ORIGINAL ARTICLE

Skip Metastases in Thyroid Cancer Leaping the Central Lymph Node Compartment

Andreas Machens, MD; Hans-Jürgen Holzhausen, MD; Henning Dralle, MD

Hypothesis: Discontinuous nodal metastasis, or skip metastasis, in thyroid cancer may display clinicopathologic features different from those seen in continuous nodal metastasis and thus may have a different prognosis.

Design: Retrospective analysis.

Setting: Tertiary referral center at a university hospital.

Patients: Two hundred fifteen consecutive patients who underwent systematic central lymph node dissection for papillary, follicular, or medullary thyroid cancer and who on histopathologic analysis exhibited nodal metastases in at least 1 lateral or mediastinal lymph node compartment.

Main Outcome Measures: Various clinicopathologic variables that were stratified for tumor entity and type of nodal metastasis (discontinuous vs continuous).

Results: Skip metastases (negative central and positive lateral or mediastinal compartments) were found in 13 (19.7%) of 66 papillary, 0 of 8 follicular, and 30 (21.3%) of 141 medullary thyroid cancers. After adjustment for multiple testing, skip metastasis was only associated with significantly fewer positive lymph nodes: 3.7 vs 12.9 nodes ($r=-0.43$, $P<.001$) in papillary thyroid cancer and 6.0 vs 17.1 nodes ($r=-0.40$, $P<.001$) in medullary thyroid cancer. No other significant correlation was identified with any other clinicopathologic variable.

Conclusions: Skip metastasis is an epiphenomenon of low-intensity nodal metastasis in thyroid cancer and entails a moderate risk of local recurrence. Consequently, clearing the central lymph node compartment should be considered when lateral or mediastinal lymph node compartments are involved.

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From the Departments of General, Visceral, and Vascular Surgery (Drs Machens and Dralle) and Pathology (Dr Holzhausen), Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany.

NODAL METASTASIS IS A common mechanism of extrathyroidal tumor cell dissemination in thyroid cancer.[1-5] This phenomenon is more prevalent in papillary and medullary thyroid cancer than in follicular thyroid cancer.[5] Recent clinicopathologic investigations have revealed that dissemination of tumor cells through the lymphatic system evolves in a stepwise sequential fashion: Spreading from the thyroid gland, the central and lateral lymph node compartments on the side of the thyroid tumor represent the first echelons of lymphatic drainage. The opposite lateral and the mediastinal lymph node compartments then follow suit.[5]

Despite the recognized sequence of lymphatic dissemination, discontinuous lymphatic spread, or skip metastasis, is not uncommon in node-positive papillary thyroid cancer.[6-8] The significance of this finding is unknown. Depending on the lymph node levels under comparison, the frequency of skip metastasis (of which the pattern of spread is unpredictable[7]) varies between 11.1% and 37.5% in node-positive papillary thyroid cancer.[6,7] As of this writing, no data on skip metastases have been published for follicular or medullary thyroid cancer.

Notwithstanding these recent advances in our understanding of lymphatic spread, the clinical significance of discontinuous, as opposed to continuous, lymphatic dissemination in thyroid cancer remains to be elucidated. The present institutional cohort study was set up to clarify the significance of skip metastases in thyroid cancer.

METHODS

PATIENT SELECTION

Between November 1, 1994, and November 30, 2002, 215 of 772 consecutive patients who were operated on at this institution for papillary (66 of 320 patients), follicular (8 of 144 patients),

Pathological and Demographic Variables in Patients With Thyroid Cancer Grouped by Presence or Absence of Skip Metastasis*

