Papillary Thyroid Carcinoma

Modified Radical Neck Dissection Improves Prognosis

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Objective: To ascertain whether modified radical neck dissection offers a survival advantage for some subsets of patients with papillary cancer of the thyroid.

Design: A retrospective cohort study of 2966 patients curatively treated at the Noguchi Thyroid Clinic and Hospital Foundation, Oita, Japan, between 1946 and 1991.

Setting: A center for the treatment of thyroid disease, where about 1400 thyroid operations are performed per year.

Patients: Between 1946 and 1991, patients with papillary cancer whose primary tumor was 1 cm or larger and who were curatively treated were studied. Of the 2859 patients, 72.1% underwent modified radical neck dissection, 8.5% underwent partial node excision, and 19.4% underwent no node excision.

Results: A univariate analysis revealed a subset of patients who benefited from modified radical neck dissection. A multivariate analysis revealed that sex (P<.001), age at the time of the operation (P<.001), size of the primary tumor (P<.001), extrathyroidal invasion (P<.001), and the presence of nodal metastasis (P<.01) are significant risk factors.

Conclusion: Patients with nodal metastasis, patients in whom the primary tumor invades beyond the thyroid capsule, and women older than 60 years can benefit from modified radical neck dissection.

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IN THE surgical management of papillary cancer, controversy exists not only about thyroidectomy but also about the extent of lymph node excision. While there are well-accepted risk factors, such as the patient's age at the time of surgery, the size of the primary tumor, and invasion of the tumor beyond the thyroid capsule, the influence of lymph node metastasis on survival is controversial. In this study, we attempted to address these issues.

A randomized trial is believed to be the most reliable and scientific way of comparing 2 therapeutic methods. However, when a randomized trial is not feasible, another approach is to determine whether a group of patients with advanced disease has a better prognosis after undergoing one surgical procedure than another group of patients with less advanced disease who has undergone a less extensive surgical procedure. If so, the more extensive surgical procedure would be justified.

We elected to use subtotal thyroidectomy and to perform modified radical neck dissection in most of our patients. Although it is unquestionably established that modified radical neck dissection reduces the recurrence rate, its influence on the survival rate still remains unclear. In this article, we report a survival advantage of modified radical neck dissection in some subgroups of patients with papillary thyroid cancer, despite the fact that these patients had more advanced disease.

RESULTS

PRIMARY TUMOR

The mean (+SD) diameter of the primary tumor was 27.1±14.5 mm. The smallest tumor was 10 mm in diameter by definition, and the largest was 150 mm in diameter. The tumor was confined within the thyroid capsule in 912 patients.

METASTASIS

Gross nodal metastasis was found in 1160 (39.1%) of the patients.

In 638 (21.5%) of the patients, nodal metastasis was not examined or counted; in 323 (10.9%) of the patients, metastasis was histologically confirmed not to be present; and in 2005 (67.6%) of the patients, metastasis was histologically confirmed to be present.
PATIENTS AND METHODS

Between 1946 and 1991, 3994 patients seen at the Noguchi Thyroid Clinic and Hospital Foundation, Oita, Japan, had papillary cancer. The following 2 groups of patients were excluded from the study: 124 patients who were not surgically treated or who underwent noncurative surgery (including 17 patients who had pulmonary metastases when they were initially seen and 92 who underwent incomplete resection) and 904 patients whose primary tumor had a maximum diameter of less than 10 mm. Therefore, 2966 patients were included in this study.

Information about living patients was obtained by periodic correspondence with the patients themselves, family members, referring physicians, and municipal records. For the deceased patients, the cause of death was confirmed by death certificates or contact with family members and hospitals. The mean follow-up interval in the patients last known to be alive was 15.6 years. Twelve (0.4%) of the patients were unavailable for follow-up, 170 died of thyroid cancer, and 333 died of unrelated causes.

The cause-specific survival rates were calculated according to the Kaplan-Meier method. Risk factor analysis was performed using the Cox proportional hazards regression model. χ² Analysis was applied for comparisons between 2 groups with a similar distribution, and the Wilcoxon rank sum test–Kruskal-Wallis test was applied for groups with an irregular distribution.

