Tumor histology is not an independent determinant of the prognosis of differentiated thyroid cancer

Verburg FA, Mader U, Luster M, Reiners C. Histology does not influence prognosis in differentiated thyroid carcinoma when accounting for age, tumour diameter, invasive growth and metastases. Eur J Endocrinol 2009;160:619-24.

SUMMARY

BACKGROUND Papillary and follicular thyroid cancer are often considered together in analyses of differentiated thyroid cancer; however, follicular cancer generally has a more aggressive course with less favorable survival rates. On the other hand, some studies suggest that the two tumors have inherently similar biologic behavior when adjusted for patient age, tumor stage and initial therapy. The aim of this study was to investigate whether there are differences in tumor-specific survival when adjusted for initial staging.

METHODS This is a retrospective study of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) that was treated at the University of Würzburg from January 1978 through December 2002. The 2002 cutoff was selected to ensure a minimum follow-up of 5 years. All patients were treated with total thyroidectomy and ^{131}I for remnant ablation except for patients with isolated papillary thyroid microcarcinoma (tumors ≤1 cm). Patients were usually treated with 40 to 95 mCi (1500 to 3500 MBq) of ^{131}I according to the thyroid remnant size. Patients had follow-up 6 to 12 months after the initial treatment when ^{131}I whole-body scintigraphy and thyroglobulin (Tg) measurements were performed after levothyroxine withdrawal or recombinant human thyrotropin (rhTSH) stimulation. Persistent or recurrent disease was treated with 190 mCi (7000 MBq) of ^{131}I. Within the first 5 years after initial therapy, patients who were considered to be free of disease had one more whole-body diagnostic scans and serum Tg measurements after thyroid-hormone withdrawal or rhTSH stimulation. Thereafter, serum Tg measurements were made during thyroid-hormone suppression of TSH and neck ultrasonography, and computed tomography scans or magnetic resonance imaging was performed as indicated. Tumor staging was done according to the World Health Organization standard at the time of surgery. Tumor size was measured on the primary tumor specimen. Patients had to undergo lymph-node surgery to be considered free of lymph-node metastases.

RESULTS The study subjects were 875 patients with PTC (71%), and 350 with FTC (29%). There were 628 (72%) women with PTC and 228 (65%) with FTC; the mean age was 46.1 years (range, 5 to 87) in the PTC patients and 52.2 years (range, 8 to 81) in the FTC patients (P<0.001, comparing PTC with FTC) (Figure 1). Mean follow-up was 10.8 years in the PTC group and 10.9 years in the FTC group. Mean (±SD) tumor diameter in PTC and FTC was 19.2±0.6 and 31.7±1.3 mm, respectively (P<0.001). Tumor was multifocal in 92 (10.5%) and 51 (14.5%) (P = 0.047), metastatic to lymph nodes in 78 (8.9%) and 18 (5.1%) (P = 0.02), and metastatic to distant sites in 64 (7.3%) and 55 (15.7%) (P<0.001) in the two histologic tumor types, PTC and FTC, respectively. The median follow-up for the entire cohort was 9.9 years, without a significant difference in the length of follow-up in the two groups of patients. Tumor-specific mortality of PTC and FTC were considerably different: the 20-year survival rates were 90.6% for PTC and 73.7% for FTC (P<0.001). If distant metastases were excluded from the analysis, the 20-year disease-specific mortality rates in FTC patients was 80.2%, which was significantly lower than that for PTC (93.1%) (P<0.001). Moreover, in patients with distant metastases, there were no significant difference between PTC and FTC (P = 0.16). In Cox regression, the independent

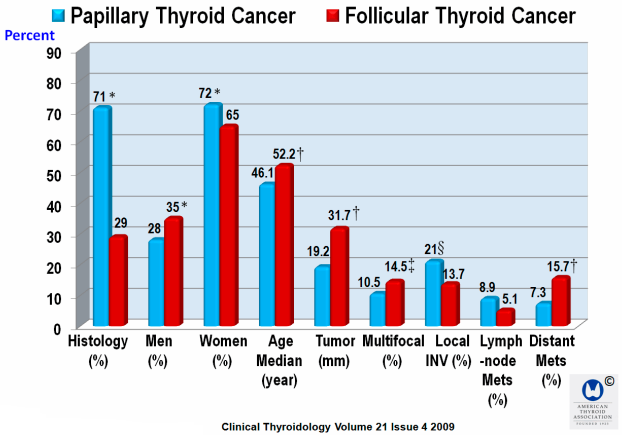

Figure 1. The comparison of characteristics between papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). *P = 0.02, †P <0.001, ‡P = 0.047, §P = 0.006, all comparing papillary with follicular thyroid cancer. INV = local tumor invasion, Mets = metastases.

