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ORGAN SPARING TREATMENT IN ONCOLOGY
September 14-16, 2000
Ljubljana, Slovenia

Radiology and Oncology is covered in *Biomedicina Slovenica, Chemical Abstracts, and EMBASE / Excerpta Medica*

2nd International Symposium on

ORGAN SPARING TREATMENT IN ONCOLOGY

September 14-16, 2000
Ljubljana, Slovenia

Organised by:
Institute of Oncology Ljubljana

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Preface

Tremendous advances have been made in the oncology during the last few decades. The organ sparing treatment approach, which allows for organ preservation leading towards better quality of life without compromising the survival of patients is one of them. New developments in systemic treatment together with improved radiation and surgical techniques resulted in even better survival without the need for extensive and mutilating surgical procedures.

Considering the great importance of organ sparing approach we decided to organize an international symposium on this topic back in 1997. The symposium was greatly appreciated by almost a hundred participants from all over Europe and it was decided to make it a repeating event. Therefore the 2nd International Symposium on Organ Sparing Treatment in Oncology, organized by the Institute of Oncology in Ljubljana, will take place on September 2000 in Slovenia.

The symposium is dedicated to continuos exchange of knowledge and personal experiences in the organ sparing treatment approach among oncologists and other health professionals involved in the care of cancer patients. We have a nice scientific program including six invited speakers and 26 presenters from different European countries who will present their work and expertise on the organ sparing approach in different cancers as well as on the quality of life of patients. Having in mind the scientific program and the high international reputation of the invited speakers I feel honored to have assumed the responsibility to be the Scientific Chairman of such an important meeting once again.

I thank all the members of the Scientific as well as the Organizing Committee who have worked hard to ensure that the 2nd International Symposium on Organ Sparing Treatment in Oncology will take place. Major merit goes to Professor Gregor Serša, the Chairman of the Organizing Committee and the Editor of Radiology and Oncology, who did a great job in organizing this event and who on behalf of the Editorial Board of Radiology and Oncology kindly offered us to publish the material of the symposium in one of their regular issues.

You are looking at the issue of Radiology and Oncology in which the manuscripts of five invited speakers at the symposium as well as the abstracts of all 26 presenters are published. Due to time pressure we took the liberty of making some editorial changes on the manuscripts in order to adjust them to the requirements of the journal without all the authors having been consulted. Hopefully the authors will not be offended by this.

I hope that the participants will enjoy the symposium and that the readers will find this issue of Radiology and Oncology useful, possibly joining us during the next symposium.

Tanja Čufer (Guest Editor)

Scientific program

2nd International Symposium on Organ Sparing Treatment in Oncology

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Breast and axilla conserving surgery in the management of early-stage breast cancer

Mogens Blichert-Toft

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The main incentive to breast conserving therapy (BCT) relates to preserving femininity and avoiding the feeling of female inferiority and a disfigured body image. Some women are even more concerned about preserving the breast rather than preserving life. The preconditions for BCT are satisfactory cosmesis, good physical function, and loco-regional disease control. If the breast is badly disfigured following BCT, there is little sense in breast conservation. The mainstay of early-stage breast cancer treatment is surgery. One option is breast conservation in case of eligibility. Radicality of the surgical procedure is emphasized whether mastectomy or breast conservation has been undertaken. Risk factors related to BCT in particular are scrutinized, and especially young age and extensive ductal components of the specimen are dealt with as independent risk factors for local control in BCT. BCT in Denmark amounts to about 30% of operations in breast cancer. This is a rather low frequency compared with figures from other countries. Consequently, the Danish eligibility criteria are discussed. The reasons for axillary dissection are emphasized. Even in small tumors below 10 mm, axillary dissection is indicated due to a considerable involvement of axillary nodes. The introduction of the sentinel node principle seems to provide a basis for conservation of healthy axillary lymph nodes in node negative patients.

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The intraoperative examination of axillary sentinel nodes

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A routine histological examination of axillary sentinel nodes predicts the nonsentinel axillary node status and may allow to spare axillary clearing in patients with breast cancer. To avoid the need for two separate surgical sessions, the results of sentinel node examination should be known intraoperatively. Routine frozen section examination of sentinel nodes, however, is liable to yield false-negative results. An extensive intraoperative examination of frozen sentinel nodes, which would attain sensitivity comparable to, that obtained by routine histological analysis has been therefore devised. The frozen sentinel nodes are subserially sectioned at 50 mm intervals. For each level, one section is stained with hematoxylin and eosin (H&E) and the other immunostained for cytokeratins using a rapid immunocytochemical assay. Immunocytochemistry did not increase the sensitivity of the examination. The general concordance between sentinel and axillary node status was 96.7%; the negative predictive value of intraoperative sentinel node examination was 94.1%. The intraoperative examination of axillary sentinel nodes is effective in predicting the axillary node status of breast cancer patients and it may be instrumental in making the decision to spare axillary clearing.

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Can axillary treatment in selected breast cancer patients be avoided?

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Purpose. *To determine the locoregional control in the patients with invasive breast cancer who had no axillary treatment.*

Patients and methods. *Axillary dissection remains an integral part of breast cancer surgery at our institute; therefore, we can report on only 30 patients with invasive breast cancer who had no axillary treatment from 3.91 till 3.99. The reasons for omitting the axillary treatment were the age and/or the prognostic factors favoring the decision on adjuvant therapy determined by the primary tumor features. All patients had clinically negative axillary nodes. 25 were post- and 5 were premenopausal with a mean age of 64.8 years (range 32-78). Five tumors were pathologically ≤ 1cm, 13 between 1-2 cm and twelve > 2 cm in diameter. Histologically, 21 carcinomas were ductal, 8 lobular and 1 papillary; 10 were grade I, 13 grade II and 7 grade III (BRE). HR were positive in 20 cases. Breast conserving surgery was performed in 24 patients, with postoperative radiotherapy in 18 and mastectomy in 6 patients. Nineteen patients received tamoxifen and 3 chemotherapy.*

Results. *Within a mean follow-up of 48 months (range 12-108), there were no axillary failures. One had a breast recurrence (treated by tumorectomy without any adjuvant therapy), no patient had distant metastases, no one died. All patients had a fully functional arm without oedema, paresthesias or pain.*

Conclusion. *Good regional control in our patients could be explained by the following: In most cases treated by conservation surgery the breast was irradiated postoperatively and the lower portion of the axilla is usually included within the tangential fields that treat the breast. In mastectomized patients, the lower axillary nodes are usually removed with the breast. Most of our patients also had systemic therapy as determined by the primary tumor characteristics. Although the number of our patients is very small, we believe that, in selected N0 patients, axillary dissection or radiotherapy to the axilla with separate fields could be omitted. Morbidity would be greatly diminished, thereby improving the quality of life without compromising regional control. The sentinel lymph node detection technique is promising, but cannot yet be used routinely in most centers.*

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The role of conservative therapy in invasive lobular carcinoma of the breast

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Introduction. *Several studies have shown that conservative surgery (CS) followed by radiation therapy (RT) provides a low incidence of local recurrences (2-4%) in the management of invasive ductal carcinoma (IDC), but the outcome of invasive lobular carcinoma (ILC) is difficult to assess because a high incidence of ipsilateral recurrences has been reported. The authors reviewed 409 patients with ILC treated by quadrantectomy and subsequent radiotherapy.*

Patients and methods. *Whole breast external beam irradiation was performed using a cobalt unit or a linear accelerator; the total dose was 46-50 Gy (2 Gy/fr); 325 patients received a boost to the tumor bed (10-20 Gy).*

Results. *Local relapses were observed in 17 patients (4.2%) and the mean time to local failure was 58.7 months (range 13-130 months); local control was 96% in T1 and 95% in T2 carcinomas. The incidence of local relapse was higher (5.9% versus 3.2%) in patients with intraductal component (IC). Recurrences underwent salvage mastectomy in 15 cases (88%); 13 of these patients are disease free, 4 developed distant metastases.*

Conclusion. *The difficulties to define the extent of the lesion and the supposed high rate of multicentricity of the tumour have limited the conservative approach to ILC in many institutions. Since ILC are often multifocal and poorly delimited, the excisional biopsy and the lumpectomy may be probably inadequate. The pattern of local recurrences in our series was characterised by a high risk in proximity of the surgical bed despite the primary surgery. Many authors suggest that the presence of an extensive IC could affect the prognosis. In our series IC was found in 134 (32.7%) cases, but it was extensive only in 77 cases; in these patients the rate of local recurrences was relevant (7.8%). The incidence of synchronous and metachronous bilateral breast recurrences was not significantly higher than in the published data concerning IDC. In conclusion, this retrospective study indicates that CS in ILC provides a good probability of local control.*

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Sentinel node biopsy in breast cancer

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Background. *Sentinel lymph node (SLN) biopsy is rapidly emerging as the most significant advancement in surgical treatment of breast cancer since the initiation of breast conservation treatment. SLN biopsy can accurately identify the node-positive patients who require axillary dissection, and spare node-negative patients an operation from which they would not have any benefit.*

The procedure is highly multidisciplinary, requiring close cooperation between nuclear medicine, surgery and pathology. It poses a new set of technical issues for each specialty, of which none has been completely resolved. Therefore, it needs to be cautiously audited during the implementation. It is generally accepted that every surgeon who wants to perform SLN biopsy should do his/her own personal series of SLN biopsies and backup axillary dissection in at least 30 cases, with a success rate of at least 90% and false negativity rate of maximum 3%. We are presenting the personal series of a single surgeon (M.S.).

Patients and methods. *We included 36 female T_{1-2} N , breast cancer patients in the study. They all received an injection of 1ml ^{99m}Tc sulphur nanocoloid of 60 MBq activity into and around the tumor. Two hours after the injection the lymphoscintigraphy was done and the projection of SLN was marked on the skin. The patients were referred to the operating room within 24 hours after the injection at the latest. There, they were injected again with 1 ml of Patent Blue peritumorally or intratumorally. After 3-5 min, an intraoperative gamma probe was used for the identification of SLN. Surgical incision was made on the spots where the skin marks had been made and blue nodes showing afferent and/or hot nodes were excised. After having retrieved the SLN, the backup axillary dissection was done. Formalin-fixed, in toto paraffin embedded SLN were cut to three or five levels. The slides were stained, additionally to HE, immunohistochemically by CAM5.2 and CK MNF116.*

Results. *Lymphoscintigraphy was done in all 36 patients. In 4 patients, we could not present SLN preoperatively. SLNs could be found in all patients after the injection of Blue Dye. We retrieved 54 SLNs (average 1.5 SLN/patient); of these, 36 SLNs were hot and blue, 9 only hot and 9 only blue. Three SLNs in three different patients were in the region of internal mammary artery while the rest were in the axilla. In 17 patients, 19 SLNs were histologically positive and 9 of these had only micrometastases. In all cases, backup axillary dissection was done. On average, 16.8 lymph nodes were retrieved per patient. In only five cases of SLN positive patients, additional positive lymph nodes were found in the axilla. When a negative SLN was found, no positive nodes were detected in the axilla.*

Conclusion. *SLN biopsy in this personal series of breast cancer patients proved to be a safe and accurate method to predict negative axillary lymph nodes. In our series, there was no false negatives. The identification of SLNs with lymphoscintigraphy and Blue Dye was successful in all cases.*

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Breast biopsy with needle localization: factors influencing complete excision of nonpalpable carcinoma

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Purpose. *Biopsy with needle localization of nonpalpable breast tumor may be diagnostic, however preferably, it should be therapeutic. The latter may be achieved if tumor is completely excised, i.e. with clear surgical margins. Our aim was to find out the factors related to complete excision of nonpalpable tumor.*

Patients and methods. *During a two-year period 215 patients (age range 32-74 years, median 55 years) underwent biopsy after needle localization of 222 nonpalpable breast lesions. Mammographic, operative and pathological factors were correlated with the outcome of surgery using contingence tables in SPSS statistical software.*

Results. *According to mammographic features, the biopsy yield rates were 67% in spicular masses, 38% in microcalcifications and 35% in tumors. A total of 96 malignant tumors were diagnosed (overall biopsy yield rate 43%): 38 in situ and 58 invasive carcinomas. Surgical margins were clear in 44, close in 20 and involved in 32 cases. Margins were likely to be clear if the tumor was mammographically spiculated and smaller than 9 mm, and if more than 50 g of tissue was excised. On the contrary, the margins were likely to be involved in micro calcifications, tumors bigger than 9 mm and if less than 50 g of tissue was excised. Reoperation was performed in 41 cases (22 mastectomy, 19 reexcision) because of non-clear margins; residuum was diagnosed in 21 of them. No residuum was observed if the tumor was mammographically spiculated; however, it was detected in 17 of 25 reoperated microcalcifications.*

Conclusion. *Complete excision of nonpalpable breast malignoma correlates with the mammographic features, tumor size and weight of excised tissue. Complete removal of large microcalcifications remain a puzzling surgical task.*

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History and evolution of endocrine therapy of breast cancer

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The first recorded observation that carcinoma of the breast would respond to hormonal manipulation was written by Beatson slightly over 100 years ago when he reported that surgical oophorectomy induced a remission in a patient with metastatic breast cancer. Oophorectomy remained the most effective therapy for metastatic pre-menopausal breast cancer for the first half of the 20th Century. The synthesis of cortisol and other adrenocortical hormone analogues in the 1950's & 1960's made possible the expansion of ablative endocrine surgery to include adrenalectomy and hypophysectomy. This "major endocrine ablation" technique allowed post-menopausal patients with metastatic breast cancer to benefit from hormonal therapy. In large series reporting the results of major endocrine ablations, an average of 30-35% of all patients achieved substantial clinical remissions in their disease. The discovery of hormonal receptors in breast cancer tumor cells and the widespread applications of biochemical and histochemical receptor testing of pathologic breast cancer specimens in the 1970's - 1980's allowed clinicians to predict with 90% certainty which patients would respond to endocrine treatments. This development substantially reduced major surgical procedures in patients who had little chance of responding. The discovery that estrogen receptor blockade with the drug tamoxifen could achieve the same result as adrenalectomy and hypophysectomy in post-menopausal women led to another revolution in the care of patients with metastatic breast cancer. Tamoxifen and other estrogen receptor blocking agents, effectively replaced surgical hormonal ablative treatments in the last third of the 20th Century. The development of clinically useful blockers of the aromatase pathway of estrogen synthesis in the adrenals, as well as agonists to block pituitary stimulating hormones, made the possibility of total estrogen blockade by non-surgical methods a reality. Algorithms for the use of these agents in clinical situations will be presented, and the recent expansion of synthetic estrogen receptor modulators (SERMS) to be used in breast cancer prevention strategies will be discussed.

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Intraoperative radiotherapy in breast cancer. How do we do it?

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Intraoperative radiotherapy consists of irradiating the tumor bed of breast cancer during operation. The geographic miss of the tumor bed is a well documented phenomenon in boost irradiation, demanding adequate techniques of high quality boost setups.

After the tumorectomy including a safety margin of 1 to 2 cm around the palpable tumor, the lateral sides are sutured side by side to be better included into the applicator. The irradiation must be localized on the tumor bed, constituted by the lateral section areas of the tumorectomy. The cross-sections of the applicator are circular with the inner diameters of 3, 4, 5, and 6 cm. The applicator is fixed in the tumor bed with a foil and is not attached to the collimator of the linear-accelerator. Our operating table is moveable alowing the transfer of the patient from the operating room to the radiotherapy treatment room in the best conditions of asepsis. There, the patient is moved from the operating table to the treatment couch. Anaesthetic surveillance of the patient is ensured by mobile and fixed monitors during the entire period of transfer and IORT. The depth dose presciption is done by CT scan of the tumor bed. The single dose is 9 Gy with 4 to 12 MeV electrons on the 90% isodose.

After the wound is healed, the patients are treated up to 50 Gy (EBRT). No additional boosting is performed. This is why EBRT is two weeks shorter than without IORT. There where no early complications associated with the use of IORT. From 5/1999 to 4/2000 conservative surgery was performed on 20 patients with stage I or II breast cancer in a dedicated IORT facility.

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192-Iridium HDR boost in breast cancer treatment - experience from 644 patients (1984-1995)

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Purpose. *Since 1984, HDR Iridium-192 brachytherapy has been used to deliver an interstitial boost to the primary tumor site in conservative breast cancer treatment. The authors present the survival data and cosmetic results of a prospective treatment method and demonstrate the safe use of Ir-192 high dose rate (HDR) implantations.*

Patients and methods. *From 1984 to 1995, 644 patients with 649 tumors have been treated (T1: 432, T2: 217, N+: 180, N-: 469). The treatment method included external beam radiotherapy (EBRT) of 45 to 50 Gy to the breast (parallel opposing portals) followed by one interstitial 10 Gy boost to the tumor bed. Adjuvant systemic therapy was given to all node-positive patients. Premenopausal patients were given six cycles of CMF (2 to 3 cycles of CMF were administered before radiotherapy and 3 to 4 cycles were continued afterwards), and postmenopausal estrogen receptor positive patients were treated with Tamoxifen. Mean follow-up of survivors was 77 months (25 to 158). Cosmetic appearance after surgery was evaluated in the first 216 patients using a 4 grade scoring. The clinical and cosmetic results were evaluated according to tumor location (medial and central: „m/c", lateral: „lat").*

Results. *Five-year actuarial data (10-yr. data in brackets): Overall survival: 89.6 % (75.0 %), local control: 96.5 % (92.0 %), disease free survival: 85.5 % (77.5 %), and disease specific survival: 92.9 % (82.2 %). The lowest local failure rate is given in ER positive patients with 1.4 % after 5 yr., and 5.5 % after 10 yr. Comparing m/c and lat, the survival parameters were highly significant in favour of the lateral tumors (p-values: OS 0.0011, DSS 0.009, DFS 0.0001, LC 0.051). There were no severe complications, except in 1 patient with periostitis and neuralgia. To exclude the influence of surgery to the cosmetic results, the mean value of 1.74 (=before RT) was normalized to 1.00. This postoperative result was compared to the cosmetic result 2 and 5 years after radiotherapy using a similar scoring: The relative value changed to 1.12 after 2 years and to 1.15 after 5 years. The rate of good to excellent results before radiation therapy was 84%, and after 5 years 74%. Normalized to 100 to exclude the influence of surgery, these results represent in 88% the changes in cosmetic appearance due to RT alone. Medial and central tumor locations result in a worse cosmesis compared to lateral tumors: The mean scores after surgery were 1.65 in lat and 2.15 in m/c ($p<0.005$). These values had not changed 5 years after RT with 1.69 and 2.13 respectively ($p<0.025$).*

Conclusion. *Our experience over more than 10 years proves the safety of the use of HDR implantations as a boost of 10 Gy in 1 fraction, delivered with careful attention to the source position for treatment, to the distance of the needles from the skin, and to the treated volume. The 5-year local relapse rate of 3.5 % (10-yr.: 8.0 %) and survival data are very similar to those reported in literature. The medial and central tumor location in the breast is associated with significant lower survival rates and significant unfavorable cosmetic results.*

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The impact of local recurrence on the survival of operable breast cancer patients treated conservatively

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The impact of local recurrence on survival was studied on 259 patients with operable breast cancer treated at the Institute of Oncology in Ljubljana in the years 1978-1988. This was a retrospective, non randomized study. All patients had breast conserving surgery (219 patients had quadrantectomy or wide excision, 40 patients had tumorectomy only).

After surgery, 129 patients received postoperative irradiation (50Gy to the breast and mostly 10Gy boost to the tumor bed), and 130 patients had no irradiation.

The objective of the study was to evaluate the difference in the recurrence rate in both groups and the impact of recurrence on survival.

From 130 patients with no irradiation after surgery 41 developed recurrences in contrast to only 16 local recurrences in 129 patients who were irradiated postoperatively (p= 0.00017). Local recurrences were more frequent after tumorectomy in comparison to quadrantectomy or wide excision (35% vs. 20%, p= 0.02).

The survival in the group of patients with local recurrence and in the group of patients without local recurrence did not differ in the first 5 years after surgery, whereas the difference in the survival of the both groups became highly significant thereafter (p=0.0076) (Figure 1)

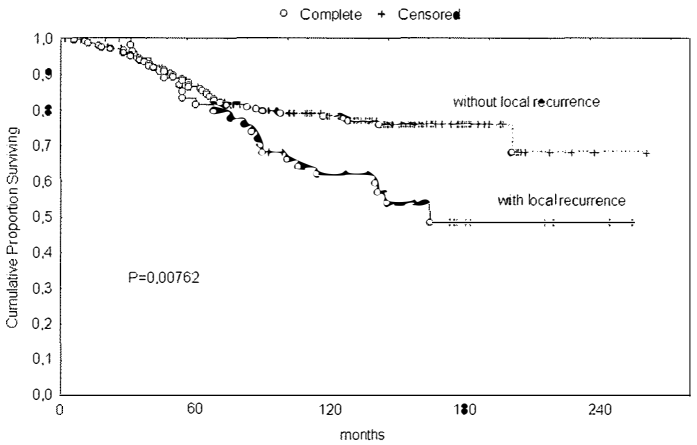

Figure 1: Survival with local recurrence (68 patients with local recurrence and 190 patients without local recurrence).

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Advanced breast biopsy instrument (ABBI) system

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Several methods have been developed in the last 10-15 years to reduce the extension of surgery in the treatment of breast cancer. First of all, it is well known that breast conservation does not impair the prognosis of patients with breast cancer and therefore the rate of brast conserving therapy has been rapidly increasing in the countries with high medical standard. For example, in our institution and within the Austrian Cooperative Study Group of Breast Cancer, the rate of breast conservation has been raised from 35% up to 75% in the last 10 years.

This has been mainly due to the fact that postoperative radiation therapy has been improved extensively.

Concerning operation in the axilla region the development of sentinel node technique has brought the opportunity to reduce the extension of surgery in the axilla and to improve the rate of postoperative morbidity. Although the logistic problems in performing this technique are evident it is necessary to enhance its use as much as possible.

Another new technique is the so-called "ABBI-system" (advanced breast biopsy instrument). This procedure is used to remove small lesion under local anaesthesia. It also allows to perform the diagnosis and treatment of minor breast cancers in one step. It is important that these techniques, the sentinel node biopsy and ABBI-system are performed in controlled trial conditions to find out the possibilities and limitations of this new method.

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Breast sparing treatment of mammary cancer

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Background. *Conservative treatment of breast cancer is a valid alternative to mastectomy in the early stage of the disease. The purpose of the paper is to establish the subgroups of patients best suited for this type of therapy and the optimum therapeutic protocol.*

Patients and methods. *This is a prospective study that overviews the outcome of four groups of patients with stage I and II of breast cancer treated by the same medical team at the Bucharest Oncologycal Institute: Group A: 123 patients who underwent conservative treatment as they met the selection criteria for this type of therapy;*

- *Group B1: 30 patients who underwent conservative treatment because they had refused mastectomy;*
- *Group B2: 40 patients who underwent conservative treatment because of medical contraindication for extended surgery;*
- *Group M: 150 patients by whom mastectomy was performed, although they would have fulfilled the selection criteria for conservative treatment.*

The most important selection criteria for conservative treatment were: unilateral, unicentric breast cancer, T<2.5cm, N0-N1, tumor/breast ratio that would allow proper excision with a convenient cosmetic outcome, and patient's wish.

Surgery for the primary tumor consisted of limited mammary resection, defined as excision of the tumor together with at least 2 cm of peritumoural mammary tissue. The amplitude of mammary resection depended on the location, size and histopathological type of the tumor and on the breast size. Axillary dissection was performed for diagnostic purposes and for local control of the axillary disease. Post-operative radiotherapy is an essential component of conservative treatment targeting the mammary gland and, under certain circumstances, the regional ganglionar areas. Chemotherapy and/or hormonal therapy were applied depending on the prognostic factors of the disease.

Results. *Local recurrence rates at 5 years were 6.9% in Group A, 25% in Group B1, 12.5% in Group B2, 1.3% in Group M. Overall survival rate at 5 years was 91.37% in Group A, 70.83% in Group B1, 62.50% in Group B2, 88.60% in Group M. The cosmetic result of conservative treatment was good in over 70% of the cases.*

Conclusion. *Results confirmed that conservative therapy, with due observance of selection criteria and of the therapeutical protocol, is an appropriate therapy for a category of patients with early breast cancer.*

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Organ sparing for rectum and quality of surgery for preventing local recurrences

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The progress in the management of rectal cancer in the last 100 years has been phenomenal. From the days of Myles abdominal perineal resection at the beginning of the 20th century we have progressed to being able to manage most rectal cancers without the need for a permanent colostomy and from a surgical procedure associated with 40% local recurrence to one with less than 5%. Adjuvant modalities with radiotherapy and chemotherapy have similarly proven useful in advanced disease to improve not only local control but also survival. Particular attention is paid to two aspects: 1) the surgical technique that is so critical in improving survival by improved local control and 2) looking at anal-preserving surgeries for advanced and low rectal cancers. It is concluded that a properly done procedure using the TME approach supported by preop radiation for advanced lesions will result in excellent local control and function in over 90% of low rectal cancers.

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Conservative treatment of anal canal cancer

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Purpose. *Sphincter preservation by radiation therapy with or without simultaneous chemotherapy has become a widely accepted standard treatment for patients with anal cancer. Our experience with 97 patients was analyzed to evaluate local control and late morbidity according to stage and treatment method.*

Patients and methods. *Between January 1983 to December 1999, 97 patients with anal cancer were treated by external beam radiotherapy (EBRT). A median total dose of 50 Gy was delivered to the primary tumor region as well to the perirectal lymph nodes. Patients were staged according the UICC Classification: 40 T1, 31 T2, 14 T3, 12 T4. Female to male ratio was 79 to 18. Mean age of all patients was 66 years. Pretreatment procedures included tumor excision or biopsy, endoscopy, transrectal sonography and examinations to exclude distant metastases. Fifty patients (51.5%) received simultaneous chemotherapy with Mitomycin C and 5-Fluorouracil. An additional boost (electron beam or implant) to the primary tumor was delivered to 67 patients (69%). Forty-seven patients received external beam therapy followed by interstitial Iridium–192 high dose rate (IR-192 HDR) implantation as boost (5 – 7 Gy) in one fraction. We obtained an optimal fixation of the needles and precise parallel needle positions with a cylinder applicator for the rectal lumen and a ring fixation system in addition to a semicircular template. To obtain an image of the implant, the patient had to be shifted to the CT-scanner by using a special transportation device. The implanted needles were visualized by CT-scan.*

Results. *Overall survival rate (OS) at 5 and 10 years was 87.3 % and 72.7% respectively, disease-specific survival (DSS) was 88% at 5 years and 10 years, local control rate (LC) was 86% at 5 and at 10 years. Mean follow up of all survivors was more than 50 months.*

Conclusion. *Radiotherapy is a standard treatment for patients with cancer of the anal canal. Additional chemotherapy showed improved local control rates and overall survival in patients with T3 and T4 tumors. Our results also indicate that the external beam therapy combined with IR-192 HDR brachytherapy as a boost is highly effective in achieving local control without severe grade 3 toxicity. Late toxicity is moderate by delivering boost doses not exceeding a volume of 60 ccm.*

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Initiation of sphincter sparing treatment for squamous cell carcinoma of the anal canal in a North American Community Hospital

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Objective. *In the United States, increasing numbers of patients are choosing to receive oncological therapy in small community cancer centers rather than in academic centers of excellence. Providing optimal therapy for uncommon malignancies such as anal cancer in the community setting can be challenging. In a hospital-based cancer center located in a rural community of 35,000, a combined modality approach to the treatment of squamous cell carcinoma of the anal canal was implemented in 1999. After one year, the results and toxicity of treatment were analyzed.*

Materials and Methods. *Patients received an initial 30.6 Gy to 36 Gy of external beam radiotherapy (EBRT) to the lower pelvis, inguinal lymph nodes, and anal canal in 1.8 Gy daily fractions, five days/week. A total dose of 50.4 to 59.4 Gy EBRT was delivered to the primary tumor using 3-D treatment planning and shrinking fields. Total dose was dependent on tumor response and exclusion of the small bowel from the final boost volume. The regional radiation oncologist, using a dedicated teleradiography system linking the regional center with the primary academic cancer center, reviewed all treatment plans with a sub-specialist radiation oncologist with an interestin GI malignancies.*

Chemotherapy was delivered concurrently with EBRT. Cis-platinum or Mitomycin-C, at the discretion of the treating medical oncologist, was administered on Day 1 and Day 28. 5-Fluorouracil, delivered as either a 96-hour continuous infusion or daily bolus injections, was administered on Days 1-4 and Days 28-31.

