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Differentiated Thyroid Cancer

Impact of Adjuvant External Radiotherapy in Patients with Perithyroidal Tumor Infiltration (Stage pT4)

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BACKGROUND. The role of adjuvant external radiotherapy in the survival of patients with differentiated thyroid cancer (DTC) is controversial. To our knowledge, no attempt has been undertaken thus far to assess the impact of this therapy with respect to the papillary and follicular types of thyroid cancer as separate entities.
METHODS. Between 1979 and 1992, 238 patients with differentiated papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) with Stage pT4 have been treated and followed in our clinic. One hundred sixty-nine patients free of metastases at the final staging, which was performed after the second radioiodine therapy, were included in this study. The standard treatment comprised total thyroidectomy, ablative radioiodine therapy, and thyroid-stimulating hormone-suppressive therapy with levothyroxin. Ninety-nine patients free of disease after the final staging received additional external radiotherapy to the neck (with a dose of 50–60 Gy), whereas the remaining 70 patients were treated with the standard treatment protocol only. Distributions of age, sex, and follow-up time were comparable in both irradiated and nonirradiated groups. Multivariate analysis of the influence of age, sex, histologic subtype, and lymph node status as well as of external radiotherapy on the time to first locoregional and distant failure (LDF), and the time to locoregional recurrence (LR), was accomplished using Cox's proportional hazard model.
RESULTS. In patients with DTC, external radiotherapy was a predictive factor for improvement of both LR ($P = 0.004$) and locoregional and distant failure ($P = 0.0003$). When the time to first locoregional and distant failure was calculated separately for patients with PTC and FTC, there was a significant difference in the PTC group in favor of irradiated patients ($P = 0.0001$), whereas there was no effect of external radiotherapy in the FTC group ($P = 0.38$). Further analyses disclosed that this effect was significantly present only in patients with PTC and lymph node involvement ($P = 0.002$), whereas those without lymph node involvement did not benefit from an additional adjuvant radiotherapy ($P = 0.27$). Because none of the patients younger than age 40 years died due to the disease nor had progressive disease during follow-up, we reassessed our results in patients older than age 40 years. The effect of external radiotherapy could be confirmed in this subgroup of patients ($P = 0.0009$) and in the subgroup of lymph node positive patients older than age 40 years with invasive PTC ($P = 0.01$).
CONCLUSIONS. In addition to total thyroidectomy, treatment with radioiodine, and TSH-suppressive therapy with thyroid hormone, adjuvant external radiotherapy improves the recurrence-free survival in patients older than age 40 years with invasive PTC and lymph node involvement.

KEYWORDS: thyroid cancer, lymph node involvement, external radiation, tumor biology, prognosis.

TABLE 1
Characteristics of Patients with DTC in Stage pT4 N0-1 M1 and Patients with PTC and FTC in Stage pT4 N0-1 M0 with (+) or without (∅) External Radiotherapy (ERT)

Patient status	Sex F/M	Mean age (yrs)	N0/N1	Mean follow-up (yrs)
DTC, N0-1M1 = (33 PTC and 36 FTC)	46/23	54 ± 15	23/46	5 ± 2.4
PTC, N0-1M0 + ERT (n = 75)	60/15	55 ± 13	47/28	5 ± 3.0
PTC, N0-1M0 ∅ ERT (n = 50)	38/12	51 ± 17	21/29	6 ± 3.1
FTC, N0-1M0 + ERT (n = 24)	18/6	53 ± 12	16/8	6 ± 3.6
FTC, N0-1M0 ∅ ERT (n = 20)	11/9	48 ± 14	14/6	8 ± 3.4

