

The Treatment Choice for Patients with Papillary Thyroid Carcinoma

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유두상 갑상선암의 치료 방법 선택에 대한 고찰

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= 국문 초록 =

유두상 갑상선암의 대부분은 서서히 진행되는 양호한 임상경과를 보이거나, 일부는 저등급 혹은 미분화 갑상선암으로 전환되는 생물학적 특성을 보인다.

저자는 유두상 갑상선암 환자 368예를 적용된 치료방법과 치료결과를 분석하여 논란이 되고 있는 치료방법들 중에서 적절한 치료방법을 찾고자 본 연구를 시도하였다.

368예중 동측엽절제술 및 협부 절제술 혹은 갑상선 아전 절제술 220예, 갑상선 전 절제술 혹은 근전절제술 143예, 종양적출술 5예였고, 이중 115예는 여러가지 형태의 경부 광칭술이 추가되었고, 150예는 수술후 방사성 동위원소 치료까지 추가되었다. 또 전 환자에서 TSH 억제제를 위한 갑상선 호르몬 투여를 하였다. 추적기간은 5년에서 12년까지 평균 8.5년이였다. Cady와 Rossi의 AMES Scoring System에 따라 저위험군과 고위험군으로 나누어 재발율과 사망율을 산출한 결과 저위험군 255예중 재발율 11.0%, 사망율 0.4%, 고위험군 65예중 재발율 36.9%, 사망율 20.0%을 보여 고위험군에서 현격히 불량한 예후를 나타내었다.

따라서 저자들은 유두상 갑상선암의 치료방법 선택은 일률적인 치료방법 보다는 환자 개인의 임상적 특성, 병기 등을 고려하여 저위험군에서는 소극적 수술을, 고위험군에서는 적극적인 수술과 수술후 보조치료를 시행하는 것이 바람직하다고 사료되었다.

Introduction

The biologic behavior of most papillary thyroid carcinomas is indolent and is characterized by slow progression over a period of years with excellent prognosis. A small number, however, have a tendency to transform into a more aggressive or a highly

lethal form such as a poorly differentiated or an anaplastic type with advancing age.

In spite of the great wealth of knowledge concerning the behavior of papillary thyroid carcinoma, there is no general agreement regarding its treatment. This controversy focuses on how much of the thyroid tissue needs to be removed and the

extent of the lymph node dissection. Furthermore, the controversy continues, not only about the extent of surgery required, but also about the indications for radioactive iodine therapy and the efficacy of thyroid-stimulating hormone (TSH) suppression therapy in controlling tumor growth.

In this paper, we attempt to provide a discussion of the different therapeutic approaches and propose guidelines for decision making in the treatment of papillary thyroid carcinoma on the basis of an analysis of our experiences and a review of the literature.

Materials and Methods

From January 1980 to December 1986, a total of 502 patients with thyroid carcinoma were treated surgically at our institution.

Among these patients, 368 (73.3%) had an established diagnosis of papillary thyroid carcinoma. There were 56 male and 312 female patients with a mean age of 42.5 years (range 12-78). The initial tumor characteristics are given in Table 1.

Selection of the appropriate treatment modality was based on the presenting characteristics of the tumors and patients, and presence or absence of

Table 1. Tumor characteristics at the initial presentation

Tumor characteristics	No of patients	%
Age <50 years	236	64.1
≥50 years	132	35.9
Tumor size		
<5 cm	316	85.9
≤5 cm	52	14.1
Extrathyroidal invasion		
No	220	59.8
Yes	148	40.2
Lateral neck node metastasis		
No	253	68.8
Yes	115	31.2
Distant metastasis		
No	352	95.7
Yes	16	4.3

regional or distant metastatic disease at initial presentation.

Once a decision to operate for a suspicious nodule was made, an extracapsular total lobectomy and isthmusectomy was performed as the initial procedure. If the nodule turned out to be a papillary thyroid carcinoma by frozen-section examination, a more definite surgery was considered. When the lesions were small (1.5 cm or less in diameter), totally confined to one lobe without extracapsular extension and unaccompanied by obvious bilateral foci, no further surgery was done except for adding central neck node dissection. Total or near-total thyroidectomy was performed for most patients with locally extensive tumors, and patients with gross involvement of bilateral lobe or multiple metastatic disease to lateral neck or distant metastatic disease.

