CO2 laser in the treatment of malignant tumours outlines the possibilities and limitations of its application. Surgical principles in oncology, i.e. radical eradication of tumours was strictly followed. It is very important to consider the exact TNM classification of the disease - its localisation and extent. The majority of epylaringeal tumours are in advanced stages at the diagnosis. Therefore, only a few are suitable for CO2 laser treatment. The video presents our CO2 laser surgery procedure.*

Material and methods: *During the last 10 years, 10 patients with tumour located in the suprahyoid epiglottis and /or on the aryepiglottic fold were treated by CO2 laser. In 7 cases, laser operation was the primary treatment and, in 3 cases, laser was used as a salvage surgery for residual or recurrent tumours after radiation failure. The tumor together with the surrounding tissue was removed with the CO2 laser beam of 20-30 Watts.*

Discussion and conclusion: *A primary and salvage laser surgery of early and not deep-infiltrated marginal tumours of the larynx was successfully carried out with minimal morbidity and excellent functional results. The authors emphasize the advantages of combination of CO2 laser and ionizing irradiation because the laser evaporation does not disturb the blood supply and oxygenation of the surrounding tissue, therefore the radiosensitivity is not decreased. A minimum invasive surgery done by CO2 laser may be indicated also after irradiation failure. The treatment with laser surgery of epilarynx tumours is a responsible decision requiring great experience, careful examination and selection of patients.*

Key words: laryngeal neoplasms-surgery; epiglottis; laser surgery

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A case of recurrence of the malignant mixed tumor of the palate after 16 years

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The tumor of the palate are comparatively rear formations. Most often they originate from the minor salivary glands situated in the palate mucous membrane. Authors present a case of recurrence of the malignant mixed tumor on the border between hard and soft palate 16 years after the first treatment - enucleation with postoperative radiotherapy. They discuss reasons for recurrence and also some other aspects of surgical treatment.

Key words: palatal neoplasms; mixed tumor, malignant; neoplasm recurrence, local

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Treatment of epidermoid anal canal carcinoma

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During the last two decades, the role of surgery in anal cancer treatment has been changing continuously. Nowadays, surgery is applied only in treatment of (recurrent) radio-and chemoresistant disease. At present, anal function-conserving radiation therapy (45-60 Gy) and concomitant chemotherapy with 5-FU and MMC are considered to be standard therapy methods applied in locally advanced tumours, whether N0 or N+. In small tumours (T1N0), chemotherapy can be omitted without jeopardizing the outcome. In future, the role of induction chemotherapy will have to be evaluated in order to see whether some other drug would contribute better to the improvement of the already favourable results.

Key words: rectal neoplasms; combined modality treatment

Introduction

Epidermoid cancer of the anus is a rare disease comprising 1-4% of malignant colorectal cancers, though 30% of all ano-rectal cancers are anal cancers. About 75% of anal cancers are anal canal cancers and are more common in women than in men (ratio 3:2 - 5:1) (Quan 1978, Beahrs 1979, Eschwege *et al.* 1985). Histologically, most cancers are of the squamous cell type of different keratinization. The lymphatic spread is mainly in three directions. The anal margin drains in the inguinal superficial region, anal canal tumours primarily in lymph nodes along the great vessels (A. mesenterica inferior, A. iliaca) and perirectal/anal lymph nodes.

Treatment of anal canal cancers is mainly a locoregional problem, distant metastases being uncommon. The age of patients has a wide range from 25 to 80 years, with a median age of about 60 years. About 75% patients have uncharacteristic symptoms with haemorrhoids, fistulas, pruritus or leucoplakia which may delay the correct diagnosis.

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Treatment

The role of surgery as primary treatment modality has gradually decreased during the last 30 years and has now been abandoned by most centres. Only very small tumours could be treated by conservative, sphincter saving surgery, and the local recurrence rate was high in these cases. Major abdomino-perineal resection and permanent colostomy was the option for most patients undergoing surgery. In spite of major surgery, the survival results were far from acceptable. Tables 1 and 2 show the results of surgery for anal canal cancer.

In Europe, radiation therapy has always played a more important role in the therapy of these tumours, compared with North America where surgery was often preferred as initial therapy. Radiotherapy was abandoned in some centres during the early decades of this century because of severe side effects. With the introduction of modern, high voltage machinery, improved brachytherapy methods and more knowledge about the natural history of this disease, the treatment results of irradiation of anal tumours gradually improved. Table 3. shows the results of primary radiation therapy for anal canal cancers.

Following the introduction of combined radiotherapy and concomitant administration of chemotherapy

(Mitomycin C and 5-Fluorouracil) by Nigro *et al.* 1974, this combination was widely adopted as the primary treatment of choice for anal cancers. This combined treatment was first used as preoperative treatment and resulted in over 60% tumour-free cases after a radiation dose of only 30 Gy (Nigro *et al.* 1981, Wanebo *et al.* 1981, Meeker *et al.* 1986). Following these encouraging results, surgery was gradually replaced by an increased radiation dose. The increased toxic effect of Mitomycin C (MMC) on hypoxic cells and on extracellular acidic environment is a clear benefit in large squamous cell cancers with considerable hypoxic regions being less sensitive to radiation (Rauth *et al.* 1983 Rockwell 1982, Dobrowsky & Dobrowsky 1995). 5-Fluorouracil (5-FU) was attributed a role of a radiosensitizing agent when administered after irradiation for longer time periods and was reported to be interacting in a supraadditive way with MMC *in vitro* (Byfield *et al.* 1982, Nakajima *et al.* 1979, Dobrowsky *et al.* 1992). It has been used in the clinic for many years in combination with radiation therapy. Table 4 shows some results from chemoradiation with MMC and 5-FU.

Table 1. Local excision for anal canal cancer - 5-year survival and local relapse rate

Author	No. of patients	Survival	Local recurrence rate
Kuehn *et al.* 1968	26	75%	8%
Stearns & Quan 1970	30	66%	63%
Beahrs 1979	21	85%	42%
Klotz *et al.* 1967	33	61%	33%
Boman *et al.* 1984	19	84%	11%
Frost *et al.* 1984	20	66%	60%

Table 2. Major surgery for anal cancer - 5-year survival

Author	No. of patients	Survival
O Brien *et al.* 1950	45	32%
Grinell 1954	13	46%
Klotz *et al.* 1967	194	50%
Kuehn *et al.* 1964	83	47%
Greenall *et al.* 1985	103	55%
Boman *et al.* 1984	114	71%

Table 3. Radiation therapy for anal cancer

Author	No. of patients	Survival	Local recurrence
Green *et al.* 1980	16	81%	25%
Cummings *et al.* 1982	51	59%	43%
Eschwege *et al.* 1985	64	46%	19%
Papillon 1982	88	68%	14%
Dobrowsky 1987	14	79%	14%

Table 4. Chemoradiation with MMC and 5-FU for anal cancer

Author	Primary tumour control	Survival
Leichman *et al.* 1985	86%	80%
Sischy *et al.* 1989	71%	73%
Papillon & Montbarbon 1987	81%	
Cummings *et al.* 1991	87%	65%
Dobrowsky *et al.* 1996	95%	73%

Other groups tested the combination of bleomycin and radiation, but it was stated that the benefit of bleomycin administration was of questionable value (Glimelius & Pahlman 1987, Svensson *et al.* 1993).

Most reports have dealt with single institutional experiences and there have not been any randomized trials until recently. Three major trials tested the effect of different chemotherapy regimens administered simultaneously with radiation therapy. An intergroup study tested whether or not the addition of MMC to 5-FU chemotherapy administered with radiation therapy was of benefit (Flam *et al.* 1996). At 4 years, colostomy rates were lower (9% vs 22%; p=0.002), colostomy-free survival higher (73% vs 59%; p=0.014) and disease-free survival higher (73% vs 51%; p=0.0003) in the MMC arm. Overall survival was not significantly different in the two arms and the MMC arm showed significantly higher toxicity.

The British UKCCCR Study made a comparison between radiation therapy with radiation therapy and concomitant chemotherapy (MMC and 5-FU) in a randomized trial in which 856 patients were treated (UKCCCR 1996). The group found a 46% reduction in local recurrence (p<0.0001) for patients treated by combined therapy. The risk of death from anal cancer was significantly reduced, but overall survival was not significantly different in the two treatment groups.

The EORTC also tested the addition of chemotherapy to radiation therapy (Bartelink 1996). After randomization of 110 patients, a higher local tumour control was reported after chemoradiation (local recurrence 9 vs 15, local recurrence and distant relapse 9 vs 10 for rt+ct vs rt, respectively; significant improvement in local tumour control: p<0.02). Overall survival was not significantly different in the two groups.

Although combined modality therapy is accompanied by an increased local toxicity and moderate haematological toxicity, it is believed to be justi-

fied by the excellent results obtained with regard to local tumour control and colostomy free survival.

In conclusion, the standard therapy for anal canal cancers consists of radiation therapy and concomitant chemotherapy with the use of 5-FU and MMC. This is the best treatment for advanced tumours, whether N0 or N+. All cases, even unresectable should be considered for this regimen. In small tumours (T1N0) chemotherapy can be omitted without jeopardizing the outcome with regard to response rate and survival. The future will show if induction chemotherapy will keep its role, or if a change of chemotherapeutic drugs (cisplatin or carboplatin and 5-FU) will further improve the already very favourable results obtained by the present therapy in this rare disease.

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Conservative treatment of anal canal cancer: Retrospective study

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Between January 1981 and May 1996, thirty patients with anal canal carcinoma were treated with a protocol of radiation therapy alone or in combination with chemotherapy. The patients were divided into 4 stages by International Union against Cancer (UICC) 1987: I stage 8 patients, II stage 16 patients, III stage 5 patients, nobody in stage IV and 1 patient in recurrence. Sixteen patients were treated with external radiation therapy alone, 8 with interstitial 192Ir implant alone, and 6 with the combination of both (dose range 30-70 Gy). Nine patients received concomitant cytotoxic chemotherapy. Toxicities were mild to moderate. Twenty-eight patients were eligible and 2 were lost to follow-up. A complete response (CR) was observed in 19 patients (68%); nobody of these patients had local recurrence and anorectal function was retained. We may conclude that radiotherapy with or without chemotherapy can provide a good local control and preserve anal function with acceptable morbidity.

Key words: rectal neoplasms-radiotherapy-drug therapy; treatment outcome

Introduction

Anal canal carcinomas are rare diseases and account for 1% to 4% of all large bowel cancers. Cancer of anal region occurs more frequently in females than in males with sex ratio of 2:1 and in people over the age of 60.[1]

In the past, the most frequently performed therapy was radical and demolitive surgery; nowadays, since anal canal cancer has good prognosis and a long survival, conservative management is preferred.

The most recent studies have shown that radiation therapy is an appropriate treatment, especially if it is associated with chemotherapy.[2,3,4] Multimodality therapy increases survival and warrants sphincter-sparing, so this combined treatment approach is now regarded as a model for successful therapy of anal canal carcinoma.[5,6,7]

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Materials and methods

From January 1981 to May 1996, thirty patients with primary anal carcinomas were treated with conservative therapy at our department; 21 were female and 9 male. The patients' age ranged between 44 and 88 years, with a median age of 71. Twenty-three patients (76.5%) had an invasive carcinoma of the squamous type, 5 of basaloid type (16.5%) and 2 of the cloacogenic type (7%).

The initial tumor stage according to the TNM-classification (UICC 1987) was for 8 patients stage I, for 16 stage II, for 5 stage III. One patient came to our observation with a local-regional recurrence; previously, this patient received external radiotherapy (a total dose of 55 Gy) in another center.

All patients in our study were eligible for a conservative therapy and nobody had abdomino-perineal resection (APR) as primary surgery treatment; complete local excision or biopsy were carried out in all cases.

All our patients were given radiotherapy treatment: 16 of them with exclusive external radiation, 8 with brachitherapy and 6 with external radiation and brachitherapy like boost.

The primary tumor region including pelvic and inguinal lymph nodes were irradiated by an anterior and posterior opposed (AP/PA) pair of fields or by a 4-field-box technique. The upper limit of the target volume was L5-S1 and lower limit included the perineum. External radiation was delivered with 10 MeV photons and a single daily fraction between 1.8 and 2 Gy in an uninterrupted course up to a medium dose of 52 Gy. Total doses varied between 30 and 65 Gy. The dose was specified at midline (AP/PA fields) or at 90% isodose (4-field-box).

In 14 cases, brachitherapy was performed; for 8 patients this was an exclusive treatment, while for 6, it was the boost of external beam radiation.

We used the template technique with iridium-192 needles and wires in all patients (low dose rate).The implant volume covered about one-third to one-half of the anal circumference; single-plane as well as double-plane implants were used. Total doses varied between 20 and 70 Gy, with a dose rate on the reference isodose according to Paris system.

Nine patients were given a concomitant chemotherapy; 3 of them with Mitomycin C (MTC)- 5 Fluorouracil (5FU) scheme and 6 with CDDP-Folinic acid-5FU scheme.

The patient who was treated for recurrence received brachitherapy treatment in two different time periods (total dose 67.4Gy) with concomitant chemotherapy.

Results

The follow-up of our series ranges between 7 to 180 months. Twenty-eight are eligible; two patients were lost from the follow-up 7 and 12 months respectively; they were without evidence of disease. Six patients died of cancer progression after a median interval of 7 months from diagnosis and three of unrelated disease. Nineteen patients (68%) are alive without evidence of disease. Out of 28 selected patients, 19 achieved a complete response (CR) in T and in N. One patient had CR in T, while no relevant modifications were seen in the metastatic nodes; he was submitted to lymphadenectomy. Eight patients showed stable disease when they underwent restaging: two of them were submitted to abdominal-perineal resection and are now alive without evidence of disease, the others six died for progression of cancer. One patient developed lymph nodes metastases 6 months after the completed treatment; he was given external radiation and he had a CR, he died for broncho-pneumonia after 46 months. The median survival of our patients is 50 months.

All patients were evaluated for toxicity, which was graded according to the WHO criteria. Nobody died from toxicity. Some patients experienced diarrhea, proctitis and perineal dermatitis; these symptoms were low grade in most of them and easily controlled with symptomatic treatments. The patient who received radiotherapy for the second time for recurrence, developed chronic proctitis. One patient has rectal angiodysplasia and she needs blood trasfusions at intervals. Anorectal sphincter function was preserved in all patients with CR. One showed stool incontinence during the year after the treatment, now normal function is recovered.

Discussion and conclusions

Our study, according to references, confirms that anal canal cancer is rare carcinoma and it occurs more frequently in females.

Anal carcinoma is a radiosensitive tumor; radiotherapy carries out good results with acceptable toxicity and gives patients the opportunity to have a surgery repair in case of stable disease or recurrence.[8,9] Our therapeutic protocol has allowed us to obtain a large number of CR (68%) with low toxicity. The analysis of failures proves that they have occurred in patients at advanced stage and with metastatic nodes.

We have come the conclusion that radiotherapy is the primary treatment and that a multimodality therapy is absolutely necessary in advanced stages.[10,11] Future objectives must include the improvement of local control rates; this could be achieved through adjustments in radiation and chemotherapy schedules.

