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The revised clinical practice guidelines on the management of thyroid tumors by the Japan Associations of Endocrine Surgeons: Core questions and recommendations for treatments of thyroid cancer

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Abstract. The Japan Associations of Endocrine Surgeons has developed the revised version of the Clinical Practice Guidelines for Thyroid Tumors. This article describes the guidelines translated into English for the 35 clinical questions relevant to the therapeutic management of thyroid cancers. The objective of the guidelines is to improve health-related outcomes in patients with thyroid tumors by enabling users to make their practice evidence-based and by minimizing any variations in clinical practice due to gaps in evidential knowledge among physicians. The guidelines give representative flow-charts on the management of papillary, follicular, medullary, and anaplastic thyroid carcinoma, along with recommendations for clinical questions by presenting evidence on the relevant outcomes including benefits, risks, and health conditions from patients' perspective. Therapeutic actions were recommended or not recommended either strongly (◎◎◎ or XXX) based on good evidence (😊)/good expert consensus (+++), or weakly (◎, ◎◎ or X, XX) based on poor evidence (😣)/poor expert consensus (+ or ++). Only 10 of the 51 recommendations given in the guidelines were supported by good evidence, whereas 35 were supported by good expert consensus. While implementing the current guidelines would be of help to achieve the objective, we need further clinical research to make our shared decision making to be more evidence-based.

Key words: Clinical practice guidelines, Papillary thyroid carcinoma, Follicular thyroid carcinoma, Medullary thyroid carcinoma, Anaplastic thyroid carcinoma

THE JAPANESE SOCIETY OF THYROID SURGERY (JSTS) and the Japan Associations of Endocrine Surgeons (JAES) have developed and published the Clinical Practice Guidelines on the Management of Thyroid Tumors 2018 [1], which is a revised edition of their previous guideline published in 2010 [2-4]. The original Japanese version of the guideline included the following sections: epidemiology, diagnosis, and non-operative management sections such as clinical questions (CQ) 1 to 9, as well as four columns for the supplement. These were drafted for Japanese readers and have been excluded from this paper. The details of the epidemiology of thyroid cancer in Japan are available elsewhere [5].

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Objective

The overall objective of the guidelines is to improve health-related outcomes in patients with thyroid tumors. The outcomes include natural history, clinical course, as well as health conditions from the patients' point of view. The task force set two goals to achieve this objective. First, the guidelines should make every clinical decision by both patients and physicians evidence-based. Physicians' daily clinical practice entails cooperation with patients to deal with unique, inevitable uncertainty of each element in the management, including diagnosis or treatment. It might be helpful to share a number (*i.e.*, evidence) indicating the degree of uncertainty in clinical decision making on a particular course of action. Second, the guidelines should facilitate standardized clinical practices for the management of thyroid tumors by physicians. Although management strategies for each patient would be decided after thorough consideration of individual situations, any variation due to gaps in evidential knowledge or experience among physicians needs to

Table 1 Quality of evidence based on the study design, threats to validity, the point estimate and confidence interval of the effect size

Quality of evidence	Study design	Threats to validity	Effect size	
			point estimate	confidence interval
Good (😊)	systematic review	less	large	small
↕	randomized controlled trial			
↕	prospective observation			
Poor (😣)	retrospective observation	much	small	large

Table 2 Recommendations based on the quality of evidence and strength of consensus

	Strongly	Weakly
Recommend	◎◎◎ *Based on good evidence (😊)* *or good expert consensus (+++)*	◎ or ◎◎ *Based on poor evidence (😣)* *or poor expert consensus (+ or ++)*
Do not recommend	XXX *Based on good evidence (😊)* *or good expert consensus (+++)*	X or XX *Based on poor evidence (😣)* *or poor expert consensus (+ or ++)*

be minimized.

Development

The task force, which comprised 18 surgeons, 4 radiologists, 2 endocrinologists, 2 pathologists, 2 supervisors, and 1 adviser, started their revision in 2014 while reviewing the methodological standards proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group and the Medical Information Network Distribution Service (Minds) of the Japan Council for Quality Health Care [6, 7]. The task force identified 44 CQs regarding epidemiology, diagnosis, non-operative management, and treatment options for each histopathological type of tumor (papillary carcinoma, follicular tumor, medullary carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma), radiation therapy, issues on advanced cases, postoperative management, and molecular-targeted therapy. Specialized librarians performed systematic searches of the literature, and the task force members reinforced the yields by identifying additional references. Studies were selected based on the following principles. First, the study population, exposure, comparison, and outcome (PECO) should meet those of the relevant CQ. We need to keep in mind, however, that the elements in PECO are rarely defined in detail compared with those in research questions. Second, the selection was performed based on the study designs in order of rank as follows: systematic reviews (including meta-analysis), randomized controlled trials, prospective observational studies, and retrospective observational studies. Both internal and external validities of the selected studies were appraised according to clinical epidemiology knowledge. Quality of evidence was assessed based on study design, threats to validity, the point estimate, and confidence interval of the effect size, and was indicated by a "face mark" as follows: 😊 as good quality and 😣 as poor quality (Table 1).

Recommendations

A pre-specified format was used for each question to describe the guidelines as follows: question, recommendation, outcomes considered, evidence, comments, and evidence tables if relevant. All the outcomes considered including benefits, risks, and patients' views were listed. Recommendations were given to the CQs where any therapeutic managements were queried. Any therapeutic actions were recommended or not recommended either strongly (◎◎◎ or XXX) based on good evidence (😊)/good expert consensus (+++), or weakly (◎, ◎◎ or X, XX) based on poor evidence (😣)/poor expert consensus (+ or ++) (Table 2). The task force did not employ any formal procedures, such as voting or the Delphi method, to formulate and to arrive at the final recommendations.

Editorial independence

Expenses to develop and publish the guidelines were covered by the JSTS and the JAES. The views or interests of the professional associations did not influence the final recommendations. No other external funding was involved in the development. All the guideline development group members reported their conflicts of interest, and these are available at the JAES website (jaes.umin.jp).

Disclaimer

The guidelines provide management directions based on the available evidence but are not aimed at enforcing the guidelines in clinical practice. They also do not impose any restrictions on the use of diagnostic or therapeutic procedures that are not included in the guidelines. As uncertainty, to some extent, is inevitable in every clinical practice, a decision based on the best evidence does not necessarily result in the best outcome. Thus, it is mandatory to fully understand through history, the physical signs, test results, and values or preferences of an individual patient as well as his/her caregivers' thoughts in order to make a sound clinical judgment, in addition to an accurate knowledge of relevant evidence. Although the task force is responsible for the contents of the guidelines, each attending physician is responsible for patient outcomes following the use of the guidelines.

Papillary Thyroid Carcinoma (PTC) (Fig. 1)

CQ 10. Risk classification of PTC

- PTC is classified into four risk classifications: very low-risk, low-risk, intermediate-risk, and high-risk.
- Classification is based on the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) classification and General Rules for the Description of Thyroid Cancer.
- It is recommended that the management of PTC be based on risk classification.

Comment

The management policy of PTC is decided based on the risk of recurrence and carcinoma death (risk-adapted approach). The UICC/AJCC TNM classification is the most popular stage classification [8, 9]. The General Rules for the Description of Thyroid Cancer in Japan, 7th edition adopts the UICC/AJCC TNM classification, 7th edition [10]. This guideline proposes risk classification based on these classification systems (Table 3).

Very low-risk PTC indicates tumors measuring 1 cm or smaller, without lymph node or distant metastasis on

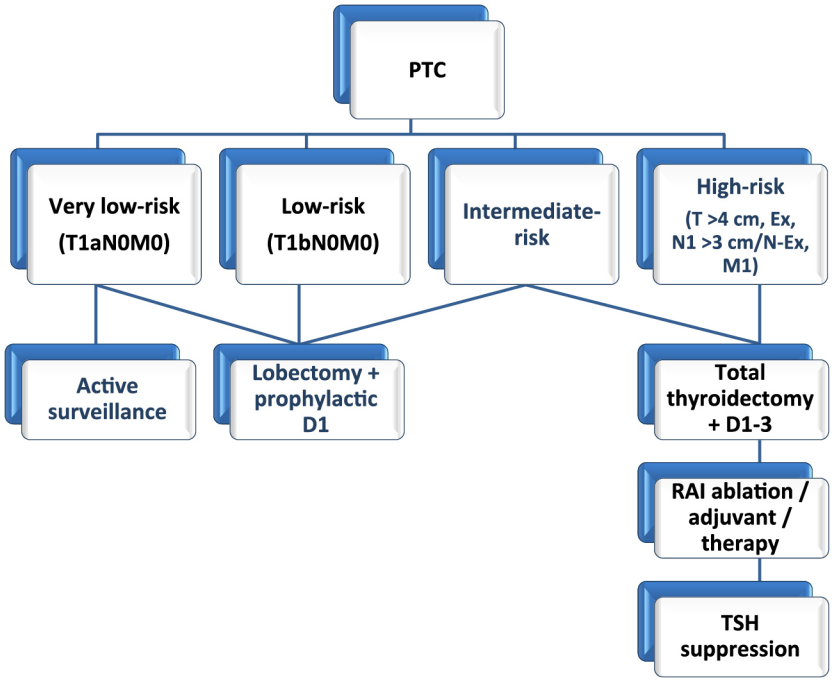

Fig. 1 Flow chart for the management of papillary thyroid carcinoma (PTC)

Ex, extra-thyroidal extension to adjacent structures except for the sternothyroid muscle; N-Ex, extra-nodal extension to adjacent structures from metastatic lymph node(s); D1, dissection of pre- and para-tracheal lymph nodes; levels I-IV in the Japanese General Rules for the Description of Thyroid Cancer classification, level VI in the American Joint Committee on Cancer (AJCC) classification; D2, dissection of unilateral lymph nodes; levels V and VI (or higher if necessary) in the Japanese General Rules for the Description of Thyroid Cancer classification, levels II-IV (or including V, VII, I if necessary) in the AJCC classification on one side; D3, dissection of unilateral lymph nodes; levels V and VI (or higher if necessary) in the Japanese General Rules for the Description of Thyroid Cancer classification, levels II-IV (or including V, VII, I if necessary) in the AJCC classification on both sides; RAI, radio-active iodine

Table 3 Risk classification of PTC

Risk	Description
Very low-risk	T1aN0M0
Low-risk	T1bN0M0
Intermediate-risk	Not belonging to the very low-, low-, or high-risk class
High-risk	At least one of the following:
	1) T >4 cm
	2) extra-thyroidal extension to adjacent structures except for the sternothyroid muscle, or extra-nodal extension of tumor in metastatic lymph node(s)
	3) clinical node metastasis >3 cm
	4) M1

imaging studies (T1aN0M0). Low-risk PTC indicates tumors measuring 1.1–2 cm without lymph node or distant metastasis (T1bN0M0). In contrast, high-risk PTC indicates tumors having at least one of the following clinical features: 1) tumor size exceeding 4 cm; 2) extra-thyroidal extension to adjacent structures except for the sternothyroid muscle, or extra-nodal extension to adjacent structures from metastatic lymph node(s); 3) clinical node metastasis larger than 3 cm; and 4) distant metastasis detected on imaging studies. Intermediate-risk PTC indicates tumors not belonging to the very low-, low-, or high-risk class. Patients having carcinoma extension corresponding to the extra-thyroidal extension on intraoperative findings may be classified as high-risk at the time of surgery because the extra-thyroidal extension is not always diagnosed preoperatively [11].

Age, gender, and histopathological findings were reported to be prognostic factors for cause-specific or disease-free survival, and various risk classifications have been proposed based on these observations [12-15]. In addition to the risk classification proposed by our guidelines, considering such factors may help to individualize management strategy for PTC.

CQ 11. Is total thyroidectomy recommended for PTC?

Recommendation

XXX Total thyroidectomy is not recommended for very low- and low-risk PTC (T1N0M0) (😊 consensus +++).

◎◎◎ Total thyroidectomy is recommended for high-risk PTC (😣 consensus +++).

◎◎ For intermediate-risk PTC, the extent of thyroidectomy (*i.e.*, total thyroidectomy or lobectomy) should be decided individually according to the prognostic factors and patient background characteristics (😣 consensus +++).

Outcomes considered

- ✓ Prognosis
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

- A 10-year disease-free survival rate was reported to be 97% for T1N0M0 PTC patients who underwent less-than-total thyroidectomy (subtotal or lobectomy with isthmectomy).
- It remains unclear whether the extent of thyroidectomy (total thyroidectomy or lobectomy) is associated with the recurrence of PTC or death due to PTC.
- No reports have been published about surgical complications related to the extent of thyroidectomy for PTC.
- No reports have been published about patient-reported outcomes.

Summary of the literature

No randomized studies have compared the efficacy of total thyroidectomy and lobectomy as surgical treatments for PTC. Some observational studies showed that total thyroidectomy was more effective than lobectomy, while other studies did not. Besides, as several studies included patients with PTC as well as those with follicular thyroid carcinoma (FTC) as their study populations, conclusions should be drawn after careful consideration.

Comparative reports between total thyroidectomy and lobectomy using disease registration database in the United States

During the last decade, some large-scale retrospective case series studies have been published using the disease registration database in the United States, including the Surveillance, Epidemiology, and End Results (SEER) database or the National Cancer Database (NCDB). However, it remains unclear whether the difference in the extent of thyroidectomy (total thyroidectomy or lobectomy) is associated with recurrence or death from PTC [16-20] (Table 4).

Studies estimating survival following total thyroidectomy or less-than-total thyroidectomy for PTC in Japan

Also, from Japan, the results of treatments using total and less-than-total thyroidectomy have been reported as retrospective cases series (Table 5). For very low- and low-risk PTC (T1N0M0), 10-year disease-free survival rate was reported to be 97% after less-than-total thyroidectomy [21], leading to the recommendation of lobectomy [21-23].

There is no evidence to support the superiority of total

Table 4 Comparative reports between total thyroidectomy and lobectomy using disease registration database in the United States

Author (year)	Database	*n*	Follow-up[$]	Outcome	Hazard ratio[#]
Haigh (2005)	SEER	5,432	7.2 yrs	OS	AMES low-risk: 1.73* AMES high-risk: 1.46
Bilimoria (2007)	NCDB	52,173	70 mo	Recurrence OS	Recurrence: 0.64 OS: 0.83*
Mendelsohn (2010)	SEER	22,724	109 mo	DSS OS	DSS: 1.10 OS: 1.07
Adam (2014)	NCDB	61,775	82 mo	OS	tumor size 1.0–2.0 cm: 1.05 tumor size 2.1–4.0 cm: 0.89
Adam (2015)	NCDB & SEER (Stage I)	43,032	NCDB: 83 mo SEER: 115 mo	OS	NCDB tumor size 1.0–2.0 cm: 1.12 tumor size 2.1–4.0 cm: 1.93 SEER tumor size 1.0–2.0 cm: 0.95 tumor size 2.1–4.0 cm: 0.94

$, median or mean of follow-up duration; OS, overall survival; DSS, disease-specific survival; #, hazard ratio of total thyroidectomy relative to lobectomy; *, statistically significant

Table 5 Studies estimating survival following total thyroidectomy or less-than-total thyroidectomy for PTC in Japan

Author (year)	Population	*n*	Surgery	Follow-up[$]	Outcome	Estimates
Ito (2010)	T1N0M0	2,638	TT or LTT	91 mo	DSS	at 10 yrs LTT: 97.2% TT: 98.4%
Matsuzu (2014)	Limited to one lobe, any N, M0	1,088	Lobectomy + lateral neck dissection	17.6 yrs	R-RFS L-RFS D-RFS DSS	at 15 yrs R-RFS: 96% L-RFS: 92% D-RFS: 98% DSS: 99%
Ebina (2014)	T >1.0 cm all patients other than high-risk[#]	967	TT or LTT	8.3 yrs	DSS DFS	at 10 yrs LTT: 99% TT: 99% at 10 yrs LTT: 91% TT: 87%

#, age >= 50 yrs, massive extra-thyroidal extension, large metastatic lymph nodes >3 cm, or M1
TT, total thyroidectomy; LTT, less-than-total thyroidectomy; $, median or mean of follow-up duration; DSS, disease-specific survival; R-RFS, remnant thyroid recurrence-free survival; L-RFS, lymph node recurrence-free survival; D-RFS, distant metastasis-free survival; DFS, disease-free survival

thyroidectomy compared to lobectomy for high-risk patients. However, total thyroidectomy followed by or in preparation for radioactive iodine (RAI) therapy and medical treatment is recommended because such patients have factors associated with poor prognosis for carcinoma recurrence and death. For intermediate-risk PTC, favorable outcomes might be expected by less-than-total thyroidectomy, as shown in Table 5, but an optimal surgical strategy should be decided by considering clinical findings and backgrounds on a case-by-case basis.

Subtotal thyroidectomy, which used to be the standard operation for PTC in Japan, is not recommended. Its benefit over lobectomy has not been demonstrated. Moreover, such patients would be at great risk of injury to the recurrent laryngeal nerves, and of developing permanent hypoparathyroidism when completion total thyroidectomy be indicated.

CQ 12. Is prophylactic lymph node dissection recommended in the surgery of PTC?

Recommendation

◎◎ Prophylactic central node dissection is recommended (😣 consensus +++).

X For low-risk PTC, prophylactic lateral node dis-

section is not recommended (😣 consensus +++).

◎ For intermediate and high-risk PTC, it is recommended that the indication of prophylactic lateral node dissection be decided based on other prognostic factors, patient's backgrounds, and her/his will (😣 consensus ++).

Outcomes considered

- ✓ Recurrence rates
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

- Prophylactic central node dissection along with total thyroidectomy is associated with a decrease in regional lymph node recurrence rates. Assuming that the decrease was a treatment effect, 43 patients need to be dissected to prevent 1 patient from developing the recurrence.
- Prophylactic central node dissection along with total thyroidectomy is associated with postoperative hypoparathyroidism. One in 9 patients and 1 in 50 patients develop temporary and permanent hypocalcemia, respectively.
- It is not evident that prophylactic lateral node dissection decreases recurrence rates in low-risk PTC.
- For cN0 PTC patients with two or more prognostic factors for lymph node recurrence, a 10-year recurrence rate exceeds 10% even if they undergo prophylactic lateral node dissection.
- Complications associated with prophylactic lateral node dissection include chyle leak (1%) and temporary nerve paralysis (<1%).
- No reports have been published about patient-reported outcomes associated with prophylactic node dissection.