Differentiated papillary and follicular adenocarcinoma are the most common histologic types of thyroid cancer. The prognosis is reported to be dependent on histologic type, tumor stage, age, sex, and local macroscopic invasion beyond the thyroid capsule.[1-7] The standard treatment for differentiated thyroid cancer (DTC) comprising total thyroidectomy (except in patients with papillary microcarcinoma), radioiodine treatment, and thyroid-stimulating hormone (TSH)-suppressive therapy with levothyroxin is widely established, whereas the role of adjuvant external radiotherapy (ERT) remains unclear.[8-14] The low incidence rate, the indolent nature of DTC, and the variety of treatment modalities used over the last 3–4 decades render retrospective studies in patients with thyroid cancer difficult. A major factor that has not been considered in these studies is the evaluation of the results respecting papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) as separate entities. Because the tumor biology and pathway of metastases in these tumor types are disparate,[15,16] the selection of subgroups of patients who could potentially benefit from locoregional ERT is essential.

A recent retrospective analysis from our hospital, including 277 patients with DTC in Stage pT3 and pT4, who were treated between 1970 and 1986 showed only a nonsignificant trend in the improvement of survival by ERT.[17] Because of the reevaluation of the UICC classification of tumor stages and the introduction of new diagnostic modalities (e.g., routine determination of thyroglobulin as a tumor marker) over the last decade, we decided to reassess the effect of ERT in patients with advanced DTC using the new TNM classification of UICC 1987, and including thyroglobulin (Tg) as a tumor marker for clinical staging. This study is based on a group of patients who has been treated and followed at regular intervals in our clinic between 1979 and 1992. Because the documentation of data before 1979 is insufficient regarding histologic and surgical reports, and lacks the tumor marker Tg, all patients seen before 1979 were excluded from our study. The goal of this retrospective case–control study was to clarify the role of ERT on locoregional and distant recurrences in patients with advanced PTC and FTC in stage pT4.

PATIENTS AND STUDY PROTOCOL

Two hundred thirty-eight patients with differentiated PTC and FTC with Stage pT4 were treated and followed in our clinic between 1979 and 1992. Patients with well documented histologic, surgical, biochemical, and radiotherapeutic records, with a follow-up time of at least 2 years, were included in this study. Mixed papillary-follicular thyroid cancers were considered as PTC (according to the WHO classification). All tumor stages were reclassified according to UICC 1987. During this process, all equivocal pathology reports were controlled by an experienced pathologist in our clinic by reviewing the specimens. Patients with undifferentiated thyroid cancer, medullary thyroid cancer, or oxyphilic (both papillary and follicular types) thyroid cancer were excluded from this study. Thyroid remnant and lymph node involvement were assessed in all patients prior to the first radioiodine treatment by radioiodine uptake test and scan as well as ultrasound of the neck.

Among the 238 cases, 69 were excluded due to initial metastases (T4 N0–1 M1). Sex, age, histology, lymph node involvement, and mean follow-up time in these 69 patients are summarized in Table 1.

One hundred sixty-nine patients were free of disease after the final staging (pT4 N0–1 M0). Seventy of 169 patients received standard therapy; 99 were additionally treated with external radiation between the first and second courses of radioiodine treatment. The standard treatment protocol in patients with DTC includes (1) total thyroidectomy before any subsequent therapy and modified neck dissection ("berry picking") in patients with lymph node involvement; (2) two courses of radioiodine treatment with a total activity of 7–12 GBq I-131 with an interval of 3–4 months; (3) lymph node metastases without sufficient iodine uptake removed by surgery; (4) TSH-suppressive thyroid hormone treatment with a dose of ~2.5 μg levothyroxine/kg body weight (basal TSH < 0.1 mU/l); and (5) external irradiation (if performed) between

TABLE 2
Characteristics of Patients with DTC in Stage pT4 N0–1 M0–1 (n = 238) with Frequency and Localization of Metastases and Follow-Up in Those with M1 after the Final Staging (n = 69)