In most patients, the central neck nodes neighboring the thyroid gland and trachea including those in the prelaryngeal, pretracheal, paratracheal, the nodes along the recurrent laryngeal nerve and the anterior-superior mediastinal nodes were removed routinely in addition to thyroidectomy.

The lateral neck node dissection was added only if nodal involvement was grossly evident.

The patients with potentially aggressive tumors such as extrathyroidal extension, lateral neck node metastases, or distant metastases received radioactive iodine therapy in the postoperative period.

Our approach to postoperative management is illustrated in Fig. 1.

Life-long thyroid-stimulating hormone (TSH) suppression therapy with thyroid hormone was instituted in all patients.

Follow-up of the patients was obtained by direct examination of the patients, serial monitoring of serum thyroglobulin (Tg) levels, ¹³¹I whole body scans, computerized tomography (CT), and other radiologic studies as necessary (Fig. 2).

Results

Surgical treatments adopted for the thyroid le-

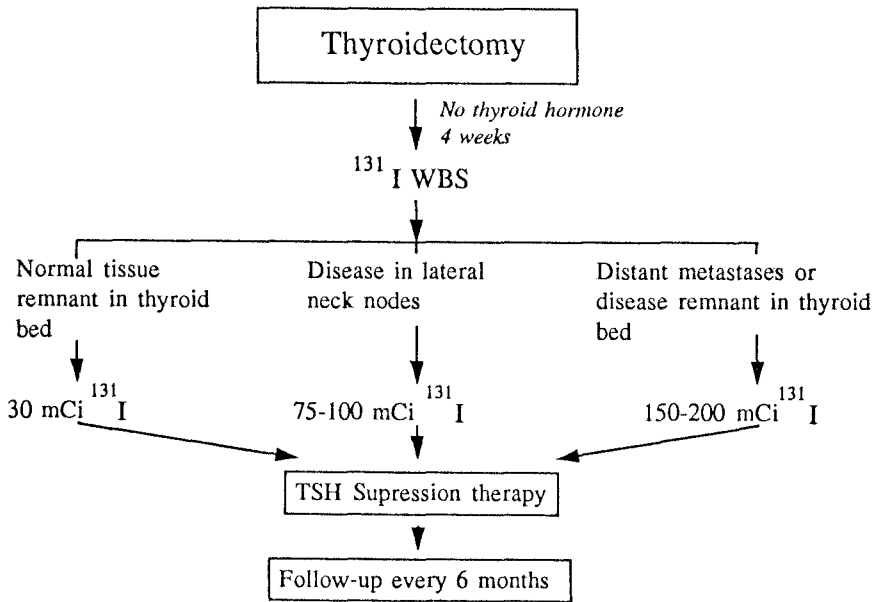


Fig. 1. Postoperative management of patients with papillary thyroid carcinoma. WBS, whole body scan ; TSH, thyroid-stimulating hormone.