Summary of literature

Prophylactic central node dissection

Effect

Three systematic reviews were published regarding the effect of prophylactic central node dissection. The newest is a meta-analysis of 17 studies (4,437 patients) by Zhao *et al.* [24]. Prophylactic central node dissection, along with total thyroidectomy was associated with regional lymph node recurrence rates with a risk ratio of 0.66 [95% CI: 0.49–0.90]. The absolute difference in recurrence rates between the dissecting and non-dissecting central compartment was 2.3%, and assuming that this corresponds to the treatment effect, dissection is required for 43 patients to prevent recurrence in 1 patient (number needed to treat [NNT]: 43). However, the 17 studies included in the meta-analysis were all observational in their designs (3 prospective, 14 retrospective studies) and patients who underwent lymph node dissection and those who did not were different in various aspects. The difference in the recurrence rates can be explained by factors other than lymph node dissection, and the risk ratio or NNT might be overestimated.

Surgical complications

Adding central node dissection to total thyroidectomy may increase the risk of hypoparathyroidism. According to Zhao *et al.*, the odds ratios of temporary and permanent hypocalcemia were 2.37 [95% CI: 1.89–2.96], and 1.93 [95% CI: 1.05–3.5], respectively [24].

Predictive factors of lymph node metastasis

Not a few studies tried to identify predictive factors of central node metastasis for cN0 PTC, in order to dissect select patients at high risk of lymph node metastasis. Ma *et al.* aggregated these predictive factors and their odds ratios in a meta-analysis of relevant studies. Following clinic-pathological characteristics were found to be associated with central lymph node metastasis: age (<45 years), male gender, tumor size >1 cm, tumor multifocality, tumor location (upper third of the thyroid), angiolymphatic invasion, extracapsular invasion, bilateral tumors, histological high-risk features and $BRAF^{v600E}$ mutation [25].

Prophylactic lateral node dissection

One systematic review regarding lateral node dissection was published in 2014, but it was not relevant because the study populations were not restricted to clinically node-negative PTC (*i.e.*, follicular thyroid carcinoma as well as clinically node-positive PTC) [26].

Effects of prophylactic lateral node dissection

The effect of prophylactic lateral node dissection on low-risk PTC was investigated in two comparative studies (Table 6) [21, 27]. Although they were observational studies, there were no statistically significant differences in the recurrence rates, and the Kaplan–Meier curves indicated very high relapse-free rates. Conversely, chylorrhea (1%) and temporary paralysis of the accessory or phrenic nerve (0.2%) were reported as complications of prophylactic lateral node dissection [27].

Recurrence after prophylactic lateral node dissection for cN0 PTC

Oncologic outcomes following the prophylactic dissection on clinically node-negative PTC were determined in three studies (Table 7) [28-30]. Ito *et al.* identified "age older than 55 years," "male gender," "significant extra-thyroidal extension," and "tumor size measuring 3 cm or larger" as predictive factors of lymph node recurrence. They recommended selective prophylactic lateral node dissection for cases having two or more of the abovementioned factors, based on their data that the 10-year lymph node recurrence-free survival rate was 88.5%

Table 6 Effects of prophylactic lateral node dissection for low-risk PTC

Author (year)	Population	*n*	Lymph node dissection	Follow-up[$]	Outcome	Estimates
Ito (2010)	cT1N0M0, solitary	2,638	CND + LND (1,545 pts) CND only (966 pts) none (127 pts)	91 mo	DFS	CND + LND = CND only = none
Ito (2011)	cN0 or N1a, not T4, not M1	1,243	CND + LND (414 pts) CND only (829 pts)	48 mo	LN-DFS	CND + LND = CND only

$, median or mean of follow-up duration; CND, central lymph node dissection; LND, lateral lymph node dissection; DFS, disease-free survival; LN-DFS, lymph node disease-free survival

Table 7 Recurrence after prophylactic lateral node dissection for cN0 PTC

Author (year)	Population	*n*	Lymph node dissection	Follow-up[$]	Outcome	Estimates
Ito (2007)	cN0	1,231	CND + LND	10.9 yrs	LN-DFS	94.2%
Bonnet (2009)	cT1N0M0	115	CND + LND	1 yr	LN-DFS	100%
Ducoudray (2013)	cN0	603	CND + bilateral LND	4.3 yrs	DFS	96%

$, median or mean of follow-up duration; CND, central lymph node dissection; LND, lateral lymph node dissection; DFS, disease-free survival; LN-DFS, lymph node disease-free survival

and 64.7% in patients with 2 and 3 or more factors, respectively [28].

Recurrence after no prophylactic lateral node dissection

Sugitani *et al.* conducted a prospective study on the management policy of performing lateral node dissection only on clinically node-positive PTC patients for a therapeutic purpose [31]. The 5-year and 10-year lymph node recurrence-free survival rates of cN0 patients who underwent central node dissection only were estimated to be 97% and 91%, respectively. Risk factors for lymph node recurrence were tumor size larger than 4 cm (risk ratio 3.6) and distant metastasis (risk ratio 46.0).

Complications

Patients may feel some symptoms related to adhesion induced by the lateral node dissection. Although the incidence is not very high, distinctive complications such as chylorrhea, accessory nerve paralysis, facial nerve paralysis, and Horner syndrome may occur. Although lymph node recurrence does not immediately affect patients' life prognoses, it significantly increases the psychological burden [32]. For intermediate-risk and high-risk patients, it is desirable to perform prophylactic lateral node dissection after due consideration of individual clinical manifestation, possible complications, and patients' way of thinking.

CQ 13. Is non-surgical active surveillance for very low-risk PTC (T1aN0M0) recommended?

Recommendation

◎◎ Active surveillance is recommended for patients with very low-risk PTC having no evidence of metastasis or extension, under an appropriate medical care system given a patient's consent, after an adequate explanation of the disease condition and the benefits/risks of the management (😊 consensus ++).

Outcomes considered

- ✓ Tumor progression (enlargement, invasion, metastasis, and carcinoma death)
- ✓ Prognosis and complication for patients who undergo surgery after active surveillance
- ✓ Health conditions from the patients' perspective

Evidence

- The 5- and 10-year rates of enlargement (3 mm or more in diameter) of very low-risk PTC (T1aN0M0) under active surveillance are estimated to be 4.9% and 8.0%, respectively.
- The 5-year and 10-year rates of patients experiencing lymph node metastasis from very low-risk PTC (T1aN0M0) under active surveillance are estimated to be 1.7% and 3.8%, respectively.
- The 5-year and 10-year rates of patients experiencing progression (tumor size reaching 12 mm or larger, or novel appearance of metastatic nodes) of very low-risk PTC (T1aN0M0) under active surveillance are estimated to be 3.9% and 6.8%, respectively.
- The 5-year and 10-year rates of the individual tumor showing enlargement (3 mm or more in diameter) for very low-risk PTC (T1aN0M0) under active surveillance are estimated to be 6.3% and 7.3%, respectively.
- Surgery after active surveillance is safe and does not affect the prognosis of patients.

・No reports have been published about the conditions of health from the patients' perspective.

Summary of literature

Enlargement or progression of the tumor under active surveillance

Two Japanese institutions reported the outcomes of prospective studies on active surveillance for very low-risk PTC (T1aN0M0). Ito *et al.* enrolled 1,235 patients who underwent active surveillance for longer than 18 months and estimated 5-year and 10-year tumor enlargement rates (3 mm or larger in diameter) to be 4.9% and 8.0%, 5-year and 10-year lymph node appearance rates to be 1.7% and 3.8%, and 5-year and 10-year clinical progression rates (tumor size 12 mm or larger, or novel appearance of node metastasis) to be 3.9% and 6.8%, respectively [33]. Fukuoka *et al.* reported that 480 lesions (384 patients) underwent active surveillance for 12 months or longer, 5-year and 10-year enlargement rates (3 mm or larger in diameter) were 6.3% and 7.3%, respectively [34]. The incidence of cases showing the novel appearance of lymph node metastasis during active surveillance (6.3 years on average) was 1%.

Features of patients or lesions showing enlargement or progression of PTC during active surveillance

Ito *et al.* estimated the 5-year and 10-year probability of enlargement of tumors by age group and reported that tumor was more likely to enlarge in young patients aged less than 40 years (9.1% and 12.1%); 40–59 years (5.0% and 9.1%); and for those aged 60 years or older (4.0% and 4.0%), respectively [33]. Also, Fukuoka *et al.* showed 5-year and 10-year enlargement rates of 9.7% and 15.0% for patients younger than 50 years, as well as 6.4% and 6.4% for those aged 50 years or older, respectively, although there was no statistical significance between the two groups [34]. They also reported that strong calcification and poor blood flow on ultrasound were features of PTC that did not progress. Sugitani *et al.* found no difference in TSH levels between enlarged and not enlarged tumors in a study, which enrolled 415 carcinoma lesions (322 patients) [35].

Conversion surgery after active surveillance and prognosis

According to the report by Ito *et al.*, 191 of the 1,235 patients who underwent active surveillance underwent conversion surgery for several reasons (total thyroidectomy for 93 patients, and lateral node dissection for 34 patients), and only 1 patient showed recurrence in the remnant thyroid [33]. Oda *et al.*, in the same institution, reported on 1,179 patients who chose and underwent active surveillance for longer than 12 months between 2005 and 2013. Surgical complications in 97 patients who underwent conversion surgery (change of will 54%, tumor enlargement 29%, the appearance of node metastasis 6%) were temporary (7.4%) and permanent vocal cord paralysis (0%), while temporary and permanent hypoparathyroidism were 35% and 1%, respectively [36]. Only one patient showed recurrence in the neck, and none of the patients showed distant recurrence or died of thyroid carcinoma. According to Sugitani *et al.*, of 230 patients who underwent active surveillance, 16 underwent conversion surgery (two underwent total thyroidectomy, and two underwent lateral node dissection) and none of these showed any adverse events or postoperative recurrence or died of thyroid carcinoma [37].

Cases unsuitable for active surveillance

Exclusion criteria for active surveillance of the two observational studies were as follows: 1) clinical node metastasis; 2) distant metastasis; 3) apparent extrathyroidal extension; and 4) tumors located adjacent to the trachea, esophagus, or recurrent laryngeal nerve. Before initiating active surveillance, confirmation is required on ultrasound and neck/chest computed tomography scan, whether these findings are present. Ito *et al.* indicated that tracheal invasion was unlikely when the tumor and tracheal cartilage surface formed acute angle, and such a tumor could undergo active surveillance. They recommend surgery for a tumor that forms an obtuse angle with the tracheal surface [38].

Although the further accumulation of cases and a longer period of active surveillance are required for the definite conclusion, it is tentatively concluded that active surveillance (and conversion surgery after becoming clinical) is an appropriate management approach for very low-risk PTC (cT1aN0M0). However, before then, sufficient explanation is required for patients, about the possibility of conversion surgery because of enlargement or appearance of node metastasis, and the possibility (although extremely low) of risks such as the appearance of distant metastasis and anaplastic transformation. Also, the choice of active surveillance should be of patients' freewill. For active surveillance, it is important to perform a reliable ultrasound examination once or twice a year. At the time of the examination, ultrasound by an experienced technician is crucial to evaluate the tumor size and appearance of new lesions and lymph node metastasis. Conversion surgery should be performed if such progression signs appear.

Follicular Thyroid Carcinoma (FTC) (Fig. 2)

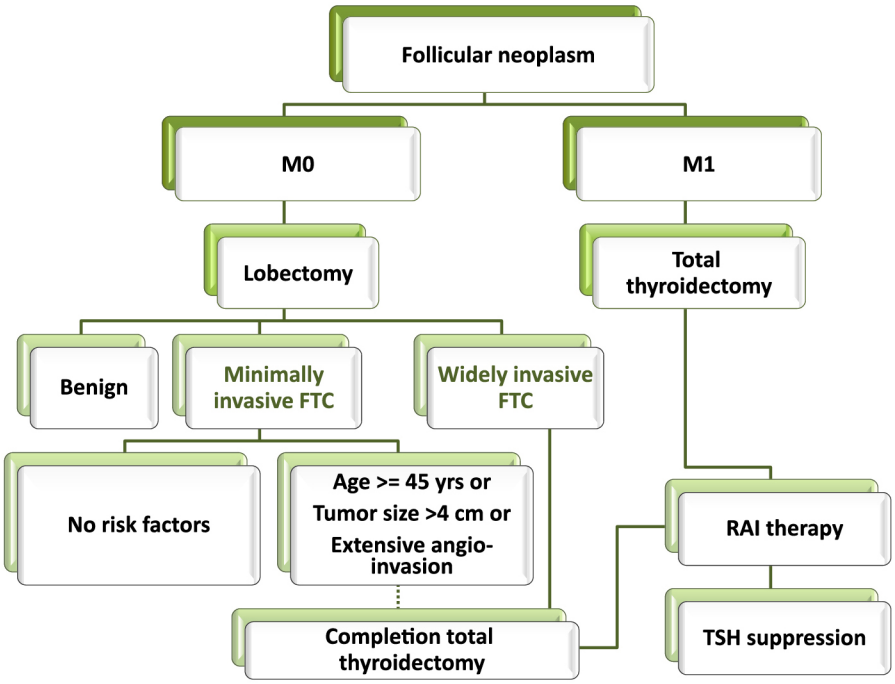

Fig. 2 Flow chart for the management of follicular thyroid carcinoma (FTC)
RAI, radio-active iodine

CQ 14. Is total thyroidectomy recommended for widely invasive FTC?

Recommendation

◎◎◎ For widely invasive FTC with distant metastasis (M1), total thyroidectomy and RAI therapy are recommended (😊 consensus +++).

◎◎◎ For widely invasive FTC without distant metastasis (M0) diagnosed after lobectomy, completion total thyroidectomy is recommended (😖 consensus +++).

No clinical trial is available for improved prognosis in completion total thyroidectomy as second surgery and successive RAI therapy for M0 widely invasive FTC. However, since the prognosis of widely invasive FTC is significantly poorer than that of minimally invasive FTC, measuring serum thyroglobulin levels following total thyroidectomy along with RAI therapy to monitor the appearance of distant metastasis or local recurrence is strongly recommended.

Outcomes considered

- ✓ Prognosis
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

- It is estimated that 20–30% of patients with M0 widely invasive FTC would show recurrence within a few years after surgery if they would not undergo RAI treatment (ablation). However, such a recurrence is unlikely to be life-threatening within ten years after surgery.
- Temporary and persistent recurrent laryngeal nerve paralysis occurs in 3% and 0.4% of patients, while temporary and persistent hypocalcemia occurs in 20% and 6% of patients who underwent surgery for FTC, respectively.
- No reports have been published about the conditions of health for total thyroidectomy from the patients' perspective.

Summary of literature

Total thyroidectomy is required for M1 widely invasive FTC because therapeutic RAI administration is essential. An important clinical question is whether total thyroidectomy followed by RAI therapy is required for M0 widely invasive FTC. As no clinical trials have been published, the issue should be addressed based on retrospective observational studies on the clinical course of M0 widely invasive FTC (Table 8).

Two reports from Japanese institutions included many patients who did not undergo RAI therapy. Ito *et al.*

Table 8 Prognosis of M0 widely invasive FTC

Author (year)	*n*	Postoperative RAI	Follow-up[$]	Outcome	Estimates
Ito (2007)	56	NA	NA	DFS CSS	at 5 yr: 86% at 10 yr: 65% at 5 yr: 97% at 10 yr: 97%
Sugino (2011)	10	0	NA	IDM	30% (3/10)
Lo (2005)	64	52	NA	IR ICD	12% (8/64) 8% (5/64)
Podda (2015)	29	76	125 mo	IR ICD	24% (7/29) 0% (0/29)

NA, not available; DFS, disease-free survival; CSS, cause-specific survival; IDM, incidence of distant metastasis; IR, incidence of recurrence; ICD, incidence of cancer death

reported a prognosis of 56 patients with M0 widely invasive FTC [39]. The Kaplan–Meier estimates of the 5-year and 10-year disease-free survival rates were 86% and 65%, while the cause-specific survival rates were 97% and 97%, respectively [39]. The number of patients who underwent RAI therapy was not available. Sugino *et al.* enrolled 10 M0 cases and reported that the incidence of distant metastasis was 30% (the follow-up period is unknown) [40]. Lo *et al.* observed 64 cases, including 52 who underwent ablation, and showed the incidences of recurrence and cancer death were 12% and 8%, respectively (the follow-up periods are unknown) [41]. Podda *et al.* estimated the incidences of recurrence and cancer death to be 24% and 0%, respectively, for patients who underwent ablation (average follow-up period, 125 months) [42].

Since it is difficult to discriminate between patients who require extensive therapies and those who do not, completion total thyroidectomy followed by RAI ablation is desirable to detect any recurrences.

Lo *et al.* reported on complications of surgery for FTC. In a series of 156 cases, including those who underwent lobectomy, the incidences of temporary and permanent recurrent laryngeal nerve paralysis were 3% and 0.4%, respectively. Of a subset of 132 cases who underwent surgery for both lobes; temporary and permanent hypocalcemia occurred in 20% and 6%, respectively [41].

CQ 15. Is completion total thyroidectomy recommended after lobectomy for minimally invasive FTC?

Recommendation

X Completion total thyroidectomy is not uniformly recommended for M0 minimally invasive FTC (㊀ consensus ++).

No clinical trials have been published regarding whether completion total thyroidectomy followed by RAI therapy improves the prognosis of patients with minimally invasive FTC.

Outcomes considered

✓ Prognosis
✓ Surgical complications
✓ Health conditions from the patients' perspective

Evidence

- Even in minimally invasive FTC, 1–9% of patients have distant metastasis at the time of initial treatment.
- It is estimated that 0–14% of patients with M0 minimally invasive FTC would develop post-operative recurrence a few years later, but life prognosis is excellent.
- No reports have been published regarding the complications of surgery for minimally invasive FTC.
- No reports have been published about the conditions of health associated with minimally invasive FTC from the patients' perspective.

Summary of literature

The incidence of distant metastasis at initial treatment (M1) in minimally invasive FTC

The incidence of distant metastasis at initial treatment (M1) in minimally invasive FTC reported by Lo *et al.*, Asari *et al.*, Sugino *et al.*, and Ito *et al.* were 1%, 9%, 9%, and 2%, respectively [41, 43-45]. As reported by O'Neill *et al.*, many M1 cases were diagnosed based on imaging studies at the time of postoperative ablation [46]. Sugino *et al.* diagnosed distant metastasis postoperatively, in two patients who underwent prophylactic completion total thyroidectomy and RAI therapy [47].