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Conservative treatment of the carcinoma of the anal canal

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Purpose: *Radiotherapy is a standard treatment in the conservative management of anal cancer. Our experience with 65 patients was analyzed retrospectively to evaluate local control, late morbidity related to stage and treatment methods.*

Materials and methods: *From January 1983 to December 1995, 65 consecutive patients were treated by external beam radiation therapy (EBRT) with (n = 31/47.7%) or without chemotherapy (n = 34/52.3 %). An additional boost to the primary tumor region was delivered to 49 patients (75.3%): 29 of these patients (44.6%) received a single interstitial HDR implant (median dose 6.48 Gy), 20 of them (30.8%) received an electron boost. Sixteen patients did not receive any boost. The interstitial HDR brachytherapy boost was delivered by a special template to ensure fixed geometry of the implanted needles. The needle implant was documented by CT imaging, so the offset and the length to be irradiated were determined.The female to male ratio was 55 : 10, median age 69 years. Tumor staging according to UICC: T1: 38.5%; T": 29.2%; T#: 13.8%; T4: 18.5; positive lymphnodes: 7.7%*

Results: *Overall survival rate (OS) was 81% at 5 years and 72% at 10 years, disease specific survival (DSS) was 86.1% at 5 years and 10 years. Local control rates (LC) were 83.6% at 5 years and at 10 years. Mean follow up of all survivors was 50 months. Simultaneous chemotherapy showed a significant improvement of LC, DSS and OS in patients with T3 and T4 tumors.*

Conclusion: *We confirm that radiotherapy is a standard treatment for patients with cancer of the anal canal. Treatment regimes should be individualized in relation to local tumor stage. Limited tumor lesions can be controlled by radiation alone. Boosting the primary tumor lesion by single HDR Iridium implantation did not show any increase in acute or late toxicity and is therefore a safe procedure.*

Key words: rectal neoplasms-radiotherapy; chemotherapy; survival rate; local control rate

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Combined radiation and chemotherapy for squamous cell carcinoma of the anal canal: Results and prognostic variables in a multiinstitutional series of 173 patients

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Purpose: This retrospective multicenter study was aimed to asses the effect of combined modality therapy in patients with squamous cell carcinoma of the anal canal, stage T1-4 N0-3 M0.
Patients and methods: Between 1985 and 1994, 173 patients underwent treatment by combined radiation and chemotherapy. A median total dose of 50 Gy was delivered to the primary, perirectal, presacral and inguinal nodes, followed by a local boost in selected cases. 5-Fluorouracil was scheduled as a continuous infusion of 1000 mg/m²/24 h on days 1-5 and 29-33, and mitomycin C as bolus of 10 mg/m² on days 1 and 29.
Results: Cancer related survival (OS), NED-survival and local control rates at 5 years were 71±5%, 59±4% and 67±4%, respectively. Anorectal function was preserved in 91% of the patients in whom the primary was controlled. Only 9.6% experienced severe late toxicity requiring surgery. In univariate analysis, T category (T1/2 vs. T3/4) was predictive for OS (83±4% vs. 53±9%, p=0.01), NED-survival (75±4% vs. 36±7%, p<0.0001) and local control (81±4% vs. 46±7%, p<0.0001). N category (N0 vs. N1-3) influenced NED-survival (66±5% vs. 33±12%, p=0.004) and local control (76±4% vs. 37±13%, p=0.003). Treatment technique (>2 fields vs. 2 fields) was found to be of prognostic value for NED-survival (70±6% vs. 50±6%, p=0.016) and local control (77±6% vs. 58±6%, p=0.018). Only in T3/4 cases the total RT-dose (< 45 Gy vs. 45 Gy) had an impact on NED-survival (42±7% vs. 23±13%, p=0.01) and local control (52±8% vs. 45±15%, p=0.03). In multivariate analysis, the T category (UICC 1992) remained the only significant variable with impact on survival (p=0.04), NED-survival (p<0.001) and local control (p=0.003).
Conclusion: Treatment with a combination of radiotherapy and chemotherapy is safe and effective for patients with anal canal carcinoma. The improvement of results in advanced stages is warranted.

Key words: rectal neoplasms; radiotherapy; chemotherapy; treatment outcome

Introduction

The potential curative effects of radiation therapy (RT) alone or radio-chemotherapy (RCT) in the preservation of anal function has been well established in squamous cell carcinoma of the anal canal.[1-12] The abdomino-perineal resection (APR) is reserved for patients with residual or recurrent carcinoma after primary RT or RCT.

As squamous cell carcinoma of the anal canal is relatively rare, it is difficult to assemble a larger series of patients treated by a single protocol so that survival rates, primary tumor control rates, patterns

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of failure as well as acute and late treatment-related toxicity can be evaluated. This paper gives the results after treatment of 173 patients with carcinoma of the anal canal treated in eight German centers.

Patients and methods

Between January 1985 and May 1994, 173 patients underwent radical treatment by combined RCT and form the study group. Patient's age, gender and histological type of the tumors are shown in Table 1. Prior to treatment all patients underwent clinical examinations including sigmoidoscopy and biopsy. Chest X-ray, laboratory tests, abdominal ultrasound and CT- scans of the abdomen and pelvis were performed routinely. On the basis of these findings tumor stages were assigned according to the UICC-system of 1987.[13] Data on cancers treated between 1985 and 1987 were revised to conform with these criteria. T and N categories are listed in Table 1. The standard treatment protocol is shown in Figure 1.

Radiotherapy

The primary tumor region including perirectal, internal-iliac and inguinal lymph nodes was irradiated using parallel opposed anteroposterior-posteroanterior fields in the early years of the study (1985-1988) and later using a 3- or 4-field box technique. External RT was delivered with megavoltage equipment (mostly 6-10 MV-photons) and single fractions between 1.6 and 2.0 Gy (median 1.9 Gy) in an uninterrupted course up to a median total dose of 49.5 Gy. The radiation dose was specified to the isocenter using multiple field techniques or to the midplane for parallel opposed fields. Otherwise specified doses were retrospectively assigned to the reference point according to the ICRU 50 guidelines. Forty-five patients received an additional boost of external RT, 31 patients using interstitial brachytherapy (BT), 12 patients Iridium-192 low-dose-rate, 11 patients Au-198 and 8 patients Iridium-192 high-dose-rate. Table 1 gives the dosages of external RT and of the Ir-192-BT for all 173 patients. Dosimetric details of the Au-198-BT patients were reported elsewhere.[14]

Chemotherapy

One-hundred and seventy-three patients received concomitant chemotherapy. 5-Fluorouracil (5-FU) was scheduled as a continuous intravenous infusion for 120 hours (1000 mg/m²/24 h) to a maximum of 1800 mg/24 h on days 1-5 and 29-33. Mitomycin C (MMC) was administered on days 1 and 29 as a single bolus intravenous injection with a dosage of 10 mg/m². The second course of chemotherapy was adjusted according to the extent of treatment related hematologic, gastrointestinal and cutaneous toxicity. A summary of the dosage of 5-FU and MMC is given in Table 1.

Table 1. Patients characteristics

Number of patients	173
Median age (range)	61 years (26–82)
Histological type	
Squamous cell carcinoma	127 (73%)
Cloacogenic carcinoma	46 (27%)
T category (UICC 1992)	Patients (%)
T1	28 (16)
T2	77 (45)
T3	46 (27)
T4	19 (11)
TX	3 (1)
N category (UICC 1992)	
N0	115 (66)
N1-3	28 (17)
NX	30 (17)
Grading (UICC)	
G1	21 (12)
G2	74 (43)
G3	49 (28)
G4	2 (1)
GX	27 (16)
External RT	
30-44 Gy	45 (26)
45-50 Gy	59 (34)
51-55 Gy	25 (14,5)
56-60 Gy	25 (14,5)
61-66 Gy	19 (11)
Ir-192 low-dose-rate	12 (7)
12 Gy	5 (3)
15-16 Gy	7 (4)
Ir-192 high-dose-rate	8 (5)
7-18 Gy	4 (3)
20-26 Gy	4 (3)
Au-198	11 (6)
5-FU (mg/m²)	
3000-4000	61 (35)
4500-8000	84 (49)
8200-12000	28 (16)
MMC (mg/m²)	
7-10	67 (38)
11-20	81 (47)
24-35	17 (10)
none	8 (5)

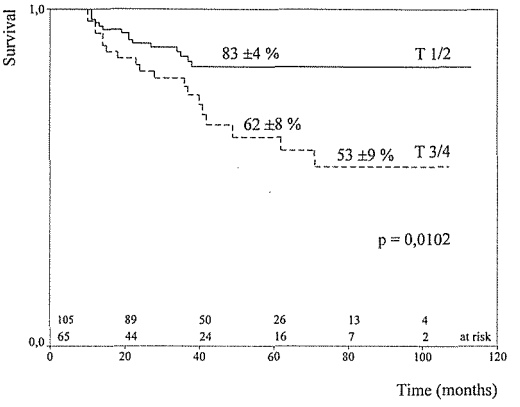

Figure 1. Cancer related survival according to T category (UICC 1992)

Follow-up assessment

Two months after the completion of therapy all patients were reassessed by digital examination, sigmoidoscopy and CT scans of the pelvis. In case of residual mass or suspicious ulcers multiple biopsies were taken under general anesthesia. Histologically verified lesions in the anal canal were counted as local disease, positive perirectal, iliac or inguinal nodes as regional disease. After negative biopsies patients were followed up at 3-month-intervals for two years from treatment and at 6-month-intervals thereafter. Median follow-up was 40 months with a range between 3 and 130 months. No patients were lost to follow-up. All events prior to May 1996 were included in the analysis. For calculating survival rates only cancer related deaths were counted (adjusted survival rate). The rates of survival, NED (no evidence of disease)-survival and locoregional tumor control were determined according to Kaplan and Meier.[15] Differences between patient groups were assessed by the log-rank-test, multivariate analysis was performed according to the Cox-regression-model.[16]

Results

Cancer related survival-, NED-survival- and loco-regional tumor control rates were 71±5 %, 59±4 % and 67±4 % at 5 years. 34 patients died of anal cancer, 14 of intercurrent disease. The survival rate for patients with T1/2-tumors was 83±4 % compared to 53±9 % in patients with T3/4-tumors (Figure 2, p=0.0102). Significant prognostic factors for all three endpoints are shown in Table 2. Only the T- and N category had a highly significant prognostic impact on NED-survival. For T3/4-tumors a total RT-dose of less than 45 Gy led to a significantly inferior NED-survival being 23±13% at five years compared to a survival rate of 42±7% following higher doses (p=0.01). Multiple field arrangements were associated with a better NED-survival of 70±6% in comparison to parallel opposed fields leading to survival rates of 50±6% (p=0.016).

Primary and regional tumor control

Two months after completion of therapy 134 (77%) patients had a clinical complete remission, 38 (22%) patients a partial remission, one patient no change. All patients with partial remission had positive biopsies, either performed as local excisions (12 patients) or multiple needle biopsies (14 patients). Significant prognostic factors for the loco-regional tumor control are shown in Table 4. Patients with smaller lesions up to a maximum diameter of 5 cm (T1/2) had a loco-regional tumor control rate of 81±4% (Figure 3) as compared to patients with larger tumors (T3/4), in whom a control rate of 46±7% was achieved (p<0.0001). Positive regional lymphnodes were associated with a poor loco-regional tumor control rate of 37±13% (Figure 4). By contrast a 76±4%-loco-regional control rate was noted in N0-cases (p=0.003). For patients with larger primaries (T3/4) a total RT-dose of less than 45 Gy led to a significantly lower tumor control rate of 45±15% as compared to 52±8% for doses above or equal to 45 Gy (p=0.03). Tumor control was also influenced by the treatment technique. The use of parallel opposed anterior and posterior fields was associated with a control rate of 58±6% which was significantly inferior to the results following treatment with multiple fields leading to a control rate of 77±6% (p=0.018).

Patterns of failure

Forty-nine (28 %) of the 173 patients experienced a local and/or regional tumor recurrence. In 26 cases there was an isolated local failure, in 7 cases a combined loco-regional failure and in another 8 cases a regional failure alone. Recurrences were noted after a time interval between 2 and 58 months (median 12 months). Twenty-six (15 %) patients experienced distant metastases between 1 and 35 months after completion of therapy. Distant metastases were combined with a local and/or regional failure in 9 cases.

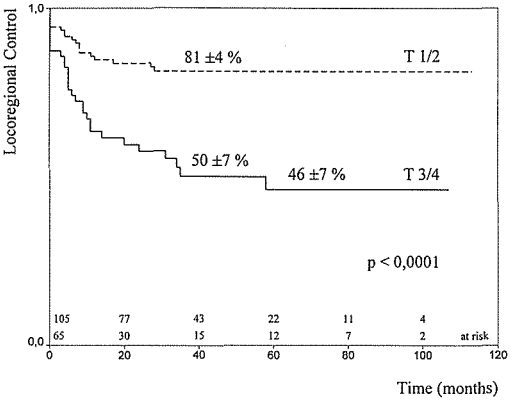

Figure 2. Locoregional tumor control according to T category.

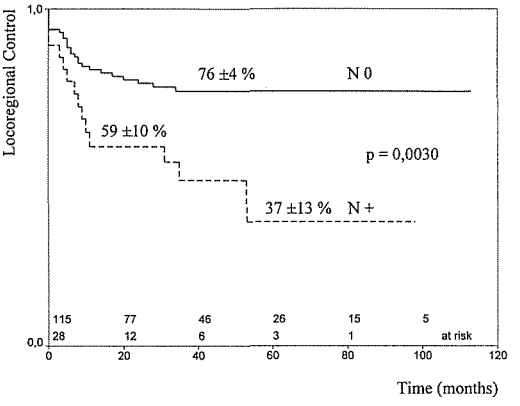

Figure 3. Locoregional tumor control according to N category.

Table 2. Significant prognostic factors for survival, NED-survival and locoregional tumor control at 5 years.

Factor	Overall survival	NED-survival	Tumor control
T category			
T1/2	83±4%	75±4%	81±4%
T3/4	53±9% (p=0.0102)	36±7% (p<0.0001)	46±7% (p<0.0001)
N category			
N0	73±5%	66±5%	76±4%
N1-3	66±11% (n.s.)	33±12% (p=0.004)	37±13% (p=0.003)
RT Dose (T3/4)			
≥45Gy	57±9%	42±7%	52±8%
<45Gy	67±16% (n.s.)	23±13% (p=0.01)	45±15% (p=0.03)
RT/CT Dose			
≥45Gy, >6g 5-FU	73±6%	61±6%	67±6%
<45Gym <6g 5-FU	69±14% (n.s.)	45±11% (p=0.042)	54±12% (p=0.11)
Treatment technique			
>2 fields	74±9%	70±6%	77±6%
2 fields	71±6% (n.s.)	50±6% (p=0.016)	58±6% (p=0.018)

n.s. not significant

Table 4. Multivariate analysis on prognostic factors for cancer related suvival, NED survival and local tumor control.

Cancer related survival				
Variable Beta	95% C.I.	Exp (Beta)		P
T category	−0,2992	0,5546-0,9910	0,7414	0,043
Technique	−0,0562	0,6880-1,2990	0,9457	0,72
RT-dose	0,0116	0,0759-1,0487	1,0016	0,53
MMC-dose	−0,0265	0,9264-1,0237	0,9738	0,29
NED-survival				
T category	−0,5591	0,4397-0,7434	0,5717	0,001
Technique	0,1781	0,9004-1,5869	1,1954	0,217
RT-dose	−0,0228	0,9447-1,0114	0,9775	0,19
MMC-dose	−0,0164	0,9436-1,0256	0,9837	0,44
Local tumor control				
T category	−0,5458	0,4302-0,7804	0,5794	0,003
Technique	0,2674	0,9436-1,8090	1,3065	0,10
RT-dose	−0,0100	0,9530-1,0285	0,9901	0,60
MMC-dose	−0,0046	0,9503-1,0427	0,9954	0,84

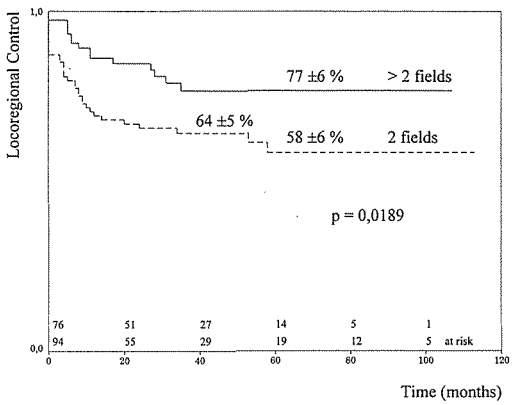

Figure 4. Locoregional tumor control according to treatment technique.

Toxicity

The various levels of acute toxicity were classified as stated by the WHO17 and are shown in

Table 3. Acute toxicity (WHO) and late treatment related toxicity (Eschwege) among 124 patients* following radiochemotherapy of anal canal carcinoma.

