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Therapeutic Strategy for Differentiated Thyroid Carcinoma in Japan Based on a Newly Established Guideline Managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons

Hiroshi Takami · Yasuhiro Ito · Takahiro Okamoto · Akira Yoshida

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Abstract
Background Therapeutic strategy for patients with differentiated thyroid carcinoma (DTC) in Japan has differed from that in Western countries. Total thyroidectomy followed by radioactive iodine (RAI) ablation has been a standard therapy in Western countries, while limited thyroidectomy has been widely accepted in Japan. We newly established guidelines for clinical practice in treating thyroid tumors based on evidence from previous publications and the accumulation of data from patients in Japan. We present our therapeutic recommendations for DTC patients based on these guidelines.
Methods From the 55 clinical questions (CQ) in our guideline, we selected CQ regarding the treatment of DTC. We commented on each and compared it with the corresponding regions in Western guidelines.
Results For papillary carcinoma, we strongly or moderately recommend total thyroidectomy for patients with tumors larger than 4 cm, clinical node metastasis, distant metastasis, or significant extrathyroid extension, while hemithyroidectomy is acceptable for T1N0M0 patients. In contrast to Western guidelines, routine central compartment dissection is recommended for papillary carcinoma in our guidelines. Completion total thyroidectomy is recommended for patients who were scheduled for hemithyroidectomy under a preoperative diagnosis of follicular neoplasm and were pathologically confirmed as having follicular carcinoma if the pathological diagnosis indicated widely invasive carcinoma or carcinoma having poorly differentiated components. RAI ablation is also recommended for DTC with aggressive clinicopathological features, but its indication is narrower than that in Western guidelines, not only because of the limitations on RAI, but also because it is our policy that patients without high-risk features do not require RAI ablation.
Conclusion It is important to treat DTC patients individually according to their clinicopathological features rather than uniformly. We hope that policies regarding the treatment of DTC patients in Western countries and Japan will find the optimal compromise in the future, leading to the best treatments for patients with thyroid carcinoma all over the world.

H. Takami
Department of Surgery, Teikyo University School of Medicine, Tokyo 173-8605, Japan

Y. Ito (✉)
Department of Surgery, Kuma Hospital,
8-2-35, Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan
e-mail: ito01@kuma-h.or.jp

T. Okamoto
Department of Endocrine Surgery and Hygiene and Public Health II, Tokyo Women's Medical University, Tokyo, Japan

A. Yoshida
Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Kanagawa, Japan

Introduction

Thyroid carcinoma is a common disease in Japan. In 2003, its incidence per 100,000 was 3.25 for males and 9.26 for females, and the age-adjusted incidence was 2.56 for males and 7.17 for females [1]. The incidences of histological types were 92.5% for papillary carcinoma, 4.8% for follicular carcinoma, 1.3% for medullary carcinoma, and 1.4% for anaplastic carcinoma based on an investigation by Japanese Society of Thyroid Surgeons (JSTS) in 2004. The

incidence of papillary carcinoma in Japan is higher than that in Western countries possibly because of sufficient dietary intake of iodine. Papillary and follicular carcinomas are often classified into differentiated carcinoma (DTC) as a single group.

Strategy for treatment of DTC in Japan has traditionally differed from that in Western countries. Western countries almost routinely perform total thyroidectomy followed by RAI ablation and thyroid stimulating hormone (TSH) suppression as the standard treatment. In Japan, in contrast, limited thyroidectomy such as lobectomy with isthmectomy and subtotal thyroidectomy has been more widely adopted than total thyroidectomy for various reasons. First, limited thyroidectomy can reduce the risk of severe complications such as bilateral recurrent laryngeal nerve paralysis and persistent hypoparathyroidism and may not require L-thyroxine administration. Second, the capacity to administer radioactive iodine (RAI) is limited by legal restrictions in Japan so only a limited number of patients can undergo RAI ablation or RAI therapy. Third, Japanese endocrine surgeons are empirically aware that most DTC lesions are indolent and show a good prognosis even though total thyroidectomy with RAI ablation and TSH suppression is not performed. Instead, since the organs in which papillary carcinoma is most likely to recur is the lymph node, prophylactic lymph node dissection has been actively performed in Japan not only for the central but also for the lateral compartment, even in patients who do not show clinical lymph node metastasis on preoperative imaging studies.

