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# Prognostic factors of papillary and follicular thyroid cancer: differences in an iodine-replete endemic goiter region

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## Abstract

Papillary (PTC) and follicular thyroid carcinoma (FTC) are known as differentiated thyroid carcinoma (DTC). Nevertheless, according to the UICC/AJCC (TNM) classification PTC and FTC are frequently analyzed as one cancer. The aim of this study is to show differences in outcome and specific prognostic factors in an iodine-replete endemic goiter region.

Six hundred and three patients with DTC treated within a 35-year-period were retrospectively analyzed with respect to carcinoma-specific survival. Prognostic factors were tested for their significance using univariate and multivariate analysis.

The histological type (PTC versus FTC) was found to be a highly significant factor – carcinoma-specific survival both in univariate ($P < 0.001$) and multivariate analyses ($P = 0.003$) was significantly different. Univariate analysis revealed patients' age, extra-thyroid tumor spread, lymph node and distant metastases, increasing tumor size, and the tall cell variant to be significant prognostic factors for PTC patients. Age $\geq$45 years, positive lymph nodes and increasing tumor size were confirmed as independent prognostic factors. Univariate analysis of FTC patients revealed age at presentation, gender, extrathyroidal tumor spread, lymph node and distant metastases, increasing tumor size, multifocality, widely invasive tumor growth and oxyphilic variant to be factors bearing prognostic significance. The presence of distant metastases and increasing tumor size could be identified as independent prognostic factors for FTC patients.

This study shows distinctive differences in prognostic factors of PTC and FTC: independent factors predicting poor prognosis are age $\geq$45 years, positive lymph nodes and increasing tumor size for PTC, and distant metastases and increasing tumor size for FTC. PTC and FTC patients should be analyzed and reported separately.

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## Introduction

Follicular cell-derived carcinomas can be divided into differentiated and undifferentiated (anaplastic) carcinomas. The term differentiated carcinoma (DTC) summarizes papillary thyroid cancer (PTC) with all its morphologic variants and follicular thyroid cancer (FTC) including the oxyphilic (Hurthle-cell) type. Within the DTC group life expectancy and the likelihood of cure vary widely (McIver & Hay 2001). Whereas some studies could not detect any differences in outcome between PTC and FTC (Tubiana *et al.* 1985, Lerch *et al.* 1997, Steinmüller *et al.* 2000), others report a significantly poorer prognosis for FTC (Brennan *et al.* 1991, Shah *et al.* 1992, Loh *et al.* 1997, Hundahl *et al.* 1998). Most thyroid cancer staging systems, including the AJCC/


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UICC (TNM) staging system do not take into account these differences and classify PTC and FTC as one tumor entity.

Age at presentation, distant metastases, tumor size and extension beyond the thyroid capsule are well-established prognostic factors for differentiated thyroid carcinoma (Hay *et al.* 1993). Nevertheless, other prognostic factors, especially the involvement of cervical lymph nodes are still discussed.

The aim of this study was to underline the differences in outcome between FTC and PTC and to ascertain whether the prognostic factors correlating with carcinoma-specific survival differ between FTC and PTC in an iodine-replete endemic goiter area.

## Materials and methods

### Demography

In a 35-year-period the data of 603 patients with DTC primarily treated at the Section of Endocrine Surgery, Division of General Surgery, Department of Surgery, University of Vienna were prospectively documented and retrospectively analyzed. The mean patients' age was $51.0 \pm 17.1$ years (median 52 years, range 10–88 years); $48.3 \pm 16.6$ years (median 49 years, range 10–86 years) for PTC and $57.9 \pm 16.4$ years (median 62 years, range 12–88 years) for FTC. The cohort consisted of 451 female (75%) and 152 male (25%) patients leading to a male to female ratio of 3:1.

