Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases

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Abstract

Objective: Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) show considerable differences in disease stage at initial presentation. The aim of this study was to investigate whether there are differences in tumour-specific survival if initial staging is accounted for.

Design: Retrospective chart review study.

Patients: The study sample comprised 875 PTC and 350 FTC patients (856 females, 369 males, mean age 47.8 years) treated in our hospital from 1978 to 2002. All patients received total thyroidectomy with subsequent I-131 ablation except for those patients with an isolated papillary microcarcinoma.

Methods: Kaplan–Meier analyses and Cox-regression analyses were performed to assess the influence of histology on thyroid cancer-specific survival.

Results: FTC patients were on average older, more likely to be male, presented with a larger tumour and more frequently had multifocal carcinoma and distant metastases than PTC patients, whereas they presented less frequently with extrathyroidal invasion or lymph node metastases. Twenty-year tumour-specific survival in PTC was 90.6% and in FTC 73.7% (P < 0.001). In multivariate analysis the presence of distant metastases (P < 0.001), age (P < 0.001), tumour size (P < 0.001) and the presence of extrathyroidal invasion (P = 0.007), but not histology (P = 0.26), were independent determinant variables for tumour-specific survival.

Conclusion: There is no difference in tumour-specific survival between PTC and FTC when accounting for the presence of metastases, age, tumour size and the presence of extrathyroidal invasion.

Introduction

Papillary (PTC) and follicular (FTC) thyroid carcinoma, derived from the same follicular thyroid cell lineage, are often grouped together as a single entity which is referred to as differentiated thyroid carcinoma (DTC), suggesting a similar clinical behaviour of these two cancer types. There are, however, important differences, especially with regard to tumour-specific survival. In several studies it has been shown that FTC patients have a considerably lower long-term survival than PTC patients (1, 2). Some prognostic scoring systems do not differ between PTC and FTC (3–5), but others do regard FTC as an adverse prognostic factor (6, 7).

The clinical presentation of PTC and FTC also differs markedly. FTC patients present with a larger diameter of the primary tumour and more often have distant metastases at the time of initial presentation (1, 2, 8, 9), both of which are considered indicators of poor prognosis with regard to recurrence-free and thyroid cancer-specific survival. On the other hand FTC only infrequently shows lymph node metastases, contrary to PTC (2, 10).

A study by Machens et al. showed that when tumour diameter is compensated for, PTC and FTC show the same rate of distant metastases (10), and FTC only develops lymph node metastases or extrathyroidal growth at a much greater tumour diameter than PTC. Most likely the more advanced stage in FTC is due to a longer diagnostic delay (10). In the light of these findings it is conceivable that FTC only appears to be associated with a poorer prognosis because it is discovered later on in the course of the disease. The aim of this study was therefore to investigate whether histology is an independent prognostic factor, causing differences in survival between PTC and FTC patients.

Patients and methods

Database

The Nuclear Medicine Clinic of the University of Würzburg, a tertiary referral centre for DTC located in Southern Germany, established the Würzburg Thyroid
Cancer Database primarily to monitor the quality of patient treatment. Secondly, the database allows for retrospective scientific population studies.

Data are recorded for each clinic visit, starting with the first visit after DTC diagnosis. Data recorded at that visit include histology, primary tumour diameter, pTNM staging and presence or absence of tumour multicentricity or local extrathyroidal invasion. Data recorded on subsequent visits included presence or absence of lymph node or distant metastases at that visit.

For patients who no longer visit our centre the registry is regularly updated through inquiry with the referring physicians as well as the death certificate registry of the German public health office. In deceased patients the cause of death was verified through review of the patients’ records, inquiry with the referring physicians and the death certificate registry.

Patients

We retrospectively reviewed data from 875 patients with PTC and 350 patients with FTC who were followed, and in most cases, also treated in our hospital from January 1978 through December 2002. The latter cut-off date was chosen to allow for a minimum follow-up of 5 years. The patients’ basic characteristics and the results of tests for differences between PTC and FTC patients are summarised in Table 1.