	Follow-up			
Patient status	**CR**	**PR**	**PD**	**D**
PTC, pT4 N0 M0 (n = 68)				
PTC, pT4 N0 M1 (n = 1)				
1 (lung)	0	0	0	1
PTC, pT4 N1 M0 (n = 57)				
PTC, pT4 N1 M1 (n = 32)				
14 (lung), 1 (bone, lung), 1 (bone), 2 (lung, liver), 15 (Tg+)	1	17	7	7
FTC, pT4 N0 M0 (n = 30)				
FTC, pT4 N0 M1 (n = 22)				
8 (lung), 5 (bone), 4 (bone, lung), 1 (skin), 4 (Tg+)	2	7	7	6
FTC, pT4 N1 M0 (n = 14)				
FTC, pT4 N1 M1 (n = 14)				
5 (lung), 5 (bone), 1 (bone, lung), 3 (Tg+)	1	5	2	6

CR: complete remission; PR: partial remission; PD: progressive disease; D: deceased at follow-up time.

the first and second course of radioiodine treatment with a dose of 50–60 Gy. The distribution of different risk factors, i.e., sex, age, histologic subtype, lymph node status, and mean follow-up time in different subgroups of patients with and without ERT, is shown in Table 1.

The final staging of patients with DTC was completed after the second course of radioiodine therapy. Following the first course of radioactive iodine therapy, most of the patients still had an elevated Tg level, which may be due to a normal thyroid remnant or a tumor residue or metastases. After the second course of iodine treatment, patients who had no signs of distant metastases on clinical examination, chest X-ray, I-131 whole-body scan at TSH level > 30 mU/l, and Tg in serum (<10 ng/ml) were considered free of metastases. The annual follow-up diagnostic program included in all patients (1) ultrasound examination of the neck, (2) chest X-ray, (3) I-131 whole-body scan 3–4 days after diagnostic activities (0.4–1 GBq), and (4) Tg in serum with IRMA (sensitivity 1 ng/ml) with a cutoff level of 10 ng/ml (Tg measurements and I-131 scans were performed after thyroid hormone withdrawal at TSH levels > 30 mU/l).

In the follow-up of patients free of disease after final staging, any histologically proven tumor mass in the thyroid bed or lymph node involvement in the neck and mediastinum was considered local recurrences. Tumor tissue detected in other organs was considered distant metastasis. An additional criterion for recurrence was the elevated Tg level (>10 ng/ml) in patients with initially normalized Tg after final staging.

The time to recurrence was considered the time to locoregional recurrence (LR) or the time to locoregional and/or distant failure (LDF). Patients with no pathological findings in the follow-up program were considered to be in complete remission. Patients who had a recurrence with no progression during 2 years of follow-up were considered to be in partial remission. All patients with progression of disease with no response to therapy were considered to have progressive disease. Five patients with PTC and one patient with FTC died during the follow-up due to tumor. There was no systematic allocation to the study or control group with respect to ERT. The general procedure since 1979 has been to include postoperative adjuvant radiotherapy in the therapy protocol of high-risk patients in Stage pT4; however, a number of patients refused this adjuvant therapy because of anxiety or noncompliance.

Although external radiotherapy was performed in most patients in our hospital, several were treated in other hospitals. In all cases, the planning target volume contained the thyroid region and the neck anterior to the prevertebral cervical fascia up to the mastoid, or sometimes the hyoid bone, the supraclavicular regions, and the mediastinum anterior to the posterior wall of the trachea down to the carina. Megavoltage photon beams and electrons were administered with a total dose of 50–60 Gy to a reference point of 1.8–2.0 Gy each fraction and five fractions per week. Spinal cord dose was lower than 44 Gy, and the dose in the planning target volume generally did not exceed 105% of the reference point dose. A boost of 6–10 Gy with 2.0 Gy per fraction was applied to the high-risk regions, using small electron fields.

