Unique Treatment Policy for Well-differentiated Thyroid Cancer in Japan: Results of a Questionnaire Distributed to Members of the Japanese Society of Thyroid Surgery and the International Association of Endocrine Surgeons

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Abstract. Although surgery has been the mainstay of treatment for patients with well-differentiated thyroid cancer, the extents of thyroid resection and lymph node dissection adopted in Japan differ from those in other countries. Furthermore, regarding the indications for postoperative radiation therapy and hormonal therapy, and treatment modalities for cancer recurrence, there are marked discrepancies between Japan and other countries. A questionnaire survey was thus conducted among domestic and overseas thyroid surgeons to ascertain the actual treatment policy for well-differentiated thyroid cancer in Japan and various foreign countries. For small papillary carcinomas of 2.0 cm or less (T1), thyroid resection was more extensive in foreign countries than in Japan, although the extent of lymph node dissection was limited in the former. For large papillary carcinomas exceeding 3.0 cm (T2), on the other hand, total thyroidectomy was the treatment of first choice for all overseas respondents, but of only 20% in Japan, despite lymph node dissection being more extensive in Japan than in other countries. Overseas surgeons were much more likely to favor postoperative TSH suppression therapy and high-dose ¹³¹I therapy. For recurrence following surgery for papillary thyroid cancer, both domestic and overseas respondents indicated surgical resection to be the most common treatment option, and favored high-dose ¹³¹I therapy as well. In Japan, however, high-dose ¹³¹I therapy is available only in a few institutions. Such limited indications for high-dose ¹³¹I therapy in Japan may reflect a discrepancy in the frequency of total thyroidectomy, a prerequisite for postoperative high-dose ¹³¹I therapy, between Japan and other countries. This is the first questionnaire study conducted in both Japan and other countries in relation to treatment modalities for thyroid cancer. The results reveal that there is a clear disparity in treatment policies between Japan and foreign countries.

Key words: Well-differentiated thyroid cancer, Treatment policy


THYROID cancer can be classified into various histological types, and above all, well-differentiated thyroid carcinomas (papillary thyroid carcinomas and follicular thyroid carcinomas) account for 85–90% of all thyroid cancers, and are further subdivided into those having a favorable prognosis, i.e., the low-risk group (85–90% of all well-differentiated thyroid carcinomas), and those having a poor prognosis, i.e., the high-risk group. The treatment policy for well-differentiated thyroid carcinoma in Japan is known to differ markedly from that in foreign countries; however, the source and nature of the treatment policy discrepancy, e.g., surgical procedures in all cases versus radiation therapy (high-dose ¹³¹I therapy and external irradiation) versus hormonal therapy (TSH suppression therapy) in postsurgical or unresectable cases, remain obscure.

Thus, we conducted a questionnaire survey among physicians enrolled in the Japanese Society of Thyroid Surgery (JSTS) and the International Association of Endocrine Surgeons (IAES) to ascertain the actual do-
mestic and overseas treatment policies for thyroid cancer. A questionnaire was distributed to them, inquiring about treatment options for well-differentiated thyroid cancer according to tumor size and the degree of prognostic risk. The replies to this questionnaire were analyzed in this study.

**Materials and Methods**

A questionnaire was distributed to 520 domestic physicians enrolled in the JSTS and 133 (26%) responded. For overseas physicians, an email questionnaire was sent to 237 members of the IAES and 83 (35%) responded. When stratified by district, domestic respondents included 6 from Hokkaido, 12 from Tohoku, 24 from Chubu, 26 from Kinki, 8 from Chugoku, 5 from Shikoku, and 14 from Kyushu and Okinawa; overseas respondents included 32 from European countries other than Northern Europe, 7 from Northern Europe, 18 from North America, one from South America, 17 from Asia, and 6 from Oceania. This reflected a geographically diverse questionnaire survey area covering several countries worldwide.

**Results**

1. **Treatment modalities for minimally invasive papillary carcinomas of the thyroid (T1)**

A 35-year-old woman was found to have a thyroid adenoma by ultrasound examination performed during a routine medical check-up. Fine needle aspiration (FNA) biopsy under ultrasonic guidance showed a papillary carcinoma, while ultrasonic imaging revealed the tumor to be located in the inferior pole of the thyroid lobe with no sign of tumor infiltration. There was no lymph node enlargement.

