Ge *et al. Holistic Integrative Oncology* (2022) 1:17
https://doi.org/10.1007/s44178-022-00015-8

Holistic Integrative Oncology

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# CACA guidelines for holistic integrative management of thyroid cancer

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## Abstract

**Purpose:** In recent years, thyroid cancer is a common clinical problem. Since guidelines for the diagnosis and treatment of thyroid nodules and differentiated thyroid cancer were revised in 2012, significant scientific advances have occurred in the field. The aim of this guidelines is to inform clinicians, researchers, patients and health policy makers on published evidence and expert consensus relating to the diagnosis and management of thyroid malignancy.

**Methods:** In order to better promote the clinical management of thyroid cancer in China, Chinese Association of Thyroid Oncology (CATO) organized relevant experts to write these guidelines based on latest relevant literatures and clinical experience of multiple centers.

The specific clinical issues and topics addressed in these guidelines were based on published evidence, prior versions of the Chinese guidelines and expert consensus.

**Results and conclusion:** The guidelines provide recommendations for the management of different types of thyroid carcinoma, including papillary, follicular, medullary, and anaplastic carcinomas.

**Keywords:** Thyroid cancer, Guidelines, Chinese Association of Thyroid Oncology (CATO)

## 1 Epidemiology and screening of thyroid cancer

Thyroid cancer is the most common malignant tumor of the endocrine system, as well as the most common malignant tumor in the head and neck. Over the past 30 years, the incidence of thyroid cancer has increased drastically worldwide, making it one of the 10 most common malignant tumors. According to the latest estimates on the global burden of cancer released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), there were 586,000 new cases of thyroid cancer worldwide in 2020, making thyroid cancer the ninth-leading cancer, of which 449,000 in women, making thyroid cancer the fifth-leading cancer in women. In China, the incidence of thyroid cancer is also rising rapidly, with an average increase of 20.43% from 2003 to 2012 annually. According to the National Cancer Center, thyroid cancer ranks seventh among all malignant tumors and fourth in women. The five-year survival rate of thyroid cancer is 98.6% in developed countries of Europe and North America, and the age-standardized 5-year relative survival rate is 84.3% in China.

### 1.1 Epidemiology of thyroid cancer

Thyroid cancer originates from thyroid follicular epithelial cells or parafollicular cells (also known as C cells). Follicular cell-derived thyroid cancer includes papillary thyroid carcinoma (PTC, accounting for 80–85% of thyroid cancers), follicular thyroid carcinoma (FTC, 10–15%), and poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC, < 2%) [1]. Parafollicular cell-derived thyroid cancer, also known

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as medullary thyroid carcinoma (MTC), accounts for approximately 1–5% of thyroid malignancies [2, 3].

The recent stark increase in the incidence of thyroid cancer is mainly due to the increasing of PTC [4, 5]. In China, the incidence of thyroid cancer is also rising rapidly, where PTC accounts for a large proportion (approximately 92%) of thyroid cancers and is much more prevalent in urban areas than in rural areas, and more prevalent in eastern China than in central or western China [6, 7].

One of the main reasons for this increase in diagnosis is the wide application of high-resolution ultrasound and fine-needle aspiration (FNA), as well as more regular health check-ups, which help to detect smaller and low-risk PTCs [5]. However, studies have also shown that the absolute incidence of thyroid cancer is increasing for all tumor sizes and age groups. Therefore, the epidemiological increase cannot be attributed to stronger diagnostic intensity alone but is the combined effect of more tests and screenings and other unknown factors [8, 9].

While the incidence of thyroid cancer is rising, the mortality rate remains relatively low and stable worldwide [10]. In the US, the mortality rate of thyroid cancer increased from 0.40 per 100,000 individuals in 1994 to 0.46 per 100,000 individuals in 2013, an average year-on-year increase of 1.1%. For PTCs with distant metastasis or those in stage IV, the average incidence increased 2.9% each year [11]. In Europe, the mortality rate of thyroid cancer is 0.5 per 100,000 men or 0.7 per 100,000 women, with little to no temporal or regional variation [12]. In China, the age-standardized mortality rate of thyroid cancer was 0.26–0.36 per 100,000 individuals from 2003 to 2012 [13]. In China, the long-term survival from thyroid cancer has significantly improved. According to 17 cancer registries, the age-standardized 5-year relative survival rate from thyroid cancer increased from 67.5% in 2003–2005 to 84.3% in 2012–2015, although the survival rate is still significantly lower than that in some developed countries [14].

In some cases, thyroid cancer linked to genetic factors. For example, 5–10% of differentiated thyroid cancers (DTC) are thought to be of familial origin and may be part of a familial tumor syndrome or may be nonsyndromic (familial non-MTC). The risk of DTC is significantly higher among first-degree relatives of the proband [15, 16]. Approximately 25% of MTCs are hereditary and caused by germline RET proto-oncogene mutation. MTC may be one of the manifestations of type 2 multiple endocrine neoplasia (MEN2).

Among environmental and dietary factors, childhood exposure to ionizing radiation is currently the only confirmed environmental risk factor for DTC. The Chernobyl disaster resulted in a significant increase in the incidence of thyroid cancer in children and adolescents in contaminated areas. This is confirmed by the increased risk of thyroid cancer in survivors of childhood malignant tumors who received radiotherapy [17, 18]. The relationship between exposure to ionizing radiation and thyroid cancer in adults is unknown. Several recent meta-analyses show that obesity may be a risk factor for thyroid cancer [19, 20]. A large population study of 5.24 million samples shows that high body mass index (BMI) is associated with an increased risk of 10 common cancers, including thyroid cancer (by approximately 9%) [21]. Both iodine deficiency and excess iodine intake can cause thyroid disease, and iodine deficiency increases the risk of radiation-induced thyroid cancer [22]. Nevertheless, no data suggest that excess iodine intake is associated with an increased risk of thyroid cancer, or that salt iodization is associated with the incidence of thyroid cancer [23, 24]. A diet of sea fish and shellfish does not increase the risk of thyroid cancer; it has a protective effect in iodine-deficient areas [25]. Moreover, intake of cruciferous vegetables has no apparent association with thyroid cancer [26].

### 1.2 Screening for thyroid cancer

At-risk populations, such as individuals with a history of childhood radiation exposure, individuals with a history of some of the aforementioned genetic syndromes and their first-degree relatives, MEN2 patients and their first-degree relatives, and the first-degree relatives of MTC patients with germline RET mutation should undergo screening for thyroid cancer [27]. High-resolution ultrasound combined with FNA can detect early thyroid cancer.

## 2 Diagnosis of thyroid cancer

### 2.1 Clinical manifestations

Most patients with thyroid cancer have no apparent clinical symptoms. Some patients have symptoms such as hoarseness, neck compression, and dyspnea/dysphagia caused by the nodules compressing the surrounding tissues. Patients with thyroid dysfunction may present clinical symptoms of hyperthyroidism or hypothyroidism. Some patients seek medical attention for enlarged cervical lymph nodes. Horner's syndrome may occur if the tumor compresses the cervical sympathetic ganglia.

MTC secretes calcitonin and 5-HT, which can cause diarrhea, palpitations, and flushing. MTC may be accompanied by MEN2, familial multiple polyposis, or certain thyroid cancer syndromes.

ATC often manifests as several simultaneous or alternating symptoms or manifests mainly as a digestive or respiratory symptom, with additional symptoms such as hoarseness and pain in the neck area. Patients usually

have a palpable plate-like hard mass in the anterior cervical area, which develops rapidly, with unclear boundaries and poor or no movement.

## 2.2 Imaging diagnosis

### 2.2.1 Ultrasound

High-resolution ultrasound is the preferred method for the assessment of thyroid cancer [28]. It is convenient, noninvasive, and inexpensive and is the most used and preferred imaging method for the thyroid gland. We recommend high-resolution cervical ultrasound for all patients with thyroid nodules detected by clinical palpation or random screening.