### Surgical strategy

Whenever cancer diagnosis was made intraoperatively, total thyroidectomy, bilateral extirpation of the lymphatic tissue along both recurrent laryngeal nerves (central lymph node dissection) and extirpation of the central jugular lymph nodes (diagnostic lymph node dissection) were the preferred forms of primary treatment. Whenever positive lymph nodes were detected by diagnostic lymph node dissection on frozen sections, a complete lateral neck dissection was performed with the aim of saving the internal jugular vein (functional lateral neck dissection). In patients with lymph node metastases fixed along the internal jugular vein, an en bloc resection of the lymph node metastases together with the internal jugular vein was performed preserving the carotid artery, the vagal nerve and the sternomastoid muscle (modified radical lateral neck dissection).

If diagnosis was made only postoperatively, the decision whether to perform a completion thyroidectomy and additional lymph node dissection depended on the patient's age, tumor characteristics and stage, as well as on the patient's choice.

Three hundred and two patients (50%) underwent primary total thyroidectomy, in a further 164 patients (27%) a completion thyroidectomy was performed and 44 patients (7%) underwent a near-total thyroidectomy leading to a total of 510 patients (85%) undergoing at least a near-total thyroidectomy.

In 79 patients (13%) the carcinoma was resected by performing a less than near-total thyroidectomy (unilateral subtotal resection: $n = 12$; unilateral lobectomy: $n = 29$; unilateral lobectomy+contralateral subtotal resection: $n = 12$; bilateral subtotal resection: $n = 26$). Thirty-nine of these 79 patients (49%) with less than near-total thyroidectomy had a papillary microcarcinoma.

In 14 patients (2%) a palliative procedure was performed, leaving behind macroscopically or microscopically visible tumor (R1/R2 resection).

Lymph node surgery was performed in 485 patients (80%). It consisted of central node dissection only in 40 patients (8%), diagnostic lymph node dissection in 269 patients (55%), functional lateral neck dissection in 72 patients (15%), and modified radical lateral neck dissection in 104 patients (21%). Patients in whom no lymph node surgery was performed were classified as pNX ($n = 118$; 20%).

### Postoperative treatment

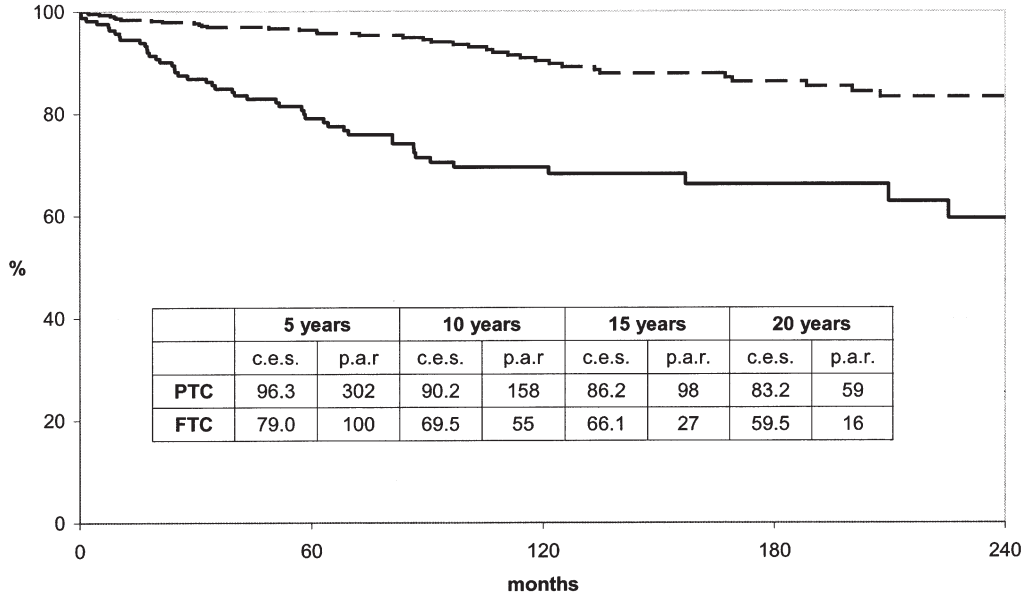
Postoperative treatment consisted of radioiodine ablation (80–100 mCi) in patients undergoing at least a near-total thyroidectomy and thyroxine suppression therapy in all patients irrespective of the patient's age, the histological tumor type, tumor size and staging or the surgical strategy.