In the most recent guidelines from the British Thyroid Association (BTA), the indication for RAI ablation for low-risk patients is regarded as questionable and the risk of a second malignancy after RAI administration is also described [2]. In Japan, total thyroidectomy is currently considered preferable for high-risk patients and that extensive prophylactic lymph node dissection for low-risk patients is unnecessary. Therefore, it seems that the therapeutic strategies in Western countries and those in Japan are moving closer to each other.

In Western countries, various authoritative guidelines have been established, such as those from the American Thyroid Association (ATA) [3], the National Comprehensive Cancer Network (NCCN) [4], the BTA [2], and the American Association of Clinical Endocrinologists (AACE)/American Association of Endocrine Surgeons (AAES) [5]. Recently, JSTS and the Japanese Association of Endocrine Surgeons (JAES) also newly established a practice guideline for thyroid tumors, including carcinoma [6]. Our guidelines promote the optimal health outcomes of patients with thyroid tumors by demonstrating the current standard of medical care and defining ideal practice based on currently available evidence. In this study, we present our therapeutic strategy for DTC based on a consensus of the members of the committee and describe the differences and commonalities between Western guidelines and our current guidelines.

Therapeutic strategies for DTC based on our guidelines

DTC consists of two different histological types, papillary and follicular carcinomas. In the ATA guideline, treatments for papillary and follicular carcinomas are described together as the treatment for DTC [3], indicating that treatment strategies for these two carcinomas are much the same. However, these two histological types have different behaviors: papillary carcinoma is likely to metastasize to the lymph node while follicular carcinoma predominantly metastasizes to distant organs. Moreover, papillary carcinoma can usually be diagnosed on preoperative imaging studies and fine needle aspiration biopsy (FNAB), whereas follicular carcinoma is normally diagnosed on postoperative pathological examination. Thus, in the Japanese guidelines, treatments for papillary and follicular carcinomas are described separately.

Our guidelines consist of 55 clinical questions (CQ), and for this article we extracted CQ that are directly related to therapy for DTC. The numbers of the CQ are the original numbers in our guidelines. We created six evidence-based recommendation ratings: A, strongly recommended based on good evidence; B, recommended based on fair evidence; C1, recommended although the evidence level is low; C2, no recommendation either for or against because of the lack of evidence; C3, recommended against because of the lack of evidence; D, strongly recommended against based on good evidence of ineffectiveness or harmfulness.

Treatment for papillary carcinoma

Observation

CQ20. Can papillary microcarcinoma (papillary carcinoma measuring 1 cm or less) be observed without immediate surgery?

Surgical treatment is mandatory for papillary microcarcinoma patients with clinical lymph node metastasis on palpation or imaging studies, distant metastasis, or significant extrathyroid extension. Patients without these features can be candidates for observation after extensive explanation of the situation and giving informed consent (recommendation rating = C1).

The recent prevalence of ultrasonography and ultrasonography-guided FNAB has facilitated the diagnosis of small carcinoma, including low-risk papillary microcarcinoma. Davis et al. [7] showed that from 1973 to 2002, there was a 2.4-fold increase in the incidence of thyroid

carcinoma but mortality remained stable during this period. They concluded that the increasing incidence reflected an increase in the detection of subclinical disease such as small and low-risk carcinomas. In Japan, the incidence of incidentally detected thyroid carcinoma on mass screening was reported to be 1000-fold higher than that of overt carcinoma [8]. Therefore, a study of the observation of low-risk and incidentally detected papillary microcarcinoma has been performed in some institutions in Japan and, to date, favorable outcomes of patients have been demonstrated [9, 10]. Although studies with a larger number of patients and with a longer follow-up are required to draw definitive conclusions, we currently suggest that observation without immediate surgery can be an option for patients with low-risk papillary microcarcinoma.

Surgical treatment

Thyroidectomy

CQ17. Does total thyroidectomy improve the prognosis of papillary carcinoma patients compared to hemithyroidectomy?

There is not sufficient evidence to indicate that total thyroidectomy improves cause-specific survival of patients with papillary carcinoma compared to that of patients who undergo hemithyroidectomy. Total thyroidectomy prevents recurrence to the remnant thyroid (recommendation rating = A) but does not decrease recurrence to the lymph node and distant organs (recommendation rating = C1). However, the committee recommends total thyroidectomy for high-risk patients (recommendation rating = B).

