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External Radiotherapy of Thyroid Cancer

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Key Words

Thyroid cancer · Radioiodine therapy · External beam radiotherapy

Schlüsselwörter

Schilddrüsenkarzinom · Radiojodtherapie – Externe Strahlentherapie

Summary

Differentiated thyroid cancer comprises papillary, mixed papillary-follicular and follicular adenocarcinomas. They are mostly hormone-sensitive and respond to thyroid-stimulating hormone (TSH) suppression. The standard treatment is total thyroidectomy. ^{131}I therapy and thyroid hormone suppression therapy. Adjuvant external radiotherapy is discussed controversially. Most authors recommend adjuvant external radiotherapy for extracapsular tumor extension. Decision on an individual basis should be made for patients with lymph node involvement. In the case of incomplete surgical resection, external radiotherapy should be applied if second surgery is not possible. For medullary thyroid cancer, external beam radiotherapy seems to be beneficial for patients with surgically inaccessible disease, with microscopic residual or gross tumor after surgery, with recurrent locoregional disease, or with surgically unmanageable metastases. Patients suffering from anaplastic thyroid cancer should receive combined treatment consisting of extensive surgery, external irradiation with total doses up to 60 Gy, and chemotherapy. The combined treatment modality leads to higher local control rates and prolongs survival.

Zusammenfassung

Differenzierte Schilddrüsenkarzinome werden in papilläre, gemischt papillär-follikuläre und follikuläre Adenokarzinome unterteilt. Sie sind meist hormonabhängig und ihr Wachstum kann durch Thyrotropin (TSH)-Suppression gehemmt werden. Die Standardtherapie umfaßt totale Thyroidektomie, postoperative Radiojodtherapie und Hormontherapie. Die Rolle der adjuvanten externen Strahlentherapie wird kontrovers diskutiert. Von den meisten Autoren wird die Indikation zur externen Strahlentherapie bei kapselüberschreitendem Tumorwachstum gestellt. Die Indikation bei Lymphknotenbefall sollte individuell gestellt werden. Bei positiven Resektionsrändern sollte, falls ein erneutes chirurgisches Vorgehen nicht möglich ist, die externe Strahlentherapie durchgeführt werden. Bei medullären Schilddrüsenkarzinomen ist die externe Strahlentherapie bei Inoperabilität, bei postoperativ mikroskopischem oder makroskopischem Tumorrest, beim loko-regionalen Rezidiv und bei inoperablen Metastasen indidziert. Bei Patienten mit anaplastischem Schilddrüsenkarzinom verspricht eine kombinierte Therapie, bestehend aus möglichst weitgehender Tumorentfernung, externer Strahlentherapie mit Gesamtdosen um 60 Gy und Chemotherapie, die beste lokale Kontrolle und das längste Überleben.

Introduction

The mainstay of treatment for differentiated thyroid cancer is surgery, consisting for the majority of patients in a total thyroidectomy, followed by ^{131}I ablation of the residual thyroid tissue and thyroid hormone suppression therapy. In the case of incomplete surgical resection, if a second surgery is not possible and in patients with extra-capsular tumor extension, additional external beam radiotherapy is useful to achieve local control. However, the indication for external beam radiotherapy is discussed controversially. In this article we summarize the present treatment options and discuss the situation where external radiotherapy might be beneficial.

Differentiated Thyroid Cancer

Differentiated thyroid cancer compries of papillary, mixed papillary-follicular, and follicular adenocarcinoma.

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Papillary thyroid cancer is slow-growing and often multicentric. It is diagnosed mostly at age 30–50. The prognosis is excellent. This tumor usually grows infiltrative and metastasizes to regional lymph nodes through lymphatic channels. Hematogenous metastases are uncommon.

Follicular carcinomas are unifocal, have a marked tendency to invade vascular channels, and metastasize hematogenously to distant sites. Lymph node metastases are uncommon. The average age at diagnosis is 50–60 years.

The 10-year survival rate of papillary thyroid cancer with 78–91% is better than of follicular thyroid cancer with 66–78% [1–3]. The more unfavorable outcome of the follicular thyroid carcinoma may depend on the more common distant metastases and the often higher age at diagnosis.

The mainstay of treatment for differentiated thyroid cancer is surgery, consisting of a total thyroidectomy and regional lymphadenectomy, followed by ^{131}I ablation of the residual thyroid tissue, and thyroid hormone suppression therapy. The indication for postoperative external radiation of differentiated thyroid cancer has remained an issue of controversial discussion, especially in the case of microscopic residual disease. It is generally restricted to those cases where local tumor control by postoperative ^{131}I therapy alone seems doubtful [4, 5]. Sautter-Bihl et al. [4] analyzed the problem of dose distribution of ^{131}I β-radiation in a simulation model by Monte Carlo techniques where tumors are tissue-equivalent spheres of various size.