Patients were monitored in a special outpatient department where a standardized follow-up protocol (clinical examination, biochemistry, including thyroglobulin levels, ultrasonography of the neck, x-ray of the lungs) was employed. All patients were seen once a year for the first 5 years and then every 2 years. The mean follow-up period was 10.8 years $\pm$ 4.2 months (median: 8.2 years). The 'patients at risk' are summarized in Fig. 1.

### Statistics

Age at presentation, gender, tumor spread, nodal status, distant metastases, primary tumor size, multifocality, histological variants and growth type, operative strategy and completeness of resection were analyzed as possible prognostic factors.

Univariate analysis of the significance of these various factors was performed using the Kaplan–Meier survival curves, and differences were assessed utilizing the log-rank test. In order to assess the independent effect of these prognostic factors, multivariate analysis was carried out




| | 5 years | | 10 years | | 15 years | | 20 years | |
|---|---|---|---|---|---|---|---|---|
| | c.e.s. | p.a.r | c.e.s. | p.a.r | c.e.s. | p.a.r. | c.e.s. | p.a.r. |
| **PTC** | 96.3 | 302 | 90.2 | 158 | 86.2 | 98 | 83.2 | 59 |
| **FTC** | 79.0 | 100 | 69.5 | 55 | 66.1 | 27 | 59.5 | 16 |

**Figure 1** Estimated cause-specific survival according to Kaplan–Meier survival curves for PTC (broken line) and FTC (solid line). c.e.s, cumulative estimated survival in %; p.a.r., patients at risk.

using the Cox proportional hazard model. Cancer-related survival was defined as the endpoint of observation.

## Results

Within the long term observation 37 of 435 PTC patients (9%) and 47 of 168 FTC patients (28%) died of thyroid cancer. The histological type (FTC vs PTC) was found to be a highly significant prognostic factor in univariate ($P < 0.001$, Fig. 1) and multivariate analysis ($P = 0.003$, risk ratio = 2.93). Therefore the following analyses of prognostic factors were performed separately for PTC and FTC patients.

### Papillary thyroid cancer

The results of univariate analysis showing the statistical significance of various prognostic factors in PTC are summarized in Table 1. Age ≥45 years at presentation, tumor extension beyond the thyroid capsule (pT4), increasing primary tumor size, distant metastases, involvement of cervical lymph nodes, incomplete resection (R1/R2 resection) and the tall cell histological variant were found to be statistically significant adverse prognostic factors, whereas gender, multifocality, operative strategy and the follicular and diffuse sclerosing histological variant bore no prognostic significance. The involvement of cervical lymph nodes was statistically significant in univariate analysis only in those patients ≥45 years of age ($P = 0.005$), whereas it did not affect prognosis in younger patients ($P = 0.38$). Interestingly, however, in these younger patients the higher incidence of cervical lymph node metastases (64% vs 34%) was striking.

Multivariate analysis confirmed age ≥45 years, primary tumor size and cervical lymph node involvement to be independent prognostic factors, whereas the presence of distant metastases and extension beyond the thyroid capsule (pT4) did not reach statistical significance on multivariate analysis (Table 2).

### Follicular thyroid cancer

The results of univariate analysis showing the statistical significance of various prognostic factors in FTC are summarized in Table 3. All analyzed factors except operative strategy and lymph node involvement in patients <45 years, turned out to be significant on univariate analysis.

Performing multivariate analysis, only distant metastases and primary tumor size were confirmed as independent prognostic factors (Table 4).