A community surgeon and/or gastroenterologist evaluated the patient eight weeks after completion of therapy. A biopsy was performed at the discretion of the endoscopist. The treating oncologists also evaluated patients at eight weeks post-treatment and at three-month intervals thereafter.

Results. *At the time of presentation, length of follow up, short term tumor control rates, and acute and delayed toxicity rates will be discussed.*

Conclusion. *A combined modality approach to the treatment of anal canal malignancies in the community setting is technically feasible with modest, but tolerable, acute toxicity. Difficulties in delivering definitive therapy in an uninterrupted fashion will be addressed at the time of presentation.*

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Cancer of the lower third of the rectum: Dilemmas between the low anterior resection and the abdominoperineal excision

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Objective. *Sphincter-saving operations are performed with the increasing frequency for patients with carcinoma of the lower third of the rectum. Stapling devices allow a safe resection of lesions closer to the anal verge. Our study compares the results of the low anterior resection (LAR) using the double stapling technique and of the abdominoperineal excision (APE) in patients with carcinoma of the lower third of the rectum.*

Patients and methods. *In the period from 1st January 1989 to 31st December 1995, 116 patients with carcinoma of the lower third of the rectum underwent potentially curative resection. Five-year survival was estimated by Kaplan-Meier statistical analysis. Patients who died within 30 days after the operation were censored. Differences in survival curves between both groups were assessed by the log rank test.*

Results. *We performed LAR in 44 of 116 (37.9%) patients and APE in 53 of 116 (45.7%). We preserved the sphincter in 52 out of 116 (44.8%)(LAR, local excision). The patients were divided according to the type of operation by the Dukes classification: LAR (A11/44 25%; B16/44 36,4%; C17/44 38,6%), APE (A12/53 22,6%; B17/53 32,1%; C24/53 45,3%). Five-year survival rate for patients with Dukes B and C tumors in the lower third of the rectum is 25% for LAR and 53% for APE. There was no statistically significant difference of survival curves between the two operations (p=0.20458, Log rank). We analyzed our results with regard to positive lymph nodes: LAR (N1 15.9%; N2 25%; N3 11,4%); APE (N1 18.9%; N2 22.6%; N3 0%). Lymphatic spread was found in 23 of 44 (52.3%) of the patients with LAR and in 22 of 53 (41.5%) of the patients with APE. Anastomotic leakage became clinically manifest in 8 out of 44 patients (18.2%). All the patients required relaparatomy and were treated with temporary loop ileostomy.*

Conclusion. *We performed LAR (52,3%) in a higher percentage of patients with lymphatic dissemination than APE (41.5%). Thus the difference in five-year survival rate is not surprising: LAR (25%), APE (53%). A more detailed preoperative staging of the tumor should be undertaken (endorectal- ultrasonography and size of the tumor). LAR should be performed in patients with small tumors or non advanced carcinoma (T1, T2). In patients where lymphatic dissemination or more advanced carcinoma (T3,T4) is identified, APE should be performed.*

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Local excision of pT1 and pT2 carcinomas of the rectum from 1996 to 1999

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Purpose. *Our aim was to present and evaluate local excisions of rectal cancer in view of preserving organ functioning and securing surgery for cure. The current follow-up and results are discussed.*

Materials and methods*. From the beginning of 1996 to the end of 1999, we treated 21 patients for rectal cancer by local excision. All patients had lesions less than 4 cm in diameter which were not extending beyond the muscularis propria by ELUS examination.*

Results. *At the moment, 13 patients are without recurrence, 3 died of cancer unrelated cause, 4 had another operation because of recurrence, 1 was lost from follow-up for unknown reason.*

Conclusion. *The number of our patients is small and hardly of statistic value. Our opinion is that local excision has its meaning as organ saving procedure if it is supported with good follow up.*

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First clinical data of a natural immunomodulator in colorectal cancer

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Background. *MSC (trade-name AVEMAR®) is a per os applicable complex of multiple, biologically active molecules obtained from fermented wheat-germ extract. Preclinical studies suggest a potent antimetastatic activity and a favorable toxicity profile. On a pilot-scale, this phase II clinical study was aimed to find out whether or not MSC as a support to surgery or plus chemotherapy adds any therapeutic benefit compared to the same combination without MSC in colorectal cancer.*

Materials and methods. *From 1998 to June 1999, 18 control patients and 12 consecutive colorectal cancer patients were enrolled into this study. All patients underwent curative surgery. The control group (18 patients) received no other therapy or adjuvant chemotherapy alone. The MSC group (12 patients) received MSC alone or plus adjuvant chemotherapy. Until now, the median follow-up has been 9 months.*

Results. *The interim data of the study provide evidence that, in the MSC group, no new metastases, neither hepatic nor other, have occurred so far. On the contrary, several new metastases have developed in the control group.*

Conclusion. *Orally administered MSC is a potent candidate to be regarded as a supportive therapy to surgery or plus chemotherapy for colorectal cancer patients.*

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Limb salvage in soft tissue sarcomas

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In 2000, most patients with soft tissue sarcomas of the axial or appendicular skeleton can expect 'to walk away' from the surgery. This compares to just 20 years ago when a relatively high percentage of patients were treated with amputation. Now the treatment has changed to one of wide local excision with a 1 cm to 2 cm margin on normal tissues and an adventitial margin on critical structures such as nerves or vessels, followed or preceded by radiotherapy. With the use of adjuvant treatments in combination with reconstructive surgery, over 90% of patients with sarcomas of the soft tissues or bone may be rendered disease free locally. The only restriction to this approach is when tumor involves the major nerve to a limb or when microscopic, clear margins cannot be obtained at the time of surgery as both of these are best treated with an amputation.

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Combined application of cisplatin, paclitaxel and radiation in the treatment of advanced squamous cell carcinoma of the head and neck

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Objective. *Encouraged by the experiences of our prospective trial (presented in 1998) and according to the international tendency to combined treatment modalities we designed a further pilot study. Due to the very promising results (phase II trials, second line chemotherapy) of the schedules containing taxans against squamous cell carcinomas of the head and neck and the lung, we introduced Paclitaxel into our concept. Paclitaxel is also known as a very effective radiosensitizer.*

Patients and methods*. Between March 1998 and April 2000, about 30 patients with advanced squamous cell carcinoma of the head and neck have been treated. The first cycle of the polychemotherapy consists of 175 mg/m^2 Paclitaxel and 75 mg/m^2 Cisplatin. The course is repeated every three weeks with reduced doses (135mg/m^2 and 60 mg/m^2 respectively) three up to five times. Radiotherapy starts immediately after the completion of the second cycle. Standard fractionation radiation therapy with a total dose of 72 Gy is applied.*

Results. *We have seen complete remissions in patients with very advanced carcinomas. This regimen seems to be highly effective against advanced squamous cell cancer of the head and neck. On the other hand, we have to face an increase of adverse side effects as well.*

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HDR brachytherapy in the treatment of cancer of the uterine cervix: Results and complications in 346 patients (1980 - 1995)

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Purpose. *The purpose is to present a safe use of intrauterine high dose rate (HDR) 192-Iridium applications in the primary treatment of cervical cancer with a combination of external beam (EBRT) and HDR brachytherapy (BT). Survival data and side effects will be presented.*

Material and methods. *From August 1980 to December 1995, 346 patients with cancer of the uterine cervix underwent primary irradiation in combination with external beam and HDR intracavitary treatment at the Department of Radiation Oncology at the Sisters of Mercy Hospital in Linz, Austria. Mean age was 60.8 years (range 30.1 to 86.6 years). All patients were classified according to the FIGO rules: Stage I 64 patients, stage II 186, stage III 93 and stage IV 3 patients. Eight patients were lost to follow up. In EBRT a dose of 1.7 to 2 Gy per day was given (4 fields per day) with a mean total dose of 37.4 Gy (range 20 - 66 Gy) over a mean time period of 46,6 days (range 35 - 77 days). The mean total BT dose was 29.2 Gy (range 4 - 46 Gy), the mean dose per fraction 8.2 Gy (range 4 - 10 Gy) and the mean number of fractions was 3.6 (range 1 to 6 fractions). The mean follow up time of survivors is 134 months. Side effects were evaluated according to the glossary of Chassagne and Sismondi.*

Results. *A complete remission could be achieved in 322 patients (93.1 %); persistent tumor was found in 24 patients at the first follow-up 3 to 5 months after the completion of irradiation. The actuarial overall survival probability for all patients at 5 and 10 years is 60.4% and 44.2 % respectively, the disease specific survival probability is 68.2 % and 62.4%. The local control rate at 5 and 10 years is 75.9 % and 73 %, and the disease-free rate 63.5 % and 58.9 respectively. According to stages I, II, and III & IV, the disease-specific survival at 5 years (event: death with or from disease) was at 91.7 %, 69.0 %, and 49.3 %, respectively, and at 10 years, it was 87.7 %, 64.4 % and 39.8 % respectively. The actuarial local control probability for stages I, II, and III & IV was 89.9 %, 75.5 %, and 66.0 %, respectively at 5 years, and 87.9 %, 72.9 %, and 61.2 % at 10 years (Kaplan-Meier calculations). From all 346 patients, 54 (15.6 %) presented with moderate or severe side effects. The actuarial rate for grade 2 complications after 5 years is 11.3 % and for grade 3 5.4 %, and after 10 years 11.9% and 6.7 %, respectively.*

Conclusion. *Intrauterine HDR brachytherapy in addition to external beam irradiation for primary treatment of invasive carcinoma of the uterine cervix provides excellent treatment results, the same as LDR applications concerning survival data and complication rates as well. Our results are matching with those of other authors very well. The method described above is a very effective tool for primary irradiation of cancer of the uterine cervix, and a safe one in experienced hands.*

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Sentinel lymph node biopsy in patients with malignant melanoma

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Background. *The issue of elective lymph node dissection (ELND) in patients with malignant melanoma is one of the most controversial issues in the history of surgical oncology. There have been four randomized prospective surgical trials which have at present reached sufficient data maturity to draw relevant conclusions. The Intergroup Melanoma Surgical Trial recruited the highest number of patients (740) and was from the very beginning designed to identify a subgroup of melanoma patients (selected by different prognostic factors) who might benefit from ELND. The results showed that ELND statistically significantly improved the survival in a group of patients with nonulcerated melanomas with the tumor thickness of 1-2 mm and the tumor location on the limb. An attractive alternative approach to selection of patients with melanoma based on prognostic factors for ELND came in early 1990's when Morton et al. devised the technique of intraoperative lymphatic mapping, sentinel lymphadenectomy and selective complete lymph node dissection (LM/SL/SCLND). LM/SL/SCLND is today considered by most authorities, as a substitute for ELND if "technological transfer" of LM/SL/SCLND, which requires a multidisciplinary team, is consistently and accurately applied. Therefore it is advised to perform LM and SC in all patients with malignant melanoma of the thickness of 1-4 mm according to Breslow.*

Patients and methods. *From January 1999 to June 2000, LM and SC were performed in 8 patients (7 male, 1 female) after the excision of primary melanoma with a 2 mm margin. Preoperative lymphoscintigraphy was performed by using ^{99m}Tc-nanocolloid and radioactive "Hot spots" of regional nodes were marked on the skin. Before the re-excision of the primary lesion, Patent Blue was injected intracutaneously around the skin lesion to help additionally identifying the sentinel lymph nodes.*

Results. *The melanoma was located on the trunk in seven patients and on the head & neck in one patient. The average tumor thickness according to Breslow was 2.83 mm. The sentinel lymph nodes were located in one lymph node basin in five patients with trunk melanoma and in two lymph node basins (both axillas) in two patients. In the patient with a scalp melanoma, the lymph nodes were located retroauriculary (1) and on the second lymph node neck level (1). The average number of sentinel lymph nodes was 2.25.*

We managed to identify 14/18 sentinel lymph nodes. Pathological exam revealed micrometastases in one lymph node in three patients. In all 3 patients, a complete lymph node dissection was performed and no additional metastases were found. The complete lymph node dissection was performed also in two patients in whom sentinel lymph nodes were not found. One of these two patients had 3 metastatic lymph nodes.

Conclusion. *LM/SL/SCLND is a valuable substitute for ELND if applied consistently and accurately. It enables more individualized approach to the patients with malignant melanoma and therefore minimizes unnecessary morbidity in patients with negative lymph nodes.*

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Partial nephrectomy in kidney tumors – our 5-year experiences

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Purpose. *In this study, a detailed analysis of partial nephrectomy applied in the treatment of kidney adenocarcinoma in the years 1990 - 1996 is presented.*

Patients and methods. *Renal tumors in early phase of growth are often diagnosed by chance. In the last 20 years, 115 (9.8%) of all 1167 diagnosed and operated hypernephromas at the Clinical Center of Ljubljana Ljubljana were treated with partial nephrectomy. The patients included in the study had adenocarcinoma renis. A detailed analysis of the results in the years 1990-1996 is presented. In this 5 years, we treated 27 patients with partial nephrectomy. We looked for clinical data, histology, location of tumor, outcome after 5 years.*

Results. *In 3 cases due to positive histologycal margin, radical nephrectomy was done later. One patient had additional resection of positive margin. Definitive histology after the 2nd operation was negative. Others 23 patients were disease-free after 5 years. The diameter of tumors in histology ranged from 2 - 4.5 cm. The location of tumors was both the upper and lower part of the kidney. The preoperative measurement of the tumor was comparable to that found in situ.*

Conclusion. *When tumor is located in proper position and is not larger than 3 cm in diameter, partial nephrectomy is a treatment of choice. Patient needs careful follow-up of local status in next the years. According to the last reports in literature, the diameter should be reduced to 2 cm due to multifocal growing pattern.*

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Tikhoff – Linberg operation and major resections of the shoulder girdle standard procedure for limb salvage in sarcoma patients

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Background and objectives. *This study was undertaken to clarify the clinical results of limb-sparing Tikhoff-Linberg procedure and major resections in patients with malignant bone and soft-tissue tumors of the shoulder girdle in our institute between 1980 and 1999.*

Patients and methods. *From 1980 to 1999, 39 patients with malignant bone and soft tissue tumors of the shoulder girdle were treated at the Department of Surgical Oncology, Institute of Oncology Ljubljana. In 27 out of 39 patients, a limb-sparing surgical procedure was possible (19 patients had a Tikhoff-Linberg procedure, and 8 major resection of bone and soft tissue). There were 15 females and 12 males with age range 14 to 71 (median 40 years). Sixteen patients had bone, 10 soft-tissue sarcomas and one with a large bone metastasis of thyroid carcinoma. Five patients had chemotherapy, 2 postoperative irradiation and 4 patients had chemotherapy and irradiation. The follow-up period in limb-sparing group ranged from 4 months to 19 years 9 months (median 6 years 4 months).*

Results. *Currently, 15 patients are alive and disease-free from 1 year 3 months to 19 years (median 7 years 6 months); two died of other diseases, 9 died of the disease (4 of metastases and 5 of local recurrence and metastases) at a mean (SD) interval of 15 months after surgery (range 6-25 months). One patient was lost from follow-up 6 months after surgery, because he was not resident of Slovenia. From 26 patients, 7 developed local recurrence from 6 months to 10 years 3 months after surgery (median 4 years 8 months) and in 3 of them, amputation was required. The bone was reconstructed only in 6 patients (in 3 with prosthesis, in 2, vascularised fibular graft was used whereas in one intraoperative extracorporeal autogenous sterilized bone graft). Hand-elbow function was excellent in 11, good in 6 and fair in 2 patients.*

Conclusion. *Classical or modified Tikhoff-Linberg operation is a suitable limb sparing procedure for tumors of the shoulder girdle. A good hand-elbow function can be perserved; however, the problem are local recurrences occurring in approximately 27 percent in this as well as in the majority of reported series.*

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Quality of life issues related to organ sparing

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Two general methods for assessment of quality of life (QL) will be described: those based on questionnaires and utility-based methods that require choice between different health states. QL must be assessed by patients, and its inclusion in clinical trials should be as rigorous as for endpoints such as survival. A primary measure of QL should be defined: in trials of organ sparing, this should reflect function of the organ that is either lost or spared. A hypothesis should be established about maintenance of a defined level of function. The primary QL endpoint should be measured for each patient at baseline and as a function of time following treatment. Other measures of QL are important to ensure that maintenance of function is not accompanied by deterioration in more global endpoints.

In trials comparing radical surgery with organ-sparing approaches, it is not necessary to use QL scales to assess the obvious. If survival is identical, organ-sparing approaches are preferred: a person who can speak has better QL than one who cannot. Assessment of QL is important when loss of function is less severe, as in breast conservation. Here most studies have confirmed better QL with lesser surgery, and anxiety about recurrence in the residual breast was uncommon. The choice between radical and organ-sparing procedures is more complex if surgery leads to substantial loss of function and organ-sparing to a lower probability of cure. Are patients willing to accept a reduction in the probability of survival in order to maintain organ function? Patients with breast cancer are unwilling to avoid toxic treatment for even a small deficit in survival, but this may be quite different if patients are faced with more severe loss of function.

The aim of organ sparing procedures is to maintain survival with a level of QL as high as possible. Methods are available for evaluating QL in patients treated by different strategies and should be included as major endpoints, together with survival, in clinical trials that investigate organ-sparing strategies. These methods will be useful in decision-aiding and especially in framing choices between improved quality and improved quantity of survival.

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Improving the quality of life of patients with TCC by sequential chemoradiotherapy

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Objective. *Radiotherapy with transurethral resection (TUR) combined either with primary polychemotherapy (with MTX, VLB, CDDP+/-ADR (MVC-RT) or concomitant monochemotherapy with VLB (RT + V)) assures a long-term survival and conservation of the bladder in more than half of the patients with invasive transitional cell carcinoma (TCC) of the urinary bladder. If the primary systemic polychemotherapy is successful, the target doses (TD) can be reduced from 62–66 Gy to 50-60 Gy. The purpose of this research was to find out whether the reduction of TD assures better quality of life to the patients.*

Patients and methods. *Of 186 patients with TCC of the bladder treated with chemoradiotherapy in the period from 1988 to 1994, 34 survivors with the conserved bladder were entered into the study. They were all requested to fill in a modified EORTC QLQ –C30 forms regarding their quality of life, to assess their problems according to the enclosed SOMA scale and to have cystometrography performed.*

Results. *We received the filled-in forms of 26 patients. Of these, 14 were treated with sequential chemoradiotherapy (MVC-RT) and received a median TD of 51.7 Gy, whereas the remaining 12 received concomitant chemoradiotherapy (RT+V) and a median TD of 63.6 Gy. Urodynamic examination was performed in 23 patients; of these, 12 were treated with MVC-RT, whereas 11 with RT+V. In view of physical, role, emotional, cognitive and social functions, generally better results were observed in the group with lower TD, though the statistically significant difference was observed only in the role functioning score (93% and 63% at a higher and lower TD, respectively; p=0.028). Moreover, considering the symptoms of chronic post-irradiation lesion of the rectum and urinary bladder, a similar observation was made. Patients having received lower TD presented with generally less serious problems, statistically marginal differences were noticed in the miction rate (p=0.06), hematuria (p=0.119) and the rate of uncontrolled defecations (p=0.131). From the cystometrography measurements, a median maximum capacity of the urinary bladder was assessed to be 348 ml (398 and 294 ml, at a lower and higher TD, respectively; p=0.05). Reduced compliance of the urinary bladder was observed in 7/23 patients (2/12 patients and 5/11 patients at a lower and higher TD, respectively; p=0193). Hyperactivity measurements did not show any significant differences. The whole group had high treatment tolerance (97.1%: 94.6% MVC-RT and 100% RT+V; p=0.0095).*

Conclusion. *A combination of TUR and MVC-RT with histological confirmation of CR by biopsy of tumor bed carried out prior to radiotherapy allows the irradiation with lower TD, thereby decreasing the toxicity of the treatment and assuring a better quality of life to patients.*

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Factors influencing rehabilitation in patients with head and neck cancer

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Purpose. *The purpose of the prospective study was to identify the factors adversely influencing the post-treatment rehabilitation in patients with head and neck cancer.*

Patients and methods. *One hundred and ten patients were examined before surgical treatment in order to find unfavorable factors: impaired hearing acuity, defective teeth, impaired pulmonary function, and speech disorders. The rehabilitation was planned according to the findings obtained. The patients evaluated their speech, swallowing, and general success of their rehabilitation (reintegration in their home environment) 12 months after the treatment. The influence of possible unfavorable factors, tumor site, and surgery extent on speech, swallowing and reintegration competence was determinate using $\chi 2$-test.*

Results. *The site of the tumor and the type of surgery did not influence the quality of rehabilitation in general. Defective teeth influenced the ability of swallowing, but not speech. Hearing loss impaired the patient's reintegration in his/her home environment. Impaired pulmonary function did not affect patient's speech. Speech was the poorest in the laryngectomized patients. However, about two thirds of all patients were satisfied with their capability of speech, swallowing and their rehabilitation in general.*

Conclusions. *Early identification of unfavorable factors, individually planned rehabilitation and intensive help of different professionals (ENT surgeon, phoniatrician, speech therapist) can ensure a proper rehabilitation of the affected functions and a suitable quality of life for patients that have undergone surgery for head and neck cancer.*

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review

Breast and axilla conserving surgery in the management of early-stage breast cancer

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The main incentive to breast conserving therapy (BCT) relates to preserving femininity and avoiding the feeling of female inferiority and a disfigured body image. Some women are even more concerned about preserving the breast rather than preserving life. The preconditions for BCT are satisfactory cosmesis, good physical function, and loco-regional disease control. If the breast is badly disfigured following BCT there is little sense in breast conservation. The mainstay of early-stage breast cancer treatment is surgery. One option is breast conservation in case of eligibility. Radicality of the surgical procedure is emphasized whether mastectomy or breast conservation has been undertaken. Risk factors related to BCT in particular are scrutinized, and especially young age and extensive ductal components of the specimen are dealt with as independent risk factors for local control in BCT. BCT in Denmark amounts to about 30 % of operations in breast cancer. This is a rather low frequency compared with figures from other countries. Consequently, the Danish eligibility criteria are discussed. The reasons for axillary dissection are emphasized. Even in small tumours below 10 mm, axillary dissection is indicated due to a considerable involvement of axillary nodes. The introduction of the sentinel node principle seems to provide a basis for conservation of healthy axillary lymph nodes in node negative patients.

Key words: breast neoplasms - surgery; lymph node excision; axilla; breast conserving; self concept

Introduction

The mainstay of early-stage breast cancer treatment is surgery. The aim of surgical intervention is primarily to ensure loco-regional tumour control. Further, meticulous surgery also embraces the intent to cure potentially curable patients.

A radical surgical approach seems most important in early-stage disease due to the limited risk of distant spread in case of small tumours, especially below 2 cm in diameter at

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diagnosis.[1,2] Similarly, age at the time of diagnosis turns out to be a considerable risk factor of distant dissemination.[2,3] Recent calculations report the V50 value where the term V50 is the tumour volume for which a distant spread has occurred in half of the patients. Under the age of 35 years at diagnosis, the V50 value was found to be 11 ml compared to 42 c.cm between 35-45 years and 35 c.cm above 45 years.[2] These data are supported by recent DBCG (Danish Breast Cancer Cooperative Group) results showing that young patients below 35 years of age at diagnosis revealed a significantly higher risk of being node positive and significantly fewer patients at that age were found to harbour tumours of malignancy grade I.[3] Further, women below 35 years of age at diagnosis had the worst prognosis with a 1.44 fold increased risk of dying from their disease. The assumption of more aggressive tumours in young patients is further emphasized by the DBCG observation that low-risk, node-negative patients less than 50 years of age at diagnosis not treated with adjuvant systemic therapy revealed a highly significant risk of dying with decreasing age. However, this trend was not found in young patients receiving adjuvant systemic therapy.[3]

There seems to be no doubt that young patients do harbour more aggressive tumours, irrespectively of tumour size. Consequently, in order to ensure loco-regional control and cure in potentially curable patients especially the young patients should be offered aggressive therapy whether or not the tumour is small.[3] The main question, however, is whether breast conserving therapy can be offered especially the young patients taking into account the peculiarities of the tumours of that particular age group.

Breast conserving therapy

Breast conserving therapy (BCT) for invasive breast carcinoma comprises a complete excision of the tumour-bearing part of the breast, axillary dissection if node positivity has been proved, and irradiation of residual breast tissue.

During the past decade, BCT has been an established and accepted method in managing the invasive breast carcinoma. In June 1990, The National Institute of Health, Bethesda, held a consensus conference aiming at the approval of BCT. The Conference concluded that "BCT is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable, because it provides survival rates equivalent to those of total mastectomy and axillary dissection while preserving the breast".[4] During the time elapsed, BCT has been applied widely, but implemented with varying degrees of frequency. With growing experience, the eligibility criteria might shift to become more restrictive.[5] Moreover, the possibility of performing skin sparing mastectomy combined with primary reconstruction of the breast in a one-stage procedure further narrows the indications of BCT. Finally, the lack of mammographic screening for breast cancer reduces the widely use of BCT.

What worries many surgeons is the fact that breast conserving surgery (BCS) infringes on the basic surgical principle, viz. to achieve surgical radicality, especially in small tumours in which therapeutic radicality is most important.[1] Although the tumour has been entirely removed, there is a high probability that residual cancerous foci are left behind in the breast by undergoing BCS.[6,7,8] Incomplete excision of cancerous tissue and close margins increase the risk of local recurrence in BCT.[8] Further, loco-regional recurrence has a detrimental effect on survival.[9,10,11]

Consequently, the key question about multifocality and multicentricity of the tumour burden remains. In their excellent work on histologic multifocality in T1-2 invasive carci-

nomas treated by mastectomy, Holland et al.[6] concluded that 37 % of tumours were unifocal showing no tumour foci in the mastectomy specimen around the index mass. In 20 %, the tumour foci were present within 2 cm, and in 43, the foci were found more than 2 cm from the reference tumour. In another study by Sismondi et al.[12], multifocality and multicentricity prevailed in young patients and in patients of 35 years of age or less compared to elderly patients, viz. 35 % vs. 19 %, 36 % vs. 16%, respectively. Similar results were obtained from another study by Anastassiades et al.[13] on multicentricity defined as one or more foci of in situ or invasive carcinoma in one or more quadrants other than the one harbouring the reference mass. Multicentricity appeared in about half of the patient series and was a frequent finding in patients 55 of years of age or less. Multicentricity prevailed in larger tumours, but was demonstrated in 16 % of tumours up to 2 cm.