High-risk patients are those with a tumor of maximal diameter >5 cm, extrathyroid extension to the mucosa of the trachea or esophagus, a large number of clinical lymph node metastases, lymph node metastasis >3 cm, and the presence of distant metastasis. Total thyroidectomy is highly recommended for high-risk patients.

Low-risk patients are those with a tumor of maximal diameter ≤2 cm and the absence of clinical lymph node metastasis (T1N0M0 in TNM classification). Hemithyroidectomy is acceptable for low-risk patients.

Other patients were classified as a being in a "gray zone" with regard to the extent of thyroidectomy, but the committee built a consensus that total thyroidectomy is encouraged for patients with tumors larger than 4 cm or clinical node metastases (N1).

The extent of thyroidectomy in Japan traditionally differed from that in most other countries. In ATA guidelines, total or near total thyroidectomy is routinely recommended for DTC except for low-risk microcarcinoma [3]. BTA guidelines recommend total thyroidectomy for most papillary carcinoma patients, especially for those with tumors greater than 1 cm, multifocal disease, extrathyroidal extension, familial disease, history of neck irradiation, and clinical lymph node metastases [2]. AACE/AAES guidelines recommend total thyroidectomy especially for high-risk patients as defined by various classification systems such as MACIS, AMES, and EORTIC and for patients with carcinoma located in both lobes, the presence of nodules in the contralateral lobe, extrathyroid extension, and local or distant metastasis [5]. In NCCN guidelines, hemithyroidectomy is accepted for patients with all the following clinicopathological features: 15-45 years old, no prior radiation, no distant metastasis, no cervical lymph node metastasis, no extrathyroidal extension, tumors smaller than 4 cm, and no signs of aggressive variant [4]. However, it is also mentioned that total thyroidectomy is "the most common" strategy even for such patients.

In contrast, limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy has been widely adopted in Japan. Several reports from Western countries demonstrated that total thyroidectomy provides a better prognosis than hemithyroidectomy [11–19]. For appropriate analysis of the data, accumulation of over 1000 cases with follow-up over a few decades is required, but it is unlikely that the level of diagnostic ability, uniformity of surgical designs, and elaborateness of follow-up would be stable over such a long period, even in a single institution. Furthermore, most patients who undergo total thyroidectomy in Western countries may also undergo RAI ablation therapy, which means that these studies may not genuinely compare total thyroidectomy with limited thyroidectomy. In contrast, several reports demonstrated negative findings for a difference in patient prognosis depending on the extent of thyroidectomy [20–24]. A report from Japan showed that recurrence of solitary T1N0M0 papillary carcinoma in the remnant thyroid of patients who underwent hemithyroidectomy had a rate of only 1% [25]. Taken together, we conclude that there is no high-level evidence of improvement in patient prognosis, especially cause-specific survival, following total thyroidectomy.

After discussion in committee of the above data and the actual situation in Japan, we achieved consensus that high-risk patients, as indicated above, should undergo total thyroidectomy. In contrast, we concluded that total thyroidectomy is unnecessary for T1N0M0 patients if no pathological lesions are present in the contralateral lobe.

Table 1 summarizes the indications for total thyroidectomy in Western and Japanese guidelines.

Lymph node dissection

CQ18. Does central compartment dissection improve the prognosis of papillary carcinoma patients?

Table 1 Indications for total thyroidectomy for patients with papillary carcinoma in various guidelines

JSTS/JAES	*Strongly recommended*: Tumor size >5 cm, extrathyroid extension to the trachea or esophagus, large number of clinical lymph node metastases, lymph node metastasis >3 cm, distant metastasis
	Moderately recommended: Tumor size >4 cm, clinical lymph node metastasis
ATA	All patients except those with low-risk microcarcinoma
BTA	Most patients, especially those with tumor size >1 cm, multifocal disease, extrathyroid extension, familial disease, clinical lymph node metastasis, radiation history
NCCN	Age <15 years or >45 years, radiation history, distant metastasis, bilateral nodularity, extrathyroidal extension, tumor size >4 cm, clinical lymph node metastasis, aggressive variant (however, also for other cases, total thyroidectomy is the most common)
AACE/AAES	High-risk patients, multifocal disease, nodule in the contralateral lobe, extrathyroid extension, local or distant metastasis

There is no evidence that prophylactic central compartment dissection improves the cause-specific survival of papillary carcinoma patients. However, it is recommended at initial surgery because reoperation for recurrence to this compartment may induce severe complications. Therapeutic central node dissection improves patient prognosis (recommendation rating = B).