Statistical differences between groups with respect to the risk factors sex, mean age, lymph node involvement, and mean follow-up time were calculated using Student's *t* test. Multivariate analysis of the influence of the prognostic factors age, sex, histologic type, and lymph node category as well as the therapeutic variable radiotherapy on the LR and the LDF was performed using the proportional hazard model according to Cox, Procedure Phreg, SAS Institute.[18] The survival distribution function or actuarial time to LDF or time to LR was calculated according to the Product-Limit Method, Procedure Lifetest, SAS Institute.[19] Time to first failure was censored at the time of last follow-up without failure, or the time of death without treatment failure, time to locoregional recurrence at the time of distant failure without locoregional failure. Distant metastasis was the failure in 11 patients, and no death without treatment failure was observed. For univariate comparisons of the survival functions, a log rank test was performed, Procedure Lifetest, SAS Institute.[19]

RESULTS

The characteristics of 238 patients with differentiated thyroid cancer in Stage pT4 N0–1 M0–1 and the frequency

TABLE 3
Frequency of Recurrences in Patients with PTC, pT4 N0-1 M0 (n = 125), Considering: External Radiotherapy, Age of Patients at Presentation, Sex, Time of Recurrence, Site of Recurrence, and Outcome

Patient status	Age (yrs)	Sex	Time of recurrence (yrs)	Site of recurrence	Outcome
pT4 N0 M0					
+ERT (n = 47)	53	f	3	LR	CR
∅ERT (n = 21)	50	m	6	LR, lung	PD
	60	f	8	LR	PD
PT4 N1 M0					
+ERT (n = 28)	56	m	3	Lung, brain	PD
	70	f	2	LR	CR
∅ERT (n = 29)	20	f	2	Tg+	PR
	21	f	2	LR	CR
	34	f	2	LR	CR
	44	f	4	LR, lung	D
	44	m	4	Tg+	D
	46	f	2	LR	PR
	53	f	4	LR	PD
	53	m	5	LR, lung	D
	55	m	3	Tg+	PD
	57	m	2	LR	CR
	60	m	8	Tg+	D
	60	f	10	LR, lung, bone	D
	65	f	3	LR	CR

PTC: papillary thyroid cancer; ERT: patients with (+) and without (∅) external radiation therapy; LR: local recurrence; Tg+: elevated thyroglobulin; CR: complete remission; PR: partial remission; PD: progressive disease; D = deceased at follow-up.

TABLE 4
Frequency of Recurrences in Patients with FTC, pT4 N0-1 M0 (n = 44) Considering: External Radiotherapy, Age of Patients at Presentation, Sex, Time of Recurrence, Site of Recurrence, and Outcome

Patient status	Age (yrs)	Sex	Time of recurrence (yrs)	Site of recurrence	Outcome
p T4 N0 M0					
+ERT (n = 16)					
	46	f	4	Tg+	PR
	55	f	5	LR	PD
∅ERT (n = 14)	20	f	5	LR	CR
	50	m	4	LR	PD
	55	f	7	Lung	PD
	72	m	9	Tg+	D
pT4 N1 M0					
+ERT (n = 8)	20	f	5	LR	CR
	60	f	5	Skin, liver	PD
∅ERT (n = 6)	24	f	5	LR	CR
	48	m	3	Tg+	PD

FTC: follicular thyroid cancer; ERT: patients with (+) and without (∅) external radiation therapy; LR: local recurrence; Tg+: elevated thyroglobulin; CR: complete remission; PR: partial remission; PD: progressive disease; D: deceased at follow-up.

TABLE 5
Influence of the Risk Factors Age, Sex, Histologic Subtype, Lymph Node Status, and the Therapeutic Variable External Radiotherapy on Locoregional and Distant Failure (According to Cox Model)

Factors	No. of patients	No. of recurrences	Risk ratio*	*P* value
Age (years)	169	28	1.0	0.29
Sex				
f	126	18	0.8	0.67
m	43	10		
Histology				
PTC	125	18	0.6	0.26
FTC	44	10		
Lymph nodes				
N0	98	9	0.3	0.006
N1	71	17		
Radiation				
+ERT	99	7	0.3	0.003
∅ERT	70	21		

PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; ERT: patients with (+) and without (∅) external radiation therapy; LDF: time to first locoregional and distant failure.

* The conditional risk ratio for each explanatory variable is given beneath the respective level of the variable.