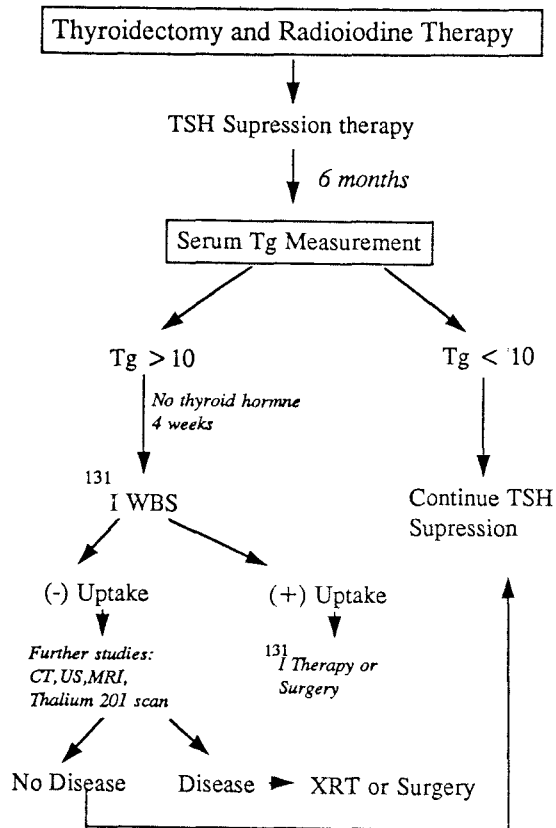


Fig. 2. Follow-up of patients with papillary thyroid carcinoma. TSH, thyroid-stimulating hormone ; Tg, thyroglobulin ; WBS, whole body scans ; CT, computerized tomography ; US, ultrasonography ; MRI, Magnetic resonance imaging ; XPT, external-beam radiotherapy.

sions consisted of ipsilateral lobectomy isthmusectomy or subtotal thyroidectomy in 220 patients(59.8%), total or near-total thyroidectomy in 143(38.9%), and debulking surgery in 5(1.3%).

An additional resection of the direct tumor extension into adjacent neck structures such as recurrent laryngeal nerve(n=17), strap muscles(n=28), tracheal wall(n=24) or esophageal wall(n=4) was carried out in 42 patients(11.4)%

Central neck node dissection was performed in 352 patients, 312(88.6%) of whom turned out to have positive nodes.

Surgical procedures adopted for the lateral neck node metastases were ipsilateral modified radical neck dissection(MRND) in 84 patients(22.8%), standard radical neck dissection(RND) in 12(3.3%), partial neck dissection(dissection of central neck nodes and interal jugular lymphatic chains) in 11(3.0%), and bilateral MRND in 8(2.2%).

Multiple cancer foci in the thyroid specimens were found in 122 patients(33.2%) by serial histologic section at 3-to-5mm intervals.

The average number of metastatic nodes in central and lateral neck nodes per patients were 3.8(range 1-18) and 18.5(range 2-42), respectively.

Adjuvant radioactive iodine was administered in 150 patients(40.8%), 38 of whom received therapeutic doses of 75 to 200 mCi for locally invasive or distant metastatic disease, and 112 patients who had no residual disease received 30m Ci to ablate the remaining thyroid tissue.

The maximum cumulative dose for ablation and therapeutic purposes were 90 and 500m Ci, respectively.

External-beam radiotherapy was used in 13 patients(3.5%) who had had a debulking surgery, or metastatic or residual disease which did not take up radioiodine.

During the follow-up period ranging from 5 to 12 years(mean 8.5years), 48 patients could not be followed-up. Among 320 patients who had been included in follow-up study, a recurrent or persistent

disease was found in 52 patients(16.3%). The site of recurrent or persistent disease were as follows: 22 lateral neck nodal region, 16 distant metastasis (10 lung, 4 bone, 2 brain), 2 nodal and distant metastasis(lung), and 12 central neck or mediastinum.

In almost all patients without evidence of recurrent disease, the serum Tg levels were less than 10ng/ml on thyroid hormone therapy, whereas in the patients with recurrent or persistent disease, the mean serum Tg levels were 52ng/ml(range 18-320).

Fourteen patients(4.4%) had died of their thyroid carcinoma, and 7 had died from other causes. The most common cause of death was airway obstruction due to extensive local disease in the central neck and mediastinum which was resistant to radioiodine or external-beam radiotherapy.

According to Cady and Rossi's AMES scoring system the 320 patients could be divided into 255 patients at low risk and 65 at high risk.

The recurrence and disease related mortality rate of the patients in the high risk group was significantly higher than that of the patients in the low risk group(Table 2).

Discussion

Since there are no prospective, randomized studies, the proper means to decision concerning extent of surgery for papillary thyroid carcinoma remains in debate. Regarding the extent of thyroid resection,

Table 2. Recurrence and death rate by the AMES scoring system*

	No of patients	Recurrence	Death
Low risk	255	28(11.0%)	1(0.4%)
High risk	65	24(36.9%)	13(20.0%)

Low risk: All younger patients without distant metastases(men, <41 years: women, <51 years), All older patients with intrathyroidal papillary cancer, primary cancer <5cm in diameter and no distant metastases.