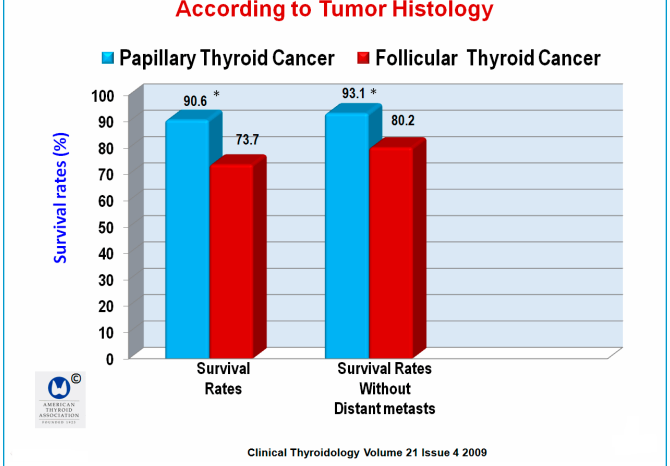

Figure 2. 20-year cancer-specific survival rates for papillary and follicular thyroid cancer with and without distant metastases. *P<0.001 comparing papillary with follicular thyroid cancer.

variables for survival were the presence of distant metastases (P<0.001), age (P<0.001), tumor size (P = 0.001), and extrathyroidal invasion (P = 0.007) at the time of diagnosis. In addition, Kaplan–Meier curves did not show significant differences between PTC and FTC for patients younger than 45 years of age with isolated nonmetastatic tumors <1 cm (P = 0.81) (Figure 2). Likewise patients 45 or older with stage IV tumors did not show significant differences in survival.

CONCLUSION The independent risk factors for tumor-specific survival were distant metastases, patient age, tumor size, and extrathyroidal invasion, but not tumor histology.

COMMENTARY

Although papillary and follicular thyroid cancer are often grouped together as a single entity referred to as differentiated thyroid cancer, the two histologically unique tumors have major genetic, biologic, and clinical differences that clearly set them apart from one another. The most obvious clinical difference is that cancer-specific mortality of follicular cancer is about twofold to threefold that of papillary cancer. A study by Hundahl et al. (1) of 53,856 cases of thyroid cancer treated in the United States from 1985 through 1995 found 10-year relative survival rates of 93% for papillary and 85% for follicular thyroid cancer—that is, cancer-mortality rates of 7% and 15%, respectively. This is in the approximate range reported by Verburg et al., who found 20-year cancer-specific survival rates of 90.6% for papillary and 73.7% for follicular thyroid cancer. The more important question is whether this is the result of inherent biologic characteristics of the tumor or as yet unidentified clinical factors. For uncertain reasons, the incidence rate of papillary cancer is approximately threefold that of follicular cancer (2). Follicular cancer tends to be diagnosed later in life, is more common in men, and is generally a larger tumor with more distant metastases at the time of diagnosis as compared with papillary cancer. On the other hand, papillary tumors tend to be more invasive and multifocal, with more locoregional lymph-node metastases than occur with follicular cancer. These obvious tumor differences lie at the surface of a much deeper and thorny set of issues. For example, the various RET/PTC oncogenes associated with papillary cancer are found in younger patients and specific RET/PTC rearrangements are associated with radiation-induced tumors, whereas as BRAF oncogenes are associated with aggressive papillary tumors such as tall-cell-variant papillary cancer, which has high recurrence and mortality rates. In contrast, encapsulated papillary cancer has almost no cancer-specific mortality. Follicular thyroid cancer, which is usually encapsulated, may have minimal tumor capsular invasion that usually portends relatively benign clinical behavior (3), while poorly differentiated follicular thyroid cancer has serious prognostic connotations (4). These tumor features must be taken into account when asking whether follicular histology per se determines the patient's outcome expressed as 20-year cancer-specific survival.

Verburg et al. found that patients with follicular cancer were on average older and were more likely to be men, and had larger primary tumors that were more often multifocal and metastatic to distant sites as compared with papillary cancer, which tended to have more extrathyroidal invasion, more lymph-node metastases, and fewer distant metastases. None of these features are strikingly different from that generally reported in the literature. The main finding of the study was that multivariate analysis identified four independent variables that predicted follicular cancer mortality: distant metastases, patient age, tumor size, and tumor invasion; however, tumor histology was not among the features predicting survival. The main conclusion of the article is that tumor-specific mortality is the same for papillary and follicular thyroid cancer when the analysis is controlled for the four factors found on multivariate analysis.

Others have found that 30-year cancer-specific mortality rates were greatest in patients with follicular cancer and that cancer mortality was most likely in the presence of adverse prognostic factors, such as advanced age, large tumor size, and distant metastases. This same study found that mortality rates for papillary and follicular thyroid cancer were similar (10% vs. 6%, P = not significant) if distant metastases were excluded from the analysis. Still others have found that histologic grade and invasive tumor is important for follicular outcome (4, 5).

Verburg et al. suggest that there are several sources of concern in their study. They were unable to confirm some of the data because in the earlier part of the study, pathology reports were rather scarce. Also, a large number of patients did not have information on the presence or absence of lymph-node metastases; and over time, there may have been shifts in tumor treatment. The authors also acknowledge that it is still not clear why patients with follicular cancer present with more advanced disease than do patients with papillary thyroid cancer.

Nonetheless, it is important to know that features such as patient age, tumor stage, and initial treatment have a major impact on the clinical outcome of both papillary and follicular cancer, which to some extent puts less emphasis on tumor histology alone when attempting to estimate the risks of tumor recurrence and cancer-specific mortality.

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