Grade	Dermatitis	Diarrhea	Anemia	Leucopenia	Thrombocytopenia	Late Toxicity
0	10 (6%)	20 (11%)	99 (56%)	59 (33%)	93 (53%)	77 (62)
1	13 (7%)	28 (15%)	18 (10%)	21 (12%)	19 (11%)	9 (7)
2	42 (24%)	45 (25%)	7 (4%)	27 (15%)	7 (4%)	26 (21)
3	56 (32%)	31 (18%)	0	16 (9%)	3 (2%)	12 (10)
4	3 (2%)	1 (1%)	0	1 (1%)	2 (1%)	

* Data on toxicity from one center not available

Table 3. The frequency of severe hematological toxicity (grade 3/4) was 22/124 patients (18%). Thirty-four percent and 19% of the patients experienced a dermatitis and enteritis of at least grade 3 (WHO), respectively. Late toxicity was scored according to Eschwege *et al.* (1985) and is shown in Table 5. Only 12 of 124 patients (9.6%) had late sequelae of grade 3, requiring surgery. The use of interstitial BT using Ir-192 high-dose-rate and Au-198 in two centers had a significant negative impact on survival without grade 3 toxicity, which was 92% without and 74% with interstitial BT of this type.

Preservation of anorectal function

A major objective of the conservative treatment of anal carcinoma by RCT or RT is the preservation of anorectal function. APR was performed in 51 (29%) of the patients, in 41 patients after local recurrence and in 10 patients for other reasons. The remaining 12 patients were scored as being partially incontinent. Thus a functioning anorectal sphincter was preserved in 110 of 173 patients (64%), and in 110 of 121 patients (91%) in whom the primary tumor was controlled by RCT.

Multivariate analysis

The following variables were included in the analysis: Total RT dose, total dose of MMC (continuous variables), treatment technique, T category (T1/2 vs. T3/4) and N category (N0 vs. N1-3), as categorial variable. The only independent and significantly related factor for survival, NED-survival and loco-regional tumor control was the T category with a p-value of 0.04, 0.001, and 0.003, respectively (see alsoTable 4).

Discussion

Carcinoma of the anal canal tends to cause sphincter muscle invasion in the early course of the disease. Adequate local excision is therefore not feasible under the prerequisite of preserving an intact anal sphincter. Local excision as a treatment strategy appears to be only appropriate for small lesions (< 2 cm) involving the anal margin and the perianal skin.[18] APR was the standard treatment for anal cancer in many centers until the mid-eighties. Five-year-survival-rates between 40% and 70% have been reported. Obvious disadvantages of the APR include the permanent loss of the anal sphincter function, a significant postoperative morbidity and mortality as well as impotence.[19-23]

Treatment options, results and late effects

It has been the ongoing and continuing policy of several French centers to use RT alone or in combination with interstitial BT for conservative treatment of anal cancer with excellent results.[1,3,10-12,18,24,25] RT alone proved to be very effective for small lesions of less than 4 cm in diameter: Local tumor control rates between 76% and 91% were reported.[3,9] For adequate local control of larger primaries, however, relatively high total doses between 60 and 65 Gy had to be applied.[3,10,11] Consequently late treatment related toxicity was noted more frequently (9-13% grade 3 according to Eschwege) requiring APR for the control of distressing symptoms. In a series reported by Touboul *et al.* only 65% of the patients with no evidence of local tumor had an intact anal sphincter.[11] By contrast, local complication rates as low as 3% together with local tumor control rates of 88% (23,24) were reported by centers using RCT with and without interstitial BT.[2,5,6,27] Nigro *et al.* (1974) pioneered in the clinical use of concomitant RCT as a neoadjuvant treatment strategy for downstaging of anal carcinoma. After 30 Gy total dose and one course of MMC/5-FU histologically negative resection specimens were obtained in almost 60% of the patients. During the following years numerous phase-II studies were conducted.

Our results of 173 patients treated between 1985 and 1994 in eight Radiation Centers compare very favorably with the literature data on survival-, NED-survival- and loco-regional control rates at of 71%, 59% and 67%, respectively. The anal sphincter function was preserved in 110 of 121 patients (91%) in whom the local tumor was permanently controlled by RCT. Noteworthy is the fact that in other series using RCT the sphincter preservation rate was as high as 80%[5,12,18] in comparison to the results following RT alone.[10,11,24]

A recent randomized EORTC study provided preliminary data concerning the issue whether RCT is superior to RT alone in advanced anal carcinoma (either node positive or > 4 cm). Both locoregional tumor control and colostomy-free survival were significantly improved in the concomitant arm.[26] In an RTOG/Intergroup study the value of additional MMC as part of the concomitant chemotherapy was investigated.[4] As has been pointed out earlier in a retrospective series by Cummings *et al.*[27] NED-survival and local tumor control rates were significantly lower after regimens omitting MMC, but using RT and 5-FU alone.

Prognostic factors

Our results clearly demonstrate that the tumor volume represented by the T category (UICC 1992) remained the only independent significant prognostic factor for survival, NED-survival and local tumor control. This was also noted in a larger series of 242 patients treated with RT alone.[10] In patients treated by RT alone and studied by multivariate analysis the size of the primary tumor was predictive for both survival and local control.[10,28,29] Local tumor control rates of 91% and 89% for tumors of less than 4 cm in diameter versus control rates of 73% and 71% for larger primaries were reported.[3,9,18]

In patients treated by RCT, local control rates for primary tumors up to 2 cm in diameter were in the range of 95-100%, for 2-5 cm 80-95% and for larger than 5 cm 65-80%.[2,5,27,30] Five-year survival rates, corrected for death from intercurrent disease, were about 95-100% when the primary was < 2 cm and in the range of 60-70% for larger tumors reflecting the good surgical salvage rates for local relapse after treatment with RCT.

It has been suggested by others[11] that a combination of preoperative RT and surgery or a more aggressive RCT including cisplatin based chemotherapy[12] could improve local tumor control and survival for patients with T4 tumors. In our series a total RT dose of less than 45 Gy with concomitant chemotherapy does not seem to be adequate for larger tumors (> 5 cm). Control rates and NED-survival were only 45% and 23% at 5 years. Following higher doses, however, results could be significantly improved (p=0.01). Surprisingly in our series refinements in the treatment technique had a significant impact on NED-survival and local control in univariate analysis. This could not be demonstrated by others.

In surgical series histopathologically confirmed involvement of perirectal, superior hemorrhoidal, pelvic or inguinal node groups was associated with 5-year survival rates of about 50%, being 25% worse than those of patients without nodal involvement[31] The presence of regional lymphnode metastases did not correlate with control of the primary tumor in patients managed with RT- or RCT protocols in the early series.[9,28] However, we found a striking difference in local tumor control for patients without regional metastases being 76% vs. 37% for patients with positive regional nodes (p=0.003). It appears that the application of routine CT-scanning of the pelvis for staging purposes may have detected enlarged nodes more accurately. Recently Myerson *et al.*[7] reported a worse disease-free survival of 52% for T1-3 N1-3 patients as compared to that of patients in T1-3 N0 stages which was as high as 88% at 10 years (p=0.03).

No data exists on patients treated by RT/RCT concerning the prognostic value of tumor DNA-content. In one large surgical series of flowcytometric DNA analysis of paraffin embedded tissue, ploidy was found to be strongly predictive for outcome, patients with diploid tumors having a 5-year survival of 75% compared to 55% for patients with aneuploid tumors.[31] Among serum markers of interest, only serum squamous cell carcinoma antigen (SCCAg) provided significant influence in one multivariate analysis predicting tumor specific death rates and recurrent carcinoma.[29]

In conclusion the results from the current study and others strongly suggest that with respect to certain prognostic factors further improvement in the therapy of anal canal cancer is possible, particularly modifications of the chemotherapeutic regimen and the radiation dose. Refinements in radia-

tion technique and fractionation schedules need to be prospectively evaluated to minimize late sequelae and to preserve anal sphincter function even in advanced cases.

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Local excision of flat adenomas of the rectum in the period from 1987 to 1991

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In a period of 5 years, 35 patients underwent operations on for flat adenomas of the rectum located at a depth of 10 cm from the anocutaneous line. All the tumours were removed by transanal submucous excision. The average period of follow-up was 22 months. Three recurrences were detected and treated with reoperation. No major complications occurred. We consider our method suitable for clinical use if combined with careful follow-up.

Key words: rectal adenomas; surgery

Introduction

This report presents the results of surgical treatment of flat adenoma of the rectum at the Proctology Unit of the Department of Gastroenterologic Surgery in Ljubljana. Thirty-five patients underwent operations during a period of 5 years. The safety and success of the surgical procedure were evaluated with regard to peri- and postoperative complications and the frequency of recurrence. Our series is too small to reveal a possible association between the histologic type of the tumour and likelyhood of recurrence.[1]

Patients and methods

In the years from 1987 to 1991, 35 patients with flat adenoma of the rectum attended our outpatient clinic. The lesions were located within 10 cm from anocutaneous line. Prior to surgery, the patients underwent colonoscopy, a routine preoperative investigation and, in case of associated conditions, also appropriate preoperative preparations. The operation was performed under epidural or caudal anaesthesia. The patients received a preoperative enema and intraoperative antibiotic prophylaxis consisting of metronidazol 500 mg and gentamicin 80 mg in a single dose. Local excision was performed with the use of Park's retractor. The submucous layer was infiltrated with physiological solution to facilitate exposure. In 11 cases, the defect was closed with a running suture. In the rest, hemostasis was achieved with individual sutures.[2,3] The removed adenomas were histologically classified according to Morson's system. The patients attended for follow-up proctoscopy a month after the procedure to rule out residual tumour. Further follow-up proctoscopies were performed at monthly intervals during the first year and annually later on.[4]

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Results

In 5-year period, 341 patients with polyps involving different parts of the large intestine were treated at our department. Among them were 35 patients with flat adenomas located at a depth of up to 10 cm from anocutaneous line. This group included 19 women and 16 men, aged between 39 and 85 years (Table 1). The distribution of operations over the 5-year period is shown in Table 2.

The base of the resected adenomas ranged in size from 1.5 to 5.5 cm (Table 3). One patient required a reoperation on for control of haemorrhage. No other major complications were encountered. The op-

erated site healed completely in all the patients. Histologic classification of the resected adenomas according to Morson's method is presented in Table 4. Three recurrences were detected at follow-up. One of them, in a male patient, showed malignant alteration. All three patients with recurrent adenomas received appropriate surgical treatment.

Table 1. Age of patients.

Age of patients by					
Decade	4	5	6	7	8
Number	2	5	9	11	8

Table 2. Beginning of treatment.

Beginning of treatment					
Year	87	88	89	90	91
Number	8	6	5	9	7

Table 3. Base diameter.

Base diameter									
In cm	1,5	2	2,5	3	3,5	4	4,5	5	5,5
Number	1	0	4	7	9	8	3	1	2

Table 4. Grade of dysplasia.

Grade of dysplasia				
Histologic type	1	2	3	Total
Villous	1	3	4	8
Tubular	0	2	8	10
Tubulovillous	0	6	11	17
Total	1	11	23	35

Discussion and conclusion

We consider our method to be favourable for the patient as hospitalization is relatively short. With careful follow up, recurrences can be detected and reoperated on before the tumours undergo malignant alteration requiring more extensive resection that may lead to permanent disability or premature death. To our judgement and by our experience and data from literature, these patients may be followed-up after the first year in the same manner as any patients with adenoma involving other parts of the colon. Likelyhood of recurrence for individual histologic types of resected adenomas could not be estimated because of inadequate size of the series and advanced age of our patients, many of whom died of other conditions in the course of follow-up.[1,4]

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MR imaging in primary irradiated prostatic carcinoma

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The main objective of our investigation was to determine the role of endorectal surface coil magnetic resonance (Endo-MR) in the monitoring of patients with prostate cancer before and after external beam radiation (EBR). A prospective study was performed on 26 patients with biopsy proven prostate cancer. All patients underwent Endo-MR prior to external beam radiation (pre-EBR). Six months after EBR (70Gy/1.8-2 Gy), another Endo-MR examination was performed until now in 14 patients (post-EBR). We used a 1.5 Tesla unit performing T1 and T2 weighted spin echo or fast spin echo sequences in axial and coronal planes. Imaging analysis included the assessment of tumor size, prostate capsule involvement and infiltration of the seminal vesicles. On all pre-EBR scans, we could identify a low intensity region in the peripheral zone on T2 weighted images correspondng to the positive biopsy findings (11 cases with tumor confined prostate, 15 cases with signs of extracapsular disease). On post-EBR scans, we obtained a variable pattern of radiation induced changes. In this presentation, the results are detailed and images from the study demonstrated. Endo-MR examination enables excellent morphological evaluation of prostate cancers and shows initial promise in demonstration of post radiation changes.

Key words: prostatic cancer; endorectal magnetic resonance imaging

Introduction

The local extent of prostatic carcinoma is difficult to asses with any conventional imaging modality. The development of a magnetic resonance endorectal surface coil (Endo-MR) has significantly enhanced the details with which the prostate and the surrounding structures can be seen.[1,2,3] The Endo-MR surface coil is mounted on a inflatable balloon; the balloon has a concave surface to seat well against the prostate.

The appearance of the prostate and the seminal vesicles on T1 and T2-weighted images is different. T1-weighted images are useful in imaging the periprostatic fat and periprostatic venous plexus; tumors are usually isodense to the normal prostate on T1-weighted images.

T2-weighted images are most useful in demonstrating the internal architecture of the prostate and seminal vesicles. The central gland is of relatively low signal, whereas the peripheral zone is of high signal. Carcinoma of the prostate presents a low signal area on T2, most commonly in the peripheral zone.

The purpose of this prospective study is to asses the value of endorectal surface coil magnetic resonance (Endo-MR) in the monitoring of patients with prostate cancer before and after external beam radiation (EBR) and to compare the imaging findings to clinical data.

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Materials and methods

Since August 1994, clinical and laboratory data (including PSA, chest x-ray, bone scan, CT of the

pelvis) were obtained on twenty-six patients (57-74 years, median 68 years) with biopsy proven prostate cancer and no evidence of distant metastases. All patients underwent Endo-MR imaging prior to external beam radiation (pre-EBR). The time interval between biopsy and MR examination was more than three weeks to ensure better differentiation between biopsy-related small areas of haemorrhage within or adjacent to the prostate and tumour-related signal intensity changes. EBR was delivered by high energy photon beams with a continuous course of 70 Gy/35-38 fx/5 days a week with a three- or four-field technique. Six months after EBR, another Endo-MR, examination was performed in fourteen patients (post-EBR) until date. We used a 1.5 Tesla unit (Gyroscan ACS, Philips) performing T1-weighted (TRE 627, TE 14) and T2-weighted (TR 2700, TE 120) spin echo or fast spin echo sequences in axial and coronal planes (slide thickness of 3 mm, FOV 210 mm). Imaging analysis of both pre- and post-EBR scans included the assessment of tumor size, prostate capsule involvement, infiltration of the neurovascular bundle and the seminal vesicles.

Results

In all 26 pre-EBR-examinations, we were able to identify a low signal intensity region in the peripheral zone corresponding to the positive biopsy findings.

In eleven patients, the tumor was confined to the prostate, but in these patients, surgery was not performed for cardiovascular or other medical reasons. In fifteen patients, evidence of extracapsular disease was observed on pre-EBR scans.

Similar to other authors,[4] we obtained a variable pattern of changes at post-EBR scans. Concerning tumor morphology, we found residual tumors of decreased size in six patients. Two tumors could no longer be identified after irradiation and one tumor could not be evaluated due to diffuse signal loss of the entire gland. No changes in tumor size and signal intensity were found in five patients; two of them had concurrent hormonal therapy.

Changes in gland morphology after EBR were observed in five patients. Increased signal on T2-weighted images in the peripheral zone and central gland was found in two patients, decreased signal in the peripheral zone in two other patients and - as described above - a uniform very low signal intensity throughout the gland on T2-weighted images was seen in one patient.

PSA levels were decreased in all patients after EBR.

Conclusion

Endo-MR provides important information for radiotherapy planning by accurate tumor staging and seems to be capable to demonstrate post radiation changes in patients with prostate cancer.

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Adenocarcinoma of the prostate treated by definitive high-dose external radiotherapy

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Between 1986 and 1994, 436 patients with localized adenocarcinoma of the prostate were treated with external beam radiation at our department. After excluding those who received a tumor dose less than 64 Gy and had insufficient follow-up data or had previous prostatectomy, we analysed a total of 384 patients (101 T1, 224 T2, 48 T3, 11 T4 - reclassified to UICC 1922). The median age was 69.7 years, the median follow-up 54.4 months. Patients with locally advanced disease were treated by pelvic fields (50.4 Gy / 1.8 Gy), followed by prostate-field conedowns (16-20 Gy /2 Gy): patients with early stage disease received only prostate field radiation (66-70 Gy /2 Gy). Five-year overall survival was 81.6% for 11, 63.8% for T2 and 64.1% for T3/4. Five year disease-free survival was 89.3% for T1, 77.2% for T2 and 56.9% for T3/4. Thirty-one patients (8%) had local recurrence, 61 patients (15%) developed distant metastases. We conclude that high dose external beam radiotherapy is very effective in local control for adenocarcinoma of the prostate but, unfortunately, many patients will continue to die from metastases and intercurrent disease.