Ultrasound signs of thyroid cancer [29, 30]: (1) a solid hypoechoic or very hypoechoic nodule(s); (2) a nodule with irregular edges; (3) diffuse dot-like hyperechoes or clustered microcalcifications; (4) vertical growth; (5) extrathyroid infiltration; (6) abnormal ultrasound imaging of cervical lymph nodes, such as hyperechoic lymph nodes, with microcalcifications, cystic degeneration, abnormal blood flow, round shape, absence of the lymphatic hilum, and a blurred cortex–medulla boundary. The ability to identify benign versus malignant thyroid nodules is related to the clinical experience of the sonographer.

Thyroid elastography and contrast-enhanced ultrasound technology are becoming more widely used for the assessment of thyroid nodules [31]. Ultrasound elastography was first used to study thyroid lesions in 2005, and its value in diagnosis and differential diagnosis has been gradually recognized. As a more standardized ultrasound diagnostic method for thyroid lesions, contrast-enhanced ultrasound provides a reliable reference for clinical diagnosis.

Recommendation 1: All patients with suspected thyroid cancer should undergo cervical ultrasound.

Recommendation 2: The ability to identify thyroid cancer is related to the clinical experience of the sonographer.

### 2.2.2 The role of other imaging modalities for the assessment of thyroid cancer

For qualitative assessment of thyroid cancer, computed tomography (CT) and magnetic resonance imaging (MRI) are not superior to ultrasound [32], but for specific areas such as the upper mediastinum [33, 34], CT and MRI are useful. CT can assess the extent of a thyroid cancer lesion and its relationship with the surrounding vital structures such as the trachea, esophagus, and carotid arteries. It is a valuable tool for preoperative surgical planning and preparing for potential intraoperative injury. For relapsed or metastatic thyroid cancer, enhanced CT can be used to see the relationship between the tumor and the surrounding tissues, and enhanced MRI can be used to identify any brain metastasis. For patients with suspected distant metastases, $^{18}$F-FDG positron-emission tomography (PET)/CT can be performed if necessary to learn about the systemic tumor burden. $^{18}$F-FDG PET alone cannot accurately distinguish benign from malignant thyroid nodules [35].

Recommendation 3: CT and MRI can help assess the extent of primary thyroid cancer and cervical lymph nodes and their relationship with the surrounding vital organs, which facilitates surgical planning.

Recommendation 4: $^{18}$F-FDG PET-CT should not be used routinely for the assessment of thyroid nodules. For patients with advanced thyroid cancer and suspected distant metastases, PET-CT can be used for systemic assessment.

Recommendation 5: For MTC with suspected relapse or metastasis, preliminary exams include comprehensive physical examination, cervical ultrasound, neck and chest CT, abdominal MRI, bone scan, and spine and pelvis MRI. If no lesions are identified, PET/CT with $^{18}$F-FDG, $^{18}$F-DOPA, or $^{68}$ Ga somatostatin receptor as the contrast agent may be performed.

### 2.2.3 Laboratory diagnosis

Before surgery, thyroid function, thyroglobulin (Tg), and thyroid antibodies should be tested as the baseline evaluation for dynamic monitoring. We do not recommend using thyroid-stimulating hormone (TSH) or Tg for the differential diagnosis of benign versus malignant thyroid tumors.

Several prospective nonrandomized studies show that routine serum calcitonin (Ctn) screening helps detect early C cell proliferation and MTC, thereby improving the detection rate and the overall survival rate of MTC [36–39]. The American Thyroid Association (ATA) is neutral about Ctn screening [40] but recognizes that Ctn screening is valuable in some populations. The China Expert Consensus recommends routine Ctn screening [41, 42] and carcinoembryonic antigen (CEA) testing before surgery in patients with suspected malignant thyroid tumors.

In MTC patients, tumor burden is often positively correlated with serum Ctn. Preoperative serum Ctn value can effectively help determine the extent of lymph node metastasis [43]. A serum Ctn value of > 20, 50, 200, and 500 pg/mL generally indicates suspected lymph node metastasis to the ipsilateral central and cervical areas, the contralateral central area, the contralateral cervical area, and the upper mediastinum, respectively. Ctn ≥ 150 pg/ml is highly indicative of disease progression or relapse. It should be noted that Ctn and CEA may be normal or even decreased in some MTC patients [44].

Recommendation 6: Tg should not be measured for the differential diagnosis of thyroid cancer.

Recommendation 7: For DTC patients, Tg and Tg antibodies (TgAb) should be routinely monitored after total thyroidectomy. Continuous monitoring is recommended to enable ongoing assessment of postoperative relapse and treatment response.

Recommendation 8: For patients with suspected thyroid malignancy, serum Ctn should be measured before surgery to classify MTC. CEA should also be measured in patients with elevated Ctn or suspected MTC.

Recommendation 9: Elevated serum Ctn reflects the MTC tumor burden. It is a valuable tool for the clinical evaluation of MTC. Images and serum Ctn should be referenced to preliminarily determine the extent of cervical lymph node metastasis and dissection.

#### *2.2.4 Aspiration*

Aspiration of thyroid cancer is done by core biopsy and FNA. Core biopsy is usually used for the histological diagnosis of thyroid lymphoma or ATC. FNA is used more often in clinical practice. For common DTC, FNA is the most sensitive and specific method for preoperative qualitative diagnosis. Preoperative FNA helps reduce unnecessary operations and assists in surgical planning.

FNA biopsy (FNAB) cytologic diagnostic results are usually reported based on the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which was first proposed in 2007 and was officially released in 2009, becoming the most widely accepted and standardized system for thyroid cytopathology. In October 2017, the revised TBSRTC (Edition 2) was released to incorporate recent progress in the field of thyroid disease. The new edition uses the same six categories of FNAB results: I) nondiagnostic or unsatisfactory (UD/UNS); II) benign; III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); IV) follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN); specify if Hürthle cell (oncocytic) type; V) suspicious for malignancy (SM); and VI) malignancy to assess the risk of malignancy and recommend usual management. Table 1 summarizes the differences between these two editions, with detailed explanations based on Bethesda category.

For DTC, the Tg level in the eluate of lymph node FNAB may assist in the diagnosis of lymph node metastasis [45]. In the case of metastatic lymph nodes of thyroid cancer, a high level of Tg will be detected in the FNA eluate. The level of Ctn in the FNAB eluate may assist in the diagnosis of MTC [46, 47].

Recommendation 10: FNAB is the most sensitive and specific method for preoperative assessment of benign versus malignant thyroid nodules.

Recommendation 11: Ultrasound-guided FNAB improves the success rate of sampling and the accuracy of diagnosis.

Recommendation 12: The levels of Tg and Ctn in FNAB eluate may assist in the diagnosis of DTC, metastatic lymph nodes, and MTC.

#### *2.2.5 Molecular testing*

For patients with clinically undiagnosed thyroid cancer, molecular testing improves the accuracy of diagnosis. For undetermined thyroid nodules (after FNAB), certain molecular markers of thyroid cancer, such as *BRAF* mutation, *Ras* gene mutation, *RET*/PTC rearrangement,

**Table 1** The risk of malignancy and recommendations for usual management based on TBSRTC category (first versus second edition)

| Bethesda Category | Risk of malignancy (%) | | | Usual management[a] | |
|---|---|---|---|---|---|
| | 2007 | 2017 | | 2007 | 2017 |
| | | NIFTP ≠ cancer | NIFTP = cancer | | |
| I I UD/UNS | 1–4 | 5–10 | 5–10 | Second ultrasound-guided FNA | Second ultrasound-guided FNA |
| I II Benign | < 1–3 | 0–3 | 0–3 | Clinical and ultrasound follow-up | Clinical and ultrasound follow-up |
| I III AUS/FLUS | 5–15 | 6–18 | ~ 10–30 | Second FNA | Second FNA, molecular marker testing, or thyroid lobectomy |
| I IV FN/SFN | 20–30 | 10–40 | 25–40 | Thyroid lobectomy | Thyroid lobectomy or molecular marker testing |
| V V SM | 60–75 | 45–60 | 50–75 | Total thyroidectomy, or thyroid lobectomy | Total thyroidectomy or thyroid lobectomy[bc] |
| V VI Malignancy | 97–99 | 94–96 | 97–99 | Total thyroidectomy | Total thyroidectomy, or thyroid lobectomy[c] |

[a] The final management strategy should consider other factors (such as clinical manifestations, ultrasound characteristics)

[b] Some studies recommend molecular marker testing to determine the scope of thyroid surgery (thyroid lobectomy, total thyroidectomy)

[c] Thyroid surgery may not be applicable if the cytological diagnosis is "suspicious of metastatic cancer" or "malignant (metastatic cancer)"

paired box gene 8 (*PAX8*)/peroxisome proliferator-activated receptor gamma (*PPAPG*) rearrangement, and gene panel results can improve the diagnosis rate [48, 49]. Molecular testing improves the accuracy of diagnosis of thyroid cancer, but it cannot be used alone to identify malignant thyroid nodules. Molecular testing should always be used together with cytological, clinical, and ultrasound findings.

