Available online at www.sciencedirect.com

ScienceDirect

EJSO 41 (2015) 766–772

EJSO the Journal of Cancer Surgery

www.ejso.com

Breach of the thyroid capsule and lymph node capsule in node-positive papillary and medullary thyroid cancer: Different biology

A. Machens*, H. Dralle

Department of General, Visceral and Vascular Surgery, Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Straße 40, Halle (Saale) D-06097, Germany

Accepted 17 October 2014
Available online 27 October 2014

Abstract

Aims: The higher incidence of extranodal growth (breach of a lymph node capsule) in the presence of extrathyroidal extension (breach of the thyroid capsule) in papillary thyroid cancer prompted conclusions that the biology of thyroid cancer is conferred to the lymph nodes, causing invasion of perinodal tissues. This study aimed at quantifying the independent contributions of clinical-pathological factors to extranodal growth in thyroid cancer.
Methods: Multivariate analyses of 1250 patients operated on for node-positive papillary (PTC; 702 patients) or node-positive medullary thyroid cancer (MTC; 548 patients), 138 and 130 of whom harbored extranodal growth.
Results: After correction for multiple testing, extranodal growth correlated with number of lymph node metastases (means of 17.0 vs. 10.1 nodes for PTC, 20.6 vs. 13.4 nodes for MTC; each $P < 0.001$) and male gender (49 vs. 35% for PTC, $P = 0.005$; 62 vs. 46% for MTC; $P = 0.002$); and in MTC also with extrathyroidal extension (46 vs. 30%; $P = 0.002$). On multivariate analysis, independent determinants of extranodal growth were number of lymph node metastases (odds ratios of 2.1, 3.7 and 3.7 for PTC ($P \leq 0.01$) and 2.7, 3.3, and 4.0 for MTC ($P \leq 0.004$) looking at 6–10, 11–20 and >20 involved nodes against a 1–5 node baseline) and male gender (odds ratio 1.6 for PTC, 1.7 for MTC; each $P = 0.02$), but not extrathyroidal extension.
Conclusions: In PTC and MTC, extranodal growth develops independently from extrathyroidal extension. This finding argues against mere transference of primary tumor characteristics to lymph nodes, pointing more to accrual of invasive properties by nodal tumor deposits.

Keywords: Papillary thyroid carcinoma; Medullary thyroid carcinoma; Primary tumor diameter; Extrathyroidal extension; Lymph node metastases; Extranodal growth; Distant metastasis

Introduction

Growth of thyroid cancer through a tissue barrier can reflect the invasive properties of the thyroid primary (breach of the thyroid capsule) or the metastatic tumor deposit (breach of a lymph node capsule). Different clinical weights have been attached to such invasive growth depending on whether it originates from within the thyroid parenchyma (extrathyroidal extension) or the lymphatic mesenchyma (extranodal growth). Although the former type of invasion is well-established and continues to form an integral element of tumor staging systems,[1,2] the latter has attracted little attention until recently. As a result, no consensus has emerged on the clinical implications of extranodal growth to date.

In 1989 appeared a first small series of 25 patients with papillary thyroid cancer (PTC) and extranodal growth describing comparable rates of regional recurrence, distant metastasis, cancer-specific death or recurrence-free survival relative to 63 controls without extranodal growth.[3] On a more powerful univariate analysis 23 years later, however, the 75 patients presenting with node-positive PTC and

* Corresponding author. Tel.: +49 345 557 2314; fax: +49 345 557 2551.
E-mail address: AndreasMachens@aol.com (A. Machens).

http://dx.doi.org/10.1016/j.ejso.2014.10.049
0748-7983/

extranodal growth had worse rates of 10-year recurrence-free survival (75 vs. 92%; $P = 0.009$) and 10-year disease-specific survival (97 vs. 100%; $P = 0.004$) than the 161 patients with node-positive PTC in the absence of extranodal growth.[4] On multivariate analysis, none of these factors remained significant. Similar findings have appeared for medullary thyroid cancer (MTC). In one series, the 12 patients with MTC and extranodal growth had worse 10-year (75 vs. 99%; $P < 0.0001$) and 20-year (56 vs. 97%; $P < 0.0001$) rates of disease-specific survival than the 106 patients with MTC without extranodal growth.[5] In another MTC study of 12 patients with and 20 patients without extranodal growth, extranodal growth was a significant predictor of overall survival (hazard ratio 3.1; 95% CI 1.1–8.5; $P = 0.03$) on univariate but not on multivariate analysis.[6]