Do you prefer surgery or one of the other options listed below?

- Surgery
- Observation without surgery
- PEIT (percutaneous ethanol injection therapy) under ultrasonic guidance

Surgical options:
- Partial thyroid lobectomy
- Thyroid lobectomy
- Subtotal thyroidectomy
- Total thyroidectomy (near-total thyroidectomy)

Lymph node dissection:
- No
- Paratracheal lymph node (central node) dissection on the affected side
- Bilateral paratracheal lymph node dissection
- Modified neck dissection on the affected side

**Tumor diameter 0.5–1 cm**

Do you prefer surgery or one of the other options listed below?

- Surgery
- Observation without surgery
- PEIT under US guidance

Surgical options:
- Partial thyroid lobectomy
- Thyroid lobectomy
- Subtotal thyroidectomy
- Total thyroidectomy (near-total thyroidectomy)

Lymph node dissection:
- No
- Paratracheal lymph node (central node) dissection on the affected side
- Bilateral paratracheal lymph node dissection
- Modified neck dissection on the affected side

**Tumor diameter 1–2 cm**

Do you prefer surgery or one of the other options listed below?

- Surgery
- Observation without surgery
- PEIT under US guidance

Surgical options:
- Partial thyroid lobectomy
- Thyroid lobectomy
- Subtotal thyroidectomy
- Total thyroidectomy (near-total thyroidectomy)

Lymph node dissection:
Table 1 shows geographical percentages of surgical procedures performed for micropapillary carcinomas of the thyroid stratified by primary tumor size in Japan and various other countries. In foreign countries, there were no geographical differences in the frequency of surgery and all of the respondents showed surgery to be the treatment of choice for micropapillary carcinomas, irrespective of tumor size. On the contrary, domestic physicians were likely to be reluctant to perform surgery for micropapillary carcinomas; about one-third favored surgical treatment for tumors measuring 0.5 cm or less, and about two-thirds favored this approach for tumors measuring 0.5–1.0 cm. Fig. 1 shows the extent of thyroid resection according to tumor size in Japan and various other countries. Total thyroidectomy was very common in foreign countries: 42–60% for tumors 0.5 cm or less, 55–64% for tumors measuring 0.5–1.0 cm, and 86–91% for tumors measuring 1.0–2.0 cm. On the contrary, the frequency of total thyroidectomy was extremely low in Japan, and thyroid lobectomy accounted for the majority of surgical options. Fig. 2 shows geographical percentages of lymph node dissection performed for micropapillary carcinomas of the thyroid and the extent of lymph node dissec-

<table>
<thead>
<tr>
<th>Primary tumor size</th>
<th>Surgical cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>Europe</td>
</tr>
<tr>
<td>0–0.5 cm</td>
<td>27%</td>
</tr>
<tr>
<td>0.5–1.0 cm</td>
<td>60%</td>
</tr>
<tr>
<td>1.0–2.0 cm</td>
<td>99%</td>
</tr>
</tbody>
</table>

Fig. 1. Extent of thyroid resection stratified by primary tumor size in minute papillary thyroid carcinoma (T1)
tion according to primary tumor size in Japan and various other countries. Overall, the percentage of lymph node dissections performed for micropapillary carcinomas tended to rise with increasing tumor size. This tendency was noted among respondents from European countries, in which physicians tended to favor more extensive lymph node dissection with increasing tumor size. Domestic respondents even more strongly favored lymph node dissection, choosing extensive lymph node dissection for tumors measuring 1.0–2.0 cm. In short, domestic physicians were less likely to favor surgical options for primary thyroid cancer than overseas physicians, and thyroid resection was less extensive. On the contrary, lymph node dissection tended to be favored in Japan.

2. Treatment modalities for large papillary carcinomas of the thyroid (3 cm: T2) (low-risk group)

A 40-year-old man presented with a mass in the right thyroid lobe. Ultrasound and CT examinations revealed a 3-cm mass localized within the thyroid gland and 2 enlarged lymph nodes each on the paratracheal and lateral sides of the internal jugular vein on the affected site. FNA biopsy led to a diagnosis of well-differentiated papillary thyroid carcinoma. Vocal cord movement was normal, and there was no evidence of distant metastasis.