There is no room for argument that therapeutic central node dissection is mandatory. Regarding prophylactic central node dissection for patients without clinical node metastasis, ATA guidelines indicate that it may be performed for T3 or T4 cases but is not necessary for T1 or T2 patients [3]. BTA guidelines recommend prophylactic central node dissection only when patients have one or more of the following high-risk characteristics: male, age greater than 45 years, tumor larger than 4 cm in diameter, and extracapsular or extrathyroidal disease [2]. NCCN guidelines indicate that prophylactic central node dissection should be considered for patients with one or more of the following characteristics: age less than 15 years or greater than 45 years, radiation history, known distant metastases, bilateral nodularity, extrathyroidal extension, tumor larger than 4 cm, and aggressive variant [4]. Prophylactic central node dissection is not recommended by the AACE/AAES guidelines [5]. Indeed, currently available data on the effect of central node dissection on prognosis are controversial [26–33]. Our guidelines also indicate that current evidence is inadequate to support the statement that patient prognosis is improved by central node dissection. However, metastasis to the central compartment is generally difficult to evaluate on preoperative imaging studies and severe complications such as injury of recurrent laryngeal nerve and persistent hypoparathyroidism may be induced by reoperation for recurrence to this compartment. Thus, we conclude that prophylactic dissection of the central compartment is of significance. This is in sharp contrast to Western guidelines.

Table 2 summarizes the indications for prophylactic central node dissection in Western and Japanese guidelines.

Table 2 Indications for prophylactic central node dissection for patients with papillary carcinoma in various guidelines

JSTS/JAES	Routinely recommended
ATA	May be performed for T3 or T4 patients
BTA	Male gender, age >45 years, tumor size >4 cm, extracapsular or extrathyroidal disease
NCCN	Can be considered for patients <15 years old or >45 years old, radiation history, distant metastasis, bilateral nodularity, extrathyroidal extension, tumor size >4 cm, and aggressive variant
AACE/AAES	Not recommended

CQ19. Does dissection of the lateral compartment improve the prognosis of papillary carcinoma patients?

Although it is not evident that prophylactic lateral node dissection improves the life prognosis of patients, it decreases the risk of recurrence to the node and improves disease-free survival (recommendation rating = B).

Patients with clinically detectable lateral node metastasis show a worse prognosis [34, 35] and careful therapeutic dissection is required. Western guidelines do not recommend prophylactic dissection of the lateral compartment. Previous data are discrepant with regard to the prognostic significance of prophylactic lateral node dissection [36–40]. In Japan, Noguchi et al. [41] showed that prophylactic lateral node dissection improves the cause-specific survival of patients, but Sato [31] had negative findings. Two more recently published articles from Japan [34, 42] recommended prophylactic lateral node dissection for patients with the following risk factors: male, advanced age, large primary lesion, extrathyroid extension, and distant metastasis. We currently conclude that prophylactic lateral node dissection can reduce the risk of recurrence to the nodes and improve disease-free survival, although evidence is lacking on whether it improves cause-specific survival.

Table 3 summarizes the indications for prophylactic lateral node dissection in Western and Japanese guidelines.

Table 3 Indications for prophylactic lateral node dissection for patients with papillary carcinoma in various guidelines

JSTS/JAES	Not determined, although its significance for reducing recurrence is recognized
ATA	Not recommended
BTA	Not recommended
NCCN	Not recommended
AACE/AAES	Not recommended

Treatment for follicular carcinoma

Most follicular carcinomas are diagnosed on postoperative pathological examination. As initial surgery, most patients undergo hemithyroidectomy under a diagnosis of follicular tumor or follicular neoplasm.

CQ22. Does classification of follicular carcinoma according to the degree of invasiveness (widely invasive and minimally invasive types) reflect the prognosis?

The classification of widely invasive and minimally invasive types can predict patient prognosis. Widely invasive carcinoma has a significantly worse prognosis than minimally invasive carcinoma. In particular, the degree of vascular invasion affects the prognosis. It is recommended that follicular carcinoma be divided into widely invasive and minimally invasive types based on postoperative pathological examination (recommendation rating = B).

Previous studies from Asian countries demonstrated a significantly worse prognosis for widely invasive carcinoma, especially carcinoma with significant vascular invasion, than for minimally invasive carcinoma [43–46]. As described below, we recommend completion total thyroidectomy for widely invasive carcinoma patients who initially underwent hemithyroidectomy. This indicates that the pathological diagnosis of whether follicular carcinoma is minimally or widely invasive is very important in determining future therapy.

