Therapeutic strategy for low-risk thyroid cancer in Kanaji Thyroid Hospital

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Abstract. It is well-known that differentiated thyroid carcinoma (DTC) has a generally indolent character and shows a favorable prognosis in comparison with many other carcinomas. The therapeutic strategy for patients with DTC in Japan has differed from that in Western countries. Total thyroidectomy followed by radioactive iodine (RAI) ablation has been standard in Western countries, whereas limited hemi-thyroidectomy and subtotal thyroidectomy has been extensively accepted in Japan. Papillary thyroid carcinoma (PTC) accounts for over 90% of all thyroid cancers in Japan. The majority of patients with PTC are categorized into a low-risk group on the basis of the recent risk-group classification schemes, and they show excellent outcomes. Several management guidelines for thyroid cancers have been published in Western countries. However, the optimal therapeutic options for PTC remain controversial, and high-level clinical evidence aimed at resolving these issues is lacking. Moreover, as socioeconomic differences in medical care exist, conventional policies for the treatment of PTC have differed between Japan and other countries. This review focuses on the special features of treatment in Japan for patients with low-risk DTC involving subtotal thyroidectomy without adjuvant therapies, rather than total thyroidectomy with RAI, with the aim of preserving quality of life. At our institution in Japan, we have had extensive experience with RAI treatment for high-risk DTC patients, and this represents a very rare situation. Here we introduce the therapeutic strategy for low-risk thyroid cancer in Japan, including the measures adopted at our institution.

Key words: Low-risk, Papillary thyroid cancer, Follicular thyroid cancer, Total thyroidectomy, Hemi-thyroidectomy

THE INCIDENCE of papillary carcinoma in Japan is higher than that in Western countries, possibly because of the sufficient dietary intake of iodine. Papillary and follicular carcinomas are often classified into differentiated carcinoma (DTC) as a single group. In terms of histological type, based on investigations by the Japanese Society of Thyroid Surgeons (JSTS) in 2004 [1] and our institution (in parentheses), the incidence of papillary carcinoma was 92.5% (92.0%), that of follicular carcinoma 4.8% (5.9%), that of medullary carcinoma 1.3% (1.0%), and that of anaplastic carcinoma 1.4% (1.2%). In the United States, the addition of iodine to dietary salts was started in the 1920s. Using the Surveillance, Epidemiology, and End Results program and data on thyroid cancer mortality from the National Vital Statistics System, Davies and Gilbert Welch [2, 3] reported that the incidence of thyroid cancer in the US increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, thus representing a 2.4-fold increase. No significant changes were seen in the incidences of the less common histological types, such as follicular, medullary, and anaplastic carcinoma. Virtually all of this increase has been attributable to an increase in the incidence of papillary carcinoma, from 2.7 to 7.7 per 100,000, representing a 2.9-fold increase. In Japan, by contrast, the incidence of thyroid carcinoma in males and females in 2003 was 3.25 and 9.26 per 100,000, and the age-adjusted incidence was 2.56 and 7.17 per 100,000, respectively [1].

The strategy for treatment of DTC in Japan has traditionally differed from that in Western countries, where total and/or near-total thyroidectomy is performed almost routinely followed by RAI ablation and thyroid stimulating hormone (TSH) suppression as the standard. In Japan, by contrast, limited forms of thyroidectomy such as hemi-thyroidectomy and subtotal thyroidectomy have been adopted more extensively than total thyroidectomy for various reasons. First, the capacity to administer radioactive iodine (RAI) is lim-
The American Thyroid Association (ATA) guidelines indicate that the treatment strategies for papillary and follicular carcinomas are much the same as those for DTC overall [6]. However, these two histological types have different behaviors: papillary carcinoma is likely to metastasize to lymph nodes, while follicular carcinoma is predominantly metastasizes to distant organs. Moreover, papillary carcinoma can usually be diagnosed by preoperative imaging studies and fine-needle aspiration cytology (FNAC), whereas follicular carcinoma is normally diagnosed by postoperative pathological examination. Here, therefore, treatments for low-risk papillary and follicular carcinomas are described separately.

