

Indications for Bilateral Modified Radical Neck Dissection in Patients With Papillary Carcinoma of the Thyroid

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Hypotheses: After subtotal thyroidectomy with modified radical neck dissection of the affected side, nodal recurrence at the contralateral cervical side indicates a poor prognosis for patients with papillary thyroid cancer. Bilateral modified radical neck dissection is beneficial for patients at high risk for contralateral nodal recurrence.

Design and Setting: Retrospective study of patients with papillary cancer who were treated surgically from January 1, 1970, through December 31, 1995, at the Noguchi Thyroid Clinic and Hospital Foundation, Beppu, Japan.

Patients: Patients (N=1776) had primary tumors greater than 10 mm in maximum diameter and underwent thyroidectomy and ipsilateral modified radical neck dissection with curative intent.

Results: Thirty-two patients (1.8%) developed contralateral lymph node metastases during the mean follow-up period of 12.1 years. The risk factors for contralateral nodal recurrence were male sex, large primary tumor, tumor extension over the isthmus, extracapsular adhesion or invasion to surrounding tissues, and the presence of gross nodal metastasis at initial surgery. These patients had a greater number of distant metastases (31.1% vs 0.7%; $P<.001$) and a lower 10-year survival rate (83.7% vs 99.3%; $P<.001$) than patients without nodal recurrence.

Conclusion: Bilateral modified radical neck dissection should be considered for patients with papillary carcinoma who show risk factors for contralateral nodal recurrence, as it could prevent a second operation and may improve their outcome.

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PAPILLARY THYROID cancer is generally associated with low morbidity and mortality rates; the disease-specific survival rate at 10 years is approximately 90%.¹ Despite the overall excellent prognosis, some patients experience recurrent thyroid cancer and die of the disease. The likelihood of disease recurrence varies with several prognostic factors, including age at diagnosis, size of the primary tumor, extracapsular invasion, and the presence of distant metastasis.²⁻⁵ However, the effect of lymph node metastasis on survival is controversial.^{1,6-10} In the early 1970s, our group¹¹ noted a high incidence of nodal metastases in patients with papillary thyroid cancer. Noguchi et al^{1,12,13} reported lymph node metastasis to be a significant prognostic risk factor and that modified radical neck dissection (MRND) improved the survival of patients with papillary thyroid cancer.

Our standard surgical therapy has been subtotal thyroidectomy with MRND of the affected side; however, some patients have shown recurrence in

See Invited Critique at end of article

the lymph nodes on the contralateral cervical side. For such patients, bilateral MRND might be considered at the initial surgery, but there have been no reports regarding the appropriate indications for bilateral MRND in patients with papillary thyroid cancer. It is also unclear whether contralateral nodal recurrence affects prognosis.

To clarify the risk factors for contralateral nodal recurrence, we examined retrospectively patients with papillary thyroid cancer who had contralateral cervical lymph node recurrence after curative surgery. We also exam-

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PATIENTS AND METHODS

From January 1, 1970, through December 31, 1995, 4466 patients with papillary thyroid cancer were treated surgically at the Noguchi Thyroid Clinic and Hospital Foundation, Beppu, Japan. Of these 4466 patients, 2069 who had primary tumors greater than 10 mm in maximum diameter underwent surgery consisting at least of thyroid lobectomy and MRND of the affected side with curative intent. To exclude any effect of local recurrence from remnant tumor or of nodal recurrence on the dissected side toward contralateral nodal recurrence, the following patients were excluded from this study: 96 with local recurrence, 6 with nodal recurrence discovered within 6 months after the initial surgery, 82 with nodal recurrence on the ipsilateral side, 91 who underwent bilateral MRND, and 18 whose medical records were insufficient for analysis. Thus, 1776 patients comprised the present study and were divided into 2 groups: 1744 without nodal recurrence (group 1) and 32 with contralateral lymph node recurrence (group 2). We compared the clinical and pathological characteristics of these 2 groups. Staging of thyroid cancer was done according to TNM classification of the Union International Contra la Cancrum, but with a slight modification.¹⁴ Because TNM classification is based on preoperative physical and imaging findings, staging is affected by various imaging methods. We could not use this system directly to classify all patients treated during the past 25 years. Tumor size was measured based on histopathological specimens. Tumor extension beyond the thyroid capsule was considered positive when adhesion or invasion was found during surgery. Regional lymph node metastasis was considered positive when gross nodal metastasis was evident during surgery. Although the staging system used in this study was not the same as the original TNM staging, we believed that it was still possible to compare the survival rates of the 2 groups.