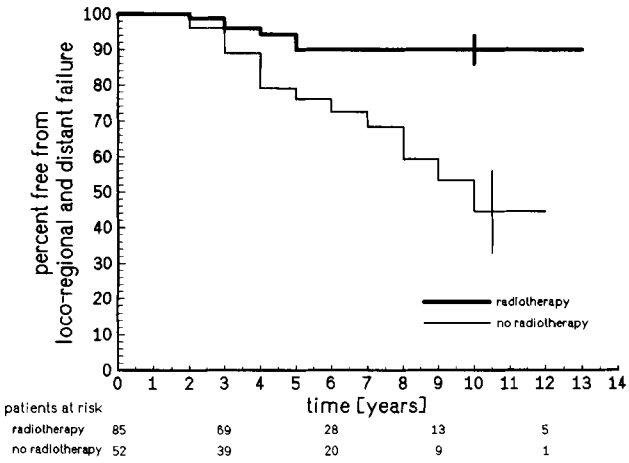

FIGURE 1. Actuarial curves for time to first locoregional and distant failure of patients aged 40 years or older with differentiated thyroid cancer with and without external radiotherapy ($P = 0.0009$, log rank test). Bars represent standard error of the percentage free from failure at 10 years.

and location of metastases in those who were not free of disease after the final staging (n = 69) are summarized in Table 2.The remaining 169 patients who were free of metastases after final staging are the subject of this report. There was no significant difference between the mean ages (Table 1) in the irradiated and nonirradiated groups of patients with PTC ($P = 0.11$) and FTC ($P = 0.21$). The mean follow-up times of the irradiated and nonirradiated

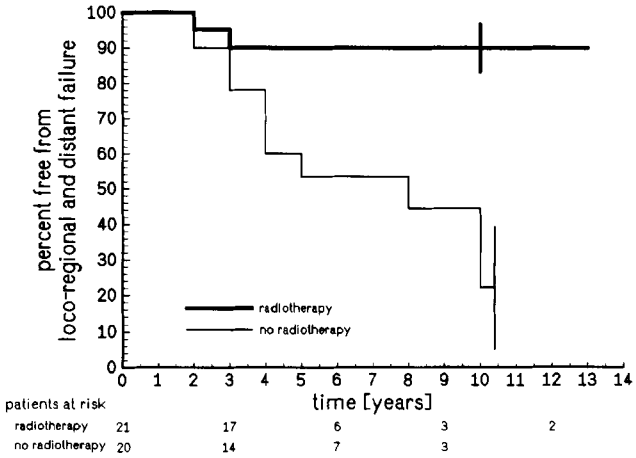

FIGURE 2. Actuarial curves for time to first locoregional and distant failure of lymph node positive patients aged 40 years or older with invasive PTC with and without external radiotherapy ($P = 0.01$, log rank test). Bars represent standard error of the percentage free from failure at 10 years.

groups (Table 1) also revealed no significant difference in the subgroups of patients with PTC ($P = 0.32$) and FTC ($P = 0.80$).

Differentiated thyroid cancer recurred in 28 patients (17%) who were judged to be free of disease after final staging; recurrences occurred after 2–10 years. The rate of recurrence in patients with PTC and FTC, taking into account external radiotherapy, age of patients at presentation, sex, time of recurrence, site of recurrence, and follow-up, are depicted in Tables 3 and 4.

Of the lymph node positive patients with PTC, 36% (32/89) were not free of disease at final staging compared to 1% (1/69) of lymph node negative patients in this group. Among patients with FTC, 36 of 80 (45%) were not free of disease at final staging (14/28 lymph node positive vs. 22/52 lymph node negative patients).

The results of multivariate analysis (according to the Cox model) with respect to LDF are shown in Table 5. Age, sex, and histologic subtype were excluded as nonsignificant variables. External radiotherapy ($P = 0.003$) and lymph node involvement ($P = 0.006$) could be estimated as significant factors. Regarding LR (data not shown here), only ERT ($P = 0.0085$) could be detected as a significant predictive factor.