Surgical options:
- □ Lobectomy
- □ Subtotal thyroidectomy
- □ Total thyroidectomy (near-total thyroidectomy)

Lymph node dissection:
- Paratracheal lymph node
  - (central node)dissection
- Modified neck dissection

Postoperative TSH suppression therapy:
- □ Throughout lifetime, as a rule
Postoperative high-dose radioiodine therapy combined with total (near-total) thyroidectomy:

- At least 5 years
- For 1–2 years
- Not conducted

As to the extent of thyroid resection, total thyroidectomy was chosen by 100% of overseas respondents but by only 20% of domestic respondents. On the contrary, subtotal thyroidectomy and lobectomy were favored by 45% and 35%, respectively, in Japan (Fig. 3). Table 2 shows geographical percentages of lymph node dissection and the extent of lymph node dissection in Japan and various other countries. Although there was a similar tendency regarding the extent of lymph node dissection worldwide, intact side lymph node dissection tended to be more frequently performed in Japan and European countries than in other areas. Fig. 4 shows the percentages using postoperative TSH suppression therapy. All overseas physicians responded that they give TSH suppression therapy for at least 5 years or throughout the patient’s lifetime; in particular, the administration of TSH suppression therapy for an entire lifetime was very strongly favored in Asia/Oceania. On the contrary, 37% of domestic physicians reported that they “do not use” TSH suppression therapy. This discrepancy between Japan and other countries may be explained by the fact that total thyroidectomy is in principle performed in all low risk patients in foreign countries.

Table 3 shows the indications for postoperative high-dose $^{131}$I therapy for large papillary carcinomas of the thyroid in Japan and various other countries. Total (or near-total) thyroidectomy is a prerequisite for postoperative high-dose $^{131}$I therapy. In Japan, the implementation of total (or subtotal) thyroidectomy was reported in 20% (27 of 132 institutions), and 28% of these 27 institutions (or 5.6% of all 132 institutions) responded that they administered postoperative high-dose $^{131}$I therapy. On the other hand, total thyroidectomy is performed in all institutions in foreign countries, and additional postoperative high-dose $^{131}$I therapy is

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**Table 2.** Extent and percentages of lymph node dissection for large papillary carcinomas of the thyroid

<table>
<thead>
<tr>
<th>Extent of lymph node dissection</th>
<th>Japan</th>
<th>Europe</th>
<th>Asia/Oceania</th>
<th>North/South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paratracheal lymph nodes on the affected side</td>
<td>100%</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lateral cervical lymph nodes on the affected side</td>
<td>93%</td>
<td>91%</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>Paratracheal lymph nodes on the intact side</td>
<td>67%</td>
<td>64%</td>
<td>53%</td>
<td>50%</td>
</tr>
<tr>
<td>Lateral cervical lymph nodes on the intact side</td>
<td>11%</td>
<td>18%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>
administered in 79–90%. Thus, there was a marked discrepancy in the administration of postoperative high-dose $^{131}$I therapy between Japan and other countries. For this radiotherapeutic modality, 18% of domestic respondents “hoped to adopt this strategy, if available”, revealing that high-dose radioiodine treatment is desired by many physicians in Japan.

3. Treatment modalities for recurrent papillary thyroid carcinomas after surgery (high-risk group)

A 60-year-old woman had undergone total thyroidectomy and bilateral modified neck dissection for papillary thyroid carcinoma 5 years previously. The tumor subsequently recurred repeatedly in the cervical lymph nodes and on each occasion, the involved lymph nodes were extirpated. At the most recent follow-up, she was found to have a fifth recurrence that involved the right lateral cervical lymph nodes.

What is your therapeutic policy in such a case (multiple answers are possible)?

□ None, other than observation
□ Extirpation of the metastatic lymph nodes
□ Modified neck dissection
□ External irradiation
□ High-dose radioiodine treatment
□ PEIT under US guidance

Table 4 shows treatment modalities for postoperative recurrent papillary carcinomas of the thyroid. Treatment policies for postoperative recurrent papillary carcinomas of the thyroid tended to be similar Japan and other countries. High-dose radioiodine treatment was more likely to be favored in Europe (73%) and Asia/Oceania (79%), and the percentage undergoing extirpation of the metastatic lymph nodes was high in North/South America (79%). The adoption of high-dose radioiodine treatment was favored overall (60% in Japan and 57–79% in foreign countries); however, external irradiation was uncommon in the treatment of recurrent papillary thyroid cancer (0–21%).