Information about patients still living was obtained by periodic correspondence with the patients, their family members, or referring physicians, or from municipal records. For deceased patients, the cause of death was confirmed by death certificate or by contact with family members or hospital personnel. The mean follow-up interval for patients last known to be alive was 12.1 years. Twenty-two patients died of thyroid cancer and 129 died of unrelated causes.

Cause-specific survival rates were calculated according to the Kaplan-Meier method. Risk factor analysis was performed using the Cox proportional hazards regression model with commercially available statistical software (JMP, version 3.1R; SAS Institute Inc, Cary, NC). Differences were considered significant at $P < .05$. Data are given as mean \pm SD, unless otherwise indicated.

ined the influence of contralateral nodal recurrence on prognosis and report herein the indications for bilateral neck dissection.

Table 1. Procedures During the Initial Surgery*

Surgical Procedure	Group 1	Group 2	Total
Total thyroidectomy	36 (2.1)	1 (3.1)	37 (2.1)
Subtotal thyroidectomy	957 (54.9)	22 (68.8)	979 (55.1)
Lobectomy, with or without isthmectomy	751 (43.1)	9 (28.1)	760 (42.8)
Total	1744	32	1776

*Data are given as number (percentage) of patients. There were no significant differences in surgical procedures between groups ($P = .09$).

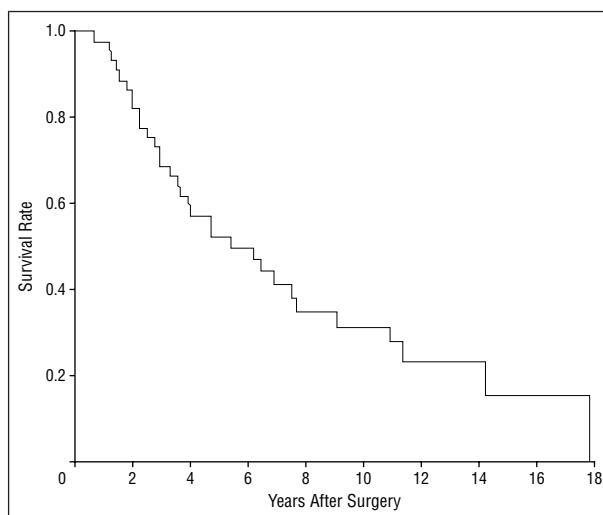


Figure 1. Disease-free survival rates in group 2 after initial surgery.

RESULTS

Total thyroidectomy was performed in 37 patients (2.1%), subtotal thyroidectomy in 979 (55.1%), and lobectomy with or without isthmectomy in 760 (42.8%). In all cases, MRND was performed on the ipsilateral side of the primary tumor. There were no significant differences in surgical procedures between groups 1 and 2 (**Table 1**).

Patients in group 2 had contralateral lymph node recurrence 5.0 ± 4.0 years (range, 0.7-17.8 years, **Figure 1**) after the initial surgery. The mean number of metastatic nodes was 3.6 ± 3.1 (range, 1-12). All nodal recurrences were found by palpation, except for 2 recurrences detected by ultrasonographic examination. All but 3 patients with lymph node recurrence were treated successfully with a second surgery. Of these 3 patients, 2 had tumors that were inoperable because of massive invasion to surrounding organs and 1 had multiple lung metastases.

Table 2 shows the number and percentage of patients in each age group according to the group. The youngest patients (<20 years) tended to have more contralateral nodal recurrences, but the difference was not significant.