Treatment

All patients received total thyroidectomy with subsequent I-131 ablation except for those patients with an isolated papillary microcarcinoma, in whom a hemithyroidectomy was performed. I-131 ablation was performed with an activity of 1500–3500 MBq I-131, depending on the size of the thyroid remnant. After ablation suppressive levothyroxin treatment was initiated. Patients returned 6–12 months after initial treatment for I-131 whole-body scintigraphy and Tg-measurement after withdrawal of levothyroxine or, in later years, after the administration of recombinant human TSH (rhTSH). If any sign of persistent disease was encountered, an additional activity of 7000 MBq I-131 was administered. In disease-free patients at least one more follow-up scan after thyroid hormone withdrawal or rhTSH injection was performed within the first 5 years of follow-up. For the first 5 years patients were followed at half-yearly intervals and thereafter at yearly intervals during TSH-suppressive therapy by means of thyroglobulin measurement and neck ultrasound. X-rays, computed tomography (CT)-scans or magnetic resonance imaging (MRI)-scans were performed on indication.

Pathological analysis and staging

Surgical specimens were analysed and classified as PTC or FTC according to WHO standard at the time of initial treatment. The present study used the histological classification given in the original pathology report.

The primary tumour diameter was determined based on macroscopic analysis of the surgical specimen, when possible. This also was true for invasive carcinoma, with the pathologist making a best estimate in widely invasive cases. For multifocal tumours, the diameter of the largest tumour focus was taken for the primary tumour diameter. In cases of an unclear diagnosis, specimens were sent to the reference pathologist on thyroid histology for Germany.

Histological grading was not determined and reported as this is not recommended by the WHO.

Classification as positive for multifocal or extrathyroidal local disease or for lymph node metastasis required histological confirmation. To be classified as free of lymph node involvement, patients had to have undergone a lymph node dissection; otherwise, they were classified as Nx and excluded from analyses concerning lymph node metastases. For classification as positive for distant metastases, non-histological evidence, such as a positive post-therapy I-131 whole-body scan, CT scan or MRI, was deemed sufficient in patients with elevated Tg-levels.

| Table 1 Comparison of characteristics between PTC and FTC patients. |
|-----------------|-----------------|-----------------|-----------------|
|                 | PTC             | FTC             | P value         |
| Number of patients | 875             | 350             | 0.02            |
| Number of male/female patients | 247/628         | 122/228         | <0.001          |
| Mean age (range) in years | 46.1 (5–87)     | 52.2 (8–81)     | <0.001          |
| Mean follow-up in years | 10.8            | 10.9            | 0.49            |
| Mean tumour diameter (mm) | 19.2 ±0.6       | 31.7 ±1.3       | <0.001          |
| Number of patients with multifocal carcinoma | 92 (10.5%) | 51 (14.5%) | 0.047 |
| Number of patients with extrathyroidal invasion | 184 (21.0%) | 48 (13.7%) | 0.006 |
| Number of patients with lymph node metastases | 78 (8.9%) | 18 (5.1%) | 0.02 |
| Number of patients classified as Nx | 199 (22.7%) | 74 (21.1%) | 0.54 |
| Number of patients with distant metastases | 64 (7.3%) | 55 (15.7%) | <0.001 |
**Statistical analysis**

For comparing two groups of categorical data a χ²-test was used. For comparing two groups for a continuous variable the Mann–Whitney test was used.

Survival was analysed using the method of Kaplan–Meier. Differences between survival curves were examined using the log-rank test.

Multivariate analysis was performed using a Cox regression employing a step-wise backward selection method based on likelihood ratios.

Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc. Chicago, IL, USA; two-tailed P levels <0.05 were considered statistically significant.

**Results**

Median follow-up in the entire study population was 9.9 years. There was no significant difference in the length of follow-up between PTC and FTC patients (P=0.49). There was no significant difference in tumour-specific survival between those treated up to 1990 and those treated from 1991 onward.