### Discussion

In addition to the TNM staging system, prognostic scoring systems based on patient age, tumor grade, ex-
tent and size (AGES) [1, 2] or based on patient age, tumor metastases, extent and size (AMES) [2–4] have been advocated for determining the prognosis of well-differentiated thyroid cancer. Taking these prognostic factors into account, a questionnaire survey was conducted, covering therapeutic options for well-differentiated thyroid cancer according to tumor size and the degree of prognostic risk. In this study, the degree of prognostic risk was based on the commonly used, worldwide, AMES system [2–4]. The results of the questionnaire survey conducted in Japan have already been reported elsewhere [5, 6]. This study was designed to assess discrepancies in therapeutic policies for well-differentiated thyroid cancer between Japan and other countries.

1. Treatment modalities for minimally invasive papillary carcinomas of the thyroid (T1)

Advances in ultrasound technology have facilitated detection of small thyroid cancers, and the thyroid cancer detection rate is thought to be approximately 0.7–1.5% for ultrasound conducted as part of a mass screening program in Japan. On the other hand, mortality from thyroid cancer accounts for only 0.5% of all cancer mortalities. Thus, there is a marked disparity between the morbidity and mortality associated with thyroid cancer. Although the incidence of thyroid cancer has also increased 240% during the last 5 decades in Western countries, the mortality from this disease has decreased to 44% [7]. Such minute thyroid cancers may remain latent and may not be associated with a fatal prognosis. Thus, whether all those minimally invasive thyroid carcinomas should be examined in detail and treated whenever detected remains controversial.

The most common treatment policy adopted in Western countries is total or near-total thyroidectomy. In addition, enlarged lymph nodes alone are extirpated and the frequency of conservative neck dissection with prophylactic intent is low. Based on a report from the National Cancer Data Base in the United States, the proportion of total or near-total thyroidectomy for papillary thyroid carcinoma was 65% during the 10-year period from 1985 to 1995, while the frequency of neck dissection was only 7% [8].

For the primary site of minute papillary thyroid carcinoma, the results of this survey showed the surgical option to be overwhelmingly the preferred choice while extensive resection was favored in foreign countries; however, total thyroidectomy is rarely performed and limited operations, such as total or partial lobectomy, are the most common surgical option in Japan. If total thyroidectomy is not performed, postoperative thyroid and parathyroid function can be preserved, but supplemental thyroid hormone therapy is commonly administered to suppress TSH even after lobectomy. The application of total thyroidectomy has some advantages in that patients undergoing this procedure have no anxiety regarding cancer recurrence or transformation into undifferentiated malignancy of the thyroid gland. Postoperative serum thyroglobulin determination is a sensitive method for the detection of recurrences and metastases in the follow-up of such patients, and there is further benefit from the postoperative use of $^{131}$I in the detection and treatment of metastases. However, in view of the fact that the incidence of potential recurrences and metastases is extremely low in the low-risk group, total thyroidectomy is not necessarily advocated as the first choice treatment for minute papillary thyroid cancer. One possibility for the treatment of minute thyroid tumors, particularly those 0.5 cm or less, is follow-up for such patients without surgical intervention. The scarcity of randomized trials makes it difficult to show conclusively which surgical option (i.e., total thyroidectomy, or lobectomy) is best for the patients. The absence of randomized prospective trials has led most opinions to be based on personal or emotional views rather than on scientific documentation.

| Table 4. Treatment modalities for recurrent papillary carcinomas of the thyroid after surgery |
|---------------------------------|--------|--------|--------|--------|
|                                 | Japan  | Europe | Asia/Oceania | North/South America |
| No other than observation       | 2%     | 0%     | 0%     | 7%     |
| Extirpation of the metastatic lymph nodes | 56%    | 61%    | 58%    | 79%    |
| Modified neck dissection        | 37%    | 36%    | 53%    | 29%    |
| External irradiation            | 14%    | 15%    | 21%    | 0%     |
| High-dose radioiodine treatment | 60%    | 73%    | 79%    | 57%    |
| PEIT under US guidance         | 5%     | 3%     | 5%     | 0%     |
Because the outcomes in both groups have been excellent, the likelihood of doing randomized prospective trials that need more than 10,000 patients to be followed up for 30–35 years is low [9].