Key words: prostatic neoplasms; radiotherapy; local control; survival rate

Introduction

Definitive external beam radiation (EBR) is an accepted modality as an alternative to surgery in the management of patients with localized carcinoma of the prostate.[1-4] We present the results of a retrospective analysis including 384 patients with adenocarcinoma of the prostate.

Materials and methods

In the period from February 1986 to May 1994, 384 evaluable patients with localized adenocarcinoma of the prostate were included in our study. The median age of the patients was 69,7 years (47 - 88 years). Pathologic confirmation of prostate cancer was obtained in all patients. In 328 patients, a transurethral resection of the prostate (TURP) was performed. Tumors were staged according to the TNM system (reclassified to UICC 1992). One hundred one patients were classified as T1, two hundred twenty four as T2, forty eight patients as T 3, and eleven as T4 tumors. The median follow-up for all patients was 54,4 months (1,3 - 161,3 months).

External beam irradiation was delivered with 23 MeV photon beams by linear accelerators with a continuous course of 50.4 Gy /1.8-2 Gy/day, 5-days a week to the pelvic lymph nodes in a four-field technique, followed by a boost to the prostate up to a total dose of 66-70 Gy using a three-field technique. Patients with a low risk for nodal metastases received treatment to the prostate and seminal vesicles alone with an adequate margin to 66-70 Gy / 2 Gy daily. The dose was prescribed to the 90 or 93% isodose. Routinely, treatment was based on CT -

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planning; individually manufactured paraffin blocks were used to protect maximally normal tissue.

Follow-up investigations comprised rectal examination, acid and prostatic phosphatase examination and/or prostate-specific antigen (PSA) - evaluation at 3-month intervals during the first three years and at 6-month intervals later on. Abdominal ultrasound and chest radiographs were performed at 6-month intervals, bone scans and CT of the pelvis were performed if clinical findings suggested progression of the disease.

Results

Actuarial 5-year overall survival rates according to UICC - stages T1, T2 and T 3-4 disease were 81.6%, 63.8%, and 64.1%, respectively.

The corresponding 5-year disease-free survival rates according to UICC - stages T1, T2, and T3-4 were 89.3%, 77.2 % and 56.9%, respectively. In 31 patients (8%), local failure was seen and in 61 patients (15.9%), distant metastases were observed.

Conclusion

Our results revealed megavoltage EBR using modern treatment facilities as a safe and effective treatment modality for loco-regional control of prostate cancer.

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Preservation of the lung function after thoracic irradiation: Role of transforming growth factor beta (TGF-β)

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TGF-β is considered as a predictor of pneumonitis in patients receiving radiotherapy. Plasma TGF-β levels were investigated in 27 consecutive patients with NSCLC stage III, who were treated with 60 Gy (2 Gy/day) radiotherapy with or without carboplatin. TGF-β was measured with a bioassay using mink lung epithelial cells transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct (normal values (SD) 9.0 ng/ml (1.9)). Mean (SD) pretreatment TGF-β value was 55.8 ng/ml (33). Only 3 patients had normal values. TGF-β was not related to age, performance score, or weight loss. No relationship between pretreatment TGF-β levels and pneumonitis was observed. There was no influence of carboplatin or radiation field size on the incidence of pneumonitis nor on TGF-β levels during treatment. All 9 patients who developed pneumonitis (CTC criteria) after treatment had, during radiotherapy, a high persistent TGF-β levels relative to pretreatment levels. Patients with the same or lower TGF-β values relative to pretreatment values did not develop symptomatic lung injury. In conclusion, elevated TGF-β levels during radiotherapy may identify patients at high risk of developing pneumonitis after treatment. Furthermore, it can help in selection of those patients who might be candidates for dose escalation.

Key words: lung neoplasms-radiotherapy; transforming growth factor beta; radiation pneumonitis

Introduction

Radiation therapy plays a significant role in the treatment of lung carcinoma, Hodgkin's disease, breast cancer and other tumors involving thoracic region. Pulmonary tissue is one of the most critical dose limiting normal tissues involved in thoracic radiotherapy. The clinical sequelae of radiation lung injury usually start with the acute onset of radiation pneumonitis at 2 to 6 months after radiotherapy with the symptoms that range from cough, fever and dyspnea to death from respiratory failure. Depending on radiation dose and volume of the exposed lung, radiation pneumonitis may resolve without further changes or may progress to the stage of chronic pulmonary fibrosis significantly affecting the quality of patients' life. Identification of those patients that might be at high risk of developing pulmonary injury after thoracic irradiation as well as those in whom the dose of radiation can be safely increased would consequently lead to the preservation of the lung function and better tumor control.

There is considerable interest in transforming growth factor beta (TGF-β) as a mediator of normal tissue injury. It is suggested that the measurement of TGF-β in the plasma during chemotherapy/radiotherapy may be useful in predicting an individual patient's risk for developing late radiation-induced normal tissue injury.[1,2] The objective of this ongoing study is to investigate the utility of plasma TGF-β levels in identification of those patients at risk for the development of radiation-induced lung injury.

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Materials and methods

Plasma TGF-β levels were investigated in this ongoing study in 27 consecutive patients with NSCLC stage III, who were treated with 60 Gy (2 Gy/day) radiotherapy with or without carboplatin. All patients underwent history and physical examination, radiographic evaluation for staging purposes and had histologic confirmation of malignancy. Pulmonary function tests including total lung capacity (TLC), vital capacity (VC), forced expiratory volume per second (FEV_1) and diffusion corrected for alveolar volume (Kco) were obtained before and after the treatment. Plasma for TGF-β measurement was obtained prior to the beginning of radiotherapy and weekly during treatment. TGF-β was measured with bioassay using mink lung epithelial cells (MLEC) transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct (normal values (SD) 9.0 ng/ml (1.9)). This bioassay is based on the ability of TGF-β to induce plasminogen activator inhibitor-1 (PAI-1) expression. MLEC were stably transfected with an expression construct containing a truncated PAI-1 promoter fused to the firefly luciferase reporter gene. Binding of TGF-β to the transfectants results in a dose-dependent increase in luciferase activity in the cell lysate assay was described by Abe *et al.*[3] and recently modified in our laboratory.[4] The endpoint of the study was the development of symptomatic radiation pneumonitis defined according to the National Cancer Institute Common Toxicity Criteria (CTC).

Results

Of the 27 NSCLC patients, 14 had squamous cell, 7 adenocarcinoma and 6 large cell carcinoma. Thirteen patients had stage IIIA and 14 IIIB NSCLC. All patients were treated with curative intent, 17 with radiotherapy and carboplatin, 10 with radiotherapy alone.

Mean (SD) pretreatment TGF-β value was 55.8 ng/ml (33). Only 3 patients (11%) had normal pretreatment values. TGF-β was not related to age, performance score, or weight loss. There was no correlation between the pretreatment TGF-β values and either the incidence or severity of pneumonitis. There was no influence of carboplatin or radiation field size on the incidence of pneumonitis nor on TGF-β levels during treatment. Pretreatment lung function values in % predicted of TLC, VC, FEV_1 and Kco (SD) were 87 (16), 86 (19), 66 (18), 116 (25), resp. Posttreatment values of TLC, VC, FEV_1 and Kco (n=25) were 83 (16), 83 (13), 65 (13), 105 (25). Changes in pulmonary function tests did not correlate with the development of pneumonitis or plasma TGF-β levels. The patients were divided into two groups according to whether or not they developed symptoms of radiation induced pulmonary injury (CTC criteria). Nine of the 27 patients developed pneumonitis. The patients who developed pneumonitis had high persistent TGF-β levels throughout the course of treatment (TGF-β ratio > 1), whereas the TGF-β levels in patients who did not develop pneumonitis stagnated or turned to normal (TGF-β ratio =< 1). This ratio is defined as the ratio between TGF-β at each week of radiotherapy normalized and the pretreatment TGF-β level. The difference in plasma TGF-β levels between the patients with and without radiation-induced pneumonitis become significant four weeks after the beginning of radiotherapy treatment (p=0.028).

Discussion

The involvement of cytokines as mediators of normal tissue injury and repair following the treatment with radiation and/or chemotherapy is currently a topic of intense laboratory and clinical research. Among the many cytokines that have so far been recognized, transforming growth factor beta (TGF-β) is of particular interest. TGF-β is a multifunctional regulator of cell growth and differentiation which stimulates connective tissue formation and decreases collagen degradation resulting in fibrosis.[5] Recent studies have reported locally produced TGF-β to be involved in the promotion of radiation-induced fibrosis in a number of tissue types.[6-10] The role of TGF-β in radiation-induced pulmonary fibrosis is, however less certain.

Finkelstein *et al.*[11] found very early fluctuations in whole lung TGF-β gene expression at 1 and 14 days after irradiation in mice. More recent results from the same group using radiation fibrosis-prone mice indicated elevated TGF-β levels in the lung that persisted at least until 8 weeks after irradiation.[12] Similar increase in mouse lung TGF-β levels have been observed following the treatment with bleomycine, or cyclophosphamide. The later phenomenon is especially pertinent to the potential enhancement of pulmonary toxicity by the combination of chemotherapy with thoracic irradiation.

An association between circulating levels of TGF-β and the incidence of pulmonary complications was first reported in patients receiving high-dose chemotherapy in the setting of autologous bone marrow transplantation for advanced breast cancer.[2] The same authors later reported preliminary findings which indicated that plasma TGF-β levels measured during radiotherapy for lung cancer may be useful in identifying patients who will or will not go on to develop symptomatic radiation pneumonitis.[1] The present study is a further confirmation that measurement of TGF-β during radiotherapy treatment may be a useful tool for identifying patients at risk for the development of radiation pneumonitis. Our data are also suggesting that other physical parameters, such as volume of irradiated lung or changes in lung function do not correlate with the risk of developing pneumonitis. This emphasizes the importance of TGF-β in the development of radiation induced lung injury. Understanding that role might further help in preservation of the lung function. Recently, it has hypothesized that normal tissue injury is not only mediated by the local production of TGF-β but also influenced by elevated circulatory level of TGF-β produced by the tumor.[13] The evidences exist that newly diagnosed breast, liver and, as our results show, lung cancer patients have elevated pre-treatment plasma TGF-β levels.[14,15] However, it is difficult to resolve what is the contribution of a normal tissue injury in TGF-β production during radiation therapy and what is produced by existing tumor.

In conclusion, elevated TGF-β levels during radiotherapy treatment may identify patients who develop pneumonitis after treatment. Further experimental and clinical investigations on the role of TGF-β and other cytokines in chemotherapy- and radiotherapy-induced injury to the lung are certainly necessary.

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Lung-sparing resection instead of pneumonectomy in patients with wide spread lung cancer

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The 5-year survival rate of the patients after lung-sparing resection (Group A) was 18.2% vs. 15.9% after pneumonectomy (Group B) ($p > 0.05$). Recurrences were detected in 63.6% of patients of group A vs. 56.9% in patients of group C (after lob - bilobectomy) ($p>0.05$).

Key words: lung neoplasms-lobectomy; pneumonectomy; survival rate

Introduction

Some authors dissuade the surgical treatment of the patients with wide spread lung cancer (Stage III) because long-term survival has remained extremely low, while the others defend extensive resection with complete mediastinal lymph node dissection for both radicality and exact staging as well as the correct adjuvant therapy indication.

Patients and methods

During the last 10 years (from 1987 to 1996), 207 patients with wide spread lung cancer (Stage III A) underwent the surgical treatment in combination with postoperative adjuvant radiochemotherapy. In 138 patients pneumonectomy was performed (Group B), 58 - lob - bilobectomy (Group C), and 11 - non-standard lobectomy with the resection of the pulmanory artery or / and of the main bronchus because of the primary tumor invasion into these structures (Group A). In all the patients, complete mediastinal lymph node dissection was made. The distribution of the patients in groups by age, gender, histological type of tumor, was comparable.

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Results

Only two patients of Group A (18.2%) had longer survival than 5 years. The first underwent pneumonectomy due to local spread of tumor (lob-bilobectomy with a sleeve resection of the main bronchus) and the second had a window resection of the main bronchus with a wedge resection of the pulmonary artery. Of 138 patients (15.9%) of Group B, after pneumonectomy, 22 survived more than 5 years. Similar results were observed in the patients of Group C; 10 patients of 58 (17.2%) lived longer than 5 years.

Most of the patients in all the analyzed groups died in the first 2 years after the operations due to local relapses and distant metastases. Recurrences in the patients after standard lob-bilobectomy (Group C) and after non-standard lob-bilobectomy (Group A) was similar (56.9% and 63.6% accordingly). There were no lethal complications of organ-preserving surgery.

Conclusion

According to the preliminary results, lung-sparing resection with postoperative adjuvant radiochemotherapy in the patients with wide spread lung cancer (Stage IIIA) can be an analternative method to pneumonectomy not only in high risk patients but in all patients where it is possible to perform it. It may also be recommended as the treatment results are no worse

than in other therapies and the quality of life quality of the patients improved.

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Brachytherapy (Ru 106) in the treatment of malignant melanoma of the choroid

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Introduction: *The authors report on the first 50 patients with primary choroidal melanoma who received primary treatment with Ru 106 plaques in 56 applications.*

Materials and methods: *We examined the records of 23 man and 27 women, treated between July 1986 and July 1992. The patients were 22-78 years old (mean 52.1 years). Height of the tumor was in the range from 2 to 7.1 mm (mean 4.5 mm) Follow-up time was from 15 to 144 months (mean 44.9 months). The dose to the apex of the tumor ranged from 82 to 120 Gy.*

Results: *Complete regression of the tumor occurred in 25 patients, partial regression occurred in 25 patients; second application of the plaque was necessary in 6 patients. Of the retreated patients, one later required enucleation because of tumor regrowth. In remaining 5 patients, regression was complete in 2 patients, and partial in 3. Enucleation was performed in 7 patients, in one because of late progression (after 110 months), glaucoma and panophthalmitis in two others, and regrowth of the tumor in the remaining 4 patients. Distant metastases were the cause of death in one patient 39 months after therapy. At that time, there were no signs of local progression. No systemic dissemination was detected at the follow-up in all other patients. 29 patients retained visual acuity grater than 0.1. Late radiogenic complications occurred in 8 patients.*

Key words: choroid neoplasms, brachytherapy, melanoma

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Quality of life in oncology: Why and how can we evaluate this aspect in cancer care?

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Since it has been recognised that QoL is an important outcome in medicine this field of research has grown rapidly. In the past decade increasing attention is being given to more systematic and quantitative ways to evaluate explicitly the impact of diseases and medical interventions on QoL. A substantial part of this research pertained to the field of cancer where cure is not always possible and treatments are mostly intrusive. The general purpose of QoL assessment in medicine is to provide more accurate evaluations of the wellbeing of individuals or groups of patients, and of the benefits and losses that may result from medical interventions. The focus of study can be to describe, to measure changes over time, to compare different populations, or to predict future outcomes. If QoL is to be evaluated, a number of decisions have to be made concerning the methodology of measurement. These decisions relate to: a) the design of the study; b) the components of QoL that will be evaluated; c) the instrument(s) to measure the relevant components; d) the subjects and e) the timing of assessment. In recent years it has become more acceptable to include QoL (mostly as a secondary) outcome measure in cancer clinical trials. Since missing QoL forms or missing data are, by definition, irretrievable, logistics and organization of the study require special measures to ensure good quality of data up-front. As QoL research is a rather new field of research there is not yet a large data base available to compose reference scores which can be used to calculate sample size and to facilitate the interpretation of results. In cancer clinical trials QoL is mostly evaluated between treatment arms in a longitudinal design. But what are significant changes over time? Surely statistical significance is not identical to clinical significance. A clinically meaningful change is statistically significant, but a statistically significant change is not always clinically meaningful. This presentation will focus on and discuss the basic principles of QoL assessment in general and in oncology in particular. Examples will be used from both the literature and current practice in the European Organization for Research and Treatment of Cancer (EORTC).