For PTC patients, molecular markers such as *BRAF* improve the accuracy of FNAB diagnosis. *BRAF* mutation is associated with DTC invasion, relapse, and mortality; therefore, a stratified system that incorporates *BRAF* mutation and detailed tumor characteristics such as the size of the primary tumor and extrathyroid infiltration will help determine the risk of relapse and whether postoperative 131I therapy may be warranted, thereby further reducing the risk of relapse [45].

Telomerase reverse transcriptase (*TERT*) mutation also plays an important role in the development and progression of advanced aggressive thyroid cancer. The risk of relapse and death is significantly higher in patients with both *TERT* mutation and *BRAF* mutation than in patients with only one or neither, suggesting that *TERT* plays an important role in the prognosis of advanced thyroid cancer.

Preoperative *RET* screening and genetic counseling assists in identifying hereditary MTC, which facilitates clinical evaluation and guides treatment. Approximately 1–7% of sporadic MTC cases have a genetic background of hereditary MTC. Therefore, genetic screening for sporadic cases can further clarify the disease classification. Patients with hereditary MTC should be advised that their hereditary *RET* mutations may be present in their family members and therefore pose a risk. *RET* mutation carriers (especially MEN2B patients) with childbearing potential should receive genetic counseling before pregnancy or delivery. *RET* screening and genetic counseling is recommended for the following populations: (1) sporadic MTC patients; (2) hereditary MTC patients and their first-degree relatives; (3) parents of patients with MEN2B manifestations in childhood or infancy; (4) patients with cutaneous lichen amyloidosis; (5) patients with Hirschsprung disease carrying a mutation in exon 10 of the *RET* gene. For RET screening, the specific target sites include (1) MEN2A screening: the main target sites are codons 609, 611, 618, and 620 of exon 10, as well as codons 630 and 634 of exon 11; (2) MEN2B screening: the main target sites are M918T mutation of exon 16 and A883F mutation of exon 15; the entire *RET* coding region should be sequenced in the case of negative results.

For hereditary MTC, risk stratification is based on different mutation sites: (1) highest risk (HST): including MEN2B patients and those with the M918T mutation of *RET*; (2) high risk (H): including those with the C634 mutation or A883F mutation of *RET*; (3) moderate risk (MOD): including hereditary MTC patients without M918T, C634, or A883F.

Recommendation 13: For undetermined thyroid nodules (after FNAB), molecular markers of thyroid cancer may be tested with FNAB samples. Preoperative ***RET*** screening and genetic counseling assists in clinical assessment and risk stratification of MTC.

#### *2.2.6 Artificial intelligence*

An artificial intelligence model trained on many ultrasound images can assist in the diagnosis of thyroid cancer. An artificial intelligence model based on a convolutional neural network can distinguish benign and malignant thyroid nodules, and its diagnostic accuracy is comparable to that of senior sonographers [49]. An artificial intelligence model trained with a large number of ultrasound images can help identify lymph node metastasis of DTC. Artificial intelligence models based on convolutional neural networks can predict lymph node metastasis of thyroid cancer based on ultrasound images of primary thyroid cancer, but its accuracy is relatively low.

Recommendation 14: Artificial intelligence models trained on many ultrasound images can assist in the diagnosis of thyroid cancer.

## 3 Treatment of thyroid cancer

### 3.1 Principles of multidisciplinary treatment of thyroid cancer

Thyroid cancer is a typical interdisciplinary disease, so the multidisciplinary team/treatment (MDT) plays a vital role in its treatment and management. Taking differentiated thyroid cancer (DTC) as an example, thyroidectomy is the main treatment method, and postoperative $^{131}$I therapy and thyrotropin (thyroid-stimulating hormone, TSH) suppression therapy are important adjuvant treatments. Systemic treatments, such as radiotherapy, chemotherapy, targeted drug therapy, even traditional Chinese medicine, are used at different stages of the disease [1]. The treatment of thyroid cancer is generally based on medical evidence and standardized diagnosis according to guidelines, with the purpose of avoiding undertreatment or overtreatment. For complex and refractory thyroid cancer, MDT consultation and management should be included whenever possible to develop appropriate treatment plans [42, 50, 51]. The MDT is chosen based on the actual situation and needs but generally includes various physicians in the subspecialties of surgery, nuclear medicine, endocrinology, oncology, radiotherapy, and Chinese medicine, as well as diagnostic experts (from, e.g., ultrasound, imaging, pathology), and other relevant

medical professionals (e.g., nutritionist, nurse, psychologist, rehabilitation therapist) [52].

### 3.2 Treatment goals for thyroid cancer

The majority of DTC patients have a good prognosis. The treatment goals are to improve the overall survival rate, reduce the risk of disease recurrence and metastasis, and achieve accurate disease staging and risk stratification. It also aims to minimize complications and unnecessary treatments [1].

Medullary thyroid cancer (MTC) has unique pathogenesis, genetic background, and syndromes. The treatment goal is to improve the overall survival. For early-stage patients, it is important to increase the cure rate and reduce the risk of recurrence and metastasis. For advanced patients, the key is to comprehensively evaluate treatment options and the benefits they would bring, thereby improving the survival rate.

Anaplastic thyroid cancer (ATC) is relatively rare and has a very poor prognosis. The treatment goal may be palliative therapy. Once ATC is diagnosed, a MDT should be formed to determine the treatment plan after careful discussion and full communication with the patient or patient surrogate. It needs to clarify whether the patient is clinically suitable for active treatment and discuss the treatment goals with the patient or patient surrogate as soon as possible. These include the end-of-life treatment options (e.g., palliative care, hospice care measures). During communication, doctors should avoid sending messages that are either too optimistic or too pessimistic [50].

Recommendation 15: In view of the particularity of ATC, the treatment goal should be based on MDT discussion and communication with the patient or patient surrogate.

### 3.3 Surgical treatment

Surgical treatment is the main treatment method for thyroid cancer, and it is also the only radical treatment method in most cases.

#### *3.3.1 Surgical treatment of DTC*

*Surgical treatment of primary tumors of DTC* Thyroidectomy for patients with DTC mainly includes total/near-total thyroidectomy and lobectomy with isthmusectomy. The scope of thyroidectomy should be based on the cTNM stage, the risk of death/recurrence, the pros and cons of various surgical methods, and the patient's preference.

In the past, due to DTC multifocal tendency and the convenience of follow-up after therapy, total/near-total thyroidectomy was the main surgical method for patients with DTC [40]. An analysis of more than 50,000 papillary thyroid cancer (PTC) cases in the National Cancer Database of the United States showed that total thyroidectomy could benefit patients with PTC larger than 1 cm by increasing the survival and reducing the risk of recurrence, yet the absolute benefit was marginal. The 10-year overall survival rates of total thyroidectomy and lobectomy were 98.4% and 97.1%, and the 10-year recurrence rates were 7.7% and 9.8%, respectively [53].

In low-risk and some intermediate-risk patients, the clinical outcomes of total/near-total thyroidectomy and lobectomy with isthmusectomy were similar [54–56]. Adam et al. analyzed 61,775 PTC cases in the National Cancer Database from 1998 to 2006, finding that after adjusting for important prognostic factors, total thyroidectomy did not increase the survival rate of PTC patients with 1–4-cm tumors. Subgroup analysis of 1–2-cm and 2–4-cm PTCs also showed the same results [55]. Compared with total/near-total thyroidectomy, lobectomy with isthmusectomy is more beneficial for reducing postoperative complications, especially serious complications such as permanent hypoparathyroidism and bilateral recurrent laryngeal nerve (RLN) injury.