CQ23. When is completion total thyroidectomy recommended as a second surgery for patients who underwent hemithyroidectomy and were diagnosed as having follicular carcinoma on postoperative pathological examination?

Completion total thyroidectomy with searching for or treating distant metastasis using RAI is recommended for patients with widely invasive follicular carcinoma and for patients with poorly differentiated components such as an insular component. However, the evidence that these therapies improve prognosis is not adequate (recommendation rating = B).

The ATA guidelines recommend completion total thyroidectomy for patients with DTC, including follicular carcinoma, that is larger than 1 cm if the patients underwent limited thyroidectomy initially because of the lack of confirmed diagnosis of carcinoma [3]. 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 classified as high-risk based on various classification systems such as UICC, AMES, MACIS, and EORTIC [5]. The NCCN guidelines recommend completion total thyroidectomy as a second surgery for patients with invasive carcinoma showing extensive vascular invasion, but accepts observation with L-thyroxine therapy to keep TSH low or normal for patients with minimally invasive carcinoma showing microscopic capsular and/or few foci of vascular invasion [4]. The BTA guidelines recommend total thyroidectomy for patients with follicular carcinoma larger than 4 cm or vascular invasion, but accepts hemithyroidectomy for lesions measuring less than 1 cm with minimal extension [2]. Other cases are regarded as a "gray zone" and no clear recommendations are made. These guidelines treat oxyphilic (Hurthle cell) follicular carcinoma separately, for which total thyroidectomy is recommended (also see CQ25).

In WHO classification, poorly differentiated carcinoma is classified as an independent histology [47], but it is not rare that tumors dissected under the preoperative diagnosis as follicular neoplasm or follicular lesion of undetermined significance are pathologically diagnosed as having poorly differentiated components. One Japanese study demonstrated that in a series of follicular carcinoma patients, involvement of poorly differentiated components is an independent prognostic factor for both disease-free and cause-specific survivals [45]. Other studies showed that cases having an insular component are more likely to have distant recurrence and poor prognosis [48, 49]. In a series of follicular carcinoma patients excluding those with poorly differentiated carcinoma, widely invasive carcinoma had a significantly worse prognosis than minimally invasive carcinoma [43, 45, 46]. Thus, in our guidelines, completion total thyroidectomy is recommended for patients with widely invasive carcinoma or carcinoma with poorly differentiated components, although evidence of whether completion total thyroidectomy followed by RAI ablation significantly improves patient prognosis is inadequate. Apart from that, male gender, advanced age, large tumor, and vascular invasion, even when minimal, have been identified as conventional prognostic factors. Although completion total thyroidectomy may not be

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

JSTS/JAES	Widely invasive carcinoma, poorly differentiated components
ATA	All patients except those with tumor <1 cm
BTA	Evidence of vascular invasion, tumor >4 cm, oxyphilic type
NCCN	Extensive vascular invasion
AACE/AAES	High-risk patients, extensive capsular or vascular invasion

required, careful follow-up is recommended for patients having these clinicopathological features.

Indications for total thyroidectomy or completion total thyroidectomy as a second surgery in the guidelines for follicular carcinoma patients are summarized in Table 4.

CQ24. Does total thyroidectomy with radioactive iodine (RAI) ablation and TSH suppression therapy improve prognosis of patients with widely invasive follicular carcinoma compared to only limited thyroidectomy?

It is not evident that total thyroidectomy with RAI ablation and TSH suppression therapy significantly improves the prognosis of patients with widely invasive follicular carcinoma. However, these therapies are considered appropriate for widely invasive follicular carcinoma considering that it has a dire prognosis (recommendation rating = B).

Western guidelines highly recommend RAI therapy especially for high-risk patients [2–5]. Mazafferri et al. [16] demonstrated favorable outcomes of patients with papillary and follicular carcinomas who underwent RAI ablation after total or near total thyroidectomy. One systemic review showed that RAI ablation may reduce the recurrence of DTC, including follicular carcinoma, but it is unclear whether total thyroidectomy and RAI ablation are effective for low-risk patients [50]. Another report recommended RAI ablation for follicular carcinoma patients with high-risk biological features such as advanced age, multiplicity, lymph node metastasis, vascular invasion, and pathologically aggressive variants [51]. To date, however, there are no published studies comparing the effect of RAI ablation on prognosis between patients with widely invasive and minimally invasive carcinoma.