The National Comprehensive Cancer Network (NCCN) has proposed the Clinical Practice Guidelines in Oncology (V.1, 2004) as guidelines for treating malignant tumors measuring 1 cm or less [10]. These guidelines recommend that thyroid tumors measuring 1 cm or less in diameter be observed without treatment and those exceeding 1 cm be subjected to a biopsy. When a biopsy has shown a tumor to be a papillary carcinoma and at least one of the following factors exists, the patient is placed in the high-risk category and total thyroidectomy is performed and, if node-positive disease is present, the procedure is combined with neck dissection: (1) age <15 years or >45 years, (2) history of radiation exposure, (3) known distant metastases, (4) bilateral disease, (5) extra-thyroidal extension, (6) tumor >4 cm in diameter, (7) cervical lymph node metastases, and (8) family history of papillary or follicular thyroid cancer. When none of the factors listed above exists, total thyroidectomy or lobectomy plus isthmusectomy is recommended.

As for the indications for lymph node dissection and the extent of dissection, the latter was found to be greater in Japan than in foreign countries, as tumor diameter increased. Overall, more extensive thyroid resection was clearly favored in foreign countries as compared to Japan, but lymph node dissection was not a common treatment option. This marked discrepancy between Japan and foreign countries may be explained by the treatment concept that high-dose $^{131}$I radiotherapy following total thyroidectomy can ultimately be administered. The presence or absence of lymph node involvement is not included in the commonly recognized worldwide systems for the degree of prognostic risk, such as AGES [1, 2] and AMES [2–4]. However, paratracheal lymph nodes, at least on the affected side, should be completely dissected in patients undergoing thyroidectomy, considering the risks of developing recurrent nerve paralysis due to postoperative regional lymph node recurrence and transformation into undifferentiated malignancy.

2. Treatment modalities for large papillary thyroid carcinomas (3 cm; T2) (low-risk group)

Surgical treatment is thought to usually be the first choice for relatively large differentiated thyroid cancers classified into the low-risk group. In the present survey, all worldwide respondents also chose surgery for treatment of this type of thyroid cancer. Patients undergoing surgery for low-risk large papillary thyroid cancer reportedly have a death rate of only 1–2%, if there is no evidence of hematogenous metastasis [3]. The results of this survey showed the frequency of total thyroidectomy to be 100% in foreign counties but only 20% in Japan. For low-risk patients with thyroid cancer, total or near-total thyroidectomy is the main standard surgical option in Western countries [11]. On the other hand, while there is a report stating that lobectomy is a preferable surgical approach [4], in another report lobectomy was described as being associated with a higher risk of locoregional recurrence [12]. Thus, there is no consensus on the standard treatment for large papillary thyroid carcinoma, nor is there substantial evidence indicating which treatment is most useful.

There is a similar tendency regarding the extent of lymph node dissection in Japan and foreign countries: cervical lymph node dissection on the affected side is chosen in the majority of low-risk patients and paratracheal lymph node dissection on the intact side is performed in approximately 60% of patients, although the dissection is slightly more extensive and this approach is more prevalent in Japan than in foreign countries. There is considerable controversy regarding the extent of lymph node dissection. However, it was reported in Japan that lymph node dissection may be associated with a decrease in local recurrence [2–4] and as such lymph node dissection is favored. However, the presence or absence of lymph node involvement is not covered by the representative prognostic scoring system adopted in Western countries.

