

Incidence of Metastatic Well-Differentiated Thyroid Cancer in Cervical Lymph Nodes

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Objective: To determine the incidence of clinically positive lateral cervical nodes at presentation and after initial treatment in patients with well-differentiated thyroid cancer.

Design: Retrospective chart review.

Setting: University-affiliated teaching hospitals.

Patients: A total of 508 patients who underwent a thyroidectomy as part of their initial treatment for well-differentiated thyroid carcinoma between January 1978 and December 1999. Neck dissections were performed only for clinically palpable cervical nodes.

Main Outcome Measures: Recurrence in the neck and survival.

Results: Forty-four patients (9%) had palpable lateral cervical lymph nodes at the time of surgery. All 31 patients younger than 45 years presenting with palpable posi-

tive nodes are alive and free of disease; 4 of 13 patients 45 years or older have died of thyroid cancer. Only 16 (3%) of 464 patients who did not undergo initial neck dissection had recurrence in lateral cervical nodes. Recurrence is more likely when the initial tumor is larger than 4 cm. In 216 patients younger than 45 years, there were 5 (2%) recurrences in lateral cervical nodes; these patients remain alive and free of disease. In 248 patients 45 years or older, there were 11 (4%) with recurrent disease in the lateral neck; 4 of these patients have died of thyroid cancer.

Conclusions: An aggressive approach to detecting and treating occult lateral cervical nodes by techniques such as jugular node sampling, sentinel node biopsy, or image-guided needle biopsy is not necessary in most patients. Attempts to detect and remove occult lateral cervical lymph node metastases might be considered in older patients with large primary tumors.

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WELL-DIFFERENTIATED thyroid cancer has an excellent prognosis. Papillary carcinoma has a 10-year survival rate of over 90%, while the 10-year survival rate for follicular carcinoma is greater than 85%.^{1,2} Clinically apparent cervical lymphadenopathy has been found at initial presentation in 23% to 56% of cases of papillary carcinoma and 5% to 13% of cases of follicular carcinoma.³⁻⁵

Various techniques have been used to detect the presence of occult metastatic disease in lateral cervical lymph nodes to determine the need for additional treatment. These include elective neck dissection⁶; random sampling of jugular nodes⁷; sentinel lymph node biopsy^{8,9}; and radiographic imaging, including whole-body radioiodine (RAI) scans, computed tomography,¹⁰ magnetic resonance imaging,¹¹ and ultrasonography.¹² Using these tech-

niques, the incidence of occult metastatic disease in the lateral cervical lymph nodes ranges from 25% to 81%.^{7,13-15}

The significance of these occult, microscopic, metastatic nodes with respect to regional recurrence and overall survival remains controversial. In this study, we examine the incidence of clinically positive lateral cervical nodes at presentation and after initial treatment in patients with well-differentiated thyroid cancer.

METHODS

This study is a retrospective chart review of patients treated within a single surgical practice. Between January 1978 and December 1999, 508 patients underwent a thyroidectomy as part of their initial treatment for well-differentiated thyroid carcinoma. Imaging studies to detect clinically occult lateral cervical lymph nodes at the time of presentation were generally not performed. Surgery was performed at 1 of 4 university-affiliated teaching

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hospitals. Patients initially treated elsewhere were excluded from the study.

Follow-up information was obtained from physician visits in 278 (55%) patients, telephone calls to the patient in 136 (27%) patients, and telephone calls to the patient's family in 83 (16%) patients. In 11 patients, follow-up was obtained from hospital cancer registries or from the Social Security Administration. Follow-up ranged from 2 to 280 (median, 68) months.

The determination of statistical significance was calculated using the Fisher exact test.

RESULTS

There were 390 (77%) women with a median age of 44 years and 118 (23%) men with a median age of 49 years. A total of 205 (53%) women and 42 (37%) men were younger than 45 years. The histologic type of the thyroid cancers in these patients is shown in **Table 1**.

A total of 389 (77%) patients underwent a total thyroidectomy, including 15 of the 16 patients who later developed recurrent disease. The surgical procedures performed for tumors of different size and histologic type are shown in **Table 2**. A total of 231 patients (45%) received postoperative RAI treatment. Of 202 patients treated before 1995, only 59 patients (29%) received RAI. From 1995 onward, 172 (56%) of the 306 patients treated received RAI. Fourteen of 16 patients who developed recurrent disease had received RAI.