The effect of ERT on LDF was calculated according to the product-limit method. In the irradiated group, the LDF ($P = 0.0003$) and LR ($P = 0.004$) were significantly prolonged compared to those in the nonirradiated group. This effect on LDF could also be confirmed ($P = 0.0009$) in patients aged 40 years or older in favor of the irradiated group (Fig. 1).

In the subgroup of patients with PTC, the effect of ERT was statistically significant ($P = 0.0001$), whereas

there was no significant effect of radiotherapy ($P = 0.38$) in the FTC group.

Because the lymph node involvement was a risk factor at staging, we analyzed the data with respect to lymph node status. The time to LDF in lymph node negative patients was longer ($P = 0.02$) than in lymph node positive patients. This significant difference could be confirmed ($P = 0.002$) in the subgroup of lymph node negative patients with PTC, whereas in patients with FTC there was no effect regarding the lymph node involvement ($P = 0.27$). Further analysis restricted to lymph node positive patient aged 40 years or older with invasive PTC confirmed the effect of adjuvant ERT ($P = 0.01$) in favor of irradiated patients (Fig. 2).

The 10-year recurrence-free survival rate in patients with PTC was slightly higher than that in patients with FTC (74% ± 7% vs. 67% ± 9%), but without statistical significance ($P = 0.59$). Six of 169 patients free of disease after final staging (all in the nonirradiated group) died from disease during the period of observation; only 3 of 11 patients with recurrences during the first 2–3 years had progressive disease, whereas the remaining eight were free of disease or in partial remission at follow-up. In contrast, all patients with recurrences after 4 years were dead or had progressive disease (Tables 3, 4).

The total radioiodine uptake assessed by radioiodine uptake test in the irradiated group was 8.10% ± 5.84% vs. 7.47% ± 3.72% in the nonirradiated group ($P = 0.37$). The absolute activity of radioactive iodine administered to ablate the thyroid remnant and lymph node metastases was 10.51 ± 4.19 GBq I-131 in the irradiated group vs. 9.57 ± 3.75 GBq I-131 in patients without adjuvant ERT ($P = 0.12$).

We observed no irreversible morbidity such as lesions of the spinal cord in the irradiated group. None of the irradiated patients who later developed recurrences was subsequently inoperable because of the ERT. Early side effects such as local erythema, lymphedema, and pharyngitis were observed in about one-third of the irradiated patients.

DISCUSSION

Differentiated papillary and follicular thyroid cancer is the most common type of thyroid malignancy, with an excellent overall prognosis. In approximately 10% of patients, the primary tumor extends through the thyroid gland capsule, which relates to a poor prognosis, with death rates ranging from 5% to 35%.[2,20] Compared to patients with other tumor stages, these patients have a higher frequency of recurrences, distant metastases, and mortality on presentation and after initial therapy.[21] The role of adjuvant ERT in survival of patients with DTC is controversial. Mazzaferi and Young[12] observed a negative effect of external radiation on recurrences in a small number of patients, which was presumably due to more advanced disease in irradiated patients than in those without radiation.[21] Simpson et al[13] reported the usefulness of external radiotherapy in patients with PTC and FTC whose tumors had no iodine uptake; 90% of patients with microscopic residual papillary carcinoma were disease-free after postoperative ERT compared to 26% with surgery alone. Fifty-three percent of patients with microscopically invasive follicular carcinoma were disease-free after surgery and ERT, whereas 38% were disease-free after surgery alone. Tubiana et al[14] reported 97 patients treated with external radiotherapy after incomplete surgical excision; survival rates were 57% after 15 years and 40% after 25 years. The incidence of local recurrence at 15 years was 11% in the irradiated group, compared to 23% in those treated with surgery alone, although the irradiated patients had larger, more extensive tumors. In a retrospective analysis, Leisner et al[10] reported a significant influence of ERT on survival ($P < 0.001$) favoring irradiated patients with DTC at Stage pT3, compared to nonirradiated patients. The 5-year survival was 68% in the nonirradiated group and 88% in the irradiated group.[10] In a previous study from our hospital,[17] the comparison of irradiated and nonirradiated patients with DTC in Stages pT3/4 showed a nonsignificant trend ($P = 0.09$) of overall survival in favor of irradiated patients. However, in none of these studies was the effect of external radiation considered with respect to PTC and FTC as separate entities. Because the tumor biology and pathway of metastasis in PTC and FTC are dissimilar,[15,16] selection of patients who could potentially benefit from locoregional ERT is essential.