Variable	Papillary Thyroid Cancer			Medullary Thyroid Cancer		
	Skip Metastasis			Skip Metastasis		
	Present (n = 13)	Absent (n = 53)	*P* Value	Present (n = 30)	Absent (n = 111)	*P* Value
T classification						
1	23	9		20	11	
2	31	21	.22	63	49	.10
3	8	6		0	4	
4	38	64		17	36	
Tumor diameter, mean, mm (95% CI)	30 (13-46)	26 (21-32)	.86	25 (18-33)	24 (21-28)	.79
Positive lymph nodes, mean (95% CI)	3.7 (2.4-5.0)	12.9 (10.1-15.7)	<.001†	6.0 (3.4-8.6)	17.1 (13.4-20.7)	<.001†
Distant metastasis‡	0	26	.06	13	35	.03
Age at onset, mean, y (95% CI)	43 (32-54)	35 (29-41)	.16	47 (41-52)	45 (41-48)	.71
Male sex	38	38	>.99	40	46	.68
Reoperation	54	70	.33	80	63	.13
Prior lymph node dissection	46	38	.75	40	39	>.99

Abbreviation: CI, confidence interval.
*Data are given as percentage of patients unless otherwise indicated.
†Significant after Bonferroni adjustment for multiple testing.
‡As ascertained at operation.

or medullary (141 of 308 patients) thyroid cancer had nodal metastases in at least 1 lateral or mediastinal lymph node compartment. These 215 patients formed the study population. There were 73 primary (34.0%) and 142 reoperative (66.0%) patients. Reoperations were all carried out with therapeutic intent when nodal macrometastases in the neck were suspected clinically or on ultrasonography or had been confirmed through fine-needle aspiration cytology or tissue biopsy, or when calcitonin levels failed to normalize after surgery for medullary thyroid cancer. All 215 patients underwent systematic dissection of the central lymph node compartment, which extends vertically from the hyoid bone to the thoracic inlet and horizontally between the carotid sheaths.[5] The lateral lymph node compartments were dissected in 95.3% (ipsilateral) and 73.5% (contralateral) and the mediastinal lymph node compartment was dissected in 37.2%. Before surgery, informed consent was obtained for each of the procedures. All specimens were subjected to pathological examination. A diagnosis of skip metastasis was only made on histopathologic confirmation of nodal metastases in the lateral or mediastinal compartment, with simultaneous freedom of nodal metastases in the central compartment on primary and reoperative surgery.

HISTOPATHOLOGIC EXAMINATION AND TUMOR STAGING

After gross evaluation by the pathologist, the entire thyroid gland was divided vertically to separate the left and right lobes. The thyroid halves were then sectioned horizontally from the superior to the inferior pole, as described previously.[9] After fixation in formalin, the whole thyroid gland was embedded in paraffin. Soft tissue and lymph nodes were processed separately. Conventional staining (hematoxylin-eosin) and, where appropriate, thyroglobulin or calcitonin immunohistochemistry were performed on every surgical specimen, using the standard avidin-biotin complex peroxidase approach. The diagnosis of papillary, follicular, or medullary thyroid carcinoma was based on the World Health Organization histological classification of tumors.[10] Staging was performed according to the American Joint Committee on Cancer[11] and International Union Against Cancer tumor-node-metastasis[12] classifications. While a diagnosis of nodal metastasis always required histopathologic confirmation, this need was waived for distant metastasis when there was unequivocal evidence on ultrasonography (liver), computed tomography, magnetic resonance imaging, positron emission tomography, scintiscan, or a combination thereof.

STATISTICAL ANALYSIS

Categorical and continuous data were tested on univariate analysis using the 2-tailed Fisher exact test and 2-tailed exact Mann-Whitney (Wilcoxon) rank sum test, respectively. Multiple testing was adjusted by using the Bonferroni method. Spearman rank correlation coefficient (ρ) was calculated to assess correlations between categorical and metric variables. The level of significance was set at $P = .05$.

RESULTS

Skip metastases were encountered in 13 (19.7%) of 66 papillary, 0 of 8 follicular, and 30 (21.3%) of 141 medullary thyroid cancers. Therefore, subsequent analyses were limited to papillary and medullary thyroid cancer.