Prognosis of minimally invasive FTC without distant metastasis (M0) (Table 9)

Using the Kaplan-Meier method, Sugino *et al.* reported

Table 9 Prognosis of M0 minimally invasive FTC

Author (year)	*n*	Postoperative RAI	Follow-up[$]	Outcome	Estimates
Sugino (2014)	324	81	NA	DFS CSS	at 10 yr: 86% at 15 yr: 76% at 20 yr: 74% at 10 yr: 98% at 15 yr: 95% at 20 yr: 93%
Lo (2005)	71	NA	NA	IR ICD	1% (1/71) 0% (0/71)
Ito (2014)	285	NA	117 mo	IR ICD	7% (19/285) 1% (3/285)
Podda (2015)	42	42	113 mo	IR ICD	0% (0/42) 0% (0/42)

NA, not available; DFS, disease-free survival; CSS, cause-specific survival; IDM, incidence of distant metastasis; IR, incidence of recurrence; ICD, incidence of cancer death

Table 10 Prognostic factors of M0 minimally invasive FTC

Author (year)	*n*	Total thyroidectomy/ Postoperative RAI	Factors for recurrence	Factors for cancer death
Sugino (2014)	324	101/81	For distant mets: Age ≥45 yrs: 9.6 (3.7–32.7)* No completion: 2.9 (1.2–9.0)*	NA
Ito (2013)	285	50/0	Age ≥45 yrs: 9.8 (2.2–43.8)* Extensive vascular invasion: 5.4 (1.7–17.0)* Tumor size >4 cm: 3.5 (1.1–11.4)*	Extensive vascular invasion: 17.0 (1.7–250)*
Podda (2015)	42	42/42	Tumor size >4 cm: OR 6.8 (1.01–45)[#]	NA

NA, not available; *, hazard ratio with 95%CI; #, odds ratio with 95%CI

the 10-year, 15-year, and 20-year distant recurrence-free survival rates of 86%, 75%, and 74%; while the cause-specific survival rates for these years were 98%, 95%, and 93%, respectively [47]. Lo *et al.* showed the incidences of recurrence and cancer death were 1% and 0%, respectively (the follow-up periods are unknown) [41]. Ito *et al.* estimated the incidences of recurrence and cancer death to be 7% and 1%, respectively, with an average follow-up time of 117 months [45]. Podda *et al.* performed total thyroidectomy and ablation for all patients and reported both incidences of recurrence and cancer death to be 0% with a mean follow-up period of 113 months [42].

Prognostic factors of minimally invasive follicular carcinoma without distant metastasis (M0) (Table 10)

As minimally invasive FTC has a better prognosis than that of widely invasive FTC, adjuvant therapy such as completion total thyroidectomy and ablation is not uniformly recommended. Nonetheless, as indicated above, even minimally invasive carcinoma may recur, and proactive treatments with completion thyroidectomy and ablation may prevent a recurrence. Recognizing the clinical and pathological characteristics of FTC associated with oncologic events could be useful for the clinical judgment of whether additional treatments are necessary.

Table 10 shows the prognostic factors of M0 minimally invasive FTC. According to Sugino *et al.*, hazard ratios associated with distant recurrence were 9.6 (95% CI: 3.7–32.7) for those aged 45 years or older and 2.9 (95% CI: 1.2–9.0) for no completion total thyroidectomy [47]. Podda *et al.* concluded that tumor size larger than 4 cm is related to recurrence with an odds ratio of 6.8 (95% CI: 1.01–44.9) [42]. Among prognostic factors investigated by Ito *et al.*, hazard ratios of increasing risk of recurrence were 9.8 (95% CI: 2.2–43.8) for those aged 45 years or older; 5.4 (95% CI: 1.7–17.0) for extensive vascular invasion; and 3.5 (95% CI: 1.1–11.4) for tumor size larger than 4 cm [48]. Besides, a factor relating to carcinoma death, extensive vascular invasion had a hazard ratio of 17.0 (95% CI: 1.7–250). In this series, all patients who died of thyroid carcinoma were aged 45 years or older, and their tumor size exceeded 4 cm [48]. In contrast, Sugino *et al.* investigated 101 cases who underwent completion total thyroidectomy and reported that none of these patients died of minimally invasive

FTC [47].

Taken together, the prognosis of patients who were pathologically diagnosed as minimally invasive FTC after lobectomy is generally excellent. Except for cases with distant metastasis, completion total thyroidectomy is not uniformly recommended. However, it may be considered for cases with more than one of the above risk factors of recurrence.

Medullary Thyroid Carcinoma (MTC) (Fig. 3)

CQ 16. What are the symptoms and findings indicative of hereditary MTC?

- Multiple endocrine neoplasia type 2 (MEN2) is suspected if there are family histories of pheochromocytoma (Pheo) and hyperparathyroidism (HPT), while familial medullary carcinoma is suspected if there is a family history of medullary carcinoma only.
- In the Japan MEN2 survey, Pheo and HPT were detected in 46% and 8% of subjects, respectively.
- Although rare, MEN2A can be accompanied by skin lichen amyloidosis and Hirschprung's disease, while MEN2B can be associated with marfanoid habitus, mucosal neuromas of the lips and tongue, intestinal ganglioneuromatosis, and corneal nerve thickening.
- Multiple medullary carcinomas located in both lobes are a finding suspected of the hereditary disease.

Summary of literature

Hereditary medullary carcinoma consists of MEN2 and familial MTC (FMTC), and MEN2 is clinically subclassified as MEN2A and MEN2B. Various associated diseases are identified in hereditary medullary carcinoma. Backgrounds of associated diseases differ according to whether *RET* gene mutation is investigated, and the location of mutated codons. Also, the incidences of associated diseases vary according to differences in the definition of MEN2 and FMTC.

Obtaining a family history of MTC, Pheo, and primary HPT (pHPT) is essential, and positive history strongly suggests that the disease is hereditary. During family history taking, any uncertainty regarding the history should be addressed by a careful re-hearing, if necessary.

For the diagnosis of hereditary medullary carcinoma, the occurrence of clinical symptoms other than for the thyroid is important. Other than Pheo and pHPT, skin lichen amyloidosis and Hirschprung's disease may comorbid as associated diseases of MEN2A. MEN2B is often accompanied by Pheo, marfanoid habitus, mucosal neuromas of the lips and tongue, intestinal ganglioneuromatosis and corneal nerve thickening. The lifetime penetration rate of medullary carcinoma in MEN2 is more than 90%, and that of Pheo and pHPT is about 30–60% and 10–30%, respectively [49-51]. Disease frequency depends on the incidence of codon 634 mutations, and the incidence of Pheo and pHPT is inevitably high in studies enrolling many patients with codon 634 mutations [52, 53]. A Japanese study on 505 cases (MEN2A 67.9%; MEN2B

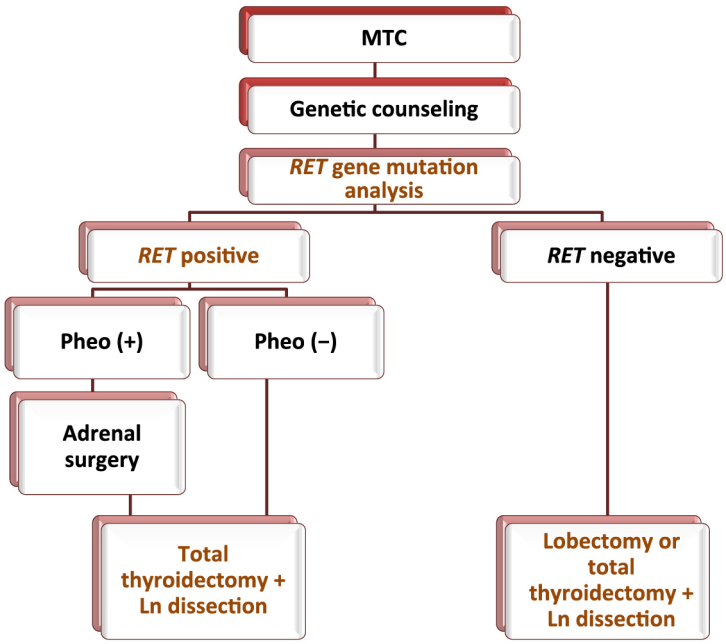

Fig. 3 Flow chart for the management of medullary thyroid carcinoma (MTC)
Pheo, pheochromocytoma; Ln, lymph node

5.7%; and FMTC 20.4%) reported that Pheo and pHPT were detected in 45.6% and 8.1%, respectively, and the incidences were very low (10 cases or smaller) for Hirschprung's disease, neuromas of the lips and tongue, intestinal ganglioneuromatosis, and skin lichen amyloidosis [54].

The majority of MEN2B is based on *de novo* mutation (no mutations are detected in parents), and, in such cases, disease detection by family history is difficult. However, this can be clinically detected by physical characteristics. FMTC is considered to be a subtype of MEN2A, and the incidence of Pheo, pHPT, and skin lichen amyloidosis is very low [55, 56]. Clinically, early-onset MTC or that with lesions in both lobes is suspected to be hereditary.

However, the sporadic disease cannot immediately be diagnosed based on the absence of family and past history, and it is impossible to correctly diagnose whether the disease is sporadic or hereditary based from the clinical standpoint alone. The definitive diagnosis of whether MTC is sporadic or hereditary should be based on *RET* gene mutation analysis.

CQ 17. Is *RET* gene mutation analysis recommended for MTC?

Recommendation

◎◎◎ *RET* gene mutation analysis is recommended for all patients with MTC (😊 consensus +++).

Outcomes considered

✓ Test performance
✓ Health conditions from the patients' perspective

Evidence

- *RET* mutations are detected by *RET* gene mutation analysis (*RET* analysis) in more than 98% of hereditary cases.
- Mutations are detected either in exon 10, 11, or 13–16.
- From the patients' perspective, the result of *RET* analysis may induce various psychological reactions, including uneasiness or relief, regardless of whether it is positive or negative.

Summary of literature

The most important issue in designing surgical strategy for MTC is to differentiate between hereditary MTC and the sporadic one. *RET* gene mutation analysis is carried out in patients who are clinically diagnosed with or strongly suspected of having MTC. By this analysis, *RET* mutation can be proved in more than 98% of hereditary cases, and mutations are detected in exon 10, 11, or 13–16 [51]. If a mutation is detected, the diagnosis is either MEN2 or FMTC, which are autosomal dominant hereditary diseases. The mutation analysis is superior to a screening test measuring the calcitonin level of family members [49, 57]. It is impossible to diagnose perfectly whether the disease is hereditary or sporadic by the family history and clinical characteristics only, and 10–15% of seemingly sporadic MTC is diagnosed as hereditary using *RET* analysis [58]. *RET* analysis is also recommended for at-risk family members when the mutation has already been identified for a patient in the family because a positive result facilitates early diagnosis and treatment. It is essential to have genetic counseling for patients or relatives, and they should give written consent before undergoing *RET* gene mutation analysis. Preimplantation diagnosis and prenatal diagnosis are not available [59].

There is a genotype-phenotype correlation in patients with MEN2. Total thyroidectomy is mandatory for hereditary MTC, while limited thyroidectomy can be performed for sporadic MTC, depending on the extent of pathological lesions [60]. The genotype is also important because the onset and degree of malignancy of MTC might differ according to the sites of mutated codons. Once the genetic test makes the diagnosis of hereditary MTC, it is essential to make or rule out the diagnosis of Pheo. If a patient has Pheo, he or she should first undergo treatment for the disease. In MEN2A, a mutation in codon 634 mutation is most likely to be associated with pHPT and mutations in exon 10 (codons 609, 618, and 620) are exclusively related to Hirschprung's disease [56].

In a study of individuals at risk of MEN2 who applied for *RET* analysis and their partners, Grosfeld *et al.* reported that favorable as well as unfavorable test results evoked various psychological reactions including both worry and relief [61]. Also, parents who were informed that their child was a gene carrier reacted with resignation, showed moderate-to-high levels of test-related and general anxiety [62].

CQ 18. Is prophylactic total thyroidectomy recommended for family members with *RET* mutations before the onset of MTC (gene carries)?

Recommendations

X Prophylactic total thyroidectomy is not uniformly recommended for asymptomatic carriers of *RET* mutations (😖 consensus +++).

Outcomes considered

✓ Prognosis
✓ Surgical complications

✓ Health conditions from the patients' perspective

Evidence

- The average age at the time of surgery for cases negative for node metastasis was 10.2 years for patients with extracellular domain mutations (codons 609, 611, 620, 630, and 634) and 16.6 years for those with intracellular domain mutations (codons 768, 790, 791, 804, and 891).
- The recurrence rate of MTC after prophylactic total thyroidectomy based on postoperative calcitonin levels is 11–12%.
- The incidence of permanent hypoparathyroidism and recurrent laryngeal nerve paralysis after prophylactic total thyroidectomy is 20% and 5%, respectively.
- No reports have been published about the conditions of health, from the patients' perspective.

Summary of literature

Total thyroidectomy can be indicated for individuals who are positive on *RET* analysis before the onset of MTC. In Europe and the United States, total thyroidectomy is recommended before the age of one year for MEN2B and before the age of five years for MEN2A [63-65]. The calcitonin stimulation test is useful to make a diagnosis of MTC for an individual who shows normal basal calcitonin level and no abnormality on ultrasonography [66]. In 2001, Brandi *et al.* proposed the timing of prophylactic total thyroidectomy based on the risk classification of MTC according to *RET* mutation sites and carriers' ages [63]. In 2009, American Thyroid Association (ATA) published the management guidelines for MTC including the risk levels and ages when prophylactic total thyroidectomy is indicated [67], and the revised version was published in 2015 [56]. The age criteria for surgery in these guidelines were based on the youngest age of occurrence of MTC reported in the literature [68]. Patients and family members should understand the benefits and the risks of prophylactic total thyroidectomy and give consent when the procedure is planned for gene carriers. However, it seems difficult to perform surgery for all children at the ages recommended in Europe and the United States guidelines.

It was revealed that C-cell hyperplasia, which is a precancerous state, is transformed to MTC with age, based on the observations of children aged 20 years or younger with *RET* gene mutations who underwent total thyroidectomy [69-71]. Machens *et al.* reported that the average age at the time of surgery for cases with negative for node metastasis was 10.2 years for patients with extracellular domain mutations (codons 609, 611, 620, 630, and 634) and 16.6 years for those with intracellular domain mutations (codons 768, 790, 791, 804, and 891) [69]. For the codon 634 mutations, the average age at surgery for C-cell hyperplasia, N0 MTC and N1 MTC were 6.9 years, 10.1 years, and 16.7 years, respectively. A study on 50 patients aged 20 years or younger with *RET* gene mutations, who underwent total thyroidectomy, demonstrated that postoperative recurrence defined by imaging studies or elevated calcitonin level (either basal or stimulated) was observed in 6 cases (12%, average age at surgery was 10 years old, average follow-up period was 7 years) [70]. Another study reported that recurrence occurred in 5 of the 46 cases (11%, average age at surgery 13 years, average follow-up periods, 6.4 years) [71]. The incidence of permanent hypoparathyroidism in these two studies was 2% and 6%, respectively. A study from Holland [72] showed that permanent hypoparathyroidism occurred in 20% of 44 cases who underwent prophylactic total thyroidectomy, and the incidence was higher in younger patients. Two patients showed temporary bilateral recurrent laryngeal nerve paralysis, and one of them experienced permanent unilateral nerve paralysis. The authors concluded that they would not recommend surgery before the age of 3 years for high-risk cases defined by the ATA risk classification (codon 634 mutations).

In Japan, there is no consensus on the appropriate age for *RET* analysis and total thyroidectomy according to the type of mutations. A study on 46 Japanese children with hereditary MTC (including patients before the *RET* gene mutation analysis became available) demonstrated that recurrence rate reached as high as 39%, particularly in those with pre-operative calcitonin level ≥2,000 pg/mL or those with two or more lymph node metastases [73]. For children with *RET* mutations, total thyroidectomy with the least surgical complications is desirable in the earlier phase of MTC. It is important to distinguish between the prophylactic total thyroidectomy before the occurrence of MTC and therapeutic surgery in the early phase of MTC. As the prophylactic surgery is not available in the national health insurance program in Japan, therapeutic total thyroidectomy in the early phase of MTC is likely to be chosen.

CQ 19. Is total thyroidectomy recommended for MTC?

Recommendations

◎◎◎ Total thyroidectomy is recommended for hereditary MTC even though the lesion is limited to one lobe because the bilateral C-cells have the potential to become cancerous (㊿ consensus +++).

◎◎ For sporadic MTC located only in one lobe, less than total thyroidectomy (lobectomy) is

recommended (㊧ consensus +++).

Outcomes considered

- ✓ Prognosis
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

- According to a nationwide study in Japan, the 10-year survival rate of patients with hereditary MTC, who underwent total thyroidectomy or not, was 94% and 90%, respectively.
- One study reported a postoperative recurrence rate of hereditary MTC after total thyroidectomy to be 14%, while the rate after the less-than-total thyroidectomy was 45%.
- Postoperative calcitonin levels came within the normal range in 74% of patients with non-hereditary MTC who underwent less than total thyroidectomy.
- One study reported that permanent hypoparathyroidism occurred in 29% of patients who underwent total thyroidectomy for hereditary MTC.

Summary of literature

Two studies were conducted regarding the prognostic outcomes and surgical designs for hereditary MTC. Iihara *et al.* showed that the 10-year survival rate after either the total thyroidectomy or less-than-total thyroidectomy was 94% and 90%, respectively. They concluded that the two surgical designs were equivalent in terms of survival [74]. Miyazawa *et al.* reported that the recurrence rate of patients, who underwent total and less-than-total thyroidectomy, was 14% and 45%, respectively [75]. Conversely, Kebebew *et al.* concluded that the disease-free survival after total thyroidectomy is significantly better, with a study population comprised of 46 hereditary and 58 sporadic MTC [76]. As hereditary MTC arises from the C-cells in both lobes, total thyroidectomy is recommended even though carcinoma lesion is clinically limited to one lobe.