In a failure analysis, Kurtz et al.[14] interestingly showed that the patients of less than 40 years of age treated for breast carcinoma by BCT had a significantly higher risk of local recurrence compared to older patients, 19 % vs. 9%, after a median follow-up period of 11 years. Kurtz et al.[15] also observed that patients with macroscopically multiple cancers treated by BCT developed recurrence in the treated breast significantly more frequently compared to the patients with a single tumour, viz. 25 % vs. 11 %, after a median follow-up of 71 months. Further, Voogd et al. pooled the data from two large randomized studies (EORTC and DBCG)[16,17] comparing the outcome of BCT with that of mastectomy. The study group found that the age below 35 years or less and extensive intraductal component were significantly associated with an increased risk of local recurrence after BCT. The median follow-up of patients still alive was 9.7 years. The hazard ratio for age was 9.2 (95 % CI 3.7-22) compared to the age over 60 years, and for intraductal component in association with index mass, the ratio amounted 2.5 (95 % CI 1.3-5.0) (personal communication).

Eligibility criteria of BCT in Denmark

In Denmark, the application of BCT has carried the stamp of cautiousness. During the years from 1983 to 1989, BCT was tested against mastectomy in a clinical randomized trial recruiting 905 patients found to be eligible for the study.[17] Very few patients had BCT in the 1980's outside the context of the DBCG protocol (82-TM). On a national scale, the percentage of BCT made up 8 % of surgical procedures in the management of operable breast carcinomas. Approximately one third of the patients below 70 years of age was found to be eligible for BCS.

In the nineties, the performance of BCT has increased. The national figure of BCT frequency constituted 24 % of surgical procedures in operable breast carcinomas, while mastectomy made up 74 %. In 2 %, the procedure was not registered in the DBCG data base.

The development of applying the BCT as a surgical option in Denmark is apparent from Figure 1. Generally speaking, the frequency is low. However, the incidence has increased over time. Further, the frequency of BCT varies among centers being highest in areas with mammographic screening for breast cancer and in the centers where the surgeon works as an integral part of a specialist breast team.

In Denmark, the treatment of breast cancer is organized and conducted by the DBCG by running nationwide predetermined protocols. Approximately 95 % of all newly diagnosed breast cancer cases are registered on case report forms and processed within the DBCG data base.[18] All of the disciplines involved in breast cancer management work within the frame of DBCG according to the agreed guidelines in order to ensure and maintain high professional standards.

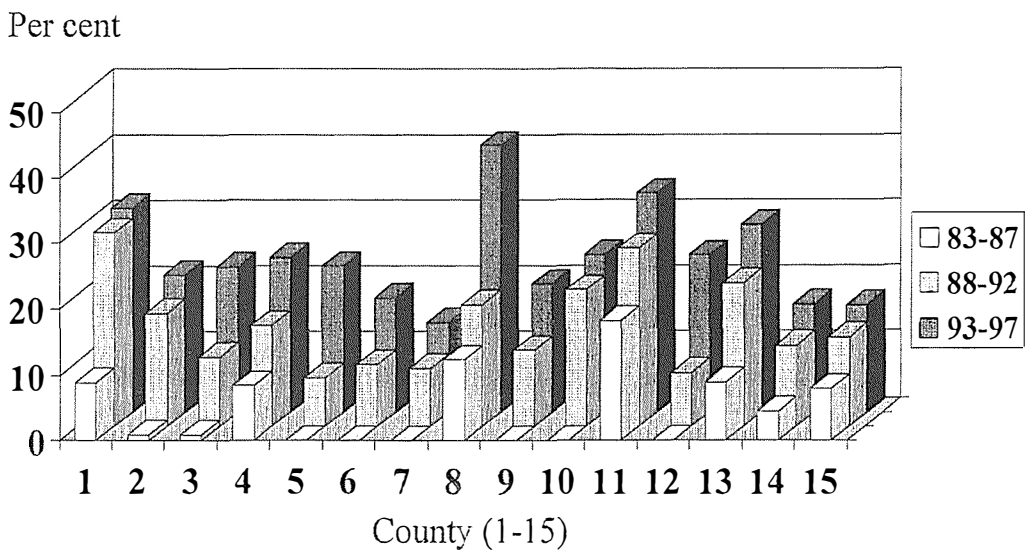

Figure 1. The distribution of BCT in Denmark from 1983 to 1997 divided into 5-year periods related to individual counties.

The decision-making whether or not to perform BCS is based on the knowledge of the natural history of breast cancer and the updated results of BCT as mentioned earlier. Consequently, grave concern is given to surgical radicality, notably in small tumours, young age, extensive intraductal components, multifocality, and multicentricity.

DBCG recommendations for BCT

1) Small tumours allowing complete excision with free margins verified histologically. In unifocal tumours with no tumour foci around the reference mass, approximately a 5mm free margin is required. In tumours with tumour foci (invasive or intraductal) present in the vicinity of the reference mass, approximately a 10 mm distance from the edge of the tumour area to the nearest margin is advised. In Denmark, the national figure of tumour size has not changed considerably over the past 20 years and is on average 26 mm, measured histologically. A relatively large tumour diameter at the time of diagnosis puts a limit to the performance of BCS.

2) An excellent to good cosmetic outcome is mandatory for the execution of BCS. To obtain a satisfactory cosmetic result, the ratio of tumour size to breast volume is decisive. A relatively large tumour size in Danish patients constitutes an obstacle to limited surgery in the management of breast carcinomas.

3) Tumour location. The preferable tumour location for BCS is in the periphery of the breast. Tumours located close to the nipple areola complex are less fit for resection and radicality is difficult to safeguard if cosmesis has to be valued. Tumours located in the lower half of the breast might also create difficulties from a cosmetic point of view. In such cases, primary breast reconstruction might constitute an alternative surgical option.

4) Patient's preference plays a role in the decision-making. The decision may be influenced by the wish to avoid radiotherapy which might not be employed in case of mastectomy. Maybe radiotherapy facilities are not available and the patient has to travel a long distance. The patient has a genuine preference for mas-

tectomy owing to safety reasons although fulfilling the eligibility criteria of BCT.

5) Surgeons preference. Undoubtedly, the surgeon's own experience, training, and firm belief has an impact on the decision whether or not to remove the breast. This factor might contribute to the varying frequency of BCT executed in the various regions in Denmark.

6) Age, definitely, influences the decision-making. Due to abundant and dense breast tissue in young age, the tumour might be difficult to delimit. Further, there is an increased risk of multifocality and multicentricity in young age as previously stated. These issues taken together with more tumour aggressiveness underline the necessity of radical and meticulous surgical removal of tumour. Under these conditions, surgeons might prefer mastectomy to BCT.

7) The policy of primary chemotherapy in large tumours to make the tumour diminish has a bearing on employing BCT. In Denmark, primary chemotherapy is employed in case of locally advanced breast cancer, but not as an up-front therapy prior to BCT.

Advantage and outcome of BCT

The main incentive to BCT relates to retaining femininity and avoiding the feeling of female inferiority and a disfigured body image. The most important prerequisites for achieving these goals in BCT are a satisfactory cosmesis, good physical function, and loco-regional disease control. On the other hand, preserving the breast does not by itself prevent emotional sequelae as seen in postmastectomy.[19,20] In particular, the younger patients undergoing mastectomy score clearly lower on body image compared to BCT.[20] The dilemma is obvious. The younger patients most in need of breast preservation are those less eligible for the procedure.

Today, BCT is an accepted method in the management of potentially curable patients found to be eligible for the method.[21] However, eligibility criteria differ between centers and even among countries and there is a considerable geographic variation in the utilization rates of BCT. The influence of these diversities upon routine BCT outcome is not thoroughly reported. However, time to loco-regional recurrence, time to distant progression, and overall survival are found to be equal in most major randomized trials comparing BCT with mastectomy, viz. NSABP-B-06, Milan I, EORTC 10801, DBCG 82TM.[16,17,21] Tumour size, nodal status, histological grade, and vascular invasion are prognostic factors for poor outcome and of the same magnitude regarding BCT and mastectomy. However, in randomized trials young age and extensive intraductal components seem to increase the risk of local recurrence in the BCT series compared with mastectomy (personal communication).

Loco-regional recurrence after BCT

The prognosis related to loco-regional recurrence (LR) after mastectomy is well known, while the situation in BCT is less clarified. A study combining the results from the EORTC[16] and DBCG[17] randomized trials on BCT vs. mastectomy revealed that LR occurred significantly earlier in the mastectomy group, on an average 1.2 years.[22] Approximately 8 % of the series had LR as the first event in a 10-year of follow-up.

Overall, 49 % with LR as a first event died within 74 months of follow-up after salvage treatment. The survival curves were comparable with 5-year survival rate of 58 % in mastectomy and 59 % in BCT. The most common local therapy of LR in BCT was salvage mastectomy and in mastectomy excision with or without radiotherapy.

Overall, 35 % of patients with LR as the first event developed a subsequent LR. There was no significant difference between the actuarial curves of BCT and mastectomy presenting 5-year actuarial LR rates of 62 % in the mastectomy group and 63 % in BCT. All subsequent LR appeared within a time span of 5.5 years after salvage therapy.

The study seems to indicate that LR as the first event after initial BCT or mastectomy basically harbours the same biological potential of spread and consequently bears the same bad prognosis.

Conservation of axillary lymph nodes

At the St. Gallen Conference, 1998, the International Consensus Panel advanced the statement that the most relevant factor for the assessment of risk in breast cancer remains the axillary nodal status and the number of nodes involved.[23] Further, agreed European guidelines claim that histological node status should be obtained in the women with invasive cancer having a planned curative operation.[24,25] Minimal requirements are four nodes retrieved and examined if a sampling procedure is done, otherwise 10 nodes examined are preferable in level I-II dissections.

The prime objectives of axillary surgery in the management of potentially curable breast carcinomas are 1) accurate staging, 2) treatment to cure, and 3) quantitative information of metastatic lymph node involvement for prognostic purposes and allocation to adjuvant treatment protocols.[26]

It is agreed that no physical examination of the axilla, no imaging techniques, and no molecular biologic markers can today replace axillary surgery for staging purposes. Understaging the axilla is detrimental to final outcome.[26,27,28]

The extent of axillary dissection has a bearing on all three outcome measures mentioned above, why "adequate" surgery generally is recommended. Normally, adequate surgery means the dissection of axillary level I and II, - and level III if suspicious nodes are palpated at that level during operation. It is important to avoid axillary failure. Ordinarily, a total axillary dissection (level I-III) provides a low risk of subsequent axillary failure, less than 1-2 %. On the other hand, if less than a total dissection has been done, the risk of axillary failure turns out to be inversely proportional to the number of nodes retrieved.[27] Axillary recurrence seems to reduce survival probabilities, causes significant patient morbidity, is difficult to salvage, and might lead to uncontrollable axillary disease.[29]

It is well established that the frequency of axillary lymph node involvement is directly proportional to tumour size. The proposal has been put forward that, in small tumours, the axillary dissection can be avoided. This suggestion seems not to be supported by the recent Danish national figures on the frequency of axillary spread based on the results from 16,660 DBCG patients below 75 years of age operated upon during the period 1990-1997 and with at least four axillary nodes removed.[26] Overall, 44 % of patients had axillary nodal spread. The percentage of node

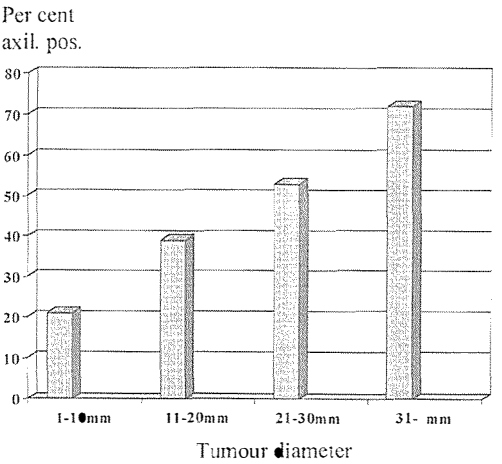

Figure 2. Distribution of node positivity by axillary dissection in operable breast carcinoma patients related to tumour size.

positivity increased from 21 % in tumours 1-10 mm in diameter as measured by the pathologist up to 72 % in tumours more than 30 mm in diameter (Figure 2). In T1a tumours, 5 mm or less, node positivity reached 16 % and in T1b, 6-10 mm, the value was 23 %. Further, it appeared that the percentage of patients with four or more positive nodes (N=7,631) increased from 23 % in node positive tumours of 1-10 mm up to 59 % in node positive tumours of more than 30 mm in diameter (Figure 3).[26] The tumour burden seems to be high even in case of small tumours. Consequently, the avoidance of axillary dissection seems not advisable, and especially not from the point of view that radical surgery seems most important in the management of the very early stages of breast cancer.[1,2]

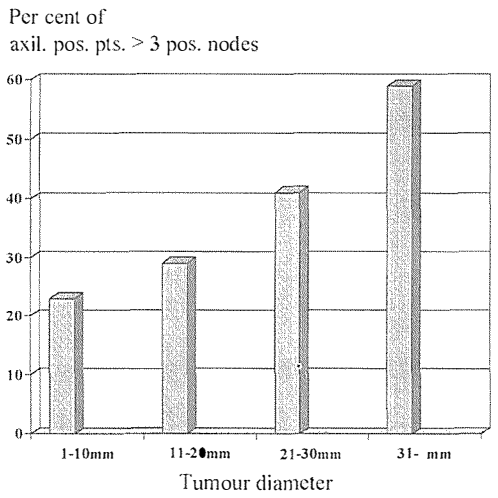

Figure 3. Percentage of patients with four or more positive axillary nodes related to tumour size in node-positive patients with operable breast carcinoma.

Sentinel node

Whether or not to clear the axilla still represents a dilemma. The procedure carries a certain morbidity and functional sequelae. Further, no advantage is gained by removing healthy lymph nodes in node negative axillas, rather on the contrary.

The introduction of the sentinel node procedure may solve the problem and contribute to the lymph node conservation in surgical oncology. The basic principle encompasses lymphatic mapping of the axilla and selective lymphadenectomy with the intention to identify a particular lymph node in a regional lymphatic basin assumed to be the first node in a direct drainage pathway. This particular node is described as the sentinel node.[30,31] If the sentinel node retains metastatic spread, the risk of involvement of non-sentinel nodes in the axilla cannot be neglected and the axilla should be dissected. If the sentinel node is not involved, no further action seems to be taken and no additional surgery is needed.

The eligibility criteria for the usage of the sentinel node method in the management of breast cancer are not yet completely agreed upon. Most commonly, the criteria laid down are tumours with a diameter less than 4 cm, unifocal lesions, and palpatory negative axillas, also negative by ultrasound and fine needle biopsy. However, in many institutions the criteria are handled more strictly. The method is so far not yet widely implemented, and a more liberal access to the procedure needs the gathering of breast cancer surgery on fewer hands in order to keep up experience, training, and high professional standards.

A crucial point for routine use of the method is documented expertise demonstrating a sufficient high detection rate of the sentinel node (preferably approximately 90 %) and an acceptable low rate of false negative node (preferably below 5 %), i.e. metastatic spread to axillary non-sentinel nodes while the node appointed the sentinel node is proved without metastasis. The detection rate of sentinel node varies with the technique used and values below 90 % are in fact given.

In most institutions of excellence the sentinel node method has been adopted as a routine procedure. The method is still under evaluation and intensive research projects are

launched. It is beyond the scope of this presentation to cover this vast field of research and progress. Undoubtedly, the sentinel node will change the policy of managing the axilla and will provide a basis for conservation of healthy lymph nodes in node negative patients.

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review

The intraoperative examination of axillary sentinel nodes

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Routine histological examination of axillary sentinel nodes predicts the nonsentinel axillary node status and may allow to spare axillary clearing in patients with breast cancer. To avoid the need for two separate surgical sessions the results of sentinel node examination should be known intraoperatively. Routine frozen section examination of sentinel nodes, however, is liable to yield false-negative results. An extensive intraoperative examination of frozen sentinel nodes which would attain a sensitivity comparable to that obtained by routine histological analysis has been therefore devised. The frozen sentinel nodes are subserially sectioned at 50 μm intervals. For each level, one section is stained with hematoxylin and eosin (H&E) and the other immunostained for cytokeratins using a rapid immunocytochemical assay. Immunocytochemistry did not increase the sensitivity of the examination. The general concordance between sentinel and axillary node status was 96.7 %; the negative predictive value of intraoperative sentinel node examination was 94.1 %. The intraoperative examination of axillary sentinel nodes is effective in predicting the axillary node status of breast cancer patients and it may be instrumental in making the decision to spare axillary clearing.

Key words: breast neoplasms - surgery; lymph node excision; axilla; lymph nodes - pathology; intraoperative period; immunohistochemistry

Introduction

The axillary sentinel node biopsy (i.e. the biopsy of the first node draining the lymph from the tumour) in patients with small primary breast carcinomas and clinically uninvolved axillary nodes is rapidly gaining wide diffusion.[1-4] Several investigations have documented that this procedure has a very high (96 to 100 %) negative predictive value with respect to the status of the remaining nonsentinel axillary nodes, and may avoid unnecessary axillary lymph node dissection (ALND) in patients with negative sentinel nodes.[5-7]

Axillary lymph node status is the most powerful prognostic parameter in breast carcinoma patients, and dictates the choice of the post-surgical adjuvant treatment. Because it is not possible to assess the node status clinically or by imaging techniques, ALND

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with the removal of at least part of the axillary nodes has represented till now the treatment of choice in ablative or conservative breast surgery.

ALND, however, may lead to several complications, like oedema, numbness, pain and weakness of the arm. Furthermore, mammographic screenings and women's consciousness have resulted in an ever increasing prevalence of patients being treated with ALND for very small primary tumours. Accordingly, these patients are less likely to have already developed axillary node metastases. Indeed, ALND will yield uninvolved lymph nodes in approximately 65-70 % of patients with small (pT1) primary tumours.[5-7]

Also, it should be taken into account that approximately 25 % of the patients who have undergone ALND and are without histopathological evidence of axillary metastases (pN0) will experience disease progression. This is most likely due to an inaccurate sampling or examination of all the nodes removed by ALND with the missing of (micro)metastatic foci. Indeed, the re-examination of axillary nodes by serial sectioning or use of more sophisticated techniques (e.g. immunocytochemistry for cytokeratins) allows to identify the missed metastases and to up-stage a similar percentage of patients.

The SNB may spare ALND in patients with uninvolved sentinel nodes, and at the same time enables the pathologists to extensively examine individual (or very few) lymph nodes by serial sectioning and use of immunocytochemical techniques. This results in the highest likelihood of detecting even the smallest metastatic deposits with a more correct staging of the disease. Indeed, the prevalence of sentinel lymph node metastases in patients with small (pT1) primaries is much higher than expected, almost reaching 35 % of the cases. In approximately 40 % of these patients, the sentinel nodes are the only involved axillary nodes, thus reinforcing the validity of the SNB concept.[8-10]

Though the short follow-up period does not allow to evaluate the clinical course of the disease in patients with uninvolved sentinel nodes, it is likely that the SNB procedure will allow to identify true pN0 patients with a very favourable prognosis.

The histopathological examination of axillary sentinel nodes

To be effective in the management of breast carcinoma patients, SNB must rely upon an extremely careful and extensive histological examination of the sentinel nodes, which must be entirely and serially sectioned at reduced intervals. Both, computer simulations and the current practice have documented that to identify small micrometastatic foci (2 mm in size or less) the sentinel nodes must be sectioned at 50-200 microns intervals, with the examination of up to 60 or more sections per node.[7,11]

The histological examination of the axillary sentinel nodes may be performed on permanent sections of formalin-fixed, paraffin-embedded tissue, or intraoperatively on frozen sections. This latter procedure has the advantage of enabling to complete the surgical treatment of the primary tumour and of the ALND in a single session. Again, even in the case of an intraoperative examination of the sentinel nodes, the nodes must be entirely and serially sectioned. Indeed, the examination of few frozen sections of only a moiety of the node (as routinely done for other purposes) will lead to an unacceptably high number of false negative diagnoses.

To overcome this drawback, we have devised a procedure for the extensive intraoperative examination of the axillary sentinel nodes.[7] The nodes are bisected and both moieties are frozen in isopentane chilled by liquid nitrogen. Fifteen pairs of frozen sections are then cut at 50 microns intervals from each moiety. Whenever lymph node tissue is left,

additional pairs of sections are cut at 100 micron intervals, until the complete examination of the node. One section of each pair is routinely stained with haematoxylin and eosin (H&E), while the other is kept unstained for the possible use of immunocytochemical reactions for cytokeratins. These are done to assess the malignant nature of suspicious cells identified in the corresponding H&E-stained sections.

In our case, the general concordance between the intraoperative examination of sentinel nodes and axillary-node status was 96.77 %, the true false-negative rate 3.22 %, the sensitivity 93.3 % and the negative predictive value 94.1 %. The time required for such an extensive examination of the sentinel nodes is approximately 40 minutes, which are normally spent by the surgeon to complete ablative or conservative mastectomy (having done the SNB first).

Immunocytochemistry and molecular biology in the examination of axillary sentinel nodes

Many reports have emphasised the role of immunocytochemistry in the accurate identification of (micro)metastases in the sentinel nodes and have recommended to perform immunoreactions for specific epithelial markers (cytokeratins) in all sentinel nodes.[12-14] It must be considered, however, that the use of immunocytochemistry does not overcome the need for an extensive sectioning of the node, which must be entirely sampled. To keep the time required and the costs of the examination of the sentinel nodes as low as possible, the use of immunocytochemistry may be confined to those cases which cannot be confidently diagnosed on purely morphological grounds. This holds particularly true for single-cell metastases commonly occurring in invasive lobular carcinomas. The percentage of cases subjected to immunocytochemistry depends upon the training and expertise of the examining pathologist on the one side, and upon the quality of the tissue sections on the other.

Even more recently, the possible role of the amplification by PCR of specific mRNA molecules to detect sentinel node metastases has been exploited.[15,16] In these procedures, RNA molecules are extracted from fresh/frozen lymph nodes, and complementary DNA is synthesised by reverse transcription. Epithelial-specific markers (cytokeratin 19, CEA, MUC1, maspin, mammaglobin, etc) are then amplified by PCR. These techniques are effective in identifying a single metastatic cell among 1,000,000 normal lymphoid cells in *in vitro* experiments. *In vivo* results, however, have been less impressive thus far. Indeed, the sensitivity of these techniques often does not reach the expected 100 % of cases known to harbour metastases (most likely due to the problems with the sampling procedures). Even more important, however, is their low specificity, with several false-positive results when the techniques are applied to uninvolved lymph nodes or to lymph nodes from patients without any neoplastic disease.

The clinical implications of micrometastases in axillary sentinel nodes

A most debated issue in the SNB procedure is related to the clinical implications of the occurrence of micrometastases in the sentinel nodes. It has been formerly discussed whether these small metastases have an impact on patients' survival, and many investigations -but not all- on the subject have documented a prognostic implication of the axillary micrometastases in the patients with long-term follow-up.

In the contest of the SNB, however, it is important to assess whether the detection of micrometastatic disease in the sentinel nodes is predictive of the occurrence of additional

metastases in the nonsentinel axillary nodes. Contrary to the findings of other groups[17,18], in our experience, approximately 25% of 150 patients with micrometastases in the axillary sentinel nodes harbour additional axillary metastases. In 75% of these cases, the additional metastases are larger than 2 mm, and their prognostic value is undisputed. Accordingly, we suggest that patients with micrometastatic disease in the sentinel nodes undergo ALND, unless they are enrolled in randomized clinical trials specifically designed to address the question of the proper surgical management of the axilla.

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review

Organ sparing for rectum and quality of surgery for preventing local recurrences

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The progress in the management of rectal cancer in the last 100 years has been phenomenal. From the days of Myles abdominal perineal resection at the beginning of the 20th century we have progressed to being able to manage most rectal cancers without the need for a permanent colostomy and from a surgical procedure associated with 40% local recurrence to one with less than 5%. Adjuvant modalities with radiotherapy and chemotherapy have similarly proven useful in advanced disease to improve not only local control but also survival. In the manuscript the particular attention is paid to two aspects: 1) the surgical technique that is so critical in improving survival by improved local control and 2) looking at anal-preserving surgeries for advanced and low rectal cancers. It is concluded that a properly done procedure using the TME approach supported by preop radiation for advanced lesions will result in excellent local control and function in over 90% of low rectal cancers.

Key words: rectal neoplasms - surgery; neoplasms recurrence, local prevention and control

The progress in the management of rectal cancer in the last 100 years has been phenomenal. From the days of Myles abdominal perineal resection at the beginning of the 20th century we have progressed to being able to manage most rectal cancers without the need for a permanent colostomy and from a surgical procedure associated with 40% local recurrence to one with less than 5%. Adjuvant modalities with radiotherapy and chemotherapy have similarly proven useful in advanced disease to improve not only local control but also survival.

In my presentation I wish to particularly look at two aspects: 1) the surgical technique that is so critical in improving survival by improved local control and 2) looking at anal-preserving surgeries for advanced and low rectal cancers.

In the last 20 years, there have been a number of prospective studies that have identified the surgeon as a prognostic factor in rectal cancer outcome. This implies that surgical techniques are critical in providing local control than the biology of the disease. Philips published the first of these in the early 1980's.

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In the prospective data base of the UK Large Bowel Project, over 1000 procedures were analyzed. For the 20 surgeons who had done greater than 30 patients and as many as 100 patients, the local recurrence varied between 5 % and 20 %. There was no difference between the local recurrence whether it was done by the resident working for the consultant or by the consultant. In another prospective data base published from Edinburgh which looked at 13 surgeons who had treated 645 rectal cancer patients, they noticed not only a major difference in postoperative morbidity, curative resection and leak rate but they also saw the local recurrence vary between 0 and 21 % as well. Ten-year survival varied between 20 % and 63 %. The Swedish Rectal Trial has also been analyzed and it has been shown that similarly in the 11 surgeons who had done greater than 25 procedures, in other words, experienced surgeons, for a total of 464 patients, the percent of abdominal perineal rate changed varied between 40 % and 80 % and the 3-year local recurrence varied between 0 and 41 %. The analysis showed that local recurrence was lower in the patients who had surgery at the university hospitals and the death was lower in specialists who had been practicing for more than 10 years. Finally, in the rectal cancer study in Germany, Hermanek has shown that local recurrence was different according to the departments the surgery was performed in. It also varied by the surgeon and was affected by low volume. There seems to be no question that in fact the surgeon is the prognostic factor in this disease in terms of local recurrence and function. What is encouraging is that local recurrence significantly influences survival. If in fact we could identify what makes the difference, then the appropriate techniques can be taught.

It is no wonder that results are so variable if we look at the standards of surgery for this disease if we look at the quality control of the NSABP R-01 Study with adjuvant treatments. The only requirements were that the tumor must be completely resected, margins tumor free, mesentery should be removed with the specimen, and the levators should be transected at the pelvis wall when possible. With our knowledge today of good rectal cancer surgery, this is a totally inadequate measure of what constitutes a proper rectal operation.

In the early 80's we became interested in local recurrence of rectal cancer and took advantage of our prospective Cancer Registry to see if the quality of surgery made a difference as determined by the pathology and surgical record. Using this data base in a retrospective manner the only things we could determine were whether the specimen was removed intact, whether the tumor was transected during the procedure, and whether there was a 2.5 cm distal margin. Using these basic criteria we identified a difference in outcome in two groups of patients. In Stage I and Stage IV patients there was no difference in the quality of surgery and the ultimate outcome. However, in Stage II and III patients there was a significant difference. In the Stage II patients the local recurrence for the adequate surgical group was 7 % as compared to 50 % in the inadequate group despite the fact that the latter had a higher rate of postoperative radiotherapy. In Stage III patients the local recurrence was 18 % for the adequate group as compared to 64 % for the inadequate group. The survival was also improved in the former group. Similarly, patients who had the inadequate resection had radiotherapy more often. In other words, radiotherapy did not make up the difference for poor quality surgery. A number of other retrospective studies identify this. The most recent one being from Edmonton AB, our sister city, which looked at patients who had perforation of the rectum during the procedure as a marker of poor surgery. In those patients who had intact specimens, local recurrence was 17 % as compared to those who had perforated specimens at 54 %. There was also a significant

drop of survival by 25 % in the latter group of patients. We also see now that reports being published using total mesorectal excision which identify in over 1800 patients only 8.6 % local recurrence. This is dramatically different from the standard studies from years past of rates of 40 %.