The indications for total/near-total thyroidectomy include (1) a history of head and neck radiation exposure or radioactive dust exposure in childhood; (2) maximum diameter of the primary tumor > 4 cm; (3) bilateral multiple foci; (4) poor pathological subtypes, such as the tall cell variant (TCV), columnar cell variant (CCV), diffuse sclerosing variant (DSV), and solid variant (SV) of PTC, widely invasive FTC, and poorly differentiated thyroid cancer; (5) distant metastases, which requires postoperative $^{131}$I therapy; (6) bilateral cervical lymph node metastasis; and (7) gross extraglandular invasion.

Relative indications for total/near-total thyroidectomy include: (1) unilateral multiple foci; (2) the maximum tumor diameter is between 1–4 cm, and (3) accompanied by high-risk factors for thyroid cancer or contralateral thyroid nodules.

The indications for lobectomy with isthmusectomy are (1) single DTC confined to one gland lobe, (2) diameter of primary tumor < 1 cm, (3) low risk of recurrence, (4) no history of head or neck radiation exposure in childhood, (4) no neck lymph node metastasis or distant metastasis, and (5) no suspicious malignant nodules in the contralateral lobe.

The relative indications for lobectomy with isthmusectomy are (1) single DTC confined to unilateral lobe, (2) diameter of primary tumor < 4 cm, (3) low risk of recurrence, (4) no suspicious malignant nodule in the contralateral lobe, and (5) minimally invasive FTC [57].

Recommendation 16: Thyroidectomy of the primary tumor of DTC patients should be determined by carefully balancing the benefits and risks. The options include total/near-total thyroidectomy and thyroid lobectomy with isthmusectomy.

*Surgical management of cervical lymph nodes in DTC* The central area is the most common site of lymph node metastasis of thyroid cancer [58, 59]. There is no controversy about therapeutic central-compartment (level VI) neck dissection for PTC patients with clinically involved central nodes, nor about prophylactic central-compartment neck dissection for high-risk PTC. Prophylactic central-compartment neck dissection for low-risk DTC patients is controversial, and the results of different studies are not consistent [1, 12, 57, 58, 60–64]. The general consensus in China is to perform central-compartment neck dissection of the affected side, under the premise of protecting the RLN and parathyroid glands.

For DTC, therapeutic lateral neck compartmental lymph node dissection is recommended, and prophylactic lateral neck compartmental lymph node dissection is not recommended [65]. Although PTC is associated with a significant incidence of occult metastases, approximately 80% do not develop into clinical metastases. Moreover, occult cervical lymph node metastasis does not reduce the survival rate of patients [66]. Therefore, prophylactic lateral neck compartmental lymph node dissection is generally not recommended for patients with clinically uninvolved central neck lymph nodes (cN0) DTC. Some studies have suggested that lateral neck compartmental lymph node dissection may be considered for some cN1a (with clinically involved central nodes) patients, such as those with extensive metastasis in the central area, locally advanced tumors, and tumors located in the upper pole [57].

Recommendation 17: For patients with clinically involved central nodes, therapeutic central-compartment (level VI) neck dissection is recommended.

Recommendation 18: For cN0 (with uninvolved central neck lymph nodes) PTC with high-risk factors (e.g., T3-T4 tumors, multiple foci, family history, childhood exposure to ionizing radiation, clinically involved lateral neck nodes), ipsilateral central-compartment neck dissection is recommended.

Recommendation 19: For cN0 PTC, central-compartment neck dissection should be chosen based on tumor factors and functional preservation.

Recommendation 20: Central-compartment neck dissection is not recommended for cN0 follicular carcinoma.

Recommendation 21: For patients with clinically involved lateral neck nodes, lateral neck compartmental lymph node dissection is recommended.

*Treatment of persistent/recurrent/metastatic DTC (prmDTC)* For the treatment of prmDTC, the following should be considered sequentially, (1) thyroidectomy for eligible patients, (2) postoperative $^{131}$I therapy for RAI-responsive disease, (3) external-beam radiotherapy or other targeted treatments (e.g., thermal ablation therapy), (4) TSH suppression treatment for stably or slowly progressive asymptomatic patients, and (5) systemic treatment or clinical trials of kinase inhibitors for patients with rapidly progressive refractory DTC [40]. Surgery is the most basic and effective treatment method for prmDTC.

Recommendation 22: Total thyroidectomy is the preferred treatment for prmDTC.

*Surgical treatment of cervical prmDTC with no invasion of surrounding organs* prmDTC is very common in clinical practice [67]. Since reoperation is often difficult and with high risk, the risks and benefits of surgery should be weighed when choosing a reoperation plan to lower the risk of tumor recurrence and death while reducing iatrogenic injury. In addition, the operation should be performed by an experienced thyroid specialist.

Small lymph nodes in the central compartment should be closely followed up. Surgical treatment can be performed when lymph nodes are enlarged and diagnosed as metastatic lymph nodes by FNAB. Lymph nodes were found in the central compartment of approximately 1/3 of postoperative patients, of whom only a small proportion (< 10%) with small lymph nodes (< 11 mm) had enlarged tumors during follow-up, and the proportion of patients finally confirmed PTC was less than 5% [68]. Therefore, the borderline was determined as a minimum diameter ≥ 8 mm, which could not only avoid the missing of potential tumors but also ensure a high certainty of FNAB and the localization of tumors during surgery [69].

Of patients with suspected involved lateral neck nodes on ultrasound, only approximately 9% had lymph nodes with a length-diameter growth > 5 mm in long-term follow-up studies [70, 71]. Therefore, close follow-up can be considered for patients with a minimum diameter of lateral cervical lymph nodes < 10 mm. For lymph nodes with a minimum diameter ≥ 10 mm, surgical treatment is performed after metastasis confirmed by FNA [71, 72].

The following factors should be considered as well to decide on the surgical treatment: the location of the tumor (proximity to surrounding organs), the scope of previous surgery, complications (e.g., hypoparathyroidism, RLN or superior laryngeal nerve paralysis), and whether the primary tumor is an aggressive histologic subtype. If the tumor is close to surrounding organs, or the primary tumor is an aggressive histologic subtype, the indications can be relaxed.

Recommendation 23: Surgical treatment is the first choice for recurrent/metastatic DTC. Close follow up should be performed for small or suspected tumors. Surgical treatment can be performed after a central lymph node with minimum diameter ≥ 8 mm or a lateral cervical lymph node with minimum diameter ≥ 10 mm is confirmed to be malignant by FNA. If the tumor is close to surrounding organs, or the primary tumor is an aggressive histologic subtype, the indications can be relaxed.

*Surgical treatment of cervical prmDTC invading surrounding organs* There is a high chance for prmDTC to adhere to or invade surrounding organs, such as the larynx, trachea, esophagus, cervical artery, and RLN. The scope of thyroidectomy for such tumors has always been controversial. The resection of visible tumors is the key to control local tumor recurrence and increase the survival rate. The surgery should be performed by specialists with rich clinical experience, and if necessary, specialists in thoracic surgery, vascular surgery, otolaryngology (head and neck surgery), bone oncology, and reconstruction surgery should also be invited.

When patients with locally advanced DTC with R0 (thyroidectomy with clear surgical margins) and R1 (microscopically positive margins) resection, the 5-year disease-specific survival rates were 94.4% and 87.6%, respectively, while the survival rate decreased significantly to 67.9% for R2 resection (visible residual tumor [73]). For patients with RLN involvement, if there is no preoperative vocal cord paralysis, it is recommended to remove the tumor as much as possible while preserving the nerve function. If there is vocal cord paralysis and tumor wraps around RLN, it is recommended to remove the tumor, and the involved nerve as well, with nerve reconstruction afterward. For patients with affected cervical blood vessels, (1) if unilateral internal jugular vein is affected, the affected internal jugular vein can be removed without vascular reconstruction; (2) if the bilateral internal jugular veins are affected, the affected vessels should be removed with vascular reconstruction. For patients with an affected common carotid artery, it is recommended to perform vascular reconstruction after excision. For patients with digestive tract and respiratory tract involvement, (1) if the tumors have not invaded the lumen, tumor removal is recommended; (2) if the tumors have invaded the lumen, it is recommended to remove the tumor and involved organs, with anastomosis/reconstruction/stoma. For patients with dyspnea, dysphagia, and other symptoms that inhibit removal, local palliative surgery (e.g., fistulation) is recommended. Postoperative radiotherapy, radioactive iodine therapy, and other systemic treatment are usually required [52, 64, 67, 70].