Table 3 shows univariate analysis of risk factors for contralateral nodal recurrence. There were more male patients in group 2 than in group 1; however, age at the time of the initial surgery was similar between the

2 groups. Maximum diameter of the primary tumor, extrathyroidal adhesion or invasion, and tumor extension to the isthmus were all significant risk factors for nodal recurrence in group 2. Patients in group 2 were also found to have more occurrences of gross nodal metastasis and a greater number of histopathologically proved lymph node metastases.

Survival rates and the number of patients in each group according to cancer stage are shown in **Table 4**. No patients were classified with T1 or M1 because of the patient selection for this study. The survival rate in group 2 was significantly lower than that in group 1, irrespective of cancer stage (**Table 4**, **Figure 2** and **Figure 3**). Although age is one of the important risk factors affecting prognosis, there were no significant differences among age groups in group 1 (data not shown). In group 2, older patients had a worse survival rate than did younger patients (**Figure 4**).

Patients in group 2 developed distant metastasis more often than those in group 1, resulting in a higher cancer death rate (**Table 5**). In group 1, all 11 patients with distant metastases had lung metastases and 3 also had bone metastases. In group 2, all distant metastases were located in the lungs (10 patients). The length of time from initial treatment to diagnosis of distant metastasis was significantly longer in group 2 than in group 1 (9.1 vs 6.2 years, $P=.04$). Thirteen patients in group 1 died of cancer; 8 of the 13 died of distant metastasis. Nine patients in group 2 died of cancer; 6 of the 9 died of distant metastasis. Two

group 2 patients died of anaplastic changes in the node with recurrence. The other 2 patients in group 2 had repeated recurrences and eventually died of non-resectable neck masses.

COMMENT

This is, to our knowledge, the first report clarifying risk factors in patients who develop contralateral cervical lymph node metastases after curative surgery and demonstrating a poor prognosis for these patients based on analysis of a large number of patients with papillary thyroid cancer.

We determined by univariate analysis that the significant risk factors for recurrence in the contralateral cervical lymph node are male sex, large primary tumor, tumor extension over the isthmus, extracapsular adhesion or invasion to surrounding tissues, and the presence of gross and many lymph node metastases at initial surgery. Generally, men with papillary carcinoma have a poorer prognosis than women.^{2,13,15-17} That men tend to have nodal recurrence may be a reason for their poorer prognosis.

Large tumor is also a risk for nodal recurrence and affects prognosis in patients with papillary carcinoma.^{3,6,7,17,18} Although a tumor diameter of 20 mm is not large, primary tumors more than 20 mm showed a high risk ratio in our study. The location of the primary tumor is also a significant risk factor for nodal recurrence. Tumors arising in the isthmus frequently cause bilateral cervical metastases.¹⁹ We found that tumor extension into the isthmus increased nodal recurrence on the contralateral side. Carcangiu et al²⁰ showed that multicentricity is associated with an increased incidence of nodal and pulmonary metastases. In the present study, intraglandular dissemination was not a risk factor for nodal recurrence. Size of the cancer may be important for nodal metastasis to the lateral cervical area. Carcinomas less than 10 mm often show nodal metastases to the paratracheal area but rarely to the jugular nodes.^{21,22} The intraglandular dissemination may typically be too small to spread to the contralateral side.

Extrathyroidal invasion increases nodal recurrence after surgery and affects the survival of patients with

Table 2. Age Breakdowns by Group*

Age, y	No. of Patients		% of Group 2 Patients in Each Age Group
	Group 1	Group 2	
<20	34	2	5.6
20-39	522	9	1.7
40-59	856	11	1.3
≥60	332	10	2.9

*There was no significant difference among age groups in occurrence of contralateral nodal recurrence ($P = .10$).

