Radiol Oncol 1998; 32(2): 213-20.

Carcinoma of the thyroid: Postoperative radiotherapy

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We report a retrospective analysis of patients with thyroid cancer who received postoperative external radiotherapy (RT) and high-dose radioiodine. Between 1982 and 1993, 69 patients with thyroid cancers of four histologic types (follicular, n=17; papillary, n=39; medullar, n=7; anaplastic, n=6) were treated by surgery, ablative radioiodine therapy (only differentiated tumours) and radiotherapy. Indications for adjuvant radiotherapy were extraglandular tumour infiltration (stage pT4) and/or incomplete surgical resection and/or extensive lymph node involvement or difficult surgical excision for repeated local recurrences. Radiotherapy was delivered by parallel opposed fields (50 Gy, 2 Gy) in a Amini-mantle-technique"; this was followed by an electron-boost (10 to 14 Gy, 2 Gy) using a midline wax bolus. The adjusted 5-year survival rate was 82.6%, the 5-year disease-free survival rate 92.1% (mean observation time 56 months, range 4 to 146 months). Statistically significant relationship was observed between adjusted survival rate and parameters like histology (p<0.00001), cervical lymph node involvement (p<0.002), metastases at presentation (p<0.001) and age (p=0.03). No severe radiation induced late complications -specifically of the spinal cord or the trachea - were recorded. Postoperative high dose radiotherapy (60 to 64 Gy), in case of differentiated thyroid tumours in combination with high dose radioiodine therapy, seems to be an effective tool to sterilise microscopic or macroscopic residual disease and can safely be delivered using modern radiation treatment techniques.

Key words: thyroid neoplasms - surgery; radiotherapy, adjuvant

Introduction

Thyroid cancer, which accounts for less than 1% of all cancer deaths[1] is described more frequently in females than in males (ratio about 2-3:1). There are four different histologic types with distinct different clinical behaviour. Papillary tumours are generally observed in young and middle-aged adults. Metastases are generally found in the lymph nodes of the neck ipsilateral to the primary lesion. Follicular thyroid carcinomas occur in a slightly older population and usually metastasise haematogeniously to distant sites with lymph node metastases being uncommon. Both so called differentiated thyroid cancers

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arise from the thyroid follicular cells while medullary carcinoma of the thyroid derives from the ĄC" - or parafollicular cells of the thyroid gland. In the medullary type tumour cells spread over blood and lymphatic routes producing metastases in the cervical lymph nodes, the lung, liver and bones. The aggressive anaplastic thyroid carcinomas occur primarily in patients older than 50 years of age, and are characterized by a rapid local growth. This tumour type mainly presents lymph node metastases and lung metastases in an early stage of disease.

The surgical resection is considered the method of choice for initial treatment of differentiated and medullary thyroid cancer as well as anaplastic tumours if the radical resection or even tumour debulking are technically feasible. The ablation of residual remnants with radioiodine usually follows in patients with differentiated thyroid cancer since that will permit subsequent whole body scintigraphy to exclude the presence of residual or metastatic disease. The value of postoperative radiotherapy (RT) is still discussed controversially. Some reports described a reduction of local recurrence, particularly after the incomplete surgery[2-8] or even a better survival rate following postoperative radiotherapy for all histologic types of thyroid cancer.[9,10] In contrary, other authors found therapeutic improvement only in specific histologic subgroups.[11,12] Other studies have denied any effect on survival[13-15] or even revealed worse results in patients treated with radiotherapy postsurgically.[16]

We present the results of a retrospective analysis of 69 patients with thyroid cancer who received postoperative radiotherapy using the wax bolus technique.

Patients and methods

Patients

Between 1982 to 1993, 69 patients (50 women, 19 men; mean age 53,5 years; range 19 to 86 years) with thyroid cancers were included in our study. Seventeen patients (13 women, 4 men) were younger than 40 years of age and 52 patients (37 women, 15 men) were older than 40 years at the time of diagnosis.