At our institution between 1993 and 2012, a total of 4560 patients with thyroid and parathyroid disease underwent surgical treatment, and 1411 patients with DTC underwent thyroidectomy and lymph node dissection. Distant metastases of DTC appeared in 100 cases (83 PTCs and 17 FTCs), including 70 lung and 30 bone and/or lung metastases. We have performed RAI therapy aggressively for distant metastases and high-risk DTC since 2005. Here we present our therapeutic strategy for low-risk thyroid cancer and describe the differences and commonalities between Western countries and Japan, with reference to our institution.

### Treatment for Low-risk Papillary Carcinoma

#### Surgical treatment (thyroidectomy)

There is insufficient evidence to indicate that total thyroidectomy improves cause-specific survival of patients with papillary carcinoma relative to that of patients who undergo hemi-thyroidectomy. Total thyroidectomy prevents recurrence in the remnant thyroid but does not reduce the incidence of recurrence in lymph nodes, or distant metastasis. However, we recommend total thyroidectomy for high-risk patients [1]. Such high-risk patients are those with a maximal...
tumor diameter of $>5$ cm, extrathyroid extension to the mucosa of the trachea or esophagus, a large number of clinical lymph node metastases, lymph node metastasis diameter $>3$ cm, and the presence of distant metastasis. Low-risk patients are those with a maximal tumor diameter of $<2$ cm and absence of clinical lymph node metastasis (T1N0M0 by the TNM classification). Hemi-thyroidectomy is acceptable for such low-risk patients (Fig. 1). Other patients are classified as lying within a “gray zone” with regard to the extent of thyroidectomy, but the majority of institutions encourage total thyroidectomy for patients with tumors larger than 4 cm or clinical lymph node metastases.

The extent of thyroidectomy in Japan has traditionally differed from that in most other countries. The ATA guidelines recommend total or near-total thyroidectomy for DTC, except for low-risk micro-papillary carcinoma [6]. The BTA guidelines recommend total thyroidectomy for most papillary carcinomas, especially those with a tumor diameter greater than 1 cm, multifocal disease, extrathyroidal extension, familial disease, history of neck irradiation, and clinical lymph node metastases [4]. The AACE/AAES guidelines recommend total thyroidectomy especially for high-risk patients, as defined by various classification systems such as the AGES, AMES, MACIS and for patients with carcinoma located in both lobes, the presence of nodules in the contralateral lobe, extrathyroid extension, and local or distant metastasis [7]. In the NCCN guidelines, hemi-thyroidectomy is accepted for patients with all of the following clinicopathological features: age 15-45 years, no prior radiation treatment, no distant metastasis, no cervical lymph node metastasis, no extrathyroidal extension, tumors smaller than 4 cm, and no signs of aggressive variants [8] (Table 2).

However, it is also mentioned that total thyroidectomy is the “most common” strategy even for such patients. On the other hand, limited forms of thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy have been widely adopted in Japan. Several studies from Western countries have demonstrated that total thyroidectomy offers a better prognosis than hemithyroidectomy [9-17]. These results might be low grade evidence, because there were not including randomized studies in almost of these reports. Furthermore, most patients who undergo total thyroidectomy in Western countries may also undergo RAI ablation therapy, which means that these previous studies may not have genuinely compared total thyroidectomy with limited thyroidectomy (Table 3). It is worth noting that several studies have failed to demonstrate any effect of the extent of thyroidectomy on outcome [18-22]. A report from Japan has indicated that rate of recurrence of solitary T1N0M0 papillary carcinoma in the remnant thyroid of patients who had undergone hemithyroidectomy was only 1%. They reported that solitary T1N0M0 patients had an excellent prognosis when they undergo thyroidectomy and elective lymph node
dissection without radioiodine therapy [23] (Fig. 1). These results suggest that RAI therapy should be recommended to high-risk papillary thyroid cancer patients. It is generally accepted that total thyroidectomy improves patient outcome, especially in terms of cause-specific survival. In Japan, there is now a consensus that high-risk patients, as indicated above, should undergo total thyroidectomy. In contrast, we have concluded that total thyroidectomy is unnecessary for T1N0M0 patients if no pathological lesions are present in the contralateral lobe. Table 2 summarizes the treatment options for thyroid carcinoma as stipulated in the Western and Japanese guidelines.