Comparisons of patient characteristics between PTC and FTC patients can be found in Table 1. It can be seen that FTC patients are on average more likely to be older, to be male, to have a larger tumour and to have multifocal carcinoma or distant metastases than PTC patients, whereas they are less likely to have extrathyroidal invasion or lymph node metastases.

In Fig. 1, it can be seen that the difference in tumour-specific mortality between PTC and FTC was considerable. The 20-year disease-specific survival rate was 90.6% in PTC patients but only 73.7% in FTC patients (P<0.001). Even if patients with distant metastases were excluded from analysis the 20-year disease-specific survival in FTC patients (80.2%) was significantly lower than in PTC patients (93.1%; P<0.001). In contrast, when only comparing those with distant metastases we found no significant difference between PTC and FTC patients (P=0.16).

All the factors in which PTC and FTC patients differed significantly at the time of presentation were entered into a multivariate analysis. In the Cox regression, sex was removed from the model in the first step, tumour multifocality in the second step, histology in the third step (P=0.26) and the presence of lymph node metastases in the fourth step. The presence of distant metastases (P<0.001), age (P<0.001), tumour size (P=0.001) and extrathyroidal invasion (P=0.007) at the time of diagnosis remained as explanatory variables for survival.

Compensating for these factors should remove the differences in survival between the two carcinomas. As an example two curves from opposite ends of the severity spectrum are analysed: in Fig. 2, patients under 45 years of age with isolated, non-metastasized tumours with a diameter <1 cm without extrathyroidal invasion (microcarcinoma) and in Fig. 3 patients, 45 years or over with distant metastases (stage IV according to the TNM system (11, 12)). In both cases the Kaplan–Meier curves do not show significant differences between PTC and FTC (Fig. 2; P=0.81, Fig. 3; P=0.52).

**Discussion**

The current study clearly shows that in differentiated thyroid cancer histology does not significantly influence prognosis. When compensating for differences in stage at the time of presentation, differences in tumour-specific survival between PTC and FTC patients disappear.
Many studies have already reported on the risk factors in DTC. In several of these studies, histology was reported to be such a risk factor. Shaha (6) introduced a staging system in which FTC patients were classified in a higher risk category than PTC patients with the same stage of disease, as did the National Thyroid Cancer Cooperative Treatment Study group staging system (7). On the other hand, the AMES (5) prognostic scoring system and various versions of the TNM (3, 4) system do not include histology as an independent risk factor. In various other studies, histology in some does (13, 14), and in others does not (15) come out as an independent prognostic factor for survival in DTC. DeGroot et al. (16) report that FTC patients have a considerably poorer prognosis than PTC patients; however, they do not report what happens when differences in disease stage at the time of presentation are compensated for. Lundgren et al. report on a nested case–control study where FTC patients turn out to have a 70% higher risk of dying from FTC; even after correction for stage at the time of diagnosis and histologic grading they still find a 40% higher risk of dying of thyroid cancer for FTC patients (17). Haq et al. report that in patients with metastasized DTC, those with FTC do significantly worse with regard to survival than those with PTC (18); Durante et al. report that patients with distant metastases, specifically those patients with less-differentiated FTC, had a poorer prognosis (19). These findings are in contrast to our findings that in patients with distant metastases there is no significant survival difference between PTC and FTC. Unfortunately we are unable to find out whether a separate subgroup of less well-differentiated FTC with metastases performs poorer than other thyroid carcinoma patients, as grading was not reported in the pathology reports.

Mazzaferri and Jhiang report that, contrary to what is observed in our patient population, survival does not differ between FTC and PTC patients if patients with distant metastases are left out (1). Most likely the FTC patients in our population still do worse because of the heightened presence of other unfavourable disease characteristics, such as higher age and larger tumours.

The differences between PTC and FTC at initial presentation, as well as the differences in survival, reported in the current study are in agreement with a similar study by Chow et al. (2).