In 1987, our own division adopted the mesorectal TME approach as described by Bill Heald. We compared our results over the last 8 years to the results of general surgeons and colorectal surgeons from 1992. Our hypothesis was that a properly procedure using the oncology principles is the most and probably the only significant determinant for maximizing local control and function. This should be reflected in the degree of training as measured by the Board-certified general surgeon, Board-certified colorectal surgeon, or an oncology surgeon. Once again we used our Cancer Registry and identified all rectal cancers done in our region of about 1 million people, and compared it to our own surgical oncology practice. There were a total of about 70 resections done in that time and the median follow-up was 2.5 to 3 years. The use of radiotherapy was significantly different in the 3 groups with the general surgeon and the colorectal surgeon using it mostly postop as compared to the oncology surgeon who used it almost exclusively preop. Secondly, the use of abdominal perineal resection was very much less for the oncology surgeon who had a sphincter-saving rate of 94 % as compared to 50 % and 60 % for the general surgeon and the colorectal surgeon. Analyzing this further, it showed that very few sphincter-saving procedures were done with tumors between 0 to 5 cm in the non-oncology surgeons as compared to 60 % for the surgical oncologist. Only two thirds of the time was the sphincter saved for a lesion between 5 and 10 cm for general surgeons and colorectal surgeons as compared to 100 % for surgical oncologists.

Finally, the local recurrence was 33 % for general surgeons, 6 % for colorectal and 0 % for surgical oncologists. This study shows that one can obtain superior local control and preserve function in most patients with rectal cancer using appropriately applied oncology principles. This study, unlike many others, also identifies training as more important than volume. We now see that in one other retrospective study reported from Edmonton, colorectal surgeons did better than non colorectal surgeons in terms of local control and survival. As well, more volume for colorectal and non-colorectal surgeons was associated with a decreased local recurrence. We also see around the world that the training approach by Bill Heald for teaching TME to Swedish and Norwegian surgeons decreased local recurrence of rectal cancer surgery from 40% to 10%. This is the most definitive proof that the proper technique is teachable and reproducible in surgeons who have an interest in rectal cancer.

What was unexpected in our study was to see how common abdominal perineal resection is still being performed for rectal cancers as compared to our group of patients. Our experience documented that even in more advanced rectal cancer sphincter-sparing procedures were possible and safe. Using preoperative radiotherapy in particular and also employing the colo-anal anastomosis an excellent functional result is possible without risking local recurrence in low rectal cancer.

We still see in the 1993 edition of a colorectal surgery text by Stanley Goldberg that the abdominal perineal resection as the 'gold' standard for this disease. In fact, the data today refutes this approach. There is no embryological anatomic, oncologic or clinical data to support this approach. Rectal cancer does not spread through lymph nodes that traverse the levators. In order to have a perineal recurrence an abdominal perineal resection is a prerequisite. Modern series show no difference in local recurrence in rectal cancer whether the anus has been preserved or removed. Heald has recently published that

in 85 curative, consecutive anterior rectal cancer resections below 5 cm in which sphincter-saving surgery was performed local recurrence was 1 % at 6 years follow-up. In detailed pathologic studies, we see that distal spread, even in advanced cancer is contained within 15 mm of distal bowel and lymph node spread in advanced cancer is contained in 2.5 cm. The majority of patient's tumor, both in the rectal wall and the lymph nodes, is contained within 1 cm.

There are now a number of studies identifying that coloanal anastomosis, particularly with a 5 cm J-pouch, give excellent long-term function with continence of 91 %. Even a straight anastomosis, which is technically easier to do gives a 70 % perfect result at 3 years. Age is not a contraindication to this approach. In one study of 40 patients the only difference in results was a higher constipation rate in patients over 75. In those patients with advanced cancers, radiotherapy can downstage the lesion to allow a coloanal or low rectal anastomosis be performed. In the two studies reported on the conversion of patients needing abdominal perineal to sphincter-saving procedure with the use of preop radiotherapy, approximately 70 % could be salvaged by radiotherapy. Local failure was about 10 % with a 70 % to 80% excellent sphincter function.

It is apparent that the literature now identifies that surgical techniques are available that reduce local recurrence even without radiotherapy to less than 5 % in T1-2 lesions and in T3, T4 lesions, radiotherapy can downstage the lesion so that sphincter-saving procedures may be performed. We also see that the mesorectum in the majority of cancers contains all local regional disease and distal spread is usually less than 1 cm allowing one to do coloanal anastomosis in low lesions. The abdominal perineal resection should, therefore, be relegated only to patients with involvement of the anal sphincter or levators.

In conclusion, a properly done procedure using the TME approach supported by preop radiation for advanced lesions will result in excellent local control and function in over 90 % of low rectal cancers.

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review

Limb salvage in soft tissue sarcomas

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In 2000, most patients with soft tissue sarcomas of the axial or appendicular skeleton can expect 'to walk away' from the surgery. This compares to just 20 years ago when a relatively high percentage of patients were treated with amputation. Now the treatment has changed to one of wide local excision with a 1 cm to 2 cm margin on normal tissues and an adventitial margin on critical structures such as nerves or vessels, followed or preceded by radiotherapy. With the use of adjuvant treatments in combination with reconstructive surgery, over 90% of patients with sarcomas of the soft tissues or bone may be rendered disease free locally. The only restriction to this approach is when tumor involves the major nerve to a limb or when microscopic, clear margins cannot be obtained at the time of surgery as both of these are best treated with an amputation.

Key words: soft tissue neoplasms; sarcoma surgery; extremities; neoplasms staging; survival rate

In 2000, most patients with soft tissue sarcomas of the axial or appendicular skeleton can expect 'to walk away' from the surgery. This compares to just 20 years ago when a relatively high percentage of patients were treated with amputation. Now the treatment has changed to one of wide local excision with a 1 cm to 2 cm margin on normal tissues and an adventitial margin on critical structures such as nerves or vessels, followed or preceded by radiotherapy. Unfortunately, this approach still results in 20 % local recurrence in the best centres around the world. In the most recent series, some from centres such as the Memorial Sloan-Kettering, we see the recurrence ranges from as low as 7 % all the way to 34 %.

We are most fortunate in our province in having a centre that supervises treatment of all cancers for a population of about 2 million people. In 1984 we established an interdisciplinary Sarcoma Group, including plastic surgeons, orthopedic surgeon, surgical oncologist, radiation oncologist, medical oncologist, and pathologists, to try to improve the results in these patients. We took advantage of the experience reported by Eilber out of Los Angeles who demonstrated a 4 % local recurrence rate in over 100 patients followed for 5 years using a preop chemotherapy and radiotherapy regime. Their morbidity rate, howev-

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er, was fairly high with a re-operation rate of 20 % and a fracture of the long bone in follow-up of 5 %.

In 1984, we began a prospective study to look at a modification of this regime, which I will report to you in the following series. This includes patients treated for soft tissue sarcoma, bony sarcoma, and pelvic sarcoma.

The first is a prospective, cohort trial of conservative surgery for soft tissue sarcomas. Our protocol administered the same amount of adriamycin as Eilber, usually by the intra-arterial route if there was a feeding vessel, at 30 mg/day continuous infusion for 3 days. Radiation followed immediately with 3 Gy for 10 days for a total of 30 Gy. This is followed by a surgical excision no sooner than 4 weeks after the completion of radiotherapy. For example, a 35-year-old woman presented with a large mass, which had been followed mistakenly for 8 months as a hematoma. A CT scan showed a large mass behind the femur, applied to the sciatic nerve. Biopsy demonstrated this to be a myxoid liposarcoma. She was treated with the intra-arterial infusion of the common iliac artery as described and radiotherapy. In the planning film prior to radiotherapy a lead wire shows a mass extending well past the greater trochanter of the hip but after therapy there was marked shrinkage of this tumor so it is difficult to see any extension. The tumor was excised taking a centimetre of normal tissue and preserving the sciatic nerve. On cross section, the tumor still had viable components that are typical of a myxoid liposarcoma but was one half the original size. She is alive now, 17 years after the surgery, with excellent cosmetic and functional result. This study reports all our patients up to 1992 so we have a minimum of a 3-year follow-up at which time 90 % of all local recurrences would be expected to have occurred. This is based on a population rather than a referral practice. We took all soft tissue limb and trunk sarcomas which were in the high-risk category of recurring, including the deep, large, high grade or recurrent tumors. Lesions that involved sciatic nerve or brachial plexus were excluded as the resection of the sciatic nerve results in a senseless and motionless limb. Patients with positive margins were offered amputation. We had 42 patients, ages 13-79, who were treated with this protocol. Two failed this protocol in that they had positive margins; one refused amputation and subsequently re-resected with a recurrence and is still free of disease. The follow-up ranged from 24 to 110 months with a mean of 5 years. This included 25 primary and 15 recurrent tumors that had failed previous attempts at surgery. The majority of these lesions are on the lower extremities, with 6 on the upper extremities, 2 on the abdominal wall, and 2 in the head and neck.

The TNM staging shown here with all but 4 patients being Stage II or greater with some being as advanced as Stage IV. The majority of these lesions are IIB and III Stages. The histologic tumor type varied among many cell types with the most common being synovial cell, leiomyosarcoma, liposarcoma, and malignant fibrohistiocytoma. Complication rate in these patients included problems with the adriamycin infusion in 10 %, wound infection, prolonged drainage in 12 %, re-operation in 2 %. Five percent had positive margins, and out of these, 1 ultimately required an amputation. The follow-up, now which was an average of 6 years since the study was completed, is 97 % local control for appendicular and 100 % for tumors on the trunk. The survival of these patients shows that only 40 % are alive at 10 years demonstrating the highly malignant potential of most of these lesions.

This protocol is unique in the literature in terms of its local control and the very low incidence and minimum of wound complications. These lesions, in our study, were all at high risk to recur as documented by the analysis from MD Anderson which showed that Stage II had a minimum of 14 % local recurrence increasing to 45 % in Stage IV.

Lesions larger than 5 cm had a 31 % incidence of local recurrence as well as this being shown for tumors with higher grade and for those having recurrences. We are still struggling, in approximately 30 %, with minor adriamycin rashes, and in 10 % significant complications. These, however, happened in the first few patients where we had intra-arterial thrombosis during infusion. It is absolutely critical that these patients be maintained on enough heparin to keep the prothrombin time well above 60 seconds. Tumors have been seen to shrink during the adriamycin infusion and these patients are hypercoagulable because of the massive procoagulant release of the dying tumor cells. We are still struggling with the problems of seroma in these large cavities and plastic surgical techniques with bringing in local muscle flaps have promised to improve this dilemma. As well, large tissue defects can now be covered with flaps which avoid the problems of wound breakdown.

We feel that this is a complex disease where the close cooperation between the surgeons and the radiotherapists is important for improving the result. We do not feel that this tumor should be approached by the surgeons who have not had special training in this area or in the absence of team support.

Overall survival of these patients with this dose of chemotherapy is unlikely to be affected. Now that local control has been accomplished in these tumors, the next and very pressing issue is to continue studying the use of adjuvant chemotherapy which to date has been disappointing in all but a few of the sarcomas such as Ewing's, osteosarcoma, and perhaps rhabdosarcoma.

In conclusion, this population-based, prospective study documents a superior approach for local control of soft tissue tumors.

We have now extended this same approach to management of sarcomas involving the bony appendicular and axial skeleton. To this day, the standard of care for these patients is, in fact, an amputation. However, with the neoadjuvant approach it may be that with the technical support for replacing bones, the same principles could apply. So along with our study of soft tissue sarcomas, we also began a parallel study for tumors involving the bone. In planning the surgery, MRI became a critical component to identify intramedullary extension of the tumor. This compares to the soft tissue tumors where CT scan alone is a very reasonable approach. Once again, our objective was to provide a microscopic clear margin with a 1 cm margin in all direction except for the bone being frequently a much more difficult task. An allograft or an alloplastic interposition graft was planned prior to the surgery. To demonstrate the approach, I am presenting 2 patients. The first one having Maffucci's Syndrome with multiple enchondromas, 2 of which had become chondrosarcoma. A total scapulectomy and removal of the proximal 2/3 of the humerus was planned and an alloplastic titanium insert was designed using the same engineering developments that have been pioneered for the space shuttle. The model of the scapula and humerus was created from the CT scan and the final constrained prosthesis designed for the surgery. The operative defect shows the arm only connected by a small skin bridge and the axillary nerves and vessels. The scapula and humerus were replaced by a prosthetic alloplastic scapula. The postoperative x-ray shows the prosthesis in place. The patient had full function of her lower arm.

The second patient is a young woman who presented with an expanding mass of the wrist with having failed a previous attempt at controlling a giant cell tumor. This tumor was locally infiltrative and destroyed the distal radius. She was treated with a preoperative radiotherapy and chemotherapy and taken to surgery 4 weeks later where the tumor was completely resected, preserving only the ten-

dons, nerves, and vessels. The resected portion was replaced by an allograft portion of radius plated in place and she has a fully functioning hand with no local recurrence 5 years later.

Our population of these patients now includes 10 patients with ages ranging from 17 to 73. Two patients were treated with shoulder replacements, 3 with replacement of pelvic bone, and 5 with lower femur replacements. Using TNM staging, they were at least Stage IIB. The pathology included 5 osteogenic sarcomas, 2 giant cell tumors, 1 chondrosarcoma, and 1 undifferentiated sarcoma. These patients all completed a metastatic work-up and for those patients with an osteogenic sarcoma or Ewing's sarcoma, preoperative systemic therapy was part of the management. All patients ended up with a functional limb but did require braces or walking aids for those having an internal hemipelvectomy and to date there has been no local recurrence. However, 1/3 of these patients developed systemic disease and ultimately succumbed. None of these patients had graft failure. One patient had a chronic infection requiring removal of the graft. During treatment approximately half of these patients had fractures of the treated bone during the time of radiotherapy but were treated with a brace until the time of surgery. This did not result in local recurrence with follow-up averaging 3 years. This experience contrasts to the analysis in the literature reported by Mankin where an above-knee amputation for osteosarcoma of the distal femur resulted in 8 % local recurrence and hip disarticulation 0 %. The survival was unchanged at 55 %. This confirms that the possibility of local recurrence does not change the propensity of the tumor to metastasize. This is an inherent property of the cell, which has taken place, as far as we can determine, many months before the initial presentation in the majority of patients. Therefore, our protocol of chemotherapy and radiation has reduced the requirements for amputations from 100 % to 11 %. One amputation was necessary in a patient with a tumor infiltrating the popliteal nerve. Fracture of the bone did not affect the subsequent therapy or local recurrence and in all these patients with reconstruction, a functional limb was retained. We currently are favoring alloplastic replacement despite the expense. However, in none of our allografts have we had a fracture although that is a well-documented, long-term complication of using this material.

In conclusion, neoadjuvant chemotherapy and radiotherapy for marginal resections of soft tissue and bony components of bone sarcomas can be done without compromising local control or long-term survival.

Finally, I will focus on a special area of experience in the management of the most difficult problem of these tumors involving the axial pelvic structure. This is particularly challenging because of the traffic of significant neural, vascular, and other organs within or surrounding this structure. However with the principles of limb salvage surgery, which we have determined both in soft tissues and appendicular skeleton, we felt that it was reasonable to apply them to tumors of the bony pelvis where the standard therapy would generally be a hemipelvectomy. Our series includes all patients with localized tumors whether they were primary or secondary. The patients had a full work-up with a bone scan, CT scan, and MRI of pelvis. The same adjuvant radiotherapy and chemotherapy protocol was used. These patients were approached with the same surgical principles of wide local excision when possible of 1cm to 2 cm. Reconstruction of the missing pelvic girdle was done either with a portion of allograft femur or an allograft pelvis. It was found that covering this bone was necessary with a myocutaneous flap to avoid the extrusion of the allograft through the skin over the iliac crest. For example, I present to you a 17-year-old male who had Ewing's sarcoma of the left

iliac bone, which extended up to the kidney. He was treated aggressively with multi-agent chemotherapy and radiotherapy and presented 9 months later for possible resection with a residual 8 cm mass on CT scan. There was a defect in his left iliac wing caused by the tumor and the MRI shows the initial extent of the mass. The patient was positioned in the lateral position for surgery where the entire iliac wing was resected from the sacral ala to just above the acetabulum. The pathology showed a few live cells in the hypocellular stroma. This is despite the fact that this tumor went from approximately 30 cm in length down to less than 8 cm. The defect was repaired with a portion of femur. The patient was alive 2 years later without evidence of recurrence. A second patient, a 27-year-old male who presented with a mass growing out of his pubis for 6 months. The x-ray shows a loss of the superior pubic ramis and the CT scan shows a large mass displacing the femoral nerve and vessels laterally. This extended into the pelvis pushing the bowel and bladder towards the contralateral side. The patient was radiated by placing an intra-abdominal prosthesis to protect the small bowel and post radiation the tumor had not particularly shrunk but had become cystic in nature. The entire ischium and pelvis were removed leaving the only connection to the axial skeleton, the femoral vessels and nerve and the sciatic nerve. An allograft pelvis was used to reconstruct. This was plated in place and he functioned with a cane because of weakness at his hip. He had normal function of his lower leg.

We had 7 patients with the following tumor characteristics, 5 being sarcoma and 2 being other carcinomas. In 3 patients, the iliac bone was resected, in 2 cases portions of the pubis, in 1 the ileum, and in 1 patient the sacrum was resected. Repair after the surgery required myocutaneous flaps in 4 of the patients and allograft bone in the defects of resection of the iliac crest and ischium. allograft bone was not used when the pubis alone was resected. In 1 patient there was a positive margin, in 1 patient there was allograft infection, and in 1 patient allograft disintegration which resulted in a subsequent hemipelvectomy. In those patients with preoperative radiotherapy as part of their planned treatment, there was no local recurrence but there was 1 patient who had systemic disease at a follow-up of 24 months. Those patients who had previously failed radiation had a higher local and systemic recurrence. In planning for these patients, the resection of the sciatic nerve would result in an insensate and functionless limb, which would render this type of surgery and reconstruction less useful. However, we have resected femoral nerve with patients being able to function extremely well even without a cane for their everyday activities. In 1 patient we have grafted the femoral nerve defect and had some rejuvenation of muscle occur.

In conclusion, pelvic girdle salvage surgery provides local control particularly with preoperative adjuvant radiotherapy and chemotherapy. Allograft replacements provide functional integrity for these patients so that they can mobilize with a minimum of walking aids.

In summary, with the use adjuvant treatments in combination with reconstructive surgery, over 90% of patients with sarcomas of the soft tissues or bone may be rendered disease free locally. The only restriction to this approach is when tumor involves the major nerve to a limb or when microscopic, clear margins cannot be obtained at the time of surgery as both of these are best treated with an amputation.

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Quality of life issues related to organ sparing

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The aim of organ sparing procedures is to maintain survival with a level of quality of life (QL) that is as high as possible. Methods are now available for evaluating QL in patients treated by quite different strategies and should be included as major endpoints, together with survival, in future clinical trials that investigate organ-sparing strategies. These methods will be useful in decision aiding for strategies leading to similar survival, and in framing choices between improved quality and improved quantity of survival.

Key words: neoplasms - surgery; organ sparing; quality of life; survival analysis

General features of quality of life assessment

There are two general methods for assessment of quality of life (QL) in patients included in clinical trials, or in patients receiving different types of treatment in the clinic: psychometric methods that are based on questionnaires completed by patients and utility-based methods that require patients to choose between different health states. In most settings it is appropriate to use a validated questionnaire that contains either discrete or continuous scales relating various components of QL. In general, such questionnaires contain items related to symptoms of disease, symptoms that are caused by treatment, and general features of physical, psychosocial and emotional health. The provision of information about these separable components of QL provides an advantage when compared to utility-based measures. Most questionnaires either include an overall scale describing health-related QL or the individual scales can be summed to provide such an estimate. It is essential that the patients complete such questionnaires since physicians are often poor judges of the QL of their patients.[1-3] Caregivers may give better estimates but cannot substitute for the patients themselves.

Quality of life questionnaires vary between those that can be used very generally for patients with quite different diseases (e.g. the Sickness Impact Profile and the Medical Outcomes Short Form 36) to highly specific

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questionnaires that evaluate patients with a given type and stage of disease. In oncology, the most widely used questionnaires are those of the EORTC [4] and the functional assessment of cancer therapy (FACT) devised by Cella and colleagues.[5] Each of these questionnaires consists of a series of core questions (the EORTC QLQ C30 and the FACT-G) that can be used with an increasing series of modules that are specific for either given types of cancer, or for given types of symptoms (such as fatigue or endocrine symptoms). These questionnaires have been extensively validated and translated into multiple languages. There is no gold standard for validation, but in general, the development of a questionnaire requires that it have the following characteristics.[4,5] There should be appropriate face or construct validity (does it measure what you want to measure?); related items should give related scores (convergent validity); unrelated items should give different scores (divergent validity); it should be reproducible (test-retest reliability); it should be responsive to change in clinical condition; and it should be predictive of outcome (predictive validity). In general QL scales are highly predictive of survival.[6]

Although QL scales are usually preferred for comparing aspects of QL among patients receiving different options of treatment, such comparisons may be difficult when treatments are radically different, as in trials of radical surgery versus an organ sparing approach. In such situations questionnaire-based approaches may be used to describe QL in patients who are treated by different modalities. These findings may then be used to describe to prospective patients the probable health state scenarios with or without radical surgery. Methods are then available which allow patients to assign a value to these health states; these values may vary between zero (equivalent to death) and one (equivalent to perfect health) and are called utilities.[7,8]

Use of quality of life scales in clinical trials

Unfortunately, most clinical trials that have included QL assessments have done this in a rather poor way. In a typical trial, a large amount of information is collected at baseline and at some specified later time in the absence of any prior hypothesis about meaningful changes in one or more QL scales. Compliance in completing the questionnaires reflects the importance assigned to them by doctors and nurses involved in the trial: it is often poor in American studies (making analysis difficult) but may be high in European and Canadian studies. Some form of analysis is undertaken after the end of the trial, such as a comparison of mean or median QL scores for randomised groups of patients obtained at or close to a fixed time, say 3 months after treatment. The problems with this approach are that it is not driven by a hypothesis, does not establish *a priori* endpoints, and does not recognise that QL is a dynamic variable, which changes at different times in different individuals. Multiple comparisons are made, some of which will be significant by chance alone. It is analogous to measuring tumour response in a chemotherapy trial by measuring the average size of tumours in a group before treatment and at some fixed time after.

The inclusion of QL endpoints in clinical trials should be as rigorous as the inclusion of more traditional endpoints such as survival. This requires recognition that QL is a property of an individual, which will change with time. It also requires that a primary endpoint of QL be defined before the start of the trial. This might be either a measure of overall QL, or a measure of a dominant symptom such as pain. In trials of organ sparing, it should be a QL attribute related to the function of the organ that is either lost or spared, depending on treatment. Using this approach, the chosen QL endpoint should be measured for each patient at baseline and as a function of

time following treatment. For example, a scale representing the ability to communicate would be appropriate in comparing patients who had undergone laryngectomy or organ-conserving approaches for treatment of laryngeal cancer. A QL response may be defined by a predetermined level of improvement, by achievement or maintenance of a predefined level of function, or by a measure of deterioration. This may occur at different times in different patients. For example, function might improve as patients adapt to loss of an organ, and might deteriorate if the conserved organ suffers late damage following conservative treatment such as radiotherapy. The proportion of patients who attain a predetermined level in a chosen QL scale, or who have a predetermined deterioration in that chosen endpoint may then be assessed by following patients with time. Other measures of QL are supportive. It is important, for example, to ensure that the improvement in a single endpoint (e.g. a measure of pain or function) is not obtained at the expense of deterioration in other more global endpoints.

Specific issues related to organ sparing

It is not necessary to use complex QL scales to assess the obvious. If one is comparing, in a clinical trial, strategies that maintain major organ function with one that causes loss of that function, and survival is identical, one does not need a QL assessment to state that the first treatment is superior. Consider, for example, the results of the VA laryngeal study which showed that chemotherapy and radiation for patients with advanced larynx cancer led to the same survival as laryngectomy followed by radiation but with two-thirds of patients keeping their larynx.[9] If the results of this study are confirmed, one does not need assessment of QL to know that the first strategy is superior. Quality of life scales are not necessary to know that a person who can speak has better QL than one who cannot. Assessment of QL becomes more important when the loss of function is less severe, as in the comparison of mastectomy versus lumpectomy plus radiation therapy for breast cancer. Here there is substantial evidence for equivalent survival, but it is important to use QL scales to ensure that patients do not suffer undue anxiety because of concern about recurrence of tumour in the residual breast. Such studies have been undertaken: most have confirmed that patients had better QL with lesser surgery, especially in domains relating to body image.[10-13]

The situation becomes more complex when a patient may be faced with the choice between radical surgery, and an organ sparing procedure, where the latter may lead to some reduction in the probability of cure or long-term survival. For example, a meta-analysis of the 3 trials comparing surgery versus radiation and chemotherapy for locally advanced laryngeal and hypopharyngeal cancer suggests a non-significant trend to poorer survival for the organ-sparing approaches.[14] If this is verified in further studies, the important question is whether patients are willing to accept a small reduction in the probability of cure or long-term survival in order to maintain speech and other important functions. A second example might relate to bladder cancer. Although data are lacking, cystectomy almost certainly gives better local control than radiation therapy (with or without chemotherapy) for muscle-invasive bladder cancer. In these situations, it is most appropriate to describe, as fully as possible, the probabilities of survival and function with the two options. Some patients will certainly accept a poorer probability of survival in order to maintain function, as demonstrated by McNeil and her colleagues, using a theoretical question about laryngectomy, many years ago.[15] At present there are few data pertaining to patient choices of this type, especially those using realistic descriptions of health

states following modern treatment, and estimates of differences in survival following radical surgery or organ-sparing approaches obtained from well-designed randomised controlled trials. Studies of patients receiving adjuvant chemotherapy for breast cancer have shown that most patients will not accept improved QL (by avoidance of toxic treatment) for even a small deficit in survival.[2,16,17] However, this might be quite different if patients were faced with more severe loss of function as would occur with laryngectomy or cystectomy.

The type of trade-off that is being made to patients in the above examples is similar to that which is used to measure utilities. A utility is a measure of QL for a given health state where perfect health has a utility of one and death has a utility of zero. The QL of a patient with a cystectomy and ileostomy is likely to be lower, in general, than the QL of a patient with a functioning bladder. If survival between the strategies that led to these two options were equal, almost all patients would accept having a functional bladder. By varying, in a theoretical presentation, the decrease in survival that would be acceptable to patients in order to retain their bladder, one can arrive at a utility for that state. For example, if patients could expect a long-term survival probability of 50% with cystectomy and were ambivalent in their choice between this option and that using a non-surgical approach with an expected long-term survival of 40%, then the utility for the state involving loss of a bladder would be 4/5 or 80%. Such utilities will vary from one patient to another, but can be useful in selecting appropriate treatments for future patients.

It is clear from QL studies that patients can adapt to loss of major function, and there are some apparent paradoxes where patients who have lost the function of a major organ may describe their overall QL as close to normal. This paradox probably occurs because of a frame-shift whereby the normal frame of reference for QL of a patient with a serious disease is different to that from a person that is healthy.[18] These evaluations can be misleading unless one uses a quality of life scale that specifically relates to the function that has been lost.

In summary, the aim of organ sparing procedures is to maintain survival with a level of QL that is as high as possible. Methods are now available for evaluating QL in patients treated by quite different strategies and should be included as major endpoints, together with survival, in future clinical trials that investigate organ-sparing strategies. These methods will be useful in decision aiding for strategies leading to similar survival, and in framing choices between improved quality and improved quantity of survival.