**Lymph node dissection**

There is no evidence that prophylactic central compartment dissection improves the cause-specific survival of patients with papillary carcinoma. Although there is no evidence that prophylactic lateral node dissection improves the life prognosis of patients, it reduces the risk of relapse to lymph nodes and improves disease-free survival [1]. However, it is recommended for initial surgery, because reoperation for relapse to this compartment carries a risk of severe complications. Therapeutic central node dissection is prognostically beneficial, and there is no room for argument that such dissection is mandatory. With regard to prophylactic central node dissection for patients without clinical node metastasis, the ATA guidelines indicate that it may be performed for T3 or T4 cases, whereas it is not necessary for T1 or T2 cases [6]. The BTA guidelines recommend prophylactic central node dissection only when patients have one or more of the following high-risk characteristics: male gender, age

| Table 2 | Extend of thyroidectomy and lymph node dissection for patients with papillary thyroid carcinoma by the major World guidelines |
|------------------|-------------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Extent of thyroidectomy |                                   |                  |                 |                  |                  |                  |
| Total or near-total thyroidectomy | Age <15 or ≥45 T>4 cm Ex (+) N (+) M (+) | Age ≥45 T>1-1.5 cm Ex (+) N (+) M (+) | T>1 cm High-risk cancer Ex (+) N (+) M (+) | T>4 cm Ex(+) N(+) M(+) | T>2 cm Ex(+) N(+) M(+) |
| Lobectomy (+isthmusectomy) | Other than above Ex (+) N (+) M (+) | Other than above Ex (+) N (+) M (+) | Other than above Ex (+) N (+) M (+) | Other than above Ex (+) N (+) M (+) | Other than above Ex (+) N (+) M (+) |
| Lymph node dissection |                                   |                  |                 |                  |                  |                  |
| Central compartment dissection N.R Ex0 N0 | N.R Ex0 N0 | N.R Ex0 N0 | [401] M0 | [401] M0 | [401] M0 | [401] M0 |
| Lateral compartment dissection N.R Ex0 N0 | N.R Ex0 N0 | N.R Ex0 N0 | N.D Ex0 N0 | N.D Ex0 N0 | N.D Ex0 N0 | N.D Ex0 N0 |

T, tumor size; N, lymph node; M, distant metastasis; Ex, extrathyroidal extension; Ex(+), extrathyroid extension to the mucosa of the trachea or esophagus; N(+), a large number of clinical lymph node metastases, lymph node metastasis>3 cm; N.R, not recommended; N.D, not determined, although its significance for reducing recurrence is recognized; NCCN, National Comprehensive Cancer Network; ATA, American Thyroid Association; BTA, British Thyroid Association; AACE/AAES, American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons; JSTS/JAES, Japanese Society of Thyroid Surgery and Japan association of Endocrine Surgeons

| Table 3 | Comparison of merit and demerit between total thyroidectomy and limited thyroidectomy in thyroid cancer |
|------------------|-------------------------------------------------|------------------|
| Merit | Demerit | |
| Total thyroidectomy | 1. easy to do radioiodine therapy | 1. postoperative hypothyroidism (need to medication) |
| 2. never to relapse remnant thyroid | 2. risk of postoperative hypoparathyroidism | 3. risk of bilateral laryngeal recurrent nerve paralysis |
| Limited thyroidectomy | 1. low risk of postoperative hypothyroidism (possibility of no medication) | 1. risk of relapse in remnant thyroid |
| 2. not to easy to do radioiodine therapy | | |
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in Japan have investigated the incidence of low-risk and incidentally detected micro-papillary carcinoma and these patients have been favorable outcome [33, 34]. These reports suggest that there is a need to discuss and carefully consider whether simple observation or thyroidectomy should be the treatment strategy for micro-papillary carcinoma.

Treatment for Low-risk Follicular Carcinoma

Most follicular carcinomas are diagnosed on post-operative pathological examination. As initial surgery, most patients undergo lobectomy or hemi-thyroidectomy under a diagnosis of follicular tumor or neoplasm. The classification of widely invasive and minimally invasive types allows some degree of prognostication. Widely invasive carcinoma has a significantly worse prognosis than minimally invasive carcinoma, and the degree of vascular invasion in particular is of prognostic significance. It is recommended that follicular carcinoma be divided into widely and minimally invasive types based on postoperative pathological examination [1].