High risk: All patients with distant metastases: All older patients with extrathyroidal papillary cancer and primary cancer >5cm regardless of extent disease.

some surgeons have advocated thyroid lobectomy including isthmusectomy or subtotal thyroidectomy, and others have recommended total or near-total thyroidectomy.

The arguments in favor of conservation surgery and that this procedure has a lower morbidity and the prognosis following this operation is comparable to that occurring after more aggressive operation²⁻³⁾. Advocates of this procedure emphasize that cancer recurrence in the opposite lobe is low, about 5 to 10%, with 15 to 20 years follow-up⁴⁾⁵⁾.

Recent report from the Mayo Clinic suggested the concept of risk groups such that papillary or follicular carcinomas could be divided into 86% of patients at low risk that revealed only a 2% mortality rate and a high risk group of 14% of patients who had a 46% mortality rate by utilizing age, pathologic grade, extent of the primary tumor, and tumor size as criteria (AGES score)⁶⁾⁷⁾.

The experience at the Lahey Clinic reported by Cady and Rossi¹⁾ was nearly identical, and advocated a risk group assessment system to determine the extent of surgery. Their scale was based solely on clinical criteria such as patient age, distant metastasis, extent of the primary tumor, and the size (AMES score).

Based upon our present knowledge and our treatment outcomes, an ipsilateral lobectomy and isthmusectomy appears adequate for the overwhelming majority of patients in the low risk group.

The arguments in favor of total thyroidectomy are that it eliminates all multifocal lesions that occurs in 30 to 87.5% of patients with papillary carcinoma and facilitates the use of radioactive iodine for the detection and treatment of recurrent or distant metastatic disease⁸⁾.

Total thyroidectomy also decreases the risk of recurrent central neck disease and decreases the chance of conversion to poorly differentiated or anaplastic thyroid carcinoma. In addition, this procedure also increases the sensitivity of thyroglobulin

measurement, which is useful for detecting recurrent disease⁹⁻¹¹⁾.

A total thyroidectomy, however, is a more technically difficult operation and is associated with a serious problems of hypoparathyroidism and recurrent laryngeal nerve injury. Thus, this extensive operation is recommended only if it can be done with very low morbidity rate.

To minimize the morbidity of total thyroidectomy, near-total thyroidectomy leaving a small rim of the posterior capsule of the contralateral lobe to preserve the parathyroid glands and recurrent laryngeal nerves has been recommended, because it lowers permanent complications and achieves therapeutic results similar to total thyroidectomy¹²⁾¹³⁾.

In general, a total or near-total thyroidectomy is recommended for most patients in the high risk group, and patients with a history of head and neck irradiation, obvious bilateral involvement or multiple neck node metastases¹⁻³⁾⁶⁾¹⁴⁾. We personally favor the near-total thyroidectomy, particularly in patients who require extensive neck node dissection in addition to thyroidectomy.

Papillary thyroid carcinoma tends to frequently metastasize to regional lymph nodes, not only to the central neck nodes but also the lateral neck nodes, and these nodal metastases are more frequently found in the younger patients. The incidence of clinically positive nodes at the time of presentation has been reported from 37 to 42.3%²⁾¹³⁾, and Noguchi et al¹⁵⁾ found that as many as 90% of patients with clinically negative necks had microscopic nodal metastases.

However, unlike for other type of carcinomas, the clinical significance of nodal metastases from papillary thyroid carcinoma remains undetermined. The majority of the studies has shown that there is no relationship between nodal metastase and survival²⁾⁴⁾⁵⁾¹³⁾.

Most Japanese surgeons have recommended elective MRND in all patients to reduce nodal recurrence

nce and to avoid a second operation¹⁵⁻¹⁸⁾, while most Western surgeons believe that the elective neck dissection does not significantly benefit the patients, even though the microscopic metastatic rate is very high. This is because the recurrent rate in patients with microscopic nodal metastases who had not undergone neck dissection has been reported as only 7 to 15%⁴⁾⁵⁾¹³⁾.