In this retrospective case–control study, we evaluated the risk factors predicting outcome in 238 patients with advanced PTC and FTC separately. To assess the impact of ERT on LDF and LR in a group of patients free of metastases after final staging (n = 169), we excluded all patients with distant metastases at final staging. Due to the higher prevalence of metastases in lymph node positive patients at staging, we analyzed our data with respect to the initial lymph node status. Local and/or distant recurrences were considered in this analysis because death due to the primary tumor occurred in only six patients who had been free of disease at final staging.

Metastases can be missed when large amounts of thyroid tissue remain after surgery,[21] which is a common finding in the posttherapy scan after first radioiodine therapy in patients with invasive tumor. Because some lung metastases are detectable exclusively by total-body I-131 scan,[22,23] a second radioactive iodine treatment was performed 3–4 months after the first therapy in this high-risk group.

We could not estimate the radiation exposure to tumor from radioiodine treatment in this retrospective

study. Thus, the efficacy of this therapy cannot be judged in different groups. However, because the absolute administered radioactive iodine and the thyroid remnant after surgery were not significantly different between groups, a lack of efficacy of radioiodine therapy in any of these groups is less likely.

Among 169 patients with DTC who were free of disease after final staging, we observed 28 (17%) recurrences. With ERT, the overall rate of recurrences could be reduced significantly ($P = 0.0003$) in the irradiated group (n = 7) compared with the nonirradiated group (n = 21). Lymph node involvement was indicated by the multivariate analysis as a further powerful predictive factor regarding LDF ($P = 0.006$). Among all cases of PTC without lymph node involvement (n = 69), we found only four events of local and distant metastasis at final staging (Table 2) and during the follow-up period (Table 3). In contrast, lymph node involvement was associated with a higher rate of metastasis at staging and in follow-up ($P = 0.002$). The prognostic importance of lymph node involvement in patients with DTC is controversial.[20,21,24-27] A probable explanation for this discrepancy is a cocorrelation of lymph node involvement with unfavorable prognostic factors. In a study by Carcangiu et al,[2] only 3 of 34 patients with PTC and lung metastases had no lymph node involvement. Massin et al[24] found a correlation between cervical lymph node involvement and pulmonary metastases. Among a group of 29 children from Belarus, all of whom developed advanced PTC in Stage pT4 and pulmonary metastases after the Chernobyl accident, we found only one case without lymph node involvement (Reiners et al, unpublished data). Nemec et al[25] found lymph node metastases in 63% of patients with lung metastases, more frequently combined with pT3 stage. In agreement with our data, Schelfhout et al[5] report extrathyroidal tumor extension and large cervical lymph nodes, or distant metastases, as the most powerful factor predicting outcome in patients with DTC. In contrast, there are reports in which nodal involvement does not seem to concur with prognosis even though it may be associated with a greater frequency of recurrence (mostly local).[20,21,26]

The controversy in the literature regarding the role of lymph node involvement could also stem from the different histologic types of thyroid malignancy, which can be influenced by different etiologic factors.[28] The prevalence of endemic iodine-deficiency goiter in Europe has been reduced in many areas by the introduction of iodination programs.[29] However, Germany remains one of the few countries with no mandatory iodine prophylaxis, with an overall prevalence of goiter of about 50%.[30] The mean urinary iodine excretion evaluated in a population from 32 different regions of Germany was as low as 72 μg/g creatinine.[31] Thus, increased risk associated with nodal involvement in our study could be a function of iodine deficiency in this area.