Recommendation 24: For recurrent cervical tumors invading the surrounding organs, R0 and R1 resection should be sought as much as possible, yet the overall factors and the advantages and disadvantages of the operation should be balanced.

*Surgical treatment of DTC with distant metastasis* Surgical resection of solitary distant metastasis improves the survival rate of patients with DTC [74]. Studies reported whether it was metastasized to the lung, bone, brain, or pancreas, patients with solitary metastases could even be cured [75–79]. The surgical indications are (1) lung metastasis: a solitary lung metastasis can be removed via surgical resection; (2) bone metastasis: for a solitary bone metastasis or when there is a high chance of bone pain, nerve involvement, or pathological fractures, surgical treatment can be considered; (3) Brain metastases: surgical treatment is recommended for solitary intracranial metastases and those with central nervous system (CNS) complications; (4) liver or pancreas metastases: solitary metastatic tumors can be removed, while balancing the surgical risks [52].

#### 3.3.2 Surgical treatment of MTC

*Surgical treatment for primary tumors of MTC* Surgery is currently the first choice and the only treatment for MTC. Currently, for hereditary MTC, the initial surgical treatment is usually total thyroidectomy. For patients with sporadic MTC, since the tumors are often bilateral and multifocal, the mainstream recommendation is total thyroidectomy. For sporadic MTC

patients with unilateral and small tumors, lobectomy with isthmusectomy can be performed, though this is still controversial [80, 81].

In some situations, MTC is diagnosed after unilateral lobectomy. In this case, the need for total thyroidectomy should be determined according to individual differences, and the potential risks and benefits of follow-up and supplementary surgery should be weighed. For patients with hereditary MTC, contralateral lobectomy should be performed since the contralateral lobe may already have tumors and the possibility of MTC in the future is close to 100%. In comparison, the incidence of sporadic MTC occurred in bilateral lobes was less than 10% [82]. Therefore, unless the patient has germline *RET* mutations, serum calcitonin after surgery or stimulation is significantly increased, or imaging shows a residual tumor, supplementary total thyroidectomy is not recommended [81, 83].

Recommendation 25: For hereditary MTC with a clear genetic test or a clear family history, total thyroidectomy should be performed, no matter the size and location of the tumor.

Recommendation 26: For sporadic MTC that has been confirmed by genetic testing, total thyroidectomy can be performed. If the tumor is unilateral and there are no other risk factors, lobectomy can be performed.

Recommendation 27: When hereditary MTC is diagnosed after unilateral thyroidectomy, total thyroidectomy should be performed.

Recommendation 28: When sporadic MTC is diagnosed after unilateral lobectomy, if the patient has *RET* germline mutations, the serum calcitonin level after surgery or stimulation is significantly increased, or imaging shows a residual tumor, total thyroidectomy is recommended.

*Surgical management of cervical lymph nodes in MTC* Cervical lymph node metastasis of MTC is similar to that of PTC. Whether the MTC is sporadic or hereditary, cN1a MTC patients should undergo therapeutic central lymph node dissection. For cN0 patients, bilateral prophylactic central-compartment neck dissection is recommended [42, 81].

For cN1b MTC patients, therapeutic lateral neck compartmental lymph node dissection should be performed. It is still controversial whether to perform prophylactic lateral neck compartmental lymph node dissection in patients with uninvolved lateral neck lymph nodes. Generally, when the number of central lymph node metastases is $\geq 4$ [84] or extraglandular invasion is found during surgery, it is recommended to perform lateral neck compartmental lymph node dissection on the affected side. If the preoperative serum calcitonin (Ctn) level is above 20, 50, 200, and 500 pg/mL, lymph node dissection should be performed in the ipsilateral central area and ipsilateral lateral area, contralateral central area, contralateral lateral area, and upper mediastinal area, respectively [85].

Hereditary MTC is called multiple endocrine neoplasia type 2 (MEN2). Such patients often have adrenal pheochromocytoma or hyperparathyroidism, which can lead to abnormal blood pressure and ion metabolism. Therefore, adrenal pheochromocytoma and primary hyperparathyroidism should be screened for before surgery. If adrenal pheochromocytoma is present, it should be treated first, and then the thyroid and parathyroid glands can be treated in the synchronous surgery.

Recommendation 29: Routine central-compartment neck dissection is recommended for patients with MTC.

Recommendation 30: For cN1b MTC patients, lateral neck compartmental and central-compartment neck dissection should be performed.

Recommendation 31: Prophylactic lateral neck compartmental lymph node dissection is generally not performed for MTC with uninvolved lateral neck lymph nodes. However, the decision must be made while considering central lymph node metastasis, serum Ctn level, and the primary tumor.

*Treatment of recurrent MTC* For patients with definite local or regional lymph node residual tumors or recurrence, a second operation should be considered. The scope of lymph node dissection can involve the central area, lateral neck, and upper mediastinal space. Ctn levels can decrease to normal levels after secondary surgery in about 1 / 3 of the patients, and the probability of subsequent distant metastasis is small if the Ctn level is significantly reduced [42].

Recommendation 32: For MTC patients with local residual tumors or tumor recurrence that can be surgically removed, a second operation should be considered.

#### *3.3.3 Surgical treatment of ATC*

ATC is a rare but highly fatal. The severity of the tumor should be clarified as soon as possible, before treatment.

With the participation of an MDT, the benefits and risks of treatment should be fully communicated with patients and their families to develop a comprehensive treatment plan. Surgery is an essential part of the treatment of ATC, especially for ATC patients with resectable tumors.

*Preoperative assessment* Due to the rapid progression of ATC, it is particularly critical to perform a rapid and accurate assessment before surgical intervention, which will help determine whether and what type of surgery is appropriate for patient. The assessment includes (1) tumor staging, including the scope of the tumor, invasion of surrounding organs, and presence of distant metastasis; and (2) comprehensive airway assessment: vocal cord activity, the extent of tumor invasion of the upper respiratory tract and digestive tract, and the conditions of the pharynx, larynx, and trachea [50].

Recommendation 33: Rapid and accurate preoperative assessment of ATC tumor staging and airway assessment should be carried out.

*Surgical options and scope of surgery for ATC patients* For patients with IVA or IVB ATC, it is necessary to determine whether the tumor is resectable. This is evaluated by such factors as the affected organs, whether satisfactory resection (R0/R1) can be obtained, and whether resection of the affected organs could lead to serious complications or risk of death. For patients with resectable ATC, after complete visible tumor resection (R0 or R1), adjuvant therapy should be followed to extend the survival time of the patient [86]. Survival in ATC patients who underwent surgery was significantly longer than in those who did not [87, 88].

For IVB ATC patients with extensive tumor invasion, it is unclear whether the resection of visceral and vascular structures can prolong survival. Radical and extensive organ resections can seriously lower their quality of life, and large surgical trauma and postoperative complications can delay subsequent radiotherapy and systemic treatment. Multiple targeted drugs have achieved good results in ATC patients [89].

IVC ATC patients gain very little benefit from surgery. If airway or esophageal obstruction occurs or is about to occur, local tumor removal may be considered to relieve symptoms [50].

Recommendation 34: For ATC that is expected to be R0/R1 (i.e., IVA and IVB), surgical treatment should be performed after MDT. Palliative surgery of ATC is not recommended.

Recommendation 35: Due to the extremely poor prognosis of ATC and the poor effectiveness of systemic treatment, extensive organ resections (e.g., laryngectomy, tracheotomy, esophagectomy, resection and reconstruction of large vessels, mediastinal dissection) are not recommended. MDT is recommended for decision-making.