Few studies have been published comparing patient outcomes after total thyroidectomy with those after less-than-total thyroidectomy in sporadic MTC. According to an observational study by Miyauchi *et al.*, post-operative calcitonin level normalized in 13 of 18 patients (72%) that underwent total thyroidectomy and in 14 of 19 patients (74%) that underwent less than total thyroidectomy [77]. In this study, all patients who underwent less than total thyroidectomy had MTC lesions limited to one lobe on ultrasound, and they were not randomly selected. The superiority of total thyroidectomy to less than total resection for improved oncologic outcomes has never been demonstrated; therefore, less than total thyroidectomy (lobectomy) is recommended for sporadic MTC that is limited to one lobe, to avoid surgical complications and life-long levothyroxine supplementation [60, 77, 78].

Rodrigues *et al.* performed a cross-sectional survey on 43 patients with MEN2 and detected permanent hypoparathyroidism in 12 of the 41 patients (29%) who underwent total thyroidectomy. Besides, as a result of psychological distress due to suffering from MEN2, 42% and 26% of patients showed anxiety and depression, respectively [79].

CQ 20. Is prophylactic lymph node dissection recommended for MTC?

Recommendations

◎◎◎ Prophylactic central node dissection is recommended (㊧ consensus +++).

◎ It is recommended to decide whether prophylactic lateral node dissection in the ipsilateral or contralateral side is performed based on calcitonin level and prognostic factors individually (㊧ consensus +++).

Outcomes considered

- ✓ Prognosis
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

- It has been reported that performing regional lymph node dissection is not associated with survival.
- Biochemical cure (*i.e.*, negative calcitonin stimulation test) was achieved in 68% of patients with hereditary MTC who underwent lymphadenectomy, and in 41% of those that did not undergo lymphadenectomy.
- The rates of ipsilateral lateral and contralateral lateral node metastases for patients with basal calcitonin levels of 20–200 pg/mL; 200–2,000 pg/mL; 2,000–10,000 pg/mL; and 10,000 pg/mL or greater were 12% *vs.* 0%; 43% *vs.* 14%; 74% *vs.* 44%; and 90% *vs.* 80%, respectively.
- No reports have been published regarding the surgical complications.
- No reports have been published about the conditions of health, from the patients' perspective.

Summary of literature

Whether lymph node dissection influences patients' prognosis has been examined in some case series studies. Kebebew *et al.* enrolled 104 patients with sporadic or hereditary MTC and showed that prophylactic lymph node dissection did not affect the patients' prognosis

[76]. Grozinsky–Glasberg *et al.* investigated 41 patients with sporadic MTC and 10 patients with hereditary MTC with or without lymph node dissection. There was no significant difference in the 15-year survival rates (80% for patients who underwent node dissection and 79% for those who did not undergo node dissection) [80]. In contrast, one report demonstrated a better prognosis of total thyroidectomy with lymph node dissection than total thyroidectomy alone, although the number of enrolled patients was small [81]. All of these were retrospective studies, and patients underwent treatment strategies in response to the degree of progression of carcinoma.

Regarding hereditary MTC, a multicenter case series study enrolling 139 patients was published [82]. The endpoint was the biochemical cure, defined as the normalization of serum calcitonin level by the stimulating test. The biochemical cure was achieved in 68% (47 of the 69 cases) of patients who underwent and in 41% (7 of the 17 cases) of patients that did not undergo systematic node dissection.

Scollo *et al.* performed total thyroidectomy and central and bilateral lateral node dissection for 54 sporadic and 47 hereditary patients to conduct a study on lymph node metastases [83]. The rate of metastases to the central node, ipsilateral lateral node, and the contralateral lateral node was 50%, 57%, and 28% for sporadic cases; and 45%, 36%, and 19% for hereditary cases, respectively. Regardless of whether the disease was sporadic or hereditary, a high prevalence of lymph node metastases to each compartment was found.

Machens *et al.* analyzed the relationship between central and lateral neck lymph node metastases in 195 patients with hereditary or sporadic MTC [84]. Among patients who had no metastases in the central lymph nodes, 10% had metastases in the ipsilateral lateral compartment, while 5% had skip metastases in the contralateral lateral compartment. Ipsilateral lateral neck involvement was found in 77% of patients who had 1 to 3 metastases in the central compartment and 98% of those with ≥4 central node metastases. As for the contralateral lateral compartment metastases, 38% of patients had 1–9 metastatic nodes in the central compartment while 77% had 10 or more central node metastases. They also investigated the relationship between calcitonin level and positivity rates of regional lymph node metastasis in 300 sporadic or hereditary MTC [85]. The rates of ipsilateral lateral and contralateral lateral node metastases for patients with basal calcitonin levels of 20–200 pg/mL; 200–2,000 pg/mL; 2,000–10,000 pg/mL; and 10,000 pg/mL or greater were 12% *vs.* 0%; 43% *vs.* 14%; 74% *vs.* 44%; and 90% *vs.* 80%, respectively.

It remains unclear whether the extent of lymph node dissection affects patients' prognosis. However, considering the node-positive rates in the central compartment, and the influence of node recurrence in this compartment on the quality of life (QoL) of patients, central node dissection is, at least, mandatory. Preoperative calcitonin level, as well as other prognostic factors such as age, tumor size, extra-thyroid extension, and clinical lymph node metastasis, are important considerations when deciding on whether to dissect the ipsilateral and contralateral lateral compartments.

Poorly differentiated carcinoma

CQ 21. What are the definition, prevalence, and prognosis of poorly differentiated carcinoma?

- Poorly differentiated carcinoma is defined as "malignant tumor originating from follicular cells, having intermediate morphology and biological behavior between well-differentiated carcinoma (papillary and follicular carcinomas) and anaplastic carcinoma." However, there have been changes in the criteria of histopathological diagnosis.
- The incidence of poorly differentiated carcinoma in Japan was estimated to be 0.3% based on the 2017 WHO classification and the Turin proposal.
- 5-year postoperative survival rate was estimated to be 44–72%.
- 10-year disease-free and cause-specific survival rates of poorly differentiated carcinoma extracted from PTC cases based on the General Rules for the Description (6th edition, 2005) were 53.8% and 80.0%, respectively.
- 10-year disease-free and cause-specific survival rates of poorly differentiated carcinoma extracted from follicular carcinoma cases based on the General Rules for the Description (6th edition, 2005) were 43% and 71%, respectively.

Summary of literature

WHO classification

Sakamoto [86] and Carcangiu [87] proposed the concept of poorly differentiated carcinoma in the 1980s, and the WHO adopted it as distinct histology from the follicular and papillary carcinomas in 2004 [88]. The histopathological growth pattern of poorly differentiated carcinoma include three components as follows: 1) solid, 2) trabecular, and 3) insular. In the 2004 WHO Classification, one histological criterion, 4) the absence of conventional nuclear findings of PTC, was added in order to exclude the solid variant of PTC. The Turin proposal adopted the strictest histopathological criteria by adding 5) the convoluted nuclei or increase in mitosis and tumor necrosis [89]. The revised 2017 WHO Classification also

adopted all the criteria, including the fifth.

General Rules for the Description of Thyroid Cancer

General Rules for the Description of Thyroid Cancer (6th edition, 2005) in Japan adopted the poorly differentiated carcinoma as independent histology [90], but in contrast to the WHO definition, the diagnostic criteria were the same as those of Sakamoto. The 7th edition (2015) of the General Rules for the Description of Thyroid Cancer adopted the 2004 WHO Classification, and defined poorly differentiated carcinoma as a lesion with solid, trabecular, insular growth in more than 50% of the tumor without typical nuclear findings of PTC [10]. It is important to note that the General Rules for the Description of Thyroid Cancer 7th edition definition and that of the 2017 WHO Classification differ because the latter followed the Turin proposal [91].

Prevalence

The prevalence of poorly differentiated carcinoma in Japan was 0.8% based on the 2004 WHO Classification (same as the General Rules 7th edition) but decreased to 0.3% when subjected to the 2017 WHO Classification (Turin proposal) [92]. Based on the 2017 WHO classification, its prevalence in North America was 1.8%, while that in Europe, especially the Alpine region dominated by North Italy, the prevalence was higher, at 4.0–6.7% [93, 94]. The difference in the prevalence may be due to the changes in the histological diagnosis criteria and also regional differences in iodine intake.

Poorly differentiated carcinoma shows a poorer prognosis than well-differentiated carcinoma (papillary and follicular carcinomas). However, the 5-year survival rates from retrospective case series studies to date vary from 44 to 72%, which could reflect the difference in diagnostic criteria, regions, and institutions [95-99].

The presence of poorly differentiated components (≥50% of the entire lesions) in PTC or FTC was found to be an independent prognostic factor [39, 92].

CQ22. Can poorly differentiated carcinoma be diagnosed pre-operatively?

・It is impossible to diagnose poorly differentiated carcinoma pre-operatively.

Summary of literature

All studies on diagnostic imaging (ultrasound, computed tomography scan, and magnetic resonance imaging) of poorly differentiated carcinoma were case reports or analyzed on a small number of cases without adequate statistical analyses.

Studies from Japan, Europe, and the United States investigated the diagnostic performance of fine needle aspiration cytology, referring to the 2004 WHO classification as the gold standard of diagnosis [100, 101]. Bongiovanni *et al.* conducted a retrospective study enrolling 40 poorly differentiated and 40 well-differentiated carcinomas collected from 6 institutions [101]. They found that the following 4 findings were characteristic of poorly differentiated carcinoma: 1) insular, solid, or trabecular pattern (sensitivity 93%, specificity 95%); 2) single-cell pattern (sensitivity 75%, specificity 83%); 3) high nuclear-cytoplasmic ratio (sensitivity 63%, specificity 82%); and 4) severe crowding (sensitivity 70%, specificity 100%). The strength of the study was that the investigators were blinded while evaluating the cytological findings, whereas the weakness was that they did not examine the reproducibility of the evaluation.

CQ 23. Is total thyroidectomy, (prophylactic) lymph node dissection, and radioactive iodine therapy recommended for poorly differentiated carcinoma?

Recommendation

◎ For poorly differentiated carcinoma, total thyroidectomy, (prophylactic) lymph node dissection, and RAI therapy are recommended (no evidence, consensus ++).

Outcomes considered

✓ Prognosis
✓ Health condition from the patients' perspective

Evidence

・It remains unclear whether the use of RAI therapy was associated with better prognosis in poorly differentiated carcinoma.
・No reports have been published about the health conditions, from the patients' perspective.

Summary of literature

No prospective studies have been published regarding whether total thyroidectomy with extensive lymph node dissection improves the prognosis of patients with poorly differentiated carcinoma. It is not appropriate to compare the results between different studies because there were considerable biases due to the pathologists and the lack of definitions (see CQ 21).

Ibrahimpasic *et al.* retrospectively validated 91 cases of poorly differentiated carcinoma diagnosed based on necrosis and nuclear mitosis and showed that pT4a (hazard ratio 6.85, 95% CI: 1.37–34.3) and mitotic index (hazard ratio 2.97, 95% CI: 1.32–6.68) were related to poor cause-specific survival [99]. Kazaure *et al.* validated 34,021 cases of well-differentiated carcinoma, 114

cases of insular carcinoma, and 497 cases of anaplastic carcinoma registered by ICD codes in the SEER database (1999–2007) in the United States [102]. The investigators found RAI therapy (hazard ratio 0.15, no data for the 95% CI) and distant metastasis (hazard ratio 15.3, no data for the 95% CI) to be factors related to survival of patients with insular carcinoma, but the details on RAI therapy were missing.

Regarding insular carcinoma, Lai *et al.* investigated 73 cases collected from 23 citations and 9 cases treated by themselves and estimated the 10-year survival rates to be 52%. Age (45 years or older) and distant metastasis were related to poor prognosis, but RAI therapy and extra beam radiotherapy were not [103].

As described above, no data are available to prove that total thyroidectomy, lymph node dissection, RAI therapy, or extra beam radiotherapy are effective in treating poorly differentiated carcinoma. However, given a poor prognosis, the suggestion to make full use of all available therapies is considered to be appropriate [104-106]. The rationale behind the recommendation is the fact that molecular target medicine is available exclusively for RAI refractory recurrent cases [107, 108].

Anaplastic Thyroid Carcinoma (ATC) (Fig. 4)

CQ 24. What is the prognosis, and what are prognostic factors of ATC?

Prognosis

The median overall survival period of ATC is less than 6 months, and its 1-year survival rate is less than 20%.

Prognostic factors

Age at diagnosis, the extra-thyroid extension of the primary lesions, distant metastasis, acute symptoms, large tumor diameter, and leukocytosis are predictors of poor prognosis.

Evidence

- Median overall survival period after the diagnosis of ATC is 3–4 months.
- The one-year survival rate is 18–20%.
- Median overall survival periods for tumor localized in the thyroid, tumor extending beyond the capsule of the thyroid, and tumor with distant metastasis are 8–9, 4–5, and 2–3 months, respectively.
- Four clinical characteristics, including acute exacerbation of symptoms, large tumor size (exceeding 5 cm), distant metastasis, and leukocytosis (white blood cell count of 10,000/mL or higher), are associated with poor prognosis. Stratifying ATC patients based on the number of positive findings of the unfavorable characteristics is highly predictive of their survival (Prognostic index).

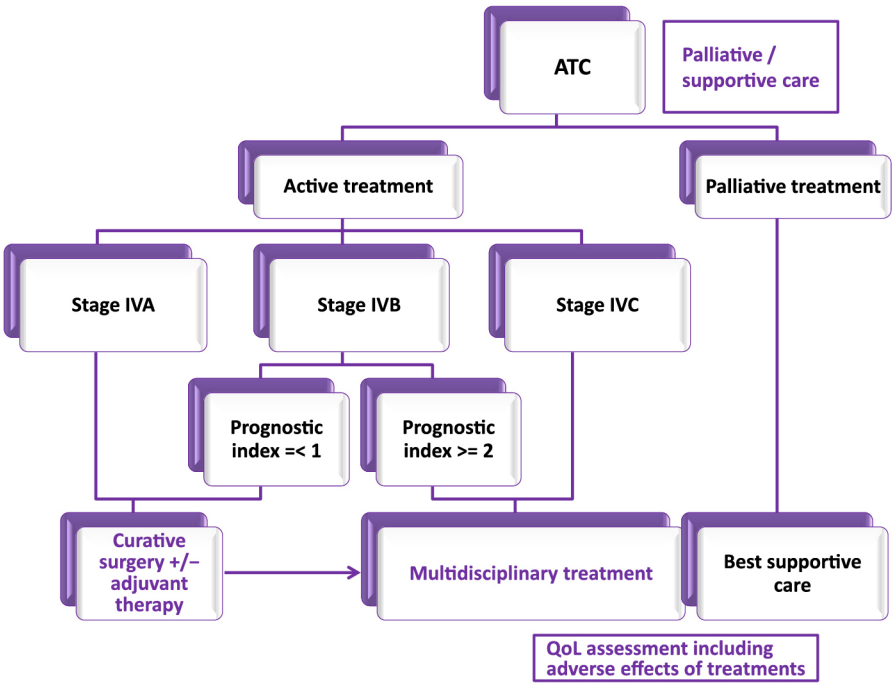

Fig. 4 Flow chart for the management of anaplastic thyroid carcinoma (ATC)

Summary of literature

Prognosis of ATC is extremely poor and previous studies showed that the median survival period after diagnosis was around 4 months, while the 1-year survival rate was 20% or less [109-113]. According to an analysis of 547 ATC amassed in Japan, median overall survival period was 3.8 months, while 1-year survival rate was 18% [114]; these results are similar to the results of an analysis of 516 cases based on SEER database in the United States (median survival period was 3 months, and 1-year survival rate was 19.3%) [115]. In the 7th UICC/TNM classification, all ATC were staged as IV, with tumor limited to the thyroid and tumor extending beyond the thyroid capsule classified as IVA and IVB, respectively, while the M1 case was classified into IVC [8]. According to the results of the analysis of 699 cases using the NCDB, median survival periods for Stage IVA, IVB, and IVC were 9.0 months, 4.8 months, and 3.0 months, respectively [116], similar to those of other studies [114, 115]. During the writing of this guideline, the UICC/AJCC TNM classification was revised to the 8th edition. Several changes were made for the T-category and stage stratification. All ATC cases were still classified as stage IV disease.

Sugitani *et al.* performed a retrospective analysis at a single institution and showed that the acute exacerbation of symptoms (duration of severe complaints such as dysphonia, dysphagia, dyspnea, and rapid growth of the tumor within 1 month), maximal tumor diameter exceeding 5 cm, existence of distant metastasis, and white blood count >10,000 mm^3 were associated with poor prognosis of ATC [117]. After that, in a prospective study, they reported the usefulness of a therapeutic strategy based on the prediction of prognosis [118]. Besides, based on the analysis of 547 cases accumulated in Japan, they showed that 4 prognostic factors described above along with extra-thyroid extension (T4b) and age (≥70 years), were significant predictors of poor prognosis and cause-specific survival rates in case subsets. The subsets were categorized based on the summation of the number of these factors, and a significant difference was shown between subsets [114]. Akaishi *et al.* reported that, based on the analysis of a single institution, age (70 years or older), leukocytosis (white blood cell count of 10,000/mL or greater), extra-thyroid extension, and distant metastasis were independent prognostic factors [119]. Age and extra-thyroid extension were regarded as significant prognostic factors also in overseas studies from the United States (based on the SEER database), Slovenia [120], and Korea [121]. In contrast, an analysis of 2,742 cases using NCDB in the United States showed that only age (85 years or older) was related to the survival periods [116]. Old patients or those having extra-thyroid extension are regarded as having poor prognosis even when they have no distant metastasis.

CQ 25. Are adjuvant therapies recommended after curative surgery for ATC?

Recommendation

◎◎ After curative surgery for ATC, the use of adjuvant therapies are recommended (😖 consensus ++).

Outcomes considered

- ✓ Prognosis of ATC following curative surgery
- ✓ Effect of postoperative adjuvant therapies on survival

Evidence

- Adjuvant therapies are likely to be performed for long-time survivors who undergo curative surgery.
- Extra beam radiotherapy and radiotherapy with chemotherapy (CRT) may extend the prognosis.
- Severe adverse events and sequelae may occur after radiotherapy or CRT.
- Additional chemotherapy after radiotherapy or CRT may extend survival.
- No effective agents and their regimen have been established.
- Molecular target medicines should not be used as postoperative adjuvant therapy.