Neck dissections were performed only for clinically palpable cervical nodes. Forty-four patients (9%) had palpable lateral cervical lymph nodes at the time of initial presentation and underwent a thyroidectomy with neck dissection (**Table 3**). In 42 patients, a modified radical neck dissection was performed with preservation of the contents of the submandibular triangle, cranial nerve XI, the

sternocleidomastoid muscle, and the internal jugular vein. The internal jugular vein was sacrificed in one patient, and both the internal jugular vein and sternocleidomastoid were sacrificed in another. Clinically positive nodes are more common in patients younger than 45 years (13%) than in older patients (5%). The incidence of positive nodes is not related to the size of the primary cancer. No patient with follicular cancer presented with positive nodes. All 31 patients presenting with palpable positive nodes who were younger than 45 years at the time of initial surgery remain alive and free of disease. Of the 13 patients 45 years and older, there have been 4 deaths (31%) from recurrent thyroid cancer, none of which were due to uncontrolled disease in the lateral neck. All 4 patients had papillary carcinoma with extensive soft tissue invasion by cancer beyond the thyroid gland.

Of the 464 patients who did not undergo an initial neck dissection, only 16 patients (3%) have developed palpable disease in the lateral cervical lymph nodes (**Table 4**). Twelve of these patients subsequently underwent modified radical neck dissections. The likelihood of recurrence is not related to the age of the patient, but is strongly correlated with the size of the tumor. Nine of these 16 patients had primary tumors larger than 4 cm. Of these 16 patients, 12 are alive and free of disease, including all 5 patients younger than 45 years. Four of 11 patients 45 years and older who had recurrence in the lateral cervical nodes have died of thyroid cancer; all had extensive extrathyroidal extension of disease.

COMMENT

In patients with well-differentiated thyroid cancer and clinically palpable lymph nodes at the time of initial presentation, most authors recommend a thyroidectomy with a neck dissection.^{16,17} However, the need to detect and treat occult, microscopically positive lateral cervical lymph nodes remains controversial, as it is unclear if the initial presence of such positive nodes affects recurrence rates. In a study of 1355 patients by Mazzaferri and Jhiang,¹⁸ cervical or mediastinal lymph node metastases were present in 567 patients (42%) at initial presentation, and 169 patients (12%) had a recurrence of disease in the neck. A multivariate analysis of these patients found that the presence of cervical node metastases at initial presentation was a significant prognostic factor for recurrence of disease.

Table 1. Histologic Data

	No. (%) of Patients		
	Aged <45 y	Aged ≥45 y	Total
Papillary carcinoma	230 (45)	217 (43)	447 (88)
Follicular carcinoma	12 (2)	20 (4)	32 (6)
Hürthle cell carcinoma	5 (1)	24 (5)	29 (6)
Total	247 (49)	261 (51)	508

Table 2. Number of Surgical Procedures Performed

	Patients Aged <45 y		Patients Aged ≥45 y		Total
	Lobectomy	Total Thyroidectomy	Lobectomy	Total Thyroidectomy	
Tumor size, cm					
<1	11	26	21	33	91
1-4	26	165	16	152	359
>4	3	16	5	34	58
Histologic type					
Papillary carcinoma	34	196	36	181	447
Follicular carcinoma	5	7	2	18	32
Hürthle cell carcinoma	1	4	4	20	29
Total	40	207	42	219	508

Table 3. Incidence of Positive Nodes at the Time of Initial Treatment

	No. (%) of Patients		
	Aged <45 y	Aged ≥45 y	Total
Sex			
Male	8/42 (19)	3/76 (4)	11/118 (9)
Female	23/205 (11)	10/185 (5)	33/390 (8)
Tumor size, cm			
<1	6/37 (16)	2/53 (4)	8/90 (9)
1-4	22/191 (12)	9/169 (5)	31/360 (9)
>4	3/19 (16)	2/39 (5)	5/58 (9)
Histologic type			
Papillary carcinoma	30/230 (13)	12/217 (6)	42/447 (9)
Follicular carcinoma	0/12	0/20	0/32
Hürthle cell carcinoma	1/5 (20)	1/24 (4)	2/29 (7)
Total	31/247* (13)	13/261* (5)	44/508 (9)

**P* = .005 (Fisher exact test).

Nodal metastasis was also found to be a risk factor for recurrence in a study by Hughes et al,¹⁹ in which 100 patients with and without positive nodes and with otherwise identical prognostic factors were matched and compared. The risk of recurrence in the older patients in the intermediate-risk group as defined by Shaha et al,²⁰ who presented with positive nodes, was 31%, compared with 8% in the group without nodal metastases. In addition, the intermediate-risk patients with positive nodes had a disease-specific mortality of 19%, compared with 0% in their matched counterparts with clinically negative nodes. The presence of positive nodes at initial presentation did not affect recurrence or survival in the low-risk group, or survival in the high-risk group. According to McHenry et al,⁷ of 70 patients with nodal disease, either clinically palpable or detected by routine cervical lymph node sampling, 13 patients (19%) had recurrence compared with 3 (2%) of 157 patients without nodal disease. A significant association between disease in the neck at presentation and the later recurrence of disease was also found by Beasley et al.²¹ However, in a study of 108 patients with positive cervical lymph nodes and 152 patients with negative nodes, Coburn and Wanebo²² found no statistical significance in the recurrence rates, which were 30% and 18%, respectively.