Key words: neoplasms; quality of life

Introduction

Historically, the main purpose of oncology has been to cure cancer, and, if cure is not possible to prolong life. Regardless of the tremendous progress in medicine in general and in oncology in particular, many patients still cannot be cured of their cancer. New treatment modalities seldom lead to revolutionary improvements of tumour control and life expectancy. On the other hand, cancer requires treatments that are mostly highly intrusive in character and often cause considerable side-effects in terms of morbidity.

Although implicitly QoL (QoL) always has been an important goal, it is only quite recently that we have come to accept that there are limitations to the strictly biological approach to evaluate cancer treatment outcomes in terms such as overall or disease free survival. Especially when two treatment options offer comparable biomedical advantages, the principal differences may lie in associated features like

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QoL. Therefore, increasing attention is being given to more systematic and quantitative ways to evaluate the impact of cancer and its treatments on QoL.

What is QoL?

It has been agreed upon that QoL is not a directly observable and measurable entity, but that it is a construct which has to be specified and defined. Without a definition a concept cannot be measured. However, despite the increasing interest and applications of QoL evaluation, still no consensus has been reached among researchers concerning the definition of this concept. Definitions of QoL are numerous and widely divergent. Nevertheless there are some issues regarding the concept of QoL that researchers in this field have agreed upon. The first agreement is that QoL is a *subjective* evaluation. It is generally accepted among QoL researchers that patients themselves are the best judges of their own QoL. However, there are circumstances in which it is difficult or even impossible that patients rate their own QoL. In these cases patients' QoL has to be assessed from the perspective of the family (e.g., partner, parents) or the caretaker (e.g., physician, nurse).

The second issue researchers have agreed upon is that QoL is not a static, but a *dynamic* entity. QoL changes as a function of time, susceptible to numerous external as well as internal influences. In other words QoL is more a transient time-dependent process than a final outcome.

The third agreement is that QoL is a *multidimensional* concept. The four basic components of the concept of QoL are physical and psychological well-being, social relations and functional capacity. Although additional components (e.g., role performance, economic status, and spirituality) or subcomponents (e.g., sexuality, body-image, self-esteem) to the main components are often being suggested, these four are generally considered to provide the core elements of the conceptual framework of QoL research.

Purpose of QoL evaluation

The general purpose of QoL assessment in medicine in general and in cancer more specific is to provide more accurate assessments of the well-being of individuals or groups of patients and of the benefits and losses that may result from medical treatment. The focus of study can be to describe QoL in individuals or in certain populations, to measure changes in QoL over time, to compare QoL in different populations, or to predict future QoL outcomes.

Although the broad area of potential applications seems to imply that QoL assessment is indicated in most medical studies, it is obvious that QoL data are more relevant in some cases than in others. The European Organisation for Treatment and Research of Cancer (EORTC) considers QoL to be a possible relevant outcome parameter in randomised phase III studies if:

1) important improvements of overall, recurrence-free, or systemic disease-free survival realistically cannot be expected to occur as a result of treatment, but significant changes or differences in at least one aspect of QoL are expected to occur;

2) one treatment demonstrates a better survival, but produces more severe toxic effects;

3) with or without treatment the disease site is associated with an extremely poor prognosis;

4) a treatment is known to be burdensome for patients;

5) a new (invasive) treatment is to be evaluated.

Measurement of QoL

If QoL is to be evaluated in a clinical study, a number of decisions have to be made concerning the design and methodology of measurement.

Design of the study

There are three main designs to evaluate the effects of treatment on QoL: by means of a cross-sectional study, a prospective cohort study, and a randomised clinical trial. The first consists of a single point evaluation at a certain interval after intervention. Although this method is relatively quick, easy, and inexpensive to conduct, it also has a number of drawbacks since the type of information obtained is limited due to the fact that data are obtained in a single point assessment. It will neither provide insight into the dynamics of the concept, nor into the magnitude of the changes or the differences between the populations. As it is now generally acknowledged that QoL changes as a function of time, a prospective cohort study is to be preferred over a cross-sectional, single point assessment. Obvious-

ly, when QoL is measured to evaluate and compare therapeutic efficacy, a randomised clinical trial is the preferred strategy. Although a few years ago QoL assessment in randomised clinical trials was more the exception rather than the rule, at present it is becoming a well accepted outcome measure.

Relevant components

As stated earlier, QoL assessment includes the evaluation of minimally four components (functional status, physical, psychological, and social well-being). In addition, other components or subcomponents can be considered relevant outcomes, depending on the specific context and the objectives of the study. The selection of these additional (sub)components can be based on expert opinions, patient interviews, reports in the literature, or can be selected based on their face validity.

Instruments of measurement

Although criteria for QoL assessment in general and selection of proper QoL instruments in particular have been formulated in the literature, the important feature remains that no gold standard exists. Instruments that have proved to meet all criteria when applied in one application may be less appropriate or even inappropriate in another. Nevertheless, there is consensus about some general criteria an instrument has to meet.

First, the instrument should have proven, good psychometric properties with respect to validity, reliability, and responsiveness to change. The latter refers to a combination of both reproducibility (i.e., identical scores in stable subjects over time), and sensitivity (i.e., the ability to demonstrate changes when the subject's state of health improves or deteriorates) (Guyatt *et al.*, 1987). Second, it should be simple, brief, and easy to administer. The rationale behind this second criterion is that these properties enhance both participation and compliance, and that they reduce both patient and staff burden. It is mainly for practical and economic reasons that a self-assessment questionnaire is preferred to a person-to-person interview.

Broadly speaking, there are three basic types of instruments: generic, disease specific and domain specific. Generic instruments focus on the main components that constitute QoL, and they are intended to be applied in a wide range of health states. This last characteristic is at the same time the main advantage of generic instruments. However, generic instruments have the disadvantages that they may not be very responsive to changes in clinical status, and they may not always focus on the most critical health outcomes of interest (Revicki & Kaplan, 1993).

Disease specific instruments have been developed especially to detect subtle, disease related effects. However, these instruments have the disadvantages that comparison of results can only be made across studies in specific populations.

Domain specific questionnaire are even more limited in their scope since they focus on one particular aspect of QoL. Examples of such questionnaires are body image, sexual functioning, or treatment related side-effects.

Timing of measurement

Since QoL is a dynamic process the timing of the assessments must be carefully scheduled. Both the number and timing of assessments have to be decided upon at a case-to-case base. They largely depend on the research question, the characteristics of the population and circumstances such as logistics and finances available. However, in broad terms it can be stated that a minimum of three assessments is usually required in randomised clinical trials to capture relevant changes in QoL over time. The first assessment is to serve as a baseline measurement and should take place prior to the start of treatment and preferably also prior to randomisation. A second assessment is performed during treatment to capture the side-effects of treatment. The timing of this assessment is usually the moment at which the side-effects are expected to be at their height. A final assessment is performed at follow-up after treatment to account for long-term effects.

Problems and limitations

Although the field of QoL research is developing rapidly, there are also a number of problems and limitations to the present approaches and possibilities. Most cancer clinical trials are being conducted in a multicenter and often also in a multinational setting. These characteristics imply specific problems and require specific measures to ensure a good quality of the data. For instance instruments to measure QoL have to be available in the various languages and have to be validated in the different cultures. Also, the institutional settings differ high-

ly with respect to logistics and organisation which requires special measures to ensure good quality of data since missing forms or missing data are, by definition, irretrievable.

Another issue is the analysis and interpretation of results. As QoL research is a rather new field of research there is not yet a large data base available to compose reference scores. In cancer clinical trials QoL is mostly evaluated between treatment arms in a longitudinal design. But what are significant changes over time? Surely statistical significance is not identical to clinical significance. A clinically meaningful change is statistically significant, but a statistically significant change is not always clinically meaningful.

Many of these problems can be expected to be resolved in the near future as guidelines for datacollection and more data become available. However, the limitations are mostly inherent to the approach and hence more pertinent in character. Whereas in the earlier days of QoL research the main emphasis lied on the description of QoL within a certain context (i.e. disease and intervention), one can now observe a shift of study purpose towards evaluation and comparison of medical interventions. As a consequence of the growing medical possibilities and demands on one hand and limitations in health care expenditures on the other hand choices in health care are becoming inevitable in Western societies towards the 21st century. This necessity of making choices becomes apparent at three different levels: the macro level for policy making, the meso level for decisions related to the medical treatment of groups of patients, and a micro level for decisions concerning the individual patient.

An important consequence of the shift towards more decisional purposes of QoL evaluation is that the instruments of measurement have to meet other requirements. To compare treatment options (and eventually combine them with other parameters such as length of life and costs data) QoL has to be expressed in a single, numerical value that is a measure of the net effect balancing both positive and negative effects of treatment. Thus as such, it includes a valuation of the consequences.

Priorities for the near future

Although much progress has been made during the last decade, there is still a long way to go before QoL evaluation can be regarded as an integrated part of standard cancer clinical practice. The rapid growth of the number of studies that include QoL as an endpoint may reflect the increasing awareness and importance of the subject on the part of the investigators, but has also pointed out more clearly the flaws and shortcomings in this new field of research. The EORTC has set the following priorities for its activities related to QoL issues.

Good quality studies

It is extremely important to have a good infrastructure and a standard approach to the collection and analysis of QoL data. To ensure adequate rates of patient accrual, compliance, and data quality, there is an urgent need for a number of standard data management strategies. These include implementation procedures, detailed instructions for data collection, explicit instructions on the administration of QoL instruments, regulations on coding of data and interpretation of missing data and incomplete forms.

Analysis and interpretation of data

An important fact is that there is no optimal method for analysing QoL data. Several methods can be used and perhaps should be used to provide better insight into the data. However, each method has its advantages and disadvantages, and different models have different assumptions that are not always met.

The interpretation of results is impeded by the lack of standards concerning what can be considered as a clinically important change in any QoL score, and the absence of standard methods to define effect sizes and to calculate sample size requirements. An important step forward would be the availability of large datasets that can be utilised in future trials for the computation of expected differences and sample sizes.

A final methodological issue relates to the integration of different outcome measures. As stated previously, cancer clinical trials have a history of parameters, all related to length of life outcomes. Further development of methods to combine length of life with QoL data is both warranted and a major challenge. Since resources for health expenditure are becoming more restricted, health economic issues have become increasingly important, also in cancer clinical trials. Combining economic data with quality and length of life data will therefore become increasingly important.

Theoretical issues

Although it has become virtually impossible nowadays to keep up with the stream of publications of empirical studies on QoL issues, the theoretical foundation and framework on QoL is still rather weak. QoL is a dynamic concept like illness. However, the way and degree these two concepts interact with each other, and which other additional factors may have an influence is still largely unknown. One such additional factor is the unknown role culture plays in QoL issues.

Conclusion

In conclusion it can be stated that during the past few years much progress has been made in the field of QoL research. Sound instruments have been developed to measure QoL and guidelines have been made on the conduct of QoL evaluation in cancer clinical trials. However, there is still a long way to go before QoL assessment has become an integral part of cancer therapy evaluation.

As we move towards the 21st century, medicine in general and oncology in particular are facing major shifts in purpose of research and health care. The progress in medical technology and the parallel growing demand of health care lead to a continuing increase of costs that become more and more difficult to afford. Hence, making decisions, setting priorities, and allocation of health care resources become inevitable. To be able to make adequate decisions, information about illness and the expected consequences of treatment is a necessary prerequisites. In this context, information concerning the expected QoL as a medical outcome is highly relevant.

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Quality of life after neck-dissection: Comparison of the oncological and functional results of the radical and modified radical neck dissection in patients with head and neck carcinomas

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The most significant prognostic factor in patients with head and neck cancer is the presence of cervical node metastases. Indications for the various techniques of neck dissection can undergo substantial variations according to the metastatic status found, biological aggressiveness of tumour, nodal volume and personal viewpoint of the attending clinician. Authors discuss the indications and contra-indications of the various surgical techniques of neck dissection and evaluate long-term results. The present paper reports on clinical experience with radical neck dissection (RND), modified neck dissection (MRND) and selective neck dissection (SelND). Between 1986-1994 623 patients with the tumors of the oral cavity, pharynx, larynx and paranasal sinuses were treated at our department. The data, such as age, gender, neck nodal stage, tumour grade and localisation of primary tumour were recorded. Neck dissection was performed in 511 cases, 351 RND, 135 MRND, 25 SelND. In 32 cases, bilateral neck dissection was performed. Neck dissection was performed in 249 patients with persistent node metastasis after radiotherapy. Survival, neck control rates and other factors in patients who had a RND, were compared with those who had MRND. Regional lymph node metastases of head and neck cancer occur in predictable pattern. Based on these patterns of nodal metastasis, the recommendations for the use of modifications of neck dissection are represented.

Key words: head and neck dissection; quality of life

Introduction

The most significant prognostic factor in patients with head and neck cancer is the presence of cervical node metastases. Indications for various techniques of neck dissection can undergo substantial variations according to the metastatic status found, biological aggressiveness of the tumour, nodal volume and personal experiences of the surgeon. Management of the neck in cancers of the upper aerodigestive tract continues to be a topic of great debate.

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In addition to lymph node metastases, survival is related to the site and stage of the primary tumour, histological pattern of invasion, status of the resection margins and, for patients with metastases, the number and anatomical level of positive nodes, and the presence and extent of extracapsular spread. These pathological features are important indicators of tumour behaviour and should be incorporated into protocols for assessment of prognosis. Although computed tomography and magnetic resonance imaging have contributed to the ability to identify metastatic disease in head and neck cancer, inadequacies in evaluating lymphadenopathy still exist. The accuracy of preoperative diagnosis of cervical lymph-node metastasis in head and neck cancer was assessed with physical examination and

– in some cases – CT assessments of the metastatic status.

Radical neck dissection (RND) is the standard treatment for cervical metastases at head and neck cancer. Although effective, RND produces significant morbidity. In an effort to reduce this morbidity, modifications of RND have been developed. These modifications can be comprehensive yet they spare some or all of the nonlymphatic structures removed by RND (MRND), or they can remove less than all the lymph node groups and are termed selective neck dissections (SelND).

Material and methods

Between 1986-1994, 623 patients with the tumours of the oral cavity, tongue, pharynx, larynx and paranasal sinuses were treated at our department. The localisation of the primary tumor is shown in Table 1.

Table 1. Localization of 442 primary tumors

Larynx	77	
Glottic		15
Supraglottic		43
Transglottic		19
Hypopharynx	87	
Mesopharynx	135	
Tonsillo-lingualis	92	
Palatum molle		10
Radix linguae		33
Cavum oris	89	
Lingua		47
Sublingua		42
Epipharynx	10	
Other tumours of the neck	44	

Neck-dissection - primary or secondary - was performed in 511 cases on 442 patients (in 69 cases bilateral neck dissection was performed) (Table 2).

Table 2. Block-dissection (primary and secondary) by the year of performance

	Primary	Secondary			Total
		After Irradiation	After Operation	Sec. Total	
1986	6	1	4	5	11
1987	15	6	6	12	27
1988	10	11	3	14	24
1989	14	15	3	18	32
1990	28	29	10	39	67
1991	39	39	8	47	86
1992	34	37	10	47	81
1993	48	41	11	52	100
1994	59	18	6	24	83
	253	197	61	258	511

Among them, there were 362 men and 80 women, with a median age of 53 years. Bilateral radical neck dissection in one stage was not performed. Frequently, the internal jugular vein was saved, and when the extension of the metastases admitted a modified neck dissection was performed. The histological finding in most cases was squamous cell carcinoma of different grade. Patients were monitored until recurrence of neck disease, or for a period of 2 years or longer. Salvage surgery for radition or surgical failures was refused by 258 patients.

Hundred and five patients with clinically negative neck had undergone modified neck dissection. In our opinion, selective removal of lymph node groups by MRND and thus saving important structures (e.g. the internal jugular vein, XI nerve, and sternocleidomastoid muscle) in clinically positive necks are appropriate in many patients. Careful selection of the types of neck dissection and judicious use of postoperative radiation therapy can optimise cure rates as well as functional and cosmetic results.

Results

Seventy-five patients, had regional recurrence most of them (45%) were seen after N3-neck operation.