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case report

Old middle cerebral infarction in a neonate

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Background. *Cerebral arterial thrombosis is a relatively rare occurrence in the neonatal period. Some children having this condition as neonates, present recurrent local seizures with radiological evidence of acute infarction. Several studies have shown this to be a rare cause of neonatal seizures.*

Case report. *We describe the case of a newborn infant with localized clonic seizures of the lower right extremity on the fourth day of life. Ultrasound examination of the brain showed only mild abnormalities. However Magnetic Resonance Imaging showed evidence of a middle left cerebral arterial infarction.*

Conclusions. *The newer imaging methods, such as central nervous system Magnetic Resonance Imaging can be helpful in the diagnosis of rarer disturbances and can further reveal cases which would otherwise pass unnoticed even where ultrasound imaging is negative.*

Key words: cerebral infarction; infant, newborn; middle cerebral artery

Introduction

Neonatal seizures can be symptoms of numerous underlying disorders in the neonate. Cerebral arterial thrombosis is a relatively rare occurence in the neonatal period. Some children with this condition as neonates have recurrent local seizures with radiological evidence of infarction. Several studies have shown that the infarction is a rare cause of neonatal seizures. Asphyxia, birth trauma or polycythemia can be predisposing factors; however, the majority of reported cases in full-term neonates are considered idiopathic. In the full-term newborns, infarction most commonly occurs in the tissue supplied by the middle cerebral artery, with the left side more often affected than the right one.[1,2]

We describe the case of a newborn infant who presented local clonic seizures of the right lower extremity on the fourth day of life. Ultrasound examination of the brain showed mild abnormalities only. Magnetic Resonance Imaging however revealed the signs of a pre-

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vious middle-left side cerebral arterial infarction, which could occur *in utero*. A reduction in size of the left cerebral peduncle was observed, and was attributed to transaxonal degeneration.

Case report

A newborn male weighted 3100 gr., was delivered after a full-term uneventful pregnancy in uncomplicated vaginal delivery. Apgar scores reported were 8 and 9 at 1 and 5 minutes respectively. For the first 72 hours, the newborn was in good condition and remained in the maternity clinic. On the fourth day after birth, three attacks of local clonic seizures in his lower extremities were reported and the newborn was admitted to our department.

Upon admission, the newborn infant was in good condition and the results of physical examination, as well as retinal examination were normal. Hematological and biochemical tests (hemoglobin, white cell count, platelet count, hemoglobin electrophoresis, glucose, calcium, magnesium, cholesterol, electrolytes and BUN) were within normal ranges. Glucose and protein levels in the cerebrospinal fluid were normal. Anion gap, blood gas, aminoacid chromatography, organic acid chromatography and homocystin serum levels, were within normal ranges. Blood, urine, and cerebrospinal fluid cultures were negative. Toxoplasma, rubella, herpes simplex virus, syphilis, and cytomegalovirus titers did not reveal any infection.

Immediately after admission, anti-convulsive therapy was administered to the newborn, initially phenobarbital followed by phenytoin and diazepam. Phenytoin and diazepam were administered for ten days and phenobarbital for two months. The newborn, during the course of hospitalization, suffered repeated episodes of localized seizures of the right lower extremity which were gradually brought under control with anticonvulsive

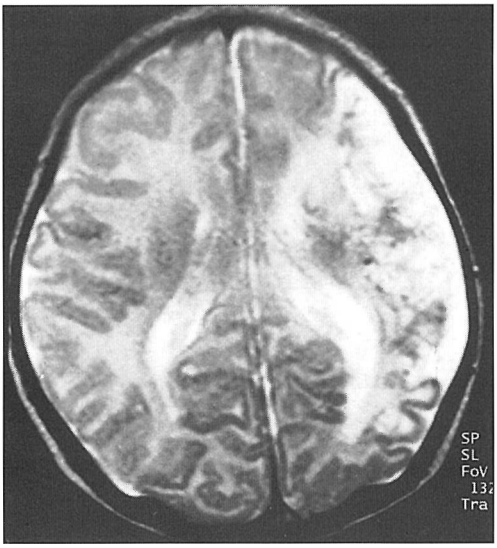

Figure 1a. Axial T_2 weighted (TR:5.400, TE:99) image through the bodies of the lateral ventricles. High signal intensity lesion in the left parietal lobe and mild dilatation of the body of the left lateral ventricle. Note the decreased size of the left peduncle in comparison with the right one.

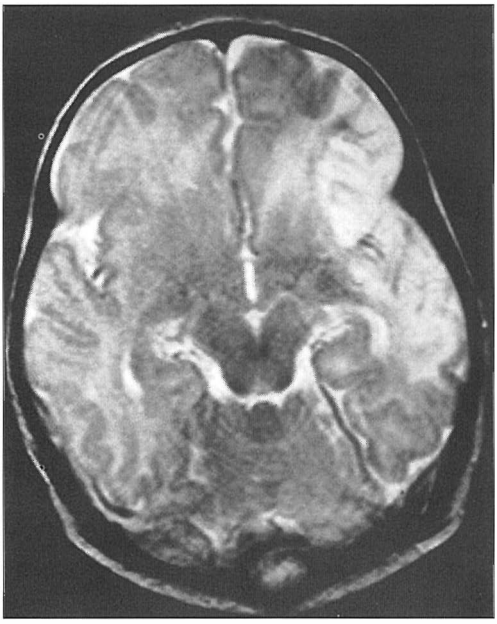

Figure 1b. Axial T_2 weighted (TR:5.400, TE:99) images through the mesencephalon. Extension of the lesion to regions of the left temporal and frontal lobes supplied by the middle cerebral artery. Note the decreased size of the left peduncle in comparison with the right one.

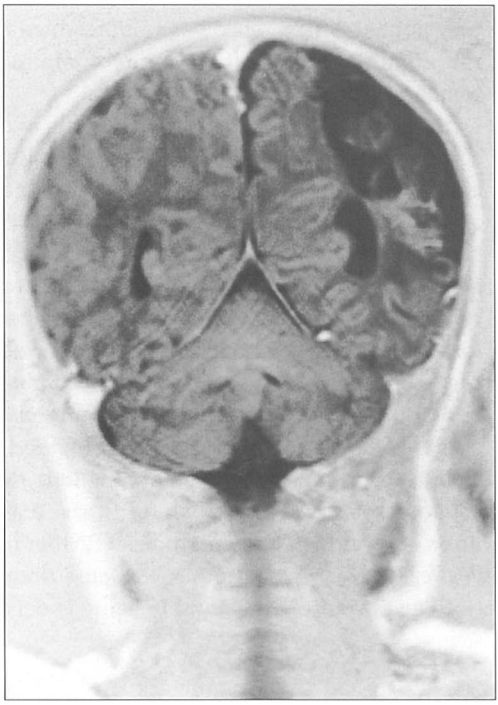

Figure 2. Coronal T_1-weighted turbo inversion recovery image. The signal intensity of the lesion did not significantly differ from the signal of the cerebrospinal fluid, indicating cystic evolution in the affected area.

therapy. Electroencephalogram findings were normal. Prothrombin and partial thromboplastin times and the fibrinogen, protein C, protein S and antithrombin III levels were also normal. No antinuclear antibodies, anticardiolipin antibodies or lupus anticoagulant were detected, either in the newborn or in his mother, while the levels of proteins C and S were within the normal ranges.

Ultrasonography examination using an ATL Ultramark-9 5 MHz transducer demonstrated a mild, non-specific increase in echogenicity in the region of the left parietal and temporal lobes. Then MR imaging (Siemens, Vision plus, 1.5T) was performed and revealed a destructive lesion with loss of brain tissue in the region supplied by the main branch of the left middle cerebral artery. The lesion was of low signal intensity on T_1 weighted images, of high signal intensity on T_2 weighted images, and exhibiting predominantly low signal intensity with some peripheral poorly demarcated areas of moderately high signal in heavily T_2 weighted images, with cerebrospinal fluid saturation (FLAIR). A mild dilatation of the left ventricle was also found. A reduction in the size of the left cerebral peduncle was observed and it was attributed to transaxonal (wallerian) degeneration (Figure 1a,b and Figure 2). After ten days treatment, phenytoin and diazepam were discontinued. The infant remained in hospital for ten more days free of seizures. The infant was discharged from our department at the age of 28 days in good condition with slight hypertonia of the right upper and lower extremities. He remains under regular observation, with monthly visits to follow his psychomotor progress and continues with the course of physiotherapy which was started during hospitalization.

The last clinical evaluation done at the age of six months did not reveal any localized neurological signs, while his psychomotor development is in accordance with his age group.

Discussion

Unilateral neonatal cerebral infarction, or neonatal stroke, can occur in both pre-term and full-term infants and usually manifest itself as localized neonatal seizures in an otherwise healthy full-term neonate; it is one of the causes of spastic hemiplegic cerebral palsy.[1]

A number of causes have been reported for neonatal localized infarction. Usually perinatal asphyxia, birth-trauma, and resuscitation by assisted ventilation, either by "bag-and-mask" or endotracheal intubation, are more common occurrences in such neonates than in healthy ones.[1] Other factors, like polycythemia, dehydration, exchange transfusion, indwelling (temporal) arterial catheters, per-

sistent *ductus arteriosus,* cocaine abuse and coagulopathy, such as protein C and S deficiency, and factor V have all been mentioned in literature. The presence of an arteriovenous malformation should also be considered.[1,2] Recently an association between cerebral infarction and antiphospholipid antibodies has been found to be a significant factor.[3] However cerebral infarction can also occur before or after birth in healthy infants without any overt underlying pathology.[1] The varied and sometimes subtle symptomatology raise the possibility that some cases may not be detected in the perinatal period.[1] The outcome of each case depends on its predisposing factors and the underlying pathology. It has been reported that full-term infants with the infarction unrelated to significant birth asphyxia usually have a favorable outcome.[4]

Although periventricular and subcortical infarction may be visualized very well by cerebral ultrasonography, it has been found that scanning with 5 and 7.5 MHz transducers is often unhelpful in the diagnosis of unilateral neonatal cerebral infarction. In the presented case, the ultrasonographic findings were nonspecific and the diagnosis of the middle cerebral artery infarct was confirmed on Magnetic Resonance Imaging. The loss of brain tissue associated with mild dilatation of the ventricle and of the regional peripheral subarachnoid space, the signal intensity of the lesion that did not differ significantly from the signal of the cerebrospinal fluid with the findings consistent with wallerian degeneration, were suggestive of a chronic infarct which had occurred during the inta-uterine development life. To our knowledge, transaxonal degeneration has not been previously documented in the first weeks of life. It has only been described in infants of more than two and half months of age.[5] Ultrasound imaging may appear normal even when interpreted in the light of information from computed tomography scanning.

In conclusion; in every newborn with seizures, especially when localized, the clinician, beside considering the usual causes for this, must be aware of the possibility of rarer causes. Cerebral infarction can even occur *in utero,* as was the case of our patient; it was revealed by Magnetic Resonance Imaging performed on the 12th day of life, despite the absence of other predisposing factors. Cerebral infarction can result in seizures or semi-paresis in newborns. The newer imaging methods, such as central nervous system Magnetic Resonance Imaging can be helpful in the diagnosis of rarer disturbances and can further reveal case which would otherwise pass unnoticed even where ultrasound imaging is negative.

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review

Do we need axillary dissection in early breast cancer?

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Background. *In the existing paradigm of the invasive breast cancer, the treatment with the axillary lymph-node dissection (ALND) and histologic staging of the axilla, which is associated with a substantial morbidity, is considered necessary for the treatment decision and local control of disease.*
However paradigms are changing and, since primary tumor characteristics are increasingly used for treatment decision and since there is a trend towards the broad application of preoperative chemotherapy, ALND is less and less important for the treatment planning. In a small subgroup of patients in whom the information on nodal status is still important it can be obtained accurately by the sentinel lymph node biopsy. For good local control of the disease, ALND can be replaced with irradiation of the axilla with substantially lesser morbidity.
Conclusions. *Abandoning ALND together with breast conserving surgery is one of the major steps towards less mutilating surgery leading to a better quality of life of breast cancer patients at the end of this millennium.*

Key words: breast neoplasms-therapy; lymph node excision; axilla; sentinel node mapping

Introduction

In the existing paradigm of the invasive breast cancer, the treatment with the axillary lymph-node dissection (ALND) and histologic staging of the axilla, which is associated with a substantial morbidity, is considered necessary for the treatment decision and local control of disease. However, paradigms are changing, and today, it is questionable if ALND is still needed for either treatment planning or local control of disease.

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Do we really need the information on nodal involvement for treatment planning in early breast cancer?

According to the information obtained from the meta-analyses of all randomized trials of adjuvant systemic therapy performed by Early Breast Cancer Trialists' Collaborative Group,[1-3] the benefits of adjuvant systemic therapy are equally shared among node posi-

tive and node negative patients. The relative benefits of the risk of recurrence and death were similar for all patients regardless of the node status. Today, the treatment decision depends much more on the primary tumor characteristics (e.g. size, hormone receptors) than on the nodal involvement. The effectiveness of the particular systemic therapy does not seem to be influenced by the number of the axillary lymph nodes involved but on the biological characteristics of the primary tumor, such as hormonal receptors, growth factor receptors and inherited resistance to chemotherapy. Innovative, intensive, dose-dense and sequential anthracycline-based chemotherapy regimens were equally found to be more effective than standard chemotherapeutic regimens in both, node positive and node negative disease[4] and it is realistic to expect that the taxane-including regimens will also turn out to be equally effective.

Presently, there is only a small subset of patients in which the indications for systemic therapy are at borderline. These are patients with small tumors, less than 1 cm in diameter. In these patients, we still need the information on axillary lymph node involvement for the treatment decision. However, by sentinel lymph node mapping, accurate information on lymph node status can be obtained in these patients without ALND. During the last few years, sentinel lymph node biopsy was found to be a highly accurate method in predicting occult lymph node metastasis. In skilled hands, it is nearly hundred percent accurate.[5-7] With the use of preoperative chemotherapy for the treatment of operable breast cancer, the information on lymph node status for the treatment planning has become obsolete. In this setting, the treatment strategy depends on much more reliable criteria, such as measurable response of primary tumor to systemic therapy. If the tumor does not respond to primary chemotherapy, a crossover to a different chemotherapeutic agent is recommended, no matter what the axillary nodal status is.

Do we still need axillary lymph-node dissection for the local control of disease?

The review of the studies that looked at the rate of axillary failure in patients with clinically node negative invasive breast cancer who received no axillary treatment[8] shows that there is a high rate of local recurrence in the axilla (from 15 to 37 %) in patients who received neither dissection nor irradiation of the axilla (Table 1). There is a very small subset of patients for whom the risk of nodal involvement is so low that ALND can be omitted. These are the patients with small microinvasive disease and patients with small, with less than 1 cm in diameter, pure tubular carcinomas.[8] In all other subset of patients with invasive breast cancer, the risk of local recurrence is too high to allow for no routine axillary treatment. Although delayed axillary node dissection is surgically possible and radical in all but about 2 % of these patients[9] and the survival of these patients does not seem to be compromised,[10] the psy-

Table 1. Axillary failure rates in clinically node-negative patients receiving no axillary treatment

Reference	No. of pts in trial	Mean follow-up (months)	Axillary failure (%)
Ribeiro et al, 1993	708	65	23
Cerotta et al, 1997	408	84	15
Lythgoe & Palmer, 1982	714	60	37
Gravesone et al, 1988	3128	60	19
Fisher et al, 1985	1079	126	19
Gatly et al, 1991	450	72	18

Table 2. Axillary failure rates in clinically node negative patients treated with axillary radiotherapy

Reference	No. of pts in trial	Mean follow-up (months)	Axillary failure (%)
Baeza et al, 1988	171	62	1
Cabanes et al, 1992	332	54	2
Dolouche et al, 1987	281	60	1
Fisher et al, 1985	352	126	3
Leung et al, 1986	446	120	0
Osborne et al, 1984	211	120	1
Peirquin et al, 1986	1040	60	2
Recht et al, 1991	335	73	1
Wazer et al, 1994	73	54	1

chologic burden of the disease recurrence for the patient is too high to be acceptable. Therefore, some kind of axilla treatment for a good local control of the disease is necessary.

In clinically node positive disease, surgical removal of the axillary nodes i.e. ALND, despite its high rate of morbidity, is still recommended. However, in clinically lymph node negative disease, nodal irradiation with a lesser degree of morbidity was found to be as effective as ALND in terms of local control of disease without compromising the patients survival. In nine published studies with follow-up times that ranged from 54 to 126 months, the percentage of axillary failure in node negative patients who received axillary nodal irradiation without ALND was only about 1 %[10-18] (Table 2). Also the results of a meta-analysis performed by Early Breast Cancer Trialists' Collaborative Group[19] showed no difference in mortality in eight trials comparing axillary surgical clearance to irradiation. Morbidity from axillary nodal irradiation seems to be minimal when compared with the extensive side effects of ALND.[20,21] The risk of arm edema is approximately half that seen in axillary nodal dissection;[22] likewise, brachial plexus injury and shoulder pain morbidity are extremely rare with radiotherapy alone.[23] Another possibility of axilla sparing treatment in clinically negative lymph-node patients is sentinel lymph-node biopsy, which allows for axillary lymph-node dissection sparing procedure in all patients with negative sentinel lymph node. This is approximately half of patients with clinically negative disease in axilla. Morbidity from sentinel lymph-node mapping does not seem to be worth mentioning.

Conclusions

In conclusion, since primary tumor characteristics are increasingly used for the treatment decision and since there is a trend towards the broad application of preoperative chemotherapy, ALND is becoming less and less important for the treatment planning. In small subgroup of patients in whom the information on nodal status is still important, it can be obtained accurately by the sentinel lymph node biopsy. For a good local control of the invasive disease ALND can be replaced with the irradiation of axilla with substantially lesser morbidity. Abandoning ALND together with a breast conserving surgery is one of the major steps towards the less mutilating surgery leading to a better quality of life of breast cancer patients at the end of this millennium.

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Factors influencing rehabilitation in patients with head and neck cancer

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Purpose. *The purpose of the prospective study was to identify the factors adversely influencing the post-treatment rehabilitation in patients with head and neck cancer.*

Patients and methods. *One hundred and ten patients with oral cavity, pharyngeal and laryngeal cancer were examined before surgical treatment in order to find unfavorable factors: hearing loss, defective teeth, impaired pulmonary function, and speech disorders. The patients evaluated the success of their rehabilitation 12 months after the treatment. The influence of possible unfavorable factors, tumor site, and type of surgery on speech, swallowing and reintegration competence was determinated.*

Results. *The site of the tumor and the type of surgery did not influence the quality of rehabilitation in general. Defective teeth influenced the ability of swallowing, but not the speech. Hearing loss impaired the patient's reintegration in their home environment. Impaired pulmonary function did not affect patient's speech. Speech was the poorest in laryngectomized patients. However, about two thirds of the patients were satisfied with their capability of speech, swallowing and their rehabilitation in general.*

Conclusions. *Early identification of unfavorable factors, and individually planned rehabilitation can ensure a suitable quality of life for patients that have undergone surgery for head and neck cancer.*

Key words: head and neck neoplasms - rehabilitation; lung volume measurements; dental status; speech disorders; hearing disorders

Introduction

In Slovenia, the incidence of cancer of the oral cavity, pharynx and larynx is increasing.[1] Unfortunately, the malignant disease is discovered in a localized stage in only 19-39 % of patients with oral cavity or pharyngeal cancer, and in 55 % of patients with laryngeal cancer.[2] Therefore, a combination of surgery and radiation therapy is necessary for a suc-

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cessful treatment in a majority of these patients. While such treatment can eradicate the malignant disease, it can also impair certain organs involved in the processes of chewing, swallowing and speech.[3,4,5,6]

A prevailing majority of the patients with head and neck cancer are older than 50 years.[2] In such a population, some chronic disorders influencing the quality of speech, chewing and swallowing can be expected.[6,7,8] For a successful rehabilitation of these important functions and reintegration of such patients in their home environment, any unfavorable factors must be identified as soon as possible and the rehabilitation must be planned individually with respect to the patient's special needs and capabilities. Therefore, a multidisciplinary approach is required.[9]

The aim of the present study was to identify the unfavorable factors, which could hinder the post-treatment rehabilitation of the patients with head and neck cancer before the beginning of therapy. The rehabilitation was planned according to the findings obtained. The authors tried to establish a correlation between the unfavorable factors, the sequels of treatment for malignant disease and the success of rehabilitation.

Patients and methods

One hundred seventy-one consecutive patients with oral cavity, pharyngeal or laryngeal cancer, who were surgically treated in two successive years, were included into a prospective study. During the study, 13 patients died because of their malignant disease, 29 patients refused participation, and 19 patients were lost from follow-up; 110 patients completed the treatment and participated in the follow-up.

Before the beginning of therapy, the patients were examined by an otorhinolaryngologist, a phoniatrician and a speech therapist. The data about the factors influencing the success of post-treatment rehabilitation (hearing impairment, the sequels of previous neurologic, pulmonary, and gastroenterologic diseases) were obtained from the patient's history and clinical examination. The hearing acuity was assessed by audiometry. The dental status was assessed with respect to the ability of chewing and speech. In all patients, pulmonary function was assessed on the basis of clinical examination, x-ray of the lungs, and measurement of pulmonary function (spirometry). The site and stage of cancer were determined. The articulation disorders, which could hinder speech after surgical treatment, were assessed by a speech therapist.

The post-treatment rehabilitation (medicamental and respiratory physical therapy, speech and swallowing therapy, prescription of hearing aids and proper training) was planned according to the findings obtained.

Twelve months after the completed treatment, the patients assessed the success of their rehabilitation in general (excellent, satisfactory or poor). They evaluated their speech and capability of swallowing (excellent, satisfactory, or poor). The results of this subjective evaluation were compared between the groups of patients who had undergone the most mutilating surgery (laryngectomy, or excision of oral cavity carcinoma with or without segmental mandibulectomy). The influence of possible unfavorable factors (impaired hearing, pulmonary function, defective teeth, speech disorders) on speech, swallowing and reintegration competence was determined using χ^2-test and Fisher exact test (Epi Info 6, Atlanta, USA).

Results

There were 102 males (92.7 %), and 8 females (7.3 %). The patients' age ranged from 37 to 81 years, their mean age being 56.2 years, standard deviation 9.4 years and median 57 years.

Forty-eight patients (43.6 %) were free of any disease that could hinder their rehabilitation after treatment for head and neck cancer. All other patients (56.4 %), had different neurologic disorders (11 patients), gastroenterologic diseases (24 patients), pulmonary diseases (20 patients), and other malignant diseases (7 patients), which could influence their rehabilitation.

In 39 patients (35.5%), the history data, the clinical findings, the x-ray of the lungs and the results of spirometry (in selected cases) suggested impaired pulmonary function. In all other patients (64.5%) the findings were normal.

In 60 patients (54.5 %), the hearing acuity was slightly impaired but did not hinder the patients in their every-day communication. In 10 patients (9.1 %), the hearing loss was moderate and in three patients (2.7 %) the loss was severe. None of the patients used a hearing aid before treatment.

A healthy and complete set of teeth was found in one patient only. Eleven patients (10 %) had suitable dentures instead of the missing teeth. Twenty-one patients (19.1 %) had healthy teeth, but more than one third of them were missing. In 59 patients (53.6 %), very defective teeth with caries were found. Eighteen patients (16.4 %) had no teeth and no dentures either.

Articulation disorders which could influence the intelligibility of speech was not found in any of the examined 57 patients.

Twenty-four patients (21.8 %) had oral cavity cancer, 17 patients (15.4%) had mesopharyngeal cancer, 21 patients (19.2 %) had hypopharyngeal cancer, and 48 patients (43.6 %) had laryngeal cancer.

The distribution of patients according to TNM classification (10) is presented in Table1.

In 19 patients, tumor excision was performed. In 16 patients, tumor excision and partial mandibulectomy was necessary. In 20 patients, conservative laryngectomy was performed. Fifty-five patients underwent total laryngectomy.

Table 1. Distribution of patients with head and neck cancer according to TNM classification (N=110)

T	N0	N1	N2	N3	Total
T1	4	1	2	1	8
T2	25	9	9	0	43
T3	15	4	9	1	29
T4	17	5	8	0	30
Total	61	19	28	2	110

In 101 patients (91.8 %), uni- or bilateral functional neck dissection was performed. In eight patients (7.3 %) radical neck dissection on one side of the neck was necessary. Only one patient had no surgery of the neck performed.

Eighty-five patients (77.3 %) received postoperative irradiation. The tumor dose ranged from 49 to 69 Gy, with mean value 55.7Gy and standard deviation 4.5Gy.

Twelve months after the completed surgical and irradiation treatment, the patients assessed their ability to swallow (Table 2) and speak (Table 3). They also estimated their rehabilitation in general (Table 4).

Table 2. Patients' self-assessment of their ability to swallow 12 months after the treatment (N=110)

Swallowing	Laryngectomized patients	Patients with oral cavity cancer	Other patients	All patients
Poor	7	8	7	22
Satisfactory	16	10	10	36
Excellent	30	6	13	49
Unknown	2	0	1	3
Total	55	24	31	110

Table 3. Patients' self-assessment of their ability to speak 12 months after the treatment (N=110)

Speech	Laryngectomized patients	Patients with oral cavity cancer	Other patients	All patients
Poor	34	6	7	47
Satisfactory	11	8	7	26
Excellent	7	10	17	34
Unknown	3	0	0	3
Total	55	24	31	110

Table 4. Patients' self-assessment of their rehabilitation in general 12 months after the treatment (N=110)

Rehabilitation	Laryngectomized patients	Patients with oral cavity cancer	Other patients	All patients
Poor	6	2	0	8
Satisfactory	19	3	4	26
Excellent	15	13	20	48
Unknown	15	6	7	28
Total	55	24	31	110

When the assessment of swallowing was compared between the laryngectomized patients and all other patients (χ^2=2.64, p=0.104), and between the patients after oral cavity carcinoma treatment and all others (Fisher exact test, p=0.091) there were no significant differences found. All the patients treated for oral cavity cancer, who had swallowing problems, had defective or missing teeth.

Speech was significantly poorer in laryngectomized patients than in all other patients (χ^2=17.26, p=0.000). The laryngectomized patients evaluated their use of esophageal speech. The patients after oral cavity carcinoma treatment assessed their ability to speak as „poor" more often than all other patients, but the difference was not statistically significant (χ^2=3.56, p=0.059).

The site of the tumor and the type of the surgery did not influence the success of rehabilitation. The assessment of rehabilitation in general was approximately the same in all the subgroups (laryngectomized subjects vs. all others: Fisher exact test, p=0.150; patients with oral cavity cancer vs. all others: Fisher exact test, p=1.000).

Only the patients with small tumors (T1 or T2) and without metastases did not receive radiation therapy. Therefore, the influence of radiation therapy could not be exactly evaluated.

A significant influence of moderate or severe hearing loss on patients' rehabilitation was found (Fisher exact test, p=0.000). On the other hand, no negative influence on their speech was noticed (χ^2=0.22, p=0.638).

The patients' speech was not influenced by their impaired pulmonary function (χ^2=0.01, p=0.938). The defective and missing teeth did not influence the patients' speech either (χ^2=0.80, p=0.372).

Discussion

The results of this study showed that in spite of the fact that in more than one half of the patients, at least one unfavorable factor was found (impaired hearing, pulmonary function, defective teeth, sequels of gastroenterologic and neurologic diseases), about two thirds of the patients were satisfied with their capability of speech, swallowing and their rehabilitation in general. We presume that such results could be attributed to the individually planned rehabilitation.