One meta-analysis study demonstrated that TSH suppression therapy reduces the risk of major adverse clinical events such as carcinoma progression, recurrence, and death [52]. However, there are no available data comparing the effectiveness of TSH suppression therapy between patients with widely and minimally invasive follicular carcinoma.

To date, there have not been any investigations comparing the effectiveness of total thyroidectomy, RAI ablation, and TSH suppression for widely invasive follicular carcinoma and it remains unclear whether these procedures significantly improve patient prognosis. However, as indicated above, widely invasive follicular carcinoma has a significantly worse prognosis than minimally invasive carcinoma, suggesting that total thyroidectomy, RAI ablation, and TSH suppression therapy are appropriate for those patients (Table 4).

CQ25. Does the prognosis of oxyphilic (Hurthle cell) follicular carcinoma differ from that of conventional follicular carcinoma?

In Europe and the United States, oxyphilic follicular carcinoma is reported to have a worse prognosis than conventional follicular carcinoma. However, their prognoses did not differ according to reports from Japan (recommendation rating = C1).

Western guidelines are indicative of the aggressive character of oxyphilic-type follicular carcinoma. In the AACE/AAES guidelines, it is classified as a rare histologic subtype that may indicate a worse prognosis [5]. The BTA guidelines indicate that total thyroidectomy should be considered for oxyphilic follicular carcinoma, although it is less likely to concentrate RAI [2]. Indeed, reports from Western countries have shown a worse prognosis for oxyphilic carcinoma [53–56]. The 10-year relative survival rate for follicular carcinoma was 85%, while that for oxyphilic carcinoma was 76% according to the National Cancer Data Base report [23]. However, two studies from Japan showed that the prognosis of oxyphilic carcinoma did not differ from that of conventional follicular carcinoma [45, 57].

In conclusion, we recommend careful postoperative follow-up for oxyphilic follicular carcinoma patients, although evidence for its dire prognosis is lacking in Japan.

Treatment for poorly differentiated carcinoma

The definition of poorly differentiated carcinoma is quite confusing in Japan. Western guidelines do not extensively discuss poorly differentiated carcinoma, possibly because the therapeutic strategy is similar to that for conventional DTC. However, in Japan, the definition of poorly differentiated carcinoma is quite confusing, so in the current guidelines we describe poorly differentiated carcinoma in detail.

CQ31. What is the definition of poorly differentiated carcinoma? How is its prognosis?

Poorly differentiated carcinoma is defined as follicular cell neoplasms that show both morphologically and

behaviorally intermediate features between follicular and papillary carcinomas of the well-differentiated type carcinoma and undifferentiated carcinoma. Its prevalence varies from 0.3 to 15%, and the 5-year cause-specific survival rate after surgery varies from 40 to 80% depending on regions and facilities. The prognosis is worse than well-differentiated carcinoma and better than undifferentiated carcinoma (recommendation rating = B).

To date, three types of poorly differentiated carcinoma have been established based on JSTS [58], WHO classification [47], and the Turin proposal [59]. These three types vary with respect to the prevalence and prognosis of poorly differentiated carcinoma: the prevalences of these three types are 10–20, 0.8, and 0.3%, respectively, in Japan [60, 61].

There are three histologic patterns (poorly differentiated components), i.e., insular, trabecular, and solid, used for the diagnosis of poorly differentiated carcinoma. Not only in the WHO classification but also in the JSTS classification, poorly differentiated carcinoma is classified into an independent histology, separate from papillary and follicular carcinomas [47, 58]. In JSTS, papillary or follicular carcinoma is diagnosed as poorly differentiated carcinoma when the lesion includes poorly differentiated components regardless of the percentages. If poorly differentiated components comprise the majority of the carcinoma lesion, it is diagnosed as poorly differentiated carcinoma in the WHO classification. Criteria for poorly differentiated carcinoma in the Turin proposal include the presence of poorly differentiated components, the absence of the conventional nuclear features of papillary carcinoma, and the presence of at least one of the following features: convoluted nuclei, mitotic activity $>3 \times 10$ HPF, and tumor necrosis [59]. In Japan, The JSTS definition of poorly differentiated carcinoma is the most widely used, but it remains debatable whether papillary or follicular carcinoma that includes a slightly poorly differentiated component should be classified as an independent histological type outside of papillary or follicular carcinoma.