Homogenous ^{131}I distribution in the whole tumor volume as well as peripheral deposition confined to the tumor surface was analyzed. Extensive dose inhomogeneities appeared in small tumors. As in local lymph node metastases tumoricidal radiation doses are not necessarily achievable by ^{131}I therapy alone, postoperative external beam radiation should be considered in the clinical situation of lymph node involvement or occult micrometastases.

Gross Residual Disease and Microscopic Residual Disease

One of the earliest reports on the use of external radiotherapy in thyroid cancer was by Sheline and co-workers [6]. In 1966 they reported on their experience with external radiotherapy in 58 patients treated between 1935 and 1964. They described the use of external beam radiotherapy in a variety of thyroid histologies and clinical situations. Given the time period of the study, the techniques of radiation used would not be considered to be adequate today. The applied doses ranged from 30 to 50 Gy, given in 15–50 days. Supplementary ^{131}I therapy was not performed. 15 patients with papillary and 4 with follicular thyroid cancer had gross residual disease or inoperable recurrence in the surgical bed. For papillary tumors with follow-up ranging from 1 to 25 years, 8 patients were alive with no evidence of disease, and 4 showed local recurrences. Of the 9 patients with palpable disease before external radiotherapy, 7 had a complete response and only 1 patient had a subsequent local relapse. The response in follicular tumors was similar.

These results suggest that external radiotherapy, even at suboptimal doses, may play a role in controlling gross disease in well-differentiated thyroid cancer and it may also contribute to local control in patients who following surgery, have microscopic residual disease in the neck. O'Connell et al. [7] described the Royal Marsden Hospital experience with 113 patients suffering from differentiated thyroid carcinoma. All of them were treated with radical external radiotherapy (60 Gy in 30 fractions, over 6 weeks). All received thyroid hormone suppression therapy with 74 undergoing additional ^{131}I therapy. Three subgroups were defined according to residual disease status. In the probably microscopic residual disease group, 2 of 25 patients (8%) developed an in-field recurrence. In the group of definite microscopic residual disease 5 of 18 (29%) patients experienced in-field recurrences. Of the 32 patients with gross residual disease complete regression occurred in 37%.

Tubiana et al. [8] reported a 40% 15-year relapse-free survival rate and a 57% 15-year survival rate in 97 patients with gross residual disease treated with external radiotherapy.

In a review of patients treated at Princess Margaret Hospital Tsang and co-workers [9] reported on 33 patients with gross residual disease, 20 were treated with external radiotherapy only and 13 had ^{131}I in addition to external beam radiotherapy. The 5-year local relapse-free rate was 62%, and the cause-specific survival rate was 65%.

Phlips and co-workers [10] reported on 94 patients with differentiated thyroid cancer seen in their department from 1974 to 1989. 38 of these patients received a course of postoperative external irradiation. The indications for additional external irradiation were directly related to the quality of the surgical resection. All patients had either macro- or microscopic residual disease or positive cervical lymph nodes with extracapsular extension. The results showed that additional external irradiation did not improve survival in this group. The 5-year survival rates were 94% for the radioiodine group and 84% for the additional external radiation group. The local relapse rate was 21% for those who received radioiodine only, as compared to 3% for those who also received external beam radiotherapy. Potential bias could be introduced by the selection of the external radiation group, consisting of patients with worse prognosis. However, external radiation highly improved the locoregional control rate in these cases. External beam radiotherapy is a local therapy given with the intention to reduce the risk of local relapse. As Phlips et al. stated, local control is certainly an important endpoint in thyroid cancer treatment because it avoids problems created by a relapse, such as recurrent nerve palsy, compression of the esophagus associated with dysphagia, and invasion of the trachea with hemoptysis. Furthermore, an increased risk for distant dissemination due to the persistence of neoplastic tissue is a potential problem.

Extrathyroidal Extension in Differentiated Thyroid Cancer

The influence of external irradiation on survival rate in differentiated carcinomas exceeding organ boundaries was assessed in the evaluation of treatment results by Leisner and co-workers [1]. 167 patients with external irradiation (I) and 73 without external irradiation (II), but otherwise identical treatment, and differentiated carcinoma stage T3 (stage T4 when modern criteria are used) were compared. Group I showed a 5- and 8-year survival of 88 and 75%, group II of 68 and 38%, respectively ($p < 0.001$). Local recurrence occurred in 10% of both groups. However, metastases were found more frequently and earlier in group II (without external beam irradiation). This led the authors to recommend external radiotherapy in differentiated

thyroid tumors with extracapsular extension. Therefore, external beam radiotherapy should be considered for patients with a risk for relapse of more than 10–20% in the thyroid bed. It is well recognized that extrathyroidal extension is a poor prognostic feature in differentiated thyroid cancer.