The administration of postoperative TSH suppression therapy was advocated by an overwhelming number of overseas respondents, reflecting that all chose total thyroidectomy for T2 patients, which essentially requires thyroid hormone therapy. There is a report stating that postoperative TSH suppression therapy can reduce the recurrence rate [13], but there is no substantial evidence to support this. Once the administration of L-thyroxine is started, for the purpose of suppressing TSH, the medication must, theoretically, be continued for the remainder of the patient’s life. If L-thyroxine is administered for several years after subtotal thyroidectomy, it is said that the residual thyroid gland may atrophy. The withdrawal of L-thyroxine there-
after is likely to compromise thyroid function and the TSH level will increase thus for a second time. There is no available evidence to substantiate the assumption that an elevation of TSH under such circumstances is responsible for cancer recurrence. Neither has the extent to which the TSH level will be suppressed been established. Initially, it was recommended that the TSH level be reduced below the detectable limit; but in recent years it has been reported that it should be at the lower limit of the normal range [14]; and a few reports have even stated that the therapeutic outcome is not improved by TSH suppression therapy [3, 15]. Bone loss is reported to be an adverse reaction associated with TSH suppression therapy in post-menopausal women [16]. Indications for TSH suppression therapy need to be further investigated.

The results of the present survey show postoperative high-dose $^{131}$I radiation therapy to be given more frequently in foreign countries than in Japan; however, this remains controversial. In foreign countries, total thyroidectomy is performed even in patients with low-risk thyroid cancer; and postoperative radiiodine treatment is in principle considered. However, there is a report stating that high-dose $^{131}$I radiation therapy is not associated with improvement in the prognosis of low-risk papillary thyroid cancer patients [17]. In the present survey, high-dose $^{131}$I radiation therapy following total or near-total thyroidectomy was chosen by 28% of domestic respondents and 79–90% of overseas respondents, revealing a marked discrepancy in the administration of radiiodine treatment between Japan and foreign countries. Total or near-total thyroidectomy is in principle performed in all institutions in foreign countries; in Japan, on the contrary, the frequency of total or near-total thyroidectomy is only 20%. The present domestic survey showed radiiodine treatment to be performed in only 8 (5.6%) institutions. This also indicates a major discrepancy in giving high-dose $^{131}$I radiation therapy between Japan and foreign countries. Furthermore, judging from the delivery record of radiiodine from the Japan Radiisotope Association to these 8 institutions, it was suspected that only 4 institutions adopt high-dose $^{131}$I radiation therapy for substantial numbers of patients, and these account for only 3% of all institutions participating in the present domestic survey.

3. Treatment modalities for recurrent papillary thyroid carcinomas after surgery (high-risk group)

We are facing a dilemma involving radical treatment for recurrent papillary thyroid carcinoma versus maintenance of the patient’s quality of life in determining the treatment policy for recurrent papillary carcinomas of the thyroid. Because the radiosensitivity of papillary thyroid carcinoma is low, surgical resection appears to be the treatment of choice for the first cancer recurrence, if the function of the laryngeal or recurrent laryngeal nerve can be preserved. Sugino et al. conducted 107 re-operations on a total of 60 patients who developed recurrent carcinoma among 419 patients who suffered from well-differentiated thyroid carcinoma. They reported that the surgery was repeated only once in most of their patients (60%) and 5 times or more in 10% [18]. In a case of postoperative recurrent papillary thyroid carcinoma, as indicated in the present survey, local resection was repeated for recurrent lymph node involvement following the initial treatment that included total thyroidectomy and bilateral neck dissection. In this case, the treatment option that should be selected for a fifth recurrence remains to be decided.