Criteria for adjuvant postoperative radiotherapy were defined either as macroscopically or microscopically incomplete surgical excision and/or tumour invasion in neighbouring structures (pT4) and/or extensive lymph node involvement or upper mediastinal involvement. Six patients (8.6%) presented with distant metastases at the time of referral. No patient had a history of prior external beam irradiation of the neck.

All patients underwent surgery; total thyroidectomy was performed in 25 patients (36%), subtotal thyroidectomy in 26 patients (37.5%), unilateral lobectomy in 9 patients (13.0%) and in the remaining 9 patients (13%) only a palliative tumour excision was possible. Six patients (8.6%) underwent the surgical excision of locoregional recurrence. In case of clinically/sonographically enlarged cervical lymph nodes a modified unilateral neck dissection was performed in 23 patients (33.1%) and a bilateral neck dissection in 3 patients (4.3%). In 17 patients (24.5%) only singular enlarged cervical lymph nodes suspected for tumour infiltration were excised (Ąberry picking"). In the remaining 26 patients (37.5%) no lymph nodes were surgically removed.

The tumour-node-metastasis classification of malignant tumours of the International Union Against Cancer (UICC) was used for the postoperative pathological staging as summarised in Table 1. All tumour stages were reclassified according to UICC 1992.[17] In 13 patients (18.7%) the excision of the

Table 1. Postoperative TNM (UICC) classification

T	< 40 years of age			> 40 years of age		
	N			N		
	0	1	X*	0	1	X
1	0	2	0	1	2	0
2	1	3	1	1	3	3 (1)**
3	0	1	0	2	4	4 (1)
4	3	5	1	5	8(2)	14(1)

NX* : No lymph nodes surgically removed
(1)**: Patients with distant metastases at diagnosis

tumour turned out to be macroscopically incomplete, in 23 (33.1%) patients microscopically. A histopathological examination of the specimens revealed 39 papillary carcinomas, 17 follicular carcinomas, 7 medullary carcinomas, and 6 anaplastic carcinomas. Papillary cancers included both, purely papillary and mixed papillary-follicular tumours.

After the surgery, the ablative radioiodine treatment was performed in 56 patients (80.6%) using a mean dose of 2,8 GBq. Six patients were treated with a second ablative radioiodine therapy for thyroid remnants. Six more patients received radioiodine treatment for loco-regional tumour recurrence and/or distant metastases additionally.

During the follow-up period 8 patients (11.5%) were treated with sequential chemotherapy regimes. All patients underwent T 4 suppression therapy.

External radiotherapy

The adjuvant radiotherapy was delivered with Co^{60} teletherapy in 88% and photon beams (8MV) in 12% of patients with a continuous course of 46 to 50 Gy, 2 Gy/d, 5 d/wk. Treatment fields encompassed all lymph nodes from the base of the skull to the upper part of the mediastinum with a boost to the actual or potential area of residual disease. The radiation treatment was carried out with opposed anterior/posterior fields in a "mini-mantle"- technique with shielding to the floor of the mouth and subapical portions of the lung. The spinal cord was blocked out from the posterior field after 42 Gy. Routinely, the treatment was based on CT planning. The dose was described to the isodose encompassing the clinical target volume (minimum 85%).

This was followed by an anterior electron boost (15 or 20 MeV) with given doses up to 60 to 64 Gy, 2 Gy/d. For each patient an individually wax bolus was manufactured to yield a maximum dose at the target volume and a minimum dose at the spinal cord. During the electron boost treatment this bolus was applied to the patient's neck to guarantee an optimal dose distribution (Figure 1, 2). In patients with tracheostomy (n=4) the wax

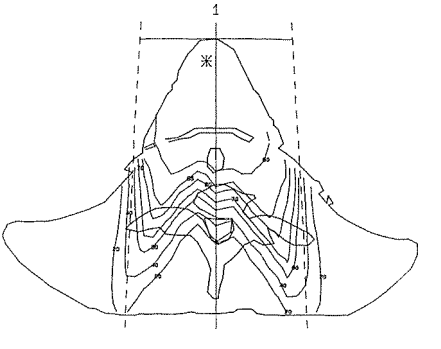

Figure 1. Dose distribution in the transversal plane using 15 MeV electron beams.