The **Table** stratifies various pathological and demographic variables for skip metastasis and tumor entity. After adjustment for multiple testing, the only significant difference between discontinuous (skip metastases) and continuous nodal metastases concerned the number of positive lymph nodes in papillary and medullary thyroid cancer. Skip metastasis consistently was associated with significantly fewer positive lymph nodes: 3.7 vs 12.9 nodes ($r = -0.43$, $P < .001$) in papillary thyroid cancer and 6.0 vs 17.1 nodes ($r = -0.40$, $P < .001$) in medullary thyroid cancer. There was no significant correlation with any demographic variable. Neither reoperation nor previous lymph node dissection produced differential rates of skip metastases in either thyroid cancer. This finding indicates that skip metastases are genuine phenomena in thyroid cancer and not simply artifacts caused by differential dissection of the central compartment and differential histopathologic analysis (de-

tection bias) owing to intensive scarring after primary operation.

COMMENT

To our knowledge, this cohort study provides the most comprehensive analysis of skip metastasis in thyroid cancer to date. There was a significant inverse correlation between the presence of skip metastasis and the total number of involved lymph nodes. The frequency of skip metastasis was 19.7% (n=66) in papillary thyroid cancer and 21.3% (n=141) in medullary thyroid cancer. These data agree well with the rates of 11.1% (n=36) to 37.5% (n=51) published in the literature for papillary thyroid cancer.[6,7] Similar rates of 13% and 15.8% have been reported for skip metastasis in T3-T4 cancer of the alveolobuccal complex[13] and squamous carcinoma of the oral tongue,[14] respectively.

THE NATURE OF SKIP METASTASIS

The phenomenon of skip metastases has been attributed to limited lymph node sampling, leading to false-negative histopathologic staging.[15] This explanation does not account for skip metastasis in thyroid cancer, as evidenced in this series by similar rates of reoperations and previous lymph node dissections in discontinuous and continuous nodal metastasis. Clearing entire lymph node compartments, the compartment-oriented lymph node dissection enables an unbiased assessment of nodal metastasis in thyroid cancer.[5] With the introduction of intraoperative lymphatic mapping using technetium-labeled sulfur or tin colloid particles, the rates of axillary skip metastases in breast cancer have plummeted from the range of 10% to 15.5%[16-18] to 0% to 0.2%.[19,20] This dramatic decline with the advent of more sophisticated detection technology supports the concept of stepwise lymphatic dissemination through successive echelons of lymph nodes. The use of routine thyroglobulin and calcitonin immunohistochemistry on every surgical specimen and pathological slide, respectively, might further lower the rates of skip metastases owing to improved capture of occult nodal metastases. As in this series of patients with papillary thyroid cancer, skip metastasis is also more frequent in breast cancer when fewer than 4 nodes are positive.[16]

CLINICAL IMPLICATIONS

The present clinicopathologic study demonstrates that skip metastasis with its erratic mode of lymphatic spread is an epiphenomenon of low-intensity nodal dissemination in thyroid cancer. Because of the recognized association between nodal metastasis and local recurrence,[5] skip metastasis in thyroid cancer is likely to entail a moderate risk of local recurrence, at least in the seemingly skipped central and the involved lateral or mediastinal lymph node compartments. Leaving positive lymph nodes in the tracheoesophageal groove unattended for a prolonged period may expose the patient to the risk of tracheoesophageal invasion.[21] Therefore, systematic lymph node dissection should follow the recognized sequence of lymph node drainage.[1-5] When lateral or mediastinal lymph node compartments are involved on histopathologic examination, clearing the central lymph node compartment should be considered, rather than waiting for nodal recurrence to emerge. Balancing patients' moderate risk of local recurrence against the risk of surgical morbidity, these patients should be referred for lymph node dissection to a specialist center where the requisite surgical skills and expertise are available.

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Corresponding author: Andreas Machens, MD, Department of General, Visceral, and Vascular Surgery, Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Straße 40, D-06097 Halle (Saale), Germany (e-mail: gensurg@medizin.uni-halle.de).

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