Table 3. Results of Univariate Analysis Between Groups

	Group 1	Group 2	P*	Risk Ratio	P†
Sex, M/F (% M)	144:1600 (8.3)	8:24 (25.0)	.002	3.90	.003
Age at first diagnosis, mean ± SD, y	46.5 ± 14.1	47.1 ± 17.2	.81	1.01	.46
Primary tumor					
Maximum diameter, mean ± SD, mm	25.8 ± 11.8	41.4 ± 16.1	<.001	1.06	<.001
>20 mm, No. (%)	1023 (58.7)	28 (87.5)	.003	4.72	.001
Extended over the isthmus, No. (%)	397 (22.8)	13 (40.6)	.02	2.39	.02
Adhesion or invasion to surroundings, No. (%)	1402 (80.4)	31 (96.9)	.047	7.53	.005
Intraglandular dissemination, No. (%)	326 (18.7)	6 (18.8)	.48	1.04	.94
Lymph node metastasis at initial surgery					
Gross nodal metastasis, No. (%)	753 (43.2)	24 (75.0)	.004	4.14	<.001
No. of metastatic lymph nodes, mean ± SD	6.3 ± 5.9	11.2 ± 7.9	<.001	1.09	<.001
>10 Metastatic lymph nodes, No. (%)	425 (24.4)	15 (46.9)	.005	2.60	.009

*For univariate analysis.

†For risk ratio.

Table 4. Cancer Stage and Survival Rates*

Cancer Stage	Group 1	Group 2
I	99.8 (769)	88.9 (13)†
II	100 (79)	0
III	98.9 (896)	80.4 (19)†
Total	99.3 (1744)	83.7 (32)†

*Data are given as survival rate after 10 years (No. of patients).
 †There was a significant difference in survival rate between groups (P<.001).

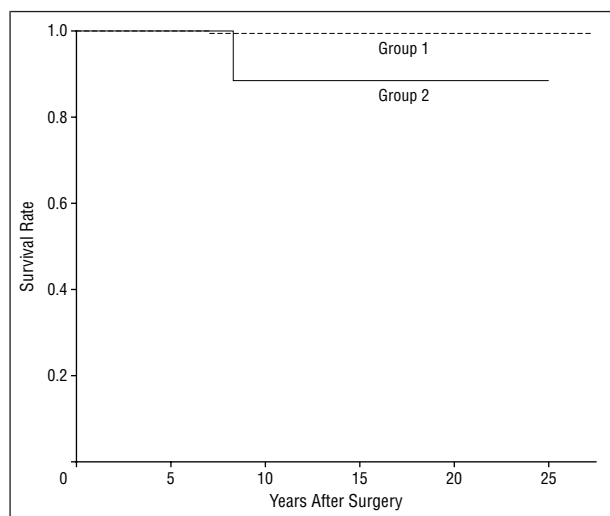


Figure 2. Disease-specific survival rate for stage I in each group. Group 2 patients showed a poorer prognosis than did group 1 patients (P<.001, log-rank and Wilcoxon rank sum tests).

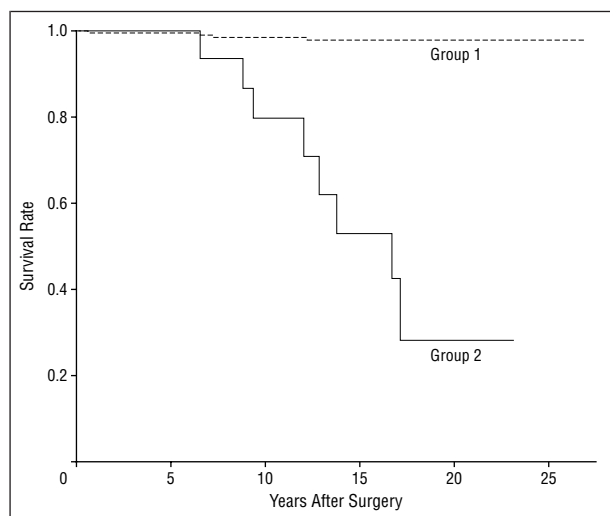


Figure 3. Disease-specific survival rate for stage III in each group. Group 2 patients showed a poorer prognosis than did group 1 patients (P<.001, log-rank and Wilcoxon rank sum tests).

papillary carcinoma.^{1,12,13,16,23} We considered extrathyroidal invasion and adhesion as a single risk factor because it was sometimes impossible to distinguish invasion from adhesion during surgery.