Table 3. Recurrence rate by the method of neck dissection

	Block-Dissection	Regional Recurrence	
RND	351	63	18%
MRND	135	11	8%
SelND	25	1	4%
	511	75	15%

Table 3 shows the recurrence rate by the metod of neck dissection.

Nodal metastases of head and neck cancer occur mostly in predictable patterns in draining lymph nodes. Based on these patterns of regional metastases, recommendations for the use of modifications of neck dissection are presented. After MRND, the function of the arm is intact, the cosmetic result of the neck is better and there is no swelling of the face, pain and weakness of shoulder.

Discussion

Radical neck dissection is a standard treatment for cervical metastases in head and neck cancer. Modi-

fications of the neck dissection reduce the risk and the mortality of the operation. In squamous cell cancers of the head and neck with either clinically negative neck or N1 stage, MRND is an adequate node sampling procedure. Quick-frozen section and histology during the operation help to determine the radicality and extension of neck dissection. Both inadequate and excessive surgery can be harmful for patients. Modified neck dissection which preserves the uninvolved accessorius nerve in the clinically positive neck in selected cases does not adversely affect survival or regional recurrence. In the clinically positive neck (N2-N3) comprehensive neck dissection with preservation of the spinal accessory nerve is oncologically sound.

Modified neck dissection which is less distressful for the patient and produces better cosmetic and functional results. It can only be applied if it does not compromise the radical approach to the treatment of the tumour disease.

Having made a great number of operations our experience is that MRND is oncologycally sufficient. In N0-N1 cases and in selected patients for N2 neck with pre- or postoperative irradiation can be effectively performed. The quality of life of the patients after MRND is better, because we have saved some anatomical structures and produced satisfactory cosmetic and functional results.

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Voice quality after radiation therapy of early glottic cancer

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Radiation therapy is generally accepted as a successful treatment modality for early glottic cancer offering an acceptable voice quality after the treatment. In order to evaluate objectively the voice quality in irradiated patients and to eliminate the influence of decreasing voice quality as a result of normal aging, the results of the acoustic analysis of voice in 20 patients with early glottic cancer treated with radiation therapy were compared to the results of 20 age-matched volounteers. The results established worse voice quality in the irradiated group but the difference was not significant except in amplitude perturbation quotient which expresses the instability of loudness.

In order to identify the factors which could influence the quality of voice after irradiation of the laryngeal carcinoma, the results of laryngoscopy and video-endostroboscopy, the data about the tumor extension and the biopsy extension, were correlated with the results of the perceptive voice evaluation and the results of acoustic voice analysis. No significant influence of the stated factors on the voice quality of the patients was established. Only the irregular glottic gap during phonation indicated to be connected with very hoarse voice.

In conclusion, radiation therapy of early glottic cancer results in an abnormal, but still satisfactory voice quality when compared to the voice quality of normal age-matched speakers. The hoarseness is the result of instability of pitch and specifically the instability of amplitude (loudness). The voice quality after the treatment can be influenced by the tumor extension and localization, the sequels of excisional biopsy, and the radiation therapy or functional disorder. All the stated factors are very intermingled and are probably acting together.

Key words: laryngeal neoplasms-radiotherapy; glottis; voice quality

Introduction

In the last twenty years, the incidence of laryngeal cancer is increasing.[1] According to the data of the Cancer Registry of Slovenia, there are approximately 30 new patients with early glottic cancer (T1NoMo and T2NoMo) every year.

Surgery and radiation therapy are successfull treatment modalities for early glottic cancer. Similar cure rates have been reported by some authors who used either conservative surgery or radiation.[2-5] According to clinical experience, surgical treatment of early glottic cancer often results in not the best voice quality.[6,7] Therefore, with respect to the voice quality, radiation therapy has been generally accepted as more suitable primary treatment modality in early glottic carcinoma.

As glottic cancer is still characteristic for males after 45 years of age, the natural process of aging of the larynx and the voice should also be considered in the evaluation of the voice quality after radiation therapy.

The aim of this study was objective evaluation of the voice quality after radiation therapy of early glottic cancer. In order to eliminate the influence of decrease of the voice quality as a result of normal aging, 20 age-matched pairs of subjects were included into the study. The goal

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of the study was also to determine which factors could influence the quality of voice after irradiation of the laryngeal carcinoma.

Patients and methods

Twenty male patients with T1 (17 patients) or T2 (3 patients) glottic cancer who were irradiated 1 to 10 years ago were included into the study. Their age ranged from 43 to 74 years (mean: 59 years).

In 10 patients, less than one half of one vocal fold was involved. Cancer extended over more than one half of one vocal fold in 7 patients and over both vocal folds in 3 patients. In 2 patients the anterior commissure was infiltrated.

For histologic evaluation of the glottic tumor, a punch-biopsy was performed in 13 patients, and an excisional biopsy was performed in 7 patients. In all of them, squamous carcinoma was assessed.

Ten patients were irradiated with 2 Gy per fraction, and 10 patients were irradiated with 2,2 Gy per fraction, five fractions per week. The prescribed tumor dose was from 61 to 68 Gy (median: 66 Gy), delivered over 33 to 48 days (median: 44 days).

The control group consisted of 20 age-matched male subjects without subjective voice disorders who were not irradiated in the neck region. Their age ranged from 42 to 74 years (mean: 58 years).

In the patients with glottic cancer who were treated with radiation therapy, mirror laryngoscopy and stroboscopy with video-telescope Storz and stroboscope Atmos were conducted to assess the morphologic changes on vocal folds (ranging from 1=no changes to 5=very severe), the vibration of the vocal folds and the glottic closure during phonation (1=complete closure, 2=narrow gap, 3= irregular gap). Signs of laryngeal muscles misuse during phonation were established as present or absent.

In the patients and the control subjects, a voice analysis was performed. A voice sample of sustained vocal "a" in duration of 3 seconds was recorded for further analysis in terms of determination of its pitch, stability of pitch and amplitude (loudness), and presence of noise. The sample was analysed with a Multi-Dimensional Voice Program (Computerized Speech Lab, Kay Elemetrics, USA) and 6 different variables were measured. First of the variables was the mean fundamental frequency (Fo). The second was the pitch perturbation quotient (PPQ) which measures the short-term (cycle-to-cycle) irregularity of pitch. The third variable was the coefficient of Fo (vFo) which reflects the very long-term variation of Fo within the analysed voice sample. The fourth was the amplitude perturbation quotient (APQ) which measures the short-term irregularity of the peak-to-peak amplitude (loudness) of the voice. The fifth variable was the coefficient of amplitude variation (vAm) which reflects the very long-term amplitude variation within the analysed voice sample. The last variable was noise-to-harmonic ratio (NHR) which is a general evaluation of noise present in the analysed signal.

The voices of the irradiated patients were evaluated by an experienced phoniatrician. The perceptive evaluation ranged from 1 for normal voice to 5 for aphonia.

The results of voice analysis in the irradiated patients were compared to the results in the control subjects. In order to identify the factors which could influence the quality of voice after irradiation of the laryngeal carcinoma, the results of laryngoscopy and video-endostroboscopy, the data about the tumor extension and the biopsy extension, were correlated with the results of the perceptive voice evaluation and the results of acoustic voice analysis. The t-test for pairs and different regression models of the statistical package Statistica v.5.0 were used.

Results

The results of voice analysis showed that all the studied variables were more abnormal in the irradiated patients than in the control subjects but no significant difference was assessed in most of them. The only variable that showed significant difference was APQ. (Table 1).

Table 1. Comparision of the variables of the acoustic voice analysis in the patients with glottic cancer who were irradiated (N=20) and in the control subjects (N=20)

Variable	Irradiated patients mean value (stand. dev.)	Control subjects mean value (stand. dev.)	p
Fo	147.55 (35.13)	141.50 (31.61)	0.51
PPQ	0.70 (0.51)	0.49 (0.37)	0.18
vFo	3.26 (4.86)	1.46 (0.72)	0.12
APQ	3.84 (1.74)	2.54 (1.18)	0.00*
vAm	14.52 (7.02)	11.88 (5.52)	0.20
NHR	0.14 (0.05)	0.14 (0.02)	0.92

According to the phoniatrician's perceptive evaluation of the voices of the irradiated patients, 1 subject had normal voice, 8 subjects had slightly hoarse voices, 9 subjects had hoarse voices and 2 subjects had very hoarse voices.

Signs of laryngeal muscles misuse were present in 13 subjects among 20 irradiated patients.

Almost no differences were found when the results of the perceptive evaluation of the patients' voices were correlated to the tumor extension, to the biopsy extension, to the morfologic changes on vocal folds, and to the signs of laryngeal muscles misuse during phonation. The only notable difference was found with the correlation of the perceptive voice evaluation to the completeness of the glottic closure. The difference could not be considered as statistically significant because of the small number of the studied patients. (Table 2).

Table 2. Correlation of the results of the perceptive voice evaluation to the tumor extension, to the biopsy extension, to the morfologic changes on vocal folds, to the signs of laryngeal muscles misuse during phonation, and to the completeness of the glottic closure in the group of irradiated patients (N=20)

Correlated variable	Normal or slightly hoarse voice (No. of patients)	Hoarse or very hoarse voice (No. of patients)
Tumor extension:		
less than 1/2 of one vocal fold	4	5
more than 1/2 of one vocal fold	5	6
Biopsy extension:		
punch-biopsy	6	7
excisional biopsy	3	4
Morphologic changes on vocal folds:		
slight	5	3
severe and very severe	4	8
Laryngeal muscles misuse:		
present	5	8
absent	4	3
Glottic closure:		
complete closure or narrow gap	8	8
irregulare gap	1	3

With the correlation of the results of the acoustic analysis of the voice samples of the irradiated patients to the tumor extension, to the biopsy extension, to the morfologic changes on vocal folds, to the signs of laryngeal muscles misuse during phonation, and to the completeness of the glottic closure, no differences were showed. (Table 3).

Table 3. Correlation of the results of the acoustic analysis of the voice samples to the tumor extension, to the biopsy extension, to the morphologic changes on vocal folds, to the signs of laryngeal muscles misuse during phonation, and to the completeness of the glottic closure in the group of irradiated patients (N=20)

Correlated variable	Fo p	PPQ p	vFo p	APQ p	vAm p	NHR p
Extension of the tumor	0.78	0.35	0.48	0.89	0.41	0.15
Extension of the biopsy	0.64	0.25	0.98	0.19	0.08	0.15
Morphologic changes on the vocal folds	0.42	0.63	0.64	0.84	0.25	0.19
Laryngeal muscles misuse	0.99	0.52	0.35	0.77	0.19	0.06
Glottic closure	0.92	0.54	0.44	0.47	0.17	0.52

Discussion and conclusions

The results of the study assessed that in the patients who were irradiated because of early glotttic cancer, the voice quality was slightly worse than in the age-matched control subjects. Only in one variable - APQ which expresses the instability of amplitude (loudness) of the voice showed to be statistically significant.

The results of the present study did not confirm the influence of the cancer extension, the biopsy extension, the signs of laryngeal muscles misuse during phonation, and the morphologic changes on vocal folds on the voice quality. The completeness of the glottic gap indicated to be important for the voice quality, the irregular gap being connected with hoarse voice.

Most of the authors reporting about the voice quality after the radiation therapy of early glottic cancer assessed abnormal voice after the treatment. Better results were obtained when the patients themselves evaluated their voices. They assessed normal or nearly normal voice in 76%[8] or even in 83% of them.[9] Worse results were established when the voices were evaluated by a professional. Morgan et al.[10] reported that speech and language therapists had found voice abnormalities in all studied irradiated patients. Similar results were established in the present study where the voice of only one patient was evaluated as normal.

As glottic cancer is still characteristic for males after 45 years of age, the natural process of aging of the voice should also be considered in the evaluation of the voice quality after radiation therapy. The

structural changes in the cartilages, ligaments, muscles, mucous membranes of the larynx, the decrease of pulmonary function, the degenerative changes in the resonance tract, the deteriorating nervous control of breathing, phonation and resonance appear and result in changes of pitch, decrease of loudness and pitch range, increasing instability of pitch and amplitude, and voice fatigue.[11] In the present study, the voices of irradiated patients were compared to the voices of age-matched volounteers. The acoustic analysis of all the studied voice samples of the patients and the volounteers established at least minor abnormalities in the stability of pitch and amplitude. The voices of irradiated patients were more unstable but the differences were not significant. Only APQ which expresses short-term irregularity of amplitude (loudness) showed to be significantly worse in the irradiated patients.

The results of other studies are similar. Hirano *et al.*[12] reported about abnormal APQ in one third of the irradiated patients. Lehman et al.[13] established significant difference in stability of pitch and amplitude of the voices of the irradiated patients in comparison with the voices of the volounteers. However, they found no differences in Fo in both groups of the studied subjects, as was also the case in the present study.

Some authors tried to evaluate which factors influenced the quality of voice after the radiation therapy of early glottic cancer. Lehman *et al.*[13] studied the influence of irradiation technique, the depth of biopsy, and the tumor localization on the results of acoustic analysis of voice and established no significant differences. The signs of laryngeal muscles misuse during phonation was assessed in 13 among 20 studied subjects. On the other hand, Benninger *et al.*[14] showed that complications during irradiation, the excisional type of biopsy, and the bilateral involvment of vocal folds are connected with bad voice quality.

In the present study, adverse influence of the tumor extension over more than one half of one vocal fold, the excisional biopsy, and very severe morphologic changes on vocal folds on voice quality was not proved. Only the irregular glottic closure during phonation (not always connected with very severe morphologic changes of vocal folds) was more often observed in very hoarse patients than in patients with better voice. What was the cause of a tissue defect or a scarr at the edge of one or both vocal folds was not established. The possible factors could be: the tumor localization or deeper infiltration, the depth of biopsy or the individual inflammatory and scirrhous response to tumor and radiation. The signs of functional disorder were established in 13 patients, therefore, the reason for bad voice quality could also be the misuse of laryngeal muscles in phonation. We can speculate that the combination of all the stated factors influence the voice quality after radiation therapy of early glottic cancer. The results of the study can only indicate the problem due to small number of included subjects.

In conclusion, radiation therapy of early glottic cancer results in an abnormal, but still satisfactory voice quality when compared to the voice quality of normal age-matched speakers. The hoarseness is the result of instability of pitch and specifically the instability of amplitude (loudness). The voice quality after the treatment can be influenced by the tumor extension and localization, the consequences of excisional biopsy, the radiation therapy or functional disorder. All the stated factors are very intermingled and are probably acting together. The role of every factor was not established yet, for this reason, a study on greater number of patients is neccessary to improve the phoniatric approach to the patients with early glottic cancer.

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Functional results after partial vertical laryngectomy

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There is an increasing popularity of the organ sparing (OS) approaches to tumour treatment also in the head-neck (HN) surgery, as these methods at the same time aim to fulfill the requirements of radical approach in oncology, yet with less aggressive surgery. Partial vertical laryngectomy (PVL) is a preferred OS method in the treatment of certain glottic malignancies. Patients soon get accustomed to their usual surroundings, but a significant deterioration of voice quality is unavoidable. In this work, we studied the act of swallowing and the effectiveness of voice therapy after PVL of various extents.

Methods: Between 1986 and 1996, the authors performed 51 PVL-s, 16 chordectomies (3 with conventional surgery and 13 with laser) and 35 hemilaryngectomies of various extents for the treatment of T1-T2 glottic tumours. The act of swallowing was tested by videofluorography on the 7th postoperative day and 8 weeks after surgery. Phoniatric therapy started immediately after the wound was healed: exercises were identical to the accepted exercises for recurrent laryngeal nerve paresis. The patients were called for indirect and direct (flexible Faryngo-Naso-Laryngoscope®, PENTAX) laryngoscopic control every week. Voice quality parameters (phonatory duration, vocal range, fundamental speech frequency) were examined before starting and 8 weeks after phoniatric therapy. Voice recordings were spectrographically analyzed, too.

Results: A marked aspiration was observed by videofluorography in 61 % (31/51) of the patients on the 7th postoperative day. The aspiration showed no correlation with the type of surgery. Eight weeks after surgery, all patients could swallow satisfactorily without any functional disturbance.An improvement in voice quality was deteced 2-3 months later; the phonatory duration and vocal range were extended. In normal social conversations the voice was audible, yet more or less hoarse in spite of the voice therapy.