TYPES OF THYROIDECTOMY AND LYMPH NODE EXCISION

Total thyroidectomy was performed in 75 (2.5%) of the patients; subtotal thyroidectomy, 1233 (41.6%) of the patients; lobectomy, 1217 (41.0%) of the patients; and partial lobectomy, 441 (14.9%) of the patients. Our routine method of subtotal thyroidectomy is to leave behind 1 or 2 g of the upper pole of the unaffected lobe, with the parathyroid gland left in situ. When intraglandular dissemination is present on the contralateral upper pole, we try to leave behind 1.0 or 1.5 g of the upper pole of any side that looks normal. Lobectomy is almost always accompanied by isthmectomy. A special explanation is required regarding patients who underwent partial lobectomy. Of the 441 patients, 71 had concomitant benign disease; of these 71 patients, 66 underwent the operation for that reason. The remaining patients had a small tumor. Of the 441 patients, 78 underwent modified radical neck dissection, 69 underwent central compartment node dissection, and the remaining 294 underwent no node excision. This procedure was mostly performed between 1970 and 1975. The modified radical neck dissection encompassed dissection of the fat and lymph node tissues around the trachea (central compartment) and those around the jugular vein extending from the common carotid artery up to the bifurcation, superior to the bifurcation the internal carotid artery to the trapezius muscle, and from the subclavian vein to the hypoglosseal nerve (lateral compartment).

Patients who underwent modified radical neck dissection had macroscopic metastasis, invasion of the primary tumor to surrounding tissue, or a preoperative diagnosis of cancer. Further analysis was performed by dividing the patients into 2 groups, those treated with modified radical neck dissection and those not treated with modified radical neck dissection, because of the few patients in the central compartment excision group. Table 1 shows the number and percentage of patients treated with each type of procedure. Patients who did not undergo this dissection had no macroscopic metastasis and minimal or no invasion to surrounding tissue. The differences between the 2 groups were summarized in Table 2.

INVASION OR ADHESION

In this type of retrospective study, adhesion and invasion of the primary tumor to the surrounding tissues were hard to differentiate strictly; therefore, they were grouped together. The incidence of invasion or adhesion of the primary tumor to surrounding tissues increased with age.

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Table 1. Lymph Node Excision in Relation to Thyroidectomy

<table>
<thead>
<tr>
<th>Type of Procedure</th>
<th>Modified Radical Neck Dissection</th>
<th>Partial Node Excision</th>
<th>No Node Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy (n = 75)</td>
<td>68 (90.7)</td>
<td>6 (8.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Subtotal thyroidectomy (n = 1233)</td>
<td>1022 (82.9)</td>
<td>90 (7.3)</td>
<td>121 (9.8)</td>
</tr>
<tr>
<td>Lobectomy (n = 1217)</td>
<td>971 (79.8)</td>
<td>87 (7.1)</td>
<td>159 (13.1)</td>
</tr>
<tr>
<td>Partial lobectomy (n = 441)</td>
<td>78 (17.7)</td>
<td>69 (15.6)</td>
<td>294 (66.7)</td>
</tr>
</tbody>
</table>

*All data are given as the number (percentage) of patients who underwent each type of procedure.

Table 2. Characteristics of Patients Who Underwent Modified Radical Neck Dissection (MRND) Compared With Patients Who Did Not Undergo MRND

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients Who Underwent MRND (n = 2139)</th>
<th>Patients Who Did Not Undergo MRND (n = 827)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative diagnosis of cancer</td>
<td>1839 (86.0)</td>
<td>292 (35.3)</td>
</tr>
<tr>
<td>Extrathyroidal invasion</td>
<td>814 (38.1)</td>
<td>98 (11.8)</td>
</tr>
<tr>
<td>Adhesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent nerve</td>
<td>628 (29.4)</td>
<td>35 (4.2)</td>
</tr>
<tr>
<td>To the esophagus</td>
<td>354 (16.5)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>To the larynx</td>
<td>116 (5.4)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>To the jugular vein</td>
<td>255 (11.9)</td>
<td>23 (2.8)</td>
</tr>
<tr>
<td>Mean diameter, mm</td>
<td>27.5</td>
<td>26.7</td>
</tr>
</tbody>
</table>

*All data are given as the number (percentage) of patients in each group. Except for mean diameter (P=.22), all differences between groups were significant (P<.001).
The incidence of nodal metastasis in male and female patients was 92.1% and 85.5%, respectively. The difference was significant (P<.009).