*Tracheotomy in ATC patients* Airway assessment is critical throughout the treatment of ATC patients, because airway conditions may change at any time during the treatment. Tracheotomy is common in patients with ATC (approximately 40%) [90], but the role of tracheotomy in radical treatment and palliative treatment of ATC is complex, and the timing is critical. On the one hand, tracheotomy can open the airway to prevent death from suffocation and to provide opportunities for other treatments. On the other hand, tracheotomy can delay radiotherapy and targeted therapy, reducing the survival rate [91]. Therefore, the decision about tracheotomy should be made based on tumor factors as well as the patient's specific situation [50].

If the tumor severely invades or compresses the airway, and conventional tracheotomy and anesthesia intubation cannot be performed, extracorporeal membrane oxygenation can be considered.

Recommendation 36: The decision about tracheotomy in ATC patients should be made based on comprehensive assessment and individual situation.

Recommendation 37: Prophylactic tracheotomy is not recommended for patients who do not or likely will not have imminent airway obstruction.

Recommendation 38: If possible, tracheotomy should be performed by an experienced surgeon under preoperative intubation anesthesia.

#### *3.3.4 Application of endoscopic/robotic thyroid surgery in thyroid cancer treatment*

Endoscopic thyroid surgery (ETS) is a major advancement in thyroid surgery of the past 20 years. With the continuous development of medical devices and equipment, especially high-definition endoscopy and robot-assisted systems, ETS has been more widely applied [92]. According to the cavity construction method, ETS can be divided into the carbon dioxide inflation method and the noninflation method. Its surgical approach can be anterior cervical (short distance) or external cervical (long distance). The anterior cervical approach is a small-incision endoscopy-assisted method such as the Miccoli

procedure. There are many external cervical approaches. The most widely used approaches in China are the anterior thoracic approach, axillary approach, bilateral axillo-breast approach, and transoral approach. Different approaches have their own advantages and disadvantages [93–100].

The main advantage of ETS is that it realizes miniaturization and concealment of the surgical incision, sometimes even leaving no scar on the body surface. Thus, it satisfies the cosmetic wishes of patients. Second, the surgical field of view is large in ETS, which is conducive to the identification and protection of the parathyroid and RLN/superior nerve. ETS has several disadvantages as well. For instance, long-distance thyroidectomy is not minimally invasive and introduces new potential complications. It also has a long learning curve and poses technical challenges. Although some large-scale studies have shown that under the premise of strict screening of cases, ETS surgery achieved the same results as open surgery, most patients who underwent ETS were low-risk PTC patients. There is no randomized controlled study and no long-term follow-up data to compare ETS with conventional surgery [101, 102]. Therefore, the choice of ETS should be strictly based on the indications and must be performed by experienced surgeons. The surgeon should always put the oncological outcome and postoperative function prior to cosmetic result.

Recommendation 39: The principles and scope of ETS treatment must be consistent with those of open surgery.

Recommendation 40: ETS should be chosen only after comprehensive consideration of the patient's will, the tumor condition, and the surgical approach needed. The choice of robotic thyroid surgery also requires comprehensive consideration of health economic factors.

#### *3.3.5 Intraoperative protection of parathyroid glands and treatment of postoperative hypoparathyroidism*

Hypoparathyroidism is a common complication of thyroid surgery. It severely lowers the quality of life of patients, especially permanent hypoparathyroidism. Therefore, intraoperative protection of the parathyroid glands is very important. The general strategy to protect parathyroid glands in thyroid surgery should follow the "1 + X" principle, where "1" means that every parathyroid gland found during surgery should be treated as the patient's only parathyroid gland, so it should be carefully protected, and it also means the surgeon should identify one parathyroid gland as accurately as possible in each thyroid surgery; and "X" means that efforts should be made to protect as many parathyroid glands as possible during surgery.

Accurate identification of parathyroid glands is the premise of protection. The refined capsular dissection technique is the key way to avoid accidental removal of parathyroid glands and protect their blood supply. The inferior parathyroid gland is often closely associated with the thymus. Therefore, if the thymus is not involved by the tumor, the thymus should be preserved during central lymph node dissection. In addition, surgical energy instruments and electrocautery should be used cautiously during operation to avoid thermal damage to the parathyroid glands [83].

Once the surgical specimen is removed, any parathyroid glands that may have been incidentally removed should be carefully examined. Autologous transplantation should be performed for parathyroid glands that have compromised blood supplies or that were incidentally resected. Parathyroid autotransplantation is most often done by the particle embedding method or the homogenous injection method. Intraoperative rapid frozen pathological examination can be performed before autologous transplantation to identify parathyroid tissue.

Recommendation 41: Refinement capsular dissection and careful examination should be conducted to protect each parathyroid gland during thyroid cancer surgery.

Recommendation 42: Intraoperative autologous transplantation should be performed for parathyroid glands that have a compromised blood supply or were incidentally resected.

#### *3.3.6 Protection of the RLN and superior laryngeal nerve and complication management during thyroid surgery*

Dysphonia caused by injury to the RLN and/or the external branch of the superior laryngeal nerve (EBSLN) is a common complication in thyroid surgery. The rate of RLN injury is approximately 3–5%, though this may be underestimated and the actual number may be close to 10%. The incidence of EBSLN injury is 5–28% [1].

Thyroid surgery, especially reoperation for recurrent tumors, is a risk factor for RLN injury. Exposure of the RLN can avoid nerve damage and ensure the thoroughness of the surgery. The surgeon should be very familiar with the anatomical structures and variations of bilateral RLNs, especially the variation of the right non-recurrent laryngeal nerve, which is often accompanied by right subclavian artery course variation. CT scans should be carefully reviewed before surgery. The existence of a left non-recurrent laryngeal nerve is extremely rare and is related to situs inversus. The protection of the RLN mainly depends on the surgeon's experience and operating technique. The surgery should be as gentle as possible, and instruments should be used while avoiding stretching and thermal damage. The surgeon should also be familiar with a variety of RLN exposure methods and select the best one according to the surgeon's preference, tumor conditions, and surgical approach taken.

The protection of the EBSLN is achieved mainly through visual recognition and region protection, or a combination of the two. Not all EBSLNs can be exposed, and the key is to clearly expose the nonvascular space between the upper pole of the thyroid and the cricothyroid muscle. If the EBSLN can be exposed, it can be protected visually; otherwise, fine dissection should be used patiently close to the upper pole of thyroid, and the branches of the upper pole vessels should be identified.

In recent years, intraoperative neuromonitoring (IONM) has been widely used in thyroid surgery. By combining functional and anatomical information, it can realize intraoperative navigation, rapid RLN identification, variation prediction, and early detection and mechanistic explanation of RLN injury. IONM is of great value in some complicated or recurrent thyroid surgeries.

Unilateral RLN injury during thyroid surgery can lead to postoperative hoarseness. Restoration of nerve function depends on the nerve preservation condition during the surgery, and neurotrophic drugs may be prescribed. Bilateral RLN injury may lead to breathing difficulties, which requires tracheotomy or chordectomy. If the nerve function has not recovered 6 months after surgery, a specialist should be consulted for further treatment. RLN tears should be repaired and reconstructed, though the effects of such methods are still not clear. Most of the symptoms of EBSLN injury can be gradually relieved or improved spontaneously through contralateral compensation. The symptoms can last from several days to several months. Generally, EBSLN function can be recovered to varying degrees within 2 to 3 months. Neurotrophic drug treatment is the main treatment for EBSLN injury.

Recommendation 43: The RLN should be routinely exposed to facilitate visual protection during thyroid surgery.

Recommendation 44: Visual recognition or regional protection should be used in thyroid surgery to avoid EBSLN injury.

Recommendation 45: For some complex, difficult, or recurrent thyroid cancers, IONM techniques can be considered to protect the RLN and EBSLN.

#### *3.3.7 Treatment of other complications*

Other common complications of thyroid surgery include postoperative hemorrhage and lymphatic fistula. The surgeon should be familiar with the thyroid and cervical anatomy, which can help to reduce the incidence of the above complications. If a complication occurs, it needs to be actively treated. For patients with neck swelling and suspected hemorrhage, pressure dressing should be avoided. Cervical hematocele should be removed as soon as possible, the airway should be kept unobstructed, and the operation area should be searched for bleeding. The treatments for postoperative chylorrhea include diet control, local compression, somatostatin application, *Pseudomonas aeruginosa* injection, reoperation, and others. For patients with long-term chylorrhea, the albumin and ion levels should be monitored to prevent hypoalbuminemia and ion disorders.