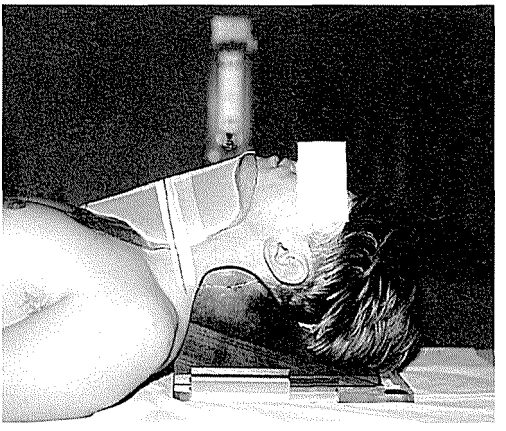

Figure 2. Positioning of the wax bolus during electron boost treatment.

bolus was not applied. In such cases the boost was given through two lateral shaped portals.

Follow up

The follow-up investigations included monitoring of thyroid hormone and thyreoglobulin/calcitonin levels, sonography of the neck, radionuclide (I^{131}) imaging studies and chest radiographs and were performed at 3- or 6-month intervals during the first 5 years and thereafter annually. The computed tomography (CT) of the neck and the chest were not performed routinely. The recurrent disease or metastases were confirmed by biopsy, if clinically feasible. Otherwise the radiological (I^{131}-whole body scan, x-ray films, CT scans) evidence of recurrence and metastases was accepted.

Data analysis

The survival curves were calculated using the Kaplan-Meier product limit method. Events for relapse-free survival were locoregional recurrence or metastasis. Survival and time to relapse were calculated from the end of the adjuvant RT. For the comparison of categorical variables, the chi square test was used. A two-sided probability level of <0.05 was considered significant. A statistical analysis was done using a software program (SPSS; Spectra Publishing; Sunnyvale, Calif.).

Results

Survival rate

The adjusted 5-year survival rate (mean observation time 56 months; range 4 to 146 months) of all patients was 82.6%. The histologic subtype was a strong determinant for survival ($p<0.00001$). Papillary carcinoma patients had a 5-year adjusted survival rate of 97,3%, follicular carcinoma patients of 76,6%, medullar cancer patients of 83.8% and anaplastic carcinoma patients of 16.7%. 11/69 patients (15.8%) died of the thyroid malignancy. All of these patients were more than 40 years of age and had tumour stage pT4 and/or M1 at the time of diagnosis. 5/69 patients (7.2%) died due to the unrelated disease without any evidence of tumour after 12, 22, 27, 50, and 74 months, respectively.

Statistically significant relationships were also found between adjusted survival rate and parameters like age ($p=0.03$), cervical lymph node involvement ($p<0.002$) and distant metastasis at the time of diagnosis ($p<0.001$).

Local recurrence rate

The 5-year disease-free survival rate of all patients was 92.1%. The local control rate was 100% for patients younger than 40 years of age including the salvage treatment. In patients older than 40 years locoregional recurrence within the irradiated field was observed in 6/52 patients (11.5%). Details are given in Table 2.

Only distant metastases at diagnosis were found to have an influence on the risk of locoregional recurrence ($p=0.04$, significant).