The patients in whom there was invasion or adhesion of the primary tumor to surrounding tissue who experienced gross nodal involvement had a better survival rate after a modified radical neck dissection was performed, as shown in Figure 1 and Figure 2, respectively.

Although the overall survival rates in the group that underwent modified radical neck dissection and in the group that did not undergo modified radical neck dissection were not statistically different, among patients with any metastases, the group that underwent modified radical neck dissection had a survival advantage (Figure 3).

**AGE**

Patients were classified into 4 age groups: younger than 20 years, between 20 and 50 years, between 51 and 60 years, and older than 60 years. Older age was a significant (P<.001) risk factor. In women older than 60 years, who composed 17.7% of the patients, modified radical neck dissection conferred a significant (P<.02, log-rank test, and P<.01, Wilcoxon rank sum test) survival advantage regardless of the risk factors (Figure 4). The 10- and 20-year cause-specific survival rates for the group that underwent modified radical neck dissection (n=373) were 92.4% and 73.2% compared with 80.3% and 56.7%, respectively, for the group that did not undergo modified radical neck dissection (n=130).

**RECURRENCE FROM REMNANT THYROID**

Recurrence in the remnant thyroid tissue was observed in 97 (3.3%) of the patients. The contralateral lobe was affected in 74 patients, the ipsilateral thyroid bed was affected in 22 patients, and the bilateral lobes were affected in 1 patient. Among these patients, 83 were successfully treated by a second operation and 1 survived with disease; of the remaining 13 (0.4%) of the patients, 11 (0.37%) died of distant metastasis and 2 (0.07%) died of local disease.

**MULTIVARIATE ANALYSIS OF RISK FACTORS**

The significant risk factors were sex (P<.001), age at the time of the operation (P<.001), maximum diameter of the primary tumor (P<.001), extrathyroidal invasion (P<.001), and presence of metastasis regardless of the size of the tumor (P<.04).

Since 1970, when we first noted the extremely high incidence of nodal metastases in patients with papillary cancer of the thyroid, we have advocated modified radical neck dissection for these patients.2,3 Recently, Simon and Goretzki1 noticed a high nodal recurrence rate and suggested the usefulness of a modified radical neck dissection. Scheumann et al2 reported improvement of the recurrence rate and the survival rate after a modified radical neck dissection; however, the indication criteria were not clarified. Although many had failed to find improvement of the survival rate after modified radical neck dissection,7,8 we were able to demonstrate the beneficial effect of modified radical neck dissection on survival in some subsets of female patients with papillary cancer of the thyroid by univariate and multivariate analyses. There are several possible reasons why previous studies have failed to demonstrate any benefit of modified radical neck dissection. This form of surgery has often been applied exclusively for advanced disease: the percentage of patients with papillary cancer of the thyroid who underwent radical or modified radical neck dissection ranged from 12.3% to 30.0% in institutions in which the procedure...
is reserved only for patients with gross nodal metastasis.\(^6\)\(^{-12}\) Moreover, because recurrence in cervical nodes can be treated easily and successfully by a second surgery, such recurrence may not have affected the survival in many instances.\(^5\)\(^,\)\(^6\)\(^,\)\(^13\)\(^{-15}\) Because of the indolent nature of papillary cancer, the probability of differences of disease-specific survival rates among groups given different treatments is small and, therefore, an analysis of many cases is necessary before any significant difference will emerge.\(^16\) Finally, not all patients benefit from modified radical neck dissection, and there are no criteria for identifying patients who are, and who are not, likely to benefit.