Recommendation 46: Close attention should be paid to the operation area and drainage fluid. If there is bleeding in the operation area, it should be treated actively while keeping the airway unobstructed. If necessary, emergency surgery should be performed for hemostasis.

Recommendation 47: For patients who have undergone lateral neck compartmental lymph node dissection, a low-fat diet is recommended postoperatively, and attention should be paid to the occurrence of drainage and chylorrhea.

#### *3.3.8 Treatment of DTC in patients with other thyroid/parathyroid diseases*

*Treatment of DTC in patients with hyperthyoidism* When hyperthyoidism (Low TSH or combined T3 and T4 increas) is present in DTC patients, thyrotropin receptor antibody (TRAb) test, thyroid iodine uptake rate, and thyroid static imaging should be conducted to identify the cause of hyperthyoidism. When DTC is combined with grave's disease (GD), toxic multinodular goiter (TMNG), and toxic adenoma (TA), the thyroid function should be restored with antithyroid drugs before any thyroid surgery [103]. Total thyroidectomy should be performed for DTC patients with GD or TMNG [103]. For those patients with DTC and TA, the clinicopathological characteristics of DTC and TA should be considered comprehensively to choose lobectomy with isthmusectomy or total thyroidectomy.

*Treatment of DTC in patients with hyperparathyroidism* When hyperparathyroidism may be present in DTC patients, dual-phase $^{99m}$Tc-MIBI scintigraphy, ion examination, 25-hydroxy vitamin D test, and renal function need to be performed. Given a history of chronic kidney disease, primary, secondary, and tertiary hyperparathyroidism can be distinguished. In addition, parathyroid MIBI scintigraphy helps to locate the parathyroid glands before surgery.

During the thyroid surgery, parathyroidectomy should be performed at the same time to treat hyperparathyroidism, and the indications for parathyroidectomy should follow the clinical guidelines for hyperparathyroidism [104, 105]. Preoperative ultrasound, MIBI, and other examinations may not accurately locate the enlarged parathyroid

glands. Intraoperative parathyroid hormone measurement can be carried out to verify the completeness of the parathyroidectomy. Parathyroid hormone and blood calcium levels should be monitored after surgery to help manage early postoperative hypocalcemia and long-term hypoparathyroidism.

Recommendation 48: Total thyroidectomy should be performed when GD or TMNG is present in DTC patients. When TA is present in DTC patients, the clinicopathological characteristics of the tumor and TA should be considered comprehensively so as to performe lobectomy with isthmusectomy or total thyroidectomy. When hyperparathyroidism is present in DTC patients, it should be treated during surgery.

### 3.4 Postoperative evaluation

#### *3.4.1 Postoperative evaluation of DTC*

*Significance and role of postoperative evaluation of DTC* Postoperative evaluation is critical in tailoring $^{131}$I therapy for DTC patients who have undergone total/subtotal thyroidectomy. Three components are primarily taken into consideration: tumor–node–metastases (TNM)-based assessment of the risk of death, assessment of the risk of recurrence, and real-time ongoing assessment. The purpose is to determine the risk of relapse and death not only based on postoperative pathology, but also considering that the risk of recurrence and specific mortality may change over time and along with prior treatment, thus the real-time disease state assessment would be the focus. In some cases, the risk of patient may be upgraded due to the finding of previously undetected metastases, which helps prevent the patient from $^{131}$I undertreatment; while for some high-risk cases based on postoperative pathology, whose risk may be downgraded after effective treatment upon real-time assessment, thus prevent them from overtreatment of $^{131}$I [106]. Therefore, the consideration by integrating TNM stage, the risk of relapse, and real-time disease status would be helpful for real-time evaluation of postoperative risk, and postoperative $^{131}$I tailoring, particularly in clarifying the purpose and potential benefits [107, 108].

*Postoperative staging (AJCC/UICC TNM, 8.$^{th}$ Edition)* The 8$^{th}$ Edition TNM staging guideline issued by American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most commonly used system for postoperative staging of DTC (Table 2) [109], which is mainly based on postoperative pathology. It assists in predicting the tumor-specific survival of DTC patients [106, 110, 111].

*The risk of recurrence of DTC* A three tiered stratification is proposed similar to the ATA guideline as low, moderate, or high in DTC patients to predict the risk of recurrence, primarily based on tumor size, characteristics of lymph node metastasis, the extent of vessel invasion, and molecular and pathological characteristics, has been demonstrated its potential in guiding clinical decision making [40]. Suspicious increase of stimulated Tg pre-131I is associated with high-recurrence risk both in adult and pediatric patients [112]. The risk of recurrence can be determined as per factors revealed by the corresponding research [1] (Table 3).

*Clinical implication of response to prior therapy in patients with DTC* Response to prior therapy such as surgery facilitates the real-time ongoing assessment to define the disease status in patients with DTC. The response assessment system was developed with reference to the system proposed by Tuttle et al. and revised by Vaisman et al. (Table 4) [113, 114]. It is used to assess the patient response to prior treatment based on pathology, real-time serological findings and imaging (structure and function).

Recommendation 49: Integrating of postoperative TNM staging, analysis of the risk of relapse, and real-time efficacy assessment helps to evaluate the risks of recurrence and death as well as the prognosis, thereby providing the basis for subsequent, e.g. $^{131}$I therapy.

*How to perform postoperative assessment* Patients at any level of risk, especially those with moderate or high risk after total/subtotal thyroidectomy, should be referred for real-time postoperative assessment.

Serological evaluation includes Tg, TgAb, and TSH. Serum Tg usually reaches nadir 3–4 weeks after surgery; rising suppressiveTg indicates persistent disease or relapse [115, 116]. Extremely low Tg without TgAb interference indicates significantly low risk of relapse and minimal or without thyroid remnant [117]. The predictive value of the postoperative Tg value will be significantly influenced by various factors including the amount of residual thyroid cancer and/or normal thyroid tissue, the TSH level at the time of Tg measurement, the functional sensitivity of the Tg, and prior treatments. Therefore, ongoing monitoring is more helpful for identifying remnant thyroid and suspicious relapse/metastasis [118, 119]. The measurement of Tg will be significantly interfered with the existence of high level of antiTg antibody. In this setting, ongoing monitoring of TgAb would be helpful to identify the disease status [120, 121]. The measurements of serum

**Table 2** TNM staging of DTC (AJCC/UICC, 8th Edition)

| Basic Indicator | Definition | |
|---|---|---|
| Tx | Primary tumor cannot be assessed | |
| T0 | No evidence of primary tumor | |
| T1 | Tumor ≤ 2 cm in greatest dimension, limited to the thyroid | |
| T1a | Tumor ≤ 1 cm in greatest dimension, limited to the thyroid | |
| T1b | Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid | |
| T2 | Tumor diameter > 2 cm but ≤ 4 cm in greatest dimension, limited to the thyroid | |
| T3 | Tumor > 4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles | |
| T3a | Tumor diameter > 4 cm, limited to the thyroid | |
| T3b | Gross extrathyroidal extension invading only strape muscles (sternohyoid, sternothyoid, thyrohyoid or omohyoid muscles) from a tumor of any size) | |
| T4 | Includes gross extrathyroidal extension beyond the strap muscle | |
| T4a | Gross extrathyroidal extension invading subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve | |
| T4b | Gross extrathyroid extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size | |
| Nx | Regional lymph nodes cannot be assessed | |
| N0 | No evidence of regional lymph node metastasis | |
| N0a | One or more cytologically or histologically confirmed benign lymph nodes | |
| N0b | No radiographic or clinical evidence of regional lymph node metastasis | |
| N1 | Metastasis to regional nodes | |
| N1a | Metastasis to level VI and VII (pretracheal, paratracheal, paralaryngeal/Delphian, or upper mediastinal lymph nodes), This can be unilateral or bilateral | |
| N1b | Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes | |
| M0 | No distant metastasis | |
| M1 | Distant metastasis | |
| Stage | Staging criteria for different age groups | |
| | < 55 years | ≥ 55 years |
| I | Any T<br>Any N<br>M0 | T1NxM0<br>T1N0M0<br>T2NxM0<br>T2N0M0 |
| II | Any T<br>Any N<br>M1 | T1N1M0<br>T2N1M0<br>T3N0M0<br>T3N1M0 |
| III | None | T4aN0M0<br>T4aN1M0 |
| IVa | None | T4bN0M0<br>T4bN1M0 |
| IVb | None | Any T<br>Any N<br>M1 |

Tg and TgAb are affected by TSH level, thus it is important to simultaneously measure TSH level.