Table 2: Rate of recurrence and follow up

TNM	Hist.	Site	Time	Treatm. (months)	Outcome	(months)
f [34]	T4 N1	med	LR	4	"S, RT"	
				22	C	95 [NED]
m[46]	T4 N1	foll	lung	7		
			liver; skin	28; 46		56 †
f [68]	T3 NX*	foll	LR	6; 11	RI	
			lung	15;22;34	RI	
			bone	44	RI	44 PR
f [65]	T3 NX	foll	lung	62; 77	RI	79 [PR]
m[57]	T4 NX	foll	LR	111;117	"S, RI; RI"	125 [NED]
f [60]	T4 NX*	pap	lung	42	"S, RI"	
			lung	49	C	65 [PR]
f [77]	T4 NX	pap	lung	110		130 †
m[46]	T1 N0	med	LR	3; 13	"S, RT;C"	93 [SD]
m[53]	T4 N1	ana	liver	23	C	34 †
f [59]	T4 NX	ana	lung	1		9 †
f [66]	T4 NX	ana	lung	3		17 †
f [7]6	T4 NX	ana	lung	31		57 †
f [78]	T4 Nx	ana	lung	3		4 †
m[56]	T2 NX* M1	foll	LR	20	"RI, C"	
	(lung)		bone	31		39 †
f [80]	T4 N1 M1	foll	lung [PD]	2	C	17 †
	(lung)					
f [49]	T4 N1 M1	pap	lung [NC]	3	RI	51 [NED]
	(lung)					
f [67]	T3 NX M1	pap	liver	20		28 †
	(bone)		lung	21		
f [50]	T4 N0* M1	med	bone [PD]	12	"RT,C"	
	(bone)		lung; LR	17; 25		37 †
f [74]	T4 NX M1	med	lung [PD]	5	C	74 †
	(lung)					

"f [34]: Female, 34 years of age"
"m[46]: Male, 46 years of age"
med: Medullary thyroid cancer
pap: Papillary thyroid cancer
foll: Follicular thyrpoid cancer
ana: Anaplastic thyroid cancer
RT: Radiotherapy
RI: Radioiodine
S: Surgery
C: Chemotherapy

*Surgery for local recurrence before referral
NED: No evidence of disease
NC: No change
LR: Local recurrence during followup
SD: Stable disease (localregional)
PR: Partial remission
PD: Progressive disease
†: Dead of disease

Distant metastases

In patients younger than 40 years of age no distant metastases occurred, whereas in patients older than 40 years of age distant metastases were observed in 10/52 patients (19.2%). Another three patients with distant failure at the time of diagnosis developed distant metastases on other anatomic sites during the follow-up period.

The rate of recurrences (taking into account age at diagnosis, histological type, site and treatment of recurrence, and follow-up for patients without and with distant metastases at referral) are displayed in Table 2.

Side effects of external radiotherapy

Acute side effects like the radiation induced laryngeo-pharyngitis and tracheitis as well as dermatitis occurred in all patients, particularly in the later phase of the external radiotherapy. Glottis oedema was seen in 3 patients (4.3%). Two patients (2.9%) experienced mild Lhermitte Syndrom but they recovered completely. Fifteen months after the radiotherapy of a gross residual anaplastic thyroid carcinoma an esophagotracheal fistula occurred in one patient (1,4%) and required percutaneous gastrotomia. Serious late irradiation induced complications of the spinal cord or the trachea were not observed.

Discussion

For many years the postoperative radiotherapy has been frequently used to prevent local failure for example in patients with breast cancer, rectal cancer or soft tissue sarcomas. The rationale of postoperative RT in patients with thyroid cancer has also the goal to prevent a local recurrence and to increase a long term survival rate. Because of the rarity of this disease and its long natural history, the evaluation of the value of postoperative RT in thyroid cancer relies mostly on retrospective studies.

The role of the adjuvant RT in papillary and follicular, so called *differentiated thyroid carcinomas,* has remained an issue of controversial discussion. Tubiana et al.[8] reported a highly significant difference in the total number of local recurrences between patients treated by surgery alone or by a combination of surgery and radiotherapy. The difference could be demonstrated in patients after the complete surgical treatment (21% vs. 14%) as well as in patients after the incomplete surgical excision (32% vs. 15%). Furthermore, the authors observed a statistically significant difference in the number of recurrences between patients who received a high-energy beam irradiation with an adequate doses of > 50 Gy compared to those with a conventional x-ray treatment with lower doses. Other previous reports describe better local control rates after a high-dose radiotherapy resulting in the improved survival rates.[9,10] the better survival rates only in patients with papillary thyroid cancer,[11,12] or the improved local control rates which did not translate into a survival benefit.[2] In 1990 Benker et al.[18] observed no beneficial effect of adjuvant radiotherapy on the survival in patients with T1-T4 tumours. The same data were reanalysed in 1996 by Farahati et al.[12] focusing only on patients with T4 tumours and an improved recurrence-free survival in patients older than 40 years with papillary histology and lymph node involvement was found.