At Kanaji Thyroid Hospital, follicular neoplasms (class III) (tumor size <5 cm, and no distant metastasis (M0)) are ordinary performed lobectomy. The patients of low-risk follicular carcinoma, minimally invasive type with no vascular invasion and follicular adenoma in post-operative pathological diagnosis are followed by a cervical ultrasound/year, thyroglobulin (Tg) and TgAb measurement/6 months, and Chest computer tomography/1-2 years (only cancer cases). On the other hand, we recommend completion total thyroidectomy with RAI ablation for patients with widely invasive carcinoma and minimally invasive carcinoma with significant vascular invasion who have initially undergone lobectomy (Fig. 2). We also recommend total thyroidectomy for the patients with highly suspicious widely invasive carcinoma and tumor size≥5 cm in pre-operative pathological diagnosis. As a matter of course, we are performed carefully informed consents to these patients (Fig. 3).

Observation or thyroidectomy?

Surgical treatment is mandatory for patients with papillary microcarcinoma in whom clinical lymph node metastasis is evident by palpation or imaging studies, or for those with distant metastasis or significant extrathyroidal extension. Patients without these features can be candidates for observation after extensive explanation of the situation and acquisition of informed consent [1]. The recent prevalence of ultrasonography and ultrasonographically guided FNAC has facilitated the diagnosis of small carcinomas, including low-risk papillary microcarcinoma. Davis et al. [3] reported that from 1973 to 2002, there was a 2.4-fold increase in the incidence of thyroid carcinoma, although mortality remained stable during this period. They concluded that this increasing incidence reflected the increased rate of detection of subclinical cases such as low-risk carcinoma. In Japan, it has been reported that the incidence of incidentally detected thyroid carcinoma on mass screening is 1000-fold higher than that of overt carcinoma [2]. Therefore, some institutions in Japan have investigated the incidence of low-risk and incidentally detected micro-papillary carcinoma and these patients have been favorable outcome [33, 34]. These reports suggest that there is a need to discuss and carefully consider whether simple observation or thyroidectomy should be the treatment strategy for micro-papillary carcinoma.
Fig. 2 The standard therapeutic guidelines at Kanaji Thyroid Hospital for low-risk follicular thyroid carcinoma

Fig. 3 The standard therapeutic guidelines at Kanaji Thyroid Hospital for high-risk differentiated thyroid carcinoma
Therapeutic strategy low-risk TC cases are regarded as lying within a “gray zone”, and no clear recommendations are offered. These guidelines treat oxyphilic (Hurthle) cell carcinoma, a follicular carcinoma variant, separately, and recommend total thyroidectomy for this type. We also have recommended completion total thyroidectomy with RAI ablation for patients with oxyphilic (Hurthle) cell carcinoma and poorly differentiated carcinoma who have initially undergone lobectomy in our hospital (Fig. 2). On the other hand, some reported from Japan suggest that oxyphilic (Hurthle) cell carcinoma does not have a poorer prognosis than ordinary follicular carcinoma [37, 40]. These results suggest that the strategy of treatment between oxyphilic (Hurthle) cell carcinoma and ordinary follicular carcinoma are maybe no problem to do same.

In the WHO classification, poorly differentiated carcinoma is classified as an independent histologic type [41], but it is not rare for poorly differentiated components to be found by pathological examination in tumors that have been resected under a preoperative diagnosis of follicular lesion of undetermined significance. Table 4 summarizes the indications for total thyroidectomy or completion total thyroidectomy as a second surgical procedure in the various guidelines for patients with follicular carcinoma.