In literature there have been several reports that the histological grade may be of importance (17, 18), especially in FTC (19). Also the extent of tumour invasion is clearly of importance in FTC: d’Avanzo et al. (20) describe that there is a difference in prognosis in those with only invasion of the tumour capsule, those with angio-invasion and those with broad extracapsular invasion. Lundgren et al. (17) also reported that widely invasive carcinoma had a worse prognosis.

Several histological subtypes have also been associated with. Unfortunately we are unable to further confirm these data as the present study solely analyses DTC in a dichotomised fashion, because especially in the earlier part of the inclusion period pathology reports were rather scarce with information on the precise extent of disease. For this study we elected to achieve the longest possible follow-up over a more detailed analysis of more detailed histological factors.

The present study is unfortunately hampered by imperfect data. This is most clearly reflected in the high percentage of patients being classified as Nx, and a relatively low percentage of patients being classified as N1. This is mostly explained by the large number of patients who undergo a hemi- or total thyroidectomy for a seemingly benign goitre, in whom a thyroid carcinoma is diagnosed only on pathologic examination of the thyroid and a dissection of the central lymph node compartment was therefore not performed.

Several other sources of biases may be identified in the present study. As the inclusion period is rather long, some shifts in treatment may have occurred and influenced survival: this is, however, unlikely as we find no significant difference in survival between those treated up to 1990 and those treated from 1991 onwards. Another source of bias is the multitude of hospitals in which patients received their primary surgery, and with it the multitude of pathologists involved in the primary classification of the tumours. There is potential for bias here: this will play a limited role as slides were consistently sent to a reference pathologist if there was doubt about the diagnosis or classification of the tumour.

Unfortunately, FTC patients present with more advanced disease than PTC patients, but it is still unclear why. Diagnosis later in the course of the disease, which may also explain the somewhat higher age at diagnosis, may cause a large part of the problem.
A cause of such late diagnosis may be that FTC cannot be distinguished on the basis of morphologic aspects of fine needle aspiration biopsy (21, 22), unlike PTC. The diagnosis of FTC requires histological confirmation, and as thyroid surgery is not without risk in many patients the careful weighing of risk of cancer versus risk of surgery may lead to a postponement of surgery for a shorter or longer time. In order to overcome this disparity in early diagnosis rates new techniques are needed. MicroRNAs or mRNA expression profile analysis as well as mutation analysis on fine needle aspirates currently show the most promise (23–26), but these techniques are still in the experimental stage and not yet ready for clinical use.

The data in the current study emphasise that PTC or FTC is not a factor in estimating the prognosis of DTC patients, rather factors like the stage of disease at diagnosis and more difficult to determine parameters such as iodine avidity matter. Also the estimation of prognosis is not a one-off event, but rather a continuously repeated procedure throughout the aftercare of DTC based on the results of treatment (27).

A second clinical point is the question of what to do with follicular microcarcinomas. In Fig. 2 it can be seen that the prognosis in follicular microcarcinomas is identical to that in papillary microcarcinomas of the thyroid. For the latter lesions it has already been shown that total thyroidectomy and I-131 ablation does not lead to any marked benefit. For the former it has, however, been assumed that total thyroidectomy and I-131 ablation do lead to an improved success of treatment, but this assumption to the best of our knowledge is not based on experimental or even observational work. On the contrary, like in our study, a study on microcarcinomas by Baudin et al. (28) showed no differences in survival or recurrence rates between papillary and follicular microcarcinoma. As there was a difference in the treatment of FTC and PTC patients with microcarcinoma the present study cannot answer whether there are benefits from differences in therapy. Therefore, further study on whether the difference in treatment between papillary and follicular microcarcinomas is justified seems warranted.

**Conclusion**

In this large DTC population, histology is not an independent determinant of the prognosis in thyroid cancer. The longer diagnostic delay in FTC patients causes them to present with more advanced disease. These advanced disease characteristics in turn are the determinants of the disease-specific survival.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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