Some authors believe that the ablative radioiodine therapy alone without a postoperative radiotherapy is sufficient for the tumour control particularly in cases of the differentiated thyroid cancer with micrometastases or microscopical residual tumour.[13,14] However, using a dosimetry simulation by Monte Carlo techniques Sauter-Biehl et al.[19] found that in tumours of r = 0.5 mm or less the percentage of a total dose deposited inside the tumour rapidly decreases and extensive dose inhomogeneities

appear. The authors pointed out that in small tumours like micrometastases in lymph nodes or in the tumour bed tumoricidal doses would not necessarily be achievable by radioiodine alone and the additional postoperative RT would be necessary to achieve a tumour control.

Contradictory results have also been observed for the effectiveness of the adjuvant RT in medullar carcinoma. Saamann et al.[16] described a lower survival rate in patients with a postoperative radiotherapy compared to those without this treatment. In this study, however, fatal recurrences in the irradiated patients occurred outside the radiation portals. In contrast to these results, other authors[3-6] found the adjuvant external irradiation with sufficient doses beneficial in preventing local recurrences in high risk patients with extraglandular invasion (pT4), particularly with lymph node metastases or after the incomplete surgery.

The local control can be achieved in the anaplastic carcinoma using radiotherapy, but the survival is usually low since many patients die of the disseminated disease. Improved results have been observed after the multimodale treatment with a combination of surgery, chemotherapy and adjuvant radiotherapy,[20-23] particularly with the hyperfractionation.[23,24] In patients with anaplastic carcinomas who lived longer than 12 months (Along survivors") Aldinger et al.[20] found histologically small areas of spindle or giant cell carcinomas while the rest of the tumour mostly consisted of well differentiated tumour cells. This observation was confirmed in our own small series of six patients in three "long term survivors" with the survival of 17, 57 and 74 months, respectively.

In the current analysis patients with thyroid cancer of all four histologic types were evaluated. To obtain a satisfactory rate of the locoregional control high radiation doses are required.[4-6,8,10,12,25] therefore a total dose of 60 to 64 Gy was chosen in order to deliver a dosage which is able to sterilise residual tumour cells - either in the tumour bed or in the lymph nodes. In our patients we observed a low local recurrence rate of 11.5% in patients older than 40 years of age which is comparable to data from the literature.[4,5,8,12,25] Various techniques have been advised to deliver a high dose to this region.[26-28] After computer assisted treatment planning parallel opposed $Cobalt^{60}$-or megavoltage photons fields in combination with electrons were used to deliver a sufficient dose to the target volume. Using an individual formed wax bolus during the anterior electron boost field made it possible to shape the electron beam isodose curves around the vertebral body to irradiate the tumour bed with a sufficient dose and to protect the spinal cord and the trachea as much as possible. Using this technique, no serious late irradiation induced complications were encountered.

Conclusion

We conclude that there is an estimable role for the adjuvant external radiotherapy after the ablative radioiodine treatment in the management of patients with differentiated thyroid cancer in stage T4 N0-2 as well as in patients with microscopic or macroscopic residual disease. In stage pT1-3 and lymph node involvement as well as in the medullary thyroid cancer treatment a decision has to be made individually considering risk factors e.g. the age of the patient, the completeness of a resection and the extent of a lymph node involvement. The combination modality treatment including surgery, chemotherapy and (hyperfractionated) external radiotherapy remains the treatment of choice in patients with anaplastic thyroid cancer to obtain a better local control and to diminish distant metastases.

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