## Discussion

The impact of histological type of differentiated thyroid carcinoma (PTC vs FTC) on prognosis continues to be debated in the literature. In the publications nothing has been reported on the iodine intake of the population studied. The majority of reported series describe a poorer prognosis for FTC (Brennan *et al.* 1991, Shah *et al.* 1992, Emerick *et al.* 1993, DeGroot *et al.* 1995, Loh *et al.* 1997, Gilliland *et al.* 1997, Hundahl *et al.* 1998), which also

**Table 1** Prognostic factors of PTC

| | ***n*** (%) | **10-year survival rate** (%) | **Log rank/*P*** |
|---|---|---|---|
| Age | | | |
| <45 years | 179 (41) | 97.5 | 0.0001 |
| ≥45 years | 256 (59) | 85.1 | |
| Gender | | | |
| Female | 329 (76) | 90.4 | 0.92 |
| Male | 106 (24) | 89.3 | |
| Extrathyroid tumor extension | | | |
| No | 354 (81) | 95.7 | 0.0001 |
| Yes | 81 (19) | 67.3 | |
| N-classification | | | |
| pN0 | 161 (37) | 93.8 | |
| pN1 | 201 (46) | 86.7 | 0.03 |
| pNX | 73 (17) | 92.3 | |
| N-classification <45 years | | | |
| pN0 | 52 (29) | 100 | 0.38 |
| pN1 | 114 (64) | 95.9 | |
| pNX | 13 (7) | 100 | |
| N-classification ≥45 years | | | |
| pN0 | 109 (43) | 90.8 | 0.005 |
| pN1 | 87 (34) | 74.9 | |
| pNX | 60 (23) | 90.2 | |
| Distant metastases | | | |
| M0 | 424 (97) | 90.9 | 0.0005 |
| M1 | 11 (3) | 65.4 | |
| Tumor size | | | |
| ≤10 mm | 171 (39) | 99.4 | 0.0001 |
| 11–40 mm | 194 (45) | 92.8 | |
| > 40 mm | 70 (16) | 71.4 | |
| Multifocality | | | |
| Unifocal | 333 (77) | 91.2 | 0.33 |
| Multifocal | 102 (23) | 86.5 | |
| Histological variant | | | |
| Tall cell | 14 (3) | 63.3 | 0.0004 |
| Follicular | 99 (23) | 90.2 | 0.28 |
| Diffuse sclerosing | 15 (3) | 100 | 0.29 |
| Operative strategy | | | |
| TTH or NTTH | 363 (85) | 91.4 | 0.96 |
| Less than NTTH | 66 (15) | 96.0 | |

TTH, total thyroidectomy; NTTH, near-total thyroidectomy.

holds true for our patients living in an iodine-replete endemic goiter region.

In Austria the iodine substitution was first started in 1923, but banned by the German *Reichsgesetzgebung* (Law) in 1938 and it was not until 1963 that the addition of 10 mg potassium iodide/kg table salt was reintroduced. This dose was doubled in 1990 to 20 mg potassium iodide/kg table salt (Eber 1998). In supplying iodized salt for goiter prevention, the daily urinary iodine excretion was increased to a median of 140 mg iodine/g creatinine and thus normalization was achieved (Galvan 1993, Eber 1998). As recently shown, the incidence of anaplastic thyroid carcinomas in Austria decreased but at the same time both the relative and absolute numbers of differentiated thyroid carcinomas rose (Bacher–Stier *et al.* 1997, Passler *et al.* 1999). The same was observed in our

**Table 2** Multivariate analysis of prognostic factors of PTC

| | *P*-value | Risk ratio |
|---|---|---|
| Age ≥45 years | 0.0002 | 11.14 |
| Male gender | 0.17 | 0.53 |
| Extrathyroid tumor extension | 0.58 | 1.28 |
| pN1 classification | 0.0008 | 5.35 |
| Distant metastases | 0.15 | 2.96 |
| Tumor size | 0.0002 | 3.30 |
| Multifocality | 0.82 | 0.91 |
| Operative strategy | 0.44 | 1.43 |

study population. However, among the DTCs there was no decrease in FTCs, which constantly make up about one third (33%) of the group of DTCs over the observation period.