Table 4 Indication for total thyroidectomy or completion total thyroidectomy as a second surgery for follicular carcinoma patients in various guidelines

<table>
<thead>
<tr>
<th>NCCN</th>
<th>Extensive vascular invasion</th>
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<tr>
<td>ATA</td>
<td>All patients except those with tumor &lt;1 cm</td>
</tr>
<tr>
<td>BTA</td>
<td>Evidence of vascular invasion, tumor &gt;4 cm, oxyphilic type</td>
</tr>
<tr>
<td>AACE/AAES</td>
<td>High-risk patients, extensive capsular or vascular invasion</td>
</tr>
<tr>
<td>JTTS/JAES</td>
<td>Widely invasive carcinoma, poorly differentiated components</td>
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NCCN, National Comprehensive Cancer Network; ATA, American Thyroid Association; BTA, British Thyroid Association; AACE/AAES, American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons; JTTS/JAES, Japanese Society of Thyroid Surgery and Japan Association of Endocrine Surgeons

which independently affected patient carcinoma death [37, 39]. The present situation suggests that the pathological issue of whether follicular carcinoma is minimally or widely invasive has a very important impact on future therapy.

Completion total thyroidectomy with a search for, or treatment of, distant metastasis using RAI is recommended for patients with widely invasive carcinoma, those with widely invasive follicular carcinoma, and those with poorly differentiated compartments such as an insular component. However, existing evidence that these therapies improve outcome is not adequate [1]. The ATA guidelines recommend completion total thyroidectomy for patients with DTC, including follicular carcinoma larger than 1 cm, if they have undergone limited thyroidectomy initially in the absence of a confirmed diagnosis of carcinoma [6]. In contrast, the AACE/AAES guidelines indicate that lobectomy may be adequate for minimally invasive follicular carcinoma showing limited capsular invasion only, although these guidelines recommend completion total thyroidectomy with RAI ablation for patients with more extensive capsular or vascular extension and for those considered to be high-risk based on various classification systems such as the UICC, AMES, and EORTIC [7]. The NCCN guidelines recommend completion total thyroidectomy as a second surgical procedure for patients with invasive carcinoma showing extensive vascular invasion, but accept observation with L-thyroxine therapy to maintain a low or normal level of TSH for patients with minimally invasive carcinoma showing microscopic capsular and/or few foci of vascular invasion [3, 8]. The BTA guidelines recommend total thyroidectomy for patients with follicular carcinomas larger than 4 cm or vascular invasion, but accept hemi-thyroidectomy for lesions measuring less than 1 cm with minimal extension [4]. Other cases are regarded as lying within a “gray zone”, and no clear recommendations are offered. These guidelines treat oxyphilic (Hurthle) cell carcinoma, a follicular carcinoma variant, separately, and recommend total thyroidectomy for this type. We also have recommended completion total thyroidectomy with RAI ablation for patients with oxyphilic (Hurthle) cell carcinoma and poorly differentiated carcinoma who have initially undergone lobectomy in our hospital (Fig. 2). On the other hand, some reported from Japan suggest that oxyphilic (Hurthle) cell carcinoma does not have a poorer prognosis than ordinary follicular carcinoma [37, 40]. These results suggest that the strategy of treatment between oxyphilic (Hurthle) cell carcinoma and ordinary follicular carcinoma are maybe no problem to do same.

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RAI Ablation and TSH Suppression Therapy

There is no evidence that total thyroidectomy with RAI ablation and TSH suppression therapy significantly improves the outcome of patients with widely invasive follicular carcinoma. However, these therapies are considered appropriate for widely invasive follicular carcinoma in view of its dire prognosis [1]. Western guidelines highly recommend RAI therapy for high-risk patients [4, 6-8]. Mazafferri et al. [14], dem-
onstrated favorable outcomes of patients with papillary and follicular carcinomas who underwent RAI ablation after total or near-total thyroidectomy. Although one systematic review has indicated that RAI ablation may reduce the incidence of recurrence of DTC, including follicular carcinoma, it is unclear whether total thyroidectomy and RAI ablation are effective for low-risk patients [42]. Another report has recommended RAI ablation for patients with follicular carcinoma showing high-risk biological features such as advanced age, tumor multiplicity, lymph node metastasis, vascular invasion, and pathologically aggressive variants [43]. To date, however, no published studies have compared the effect of RAI ablation on prognosis between patients with widely and minimally invasive carcinoma.

One meta-analysis has concluded that TSH suppression therapy reduces the risk of major adverse clinical events such as carcinoma progression, recurrence, and death [44]. However, there are no available data comparing the effectiveness of TSH suppression therapy between patients with widely and minimally invasive follicular carcinoma. It is noteworthy that no previous investigations have compared the effectiveness of total thyroidectomy, RAI ablation, and TSH suppression for widely invasive follicular carcinoma, and it remains unclear whether these procedures significantly improve outcome.