Samaann et al. [11] demonstrated on 1599 patients, treated at the M. D. Anderson Cancer Centre, that the risk for local recurrence increased with the extension of local tumor. If the tumor was confined to the thyroid gland, local recurrence rate was 19%, with nodal involvement it increased to 22%; but if there was infiltration of the soft tissues, it increased to 36%. Survival at time of follow-up (median 11 years) was 93 and 94% for the first two groups, respectively, but decreased to 82% in patients with extrathyroidal extension and soft tissue involvement. Local recurrence was the most common cause of death.

Lerch and co-workers [12] found no significant influence of lymph node involvement on survival. In their group of 500 patients, higher mortality of patients with lymph node involvement was associated with high tumor stage (T4) and presence of distant metastases (M1). They stated that lymph node involvement may influence recurrence. Adjuvant external beam radiotherapy was not used in their study.

Tubiana et al. [8] reported on 66 patients who received adjuvant radiotherapy postoperatively for extensive regional lymph node involvement, tumor invasion of the neighboring muscles, or difficult surgical excision of recurrence after previous operation. The relapse-free survival and the overall survival rates for this group of patients given external beam radiotherapy with or without ^{131}I was lower than for the group treated with surgery alone. However, external beam radiotherapy was performed on patients with less favorable prognosis. When the high-risk cases were pooled with the patients who had gross residual disease, the number of local recurrences was 14%, as compared to 21% out of 336 patients who did not receive external beam radiotherapy ($p < 0.05$).

The importance of giving an adequate dose of external beam radiotherapy was demonstrated by a lower infield recurrence rate in patients who received doses greater than 50 Gy. These results suggest that adequate external beam radiotherapy improves local control in patients who are at risk of local relapse.

Benker and co-workers [13] from Essen/Germany reviewed 932 patients. 346 had undergone external beam radiotherapy with a total dose from 40 to 70 Gy prior to ^{131}I therapy. Survival was not prolonged following postoperative external beam radiotherapy. However, a subgroup analysis of patients older than 40 years with tumors > 4 cm or with tumors with extrathyroidal extension, revealed a 10-year survival rate of 48% for those treated without external beam radiotherapy as compared to 58% for those who received external beam radiotherapy (this difference was not statistically significant). More recently, Farahati et al. [14], also from Essen, reported on an increased freedom from locoregional and distant failure for patients over the age of 40 with extrathyroidal extension and lymph node involvement from papillary carcinoma who were treated with adjuvant external radiation therapy. It is important to note, that all patients had standard therapy of total thyroidectomy, 2 courses of ^{131}I, and thyroid-stimulating hormone (TSH) suppression. The only treatment variable was the use of adjuvant external beam radiation therapy following the initial ^{131}I therapy. External beam radiation therapy was a predictive factor for improvement in time locoregional recurrence ($p = 0.004$) and locoregional and distant failure ($p = 0.0003$).

The participants of a German nuclear medicine meeting (1991, in Heidelberg) [15] advocated adjuvant external radiotherapy after surgery and ablative radioiodine therapy in patients suffering from a well-differentiated thyroid carcinoma with extrathyroidal extension. Surgery is performed with the intention of total thyroidectomy. Only in very few cases macroscopic residual tumor is present after surgery. In this case, if second surgery is not possible, we would recommend to give ^{131}I therapy followed by external beam radiotherapy and to continue with ^{131}I therapy.

Prognostic Factors

Tennvall and co-workers [16] investigated other significant prognostic factors than those proposed by the EORTC Co-operative Group. The EORTC Co-operative Group identified prognostic significance for age, sex, cell type, clinical extent of tumor, lymph node involvement, and presence of distant metastases. Adamietz and co-workers [2] identified the same factors during their rather long median follow-up of 11 years with advanced age being the most important prognostic factor.

In the study of Leisner et al. [1], men died 1.5 times more frequently than women. The 10-year survival rate was 90% in patients below the age of 50 years in contrast to 60% in older patients. Patients with papillary carcinoma showed a 10-year survival rate of 78%, whereas 66% of all patients with follicular carcinomas survived longer than 10 years.

Saur and co-workers [3] also revealed age, tumor invasion, and distant metastases as being of significant prognostic value. No correlation was demonstrated for sex and tumor histology. The authors recommend external beam radiotherapy in cases of incomplete tumor resection, in the presence of lymphangiosis carcinomatosa, and in anaplastic transformation.

Comparison of existing studies is difficult because of the diverse treatment modalities, e.g. extent of surgery, ^{131}I therapy, irradiated volume, and applied doses. Further obstacles are introduced over the years by changes of the staging system.

The only way to define the role of external beam radiotherapy is to perform a prospective randomized trial of external beam radiotherapy against no external beam radiotherapy in patients considered to be at increased risk of relapse in the thyroid bed. Such a randomized trial has been opened for patient recruitment in December 1999 by the University of Münster/ Germany. Results may be available in approximately 10 years.