It has been proposed that more aggressive attempts should be made to detect the presence of occult positive nodes in patients with well-differentiated thyroid cancer. The use of sentinel lymph node biopsy in papillary cancer was studied by Fukui et al⁹ in 22 patients who underwent a thyroidectomy and modified radical neck dissection. Sentinel lymph nodes were identified in 21 patients, with concordance between the status of the sentinel node and the remaining lymph nodes in 19 of 21 patients. In the 7 patients in whom metastatic disease was found, 5 patients had positive sentinel nodes, while 2 of the remaining 14 patients with negative sentinel nodes initially were later found to have metastatic lymph node disease. In a series of 227 patients who underwent random lymph node sampling, McHenry et al⁷ found that only 6% of patients had clinically palpable nodal dis-

Table 4. Incidence of Recurrent Thyroid Cancer in Lateral Cervical Lymph Nodes After Initial Treatment

	No. (%) of Patients		
	Aged <45 y	Aged ≥45 y	Total
Sex			
Male	1/34 (3)	5/73 (7)	6/107 (6)
Female	4/182 (2)	6/175 (3)	10/357 (3)
Tumor size, cm			
<1	0/31	1/52 (1)	1/83* (1)
1-4	2/169 (1)	4/159 (3)	6/328* (2)
>4	3/16 (19)	6/37 (16)	9/53* (17)
Histologic type			
Papillary carcinoma	4/200 (2)	10/205 (5)	14/405 (3)
Follicular carcinoma	0/12	0/20	0/32
Hürthle cell carcinoma	1/4 (25)	1/23 (4)	2/27 (7)
Total	5/216 (2)	11/248 (4)	16/464 (3)

**P* < .001 (Fisher exact test).

ease, while an additional 25% had occult microscopic metastases. Scheumann et al⁶ compared 195 patients who underwent either selective removal of enlarged lymph nodes (“berry picking”) or modified neck dissection. In the patients who underwent neck dissection, there was a statistically significant reduction in the rate of recurrence and an improvement in overall survival.

However, in a study of 278 patients by Attie et al,¹⁴ in which 115 of 222 patients without clinical evidence of nodal disease underwent an elective neck dissection, 79 patients (69%) were found to have microscopic evidence of disease. None of these patients had a recurrence of disease in the neck or death from the primary disease.

In our study, we found a lower incidence of disease in cervical lymph nodes at initial presentation and of later recurrence in these nodes than in previously published studies. There are several factors that could explain this difference. There could be a selection bias in our patient population. Patients presenting with more advanced cancers might be referred to a large urban center 20 miles (32 km) away rather than being treated in our community.

It is likely that patients treated during the 21 years included in this study are presenting with less advanced tumors than those reported in series including patients treated as many as 50 years ago. Of patients in this series, 88% had tumors that were 4 cm or smaller. Although the incidence of clinically positive nodes at the time of initial treatment is not related to the size of the primary tumor, the likelihood of recurrence in the lateral neck correlates strongly with the size of the primary tumor.

Earlier series, reporting cervical lymph node metastases in patients with follicular cancer, may have misclassified some cancers that would now be considered follicular variants of papillary cancer. In our series, of the 16 recurrences in cervical nodes, 14 patients (88%) had papillary carcinoma and 2 had Hürthle cell cancer. There were no lymph node metastases in patients with follicular carcinoma.

The median duration of follow-up in this study is 68 months. It is possible that with longer follow-up, additional patients with recurrence in cervical nodes will be

identified. It is also possible that some patients who were lost to follow-up did not return because they developed recurrent cancer. The number of such patients, however, is expected to be small. According to McConahey et al,¹³ the incidence of recurrent disease in the cervical nodes was greatest in the first 3 years after initial treatment. The incidence was 16.3 per 1000 person-years in this time period compared with 2.5 per 1000 person-years subsequently. Our follow-up should therefore be of adequate duration to detect most recurrences. Finally, it is possible that the low recurrence rate in cervical nodes is related to our treatment approach with many patients receiving RAI.

In patients 45 years old or older with tumors larger than 4 cm, recurrence in the lateral neck is more common and such recurrence more likely to be associated with a fatal outcome than in the remainder of the patients studied. Although we have no evidence to suggest that a more aggressive approach to these patients will improve survival, attempts to detect and remove occult lateral cervical lymph node metastases might be considered in this small group of patients.

CONCLUSIONS

The incidence of clinically apparent cervical lymph node metastases at presentation in patients with well-differentiated thyroid cancer is low. Although many patients have occult, microscopic lymph node metastases, few will develop clinically significant disease in the lateral neck. The low rate of recurrence of disease in lateral cervical lymph nodes demonstrated in our study suggests that an aggressive approach to detect and treat such metastatic microscopic disease is not necessary in most patients. Because of the higher risk of recurrence in the neck and the poor prognosis associated with such recurrence in patients 45 years and older with tumors larger than 4 cm, attempts to detect and remove occult lateral cervical lymph node metastases might be considered in this group.

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