CQ32. Can poorly differentiated carcinoma be diagnosed preoperatively?

Although the utility of fine-needle aspiration biopsy for preoperative diagnosis of poorly differentiated carcinoma has been reported, it is not clearly evident that poorly differentiated carcinoma can be preoperatively diagnosed (recommendation rating = C2).

There is no evidence that poorly differentiated carcinoma can be definitely diagnosed on preoperative imaging studies and cytology, although some case reports and retrospective studies that have included a limited number of cases have been published.

CQ33. Do total thyroidectomy and prophylactic lymph node dissection improve the prognosis of patients with poorly differentiated carcinoma?

Poorly differentiated carcinoma has a high grade of malignancy and total thyroidectomy and extensive lymph node dissection are reasonable and appropriate for treatment if it is preoperatively suspected. However, there is insufficient evidence that these procedures improve patient prognosis (recommendation rating = C1).

Although there are no prospective studies available, studies in Western countries have recommended total thyroidectomy with lymph node dissection followed by RAI therapy or external beam radiation therapy for poorly differentiated carcinoma [62–64]. In contrast, some studies have shown negative results for the effectiveness of total thyroidectomy [65–67], but they seem to have problems with respect to statistical analysis. Since poorly differentiated carcinoma generally has a poor prognosis, common sense suggests that total thyroidectomy with extensive lymph node dissection should be recommended for patients preoperatively diagnosed as having or suspected of having poorly differentiated carcinoma, although evidence of whether such a procedure can prolong patient prognosis is lacking.

CQ34. Does additional surgery improve the prognosis of patients who underwent hemithyroidectomy under a diagnosis of papillary or follicular carcinoma but later diagnosed as having poorly differentiated carcinoma on postoperative pathological examination?

Completion total thyroidectomy for patients who underwent hemithyroidectomy under a diagnosis of follicular neoplasm is meaningful if they were diagnosed as having poorly differentiated carcinoma. However, it is not adequately evident that additional surgery for poorly differentiated carcinoma significantly improves prognosis (recommendation rating = C1).

See also CQ23. The recommendation rating for this CQ is C1 because there are currently no data supporting the improvement of patient prognosis following completion total thyroidectomy.

CQ35. Do therapies other than surgery improve the prognosis for patients with poorly differentiated carcinoma?

Although the partial effectiveness of RAI ablation therapy, external beam radiotherapy, and chemotherapy has been reported, it cannot be definitively concluded that these procedures improve prognosis (recommendation rating = C1).

There is consensus regarding the application of RAI therapy for distant metastasis and external beam

radiotherapy for local control. However, the recommendation rating is C1 because there are no data demonstrating the improvement of patient prognosis following these procedures.

Application of RAI ablation

CQ40. What is the application and role of ablation?

Ablation implies the elimination of the remnant thyroid after total or near total thyroidectomy using ^{131}I. It is reported that ablation improves the local control rate and the disease-free survival rate, especially in high-risk patients who underwent total thyroidectomy. However, it remains debatable whether ablation improves the prognosis for survival (recommendation rating = B).

Western guidelines recommend RAI ablation for high-risk patients. In contrast, the AACE/AME guidelines indicate that RAI ablation for low-risk patients should be determined in a case-by-case fashion [5]. In the ATA guidelines, RAI ablation is not recommended for patients with carcinoma smaller than 1 cm without high-risk features [3]. The BTA guidelines indicate that the benefit of RAI ablation for low-risk patients may be questionable [2]. 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 [4].

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 continuous high thyroglobulin level after total thyroidectomy. Furthermore, for aggressive histological types such as tall cell variant, diffuse sclerosing variant, columnar cell carcinoma, widely invasive follicular carcinoma, and poorly differentiated carcinoma having insular/scirrhous/trabecular growth patterns, RAI ablation therapy is preferable.

According to a domestic questionnaire in 2006, 46% of patients were considered to undergo RAI therapy, but this includes 18% with "wishful selection," that is, RAI therapy was considered preferable for these patients if it were available.

In another CQ (CQ41), our guidelines describe that the appropriate dose of RAI for ablation depends on the quantity of remnant thyroid, but it may range from 30 to 100 mCi (recommendation rating = C1).

Actual state for RAI therapy in Japan

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 bedspace 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 these patients will undergo RAI therapy. Responses to a recent questionnaire for institutions where RAI therapy is available showed that the waiting time for RAI therapy is very long at 4.4 months on average and 18 months maximum, indicating that available beds for RAI therapy are all taken.