Conclusions

In management of differentiated thyroid cancer, surgery and ^{131}I therapy are standard treatment. The use of adjuvant external radiotherapy remains controversial. Most authors recommend adjuvant external radiotherapy for extracapsular tumor extension. For patients with lymph node involvement the decision should be made with respect to the prognostic factors on an individual basis. In the case of incomplete surgical resection, external beam radiotherapy should be applied if re-operation is not possible.

In the thyroid bed doses of 60–66 Gy should be applied. The cervical lymph nodes up to the hyoid bone, the supra- and

infraclavicular lymph nodes and the nodes in the ventral and upper mediastinum should receive doses of 50 Gy using single doses of 1.8–2.0 Gy. The dose at the spinal cord should be limited to 40 Gy.

The potential benefit of external irradiation must be weighted against possible acute side effects (e.g. dry desquamation and rarely moist desquamation, mucositis, and weight loss) and late effects (fibrosis and nerve palsy). The acute side effects are reversible. Due to their self-limiting nature a high frequency of dry desquamation and mucositis can be accepted. The late side effects are usually irreversible and therefore mostly considered as the dose-limiting end point. However, with the recommended doses the incidence of severe late effects is very low.

Medullary Thyroid Cancer

External irradiation for medullary thyroid cancer is discussed controversially in the literature. Prospective randomized trials have not yet been performed due to the rarity of the disease. All reported series are retrospective by nature. Recent data indicate that external radiotherapy can be used for curative treatment in patients with microscopic residual or gross disease after surgery [17, 18]. Tubiana et al. [8] reported similar survival rates for patients who received postoperative irradiation and for those who received surgery alone. Since the tumor was more limited in the patient group who received surgery alone, complete surgical excision was easier to achieve and involvement of the cervical lymph nodes was less frequent and less extensive [19]. Jensen and colleagues [20] reported on 5287 cases of thyroid cancer. 191 patients (4%) suffered from medullary cancer. 70% of these patients were treated with surgery alone. Surgery plus irradiation showed 100% survival at 5 years, compared with 91% survival after surgery alone.

In patients with microscopic residual disease the recommended dose is 60 Gy administered within 6–7 weeks. In cases with remnant gross disease or surgically unmanageable tumors, 65–70 Gy is advocated, with a reduced volume after 50–60 Gy. With bone metastases or inoperable mediastinal lymph node metastases, external irradiation is the most effective therapy and yields prolonged palliation in 75% of the patients.

Conclusion

External beam irradiation seems to be beneficial for patients with surgically inaccessible disease, for patients with microscopic residual or gross postoperative disease, for patients with recurrent locoregional disease, and in cases of metastases which are impossible to manage by surgery [21].

Anaplastic Thyroid Cancer

Levendag and co-workers [22] reported on 51 patients with anaplastic thyroid carcinoma. 45% had some kind of surgery, however, only 1 had radical surgery with microscopically free margins. 75% of the 28 patients without distant metastases at the beginning of radiotherapy treatment developed distant metastases within 6 months. The overall survival was poor. 94% died within the first year. Patients who received doses of less than 30 Gy had a median survival of only 0.6 months, which might be caused by the aggressive nature of the disease. In contrast, patients who received doses above 60 Gy had the best prognosis with 20% 1-year survival and a median survival of 5.3 months. The main cause of death was residual tumor and local relapse. Complete response to radiotherapy at the end of treatment seems to correlate with the best prognosis (8 months median survival vs 1.6 months for none or incomplete responding tumors). Junor et al. [23] noted higher survival rates with increased radiation dose as well.

Combined Therapeutic Modality

Kim and Leeper [24] reported on 19 patients with anaplastic giant and spindle cell carcinoma of the thyroid. 10 of them underwent subtotal thyroidectomy and modified neck dissection, 9 received only biopsy of the tumor. None of the patients showed any evidence of distant metastases at the time of treatment. After diagnosis, all of them received a combined therapeutic regimen consisting of administration of adriamycin (10 mg/m^2, or a maximum of 20 mg), once weekly before hyperfractionated radiotherapy (1.6 Gy twice a day, 3 days/week, total dose 57.6 Gy in 40 days) was performed. Initial complete tumor response rate was 84%. Local tumor control rate 2 years after combined therapy was 68%. The median survival time was 1 year, which is still significantly higher compared to the 5.3 months found by Levendag et al. [22] with high-dose irradiation alone. However, most patients promptly developed distant metastases and died from tumor-related causes. Other authors found similar results with combined radiochemotherapy [25, 26].

Conclusion

Patients treated with combined extensive surgery, irradiation with total doses up to 60 Gy, and chemotherapy, appear to have the best survival rates.

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