One third of the patients after the treatment of oral cavity cancer, and only one eighth of the laryngectomized patients had problems on swallowing. All the patients treated for oral cavity cancer that had swallowing problems, had defective or missing teeth and also had chewing problems. It appears that defective teeth are a characteristic feature of the population of patients with head and neck cancer. Still, the authors believe that the most important reasons for swallowing problems are postirradiation sequels[11,12], and inadequate compensatory patterns in the operated field.

Almost all laryngectomized patients with swallowing problems were treated for hypopharyngeal cancer. Laryngectomy and partial pharyngectomy were required in all the cases. Loss of tissue and possible stenosis of the pharyngeal canal may be important reasons for swallowing difficulties in these patients.

Hearing loss was expected to be an important factor that could hinder the control of speech in new anatomic situation after the treatment of cancer in the head and neck region.[6] It turned out, however, that hearing

loss did not affect the patients' speech but it did hinder their rehabilitation in general. All the patients with moderate or severe hearing loss received hearing aids and proper training during their stay in hospital. It is possible that they were not using their hearing aids after having returned home, which rendered their communication with their relatives and friends more difficult.

The authors cannot be satisfied with the results of speech rehabilitation of the laryngectomized patients. Only one third of the patients were satisfied with their esophageal speech. The patients were taught the principles of esophageal speech during the first month after surgery. However, all the laryngectomized patients were irradiated postoperatively. During irradiation, which started usually three weeks after surgery, the increasing radiomucositis hindered further improvement in esophageal speech. A certain number of patients started to use an electrolarynx instead. No patient received a tracheoesophageal prosthesis during the time of the study.

Some authors believe that voice is not a primary determinant of the quality of life.[13,14] Altered speech is consistent with a satisfactory quality of life. The results of the present study were similar. Only six laryngectomized patients were not satisfied with their reintegration in their home environment; only three of them thought this was due to the loss of their natural voice.

In conclusion, early identification of unfavorable factors before the beginning of treatment, individually planned rehabilitation and intensive help of different professionals (an otorhinolaryngologist-surgeon, a phoniatrician, a speech therapist) after the treatment can ensure a proper rehabilitation of the affected functions and a suitable quality of life for patients that have undergone surgery for head and neck cancer.

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Ependymomas in adult patients: Results of adjuvant radiotherapy

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Background. *As ependymomas are rare tumours and experiences base on the results of retrospective studies, we assess the survival and pattern of recurrence in eight adult patients with intracranial or spinal ependymoma who were treated with adjuvant radiotherapy.*

Patients and methods. *The data of a series of adult patients with low/intermediate (7) or high-grade (1) ependymomas receiving postoperative radiotherapy are presented. Between 1985 and 1994, eight patients (mean age 41 years, range 18-55 years) with intracranial (2) or spinal (6) ependymoma were irradiated either after macroscopically complete surgery (4), or incomplete surgery (1) or for salvage after incomplete resection of local recurrence (3). Radiotherapy with a mean dose of 52 Gy (range, 50-54Gy) was given to generous local fields with boost, not to the entire craniospinal axis.*

Results. *Median follow-up was 101 months (range, 12-146 months); the 5-year overall survival and disease-free survival were 100 % and 8ž %, respectively. Infield failure occurred in one patient with intracranial and one with spinal ependymoma 77 months after radiotherapy in both cases. Initially, these two patients had been irradiated after incomplete resection of a recurrent tumour. Two patients with spinal cord tumours showed outfield failure in the spinal cord 38 and 86 months after radiotherapy. No irradiation induced late effects were observed.*

Conclusions. *Adjuvant radiotherapy after incomplete surgery and/or local recurrence and/or high-grade tumours seems to be efficient to prolong local control in this rare disease.*

Key words: ependymoma-surgery-radiotherapy; radiotherapy, adjuvant; adult

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Introduction

Ependymomas derive from ependymal cells lining the ventricular system and the central spinal canal. They are rare tumours and experiences base on the results of retrospective studies.[1-14] About 60% of the intracranial ependymomas are located infratentorially, most commonly in the fourth ventricle, while 40% evolve supratentorially.[15] About half of supratentorial tumours are located intraventricularly, while the remainder appear to be intraparenchymal, arising perhaps from remote fetal ependymal cell rests.[16] Intracranial ependymomas generally occur in children and young adults. Spinal cord tumours, however are seen more frequently in adult patients in the fourth and fifth decade with the lumbosacralis axis as a common site.

This study reviews survival and pattern of recurrence in eight adult patients with intracranial or spinal ependymoma.

Material and methods

Patients characteristics

From August 1984 through April 1995, eight adult patients with histologically proven ependymoma received radiotherapy at some phase in their treatment. Four patients were irradiated postoperatively after macroscopically complete surgery, one patient after incomplete surgery, and three patients underwent incomplete surgery and postoperative radiotherapy for salvage. Details are given in Table 1. There were 4 male and 4 female patients, their median age was 44 years (range, 18-55 years).

Two patients had an intracranial tumour; one supratentorial ependymoma was found in the third ventricle and one infratentorial tumour was located in the fourth ventricle. Six patients had ependymomas of the spinal cord, which were located in the thoracolumbar and lumbar region in three patients, respectively. No patient had evidence of distant metastases.

The tumours were classified according to the degree of histologic differentiation, there were seven low/intermediate-grade and one high-grade tumour. Myxopapillary subtype was found in one patient, papillary in three, cellular and anaplastic subtype in one case, respectively. No information on histologic subtype was evident in 2 patients.

In earlier years diagnostic evaluation of the primary tumour included ventriculography and myelography, whereas in recent years, computed tomography and magnetic resonance imaging have usually been performed.

Most frequent symptom in patients with spinal tumours was low-back pain. Few days before diagnosis, the tumour caused spastic hemiparesis in three patients. In one patient with spinal ependymoma no information about the kind and duration of symptoms was available. Both patients with intracranial tumours had suffered from headache for 3 years and 2 months, respectively. Few days before diagnosis, the symptoms of increasing intracranial pressure were recorded. Details are shown in Table 1.

External radiotherapy

Seven patients received a mean dose of 52 Gy (50-54 Gy) to the tumour bed including a safety margin and an additional boost; one patient had a whole-brain irradiation followed by a boost. No irradiation of the entire craniospinal axis was performed. Daily doses were 1.7 - 2.0 Gy 5 days per week. All fields were treated daily. Photon beams were used in five patients, two patients were irradiated with electrons and, in earlier years, one patient had a Cobalt-60 therapy. Treatment planning CT scans for the determination of the target volume were done routinely. No patient had chemotherapy additionally.

Table 1. Patient's characteristics including the treatment modality and outcome

Age	Site	Grade	Symptoms		Initial	Time to	Surgery and	Progression			Outcome
			Kind	Duration	surgery	failure	radiation dose	Intervall	Site	Treatment	
18	supratentorial	I	Headache Vertigo Neck stiffness	2 mos 3 days	R0	122 mos	R2 + 50 Gy	77 mos	Infield	Radiosurgery	111mos^{AWD}
30	supratentorial	cell.I- I	Headache Nausea, Emesis	3 years 6 days			R0 + 54 Gy				119 mos^{NED}
53	Th12- S1	I	Dysbasia Hemiparesis	3 mos 6 days			R1 + 52.2 Gy				12 mos^{NED}
44	TH12- L1	myxopap.II	Low back pain Hemiparesis	2 mos 4 days			R0 + 50 Gy	38 mos 23 mos	Outfield $^{(Th9)}$ Outfield $^{(L4-S3)}$	RX R2+50Gy	84 mos^{DOD}
55	L3-4	pap.II	Low back pain	2 mos			R0 + 54 Gy				111 mos^{NED}
44	Th10- L1	pap.I	?	?	R0	46 mos	R2 + 54 Gy	77 mos	Infield	~	91mos ^{DSM}
30	L3-4	anapl.III	Hemiparesis	2 days			R0 + 54 Gy				41mos^{NED}
52	L2- L4	pap.I	Low back pain	17 mos	R0	74 mos	R1 + 54 Gy	86 mos 44 mos	Outfield $^{(Th6-8)}$ Outfield $^{(Th2-3)}$	RX R1+ 52.2Gy	146 mos^{AWD}

mos: months; cell: cellulary; myxopap: myxopapillary; pap: papillary; anapl: anaplastic
AWD: Alive with disease, NED: No evidence of disease, DOD: Dead of disease, DSM: Dead of second malignancy
R0: Radical surgery; R1: Microscopically incomplete surgery; R2: Macroscopically incomplete surgery; RX: unknown radicality

Follow up

The median follow-up was 101 months (range, 12- 146 months). Patients were seen in follow-ups every 3 months for 3 years and every 6-12 months thereafter. Follow up investigations included myelography in earlier years, later on, computed tomography or /magnetic resonance imaging were performed.

Data analysis

Estimates of rates for overall and disease-specific survival were calculated using the Kaplan-Meier product limit method.[17] The timing of all events was calculated from the last day of radiotherapy.

Results

Radiation treatment was well tolerated. Acute discomfort included reversible focal loss of hair and/or moderate skin erythema; no late side-effects were observed.

All patients were evaluable for survival and local control. Overall 5-year survival was 100 %. The median disease-free survival was 86 months, the 5-year disease-free survival was 86 %.

Two patients failed locally within the radiation field. In one patient with an intracranial ependymoma, radiosurgery was performed for salvage, the other patient received no further treatment; he died secondary to primary pancreatic cancer. Initially, both patients had been irradiated for local recurrence. Two patients with spinal cord tumours developed outfield failures. Details are summarised in Table 1. No distant failures were observed.

Discussion

Failure to control disease at the primary site seems to be the major problem. Most patients

with intracranial ependymomas who develop spinal metastases also fail locally and die of their local disease. In rare cases, distant metastases have been reported.[14, 18]

Prognostic factors

Clinical variables like age,[2,3,12,13] gender,[3,13] tumour grade,[4,7,11-13] histological subtype[1,4] and tumour location,[3,6,12] have been discussed to be potential prognostic factors. Some reports have seen no significant difference in survival rates based on age, [2,3,13] others have found a trend for better progression-free survival [7,12] or a significant better actuarial survival in patients older than 16 years of age[7].

While some authors[3] have found no significant correlation with gender and survival, Vanuytsel et al.[13] obtained a significant better overall and progression-free survival in female patients. Tumour grade has been most frequently identified as significant variable. [4,7,11,13] Seven out of eight of our patients with spinal and intracranial ependymomas had low/intermediate-grade tumours with a 5-year disease-specific survival rate of 86 %; these numbers are in keeping with the results of other reviews.[2,4,11] Tumour location was the only factor that influenced absolute survival in a review of Mc. Laughlin et al.[6], these findings have not been confirmed by others.[3,12]

Another possible prognosticator which was evaluated by some authors is the duration of symptoms prior to diagnosis.[11,14] The clinical presentation of ependymoma depends on the location of the tumour; it can be unspecific like headache or low-back pain, which may lead to delayed diagnosis. Wen et al.[14] report a median duration time of 18 months in patients with spinal ependymomas, 40% of the patients had symptoms for more than 3 years prior to their initial visit. Median length of symptoms of 14 months was noted by Waldron et al.[11], but this clinical variable had no impact on recurrence-free and cause-specific survival on multivariate analysis.

Intracranial ependymoma

Surgical resection and radiotherapy are accepted as standard treatment, but it remains disagreement regarding the volume that should be irradiated. For the treatment of high-grade supratentorial ependymoma with no evidence of dissemination, some authors recommend craniospinal irradiation (CSI),[12] others however, saw no benefit of the use of CSI and found whole brain irradiation with boost a justifiable approach.[7,13] Craniospinal irradiation remains standard treatment when spinal seeding is radiographically or pathologically evident. For localised supratentorial low-grade tumours general agreement exists on local confined fields [7,13] either generous local irradiation or whole-brain irradiation with boost.

The spread to the subarachnoidal space is considered to be higher for tumours arising in the posterior fossa and for high-grade tumours. Therefore, for high-grade infratentorial tumours, CSI is considered as treatment of choice by most authors.[2,7,12] In case of low-grade infratentorial tumours, treatment policies include local fields [7,13] and CSI.[12]

Local infield failure occurred in one of our two patients with intracranial ependymomas 77 months after macroscopically incomplete resection of local recurrent tumour and postoperative radiotherapy (50 Gy); stereotactic radiosurgery was performed for salvage in this patient.

Spinal ependymoma

Spinal ependymomas have a long natural history. Both, the length of symptoms prior to diagnosis as discussed above and the development of late recurrences illustrate this. Recurrences later than 10 years following initial diagnosis and therapy have been reported[11] - therefore long-term follow-up is needed to assess treatment results.

Surgical resection is the mainstay of treatment for the majority of these tumours; with the improvement of neurosurgical instrumen-

tation, the morbidity of the radical approach has decreased extremely. However, radical surgery is not possible in all cases. The role of postoperative radiotherapy is controversial for the patients with spinal ependymomas. Some authors consider surgery alone to be efficient[9], others recommend postoperative radiotherapy only for intermediate/high-grade tumours[8,11] or after incomplete resection;[5,6,8,11,14] generally, a local field irradiation is considered sufficient.[6,10,11] Wen et al.[14] recommend a dose of 45-50 Gy if the tumour has been incompletely resected or if it has been removed in a piecemeal fashion and not in an en bloc fashion. If the tumour has been removed in a piecemeal fashion the authors recommend a thecal sac irradiation additionally. Waldron et al.[11] also suggest postoperative irradiation of intermediate or poorly differentiated tumours, irrespective of the degree of resection, as well as in incompletely resected tumours. Given the dose limitations by the spinal cord tolerance levels, the radiation doses reported in the literature range between 40 and 54 Gy.[2,7,8,12,14] A report by Stuben et al.[7] showed a significant difference in progression free survival (PFS) probability between the patients treated with doses up to 45 Gy and those patients receiving more than 45 Gy (36% vs. 54% 5-year PFS). In our patients with spinal ependymoma, a mean dose of 53 Gy was used and infield failure was obtained in one patient. He had been irradiated for local recurrence after macroscopically incomplete surgery; the patient died due to pancreatic cancer. In two patients, one papillary and one myxopapilary subtype, outfield failures were seen. (Table 1). One may argue, that larger fields might have reduced the risk of these events.

Conclusion

Adjuvant radiotherapy either after incomplete surgery and/or local recurrence and/or high-grade tumours seems to be efficient to prolong local control in this rare disease.

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Antibodies to p53 - can they serve as tumor markers in patients with malignant lymphomas?

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Background. *Tumor suppressor gene p53 is mutated in approximately 21 % of patients with nonHodgkin's lymphomas (the percentage varying from 0 up to 67 % depending upon the histological type). Most of the mutations are point missense mutations resulting in nuclear accumulation of altered protein. Roughly one third of patients with overexpression of p53 protein develop circulating anti p53 antibodies. The present study was aimed at defining the usefulness of serial serological determinations of autoantibodies to p53 for clinical follow up of NHL patients.*

Patients and methods. *Serum levels of antibodies to p53 were determined in various time intervals in three lymphoma patients (who had elevated serum levels at the time of diagnosis) for maximum two years using the commercially available ELISA kit p53-Autoantikoerper ELISA 2. Generation.*

Results. *In all three cases the temporal patterns of anti p53 antibodies reflected accurately disease progression or regression, and even foretold a relapse ten months in advance. The reflection of disease regression by autoantibodies lagged approximately three months behind the morphological disappearance of the disease due to a long half life of the antibodies.*

Conclusion. *Our results confirmed the usefulness of antibodies to p53 as tumor markers for follow up of lymphoma patients, yet the subset of patients that could be appropriately followed up with this method is very limited due to the low proportion of patients that develop immune response to p53 protein.*

Key words: lymphoma, non-Hodgkin; tumor markers, biological ; protein p53

Introduction

p53 is a tumor suppressor gene the alterations of which are among the most frequent genetic changes detected in human neoplasms. Normal p53 acts as a "guardian of the genome" by preventing the proliferation of cells with damaged DNA. This function is achieved by the production of normal (wild type) p53 protein which acts on downstream

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genes to arrest the cell cycle until the DNA damage is repaired, or if the damage is irreversible, to cause apoptosis.[1,2] The loss of wild type function usually occurs by a two-step mechanism comprising mutation of one copy of the p53 gene and deletion or inactivation of the remaining wild type allele. The outcome of the mutation is the synthesis of a protein with a changed conformation, a longer half life, and disordered function in terms of cellular growth.[3]

The incidence of p53 mutations in nonHodgkin's lymphomas (NHL) varies according to histological type and disease stage - it is high in aggressive lymphomas (Burkitt's and diffuse large B cell lymphomas) and lower in intermediate and indolent lymphomas. Regardless of the type - the incidence is generally higher in case of a relapse or after progression. Most of the mutations are missense mutations clustered in exons 5 to 8 of one p53 allele and are usually associated with deletion of the other allele, through 17p deletion.[4]

Different authors[5-11] reported that p53 protein can become immunogenic in various human tumors *in vivo*, indicating that alterations in the expression or properties of p53 associated with tumor development can be detected by screening the sera of cancer patients for anti p53 antibodies. The formation of autoantibodies to p53 is directed against two immunodominant regions located at the carboxy and amino termini of the protein outside the central mutational hot spot region [7] and is observed only in patients with p53 missense mutations that express detectable levels of p53 protein in their tumor cells.[8] The p53 specific immune response does not develop in cancer patients bearing stop, splice/stop, splice or frameshift mutations of p53 gene in tumor cells.[8]

According to the literature autoantibodies to p53 were identified in 2.6 % [10] up to 21 % [6] of the tested sera of NHL patients. In our previous study the percentages of p53 antibody positive sera also varied greatly between different histological subtypes of NHL. In this paper we present a small study examining the usefulness of serial serological determinations of autoantibodies to p53 for clinical follow up of NHL patients.

Materials and methods

Patients

Three patients (two male and one female patient, ages 25, 64, and 47 years, respectively) with different types of NHL (REAL classification)[12] in which autoantibodies to p53 were detected at the time of diagnosis were followed up for maximum two years. In all three patients also p53 protein overexpression (indicating an underlying mutation of p53 gene) was identified immunohistochemically.

Sample collection

Blood was collected in variable time intervals over a maximum two year period and sera were separated from the clot by centrifugation. The sera were then aliquoted and stored at -20°C until analysis. The samples were diluted in sample dilution buffer before assaying (so that the measurement results fell inside the area of a standard curve) and the determinations were executed according to manufacturer's instructions.

Serum determinations

Serial determinations of autoantibodies to p53 were performed using the commercially available ELISA kit p53-Autoantikoerper ELISA 2. Generation (Dianova, Hamburg, Germany). The assay is based on a sandwich technique with human recombinant p53 protein coated to the microtiter plate wells which binds the anti p53 autoantibodies of the

serum sample and a goat anti human IgG antibody (as the detection antibody) conjugated to peroxidase. The bound enzymatic activity is determined by addition of a chromogenic substrate and by measuring the resulting colored solution with a spectrophotometer. The concentration of the sample or the standard is directly proportional to the absorbance value measured.

Results

Patient A was diagnosed with Burkitt's lymphoma stage IV and was treated with aggressive chemotherapy that included high dose methotrexate, cyclophosphamide, ifosfamide, vincristine, adriamycin, etoposide, cytosine arabinoside and corticosteroids plus chemotherapeutic central nervous system prophylactic therapy according to BFM protocol. He responded well to primary treatment and there were no clinical signs of residual disease upon completion of the therapy. However, three months later he was admitted to the hospital with a massive relapse. Salvage chemotherapy was introduced, but with no effect, so the patient died of lymphoma shortly thereafter. The levels of antibodies to p53 were elevated prior to treatment, showed only a minor decrease during the primary treatment and started to rise before the primary treatment was completed. From there on the levels increased continuously reflecting the disease progression (Figure 1).

Patient B was diagnosed with an inoperable diffuse large cell B lymphoma of the stomach involving also paraaortic lymph nodes. He was treated with six cycles of CHOP regimen (cyclophosphamide, epidoxorubicin, vincristine, corticosteroids) plus radiation and achieved a complete remission. Surprisingly, during the two years of follow up there was no evidence of recurrence. Pretreatment levels of antibodies to p53 in this patient were elevated, but fell to normal (below the cut-off limit determined by the kit producer) as a consequence of successful treatment lagging approximately

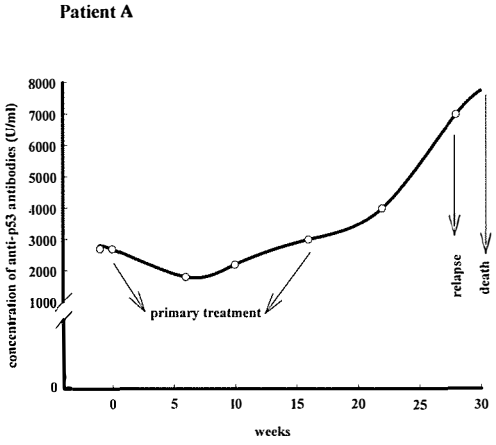

Figure 1. Consecutive serum levels of autoantibodies to p53 protein in a patient with Burkitt's lymphoma reflected the dynamics of the disease. The patient responded well to primary treatment, but experienced a relapse (three months later) that was resistant to salvage therapy. The relapse was foretold by the increasing levels of autoantibodies to p53 protein already before the primary treatment was finished.

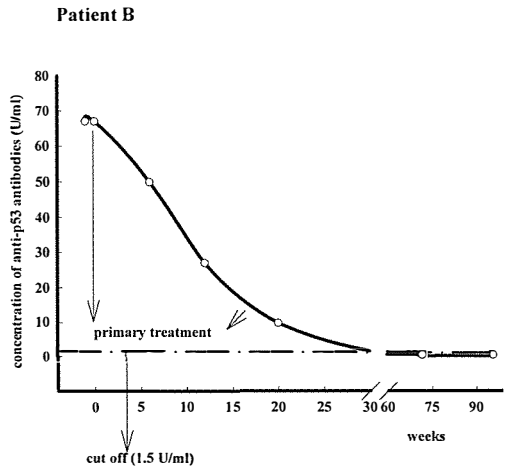

Figure 2. The downward trends in serum levels of autoantibodies to p53 protein confirmed the success of primary treatment in a patient with inoperable diffuse large cell B lymphoma of the stomach. The levels fell below the cut-off limit approximately three months after morphological disappearance of the disease.

two to three months behind the morphological disappearance of the disease (Figure 2).

Patient C was diagnosed with follicle center cell lymphoma grade III and stage III. She was treated with ten cycles of CHOP regimen (cyclophosphamide, epidoxorubicin, vincristine, corticosteroids) plus radiation of the residuum after chemotherapy and with this combined treatment achieved a complete remission. Ten months later a relapse was detected and she was treated with salvage chemotherapy, but progressed during the treatment. Radiation therapy was applied to the bulky masses in the mediastinum - again with poor success, so the patient died of lymphoma shortly thereafter. The levels of antibodies to p53 were elevated prior to treatment and decreased somewhat reflecting the response to primary chemotherapy - but never reached the cut-off level. Two months upon completion of CHOP regimen the levels of antibodies to p53 started to rise again foretelling the relapse ten months before it was actually confirmed. During the salvage therapy there was a continuous increase in the antibody levels (Figure 3).

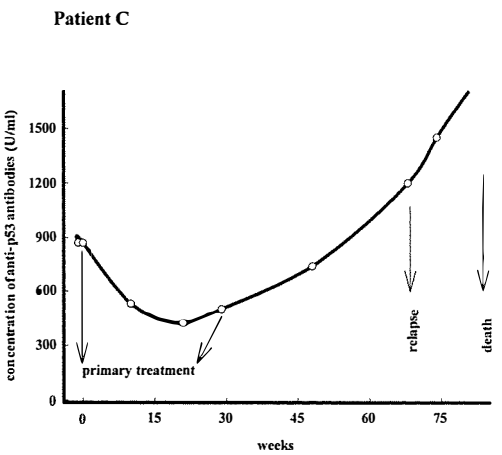

Figure 3. The serum levels of autoantibodies to p53 protein indicated the disease status in a patient with follicle center lymphoma grade III. The patient achieved a complete remission with the primary treatment, but relapsed ten months later and responded poorly to the salvage therapy. The relapse was foretold ten months in advance by the continuous increase in the serum levels of autoantibodies.

Discussion

In contrast to various types of solid tumors (e.g. prostate cancer, breast cancer, colorectal cancer, germ tumors), in lymphomas there are no appropriate serum tumor markers for the easy follow up of the patient's disease status, with lactic dechydrogenase (LDH) and beta-2-microglobulin being the best approximations to the definition of a serum lymphoma tumor marker.[13] However, in a certain proportion of NHL patients with overexpression of p53 protein in their tumor cells (due either to mutation of p53 gene or stabilization of the gene product by mechanism other then point mutation), this protein somehow becomes immunogenic, resulting in the production of autoantibodies to p53 protein.[6,10] It has been suggested that the appearance of such antibodies in the sera of cancer patients is a very early event - present already at the diagnosis.[7,14] The specificity of the autoantibodies to p53 protein is 100 % [11], but they are present in malignancy in general, and are not an indicator of the type of malignant disease. Therefore, the antibodies show some prerequisites for a good tumor marker also in some lymphoma patients. The frequency of autoantibodies' development, on the other hand, is relatively low, for example approximating only 25 % of patients with hepatocellular carcinoma[11], which is due to the facts that p53 is not mutated in every patient with malignant disease, and that the appearance of antibodies to p53 (protein) is not an obligatory consequence of p53 overexpression in tumor cells.

In our three cases the early presence of anti p53 antibodies, as well as their specificity, were confirmed, while only 8 % of NHL patients developed an immune response to overexpressed p53 protein.

On the other hand, in accordance with observations of Angelopolou *et al.*[10] our results clearly demonstrated that the levels of anti p53 antibodies correlated well with the disease progression or regression, even foretelling the disease progression ten months before it was actually confirmed. In contrast to conventional tumor markers, which are known to have a shorter half life, the temporal patterns of antibodies reflecting tumor regression lagged approximately two to three months behind the morphological disappearance of the disease. This delay is explainable with the relatively long serum half lives of the antibodies, and the time required for the immune system to adapt to an altered immunological stimulus.

In conclusion, even though the existence of anti p53 antibodies in patients with NHL is a relatively rare event - namely, overexpression of p53 protein is found in approximately 21 % of NHL (varying with the histological type and the antibody used in immunohistochemical methods)[15-17], of which only a part develop an autoimmune response to p53 protein (for percentages see the Introduction) - these autoantibodies, when present, show the qualities of a good serum tumor marker and represent one of the simplest methods to follow up a subset of NHL patients. Moreover, due to the fact that the presence of antibodies to p53 protein in patients with different solid tumors was associated with more aggressive tumor types, shorter tumor free intervals and poor prognosis [18,19], there is another strong argument speaking in favor of detecting antibodies to p53 protein in order to define the subset of patients being particularly at risk for an unfavorable outcome.

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Radiol Oncol 2000; 34(3): 307-8.

Advanced course on ethics in oncology

June 25-28, 2000, Bled, Slovenia

An Advanced Course on Ethics in Oncology was held from 25th to 28th of June 2000 in Bled, Slovenia. The course was organized by the Institute of Oncology from Ljubljana, Slovenia and sponsored by the European School of Oncology. It was carried out under the high patronage of the first lady of Slovenia Mrs. Štefka Kučan. 57 participants from 15 different countries attended the course, most of them from Slovenia and Eastern Europe.