Gross nodal metastasis is a significant risk factor for postoperative nodal recurrence.^{16,23} Many metastatic

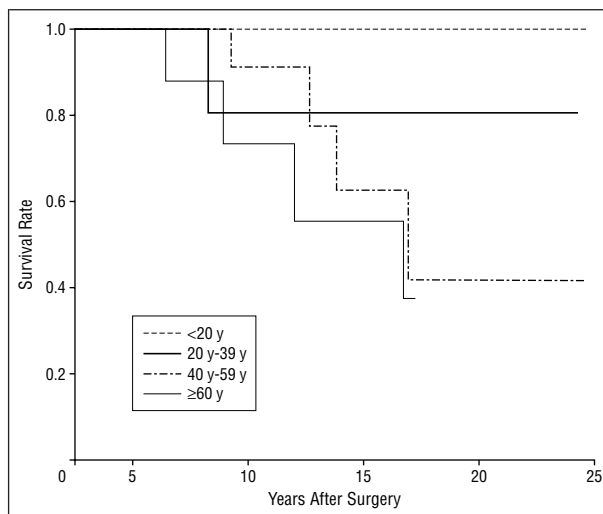


Figure 4. Disease-specific survival rate of each age group in group 2. Older patients had a worse survival rate than did younger patients, but the difference was not significant (P=.32, log-rank test; P=.39, Wilcoxon rank sum test).

Table 5. Outcome*

	Group 1	Group 2
Distant metastasis	11 (0.6)	10 (31.2)†
Death from thyroid cancer	13 (0.7)	9 (28.1)†

*Data are given as No. (percentage) of patients.
 †There was a significant difference for outcome between groups (P<.001).

nodes on the ipsilateral side might lead to recurrence on the contralateral node, since lymph node metastases occur successively as follows: paratracheally, ipsilaterally, then contralaterally.^{11,24,25}

In this study, we found a poor prognosis for patients with papillary thyroid cancer who developed contralateral nodal recurrence when compared with patients without nodal recurrence, irrespective of cancer stage. There has been controversy about whether lymph node recurrence affects the survival of patients with papillary thyroid cancer; some authors report no relation between nodal recurrence and prognosis.⁶⁻⁸ Discrepancies between their conclusions and ours can be explained by the selection of patients, surgical procedures, postoperative adjuvant therapy, and follow-up regimen. Their data include a variety of patients who developed nodal recurrence after surgery with or without lymph node dissection; therefore, it is difficult to evaluate accurately the effect of nodal recurrence on their prognoses. It is important to select an adequate number of patients treated with the same surgical procedure. We did not treat patients with radioiodine after curative surgery. In many institutions, radioiodine therapy has been used to treat selected patients after total thyroidectomy, regardless of whether neck dissection was performed. In such circumstances, small metastatic lymph nodes may be eradicated by radioiodine. Finally, a large number of patients and long follow-up periods (>10 years) are necessary to

draw significant conclusions, because most patients with papillary thyroid cancer have a good prognosis irrespective of therapy.

A major cause of death among patients with papillary thyroid cancer was distant metastasis, especially lung metastasis. There is some evidence that lymph node metastasis might cause distant metastasis. McHenry et al⁹ showed cervical node metastasis to be associated with recurrence and distant metastasis. Yamashita et al¹⁰ recently reported that the presence of extranodal invasion in patients with thyroid carcinoma is an indicator of distant metastasis and poor prognosis. We have reported that MRND improves the prognosis for patients with papillary thyroid cancer, especially those with gross nodal metastasis, primary tumor invasion beyond the thyroid capsule, and age greater than 60 years.^{1,12,13} Modified radical neck dissection might prevent distant metastasis from nodal metastasis. In our study, the period between initial surgery and the discovery of distant metastasis was longer in patients with nodal recurrence than it was in patients without it. It is possible that in some patients with nodal recurrence, the distant metastasis arose from the nodal recurrence. In the patients with other cancer, Anderson and Dische²⁶ showed that persistent cancer increases the risk of distant metastasis to other organs. Therefore, it is possible that bilateral MRND not only reduces the need for secondary surgery for contralateral nodal recurrence but also improves the prognosis for selected patients.