Summary of literature

The prevalence of ATC, limited to the thyroid (Stage IVA), is reported to be 6–13% [114, 115, 119, 121, 122]. Curative surgery is possible for cases, even though the tumor has extended to the surrounding tissues (Stage IVB), by combining the resection of the trachea, larynx, esophagus, recurrent laryngeal nerve, and strap muscles [123]. Haymart *et al.* investigated the prognosis of 2,742 patients with ATC in the NCDB and showed that the median survival period of Stage IVA patients who underwent thyroidectomy was only 4.3 months (95% CI 3.1–7.4) [116]. It was shorter than the survival periods of patients who underwent radiotherapy (9.3 months), chemotherapy (6.4 months), and CRT (11.2 months), in addition to thyroidectomy. Yoshida *et al.* studied the prognosis of patients with incidentally detected ATC on postoperative pathological examination and showed that the 1-year survival rate of patients who underwent surgery was only 50%, which was much poorer than that of patients who underwent additional chemotherapy or radiotherapy, at 87% [124]. Kim *et al.* reported that most of the long-time survivors out of 121 patients with ATC in a

multicenter study underwent external radiotherapy after curative surgery [121]. Sugitani *et al.* showed that in Stage IVA patients, radiotherapy after curative surgery extended the survival, although the difference was not statistically significant (6.5 *vs.* 13.0 months, $p = 0.078$), based on the data from the Anaplastic Thyroid Carcinoma Research Consortium of Japan (http://www.atccj.com/) enrolling 677 patients [114]. Although adding chemotherapy to curative surgery with radiotherapy for Stage IVA patients did not extend the overall survival (13.0 *vs.* 10.5 months), the strategy significantly extended the survival of Stage IVB patients (6.5 *vs.* 14.0 months). Chen *et al.*, however, reported that radiotherapy did not improve the prognosis in patients with Stage IVA ATC based on the analysis of 261 cases in the SEER database [125]. All of the observations are inconclusive because they were retrospective in their designs and details of the agents and their regimen were unknown. Besides, there is the possibility of bias that adjuvant therapies were more likely to have been given to patients who were expected to have long-term survival.

Chemotherapy for ATC is associated with a high incidence of hematological toxicity and other adverse events. Similarly, radiotherapy has been reported to cause dermatitis, pharynx/larynx inflammation, and dysphagia frequently, as well as less frequent sequelae such as spinal cord injury [116], pneumonitis, and esophageal stricture [126]. Hyper-fractionated radiation therapy [116] and intensity modulating radiation therapy [126] can be an alternative to avoid such side effects. Molecular target medicine has an indication for only unresectable thyroid carcinoma, but not as adjuvant therapy after curative surgery. Also, no reports are available for the outcomes and adverse events of molecular target medicines when used as adjuvant therapy. Taken together, post-operative extra beam radiotherapy and chemotherapy as adjuvant therapies may be beneficial for patients who undergo curative surgery, but adverse events and sequelae may occur, preventing the patients from undergoing adequate therapies as planned. Before initiating adjuvant therapies, risk and benefit should be adequately considered for an individual patient, based on the prognostic factors and the patient's age.

CQ 26. Is multidisciplinary treatment recommended for unresectable ATC?

Recommendation

◎◎ For unresectable ATC, multidisciplinary treatment is recommended (😖 consensus ++).

Outcomes considered

✓ Effectiveness

Evidence

- Although multidisciplinary treatment has a limited effect overall in extending the prognosis of patients with ATC, prolonged survival has been demonstrated for patients with successful responses.
- Local control can be achieved by radiotherapy or chemoradiotherapy.
- Chemotherapy by taxane showed response rates ranging from 14% to 23%, and long-term survival can be expected if a response enables curative surgery.
- Chemotherapy has never been shown to be effective for distant metastasis.
- Molecular target medicine is available, but further studies are necessary for its safety and effectiveness.
- Each therapy may have serious adverse events that impair the QoL.

Summary of literature

Palliative surgery, followed by radiotherapy and chemotherapy, are often used as a multidisciplinary therapy for a patient with unresectable local extension or distant metastasis, which are common conditions at the time of diagnosis of ATC, to improve the QoL and survival. No prospective studies, however, examined the effectiveness of multimodal therapy on survival and QoL in patients with unresectable ATC. Large-scale retrospective studies showed that the prognosis of patients who underwent multimodal therapy was better compared to those who did not undergo the therapy [114, 116, 122]. In contrast, survival rates of ATC have not changed during these 20 years [122]; it remains unclear whether conventional multimodal therapy can improve the prognosis of all patients with ATC.

According to an exploratory case series studies in a single institution, long-term survivors are likely to undergo all treatments including surgery, radiotherapy, and chemotherapy [126, 127]. Especially, therapies including extra beam radiotherapies (*i.e.*, preoperative radiotherapy, postoperative radiotherapy, or chemoradiotherapy) were associated with long-term relapse-free survival and overall survival [126-130].

The response rate of the weekly paclitaxel was reported to be 31%, and Stage IVB patients who could undergo curative surgery after paclitaxel administration showed favorable outcomes [131]. A prospective study confirmed its tolerability and reported that the response rate was 23%, the median overall survival period was 6.7 months, and the 1-year survival rate was 26.8% [132]. The study also showed that some of the patients, in whom the complete post-treatment surgical removal of the tumor was feasible, survived significantly longer than those without curative surgery after chemotherapy, indicating effectiveness as pre-operative induction therapy.

Similar effectiveness (response rate 14%, disease-control rate 43%) was reported for docetaxel [133]. However, no studies have demonstrated the effectiveness of the drugs to control distant metastasis.

Lenvatinib is the only drug that is effective and approved for treating ATC in Japan [134]. The effectiveness of sorafenib for ATC is uncertain (see CQ 44) [135].

Although the combination of multiple therapies is often necessary to treat unresectable ATC, it is often hard to predict responses of the disease to such a strategy. In any case, a well-informed decision is mandatory because available therapies may cause adverse events frequently.

CQ 27. When a recurrent lesion from a differentiated thyroid carcinoma (DTC) is diagnosed as anaplastic thyroid carcinoma, is a treatment strategy for anaplastic thyroid carcinoma recommended?

Recommendation

◎◎◎ Treatment strategy for ATC is recommended for a recurrent lesion diagnosed as ATC in a patient with DTC (😖 consensus +++).

Outcomes considered

✓ Prognosis of patients diagnosed as ATC for recurrent lesions from DTC

Evidence

- As ATC does not express the TSH receptor, TSH suppression therapy is not indicated.
- As ATC does not intake iodine, RAI therapy is not indicated.
- Prognosis of ATC incidentally detected in the resected specimen of metastatic/recurrent lesions could show a longer survival period than that of non-incidental ATC.
- Palliative surgery may improve QoL and prognosis.

Summary of literature

Some cases show histological components of ATC in recurrent lesions of differentiated carcinoma (anaplastic transformation) [136]. Carcinoma cells after anaplastic transformation do not express the TSH receptor [137] or have the ability of thyroglobulin production [138] and iodine intake. Thus, unlike DTC, TSH suppression therapy, and RAI therapy are not indicated for ATC. For such cases, therapeutic strategies the same as those for primary ATC should be selected. A report analyzing 677 cases of ATC accumulated in Japan showed that the median survival period was 5.8 months and a 1-year survival rate was 30% for cases with anaplastic transformation in cervical lymph nodes, which were better than those of common ATC [114]. However, the prognosis of 6 cases with anaplastic transformation in distant recurrence lesions was very poor, with a median survival period of only 1.5 months and a 1-year survival rate of 0%. Curative surgery is expected to improve the patient's prognosis only when recurrent lesions in the lymph nodes exhibit incidental components of ATC [139]. Palliative surgeries such as tracheotomy to avoid asphyxia have certain roles in improving the patient's prognosis and QoL [136, 140].

Because ATC has been shown to have gene abnormalities in common with DTC [141], the molecular target therapy may be effective. However, as various novel phenotypical abnormalities that were not detected in DTC have been observed in ATC [138, 142-144], its effectiveness may not be the same as that for DTC.

CQ 28. Is a provision for palliative care recommended for patients with ATC?

Recommendation

◎◎◎ Provision of palliative care is recommended (😖 consensus +++).

Outcomes considered

✓ The usefulness of the provision of palliative care for patients with ATC.

Evidence

- No reports have been published demonstrating the usefulness of the provision of palliative care for patients with ATC.

Summary of literature

Progression of ATC is extremely rapid, and a therapeutic action should often be initiated before a patient's recovery from psychological damage, denial, and confusion to recognition, acceptance, and accommodation of the disease diagnosed. Psychological damage can also be huge, particularly when a patient experiences a physical or functional loss due to a treatment such as a tracheotomy. It is not rare that disease progresses more rapidly than not only the patient's but also the physician's expectation, and treatment and care for patients might fall behind the curve, which may lead to the failure of building a trust relationship. Most patients are not able to attain complete cure, and they have 6 months to live on average, which is as long as the so-called "terminal stage of carcinoma." Active anticancer therapies may even be discontinued due to consideration for the response to therapies. Besides, in cases where treatments are not successful, the patient's condition rapidly worsens by the day. As symptoms associated with bodily and spiritual

Table 11 Radioactive iodine: classifications and definitions

	Remnant ablation	Adjuvant therapy	Cancer treatment
Target	Patients with no residual tumor cells	Patients with minute cancer cells	Patients with gross residual cancer cells or distant metastasis
Intention	To eliminate remnant normal follicular cells	To destroy microscopic residual cancer cells	To treat persistent disease
Purpose	To facilitate detection of recurrence by measuring thyroglobulin	To improve disease-free survival and disease-specific survival	To improve disease-specific survival
Dose	1.1 GBq (30 mCi)	3.7–5.6 GBq (100–150 mCi)	3.7–7.4 GBq (100–200 mCi)

pain are common, unless appropriate relief of symptoms by supportive care is provided, psychological reactions of a patient and his/her family may be so overwhelming that both the patient and the medical sides find it difficult to achieve treatment satisfaction. Both sides have many opportunities to feel mental stress such as uneasiness and depression, and it is far from easy for both to face the disease upfront.

For patients diagnosed with ATC, it is mandatory to provide holistic best supportive care just by following-up with the diagnosis as far as possible, to avoid the decrease in patient's QoL. Providing ongoing best supportive care should be aimed at cooperating with attending staff and making up a multidisciplinary medical team. All medical staff involved in cancer care should make every effort to acquire knowledge and skills, using any opportunities to learn palliative care. Because ATC may change in intense medical condition, physicians can experience cases for which long-term treatment plan is difficult to discuss. It is also not rare that communication with persons other than the patient is required. For medical staff, it is very important to maintain continuous communications with the patient and his/her family members from the initiation of therapy so that they can provide an opportunity to discuss the discontinuation of anticancer therapies and how to reach the end-of-life.

Radiation Therapy

Radioactive iodine: classifications and definitions

It is important to classify RAI therapy into three categories, according to the disease condition and the purpose of therapy: ablation, adjuvant therapy, and treatment (Table 11).

Radioactive iodine: response evaluation

Response to RAI should be evaluated not only based on diagnostic imaging, but also symptoms, physical findings, serum thyroglobulin, and anti-thyroglobulin antibody measurements.

Commentary

Due to the lack of hospital rooms available for RAI therapy in Japan, many of the patients who were candidates for adjuvant RAI were treated with ablative RAI. This fact may cause misunderstandings in communications between foreign experts and Japanese counterparts concerning the patient population, purpose, and the dosage of the therapy. In the newest ATA guidelines published in 2015 [145], RAI is classified into three categories: "ablation" [145, 146] for patients who are considered to be free from tumor cells, to eliminate the remnant normal follicular cells; "adjuvant therapy" for patients who may have minute carcinoma nests because of invasion into adjacent structures or organs; and "treatment" for patients with gross residual carcinoma or distant metastasis (Table 11) [147]. What has been referred to as "ablation" in Japan is often equivalent to "adjuvant therapy" in the ATA guidelines because of the following reasons. First, in the past, the resources for RAI therapy were quite limited in Japan. Therefore, the therapy equivalent to "ablation" defined by ATA has scarcely been performed. Second, since the therapy with 1.1 GBq (30 mCi) of RAI became available at outpatient clinics in Japan in 2010, many patients who were candidates for adjuvant therapy with 3.7 GBq (100 mCi) of RAI were treated this way under the name "ablation." It is, however, strongly recommended to use relevant terms under the same international definitions, so that we will be able to perform comparable clinical studies in Japan with other countries.

Molecular target medicines are available for RAI-refractory patients with DTC [148]. Therefore, it is mandatory to judge the effectiveness of RAI therapy appropriately. Issues regarding treatment effects for each organ where carcinoma metastasizes or remains appear in CQ 32. Evaluation of response to RAI therapy should be based on comprehensive judgment by imaging studies, thyroglobulin and anti-thyroglobulin levels, and symptoms. For example, measuring thyroglobulin is effective in estimating the systemic tumor volume, and its doubling-time is related to the patient's prognosis, but

worsening of the disease does not always occur in all remnant lesions uniformly. Only a portion of the remnant lesion may rapidly progress and become critical. Therefore, it is important to individually evaluate the disease progression in each metastatic lesion, together with monitoring thyroglobulin for the systemic evaluation. Also, the treatment strategy might be reconsidered at the right time to avoid an aimless continuation of RAI therapy.

CQ 29. Is post-operative radioactive iodine therapy recommended for differentiated thyroid carcinoma?

Recommendation

◎◎◎ Post-operative *adjuvant* RAI therapy is recommended for high-risk PTC without distant metastasis (M0) (😣 consensus +++).

◎ Post-operative *ablative* RAI therapy is considered for intermediate-risk PTC after due consideration of the prognostic factors of each patient (😣 consensus ++).

XXX Post-operative *ablative* RAI therapy is not recommended for low-risk PTC (😣 consensus +++).

◎◎◎ Post-operative *ablative* or *adjuvant* RAI therapy is recommended for widely invasive FTC without distant metastasis (M0) (😣 consensus +++).

XX Post-operative *ablative* RAI therapy is not recommended for minimally FTC (😣 consensus ++).

Outcomes considered

- ✓ Effectiveness of RAI (disease-free survival rates, cause-specific survival rates)
- ✓ Adverse effects associated with RAI
- ✓ Health condition from the patients' perspective

Evidence

- Low-risk PTC: RAI therapy has not been demonstrated to be effective in suppressing the low rates of recurrence or carcinoma death from low-risk PTC.
- Intermediate-risk PTC: According to a large-scale, retrospective analysis of the NCDB in the United States, RAI administration was associated with a better overall survival with an estimated hazard ratio of 0.71 for the entire population and 0.64 for the subset of patients <45 years-old, respectively, with *intermediate-risk PTC defined by* the *ATA risk criteria*.
- High-risk PTC: According to a large-scale, retrospective analysis from the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) in the United States, use of RAI (given for any reasons or as an adjuvant therapy) for Stage III or IV patients with *DTC* was associated with improved survival, and their risk ratios were estimated to be 0.74 for all-cause mortality, 0.68 for carcinoma death, and 0.76 for carcinoma recurrence.
- Widely invasive and minimally invasive follicular carcinomas: See CQ 14 and 15.
- Acute side effects, gastrointestinal symptoms, and radiation sialadenitis occurred in 60–70% of patients. Temporary effects on gonadal function and bone marrow may occur. Therapy-induced carcinoma may occur with an increase in dose, but the incidence is very low.
- Patients reported that "diagnosis of thyroid carcinoma is a life-changing event," "it is not easy to determine to undergo RAI therapy," and "experienced various symptoms after RAI therapy."

Summary of literature

Readers are advised to keep the following cautions in mind when going through the summary of the literature.

1. Some studies included both PTC and FTC under the name "differentiated carcinoma (DTC)" for the study population. Moreover, the risk classification definitions differed among studies and are different from those in the present guidelines.

2. As for the RAI therapy, the distinction between "ablation," "adjuvant therapy," and "treatment" was not always made even in relevant reports from foreign countries.

3. The doses of RAI also varied among the studies.

Effectiveness of RAI

(a) Low-risk PTC or DTC: Lamartina *et al.* reviewed studies on RAI therapy for low-risk DTC (T1-3N0M0) defined by ATA guidelines, and concluded that "adjuvant therapy" was not related to a decrease in carcinoma recurrence and death [149]. A meta-analysis of observational studies by Hu *et al.* also concluded that "ablation" for microcarcinoma was not associated with a decrease in cancer recurrence and cancer death [150].

(b) Intermediate-risk PTC or DTC: Based on their reviews of the literature regarding the effectiveness of RAI on intermediate-risk DTC (T1-3N1a-bM0) defined by ATA guidelines, Lamartina *et al.* found that the results were inconsistent. Ten studies showed positive results for suppressing disease recurrence, whereas the other 14 investigations reported negative results [149]. Ruel *et al.* investigated the relationship between RAI therapy and all-cause mortality for 21,870 cases of intermediate-risk PTC (pT3N0cM0-x, pT1-3N1cM0-x) by ATA guidelines' definitions registered in the NCDB in the United States [151]. The hazard ratio obtained by adding RAI therapy (called "adjuvant") was 0.71 (95% CI: 0.62–

0.82) for the entire population and 0.64 (95% CI: 0.45–0.92) for patients younger than 45 years. If the observed differences were assumed to be due to the treatment effects of RAI, NNT would be 54 (95% CI: 39–67) for all the patients, while NNTs for those aged <45 and aged ≥65 years would be 162 (95% CI: 90–800) and 22 (95% CI: 11–233), respectively. The results might be encouraging, but their external validity would be limited because the definition of intermediate-risk differs from those in the present guidelines. It is also likely that the dosages of RAI were different from those used in Japan, although the investigators did not provide the data (or due to lack of data in the database).

(c) High-risk PTC or DTC without distant metastasis: The NTCTCSG reported that the use of RAI ("adjuvant") was associated with improved survival in Stages III and IV, defined as high-risk patients, among 2,936 patients with DTC. The estimated risk ratios were 0.74 (95% CI: 0.63–0.91) for all-cause mortality, 0.68 (95% CI: 0.53–0.88) for carcinoma death, and 0.76 (95% CI: 0.60–0.68) for carcinoma recurrence [152]. It is not certain whether the use of adjuvant RAI is effective in reducing recurrence and cancer mortality for patients with high-risk PTC defined by the present guidelines. However, considering the relatively high probability of the oncologic events in the long-term, the guidelines recommend the use of adjuvant RAI for the high-risk patients using the same dose used for the treatment (see also CQ 31) [153].