Recently, Clain et al.[7] reported a significant correlation between extrathyroidal extension and extranodal growth in 193 patients with differentiated thyroid cancer: 41 (72%) of their 72 patients with extrathyroidal extension had extranodal growth, as opposed to only 12 (10%) of their 121 patients without extrathyroidal extension ($P < 0.001$). This striking finding prompted the authors to conclude that the biology of the primary thyroid tumor was conferred to the lymph node in that the presence of extrathyroidal extension resulted in a significantly higher incidence of extranodal growth. If confirmed, this observation may have important clinical ramifications for PTC, supporting the upstaging of patients with minimal extrathyroidal extension,[7] and conceivably also for malignancies other than follicular cell-derived thyroid cancer.

The present validation study of 702 patients with node-positive PTC and 548 consecutive patients with node-positive MTC was set up to clarify, separately for each tumor entity, the dependence or independence of extranodal growth from extrathyroidal extension by quantifying the individual contributions of various clinical-pathological risk factors to extranodal growth on multivariate analysis.

Patients and methods

Study population

Between November 1994 and May 2014, 702 of 1367 patients with PTC and 548 of 898 patients with MTC (144 patients with hereditary and 404 patients with sporadic disease) underwent initial neck surgery or reoperation at this institution for node-positive PTC or node-positive MTC. Patients with sporadic and hereditary MTC, faring the same after adjustment for extent of disease,[8] were evaluated as one group. Because extranodal growth (breach of a lymph node capsule) by implication required the presence of tumor deposits within at least one lymph node, the 665 patients with node-negative PTC and the 350 patients with node-negative MTC were not included in this investigation. For retrospective analysis of existing data sets from routine patient care, no institutional review board approval is required under German national law and applicable institutional regulations.

Total thyroidectomy and compartment-oriented surgery

All 1250 patients with node-positive PTC or node-positive MTC had total thyroidectomy, except for 5 PTC patients and 1 MTC patient, with systematic lymph node dissection of the central neck compartment using the compartment-oriented approach.[9] The central lymph node dissection (level VI on either side of the neck) also comprised level VII when one of these levels, or both, were clinically involved. The lateral neck compartments had been dissected systematically in 515 patients with PTC (73%) and 475 patients with MTC (87%) ipsilateral to, and in 193 patients with PTC (27%) and 413 patients with MTC (75%) also contralateral to the largest primary thyroid tumor. Systematic lymph node dissection of the mediastinal compartment, extending between the brachiocephalic vein and tracheal bifurcation, had been carried out in 40 (6%) patients with PTC and 130 (24%) patients with MTC by way of complete median sternotomy. All operations were conducted using optical magnification and bipolar coagulation, as described previously.[10] Informed consent was obtained before each operation that represented standard practice of care in accordance with the practice guidelines of the German Cancer Association.[11] Distant metastases per se were not an exclusion criterion because of the recognized longevity of patients with metastatic PTC and MTC.

Pathologic examination of surgical specimens

All specimens were subjected to histopathologic examination and embedded in paraffin. Conventional staining (hematoxylin and eosin) and thyroglobulin and calcitonin immunohistochemistry was performed as appropriate on every surgical specimen. PTC was diagnosed according to the World Health Organization's International Histological Classification of Tumors.[12,13] Poorly differentiated thyroid cancer, meeting the World Health Organization's International Histological Classification of Tumors criteria[13] and displaying PTC morphology, was classified as poorly differentiated PTC. The diagnosis of tall cell variant of PTC required that the height of the neoplastic cells be at least twice the width in an otherwise typical PTC.[14] Pathologic reports from outside institutions were reviewed as necessary. Primary tumor diameter was based on direct measurements on the surgical thyroid specimens. When multiple tumors were present, only the size of the largest thyroid cancer was taken. Extrathyroidal extension (breach of the thyroid capsule by the tumor) was defined as tumor spread by continuity beyond the thyroid capsule, whatever the extent of that invasion. All lymph node