The course was exceptional in many ways, one of them certainly being the beautiful setting of Lake Bled and Grand Hotel Toplice, where the course was held. Its topic, biomedical ethics, has an increasingly important role in medicine, not only in Western Europe and in the USA but also in the Eastern Europe, where most of the course participants came from. For many of them, the course offered the first formal teaching on the subject, as well as a unique chance of debating ethical issues with distinguished invited speakers. Among the course's invited speakers were prominent international authorities in the field of biomedical ethics: **Prof. Matjaž Zwitter** from the Institute of Oncology, Chairman of the organizing committee and co-author of the book Communication with the Cancer Patient – Information and Truth, **Prof. Raanan Gillon**, Editor of the Journal of Medical Ethics and Senior Editor and co-author of the textbook Principles of Healthcare Ethics, **Prof. Povl Riis**, co-author of the Second Declaration of Helsinki and an expert on ethical issues in biomedical research, **Georges B. Kutukdjian**, Senior Director of the Division of the Ethics of Science and Technology at UNESCO, **Mgr. Charles G. Vella**, Member of the Ethics Committee of the Cambridge Journal of Bioethics and author of a number of books on family, counseling and ethics, **Prof. Tore Nilstun**, Vice-Chairman of Research Ethics Committee at IARC and of Clinical Ethics Committee at Lund University Hospital, **Prof. Jože Trontelj**, Chairman of Slovenian National Medical Ethics Committee and co-author of the Oviedo Convention, **Nora Kearney**, Senior Lecturer in Cancer Nursing at the University of Glasgow and immediate past President of the European Oncology Nursing Society, **Prof. Gregory L. Larkin**, author of many publications on ethical issues, including the Code of Ethics for Emergency Physicians, and others.

The course did not or better could not cover only the ethical issues within oncology. In the brief and thorough introduction to medical ethics by Prof. Gillon and Mgr. Vella we learned about the four basic principles of medical ethics, **respect for autonomy, beneficence, non-maleficence and justice**, and their implementation in medical practice. The course continued with more detailed lectures about the ethical principle of autonomy in medical practice, ethics of clinical research, dying and euthanasia, and medical utility (the ethical principle of justice in the face of scarce medical resources). Some of the lectures included cases illustrating some common ethical dilemmas clinicians encounter in their daily practice. Each lecture was followed by ample amount of time for discussion, which is the most important instrument in teaching bioethics. As most of the lecturers actively practice medicine, they could provide practical and useful insights as well as academical answers to our questions and dilemmas. The best part of the course was therefore the round table discussion that took place on the third day. By that time, informal and

friendly atmosphere of the course was already established and enabled an open and lively discussion on ethical topics that participants pointed out as most problematic. We talked about inappropriate prolongation of life, patients' false hopes in connection with new treatments and problems in informing the patient about the prognosis of incurable cancer. We all agreed that doctor-patient relationship is based upon and can be improved by physician's knowledge of medical ethics and good communication skills. Both these topics are insufficiently taught to medical students, especially in the Eastern European countries.

Social program of the course was not as abundant as the lectures, but it helped to establish an informal and friendly atmosphere. The ice was certainly broken by a rowing regatta to the Island of Bled, where some of us more or less successfully tried to make the lucky bell ring. The gala dinner, which was held in the romantic Bled Castle, was enriched by a special „main course", the dinner talk by Prof. Borut Telban from Slovenian Academy of Sciences and Arts. Prof. Telban is an anthropologist who spent three years doing research among the tribes in the Papua New Guinea. He gave us an account on human values in those communities, which is a unique perspective not many of us will ever have a chance to experience.

As this was the first international course on biomedical ethics in oncology and in this geographical area, it answered some but opened many new questions about this important topic. The participants stated that the course fulfilled their expectations and agreed that courses on biomedical ethics are much needed and will therefore have to be repeated, preferably including a more practical approach, based on case reports and enabling a guided discussion about concrete ethical dilemmas.

Patricija Ećimović

Radiol Oncol 2000; 34(3): 251-9.

Kirurško zdravljenje zgodnjega raka na dojki z ohranitvijo dojke in aksilarnih bezgavk

Blichert-Toft M

Cilj vseh prizadevanj v kirurškem zdravljenju raka dojke z ohranitvijo dojke je ohranjanje ženskosti, pri čemer se trudimo s čim manjšo iznakaženostjo zunanjega izgleda čim bolj omejiti občutek manjvrednosti. Mnogo žensk bi raje ohranilo dojko kot življenje. Osnovni pogoji, ki jih mora izpolniti vsak kirurški poseg z ohranitvijo dojke, so naslednji: zadovoljiva kozmetična rekonstrukcija, funkcionalnost in lokoregionalni nadzor nad boleznijo. Če je po operaciji izgled dojke hudo iznakažen, ohranitev dojke ni smiselna. Osnovna metoda zdravljenja zgodnjega raka dojke je operacija. Poseg z ohranitivijo dojke je možen le, če je za bolnico ustrezen. Radikalnost kirurškega posega je še posebej pomembna po opravljeni mastektomiji ali kirurškemu zdarvljenju z ohranitvijo dojke. Posebej natančno je treba proučiti dejavnike tveganja kirurškega zdravljenja z ohranitvijo dojke, zlasti mladost bolnice in razvejanost izvodil v vzorcu, dva dejavnika, ki ju obravnavamo kot neodvisna dejavnika tveganja za lokalni nadzor bolezni po opravljenem posegu z ohranjeno dojko. Od vseh kirurških zdravljenj raka dojke na Danskem jih je 30 % opravljenih z ohranitivjo dojke. Ta delež je razmeroma nizek v primerjavi z ostalimi državami. Prav zato smo odločili za razpravo o kriterijih, ki danes veljajo na Danskem in odločajo o ustreznosti tega postopka. V razpravi poudarjamo tudi razloge za odstranitev aksilarnih bezgavk, ki jo priporočamo celo pri tumorjih, manjših kot 10 mm, pri katerih ugotavljamo precejšnjo prizadetost bezgavk. Z uvajanjem postopka, ki temelji na odkrivanju 'stražarske' bezgavke, postavljamo temelje metodi ohranjanja neprizadetih aksilarnih bezgavk pri bolnicah z negativnimi bezgavkami.

Radiol Oncol 2000; 34(3): 261-4.

Odkrivanje stražarskih aksilarnih bezgavk med operacijo

Viale G

Z rutinskim histološkim odkrivanjem stražarskih aksilarnih bezgavk je mogoče predvideti, katere od bezgavk niso prevzele stražarske naloge. Bolnicam z rakom dojke tako lahko prihranimo odstranitev vseh aksilarnih bezgavk. Če se želimo izogniti dvem kirurškim posegom, je treba med operacijo opraviti preiskavo stražarske bezgavke in kirurga obvestiti o rezultatih preiskave. Rezultati rutinske preiskave z zamrznjenim rezom so pogosto negativno napačni. Zato smo se raje odločili za obsežnejšo intraoperativno preiskavo zamrznjenih bezgavk, s katero bi lahko dosegli občutljivost, ki bi bila primerljiva z občutljivostjo rutinske histološke analize.V prvi seriji v zamrznjene bezgavke zarežemo vsakih 50 μm. Na vsaki od ravni eno rezino obarvamo s hematoksilinom in eozinom, drugo pa z imunskim barvilom za citokeratine, pri čemer uporabljamo nagli imunocitokemični preizkus. Z imunocitokemijo nismo uspeli povečati občutljivosti preiskave. Razmerje med statusom stražarskih in aksilarnih bezgavkami je bilo 96,7-odstotno; negativna napovedna vrednost preiskave stražarske bezgavke med operacijo je bila 94,1-odstotna. Preiskava stražarskih bezgavk med operacijo je učinkovita metoda za ocenjevanje stanja aksilarnih bezgavk pri bolnicah z rakom dojke in je lahko zelo uporabna v odločitvah o ohranitvi ali ostranitvi aksilarnih bezgavk.

Radiol Oncol 2000; 34(3): 265-8.

Terapija z ohranitvijo rektuma an kvaliteta operativnega posega pri prevenciji lokalnih recidivov

Temple WJ

Zdravljenja rektalnega raka je v zadnjih 100 letih izjemno napredovalo. Od časov Mylesove obdominalne perinealne resekcije je prišlo do napredka v začetki 20. stoletja, ko ni potrebna več stalna kolostoma in je redikalni kirirški poseg povezan samo z 5 % lokalnih recidivov. Adjuvantno zdravljenje z radioterapijo in kemoterapijo se je pokazalo uspešno pri napredovalem raku, ne samo pri kontroli lokalne bolezni ampak tudi izboljšanju preživetja. Članek obravnava z veliko pozornostjo predvsem dve gledišči: 1) tehniko kiruškega posega s katero lahko povečamo preživetje in lokalno kontrolo rasti tumorja, in 2) kirurgijo anusa z ohranitvijo funkcije organa in in zboljšanja lokalne kontrole rasti tumorja. Ugotavljamo, da s pravilnim kirurškim posegom ob uporabi TME tehnike, in souporabi preoperativnega obsevanja napredovalih tumorjev, lahko dosežemo več kot 90 % kontrolo lokalne rasti tumorjev spodnjega dela rektanega kanala.

Radiol Oncol 2000; 34(3): 309-15.

Radiol Oncol 2000; 34(3): 269-73.

Terapija z ohranitvijo organov pri zdravljenju sarkomov mehkih tkiv

Temple WJ

Sedaj, v letu 2000 lahko večina bolnikov s sarakomi mehkih tkiv pričakuje, da bo hodila po operaciji, kar predstavlja velik napredek v primerjavi z zdravljenjem pred 20 leti, ko je bila amputacija okončin standardni način zdravljenja. Danes se zdravi s široko lokalno ekscizijo z varnostnim robom 1-2 cm v zdrava tkiva, v kombinaciji z radioterapijo pred ali po operaciji. Lokalno lahko na tak način z rekonstrukcijsko kirurgijo in adjuvantnim zdravljenjem dosežemo 90% kontrolo rasti tumorja. Edina omejitev za tak poseg je, ko je bolezen napredovala in objela živce okončine, ali če ne moremo pri operaciji doseči čistih robov, takrat je še vedno potrebna amputacija okončine.

Radiol Oncol 2000; 34(3): 275-9.

Razmišljanja o kakovosti življenja in zdravljenju z ohranitvijo organov

Tannock IF

Z zdravljenjem z ohranitvijo organov želimo v času preživetja zagotoviti čim višjo kakovost življenja. Danes že poznamo metode za ocenjevanje kakovosti življenja bolnikov, ki jih zdravimo na zelo različne načine. V načrtovanih kliničnih raziskavah, ki proučujejo strategije zdravljenja z ohranitvijo organov, bi bilo potrebno kakovost življenja uvrstiti med raziskovalne teme, tako kot preživetje. Takšne metode bodo v veliko korist in pomoč pri določanju strategij, ki zagotavljajo podobno preživetje, in odločanju med izboljšanjem kakovosti ali količinskosti preživetja.

Radiol Oncol 2000; 34(3): 281-4.

Nesvež možganski infarkt pri novorojencu

Hatzidaki E, Prassopoulos P, Korakaki E, Evangeliou A, Voloudaki A, Giannakopoulou C

Izhodišča. Možganska arterijska tromboza je razmeroma redka pri novorojencih. Pri otrocih, kjer kmalu po rojstvu nastane takšna tromboza, se ponavljajo lokalni akutni klonični krči z radiološko značilnimi znaki akutnega možganskega infarkta. Veliko študij potrjuje, da je ta pojav pri novorojencih zelo redek.
Prikaz primera. V članku poročamo o primeru novorojenca, ki je tretji dan po rojstvu prestal napade kloničnih krčev, ki so bili omejeni na desno spodnjo okončino. Ultrazvočna preiskava možganov je pokazala le manjše anomalije, preiskava z magnetno rezonanco pa je odkrila arterijski infarkt v srednjem delu možgan levo.
Zaključki. Novejše metode slikovne diagnostike, na primer slikanje centralnega živčnega sistema z magnetno rezonanco, so zelo uporabne v diagnostiki manj pogostih bolezenskih motenj in pri odkrivanju primerov, ki jih po negativni preiskavi z ultrazvokom ne bi izsledili.

Radiol Oncol 2000; 34(3): 285-8.

Ali je še potrebna popolna odstranitev pazdušnih bezgavk pri bolnicah z omejenim rakom dojk?

Čufer T

Izhodišča. Popolna odstranitev pazdušnih bezgavk (POPB) s histološkim pregledom le-teh še vedno velja za potreben kirurški poseg v okviru zdravljenja omejenega raka dojk. Ta poseg, ki ima pogosto neželene kasne podsledice, naj bi bil potreben za odločitev o dopolnilnem sistemskem zdravljenju in za lokalno kontrolo bolezni. Vedno bolj pa se zastavlja vprašanje, ali je temu res tako. Glede na to, da se dopolnilno zdravljenje vedno bolj načrtuje na podlagi bioloških lastnosti prvotnega tumorja in zaradi vse pogostejše uporabe predoperativnega sistemskega zdravljenja, je POPB vse manj pomembna za načrtovanje zdravljenja. Pri majhni skupini bolnic, pri katerih pa je za izbor dopolnilnega zdravljenja še vedno potrebna informacija o prizadetosti pazdušnih bezgavk s tumorjem, lahko POPB nadomesti biopsija varovalne bezgavke. Dobro lokalno kontrolo bolezni je ob manjših kasnih posledicah mogoče doseči tudi z obsevanjem pazduhe.
Zaključki. Skupaj z ohranitvijo dojke je opustitev kirurške odstranitve vseh bezgavk v pazduhi eden glavnih korakov k izboljšanju kvalitete življenja bolnic z omejenim rakom dojk.

Radiol Oncol 2000; 34(3): 309-15.

Radiol Oncol 2000; 34(3): 289-94.

Dejavniki, ki vplivajo na rehabilitacijo bolnikov z rakom glave in vratu

Hočevar-Boltežar I, Šmid L, Žargi M, Župevc A, Fajdiga I, Fischinger J, Jarc A

Namen raziskave. S prospektivno raziskavo so avtorji poskušali ugotoviti, kateri dejavniki negativno vplivajo na rehabilitacijo bolnikov z rakom glave in vratu po končanem zdravljenju.
Bolniki in metode dela. Pri 110 bolnikih z rakom ustne votline, žrela in grla so avtorji pred kirurškim zdravljenjem ugotavljali morebitne neugodne dejavnike: naglušnost, pomanjkljivo zobovje, zmanjšano pljučno funkcijo in govorne motnje. Dvanajst mesecev po končanem zdravljenju so bolniki ocenjevali uspešnost rehabilitacije. Avtorji so ugotavljali vpliv naštetih neugodnih dejavnikov, lokalizacije tumorja in vrste kirurškega zdravljenja na bolnikov govor, sposobnost požiranja in reintegracije v domače okolje.
Rezultati. Lokalizacija tumorja in vrsta kirurškega zdravljenja nista vplivali na splošno uspešnost rehabilitacije. Pomanjkljivo zobovje je zmanjševalo sposobnost požiranja, ni pa vplivalo na govor. Naglušnost je negativno vplivala na vključevanje bolnika v domače okolje. Zmanjšana pljučna funkcija ni vplivala na bolnikov govor. Govor je bil najslabši pri laringektomiranih bolnikih. Kljub temu sta bili dve tretjini bolnikov zadovoljni s svojo sposobnostjo govora, požiranja in rehabilitacije po zdravljenju na splošno.
Zaključki. Zgodnje odkrivanje neugodnih dejavnikov in individualno načrtovana rehabilitacija lahko omogočita primerno kakovost življenja bolnikov, kirurško zdravljenih zaradi raka glave in vratu.

Radiol Oncol 2000; 34(3): 295-300.

Ependimom pri odraslih bolnikih: rezultati zdravljenja z adjuvantno radioterapijo

Mayer R, Prettenhofer U, Quehenberger F, Guss H, Hackl A

Izhodišča. Ependimom je zelo redek tumor. Ker izkušnje o zdravljenju temeljijo predvsem na retrospektivnih študjah, smo tudi mi preživetje in ponovitev bolezni proučevali na osmih odraslih bolnikih z ependimomom v lobanji ali na hrbtenici, ki smo jih predhodno zdravili z adjuvantno radioterapijo.

Bolniki in metode. V študiji smo predstavili 7 bolnikov z ependimomom z nizko in srednjo stopnjo in 1 bolnika z visokostopenjskim ependimomom. Vsi so bili po operaciji zdravljeni še z radioterapijo. Od 8 bolnikov s povprečno starostjo 41 let (18-55 let), ki so bili zdravljeni od 1985 do 1994, sta 2 bolnika imela ependimom v lobanji, 6 pa na hrbtenici. Pri 4 bolnikih je bil ependimom makroskopsko popolnoma odstranjen, pri 1 je bil delno odstranjen, pri 3 pa je bil potreben dodatni kirurški poseg po nepopolni odstranitvi lokalno ponovljene bolezni. Obsevalno polje ni obsegalo celotne kraniospinalne osi. Povprečni obsevalni odmerek je bil skupno z dodatnom obsevanjem 52 Gy (50-54 Gy).

Rezultati. Povprečni čas sledenja bolnikov je bi 101 mesec (12-146 mesecev), petletno preživetje je bilo 100 %, preživetje brez znakov bolezni pa 86 %. Recidiv znotraj obsevalnega polja smo zasledili 77 mesecev po radioterapiji pri 1 bolniku z ependimomom v lobanji in pri 1 bolniku z ependimomom na hrbtenici. Oba bolnika smo obsevali po delni odstranitvi ponovno zraslega tumorja. Recidiv zunaj obsevalnega polja pa smo opazili pri 2 bolnikih s tumorjem na hrbtenici in sicer pri prvem 38 mesecev po zaključenem obsevanju, pri drugem pa po 86 mesecih. Pri nobenem bolniku nismo zasledili kasnejših stranskih učinkov obsevanja.

Zaključek. Adjuvantna radioterapija se zdi učinkovita za ohranitev lokalnega nadzora te precej redke bolezni predvsem pri bolnikih, kjer smo samo delno odstranili tumor, ali pri tistih, kjer je prišlo do ponovitve bolezni ali pa je bil tumor visoke malignostne stopnje.

Radiol Oncol 2000; 34(3): 301-6.

Serumska protitelesa proti proteinu p53 kot tumorski označevalci za sledenje bolnikov z Ne-Hodgkinovimi limfomi?

Jezeršek B, Novaković S

Izhodišče. Mutacije tumorskega supresorskega gena se pojavljajo pri približno 21 % bolnikov z Ne-Hodgkinovimi limfomi (odstotek variira od 0 do 67 % glede na histološki tip Ne-Hodgkinovega limfoma). Prevladujejo t.i. mutacije s spremenjenim smislom (mutacije"missense"), ki posledično privedejo do kopičenja spremenjenega proteina v jedrih tumorskih celic. Približno tretjina bolnikov, pri katerih se spremenjeni protein p53 kopiči v jedrih tumorskih celic, se na takšno kopičenje odzove z nastankom krožečih protiteles proti proteinu p53. S pričujočo raziskavo smo želeli določiti dinamiko gibanja serumskih protiteles proti proteinu p53 glede na trenutno stanje bolezni in na osnovi tega sklepati o vrednosti protiteles proti proteinu p53 kot tumorskih označevalcev za sledenje bolezni.

Bolniki in metode. Serumsko koncentracijo protiteles proti proteinu p53 smo določali v različnih časovnih razmikih (v skupnem trajanju največ dveh let) pri treh bolnikih z Ne-Hodgkinovim limfomom in sicer z ELISA metodo p53-Autoantikoerper ELISA 2. Generation.

Rezultati. Pri vseh treh bolnikih je dinamika gibanja serumskih protiteles proti proteinu p53 natančno odražala izboljšanje ali poslabšanje maligne bolezni, naraščanje koncentracije protiteles smo namreč opazili celo že deset mesecev prej, preden smo klinično potrdili ponovitev bolezni. Upadanje koncentracije protiteles proti proteinu p53, kot odraz zmanjševanja tumorske mase, pa je zaostajalo približno dva do tri mesece za klinično sliko, kar je seveda posledica dolgega razpolovnega časa omenjenih protiteles.

Zaključek. Naši rezultati potrjujejo, da so serumska protitelesa proti proteinu p53 primerna kot tumorski označevalci za sledenje bolnikov z Ne-Hodgkinovimi limfomi. Žal pa je število bolnikov, pri katerih lahko uporabimo takšen način sledenja, zelo omejeno, ker se le manjši delež bolnikov na kopičenje spremenjenega p53 proteina v jedrih tumorskih celic odzove z nastankom protiteles.

Notices

*Notices submitted for publication should contain a mailing address, phone and/or fax number and/or e-mail of a **Contact** person or department.*

Lymphoma

October, 2000

The ESO postgraduate course will take place in Izmir, Turkey.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Radiation therapy

October 2-6, 2000

The 9th International Symposium on Neutron Capture Therapy for Cancer will take place in Osaka, Japan.

E-mail igcong@po.iijnet.or.jp

Oncology

October 4-6, 2000

The 4th National Congress of Federation of Spanish Societies of Oncology (F.E.S.E.O.) will be offered in La Caruna, Spain.

Contact Technical Secretariat, Orzan Congres, S.L.; call +34 981 169 855; or fax +34 981 247 908

Neuroradiology

October 5-7, 2000

Johns Hopkins Neuroradiology Review will be offered in Baltimore Mariott Inner Harbour Hotel, Baltimore, Maryland, USA.

Contact Johns Hopkins University School of Medicine, Office of Continuing Medical Edication, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205; call (419) 955 2959; or fax (410) 955 0807

Oncology

October 6-7, 2000

The ESO course on "Fatigue/Exhausting in Cancer Patients" will take place in Milan, Italy.

Contact ESO Office, Viale Beatrice d'Este 37, 20122 Milan, Italy; or call +39 0258317850; or fax +39 0258321266: or e-mail esomi@tin.it

Surgical oncology

October 6-7, 2000

The ESO training course will take place in Herakleion, Greece.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Radiation oncology

October 8-12, 2000

The ESTRO teaching course on "Evidence-Based Radiation Oncology: Principles and Methods" will be offered in Lleida, Spain.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Radiobiology

October8-12, 2000

The ESTRO teaching course on "Basic Clinical Radiobiology" will be offered in Bratislava, Slovakia.

Contact ESTRO office, Av. E. Mounier, 83/4, B-1200 Brussels, Belgium; or call +32 7759340; or fax +32 2 7795494; or e-mail info@estro.be; or see Internet http://www.estro.be

Radiation oncology

October 8-12, 2000

The Joint Meeting DEGRO-OGRO-DGMP will be offered in Munchen, Germany.

See Internet http://www.degro.org

Bioelectromagnetism

October8-12, 2000

The „3rd International Conference on Bioelectromagnetism" and „1st Slovenian-Croatian Meeting on Biomedical Engineering" will be offered in Bled, Slovenia.

Contact Prof. Damijan Miklavčič - president, Faculty of Electrical Engineering, University of Ljubljana, Tržaška 25, Sl-1000 Ljubljana, Slovenia; or call +386 61 1768 264; or fax +386 61 1264 658; or e-mail 3rdICBEM@svarun.fe.uni-lj.si; or see Internet http://www.albatros-bled-sp.si

Oncology

October 12-14, 2000

The ESO training course on "Oncology through the Ages: Historical, Philosophical and Ethical Aspects" will take place in Athens, Greece.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Medical oncology

October 13-17, 2000

The 25th ESMO Congress will take place in Hamburg, Germany.

Contact ESMO Congress Secretariat, Via Soldino 22, CH-6900 Lugano, Switzerland; or call +41 91 950 0781 or fax +41 91 950 0782; or e-mail esmo@dial.eunet.ch; or see Internet http:/www.esmo.org

Radiation therapy

October 22-25, 2000

ASTRO Annual meeting will be held in Boston, Massachusetts, USA.

Contact American Society for Therapeutic Radiology and Oncology Office, 1891 Preston White Drive, Reston, VA 20191, USA; web site: www.astro.org

Soft tissue sarcomas and bone tumours

October 26-28, 2000

The ESO training course will take place in Ankara, Turkey.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

Oncology

October 27-29, 2000

The ESO training course on "Angiogenesis: Indications in the Prognosis and Treatment of Cancer" will take place in Alexandroupolis, Greece.

Contact ESO office for Balkans and Middle East, N. Pavlidis, E. Andreopoulou Medical School, Department of Medical Oncology, University Hospital of Ioannina, 45110 Ioannina, Greece; or call +30 651 99394 or +30 953 91083; or fax +30 651 97505

As a service to our readers, notices of meetings or courses will be inserted free of charge.

Please sent information to the Editorial office, Radiology and Oncology, Vrazov trg 4, Sl-1000 Ljubljana, Slovenia.

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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education - A Report for the Third Quarter of 2000

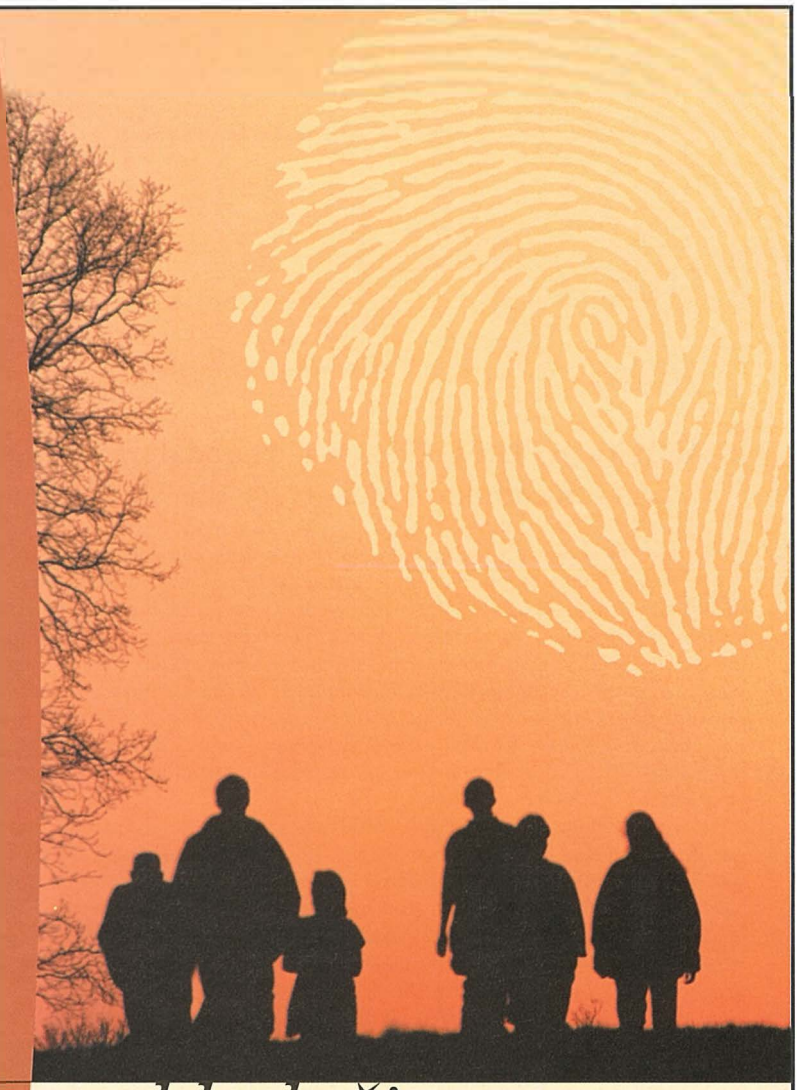
During the summer recess in the months from June through to August of the year 2000 the activity of "Dr. J. Cholewa Foundation" for cancer research and education continued as outlined in the plan that was agreed upon at the meetings of it's Scientific Board and Board of Directors in the end of the previous year. The plan for the year 2000 represents the continuation of the previous activity of the Foundation that includes the support for the research activity associated with cancer in Slovenia, grants for the participation of the medical professionals involved in the research and treatment of cancer and cancer education from Slovenia on various symposia, congresses and other meetings with cancer related topics, especially if they plan to participate actively presenting the results of their work. The Foundation also supports the publication of two cancer periodicals that are edited and printed in Ljubljana, Slovenia.