Conclusions: After PVL the laryngeal closure seems to be preserved enough to prevent aspiration in all patients and allows oral feeding at will. On the basis of our data we can also conclude that the voice that seems better from the subjective point of view also shows better acoustical structure by objective analysis. The voice after OS laryngeal surgery is satisfactorily audible in normal social conversations, though more or less hoarse in spite of voice therapy.

Key words: laryngeal neoplasms; laryngectomy-methods; voice quality; speech therapy

Introduction

In case of malignant laryngeal tumour it is very important to select the type of surgery that is oncologically suitable but affects as small part of the larynx as possible.[1,2] The function preserving approach, trying to preserve the voice of the patients is becoming increasingly widespread in laryngeal surgery.[3-5] After the wound is healed, it is very important to help the patients to re-accustom to their surroundings as soon as possible and to regain their work abilities. Partial laryngectomy allows unhindered breathing without a tracheostoma thus allowing faster returning to the usual life. The quality of voice drops significantly after surgery. After partial vertical laryngectomy, voice can be formed only if the preserved side of the larynx finds some support on the resected side. In this type of surgery, the postoperative scar and the vocal cord of the

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preserved side usually form the glottis.[6] On the other hand, with the preserved laryngeal closure the aspiration during swallowing may be avoided and oral feeding allowed.[7,8]

In this work, we studied the act of swallowing and the possibilities of voice therapy and speech rehabilitation after partial vertical laryngectomy of various extents.

Patients and methods

Between 1986 and 1996, 51 partial vertical laryngectomies for T1 carcinomas of the larynx were performed at our department. The number of chordectomies was 16; 3 of these were done with traditional surgical methods and we have used surgical lasers in the other 13 cases. Twelve frontolateral vertical resections were performed, while among the other 23 hemilaryngectomies, there were 8 Moser type and 15 Hautant type interventions. The mean age of the patients was 57 years (31-74) at the time of the surgery. There were 48 male and three female patients. The results of the histologic examination showed in all cases squamous cell carcinoma.

After the removal of the endolaryngeal tampon and the closing of the temporary tracheostoma we were monitoring the condition of the larynx by indirect laryngeal examination and started with the voice exercises aimed at forming the best possible voice quality as soon as possible. The postoperative *voice therapy exercises* were practically identical to the accepted voice exercises for recurrent nerve paresis:[3,4,9] 1. hard voice-starting exercises; 2. voluntary coughing exercise; 3. phonation of deep voices, Gutzmann's subtonal grunting; 4. digital compression to increase the adductive tendency of the intact vocal cord; 5. head turning exercises for decreasing voice cord level inequality.

The voice exercises were performed first under permanent control then later independently, at home several times a day and the patients were called in for a laryngoscopic control examination every week. The exercises were modified according to the results of the laryngoscopic examination. After complete wound healing and the subsequent 2-3 month voice therapy, the voice characteristics (frequency of sound speech, phonatory duration, vocal range) were examined. Beside the indirect laryngeal examination, the patients were also examined by a flexible PENTAX Faryngo-Naso-Laryngoscope®. After the completed voice therapy, voice recording was made in a sound-treated room. The recordings were later analyzed with a CSL 50® digital acoustic analyzer up to a frequency of 5000 Hz with a band-width of 146 Hz.

The swallowing ability was tested by videofluorography (100 ml Gastrografin® - Schering, water-soluble contrast material) on the 7th postoperative day and 8 weeks after surgery.

Results

An improvement of the voice quality was noted after about 2 months of voice training, in the beginning only during the exercises, but later in normal speech, too (Table 1).

Table 1. Improvement of some parameters of voice quality after two months of voice training

	normal	after surgery	after voice therapy
Fundamental frequency (Hz)	98–130	90–110	96–118
Phonatory duration (sec)	20–25	5–10	10–15
Vocal range (octave)	2–2½	< 1	1–1½

The fundamental frequency in speech became deeper - according to the larynx condition - due to the turning off the undesirable compensation mechanisms. The improvement of the *phonatory duration* usually indicated a decrease in the glottic closing deficiency, but it was still far from the physiologic range. The ability to modulate might have improved a bit, but the *vocal range* remained narrow in spite of the voice therapy. The *ability to increase voice loudness* also increases due to the relaxation and breathing exercises and the training to increase the speed of the airflow.

The results of the objective analysis and the subjective judgment were identical. The recordings that seemed to have a better acoustical structure as determined by *spectrographic analysis* were also considered subjectively better by the listeners, the speech was more understandable.

A marked aspiration by videofluorography was observed in 61 % of the patients (31/51) on the 7th postoperative day. Aspiration showed no correlation with the type of surgery. All patients could swallow satisfactorily 8 weeks after surgery without any functional disturbance.

Discussion

There were only temporary functional disturbances in the swallowing act among our patients without any correlation with the applied type of organ sparing surgery. After 2 months, the laryngeal closure was healed enough to prevent aspiration in all patients and allowed a normal, oral feeding at will.

The voice condition is checked after the wound has been healed but before the speech exercises. The fundamental frequency in speech usually becomes deeper or similar to the voice of the false vocal cords. Phonatory duration is significantly shorter, the vocal range becomes very narrow, less than 1 octave, the ability to increase voice loudness decreases, the voice becomes faint.[10-12] Speech is an exhausting act due to the high ratio of wasted air caused by the closing deficiency of the glottis. We have observed that the "phonatory dyspnea" is usually characteristic in most of the patient as well as the inspiratory and expiratory phonation. Phonation is made harder by the frequent level difference between the scar of the operation area and the intact vocal cord. Voice training should be started as soon after wound healing as possible to prevent the formation of incorrect helping mechanisms (whispering, forced high pitch or head-voice, strained neck muscles) due to aphysiologic compensation attempts. The purpose of the exercises is to increase the overcompensation activity of the intact vocal cord, resulting in the improvement of the glottal closing deficiency, the intact vocal cord touches the scar or gets significantly closer to it.[7] Voice training must be tailored to each patient's needs. Intensive relaxation exercises are also necessary to compensate high stress of neck muscles caused by the aphysiologic compensation attempt, while the high ratio of air-wasting requires breathing and loudness-increasing exercises.

On the basis of our studies we can state that the voice which seemed better from the subjective point of view showed a better acoustic structure in the objective analysis, too. A very important factor is the success of the voice training aimed at the improvement of voice quality. The patients´ will and belief in the necessity of the treatment is an absolute requirement. There is no definitive correlation between the type of the applied organ sparing surgery and the phonatory defect. The sound quality may be different even in the case of identical operations due to individual differences in the size of the glottis, the extension, rigidity and elasticity of the scar tissue and the compensation abilities. Granulation tissues at the scar area and scary adhesions may spoil voice quality. Still, the voice forming after function preserving laryngeal surgery usually ensures good audibility in normal conversational speech and most of the patients can continue their life without serious problems.

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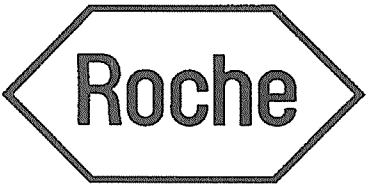

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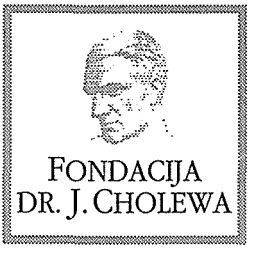

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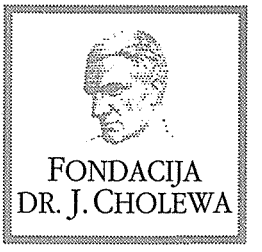


Activity of "Dr. J. Cholewa Foundation" for cancer research and education – report for the first half of 1997

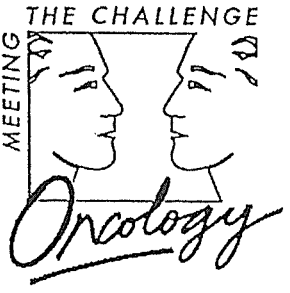
"Dr. J. Cholewa Foundation for cancer research and education continued with its activity as it was outlined at the meetings of the Executive council of the Foundation. The financial report presented by Foundation's President Mr. S. Fatur and the report about its activity in 1996 and a suggestion for the activity in 1997 presented by Dr. B. Štabuc, PhD, were both taken into notice by the members of the council at the meeting that took place in February 1997. As on the meetings that took place during the second half of 1996 it was agreed that the activity of the Foundation should in general be extended and intensified.

The Foundation will in 1997 continue with its policy of providing research and educational grants to those interested in the problems of oncology in the Republic of Slovenia. One or two research grants will be provided to the candidates that will fulfill the criteria as defined by the Foundation. It is possible that in the future the applications for the research grants may be reviewed and assessed in collaboration with noted experts from other countries, as to further the quality of research supported by the Foundation. Educational grants will be awarded to physicians and nurses involved in the treatment of cancer patients and in cancer research. In this way the collaboration can especially be extended with the European School of Oncology from Milan, as it was already agreed on the previous meetings of the Executive council of the Foundation. It was especially pointed out that the possibility of obtaining educational grants from the Foundation should not be limited exclusively to the applicants from major hospitals and medical centers. All the applicants awarded the educational grant for attending a scientific congress, symposium, or courses and meetings organized by the European School of Oncology should in the future be obliged to spread their newly acquire knowledge as much as possible.

The Foundation will continue to support the regular publication of "Radiology and Oncology" scientific journal. In the same way support will be provided for the regular publication of "Challenge", the newsletter of the European School of Oncology. Both these publications offer interesting and relevant scientific information to all interested in the problems of oncology, in the case of "Challenge" specifically with problems associated with countries with scarce financial resources.

The Foundation is grateful to the authorities of the city of Ljubljana for their continous and effective help and goodwill, that has resulted in the opening of its new office.

Andrej Plesničar, MD, MSc
Tomaž Benulič, MD, MSc
Borut Štabuc, MD, PhD



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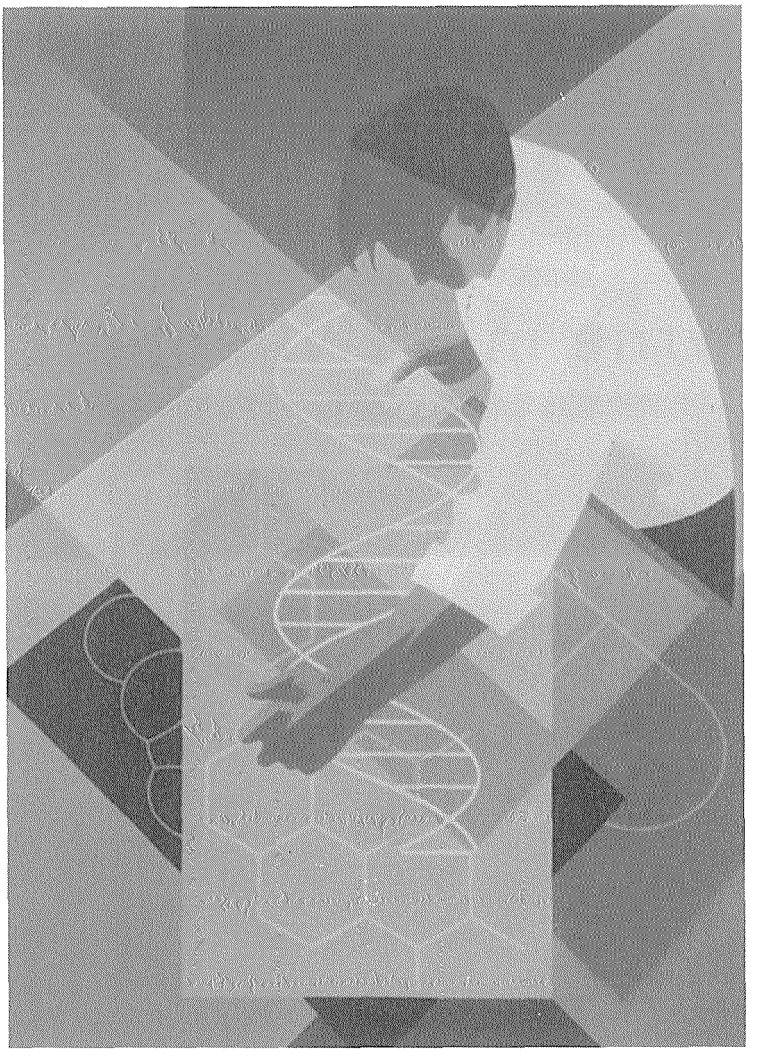

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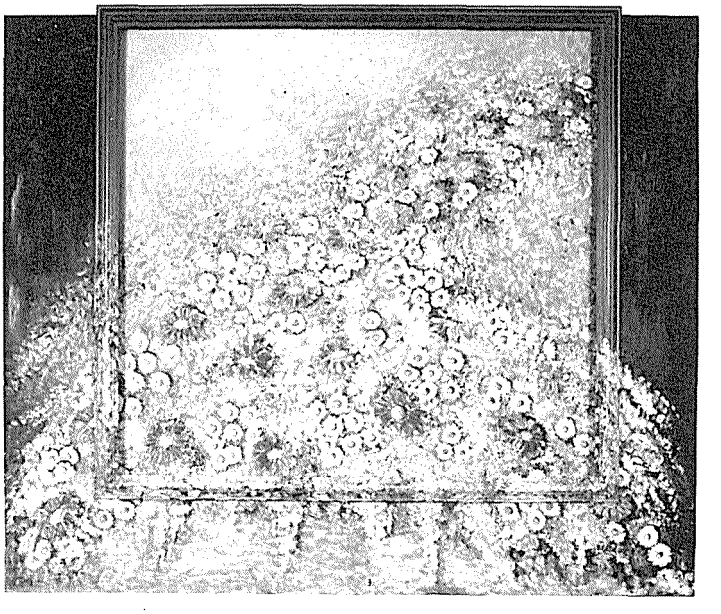

- centralno delujoči analgetik za lajšanje zmernih in hudih bolečin
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Kontraindikacije: Otroci do 1 leta starosti, akutna zastrupitev z alkoholom, uspavali, analgetiki in drugimi zdravili, ki vplivajo na CŽS, zdravljenje z inhibitorji MAO. **Interakcije:** Pri sočasni uporabi zdravil, ki delujejo na osrednje živčevje, je možno sinergistično delovanje v obliki sedacije pa tudi močnejšega analgetičnega delovanja. **Opozorila:** Pri predoziranju lahko pride do depresije dihanja. Previdnost je potrebna pri bolnikih, ki so preobčutljivi za opiate, in pri starejših osebah. Pri okvari jeter in ledvic je potrebno odmerek zmanjšati. Bolniki med zdravljenjem ne smejo upravljati strojev in motornih vozil. Med nosečnostjo in dojenjem predpišemo tramadol le pri nujni indikaciji. Bolnike s krči centralnega izvora skrbno nadzorujemo. **Doziranje:** *Odrasli in otroci, starejši od 14 let:* 50 do 100 mg 3- do 4-krat na dan. *Otrokom od 1 leta do 14 let* dajemo v odmerku 1 do 2 mg na kilogram telesne mase 3- do 4-krat na dan. **Stranski učinki:** Znojenje, vrtoglavica, slabost, bruhanje, suha usta in utrujenost. Redko lahko pride do palpitacij, ortostatične hipotenzije ali kardiovaskularnega kolapsa. Izjemoma se lahko pojavijo konvulzije. **Oprema:** 5 ampul po 1 ml (50 mg/ml), 5 ampul po 2 ml (100 mg/2 ml), 20 kapsul po 50 mg, 10 ml raztopine (100 mg/ml), 5 sveč po 100 mg.