**Application of RAI Ablation**

Ablation implies the elimination of the remnant thyroid using $^{131}$I after total or near-total thyroidectomy. It is reported that ablation improves the local control rate and the disease-free survival rate, especially in high-risk patients who have undergone total thyroidectomy. However, it remains debatable whether ablation improves the prognosis in terms of survival [1]. Western guidelines recommend RAI ablation for high-risk patients. In contrast, the AACE/AMES guidelines indicate that the use of RAI ablation for low-risk patients should be decided on a case-by-case basis [7]. In the ATA guidelines, RAI ablation is not recommended for patients with carcinomas smaller than 1 cm without high-risk features [6]. The BTA guidelines indicate that the benefit of RAI ablation for low-risk patients may be questionable [4].

These guidelines also comment on the risk of second malignancy after RAI, and that the application of RAI ablation should be individualized and selective. The NCCN guidelines recommend total-body RAI imaging 2-12 weeks after total thyroidectomy and RAI ablation using 30-100 mCi only when patients show thyroid bed uptake. The guidelines also recommend RAI treatment using 100-200 mCi when responsive residual tumors are suspected or proven on imaging [8].

In Japan, as indicated below, the capacity to administer RAI is limited. However, we actively recommend RAI ablation for patients demonstrating significant extrathyroid extension, vascular invasion, multiple lymph node metastases, and a continuously high thyroglobulin level after total thyroidectomy. Furthermore, for aggressive histological types such as the tall cell variant, diffuse sclerosing variant, columnar cell carcinoma, widely invasive follicular carcinoma, and poorly differentiated carcinoma having insular, scirrhous, or trabecular growth patterns, RAI ablation therapy is preferable.

In Japan, the number of patients who undergo RAI therapy has been increasing annually: 481 patients in 1987, 1350 patients in 1997, and 2373 patients in 2007. However, the number of bed spaces decreased from 188 in 2002 to 158 in 2007. The number of patients requiring RAI therapy is estimated to be 6800 per year, which means that only 35% of them will receive it. Responses to a recent questionnaire distributed to institutions where RAI therapy is available showed that the waiting time for RAI therapy is very long, 4.4 months on average and 18 months at most, indicating the high demand for beds for patients requiring RAI therapy. A breakthrough measure for management of this situation has been the use of 30 mCi RAI ablation on an outpatient basis, as verified by the Japanese Society of Nuclear Medicine. It remains debatable whether this is an appropriate dose for RAI; it is unclear whether 30 mCi for ablation will provide the same effect as 100 mCi [45].

At Kanaji Thyroid Hospital, the numbers of patients who undergo RAI ablation and therapy have been 264 and 394 patients, restrictively, since 2005 to 2012. RAI at Kanaji Thyroid Hospital has been performed for high-risk patients with DTC in accordance with standard therapeutic guidelines (Fig. 3). Our data showed that distant metastases were significantly more common in patients with follicular thyroid cancer than in those with papillary thyroid cancer. The survival rate was not clearly significant difference between papillary and follicular carcinoma patients. However the patients of follicular carcinoma were a poorly prognostic tendency than that of papillary carcinoma. We recommend that RAI ablation should be performed less
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for each patient. For example, routine total thyroidectomy may prevent relapse in the remnant thyroid and enable physicians to perform RAI ablation or RAI therapy immediately. However, the prognosis for low-risk patients remains excellent, even if they undergo hemithyroidectomy alone without RAI ablation or TSH suppression therapy. Furthermore, the risk of a second malignancy after RAI therapy has become a concern. At least in Japan, an area with sufficient dietary intake of iodine, total thyroidectomy is definitely not needed in low-risk patients. In contrast, we showed that only 5 out of 373 patients (1.3%) with solitary PTC 2 cm or less demonstrating low-risk thyroid cancer features (Table 1) developed distant recurrence and no patients died of low-risk papillary carcinomas (T1N0M0) in our institution. These findings strongly support our recommendation (Fig. 1). On the other hand, in our institution the relationship of low-risk PTC between recurrence to remnant thyroid, lymph nodes, and distant organs was 1 patient (0.3 % of patients who underwent limited thyroidectomy), 4 patients (1.3 %) and 4 patients (1.3 %), respectively. These findings suggest low-risk PTC patients who underwent limited thyroidectomy had excellent prognosis. The indications for total thyroidectomy are still debatable, but we strongly recommend it for patients with tumors larger than 4 cm, clinical lymph node metastasis, distant metastasis, or significant extrathyroidal extension.