The results of the present survey showed a similar tendency for postoperative recurrent papillary thyroid carcinoma treatment in Japan and foreign countries, i.e. surgical options, including lymph node extirpation (around 60%) and neck dissection (around 40%), tended to be prevalent. In carcinoma cases with multiple recurrences, as illustrated by the case presented herein, radiiodine treatment was favored in Japan, as well as in foreign countries, suggesting that this type of treatment is regarded as systemic radiotherapy, considering metastases to other anatomical sites. However, indications for high-dose $^{131}$I radiation therapy are limited, considering that the accumulation of $^{131}$I, younger patients, and small metastatic foci are factors associated with benefit from this treatment. The development of myelocytic leukemia is sporadically reported as an adverse effect of high-dose $^{131}$I radiation therapy, but its incidence is extremely low. In view of the fact that radiiodine treatment is beneficial in controlling thyroid cancer, it seems unnecessary in the meanwhile to consider the potential risk of developing a secondary cancer. Because no adverse radiation effects other than myelocytic leukemia are likely, indications for radiiodine treatment should be expanded. In Japan, high-dose $^{131}$I radiation therapy was chosen at a higher fre-
quency (60%) than expected. This frequency may have included the preference for this therapy, if available. In fact, although there are an estimated 6,800 thyroid cancer patients per year who are potential candidates for radioiodine treatment, the actual number of patients treated with radioiodine was approximately 1,500 from nearly 70 institutions, accounting for 22% of the estimated number (personal communication from the Japan Radioisotope Association). This figure was far lower in Japan than in foreign countries. The present domestic survey failed to reveal the actual practice of high-dose $^{131}$I radiation therapy. Although the clinical significance of this radioiodine treatment is well recognized in Japan, many candidates are unlikely to receive it. This can be explained by the fact that very limited availability of high-dose radioiodine treatment leads to difficulty in the immediate actual application of this modality, even though it is required in many patients with thyroid cancer. The following explanations are possible: legal restrictions against high-dose $^{131}$I radiotherapy are very strict and the NHI (National Health Insurance Drug Price Standard) reimbursement for this treatment is extremely low. This situation requires further general improvement. Some institutes in the U.S.A. reported the preliminary results of cases of differentiated thyroid cancer, treated with 1100 MBq (<30 mCi) $^{131}$I as out-patients [19]. The final result of this treatment is still controversial but the application of it should also be considered in Japan.

The present survey revealed that the acceptance of external irradiation is extremely low. We radiation oncologists believe that external irradiation is beneficial as a local treatment for selected patients with recurrent thyroid cancer. In general, external irradiation is indicated in cases with unresectable tumors or a clear positive margin that may not be controllable with radioiodine treatment, profound cancer involvement of surrounding tissue for which postoperative recurrence is very likely, postoperative cancer recurrence for which surgery is not feasible, and recurrence following aggressive $^{131}$I treatment. In view of the fact that thyroid cancer is less radiosensitive, it is reasonable and not surprising that surgery was the most prevalent therapeutic option for thyroid cancer in this survey. Nevertheless, we believe that external irradiation should be selected to prevent postoperative cancer recurrence.

In the present survey, recombinant humanized TSH (rhTSH), which has not been approved in Japan, was not included as one of the questionnaire entries. In foreign countries, rhTSH is widely used as an alternative to TSH suppression therapy in patients with well-differentiated thyroid carcinoma following total thyroidectomy, in combination with thyroglobulin measurements for the detection of cancer recurrence, diagnostic $^{131}$I scintigraphy, and high-dose $^{131}$I radiation therapy. Examination or treatment with rhTSH should be instituted a few weeks after discontinuation of oral administration of thyroid hormone, probably leading not only to an improvement in the patient’s quality of life, but also to prevention of the proliferation of tumor cells during the period after thyroid hormone discontinuation. Indications for rhTSH have already been well established in foreign countries and are widely used in various countries ranging from Eastern Asia to South America [20]. The present survey inquired only as to whether rhTSH is used or not. The results revealed that lack of availability of rhTSH is limited to Japan. We expect rhTSH to be approved in Japan in the very near future.

Conclusions

A large-scale questionnaire survey was conducted to clarify the discrepancies in treatment options for well-differentiated thyroid cancer between Japan and various foreign countries. The results revealed the more prevalent therapeutic options in foreign countries, as compared to Japan, to be: (1) total thyroidectomy even for minimally invasive small thyroid carcinoma (T1), (2) high-dose $^{131}$I radiation therapy even for large papillary thyroid carcinoma with a favorable prognosis (T2, low-risk group), (3) high-dose $^{131}$I radiation therapy, and (4) long-term TSH suppression therapy. On the other hand, thyroid resection is relatively less extensive in Japan, and lymph node dissection is more likely to be favored as the treatment of choice. The rationale for performing total thyroidectomy is based on the concept of radical treatment of cancer followed by high-dose $^{131}$I radiation therapy. Taken together, these observations indicate that there is a marked discrepancy in various therapeutic options, including the use of rhTSH, for thyroid cancer between Japan and other countries. As long as no reasonable explanation for such discrepancies can be given to overseas physicians, Japan is seen as being unreasonable, and possibly even backward, by the rest of the world in its treatment of thyroid cancer patients.
References