It is planned that one or very probably two grants will be awarded for cancer research. The experts involved in cancer research are to be invited to submit the proposals for themes either from basic research in cancer, research including clinical studies of treatment of cancer, or themes from epidemiological research of cancer. The research themes are supposed to be submitted by the Slovenian experts and major part of the research work is expected to take place in Slovenia. As the efficacious research work often depends on regular and intensive contacts with other researchers or research groups it is thus imperative for the Foundation to provide sufficient funds or other stimulation to Slovenian researchers, clinicians and educators involved in any way with cancer to continue to communicate and to meet experts dealing with cancer in other countries. Several smaller grants will thus be provided to cancer experts from Slovenia to participate in cancer congresses, symposia and international cancer education activity world-wide. The Foundation has in the recent years successfully co-operated with the European School of Oncology from Milan, Italy, in this matter and hopefully this co-operation will continue in the future. It is fair to assume that the Foundation will also support the organisation of all meetings, symposia and conferences with themes related to cancer in Slovenia.

The Foundation will continue to support the regular publication of "Radiology and Oncology" and "Challenge ESO Newsletter" international journals. Both journals publish articles and reports associated with various aspects of cancer and are both edited and printed in Ljubljana, Slovenia. Due to the change of nature of the co-operation between the European School of Oncology and the Foundation several changes are expected to take place in the editorial policy and possibly in the appearance of the "Challenge ESO Newsletter"

The "Dr. J. Cholewa Foundation" for cancer research and education is continuing with it's activity as outlined in the relevant documents. It is planned that the activity of the Foundation will be further expanded in the months and years to come.

Andrej Plesničar, MD
Borut Štabuc, MD, PhD
Tomaž Benulić, MD



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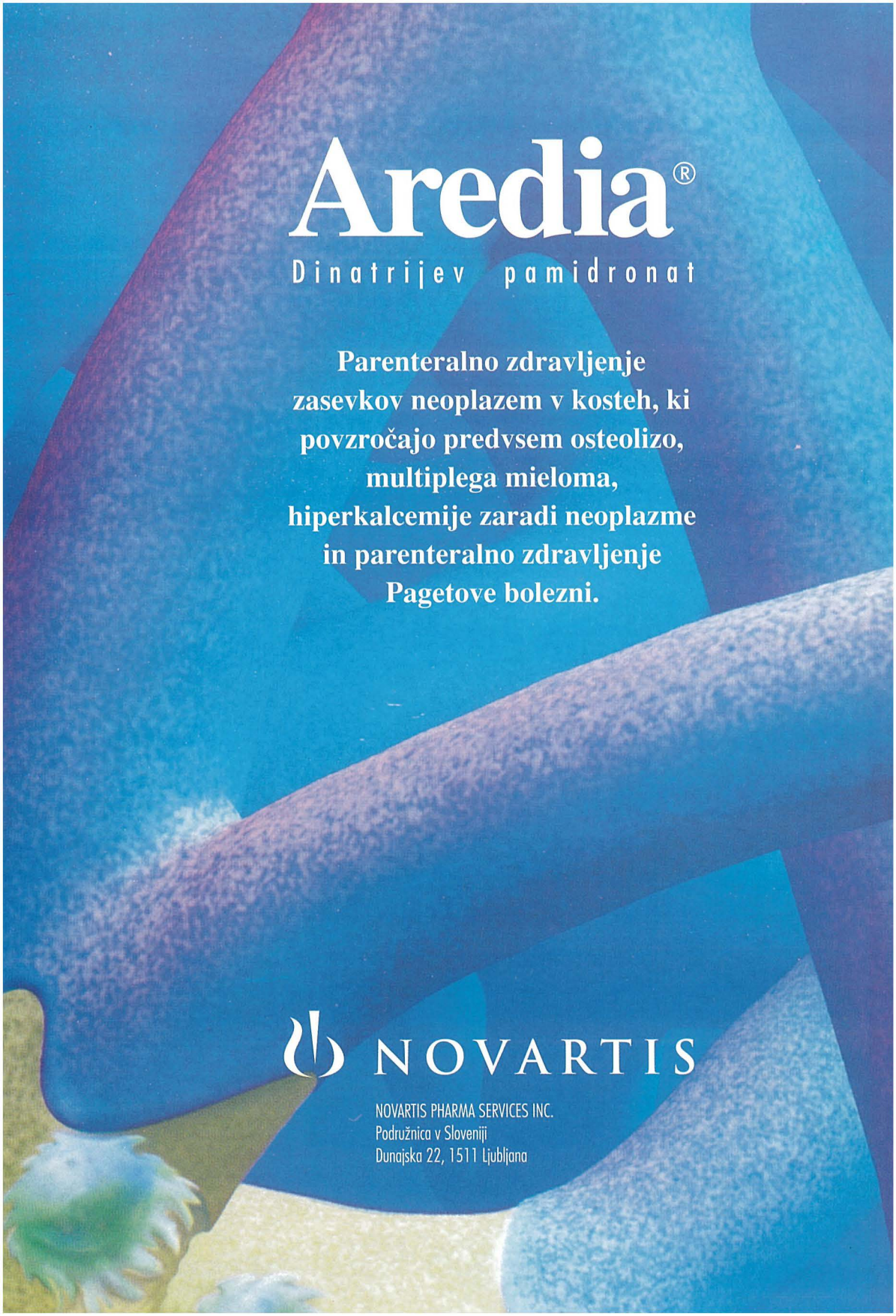
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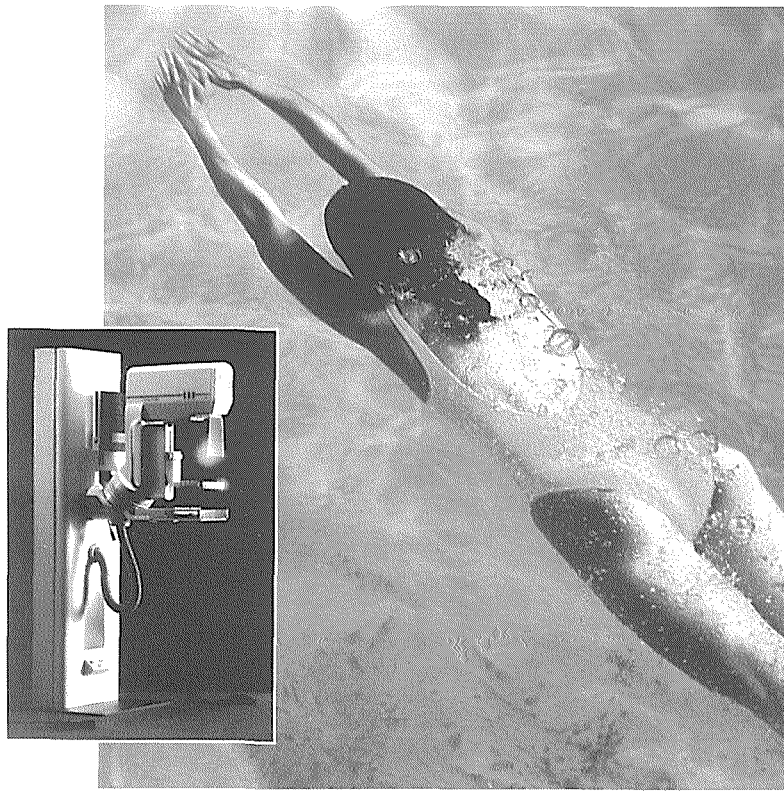

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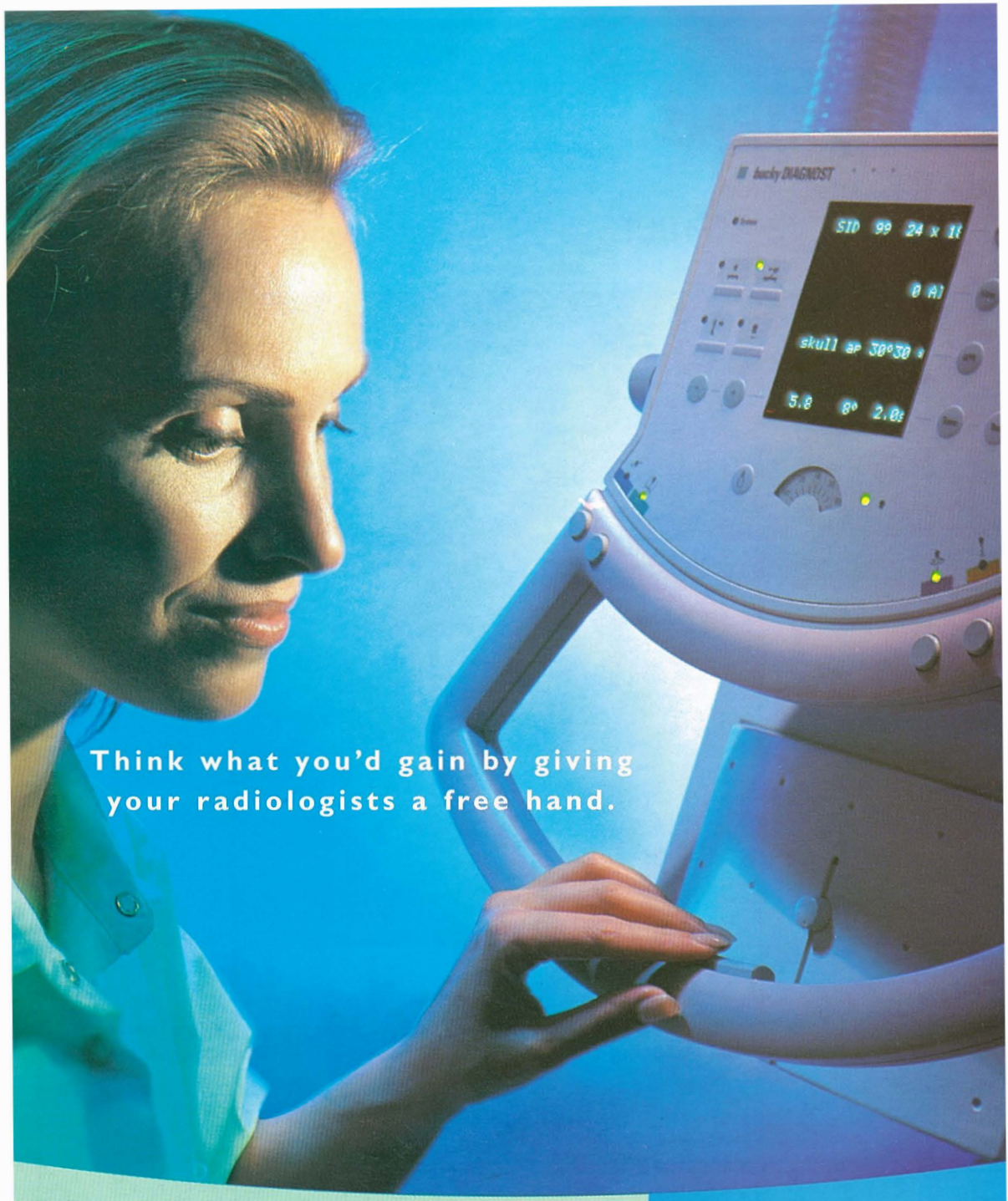

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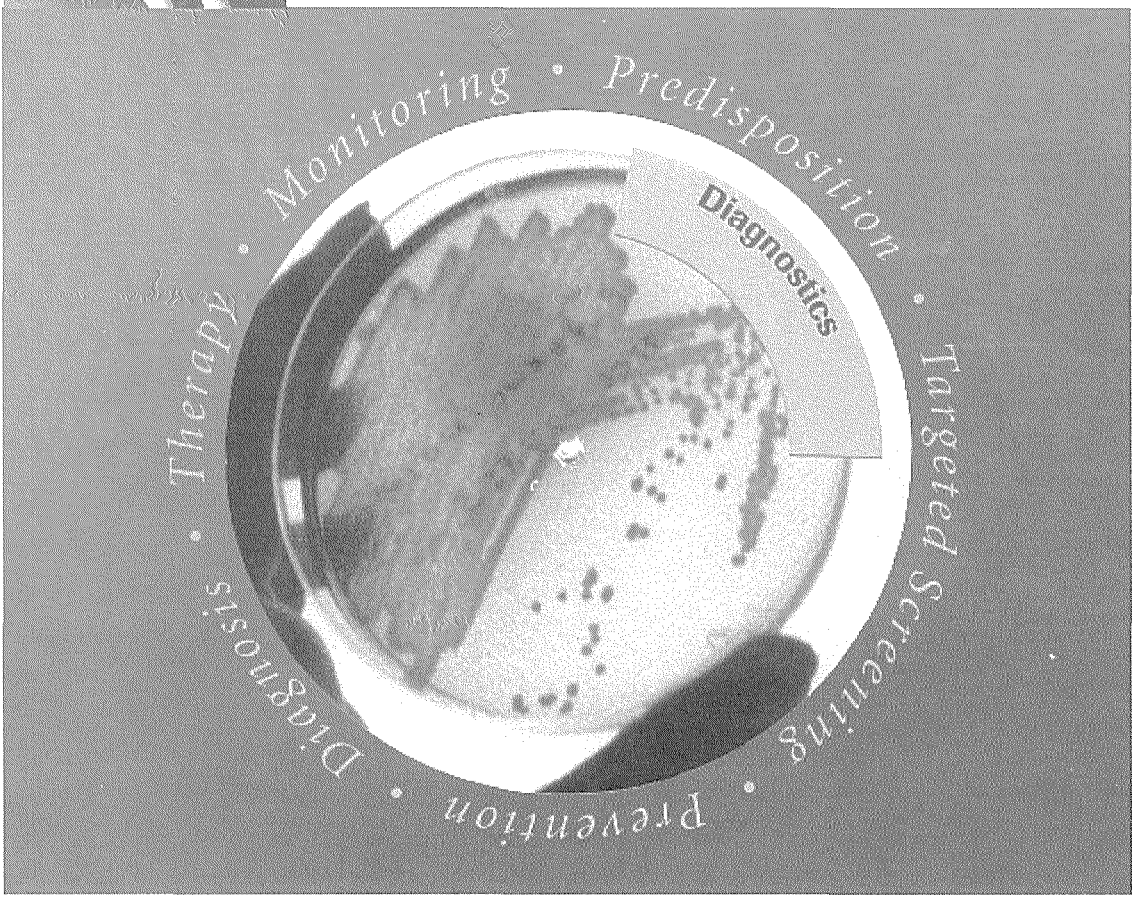

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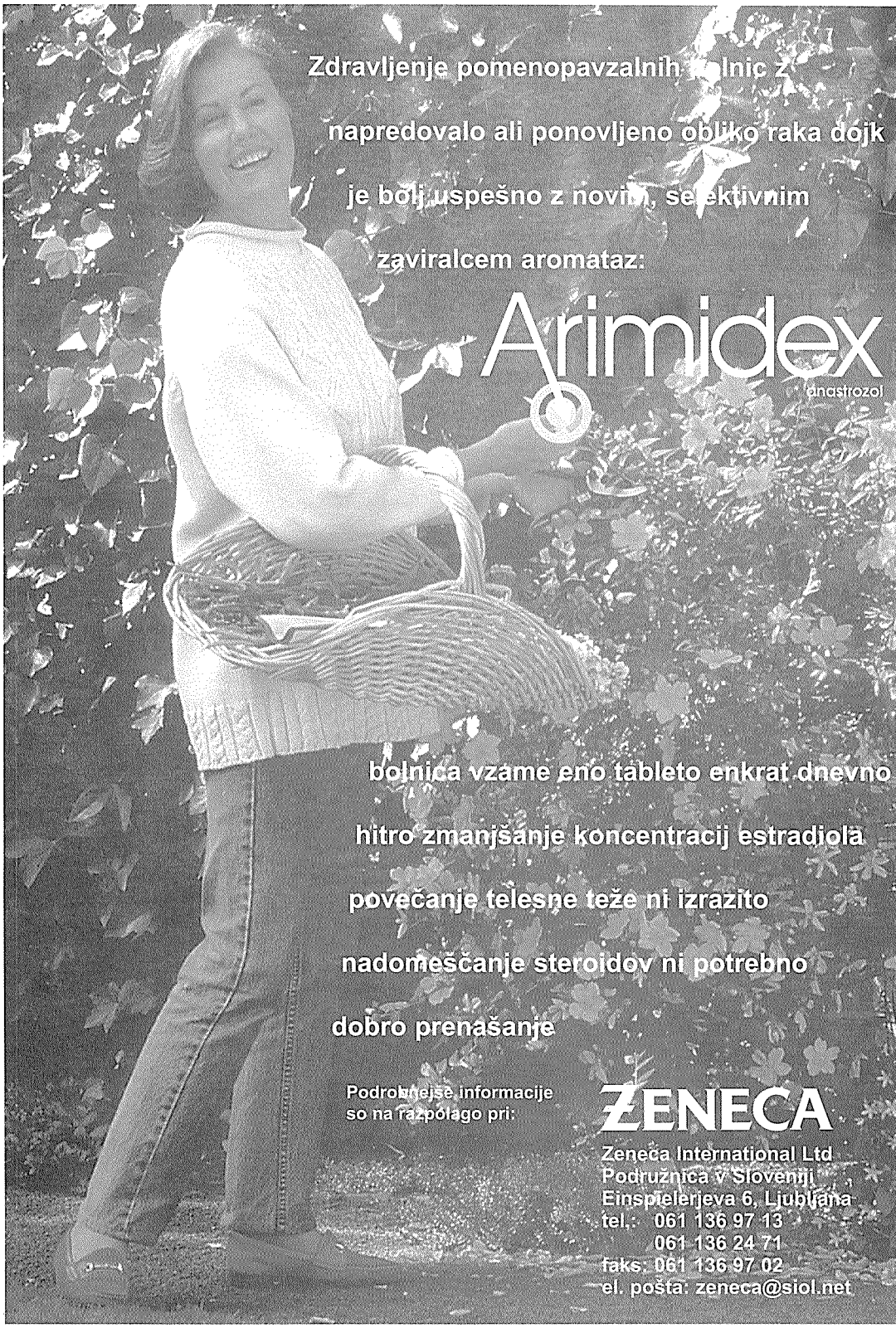
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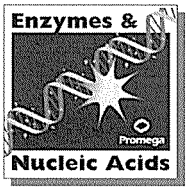

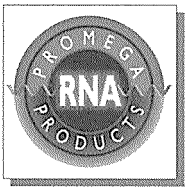

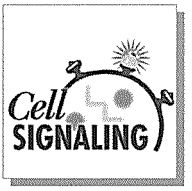

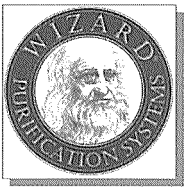

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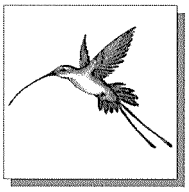

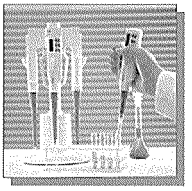
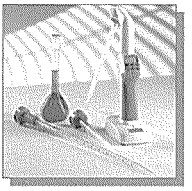
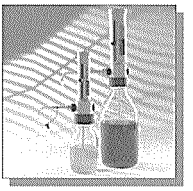

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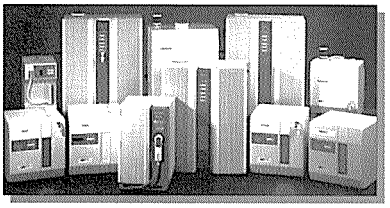

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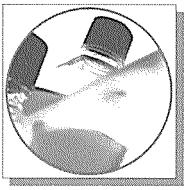

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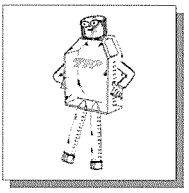
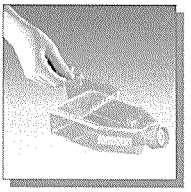
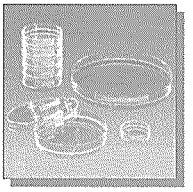
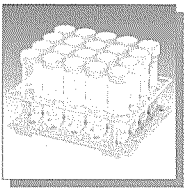
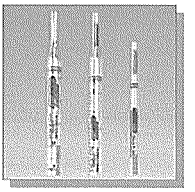

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Manuscript written in English should be submitted to the Editorial Office in triplicate (the original and two copies), including the illustrations: *Radiology and Oncology,* Institute of Oncology, Vrazov trg 4, SI-1000 Ljubljana, Slovenia; (Phone: +386 61 132 00 68, Tel./Fax: +386 61 133 74 10, E-mail: gsersa@onko-i.si). Authors are also asked to submit their manuscripts 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).

All articles are subjected to editorial review and review by independent referee selected by the editorial board. Manuscripts which do not comply with the technical requirements stated herein will be returned to the authors for correction before peer-review. Rejected manuscripts are generally returned to authors, however, the journal cannot be held responsible for their loss. The editorial board reserves the right to ask authors to make appropriate changes in the contents as well as grammatical and stylistic corrections when necessary. The expenses of additional editorial work and requests for reprints will be charged to the authors.

General instructions• Radiology and Oncology will consider manuscripts prepared according to the Vancouver Agreement (*N Engl J Med* 1991; **324:** 424-8, *BMJ* 1991; **302:** 6772; *JAMA* 1997; **277:** 927-34.). Type the manuscript double spaced on one side with a 4 cm margin at the top and left hand side of the sheet. Write the paper in grammatically and stylistically correct language. Avoid abbreviations unless previously explained. The technical data should conform to the SI system. The manuscript, including the references may not exceed 15 typewritten pages, and the number of figures and tables is limited to 4. If appropriate, organize the text so that it includes: Introduction, Material and methods, Results and Discussion. Exceptionally, the results and discussion can be combined in a single section. Start each section on a new page, and number each page consecutively with Arabic numerals.

Title page should include a concise and informative title, followed by the full name(s) of the author(s); the institutional affiliation of each author; the name and address of the corresponding author (including telephone, fax and e-mail), and an abbreviated title. This should be followed by the *abstract page,* summarising in less than 200 words the reasons for

the study, experimental approach, the major findings (with specific data if possible), and the principal conclusions, and providing 3-6 key words for indexing purposes. Structured abstracts are preferred. If possible, the authors are requested to submit also slovenian version of the title and abstract. The text of the report should then proceed as follows:

Introduction should state the purpose of the article and summarize the rationale for the study or observation, citing only the essential references and stating the aim of the study.

Material and methods should provide enough information to enable experiments to be repeated. New methods should be described in detail. Reports on human and animal subjects should include a statement that ethical approval of the study was obtained.

Results should be presented clearly and concisely without repeating the data in the tables and figures. Emphasis should be on clear and precise presentation of results and their significance in relation to the aim of the investigation.

Discussion should explain the results rather than simply repeating them and interpret their significance and draw conclusions. It should review the results of the study in the light of previously published work.

Illustrations and tables must be numbered and referred to in the text, with appropriate location indicated in the text margin. Illustrations must be labelled on the back with the author's name, figure number and orientation, and should be accompanied by a descriptive legend on a separate page. Line drawings should be supplied in a form suitable for high-quality reproduction. Photographs should be glossy prints of high quality with as much contrast as the subject allows. They should be cropped as close as possible to the area of interest. In photographs mask the identities of the patients. Tables should be typed double spaced, with descriptive title and, if appropriate, units of numerical measurements included in column heading.

References must be numbered in the order in which they appear in the text and their corresponding numbers quoted in the text. Authors are responsible for the accuracy of their references. References to the Abstracts and Letters to the Editor must be identified as such. Citation of papers in preparation, or submitted for publication, unpublished observations, and personal communications should not be included in the reference list. If essential, such material may be incorporated in the appropriate place in the text. References follow the style of Index Medicus. All authors should be listed when their number does not exceed six; when there are seven or more authors, the first six listed are followed by "et al.". The following are some examples of references from articles, books and book chapters:

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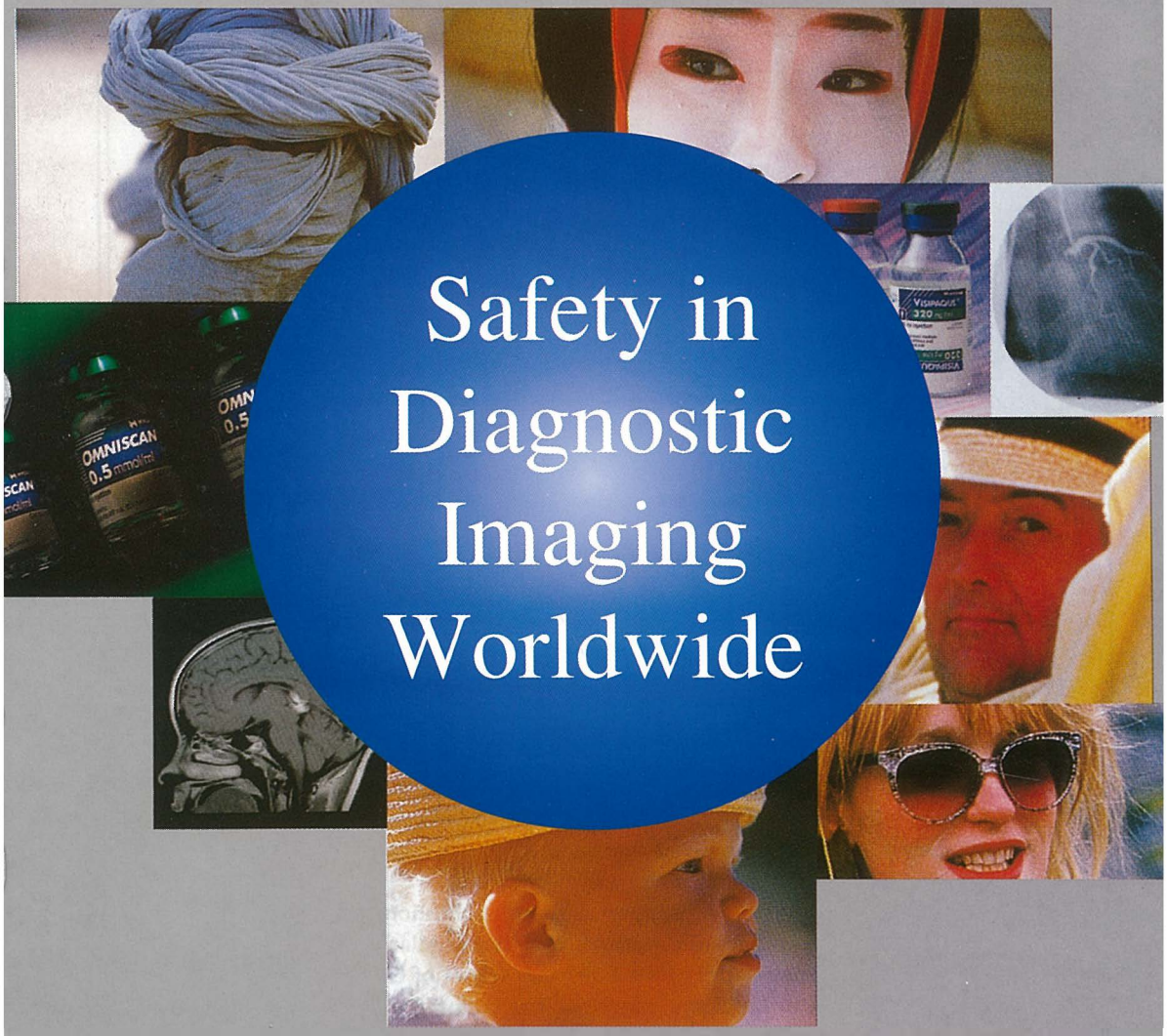

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