Adverse effects associated with RAI

(a) Acute phase

Gastrointestinal symptoms: Gastrointestinal symptoms such as appetite loss and nausea occur in 60–70% of patients [154]. The incidence of vomiting, however, is rare, at less than 10%. Constipation is likely to occur due to hypothyroidism induced by levothyroxine withdrawal. Anti-emetics and laxatives are effective as appropriate.

Radiation sialadenitis: It occurs with a high incidence, at 60–70%, including minor incidents [155]. It has not been concluded whether the administration of the secretagogue of saliva such as lemon candy is appropriate [156]. The administration of anti-inflammatory agents may alleviate strong symptoms. With the repeated RAI treatments, salivary gland swelling may occur during the meal by conduit stenosis, and gradual decrease in saliva secretion may lead to the discontinuation of the treatment. Dysgeusia may appear but certainly resolves. A high incidence of lacrimal gland dysfunction has been [157], but it rarely becomes a clinical problem.

Pain and swelling in the anterior neck: Symptoms may appear due to radiation thyroiditis in 20% of patients with a remnant thyroid [158]. Painless anterior neck swelling may also occur even if the patients had their thyroid completely removed [154]. Usually, the symptoms become noticeable within 48 hours following the RAI therapy and may cause stridor, although quite rare, which needs close attention.

Eliciting neurological symptoms: As there is a risk of eliciting neurological symptoms due to tumor enlargement by radiation swelling or TSH stimulation, the use of RAI therapy is contraindicated in patients who have metastases to the brain or invasions into the canalis vertebralis [159].

Effects on young women: Temporary amenorrhea occurs in 20–30% of women with childbearing potential, and premature menopause may occur [160]. RAI therapy is contraindicated in pregnant women, but conception after the treatment does not bring the risk of agenesis or fetal anomaly [160]. One study reported that conception within 1 year after RAI therapy was associated with an increase in abortion [161], but another report refuted the association [160]. Oligospermia may occur in male patients, but it is usually temporary and rarely lead to gonadal dysfunction, resulting in infertility with RAI therapy repeated a few times [162].

Peripheral blood cell count abnormality: A mild decrease in the numbers of peripheral blood cells may occur, but it is only temporary [154], although the phenomena may persist with repeated RAI therapy. For patients with renal dysfunction, RAI dose reduction should be considered to avoid increased exposure to the bone marrow.

(b) Late phase

Radiation pneumonitis and pulmonary fibrosis: There is a rare but distinct risk of radiation pneumonitis and pulmonary fibrosis in cases with strongly accumulated RAI in diffuse lung metastases [154]. A fatal case due to acute respiratory failure was reported [163]. The dose accumulating in the lung 48 hours after administration should not exceed 80 mCi.

Secondary carcinogenesis: A meta-analysis including two multi-center studies concluded that the risk of developing a second primary malignancy was greater in thyroid cancer survivors treated with RAI than in those without RAI (relative risk, 1.19 (95% CI: 1.04–1.36) [164]. The potential concern of the adverse effect, however, does not preclude the use of RAI for the high-risk PTC because the estimated risk is small. No reports showed an increased risk of developing second primary malignancy following RAI therapy with a dose of ablation (1.1 GBq, 30 mCi). Careful considerations are essential to decide on RAI therapy for pediatric cases because relevant studies have rarely been reported [165].

Health condition from the patients' perspective

Sawka *et al.* performed a qualitative study on 16 patients with differentiated carcinoma in order to investi-

gate the experience of the diagnosis of thyroid carcinoma and RAI therapy in the patients [166]. The focus group sessions with the thyroid cancer survivors identified some themes as follows: the life-changing experience of thyroid cancer, the experience of receiving counseling and decision-making on adjuvant RAI treatment, and experience after RAI treatment. The representative comments for the first theme are as follows:

- ➢ "The experience of being diagnosed with thyroid cancer changed the survivors' lives and the outlook on life."
- ➢ "The diagnosis was followed by feelings of fear and uncertainty about the future."
- ➢ "being told that thyroid cancer was a "good cancer" was generally not reassuring to survivors and was accompanied by feelings that their diagnosis was being dismissed as unimportant."

Subsequent narratives corroborated the second theme:

- ➢ "The primary information source related to thyroid cancer treatment, including RAI, was thyroid cancer specialty physicians,"
- ➢ "contradictory messages about the utility of adjuvant RAI treatment were received from physicians and internet sources,"
- ➢ "plain-language information about the risks, benefits, and uncertainty about RAI treatment was desired,"
- ➢ "The desire for numerical data on disease prognosis and treatment benefits varied,"
- ➢ Moreover, "individuals varied in their desire to be involved in decision making on RAI treatment."

Finally, the following words emerged related to the third theme:

- ➢ "more than half of the participants reported some short- or long-term emotional or physical negative effects attributed to RAI treatment,"
- ➢ Furthermore, "side-effects due to RAI treatment were not always recognized by the treating physicians, at follow-up."

The focus group participants provided several key recommendations for healthcare providers to incorporate in counseling patients with well-differentiated thyroid carcinoma about RAI treatment. These include explaining the rationale for RAI remnant ablation based on individual patient's situation; explain the benefits and risks of RAI treatment and related uncertainty in plain language; team-based thyroid cancer care and avoidance of conflicting recommendations among healthcare providers; and information sharing about current clinical practice and guidelines [166].

CQ 30. Is iodine restriction recommended before radioactive iodine therapy?

Recommendation

◎◎◎ In order to improve the accumulation of RAI to the normal remnant thyroid or malignant thyroid tissue, iodine restriction is recommended (😣 consensus +++).

Outcomes considered

- ✓ Effectiveness (success rate of ablation, disease-free survival rates, cause-specific survival rates)
- ✓ Adverse effects
- ✓ Health condition from the patients' perspective

Evidence

- ・No investigations have addressed the current status and effectiveness of iodine restriction in Japan.
- ・No studies have examined whether iodine restriction at the time of RAI therapy is associated with improved long-term survival.
- ・There was a report of a case who developed hyponatremia during iodine restriction.
- ・No reports have inquired about the patients' perspective.

Summary of literature

Although there are some relevant reports in the literature, the fact that operational definitions for iodine restrictions, RAI therapy, and success of ablation differ among the studies made any comparisons difficult. Besides, implementing an appropriate iodine restriction before RAI therapy may not be easy because of the iodine-rich environment in Japan as compared to other areas such as Europe or North America. According to the survey conducted by Misaki *et al.*, there were wide variations regarding the method, duration, assessment, and goal of the restriction among the 105 institutions in Japan that responded to the queries [167]. Although experts are consistent with the fact that iodine restriction is mandatory before RAI therapy, they also recognize that it would be difficult for Japanese people to restrict the intake of iodine to the same extent as recommended in Western countries.

A systematic review by Sawka *et al.* showed the effectiveness of iodine restriction [168], but Li *et al.* emphasized the necessity of further research because most of the published studies were retrospective in their designs [169]. Besides, it may not be appropriate to extrapolate research findings in foreign countries to Japanese patients for reasons indicated above.

Li *et al.* pointed out that several case reports have been published, citing the development of hyponatremia

during iodine restriction while preparing for RAI therapy [169]. Patients' perspective has never been addressed in the literature concerning iodine restriction.

Iodine restriction is refraining from the intake of foods and avoiding the administration of medicine with a high content of iodine. Meals without ingredients having a high content of iodine and cooked using ingredients with low iodine as far as possible, are called "iodine-restricted diet" or "low-iodine diet." A standard iodine-restricted diet is a diet with an iodine intake of 50 μg/day or less. Patients should be started on the iodine-restricted diet at least two weeks before RAI therapy. Thyroid hormone (liothyronine, T3: levothyroxine, T4), antiarrhythmic agent (*e.g.*, amiodarone), medications for a peptic ulcer (*e.g.*, "MAJIRIN A," "GASUTOROFIRIN,"), and liver failure (*e.g.*, "AMINOLEBAN,") contain high dose iodine. Examples of solutions containing a large amount of iodine are Lugol's solution, iodine-containing gargles, and iodinated contrast agents. Iodine restriction at RAI therapy for thyroid carcinoma should be strictly performed because iodine uptake is low in carcinoma cells as compared with normal follicular cells. The fact that people take iodine-rich foods so often makes it difficult to address the standards of the iodine-restriction diet in Japan. Thus, registered dietitians play a key role in delivering dietary advice and for consultations. The use of a commercially available iodine-restricted diet can be a good alternative as an iodine-restricted diet at home may be a big burden for patients and their families.

About the waiting period after the use of iodinated contrast agents, 1–3 months may be appropriate, although valid evidence is lacking [170].

CQ 31. What is the appropriate dose of radioactive iodine for radioactive iodine therapy?

Recommendation

- 1.1 GBq (30 mCi) for ablation.
- 3.7–5.6 GBq (100–150 mCi) for adjuvant.
- 3.7–7.4 GBq (100–200 mCi) for treatment.

Summary of literature

Not a few studies have investigated suitable doses for post-operative RAI therapy. Many of them compared between administration of 1.1 GBq (30 mCi) and 3.7 GBq (100 mCi) [171-177]. However, it is not appropriate to draw any conclusions by simply reviewing such studies because of differences in characteristics of the patient populations and purposes of RAI therapy. It would be appropriate to determine the dose of RAI considering both risks of oncologic events and the purpose of the therapy.

A randomized controlled trial demonstrated that the dose of 1.1 GBq (30 mCi) was sufficient for ablation in patients with low-risk PTC [147], while the ablative RAI, however, is not indicated for low-risk PTC in Japan. For intermediate-risk PTC with microscopically residual malignant thyroid tissue, the administration dose is set at the same as the dose for macroscopic remnant carcinoma or distant metastasis [151, 153, 178]. However, it should be noted that the effectiveness of 1.1 GBq (30 mCi), which is the upper limit of administration in outpatient clinics in Japan, has not yet been established as adjuvant therapy.

CQ 32. Is radioactive iodine therapy recommended for recurrences (local recurrence, lymph node metastasis, and distant recurrence) in differentiated thyroid carcinoma?

◎◎◎ The decision for the use of RAI therapy should be made after thorough consideration of disease progression as well as location, number, and size of recurrent lesions (😖 consensus +++).

◎◎◎ RAI therapy is strongly recommended for lung metastasis (😖 consensus +++).

◎◎◎ RAI therapy is strongly recommended for bone metastasis (😖 consensus +++).

◎ RAI therapy is weakly recommended for either local recurrence or lymph node metastasis that is inoperable but requires therapy (😖 consensus ++).

XXX RAI therapy is not recommended for brain metastasis (😖 consensus +++).

XXX RAI therapy is not recommended for metastasis to other organs than above (😖 consensus +++).

XXX RAI therapy is not recommended for cases without apparent recurrence lesions but with high thyroglobulin level (😖 consensus +++).

Outcomes considered

- ✓ Effectiveness (response rate of therapy, survival rates)
- ✓ Complications associated with therapy
- ✓ Health condition from the patients' perspective

Evidence

- The response rate for lung metastasis showing iodine accumulation has been estimated to be 17% for complete response (CR), 44% for partial response (PR), 33% for stable disease (SD), and 6% for progressive disease (PD).

- 5-year, 10-year, and 15-year survival rates of cases with lung metastasis showing iodine accumulation have been estimated at 87%, 69%, and 56%, respectively.
- 5-year, 10-year, and 15-year survival rates of cases with lung metastasis without iodine accumulation have been estimated at 70%, 38%, and 21%, respectively.
- The rate of CR for bone metastasis was 50% in 8 cases aged 45 years or younger, and 21% for 99 cases older than 45 years.
- As an adverse event, the incidence of blood system disorders was reported as 37%.
- No reports have inquired about the patients' perspective.

Summary of literature

Surgical treatment should be the first choice for the recurrence of differentiated carcinoma. For patients with inoperable local recurrence and distant metastasis, RAI therapy has a role. It is important to consider anatomical location, number, and size of recurrent lesions as well as the severity of disease progression to determine therapeutic strategies.

Lung metastasis

For micro-metastases to the lung with I-131 accumulation, aggressive treatment is desirable because effects are the most highly expected [179-183]. Especially for minute metastatic lesions with I-131 accumulation, which are undetectable on imaging studies, RAI therapy is effective, and CR may occur in 30–80% of patients [179-183]. For young patients, response to therapy is excellent [181, 183, 184]. In contrast, it is less effective for cases older than 40 years and with macro-nodular lesions [182, 183]. I-131 accumulation to the lung metastasis generally contributes to the improvement of vital prognosis of patients and 15-year survival rate of patients with lung metastasis with I-131 accumulation that disappeared after treatment is excellent, at 89% [179]. RAI therapy may lead to pulmonary fibrosis, a rare but serious complication in patients showing diffuse accumulation to the lung [185].

Bone metastasis

No studies have investigated the efficacy of RAI therapy on bone metastasis only. Petrich *et al.* treated bone metastases of 107 DTC patients with RAI therapy between 1965 and 1997. The CR rate was 50% among patients aged 45 or younger and 21% among those older than 45 years, although the outcome was not clearly defined [186]. Overall, 37% of the patients experienced hematologic disorders (anemia, leukopenia, and thrombocytopenia) as adverse events of the therapy. Bernier *et al.* investigated the overall survival of 109 DTC patients with bone metastasis treated between 1958 and 1999 and found that the use of RAI therapy ≥200 mCi was associated with a decrease in mortality rate [187].

Local and lymph node recurrence

For local recurrence and lymph node metastasis large enough to be detected by physical examination or conventional imaging studies, surgical resection is desirable because RAI therapy is generally ineffective [188]. However, the treatment may be applicable for recurrences with no indication of surgery, as exceptional cases were reported [189]. RAI therapy may work as adjuvant therapy following resection [190, 191], but one study refuted its efficacy [192].

Brain metastasis

Surgery and extra beam radiotherapy are the first-line treatments to control brain metastasis from DTC (see CQ 34). RAI does not accumulate well in brain metastasis [193], and if accumulated, it may cause brain edema. Therefore, RAI therapy is not a treatment of choice for brain metastasis. For patients with metastases in the lungs or bones as well as in the brain, RAI therapy can be an option to treat lesions in the lungs or bones after controlling brain metastasis by other modalities with caution for radiation-induced brain edema.

Metastasis to other organs

DTC may spread to other organs such as the liver, kidney, and adrenal gland. The lesions are likely to be a part of metastases to multiple organs or detected in far advanced cases with huge unresectable tumors, indicating that RAI therapy is not very effective [194, 195].

Cases with high thyroglobulin levels whose metastatic lesions are not detected by routine imaging studies

Routine imaging studies may not detect metastatic or recurrent lesions despite a high thyroglobulin level in patients. Scintigraphy after the administration of the therapeutic dose of RAI may be used to detect such lesions [196, 197], but it is unclear whether the therapy improves survival [196, 198].

CQ 33. Is recombinant human thyroid-stimulating hormone (rhTSH) recommended to increase thyrotropin level at the time of radioactive iodine administration?

Recommendation

◎◎◎ The use of rhTSH is recommended as a substitute for levothyroxine withdrawal before I-131 whole-body scan (WBS), serum thyroglobulin test, and ablation (☺ consensus +++).

Outcomes considered

- ✓ Diagnostic ability
- ✓ Rate of successful ablation

✓ Adverse events
✓ Health condition from the patients' perspective

Evidence

- The use of rhTSH has advantages as compared to the withdrawal of thyroid hormones in terms of shorter duration of testing, avoiding hypothyroidism that may impair patients' QoL, and preventing potential carcinoma cell growth.
- Diagnostic performance of WBS with the use of rhTSH is equivalent to that for the use of thyroid hormone withdrawal.
- The rate of successful ablation with the use of rhTSH is equivalent to that for the use of thyroid hormone withdrawal.
- The use of rhTSH is more expensive than the use of thyroid hormone withdrawal.
- Adverse events from rhTSH administration include headache, nausea, vomiting, general fatigue, and dizziness.

Insurance adaptation of rhTSH

The use of rhTSH is covered by the health insurance system in Japan, as indicated below.

♦ WBS, along with thyroglobulin (Tg) test or Tg test alone following total or near-total thyroidectomy for differentiated carcinoma.
♦ Remnant thyroid tissue ablation by I-131 for patients without distant metastasis following total or near-total thyroidectomy.

Summary of literature

Diagnostic performance

Equivalent diagnostic performance of WBS can be achieved with the use of rhTSH as compared to the use of thyroid hormone withdrawal [199].

Rate of successful ablation

Two large-scale multicenter randomized control studies comparing two TSH-stimulation methods (thyroid hormone withdrawal and rhTSH) and two RAI doses (1.1 GBq and 3.7 GBq) in a 2-by-2 design indicated that the ablation rate was equivalent between the RAI doses and between the thyrotropin-stimulation methods while adverse events with the use of rhTSH were fewer than those with the conventional method [146, 147]. The ATA guidelines also endorse the use of rhTSH for ablation [145].

Adverse events associated with therapies

Various symptoms associated with hypothyroidism (*e.g.*, sensitivity to cold, bodyweight increase, constipation, bradykinesia, frigid skin sensation, eyelid edema, cardiac and renal dysfunctions, decline in cognitive function) are inevitable for a few weeks following the use of the thyroid hormone withdrawal method which induces marked elevation of intrinsic TSH [200-205]. In addition to these consequences, the conventional method has other drawbacks such as the long preparatory period (two weeks or longer) for diagnosis, persistent symptoms from hypothyroidism even after examination, and the risk of carcinoma cell growth. In contrast, the use of rhTSH has several advantages in terms of maintaining the QoL, shortening of the preparatory periods for diagnosis, avoiding hypothyroidism, having less chance of damage to the salivary gland [206], minimizing the stimulation of cancer cell growth [207, 208], and alleviating radiation exposure by maintaining the renal function [209, 210]. Adverse events associated with the use of rhTSH include headache, nausea, vomiting, general fatigue, and dizziness, although they are rare. Contraindication to the use of rhTSH includes patients with a history of hypersensitivity for the thyrotropin preparation and a woman who is or may be pregnant or lactating women.

Health condition from the patients' perspective

The use of rhTSH does not impose impairments in QoL associated with hypothyroidism, while its disadvantage concerns the high medical expenses.

Concerning the adjuvant settings or therapeutic use of RAI for patients with residual or distant metastases, the ATA guidelines do not endorse the administration of rhTSH, although its effectiveness has reportedly been found to be equivalent to that of levothyroxine withdrawal method according to prospective studies as well as meta-analyses [211-217]. In individual cases, it is necessary to consider the risks and benefits before deciding whether or not to use rhTSH for the preparation of adjuvant therapy.