Univariate analysis showed a highly significant difference in carcinoma-specific survival between PTC and FTC. It was also possible to confirm the histological type as an independent risk factor in multivariate analysis. This is in contrast to studies carried out by Tubiana *et al.* (1985), Lerch *et al.* (1997), Steinmüller *et al.* (2000) and Levi *et al.* (2000).

Age at presentation is a well-established strong prognostic factor for differentiated thyroid carcinoma (Shah *et al.* 1992, Lerch *et al.* 1997, Gilliland *et al.* 1997, Cady 1998, Mazzaferri 1999, Beenken *et al.* 2000). In our patient cohort, age at presentation was a strong and independent prognostic factor only for PTC, whereas in FTC the statistical significance in univariate analysis could not be confirmed through multivariate analysis. The same observation was made by Chow *et al.* (2000*a*,*b*) in a cohort of 842 patients with differentiated thyroid carcinoma, who were retrospectively studied at the Queen Elizabeth Hospital in Hong Kong. The fact that age at presentation is not of any prognostic importance in FTC has already been described by others (DeGroot *et al.* 1995, Steinmüller *et al.* 2000, Witte *et al.* 2002). On the other hand, some authors identified older age as a poor prognostic factor in patients with FTC (Byar *et al.* 1979, Brennan *et al.* 1991, Emerick *et al.* 1993, Zidan *et al.* 2000).

Another reported prognostic factor is gender (McConahey *et al.* 1986, Salvesen *et al.* 1992, Shaha *et al.* 1996, Gilliland *et al.* 1997, Mazzaferri 1999, Levi *et al.* 2000, Hellman *et al.* 2001). In our group of patients, male gender had a statistically significant impact on poorer prognosis only in univariate analysis in FTC patients, whereas it could not be confirmed to be an independent risk factor in multivariate analysis. Other authors have also failed to prove gender as an independent prognostic factor (Simpson *et al.* 1987, Segal *et al.* 1996, Loh *et al.* 1997).

Tumor extension beyond the thyroid capsule (pT4) is described as being one of the strongest prognostic factors in DTC, therefore resulting in its use in most staging systems (Carcangiu *et al.* 1985, Cady & Rossi 1988, Shah *et al.* 1992, Shaha *et al.* 1994, Lerch *et al.* 1997, Mazzaferri 1999). Surprisingly, this prognostic factor did not bear any independent importance in multivariate analysis in either our PTC or our FTC patient cohort.

One of the most discussed prognostic factors for DTC is the presence of cervical lymph node metastases. We did not find any prognostic impact in patients <45 years of age. In patients ≥ 45 years of age involvement of cervical lymph nodes was associated with a poorer prognosis in PTC and FTC patients. This finding is in complete accordance with the work of Hughes *et al.* (1996) and may lead to a more extended lymph node dissection in these 'high risk' patients. Nevertheless, the independent prognostic significance could only be confirmed for PTC, but not for FTC. This finding conforms to that of DeGroot *et al.* (1995), who did not find any significant correlation between positive cervical lymph nodes and carcinoma-related death in FTC patients. It is, however, in contrast to Witte *et al.* (2002), who describe a significant impact of lymph node involvement on prognosis of FTC. Generally, studies exist which indicate a correlation between cervical lymph node involvement and poor prognosis in differentiated thyroid carcinomas (Akslen *et al.* 1991, Mazzaferri & Jhiang 1994, Scheumann *et al.* 1994, Lerch *et al.* 1997, Loh *et al.* 1997, Mazzaferri 1999, Kebebew & Clark 2001), whereas others are not able to do so (Hay 1994, Pacini *et al.* 1994, Grebe & Hay 1996, Yamashita *et al.* 1997, Sanders & Cady 1998, Steinmüller *et al.* 2000). A Japanese study by Yamashita *et al.* (1997) showed large nodular deposits ( > 10 mm) and extracapsular invasion of lymph node metastases to be associated with poor prognosis in patients with papillary thyroid carcinoma.