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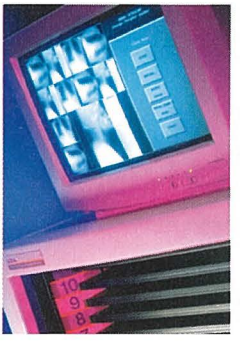

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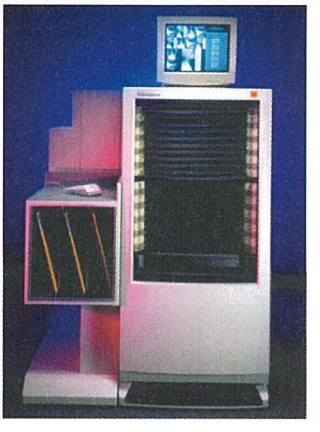

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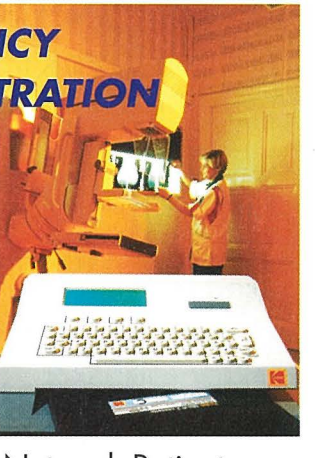

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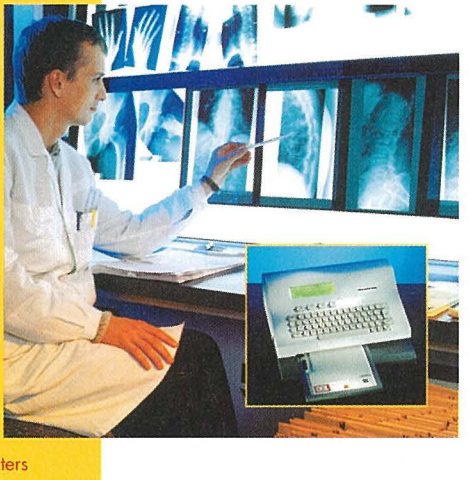

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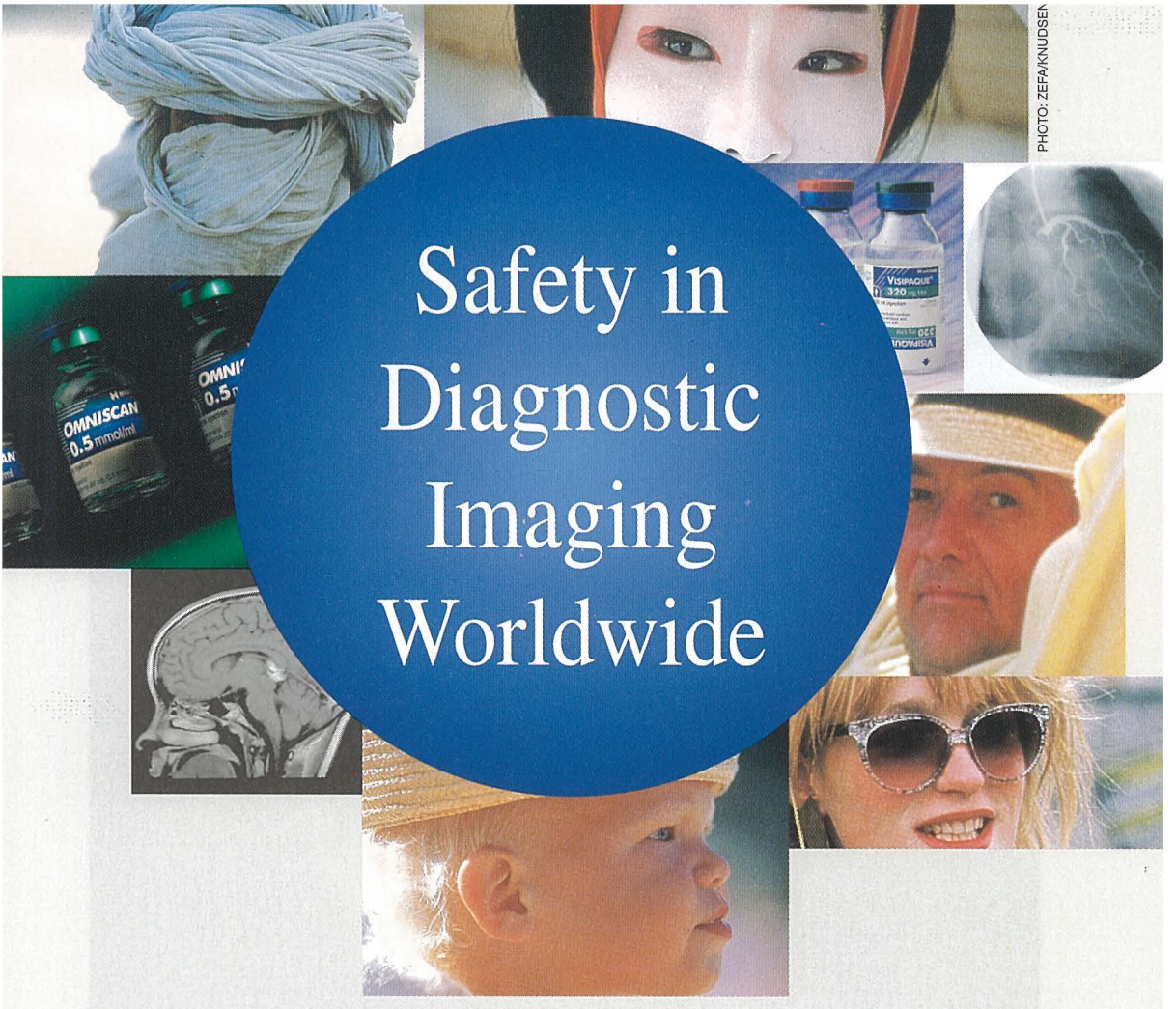

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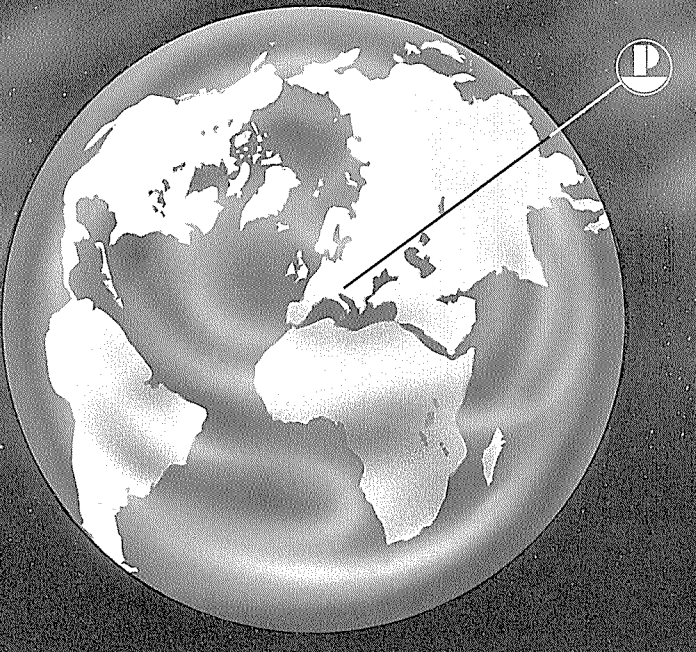

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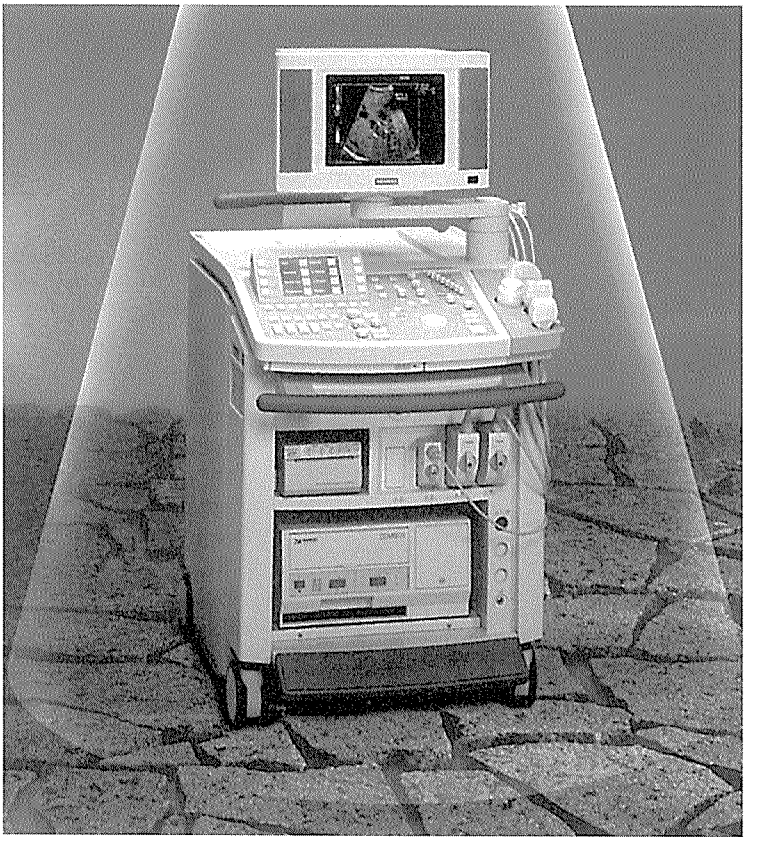

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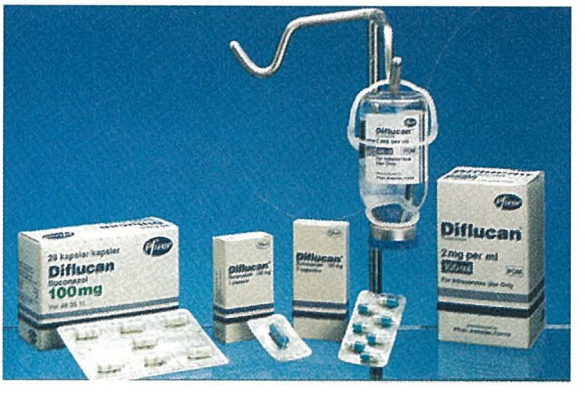

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Indikacije in odmerki: obrni. **Uporaba pri starejših:** kot zgoraj, razen pri ljudeh z ledvičnimi okvarami - glej popolne informacije za predpisovanje. Ne priporočamo uporabe pri otrocih mlajših od 16 let, razen kadar se zdi to lečečemu zdravniku nujno potrebno - glej popolne informacije za predpisovanje in priporočljive odmerke za otroke starejše od enega leta. Bolniki z ledvičnimi okvarami: morda so potrebni manjši odmerki - glej popolne informacije za predpisovanje. **Dajanje zdravila:** DIFLUCAN lahko dajemo oralno ali v obliki intravenske infuzije. Odmerki so pri oben načinih enaki. **Kontraindikacije:** Znana preobčutljivost na flukonazol ali sorodne triazole. **Opozorilo:** Pri bolnikih, pri katerih pride do pomembnega povečanja jetrnih encimov, moramo pred nadaljevanjem zdravljenja z DIFLUCANOM oceniti razmerje med tveganjem in koristnostjo. Poročajo tudi o anafilaktičnih reakcijah. **Varnostni ukrepi:** Ker so na voljo le omejeni podatki, odsvetujemo uporabo pri nosečnicah, razen kadar se zdi to lečečemu zdravniku nujno potrebno. **Dojenje:** ne priporočamo uporabe. **Interakcije z drugimi zdravili:** Potrebno je skrbno spremljanje bolnikov, ki istočasno jemljejo antikoagulanse, oralno sulfonilurejo ali fenitoin, ciklosporin in teofilin. Pri bolnikih, ki istočasno jemljejo rifampicin, so morda potrebni večji odmerki DIFLUCANA. **Stranski učinki:** Najpogostejši stranski učinki so vezani na gastrointestinalni trakt: slabost, abdominalno nelagodje, diareja in vetrovi. Poročajo tudi o kožnem izpuščaju. Pri bolnikih s hudo osnovno boleznijo so med zdravljenjem z DIFLUCANOM in primernimi učinkovinami opazili spremembe v testnih rezultatih ledvičnih in hematoloških funkcij ter bolezenske spremembe jeter, vendar pa sta klinična pomembnost in povezava z zdravljenjem še nepotrjeni.
Na željo posredujemo dodatne informacije. Pred predpisovanjem DIFLUCANA se je potrebno seznaniti s celotnimi informacijami za predpisovanje zdravila.

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Submission of manuscript: Manuscripts written in English should be submitted in triplicate (the original and two copies), including the illustrations to the Editorial Office: *Radiology and Oncology*, Institute of Oncology, Vrazov trg 4, SI-1105 Ljubljana, Slovenia; (Phone: + 386 61 1320068, Fax: +386 61 13 14 180, e-mail: oshrestha@mail.onko-i.si). Authors are asked to submit their manuscripts also on a 3.5" 1.44 Mb formatted diskette. The type of computer and word-processing package should be specified (Word for Windows is preferred).

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Dent RAG, Cole P. *In vitro* maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981, **43:** 486-95.

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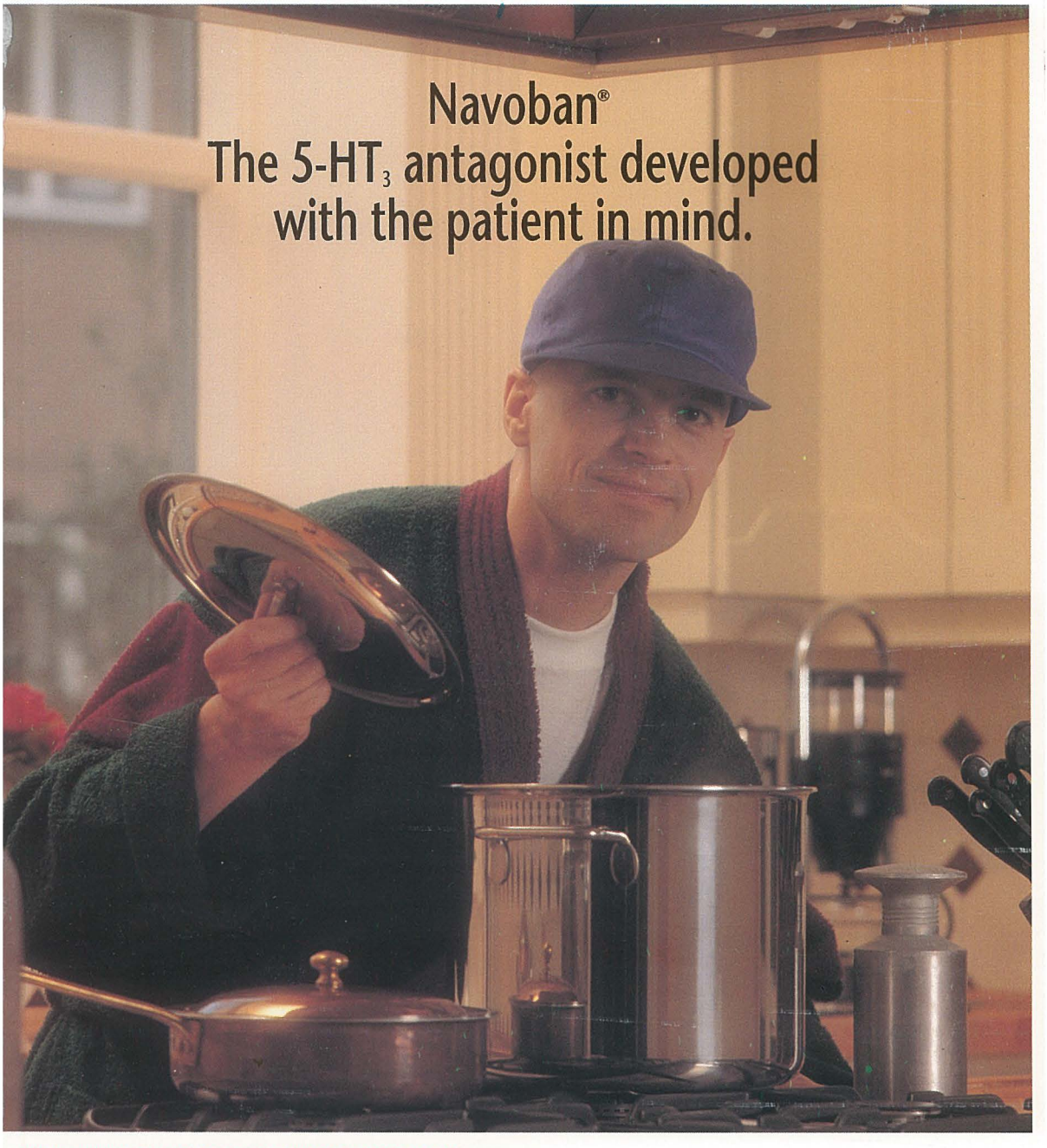

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