The decision to recommend the use of ERT for patients with PTC has major implications. Although PTC, a relatively common tumor, carries a prognosis of generally excellent survival, in a subgroup of patients the cocorrelation of lymph node involvement and perithyroidal tumor infiltration seems to affect the prognosis adversely. Nonirradiated patients with advanced PTC tended to have frequent recurrences in our study. Adjuvant radiotherapy, in contrast, has limited this tendency significantly in the irradiated group of patients ($P = 0.0001$).

Since none of the patients younger than age 40 years died due to tumor or had progressive disease on follow-up, we analyzed our data on patients aged 40 years or older, which confirmed the usefulness of ERT in the irradiated group ($P = 0.0009$). A further analysis showed the efficiency of this adjuvant therapy in a subgroup of lymph node positive patients aged 40 years or older with invasive PTC ($P = 0.01$).

These data underscore the effect of ERT for local control of recurrence rate in patients with invasive PTC. PTC spreads typically to the local lymph nodes and to the lungs.[15] Anatomical connection between the intraglandular lymph system surrounding follicles and lymphatic vessels outside the organ through the surface of the thyroid gland is well defined.[32-34] By infiltration of transglandular structures in invasive PTC (Stage pT4), the tumor cells not only disseminate through this anatomical channel but also infiltrate the surrounding soft tissue and perithyroidal lymphatic network. This phenomenon can lead presumably to an extraglandular predominance of tumor cells in lymph node positive patients and cause tumor dissemination. Indeed, β-emitting I-131 deposits the radiation dose intraglandularly within a few millimeters, which can ablate the thyroid remnant in patients with DTC, sparing surrounding tissue. Small micrometastases and moderately differentiated tumor cells could escape sterilization by radionuclides administered at activity levels sufficient to eradicate the larger tumors and well differentiated tumor cells.[35,36]

Compared with the situation of early recurrences, the prognosis for delayed recurrences was mostly poor and combined with distant metastases. It is probable that distant metastases initiate from the residual tissue after a long period of time. We suppose that, in patients with PTC and perithyroidal tumor infiltration, adjuvant ERT can destroy remaining viable tumor cells locally and prevent the indolent lymphatic dissemination. Thus, in the management of lymph node positive patients over age 40 years with invasive PTC but without distant metastases, adjuvant ERT should be applied in addition to standard treatment.

Not all patients with PTC respond to ERT. For local

control by radiotherapy, all the micrometastases theoretically must be within the radiation field. Thus it is not surprising that patients with viable tumor cells beyond the radiation field do not benefit from this additional treatment.

Follicular thyroid cancer is less common than PTC. Acquiring data with a sufficient number of patients in each subgroup is difficult. In agreement with data from Young et al,[37] the overall recurrence rate was not affected by the presence of lymph node involvement ($P = 0.27$); this suggests that this tumor, in contrast to PTC, does not preferably metastasize by the lymphogenic pathway. Occurrence of skeletal involvement as one of the most frequent sites of distant metastasis regardless of lymph node involvement (Tables 2, 4) confirms the mainly hematogenic dissemination of this tumor. Our study demonstrates that this pattern of metastasis could not be affected by adjuvant radiotherapy ($P = 0.38$).

In conclusion, an effort was undertaken to assess the impact of ERT on the outcome in subgroups of patients with advanced DTC in Stage pT4. We conclude that patients over the age of 40 years, with invasive PTC, who had nodal involvement at presentation but were thought to be disease free after initial therapy, benefit from an additional adjuvant ERT. Since the rate of recurrences in patients with PTC without lymph node involvement at final staging as well as in follow-up was notably low, additional routine ERT in this group should be discouraged. Considering the limited number of patients with FTC, we cannot definitely exclude an advantage of ERT in this group; however, taking into account the results of this study and the different pathways of metastasis, an additional, routine ERT seems unnecessary.

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