In Japan, there is now a consensus that central node dissection should be performed routinely for papillary carcinoma. This is in sharp contrast to the situation in the West, although both Western and Japanese guidelines recognize that subclinical central node metastasis does not affect outcome. However, it is true that relapse in this region may cause severe complications at reoperation, such as recurrent-laryngeal nerve injury and persistent hyperparathyroidism. Central node dissection does not require wound extension and is not very time-consuming when performed during primary surgery. Accordingly, we recommend routine central compartment dissection for patients with papillary carcinoma excluding micro-papillary carcinoma. Only micro-papillary carcinoma is enough performed lobectomy or observation.

At Kanaji Thyroid Hospital, follicular neoplasms (class III) (tumor size <5 cm, and no distant metastasis (M0)) are ordinary performed lobectomy. The patients of low-risk follicular carcinoma, minimally invasive type with no vascular invasion in post-operative patho-

Table 5  The high-risk relapse clinicopathological factors from distant metastases cases in Kanaji Hospital

<table>
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<tr>
<th>Factors</th>
<th>n</th>
<th>%</th>
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<tr>
<td>Papillary thyroid cancers</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Variant components</td>
<td>9</td>
<td>10.8</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>37</td>
<td>44.6</td>
</tr>
<tr>
<td>Cervical lateral lymph node metastases</td>
<td>58</td>
<td>69.9</td>
</tr>
<tr>
<td>Follicular thyroid cancers</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Tumor size &gt; 4.5 cm</td>
<td>8</td>
<td>47.1</td>
</tr>
<tr>
<td>Widely invasive carcinoma</td>
<td>2</td>
<td>11.8</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>2</td>
<td>11.8</td>
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than 180 days after total or near-total thyroidectomy (Fig. 4). Similarly, Higashi et al. [46] have suggested that delaying initial RAI ablation until beyond 180 days after total thyroidectomy may result in poor survival for high-risk DTC patients. The clinicopathological factors of patients with DTC associated with a high risk of relapse due to distant metastases, as assessed at Kanaji Thyroid Hospital, are summarized in Table 5.

Discussion

Although DTC generally shows an indolent character and is slow-growing, cases demonstrating certain clinicopathological features are likely to show relapse and even become life-threatening. Therefore, the therapeutic strategy for DTC should vary according to the biological characteristics of the thyroid carcinoma. Every treatment, including the extent of thyroidectomy, lymph node dissection and RAI ablation, has limitations and advantages. It is important for physicians to select the best treatment with flexibility, rather than uniformity,
logical diagnose are followed by a cervical ultrasound/year, thyroglobulin (Tg) and TgAb measurement/6 months, and Chest computer tomography/1-2 years. We also recommend completion total thyroidectomy after lobectomy for patients with widely invasive follicular carcinoma and minimally invasive follicular carcinoma with vascular invasive infiltrating type (Fig. 2), or poorly differentiated carcinoma. The data accumulated in Japan indicate an excellent prognosis for patients with low-risk DTC.

Lack of opportunity to administer RAI ablation, partly because of the lack of an appropriate fee structure, is problematic. The indications for RAI ablation in Japan tend to be narrower than those used in the Western guidelines, but it is clear that high-risk cases require RAI ablation and therapy. We expect that administration of 30 mCi ablation on an outpatient basis will continue, but there is a need to determine the actual effective dose required for RAI ablation.

In summary, we have presented an outline of the current Japanese standard therapeutic strategies for low-risk DTC in comparison with the strategies stipulated in the Western guidelines. We hope that patients with thyroid cancer, wherever they are in the world, will be suitably evaluated so that they always receive the most appropriate treatment.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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