As a breakthrough to manage these circumstances, the adequacy of RAI ablation using 30 mCi on an outpatient basis was verified by the Japanese Society of Nuclear Medicine. It remains debatable whether this is an appropriate dose of RAI; it is not evident that 30 mCi will provide the same effect as 100 mCi for ablation [68]. However, it is expected that outpatient therapy for ablation can resolve the prolonged waiting period and leave the allotted beds for patients with remnant disease or distant metastases that require larger amounts of RAI administration. Data have been accumulated that administration of 30 mCi on an outpatient basis can be performed safely and is not legally restricted. However, in order to diminish exposure to the public and to prevent public fear, institutions that administer 30 mCi in the outpatient department are obligated to send representative staff to a lecture class on the appropriate usage of RAI under the direction of the Ministry of Health, Labor and Welfare. At present, administration of 30 mCi by the outpatient department has not yet started but is expected to start in the near future.

Comments

DTC generally shows an indolent character and is slow-growing, but cases demonstrating certain clinicopathological features are likely to show recurrence and even become life-threatening. Therefore, therapeutic strategy for DTC should vary according to the biological characteristics of the carcinoma. Every therapy, including the extent of thyroidectomy and 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 for each patient. For example, routine total thyroidectomy may prevent recurrence to the remnant thyroid and enable physicians to perform RAI ablation or RAI therapy immediately. However, the prognosis for low-risk patients remains excellent, even when they undergo hemithyroidectomy only without RAI ablation or TSH

suppression therapy. Furthermore, the risk of 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. The indication of total thyroidectomy is still debatable, but we strongly or fairly strongly recommend total thyroidectomy for papillary carcinoma patients with a tumor larger than 4 cm, clinical lymph node metastasis, distant metastasis, or significant extrathyroid extension. We also recommend, although not strongly, completion total thyroidectomy after lobectomy for widely invasive follicular carcinoma patients or poorly differentiated carcinoma patients. However, our indications for total thyroidectomy in patients with DTC remain narrower than those in Western guidelines, not only because of the limited capacity to perform RAI, but also because of our accumulated data showing the excellent prognosis of low-risk patients.

Regarding lymph node dissection, we obtained consensus that central node dissection should be routinely performed for papillary carcinoma. This is in sharp contrast to Western guidelines, although both Western and Japanese guidelines recognize that subclinical central node metastasis does not affect patient prognosis. It is true, however, that recurrence in this region may cause severe complications such as recurrent laryngeal nerve injury and persistent hyperparathyroidism at reoperation. Central node dissection does not require wound extension and is not very time-consuming during the primary surgery. We thus recommend routine central compartment dissection for papillary carcinoma in our guidelines. In many institutions in Japan, prophylactic lateral node dissection has been actively or even almost routinely performed, while many Western surgeons have had a "wait and see" policy. In these guidelines, routine prophylactic lateral compartment dissection is not recommended because strong evidence for improvement of patient prognosis following this procedure is lacking. However, it is also true that such dissection reduces the recurrence to the nodes and cases predicting that a high incidence of recurrence may be an indication for prophylactic dissection. Our guidelines do not clearly determine the indications for prophylactic lateral node dissection, and whether it should be performed should be up to the discretion of the surgeon who should consider the biological features of the carcinoma of each patient.

The guidelines discussed here provide a rather detailed account about poorly differentiated carcinoma because the definition of poorly differentiated carcinoma in Japan differs from that in Western countries. It remains debatable whether poorly differentiated carcinoma should be classified as a separate histological type from papillary or follicular carcinoma in JSTS. In Japan, there are three types of poorly differentiated carcinoma and the first question to be settled is the coherent definition of the term before further studies.

Lack of ability to administer RAI ablation, partly because of the lack of an appropriate fee structure, is problematic. The indications for RAI ablation tend to be narrower than those used in Western guidelines, but it is clear that high-risk cases require RAI ablation and RAI therapy. We expect administration of 30 mCi for the purpose of ablation in an outpatient department to ensure beds for those requiring administration of larger amounts.

In summary, we presented our current standard therapeutic strategies for DTC extracted from our newly established guidelines and compared these strategies with those in Western guidelines. We hope that patients with thyroid carcinoma will be able to obtain the most suitable treatment everywhere in the world as the treatment strategies become more unified between physicians in Western countries and Japan.

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