Within our group of patients, distant metastases at presentation were an independent prognostic factor only for FTC, but not for PTC, where only univariate analysis was of statistical significance. This is in contrast to the majority of published studies (Cady & Rossi 1988, DeGroot *et al.* 1990, 1995, Loh *et al.* 1997, Shaha *et al.* 1998, Chow *et al.* 2002*b*) which report distant metastases also to be a strong independent prognostic factor for PTC. This may, however, be due to the low number of PTC patients presenting with distant metastases ($n = 11.3\%$) in our study population.

The primary tumor size was the only prognostic factor which merited independent statistical significance on multivariate analyses for both PTC and FTC. On the whole, increasing tumor size is a prevalent and accepted factor for poorer prognosis (McConahey *et al.* 1986, DeGroot *et al.* 1990, Akslen 1993, Hay *et al.* 1993, Loh *et*

**Table 3** Prognostic factors of FTC

| | ***n*** (%) | **10-year survival rate** (%) | **Log rank/*P*** |
|---|---|---|---|
| Age | | | |
| <45 years | 35 (21) | 97.0 | 0.0007 |
| ≥45 years | 133 (79) | 62.8 | |
| Gender | | | |
| Female | 122 (73) | 75.4 | 0.004 |
| Male | 46 (27) | 53.5 | |
| Extrathyroid tumor extension | | | |
| No | 138 (82) | 80.4 | 0.0001 |
| Yes | 30 (18) | 24.3 | |
| N-classification | | | |
| pN0 | 106 (68) | 81.8 | 0.0001 |
| pN1 | 17 (10) | 42.0 | |
| pNX | 45 (22) | 52.0 | |
| N-classification < 45 years | | | |
| pN0 | 29 (83) | 96.4 | 0.71 |
| pN1 | 1 (3) | 100 | |
| pNX | 5 (14) | 100 | |
| N-classification ≥ 45 years | | | |
| pN0 | 77 (58) | 76.5 | 0.002 |
| pN1 | 16 (12) | 37.5 | |
| pNX | 40 (30) | 47.6 | |
| Distant metastases | | | |
| M0 | 131 (78) | 80.7 | 0.0001 |
| M1 | 37 (22) | 35.9 | |
| Tumor size | | | |
| ≤10 mm | 9 (5) | 75.0 | 0.0001 |
| 11–40 mm | 82 (49) | 90.0 | |
| > 40 mm | 77 (46) | 45.6 | |
| Multifocality | | | |
| Unifocal | 148 (88) | 74.3 | 0.0006 |
| Multifocal | 20 (12) | 33.3 | |
| Histology | | | |
| Minimally invasive | 99 (59) | 86.7 | 0.0001 |
| Widely invasive | 69 (41) | 49.8 | |
| Histological variant | | | |
| Oxyphilic | 39 (23) | 54.0 | 0.04 |
| Non-oxyphillic | 129 (77) | 75.1 | |
| Operative strategy | | | |
| TTH or NTTH | 147 (92) | 72.3 | 0.77 |
| Less than NTTH | 13 (8) | 75.5 | |

TTH, total thyroidectomy; NTTH, near-total thyroidectomy.

*al*. 1997), although some investigators (Chow *et al*. 2000*a,b*) have failed to prove increasing tumor size as an independent risk factor.

A few authors describe multifocality as a strong indicator of poor prognosis (Carcangiu *et al*. 1985, Mazzaferri & Jhiang 1994). It is generally acknowledged to be a controversial and inconsistent prognostic factor (Kebebew & Clark 2001). We were also unable to determine the independent impact of multifocality on prognosis of PTC and FTC in our study.