CQ 34. Is extra beam radiotherapy recommended for advanced and recurrent differentiated thyroid carcinoma?

Recommendation

◎ For patients suffering from symptoms caused by advanced or recurrent thyroid carcinoma, extra beam radiotherapy is recommended to alleviate the symptoms, given that salvage surgery, RAI therapy, or molecular target drugs are not indicated (😖 consensus +).

Summary of literature

Indication for the primary lesions of thyroid carcinoma

Extra beam radiotherapy has a limited role in the management of DTC due to its low sensitivity to the treatment [218-220]. During the last two decades, some retrospective studies showed its effectiveness in inoperable, residual, or recurrent tumors as well as in recurrent

lymph node metastases [221-227]. Its usefulness, combined with chemotherapy, was also reported [228]. Adding extra beam radiotherapy for patients with microscopic residual tumor might also be useful in decreasing local recurrence rate [229, 230]. Other studies, however, refuted its effectiveness in managing advanced or recurrent cases [231-233].

About the technical aspects of extra beam radiotherapy, the wide radiation field, including the upper mediastinal lymph nodes area, achieved a high rate of local disease control [234, 235], and the radiation dose of 50 Gy or greater was associated with decreased recurrence rate [236]. Three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) enhance radiation doses to the tumors while preventing damage to the spinal cord by reducing the doses to healthy tissues [226, 229, 230, 232, 237]. The indication of extra beam radiotherapy might be extended in the future [226, 230, 237].

Indication for metastatic lesions of the thyroid carcinoma

Indications of extra beam radiotherapy include patients whose metastatic lesions are responsible for, or likely to cause symptoms such as pain due to bone metastasis, neurological symptoms due to brain metastasis, bleeding, wheezing, superior vena cava obstruction, or dysphagia due to local recurrence. The treatment is effective in alleviating symptoms caused by metastases to the bone, brain, and lung [238]. Surgical removal was preferred for brain metastasis to avoid brain edema caused by RI therapy [239]. The short-term irradiation using the 3DCRT is an effective alternative to manage brain metastases [240].

Advanced differentiated carcinoma

CQ 35. Is resection of the recurrent laryngeal nerve invaded by thyroid cancer recommended?

Recommendation

◎◎◎ Resection of the invaded recurrent laryngeal nerve is recommended for patients who show symptoms or findings of nerve paralysis preoperatively (㊧ consensus +++, see CQ 36).

◎◎ Preserving the nerve by shaving-off the invading tumor, if possible, is recommended for patients who do not show symptoms or findings of nerve paralysis preoperatively (㊧ consensus +++).

Outcomes considered

✓ Prognosis
✓ Phonatory function
✓ Health condition from the patients' perspective

Evidence

- Recurrence of the tumor at the shaved site was estimated to be 5% in patients whose extra-thyroidal extension of PTC was limited to the recurrent laryngeal nerve.
- The shaving-off procedure might be followed by permanent vocal cord paralysis with a probability of 8–17% in patients who did not show symptoms or findings of nerve paralysis preoperatively.
- The phonatory function was maintained in 83% of cases who underwent partial layer resection of the recurrent laryngeal nerve when its diameter was less than half.
- No reports have inquired about the patients' perspective.

Summary of literature

Patients with symptoms or findings of nerve paralysis preoperatively

When the vocal cord paralysis is obvious, nerve reconstruction following curative dissection is recommended as it is difficult to preserve the nerve without leaving remnant carcinoma. No studies have investigated whether dissection of the recurrent laryngeal nerve is related to the prognosis, phonatory function, and health condition from the patients' perspective for cases with nerve paralysis pre-operatively.

Patients without symptoms or findings of nerve paralysis preoperatively

Nishida *et al.* performed nerve preservation (shaving) for 23, and nerve dissection for 27 of 50 cases (45 PTCs and 5 FTCs) whose intra-operative findings indicated extra-thyroidal extension to the recurrent laryngeal nerve invasion. None of the cases underwent RAI therapy. Disease-free survival rates up to 10 years after surgery were 35% and 44%, and survival rates were 78% and 52% for the nerve-preserving and dissection group, respectively, indicating that the survival rates of those in the dissection group were lower than for those in the nerve-preserving group. Four patients (17%) in the nerve-preserving group experienced permanent vocal cord paralysis [241].

Kihara *et al.* observed 18 cases that underwent "partial layer resection" whose preserved recurrent laryngeal nerve became less than half in diameter and reported regarding vocal cord function immediately after surgery that, 2 had no paralysis, 13 showed temporary paralysis, and 3 had permanent paralysis, and phonatory function was maintained in 15 (83%) patients 1 year after surgery [242].

Lang *et al.* performed shaving for 39 and recurrent laryngeal nerve dissection for 38 of 77 cases with invasion to the nerve on intra-operative findings; of these, 26 patients had an extra-thyroidal extension to other organs as well. Post-operatively, 69% and 57% of patients underwent RAI therapy (3.0–5.5 GBq) and extra beam radiotherapy (40–50 Gy), respectively. Three patients (8%) who underwent shaving showed permanent vocal cord paralysis. In the Kaplan–Meier analysis, the local recurrence-free survival rate was 77% and 79%, while cause-specific survival rate was 76% and 66% for patients who underwent shaving and nerve dissection, respectively [243].

Lee *et al.* investigated 34 cases with an invasion of PTC exclusively to the recurrent laryngeal nerve and reported that the nerve was preserved by shaving in 20 cases and resected in the remaining 14. Post-operatively, all underwent RAI therapy (3.7–7.4 GBq), while 79% underwent TSH suppression. Two patients (10%) who underwent nerve shaving had permanent vocal cord paralysis. Four patients (20%) who underwent shaving showed recurrence, but recurrence to the shaving lesion was detected in only one of them (5%). None of the patients died of carcinoma during the post-operative follow-up (average 85 months) [244].

CQ 36. Is recurrent laryngeal nerve reconstruction recommended for cases that underwent nerve resection?

Recommendation

◎◎◎ Nerve reconstruction is recommended at the same time as the nerve resection (😊 consensus +++).

Outcomes considered

- ✓ Phonatory function
- ✓ Health condition from the patients' perspective

Evidence

- Phonatory function recovers within 1 year after nerve reconstruction.
- No reports have inquired about the patients' perspective.

Summary of literature

Nerve reconstruction at the time of nerve resection is recommended because the phonatory function recovers by preventing atrophy of the vocal muscle. However, misdirected regeneration of the nerve is inevitable, and the improvement of vocal cord movement cannot be expected [245].

There are some surgical techniques in recurrent laryngeal nerve reconstruction. Miyauchi *et al.* reported: 1) end-to-end anastomosis; 2) free nerve grafting; 3) anastomosis to the ansa cervicalis with the recurrent laryngeal nerve; 4) anastomosis to the vagus nerve with the recurrent laryngeal nerve. Maximum phonation time (MPT) of patients with recurrent laryngeal nerve paralysis is shorter than that of healthy persons, but MPT 1 year after surgery of cases with nerve reconstruction was significantly longer than that of cases without reconstruction. Average time to the recovery of the vocal cord function evaluated by MPT was 67 days, 89 days, 147 days for patients who underwent end-to-end anastomosis (5 patients), free nerve grafting (8 cases), anastomosis to the ansa cervicalis (19 cases), and the anastomosis to the vagus nerve (2 cases), respectively [246]. There was a gender difference in the MPT, but not in the phonation efficiency index [247]. Other studies also corroborated the finding that phonatory function was better in patients with reconstruction than those without reconstruction or those with other treatments, including thyroplasty and arytenoid adduction [248-251].

Two-Stage reconstruction is also useful in improving phonatory function, although simultaneous procedure would be desirable [252, 253]. Li *et al.* suggested that the reconstruction performed within two years after nerve injury led to better outcomes [252].

CQ 37. Is the resection of the tracheal wall invaded by thyroid cancer recommended?

Recommendation

◎◎ Resection of the invaded tracheal wall is recommended. However, the indication and procedure of resection should be determined with thorough consideration of disease stage, the extension of the tumor spread, risk of surgical complications, postoperative QoL, prognosis, and the skill of the treatment team (😖 consensus +++).

Outcomes considered

- ✓ Prognosis (local [tracheal] recurrence, carcinoma death)
- ✓ Surgical complications
- ✓ Health condition from the patients' perspective

Evidence

- The recurrence rate after shaving (tracheal wall) was about 5%.
- Anastomotic failure after tracheal resection may result, although rare, in serious outcomes.
- No reports have inquired about the patients' perspective.

Summary of literature

As DTC invading the trachea may cause airway stenosis, surgical treatment has a great role. However, an extended resection of the aero-digestive tract may be associated with postoperative symptoms related to respiration and swallowing, as well as serious complications. An indication for tracheal resection should be determined after thorough considerations of both the postoperative QoL and the life expectancy predicted by the individual's disease stage.

Vital prognosis after tracheal resection

It has been reported that the prognosis of patients with tracheal invasion who undergo curative tracheal resection is better than for those who did not undergo tracheal resection or who undergo non-curative resection [254-258]. These observations, however, do not prove the causal relationship between the extension of surgical treatments and prognosis of patients because it is easily conceivable that cases without resection or with imperfect resection exhibit more advanced stages than those with curative resection. Besides, the reported life expectancy cannot be applied to an individual patient because the study populations in the literature varied in the extent of disease progression as well as treatments received.

Tracheal resection or shaving?

For patients with deep invasion by DTC reaching the tracheal lumen (tracheal mucosa), tracheal resection is mandatory. For those without deep invasions but with apparent involvement of the trachea, a sharp dissection of the surface layer around the invasive lesions together with the tumor, without reaching the tracheal lumen, namely shaving, is possible, although tracheal resection is also an alternative. Tracheal resection may be superior to the shaving procedure in terms of curability, but plastic surgery such as tracheocutaneostomy or one-stage reconstruction is mandatory. Outcomes that should be considered in selecting surgical designs include complication risks associated with tracheal resection, health conditions from the patients' view, and potential local recurrence following shaving surgery.

Shadmehr *et al.* reported that 2 of the 18 cases that underwent tracheal sleeve resection and reconstruction experienced anastomotic failure, and 1 of them died of sepsis as a sequela to mediastinitis [257]. Tsai *et al.* also experienced 2 cases of anastomotic failure among 18 cases that underwent tracheal resection, and 1 died of the rupture of the large vessel [258].

The local recurrence rate following the shaving of the tracheal wall invaded by DTC is about 5% [258-262]. Tsai *et al.* reported the corresponding figure to be 50% in a study population in which all of the patients were positive for carcinoma in the resection stump after shaving [258].

No reports have inquired about the patients' perspective after tracheal resection.

CQ 38. For patients with apparent invasion reaching to the tracheal lumen, is sleeve resection with reconstruction recommended rather than partial resection of the trachea (wedge resection or window resection)?

Recommendation

◎ It is recommended that the treatment team gives through considerations on the patient's disease status (anatomical location of the tumor, disease stage, comorbidity, predicted prognosis), risk of surgical complications, expected postoperative quality of life, patient's or caregivers' preferences as well as expected skills of the team when sleeve resection followed by reconstruction is indicated (😣 Consensus +++).

Outcomes considered

- ✓ Prognosis (local [anastomosis sites] recurrence)
- ✓ Surgical complications
- ✓ Health conditions from the patients' perspective

Evidence

For sleeve resection with reconstruction (end-to-end anastomosis) of the trachea,

- The incidence of recurrence to the anastomosis sites was reported to be 0%.
- The incidence of failure of the anastomosis was reported to be 0–10%.
- The incidence of operative death was reported to be 0–8%.
- No reports have inquired about the patients' perspective.

Summary of literature

Tracheal resection is required when the invasion of DTC reaches the tracheal lumen (tracheal mucosa). Sleeve resection followed by reconstruction (end-to-end anastomosis) or partial resection (wedge resection and window resection) is the surgical procedure for the lesion. In preparing for the surgical treatments, the available skills of the team, as well as the patient's condition (disease stage, comorbidities, tolerability to operation, and preferences), need to be thoroughly considered. Outcomes considered here include the risk of local recurrence, surgical complications, and health conditions from the patient's view of each surgical procedure.

Ozaki *et al.* reported that none of the 21 cases showed recurrence after sleeve resection of the trachea recon-

structed by end-to-end anastomosis [263]. Ebihara *et al.* reported that 7 of the 41 patients (17%) who underwent window resection followed by closure of the tracheocutaneostomy showed recurrence [264].

Anastomotic failure is one of the serious complications of the end-to-end anastomosis. Ozaki *et al.* reported that none of their cases showed serious complications [263]. Grillo's group observed that among 69 cases with the reconstruction of the trachea, anastomotic failure occurred in 3 (4%), surgery-related death (airway obstruction by laryngeal edema) in 1 (1%) [265]. Musholt *et al.* described nine events of serious complications, including two deaths [266]. Of 40 cases by Nakao *et al.*, anastomotic failure occurred in 4 (10%) and 3 of these died (in two, due to the perforation of the artery and mediastinitis in one) [267]. Lin *et al.* reported 2 cases (10%) of anastomotic failure among 19 patients that underwent tracheal reconstruction [268].

Although life expectancy such as disease-specific survival or overall survival may also be an important consideration in advanced cases, the information was not adopted here as evidence because the outcome may be significantly affected not only by local control but also by disease status in distant organs.

Postoperative therapy (including for recurrence and metastasis)

CQ 39. Is thyrotropin suppression therapy recommended for differentiated thyroid carcinoma as a postoperative adjuvant therapy?

Recommendation

XXX For low-risk or very-low risk PTC, TSH suppression therapy is not recommended (😊 Consensus ++).

◎◎ For intermediate-risk PTC, it is recommended to determine the indication of TSH suppression therapy based on the intra-operative findings and pathological findings (😣 Consensus +++).

◎◎ For high-risk PTC; TSH suppression therapy is recommended (😣 Consensus +++).

◎◎ For widely invasive FTC, TSH suppression therapy is recommended (😣 Consensus +++).

Outcomes considered

- ✓ Prognosis
- ✓ Adverse events
- ✓ Health conditions from the patients' perspective

Evidence

- TSH suppression therapy is not effective in preventing oncologic events in patients with low-risk or intermediate-risk PTC whose absolute risks of the failures are quite small.
- "Subnormal" TSH suppression is associated with reduced risk of recurrence and cancer death from DTC (risk ratio: 0.05–0.37).
- TSH suppression therapy may be associated with cardiovascular death and reduced bone mineral density.
- Stopping TSH suppression therapy was not associated with improvements in patients' QoL.

Summary of literature

Effectiveness

McGriff *et al.* concluded that TSH suppression therapy was associated with favorable prognosis following a systematic review of the literature [269]. By aggregating data from 10 observational studies, the reported estimated risk ratio of any oncologic outcomes of disease progression, recurrence, or death was 0.71 (95% CI: 0.60–0.88). However, the interpretation of the risk ratio is difficult because both the internal and external validity of the meta-analysis had serious flaws [270].

Only one randomized controlled trial to determine the effectiveness of TSH suppression therapy was conducted by Sugitani and Fujimoto in Japan [271]. Among 433 study participants with PTC, those with high-risk features were relatively few, including extra-thyroidal extension (15%), apparent lymph node metastasis (38%), and receiving total thyroidectomy (15%). The investigators randomly assigned study participants to either the TSH suppression group (<0.01 μU/mL) or non-suppression group and followed them up for an average of 6.9 years. The Kaplan–Meier estimates of 5-year disease-free survival rates were 91% and 89%, and for the 5-year cause-specific survival rates were 99% and 98% in the TSH-suppression group and the non-suppression group, respectively. The investigators concluded that thyroid-conserving surgery without TSH suppression should be considered for patients with low-risk PTC.

In contrast, some observational studies indicated that TSH suppression therapy might be effective. A prospective observational study with 366 DTC patients showed that the degree of TSH suppression was associated with favorable prognosis [272]. Carhill *et al.* demonstrated that TSH score 2.0–2.9 (subnormal) was associated with decreased risk of recurrence and death compared to TSH score 3.0–4.0 (normal elevated). TSH score 1.0–1.9 (undetectable), however, was not associated with further reduction in the risk when compared with subnormal TSH [273]. Multivariable analysis of low- and intermediate-risk DTC patients defined by the ATA guidelines failed to demonstrate the favorable association

between TSH suppression therapy and decreased carcinoma recurrence [274].

Adverse events

TSH suppression therapy may be associated with some adverse events such as bone and cardiovascular sequelae as well as psychological manifestations, but their causal relationships have been controversial [275]. Sugitani and Fujimoto demonstrated that bone mineral density significantly decreased in females aged 50 years or older who were allocated to TSH suppression therapy in a randomized controlled study [271, 276]. Klein Hesselink *et al.* revealed that cardiovascular death and all-cause mortality were 3.35 times and 4.40 times higher in DTC patients on TSH suppression than in the general population, respectively [277].

Patient-reported outcomes

Eustatia-Rutten *et al.* conducted a randomized controlled trial where QoL was compared between DTC patients with TSH suppression therapy for more than ten years (control group) and those whose TSH levels were normalized following the long-term suppression (intervention group). The investigators did not use any scales specific to thyroid disorders but administered instruments to measure the general QoL, including Short Form 36 (SF-36), multidimensional fatigue inventory (Mfi-20), Hospital Anxiety and Depression Scale (HADS), Social Relationship Scale (SRS), and Self-Rating Depression Scale (SDS). At 6 months after the intervention, only "Role restriction due to physical problems" in SF-36 (better in TSH suppression group) and "decreased motivation" in Mfi-20 (better in TSH normalization group) showed statistically significant differences [278].

CQ 40. Is chemotherapy recommended for advanced/recurrent differentiated thyroid carcinoma?

Recommendation

X It is recommended not to use cytotoxic anti-cancer chemotherapy for advanced/recurrent DTC (😖 Consensus ++).

Outcomes considered

- ✓ Anti-cancer effect
- ✓ Adverse events
- ✓ Health conditions from the patients' perspective

Evidence

- Response rates (CR + PR) for doxorubicin were reported to be 5% in one report and 31% in another report.
- The response rate for gemcitabine plus oxaliplatin was 57%.
- No reports have inquired about the patients' perspective.