Recent advances of statistical models and computer technology enabled us to analyze many patients with multiple risk factors.\(^2\)\(^,\)\(^9\)\(^,\)\(^17\)\(^{-20}\) With the use of multivariate analysis, the age of the patients at the time of the operation, the size of the primary tumor, the presence of gross nodal involvement, and the presence of remote metastasis when they were specifically mentioned have been agreed on as the risk factors in the literature we examined.\(^13\)\(^,\)\(^17\)\(^,\)\(^21\)\(^{-23}\) However, a scoring system or a classification of patients based on prognosis, inclusive of nodal metastasis, is only given in the article that we previously published.\(^20\)

Aside from these rather sophisticated mathematical methods of analysis, Cady et al\(^24\) made a simple and practical rating system named AMES, which is essentially based on the age of the patient, the presence of remote metastasis, the extension of the primary tumor beyond the thyroid capsule, and the size of the primary tumor. They further developed the concept of risk group definition. With the use of multivariate analysis, as well as histological grading, Hay et al\(^25\) proposed a new scoring system inclusive of histological grading, known as AGES, which denotes age of the patient, histological grade of the tumor, extension beyond the thyroid capsule, and size of the primary tumor. They further developed and improved their scoring system by excluding histological grading and including completeness of the resection, invasion of the primary tumor to surrounding tissues, and size of the primary tumor.\(^23\) None of these scoring systems but ours singularly ignored nodal involvement, despite the fact that multivariate analysis clearly proved that gross nodal involvement is one of the risk factors.

Routine or frequent use of radioactive iodine with the objective of ablating microscopic cancer foci is recommended by those who advocate total thyroidectomy.\(^5\)\(^,\)\(^6\)\(^,\)\(^26\)\(^{-28}\) Those who do not perform total thyroidectomy routinely use radioactive iodine in selected patients.\(^29\)\(^,\)\(^30\) We employ radioactive iodine only when remote metastasis is evident and when the metastasis can accumulate radioactive iodine, not only because of the strict regulation of radioisotopes in Japan but because we also believe that calcitonin secretion must be preserved.

In our series, male patients had a higher incidence of nodal metastasis. This observation agreed with the observations of Tisel et al,\(^12\) Tscholl and Hedinger,\(^31\) and Ahuja et al.\(^32\)

Although we are aware that total thyroidectomy is a safe procedure when it is performed by skilled and well-experienced surgeons,\(^33\)\(^{-35}\) we still try to avoid total thyroidectomy for the simple reason that it does not seem to improve the survival rate. Because of this policy, we paid particular attention to recurrence at the remnant thyroid. Of the 2966 patients who we observed on average for 15.6 years, only 13 (0.4%) died of causes related to recurrence in the remnant thyroid or thyroid bed; among these patients, only 2 (0.07%) died with neck disease. Many other researchers are also unable to find any survival advantage of total thyroidectomy.\(^7\)\(^,\)\(^19\)\(^,\)\(^36\)\(^{-40}\) Samaan et al\(^41\) indicated that total thyroidectomy was associated with a longer disease-free interval and less recurrence. However, in their more recent article,\(^41\) a higher survival rate was reported.\(^42\) We wonder whether the total thyroidec-
tories were performed by more experienced surgeons compared with the less extensive thyroidectomies. The bone mineral content is reduced after total thyroidectomy. Therefore, if there is no benefit associated with total thyroidectomy in appropriately selected patients, then the increased risk of osteoporosis should be avoided.

Most researchers agree that older patients with differentiated thyroid cancer have a relatively poorer prognosis. In the men and women in our study, age was one of the most important risk factors. Women older than 60 years accrue a survival advantage when they undergo modified radical neck dissection, regardless of other risk factors.

Univariate and multivariate analyses of modified radical neck dissection indicated a survival advantage in older women. However, women younger than 55 years, those without gross metastasis, and those without extrathyroidal invasion seemed to derive no benefit from this procedure.

The size of the primary tumor is also recognized as one of the risk factors by many researchers. In this study, the size was a significant risk factor per multivariate analysis.

Invasion of the primary tumor beyond the thyroid capsule is one of the risk factors reported by others. The incidence of invasion of the primary tumor to surrounding tissues progressively increases with age. The influence of age on prognosis is not explained by invasion alone; inversely, the invasiveness of the primary tumor might be under the influence of a factor or factors possibly related to age.

Thus, we found that modified radical neck dissection improved the outcome in some subsets of patients with papillary cancer of the thyroid: specifically, those in whom gross nodal metastasis was noticed before or during surgery, those in whom the primary tumor invaded beyond the thyroid capsule, and those who were older than 60 years.

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REFERENCES