In general, younger patients with papillary thyroid cancer have better prognoses than older patients, despite more frequent lymph node metastases.^{13,16,23,27} This was confirmed by our study, suggesting that bilateral MRND (prophylactic for the contralateral side) could prevent a second surgery for nodal recurrence but that it may not affect prognosis in young patients. In contrast, the survival of older patients decreased when they had contralateral nodal recurrence. Older patients with risk factors for contralateral nodal recurrence are the best candidates for bilateral MRND.

In conclusion, the risk factors for contralateral nodal recurrence are male sex, large primary tumor, tumor extension over the isthmus, extracapsular adhesion or invasion to surrounding tissues, and the presence of gross nodal metastasis at the time of the initial surgery. Contralateral nodal recurrence indicates distant metastases and poor prognoses in patients who receive curative surgery with ipsilateral MRND. Bilateral MRND (prophylactic for the contralateral side) may be recommended for such patients.

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The authors of this study are advocating prophylactic contralateral modified neck dissection for patients they define as being at high risk for developing contralateral neck disease. These data were based on the fact that contralateral nodal recurrence was associated with a poor prognosis. I believe their data define a group of patients with poor prognosis, but the authors fail to provide data that would indicate that bilateral neck dissection would alter outcome.¹⁻³

Historically, surgeons in the United States performed prophylactic ipsilateral lymph node dissection in patients diagnosed as having papillary thyroid cancer. Almost all have abandoned this, since the incidence of recurrent disease in patients without clinical evidence of metastasis to the lymph nodes who were not treated with elective neck dissection was much lower than the 30% to 70% of patients with occult metastasis who underwent prophylactic node dissection. Most surgeons came to the conclusion that these occult tumors either regressed or remained in a dormant state. Support for desisting prophylactic lymph node dissection comes from the many studies that have generated prognostic scoring systems that have not found lymph node involvement to affect survival. The Mayo Clinic's MACIS (metastasis, age, completeness of resection, invasion, and size) prognostic scoring system is based on the largest number of patients (N=1779), with a mean follow-up of 12.7 years.⁴ In their analysis, the presence of lymph node involvement did not affect survival. Even the TNM staging system places all patients younger than 45 years without distant metastases in stage I.

In contrast, Ohshima and colleagues have long favored prophylactic ipsilateral node dissection and have provided data that suggest that this is the best treatment. However, they do not use postoperative radioactive iodine treatments, and it is possible that this is one of the factors that has led them to conclusions that are different from those of many other thyroid surgeons. Individuals identified by Ohshima and colleagues as being at high risk for developing contralateral neck disease would receive radioactive iodine treatment in many other centers. Many of their patients who had contralateral neck disease also had distant metastasis, which indicates that the patient has a biologically more aggressive tumor. Radioactive iodine in this setting may be the preferred treatment, since it treats local and distant disease.

Overall, it seems that prophylactic contralateral lymph node dissection probably is not justified, especially considering the potential morbidity of the surgery. These morbidities include paralysis of the spinal accessory nerve, injury to the brachial plexus, injury to the sympathetic trunk, hypoglossal nerve injury, and lymphorrhea. Lymph node dissection should be reserved only for those patients who develop clinically positive nodes. Those patients who are considered to be at higher risk should be followed up more closely by checking serum thyroglobulin levels, which might provide early evidence of distant disease; in such a setting, radioactive iodine treatment would be more valuable. The authors have a lot of experience in this area, and they continue to provide useful information for disease management.

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Surgical Anatomy

Branchial cleft abnormalities (cleft, fistula, cyst), when present, are remnants of the first, second, or third branchial cleft: (1) from the cartilage of the external auditory canal to the skin of the neck, beneath the center of the body of the mandible; (2) from the tonsillar fossa to the skin anterior to the sternocleidomastoid muscle; and (3) extending between the bellies of the sternocleidomastoid muscle above the clavicle.

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