Summary of literature

Doxorubicin is a cytotoxic anticancer drug that has been examined for its effectiveness in DTC, in several studies. Shimaoka *et al.* conducted a randomized controlled trial on patients with advanced differentiated, medullary and ATCs to compare the effectiveness between doxorubicin as a single agent (60 mg/m^2 every 3 weeks) *versus* doxorubicin (60 mg/m^2 every 3 weeks) plus cisplatin (40 mg/m^2 every 3 weeks) [279]. The response rates among 35 patients with advanced DTC for CR was 0% (95% CI: 0–21%) and for PR was 31% (95% CI 11–59%) for the monotherapy (16 cases); and for the combination therapy, for CR was 11% (95% CI: 1–31%) and for PR was 5% (95% CI: 0.1–26%), respectively. Severe adverse events were observed in 4% of patients on doxorubicin alone and in 12% for the combined regimen, without treatment-related death. Droz *et al.* estimated the response rate of 5 regimens including doxorubicin, to be 3% for 49 patients with advanced DTC with metastasis [280]. Matuszczyk *et al.* administrated doxorubicin as a single agent (8 cycles of 15 mg/m^2 weekly or three cycles of 60 mg/m^2 every 3 weeks) for patients with advanced, RAI resistant PTC or FTC. With the follow-up period of 11 months, PR, SD, and PD were observed in 5%, 42%, and 53% of patients, respectively [281].

A retrospective study demonstrated that doxorubicin, in combination with interferon-alpha, showed a similar response rate to, but often, more adverse events than doxorubicin alone [282]. A prospective study examining the anti-tumor activity of etoposide was stopped at interim because it resulted in no response for all patients [283].

Spano *et al.* conducted a retrospective analysis of the combination therapy of gemcitabine and oxaliplatin in 14 patients with RAI refractory DTC. As the estimated response rates were 57% (CR 7%, PR 50%, and SD 28%) with a wide confidence interval (95% CI: 29–82%), the investigators concluded that the effectiveness of the regimen needs to be tested prospectively with many more patients, sufficient to adequately narrow the confidence interval [284].

No cytotoxic anti-cancer agents have been approved or covered by the health insurance system for DTC in Japan. Furthermore, as the confidence intervals of reported response rates vary widely, the clinical use of any regimens is not recommended.

CQ 41. Is alternative medicine recommended for thyroid carcinoma?

Recommendation

XXX Any use of alternative medicine is not recommended because its effectiveness of anti-tumor

activity or survival benefit in patients with thyroid cancer has never been demonstrated (😣 Consensus +++).

Outcomes considered

- ✓ Anti-cancer effect
- ✓ Palliative effect on symptoms
- ✓ Adverse effects
- ✓ Health conditions from the patients' perspective

Evidence

- None.

Summary of literature

Alternative medicine for carcinoma patients has been classified into five categories: 1) alternative medical system (*e.g.*, traditional medicine, ethnic therapies, and oriental medicine), 2) energy therapy (*e.g.*, qigong and reiki), 3) physical therapy (*e.g.*, chiropractic and massage therapy), 4) mind and body interventions (*e.g.*, psychotherapy, hypnosis, and meditation), and 5) therapies based on pharmacology and biology (*e.g.*, Chinese medicine, shark cartilage, Agaricus, diet remedy, and immunotherapy).

To date, only one report has been published about alternative medicine for thyroid carcinoma, which was a survey investigating the frequency of its use [285].

Molecular target medicine therapy

CQ 42. Is the administration of molecular target medicine recommended for advanced/recurrent DTC?

Recommendation

◎◎◎ The use of molecular target medicine is recommended for definitely progressive DTC refractory to RAI therapy (😊 Consensus +++).

Outcomes considered

- ✓ Effectiveness
- ✓ Adverse effects
- ✓ Health conditions from the patients' perspective

Evidence

- The median progression-free survival period was prolonged for 5 months by sorafenib and 15 months by lenvatinib as compared to the placebo control, respectively.
- The NNT for controlling disease during six months after initiation of therapy was 5 for sorafenib and 2 for lenvatinib, respectively.
- Major adverse events (NNH; number needed to harm ≤5) included hand-foot syndrome (2), diarrhea (2), hair loss (2), exanthema/desquamation (3), loss of weight (3), hypertension (4), fatigue (4), loss of appetite (4), stomatitis (5) for sorafenib, and hypertension (2), diarrhea (2), loss of appetite (3), weight loss (3), angular cheilitis (3), fatigue (3), acromelic erythrodysesthesia syndrome (3), proteinuria (3), nausea (4), vomiting (5), headache (5), and speech disorder (5) for lenvatinib.
- No reports have been published regarding health conditions regarding treatment by molecular target medicine from the patients' perspective.

Summary of literature

Sorafenib is a tyrosine kinase inhibitor targeting VEGFR-1-3, RET, RAF, PDGFR-beta. The DECISION trial, a randomized phase III study, compared sorafenib to placebo with the RAI-refractory locally advanced or metastatic DTC study population showing disease progression during the previous 14 months without any medical treatments such as molecular target medicine, thalidomide, or chemotherapy [107]. Sorafenib significantly prolonged disease progression-free survival by five months, decreased the risk of disease progression by 41%, and showed response rate of 12%. No significant difference was observed for overall survival between the groups because crossing over from placebo to sorafenib was permitted after disease progression. Major adverse events included hand-foot syndrome (76.3%), diarrhea (68.6%), hair loss (67.1%), exanthema/desquamation (50.2%), and fatigue (49.8%), and those ≥grade 3 were hand-foot syndrome (20.3%), diarrhea (5.8%), fatigue (5.8%), weight loss (5.8%), and exanthema/desquamation (4.8%). The active treatment was stopped due to adverse events in 18.8% of the entire population, and 50% of Japanese patients.

Lenvatinib is a tyrosine kinase inhibitor targeting VEGFR-1-3, fibroblast growth factor receptor (FGFR)-1-4, RET, c-KIT, and platelet-derived growth factor receptors (PDGFR). In a randomized controlled phase III study, the SELECT trial, lenvatinib was compared with placebo for its effectiveness in patients with RAI-refractory locally advanced or metastatic DTC showing disease progression during the previous 13 months with or without one regimen targeting VEGFR [108]. Lenvatinib significantly prolonged disease progression-free survival for 14.7 months, decreased the risk of disease progression by 79%, and showed response rate of 65%. For those having a history of treatment with targeting VEGFR, the disease progression-free survival period was significantly prolonged at 15.1 months with the hazard ratio of 0.22. No significant difference was observed in the overall survival because some of the

patients who showed disease progression with placebo crossed over to the active treatment. The median disease progression-free survival period of the placebo group in the SELECT trial was shorter than that in the DECISION trial (3.6 months *vs.* 5.8 months), suggesting that patients registered in the SELECT trial had more aggressive disease than those in the DECISION trial. Major adverse events were hypertension (67.8%), diarrhea (59.4%), fatigue (59.0%), appetite loss (50.2%), weight loss (46.4%), and nausea (41.0%), and those ≥grade 3 included hypertension (42%), weight loss (10%), proteinuria (10%), and fatigue (9%). In Japanese patients, the incidences of hypertension (all grades 87%; ≥grade 3 80%), proteinuria (all grades 63%; ≥grade 3 20%), hand-foot syndrome (all grades 70%; ≥grade 3 3%) were higher than those in the entire series, but those who stopped the treatment were less (entire series 14.2%; Japanese subset 3.3%) [286].

Indication of molecular target medicine and timing of treatment initiation

Indication

Although both lenvatinib and sorafenib were approved for the treatment of "unresectable thyroid carcinoma," either drug should not be indicated solely based on the condition termed "unresectable" [287, 288]. For unresectable differentiated carcinoma, RAI therapy should be considered first, and molecular target medicine is indicated only when RAI therapy has no role in the management.

At present, safety and efficacy are not established for administrating molecular target medicines as adjuvant therapy. As they are angiogenesis inhibitors, there are risks of delayed wound healing and bleeding. Therefore, it is not recommended to perform surgery after tumor shrinkage by molecular target medicines and to administer either drug as an adjuvant therapy to patients with a high risk of recurrence. Furthermore, it has been reported that the use of drugs was associated with serious complications such as serious or even fatal bleeding in patients with a history of radiotherapy for recurrent tumors and those with invasion to the artery or the skin. The molecular target therapy is not indicated for such patients, especially for those having skin invasion.

Timing of initiation of therapy

The timing of therapy initiation should be carefully discussed, because recurrent/metastatic lesions often grow slowly, even if they are RAI refractory. In the National Comprehensive Cancer Network (NCCN) guidelines, the administration of molecular target medicine is considered for patients with rapidly growing lesions or symptomatic disease [109]. In ATA guidelines [145], in addition to these, the administration should also be considered for life-threatening lesions (expected worsening symptoms or life expectancy less than 6 months), but the decision may be difficult. Postponing (deferring) administration for asymptomatic patients until their metastatic lesions become symptomatic or till rapid growth may be a disadvantage to the patients. Such disadvantages may include increased risk of bleeding due to invasion to the artery or the skin and worsening of their QoL, which may lead to the chance of administration being missed. Therefore, even for asymptomatic patients, active surveillance is recommended if they have recurrent lesions or metastases. Imminent danger of bleeding, damage to QoL, and disease progression should be appropriately monitored based on the risk of invasion of recurrent/metastatic tumors to the artery, vertebral canal, trachea, esophagus, and skin as well as tumor enlargement; by regular imaging studies and changes in the levels of thyroglobulin and its antibody. Treatment should not be started unconditionally for all lesions with rapid growth or symptoms, but its indication and timing of administration should be decided by considering the benefits and harms associated with the therapy as well as the patients' general status.

Management of adverse events

Adverse events associated with molecular target medicine can be severe, particularly at the beginning of an administration. Detailed management in response to any side effects such as temporary withdrawal, dose reduction, and restarting of drugs is essential to maintain the patients' QoL as the medication period can be long. Informed consent should be obtained from a patient and his/her family before starting the therapy with due recognition of fatal adverse events such as myocardial infarction, hemorrhagic cerebral infarction and massive bleeding. It is mandatory to have doctors who are familiar with the management of adverse events, to prepare the facilities for supporting and educating the patients, this is because early recognition and management of any side effects are important to prevent the discontinuation of therapy.

Selection of molecular target medicine

Lenvatinib and sorafenib are available for unresectable DTC in Japan. The goal of therapy is to keep patients alive as long as possible without impairing their QoL. Successful management may lead to the relief of symptoms along with minimal experience of adverse events that should be essential to maintain QoL, but no reports have been published regarding patients' perspective.

Although no direct comparative data between lenvatinib and sorafenib have been published, their efficacy and profile of adverse events differ from each other based on comparative studies with placebo. Sorafenib has a high frequency of skin toxicity, and in Japanese patients, more frequently, discontinuation occurs due to these adverse

events than in foreign patients. In contrast, in lenvatinib, the incidence of hypertension, loss of appetite, and fatigue are frequently observed, but they could be managed by cessation and drug dose reduction. The incidence of hand-foot syndrome ≥grade 3 was also infrequent and the drug was discontinued in only one patient (3%).

The NCCN guidelines described that administration of lenvatinib or sorafenib should be considered for patients with DTC having rapidly enlarging RAI-refractory recurred lesions or having symptoms due to metastases. As the efficacy rate (CR + PR) of the former was 65%, while the rate of the latter was 12%, the NCCN guidelines committee regarded lenvatinib as the "preferred agent" [109]. In a clinical setting, shared decision making is desirable while presenting evidence on efficacy, toxicity, and durability of both drugs.

The efficacy of these agents as a second-line treatment for patients with a history of treatment with drugs targeting VEGFR has not been verified.

CQ 43. Is the use of molecular target medicine recommended for advanced/recurrent medullary thyroid carcinoma (MTC)?

Recommendation

◎◎◎ Administration of molecular target medicine (vandetanib) is recommended for definitely progressing advance/recurrent MTC (😊 consensus +++).

◎◎ Administration of molecular target medicine (sorefenib or lenvatinib) is recommended for definitely progressing advance/recurrent MTC (😊 consensus +++).

Outcomes considered

- ✓ Efficiency
- ✓ Adverse events
- ✓ Health conditions from the patients' perspective

Evidence

- The median disease progression-free survival period was prolonged for 11 months by the administration of vandetanib as compared to the placebo control.
- NNT of disease control by vandetanib (within 6 months after initial treatment) was 5.
- Major adverse events (NNH ≤5) were diarrhea (3), exanthema (3), TSH elevation (3), and hypertension (4).
- Vandetanib administration significantly prolonged the pain progression-free survival period from the patients' perspective (hazard ratio 0.61).

Summary of literature

Vandetanib is a tyrosine kinase inhibitor targeting VEGFR, RET, and endothelial growth factor receptor (EGFR). A randomized phase III trial (Zeta trial) comparing vandetanib *versus* placebo was conducted for unresectable locally advanced or metastatic MTC. Vandetanib significantly prolonged progression-free survival period as a primary endpoint at 64% and decreased the risk of disease progression (hazard ratio 0.46) [289]. The response rate of vandetanib was 43.7%. No significant difference was observed in overall survival between the groups, probably due to the crossing over from placebo to vandetanib in some patients. The major adverse events included cutaneous symptom (82.7%), diarrhea (46.8%), hypertension (26.4%), nausea (23.4%), and fatigue (18.6%), and those ≥grade 3 were diarrhea (10%), hypertension (9%), QTc elongation (8%), and malaise (6%).

Lenvatinib showed a response rate of 22% (95% CI: 3–60%), and median disease progression-free survival of 9.2 months for MTC in a phase II trial for all histology of thyroid carcinoma [134, 287]. In a phase II study for MTC conducted in foreign countries, lenvatinib demonstrated a response rate of 36% (95% CI: 24–49%) and median progression-free survival of 9 months [290].

Sorafenib showed a response rate of 25% (95% CI: 3–65%) for MTC in a phase II study for ATC and MTC in Japan [135].

Indication of molecular target medicine and timing of treatment initiation

Although vandetanib was approved for the treatment of "unresectable MTC," the drug should not be indicated solely based on the condition termed "unresectable." Most MTCs are not rapidly progressive, and indication and timing of treatment should be decided upon by considering the benefits and risks associated with the therapy, as well as the patients' general conditions.

Management of adverse events of molecular target medicine

Although rare, the use of vandetanib is associated with interstitial lung diseases such as interstitial pneumonia, pneumonitis, fibrosis, and acute respiratory distress syndrome. Careful observations by checking for symptoms such as shortness of breath, dyspnea, cough, and fatigue, as well as chest imaging studies, are mandatory. A regular check-up using an electrocardiogram is also essential to rule out QTc prolongation. Physicians need to pay attention to the occurrence of diarrhea and cutaneous toxicity such as photosensitivity [291].

Selection of molecular target medicines

In Japan, vandetanib is available to treat "unresectable MTC." Lenvatinib and sorafenib are available for "unresectable thyroid carcinoma." Thus, the three drugs can be used for unresectable MTC. Although direct comparative

studies of these three have not been reported, clinical evidence of vandetanib against MTC is the most valid because phase III study with placebo was performed. Also, the use of vandetanib is tolerable because of the low incidence of adverse events ≥grade 3 and that of discontinuation due to adverse events. Therefore, vandetanib is strongly recommended for unresectable MTC rather than the remaining two drugs.

No clinical study data are available regarding MTC patients who have a history of treatment with drugs targeting VEGR. When considering the administration of other drugs after the treatment with lenvatinib or sorafenib, factual information should be provided to the patients in a discussion on further management.

CQ44. Is the administration of molecular target medicines recommended for advanced/recurrent anaplastic thyroid carcinoma (ATC)?

Recommendation

◎◎ Administration of molecular target medicine (lenvatinib) for unresectable advanced/recurrent ATC is recommended, given the judicious judgment on the expected effects and possible risks (😊 consensus ++).

Outcomes considered

✓ Effectiveness

Evidence

・The PR rates of ATC are 27% (95% CI: 6–61%) and 24% (95% CI: 7–50%) for lenvatinib and 0% (95% CI: 0–31%) and 10% (95% CI: 1–32%) for sorafenib.

Summary of literature

According to company data of lenvatinib, its PR rate for ATC was 27% (95% CI: 6–61%) [287]. Also, in a phase II study for all thyroid carcinoma histology, the response rate and median progression-free survival for ATC by lenvatinib were reported to be 24% (95% CI: 7–50%) and 7.4 months, respectively [134].

In a phase II study of sorafenib for ATC in Japan, the response rate was 0% (95% CI: 0–31%), indicating that sorafenib is not effective for ATC [135]. Besides, in a foreign phase II study for ATC, sorafenib was not effective because the response rate and median progression-free survival rate were 10% (95% CI: 1–32%) and 1.9 months, respectively [292].

Indication of molecular target medicine and time for initiation of therapy

As unresectable ATC is very aggressive and shows dismal prognosis, the indication of molecular target medicine should be immediately considered once the diagnosis is made, even in asymptomatic cases. As described in the section on molecular target medicine for DTC (CQ 42), the benefit of therapy should be balanced against the risks of developing fistula and bleeding, through the evaluation of tumor invasion to the surrounding organs such as the esophagus, trachea, great vessels, and the skin. Although ATC is likely to recur after surgery, the use of lenvatinib as preoperative induction therapy or postoperative adjuvant therapy is not recommended because its safety and effectiveness have not been established yet. Similarly, perioperative use is not recommended because it may delay wound healing.

Management of adverse events of molecular target medicine

See CQ 42.

Selection of molecular target medicine

Lenvatinib is the only available drug for the treatment of advanced/recurrent ATC in Japan. The effectiveness and safety of sorafenib for ATC have not yet been established [135].

Future directions

What we found through the revision work was that relevant evidence was lacking for many of the clinical questions posed in the new guidelines. Only 10 of the 51 recommendations for the therapeutic management of thyroid cancers were supported by good evidence, whereas 35 recommendations were aided by good expert consensus. While implementing the current guidelines would be of help to achieve the objective, we need further clinical research to make our shared decision making to be more evidence-based. Besides, some novel developments such as molecular testing for thyroid nodules with indeterminate cytology need to be addressed in the near future. It would be essential to construct a system that enables us to distribute new findings in a timely manner so that physicians caring for patients with thyroid tumors can catch up with state-of-the-art and latest knowledge.

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Disclosure

All the guideline development group members reported their conflicts of interest, and these are available at the JAES website (jaes.umin.jp).

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