Beyond the different histological variants of PTC, only the tall cell variant bore any conclusive evidence as a strong predictor of poor prognosis, whereas the follicular and diffuse sclerosing variant did not reveal any

**Table 4** Multivariate analysis of prognostic factors of FTC

| | *P*-value | Risk ratio |
|---|---|---|
| Age ≥45 years | 0.38 | 2.00 |
| Male gender | 0.35 | 1.42 |
| Extrathyroid tumor extension | 0.39 | 1.50 |
| pN1 classification | 0.32 | 1.66 |
| Distant metastases | 0.0001 | 5.38 |
| Tumor size | 0.006 | 2.84 |
| Multifocality | 0.11 | 2.06 |
| Minimally invasive growth | 0.13 | 0.51 |
| Operative strategy | 0.64 | 1.45 |

statistically significant differences in the survival rate compared with pure PTC. These findings are in accordance with other studies (Johnson *et al*. 1988, Taylor *et al*. 1998) published on this subject, which show the tall cell variant as an indicator of poor prognosis, the diffuse sclerosing variant to be of intermediate risk (Carcangiu & Bianchi 1989, Chan 1990), and the follicular variant as well as pure PTC as having a positive prognosis (Chen & Rosai 1977, Carcangiu *et al*. 1985, Tielens *et al*. 1994, Ortiz Sebastian *et al*. 2000).

Growth characteristics of FTC (minimally or widely invasive) were statistically significant in univariate analysis, but could not be confirmed as independent risk factors. This is in concordance with DeGroot *et al*. (1995), but in contrast to others (Tubiana *et al*. 1985, Schlumberger 1998). This also holds true for the oxyphilic or Hurthle cell variant of FTC, which could not be found to be of prognostic significance in our patients, which was also not the case in most other reports (Grant 1995, Chen *et al*. 1998, McHenry *et al*. 1999).

A very important, but nevertheless controversial issue is the question as to whether the extent of thyroid surgery has an impact on survival in patients with DTC. Most authors recommend total or near-total thyroidectomy in order to reduce the risk of recurrence and thus improve survival (Clark 1982, Samaan *et al*. 1992, Mazzaferri & Jhiang 1994, Loh *et al*. 1997, Hay *et al*. 1998, Duren *et al*. 2000), while others prefer less radical surgery for all low risk patients regardless of the T-classification (Cady 1998). This recommendation is supported by studies of DeGroot *et al*. (1995) who could not find an increase in carcinoma-specific mortality when less radical surgical procedures were chosen.

We also could not find a statistically significant difference in carcinoma-specific survival between the two groups, namely, total or near-total thyroidectomy and less than near-total thyroidectomy. Fourteen patients with palliative (R2) resection were not included in this analysis. Only 79 patients (13%) underwent a less than near-total thyroidectomy. Of these 79 patients, 39 (49%) had a papillary microcarcinoma. The percentage of patients in low risk groups was higher in the less radical surgery group (UICC-AJCC: 89% vs 70%; AMES: 86% vs 70%; MACIS: 90% vs 80%). What can be deduced from the above findings is that a type of patient selection process exists, and consequently, the analysis regarding operative strategy may not be correct. The authors therefore still recommend total thyroidectomy for all patients in which the diagnosis of thyroid carcinoma is made pre- or intraoperatively. A less than near-total thyroidectomy should be permitted only in those patients with unifocal tumors and pT1-classification without lymph node metastases. This procedure is underlined by the fact that the percentage of patients in high-risk groups is higher and the prognosis within the risk groups is poorer within Europe compared with North America and Australia (Passler *et al*. 2003).

## Conclusions

PTC and FTC are summarized as differentiated thyroid carcinoma in the majority of reports. It should, however be noted that some important differences exist. At least in an iodine-replete endemic goiter region, FTC patients present with a higher age, as well as with more frequent distant and less frequent lymph node metastases and significantly poorer carcinoma-specific survival. Furthermore, this study shows distinctive differences in prognostic factors for the two entities: independent factors predicting poor prognosis are age ≥45 years, positive lymph nodes and increasing tumor size for PTC, and distant metastases and increasing tumor size for FTC. The authors therefore believe that patients with PTC and FTC should be reported separately.

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