Thus, in most Western countries, neck dissection has been recommended only in patients with clinically positive neck nodes.

In this situation, a Bocca type MRND preserving the internal jugular vein, spinal accessory nerve, sternocleidomastoid muscle and submandibular space has been widely accepted²⁾⁴⁾⁵⁾¹³⁾¹⁹⁾²⁰⁾. We do not feel the berry-picking type of node dissection is adequate. The standard RND is rarely indicated except for patients with massive and direct invasion to the jugular vein or sternocleidomastoid muscle²⁾⁴⁾⁵⁾²⁰⁾.

It is well known that the central neck node metastases are more likely to have clinically significant problems than metastases in the lateral neck nodes²¹⁾. When a recurrence occurs in this anatomic area, it is very difficult to reoperate and control these type of local recurrences.

Frankenthaler et al²²⁾ reported that up to 90% of the patients with papillary carcinoma had microscopic metastases to the pretracheal and paratracheal nodes.

Therefore, even though the central neck nodes appear normal at the time of exploration, we suggest a complete dissection of these lymphatic chains with thyroidectomy.

Postoperative radioiodine therapy has been used more frequently in recent years, based on a reduced recurrent and death rate in patients treated with both radioiodine and thyroid hormone⁴⁾⁵⁾¹³⁾²³⁾. It appears that there is general agreement that a therapeutic dose of radioiodine effects an optimistic progress in most patients with residual disease or recur-

rent disease and in patients with distant metastases, but the routine use of radioiodine ablation for thyroid remnants has not been universally accepted¹⁾⁶⁾⁷⁾. At our institution, however, we continue to recommend routine radioiodine ablation in patients who have had total or near-total thyroidectomy, because we believe that it is useful for increasing the sensitivity of Tg measurement and of ¹³¹I whole body scan during the follow-up as well as for reducing the incidence of recurrent disease.

External-beam radiotherapy has been only considered with a palliative intent in patient with residual or recurrent diseases not amenable to surgical excision or radioiodine therapy.

As is well known, life-long thyroid hormone replacement therapy has been recommended for all patients whether or not the entire thyroid has been removed. This is necessary to maintain euthyroidism and to achieve maximal suppression of TSH. Because TSH may have a growth-promoting effect on thyroid carcinoma and stimulating effect in the transformation of well differentiated carcinoma to a less well differentiated carcinoma³⁻⁵⁾¹³⁾.

In the follow-up of papillary thyroid carcinoma, periodic check-ups of serum Tg levels, chest X-ray, high-resolutional ultrasonography, isotope bone scans, CT or thallium 201 scan have been considered useful for the detection of cancer recurrence or metastases¹³⁾²¹⁾²³⁾.

In patients who had had a total or near-total thyroidectomy, the role of radioiodine in postoperative follow-up has been reasonably well accepted⁸⁻¹⁰⁾ but nowadays the measurement of serum Tg has been taking the place of the role of radioiodine in the screening for recurrent or metastatic disease²⁴⁾²⁵⁾.

We believe that the measurement of serum Tg is a very useful test because of its simplicity, low cost, and availability, and because it also can decrease the frequent needs for taking ¹³¹I whole body scans.

Conclusion

Review of this series suggests the following :

1) Selection of the appropriate treatment usually is based on the particular clinical situation encountered.

2) A total of near-total thyroidectomy is indicated for most patients at high risk and conservation surgery is recommended for the patients at low risk.

3) Central neck node dissection is indicated in all patients whether or not metastases are evident while MRND is recommended only for the patients with gross nodal involvement.

4) The use of radioactive iodine following total or near-total thyroidectomy can be applied either to ablate thyroid tissue remnants, treat residual disease or distant metastases, or both, and all patients should be placed on life-long TSH suppression therapy regardless of the amount of thyroid tissue remnant.

5) In those who have total or near-total thyroidectomy with subsequent radioiodine ablation, monitoring of serum Tg levels and sequential radioactive iodine scanning can detect recurrent or distant metastatic disease.

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