Postoperative imaging evaluations usually include cervical ultrasound and diagnostic iodide whole-body scanning (DxWBS), other studies may be considered as needed, such as plain CT, whole-body bone scan, magnetic resonance imaging (MRI), and $^{18}$F-FDG positron-emission tomography (PET)/CT. In case of discrepancy between imaging and serology, fine-needle aspiration (FNA) or histological examination and molecular testing may be considered to further determine the nature of the suspicious lesions seen on imaging.

Recommendation 50: Postoperative ongoing assessments include real-time monitoring of serology (TSH, Tg, TgAb) and imaging (such as DxWBS, cervical ultrasound) to provide the basis for subsequent $^{131}$I therapy, efficacy prediction, and ongoing assessment.

#### *3.4.2 Postoperative evaluation of MTC*

*Evaluation of the efficacy of the initial operation and the risk of relapse* After the initial operation of MTC, the surgical outcome and the risk of relapse and metastasis should be evaluated to develop treatment and follow-up

**Table 3** The Risk Stratification of DTC

| Risk Stratification | Criteria |
|---|---|
| Low risk (≤ 5%) | - All of the following criteria:<br>No local or distant metastases;<br>All macroscopic tumor has been resected;<br>No tumor invasion of loco-regional tissues and structures;<br>No aggressive histology (e.g., tall cell, hobnail, columnar cell carcinoma);<br>In either RAI diagnostic whole-body scan or post-$^{131}$I treatment whole -body scan, there no RAI-avid foci or metastasis outside the thyroid bed;<br>No vascular invasion;<br>cN0 or pN1: ≤ 5 lymph node micrometastases (< 0.2 cm in largest dimension)<br>- Follicular variant (FV) of papillary thyroid carcinoma (PTC) limited to the thyroid, without capsular invasion<br>- Well-differentiated FTC confined to the thyroid, with capsular invasion and < 4 vessel invasions<br>- Papillary thyroid microcarcinoma (PTMC) limited to the thyroid, unifocal or multifocal, with or without *BRAF*$^{V600E}$ mutation |
| Intermediate risk (6–20%) | - Microscopic tumor invasion of the perithyroidal soft tissues<br>- RAI-avid metastatic on whole-body scan after the first $^{131}$I treatment session<br>- Aggressive variant of DTC (such as tall cell, hobnail, columnar cell)<br>- PTC with vessel invasion<br>- clinical N1 or: > 5 pathological N1 with all involved lymph nodes metastases < 3 cm in largest dimension<br>- Multifocal PTMC with extrathyroidal extension and *BRAF*$^{V600E}$ mutated (if known) |
| High risk (> 20%) | - Macroscopic invasion of tumor into perithyroidal soft tissues (gross ETE)<br>- Incomplete tumor resection<br>- Distant metastases<br>- Postoperative serum Tg suggestive of distant metastases<br>- pathologic N1 with any metastatic lymph node ≥ 3 cm in largest dimension<br>- Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion) |

plans. The prognosis of MTC depends mainly on the tumor stage at the time of initial diagnosis and the outcome of surgical resection. In addition, patient age, mutation site, and postoperative calcitonin doubling time are closely related to the prognosis [81, 122].

Significance of TNM staging in postoperative evaluation of MTC (Table 5) The outcome of the initial operation is a key factor in the prognosis. In 2013, Tuttle and Ganly outlined the risk stratification for DTC and proposed four categories for MTC after the initial operation: (1) biochemical response: complete tumor resection, undetectable Ctn; (2) structural response: elevated tumor markers (Ctn and carcinoembryonic antigen (CEA)), without imaging evidence of lesions; (3) anatomical remnant: ongoing anatomical remnant or distant metastasis; and (4) indeterminate disease response: nonspecific imaging abnormalities, biochemical abnormalities, or undetectable anatomical remnant. The 10- year survival rate is 95–97% in patients with biochemical response [123], and the 5- and 10- year survival rates are 80–86% and 70% in patients with persistently elevated Ctn, respectively [124].

Recommendation 51: All MTC patients should be followed up for life. The follow-up procedures and schedule should be determined from gene mutations, TNM stage, surgical outcome, postoperative Ctn and CEA, and Ctn doubling time.

#### *3.4.3 Postoperative evaluation of ATC (Table 6)*

For ATC, preoperative evaluation rather than postoperative evaluation is more important. Most ATC patients have a high tumor burden with rapid progression. The tumor stage may change rapidly and should be determined promptly and accurately at the time of diagnosis to determine the surgical indications and potential surgical options. Postoperative evaluation should first clarify the type of surgery and the type of margin to determine the disease state and subsequent treatments (Table 6), while taking into account the patient's general condition, including treatment tolerance, as well as the risks and benefits of radiotherapy and systemic treatment.

ATC patients who have undergone R0 or R1 resection may receive standard fractionated intensity-modulated radiotherapy (IMRT) combined with systemic therapy if their general condition is good without signs of metastasis and they want to receive active treatments. Radiotherapy should start 2 to 3 weeks (no later than 6 weeks) after operation, once swelling has subsided. Cytotoxic chemotherapy usually starts before radiotherapy and may be started within the first week after surgery if possible [50].

Patients who have undergone R2 resection or have unresectable disease (without metastatic disease) but are in good general condition may receive standard fractionated IMRT and systemic chemotherapy if they want to receive active treatments. In addition, ATC patients

**Table 4** Stratifications of response to therapy in patients with DTC

| Efficacy | Excellent Response (ER) | Indeterminate Response (IDR) | Biochemical Indeterminate Response (BIR) | Structural Indeterminate Response (SIR) |
|---|---|---|---|---|
| Definition | Negative imaging and either suppressed Tg < 0.2 ng/ml or stimulated Tg < 1 ng/ml; | Nonspecific findings on imaging studies; Faint uptake in thyroid bed on RAI scanning suppressed Tg: 0.2 ng/ml ≤ Tg < 1 ng/ml, or stimulated Tg: 1 ng/ml ≤ Tg < 10 ng/ml; or anti-Tg antibody (TgAb): stable or declining in the anbsence of structural or functional disease; | Negative imaging Suppressive Tg ≥ 1 ng/ml or stimulated Tg ≥ 10 ng/ml or rising TgAb level | Structural or functional evidence of disease with any Tg level with or without TgAb |

**Table 5** TNM staging of MTC (8th Edition)

| Stage | |
|---|---|
| I | T1N0M0 |
| II | T2-3N0M0 |
| III | T1-3N1aM0 |
| IVa | T4aN0-1bM0/T1-3N1bM0 |
| IVb | T4N0M0 |
| IVC | Tx-4bNx-1bM1 |

**Table 6** TNM staging of ATC (8th Edition)

| Staging | |
|---|---|
| IVa | T1-3aN0M0/T1-3aNxM0 |
| IVb | T1-3a N1M0 |
| IVb | T3bNx-1bM0 |
| IVb | T4Nx-1bM0 |
| IVC | Tx-4bNx-1bM1 |

with *BRAF*$^{V600E}$ mutation may also receive BRAF/MEK inhibitors.

Patients with unresectable disease per initial evaluation may undergo surgery if the tumor is considered resectable after radiotherapy and/or systemic chemotherapy (with or without BRAF/MEK inhibitors).

### 3.5 Postoperative $^{131}$I therapy for DTC

#### *3.5.1 Clinical significance of $^{131}$I therapy for DTC*

For DTC, $^{131}$I therapy plays the following roles:

(1) Treatment of persistent disease (TPD): treatment for unresectable local or distant metastases, with the goal of delaying disease progression, improving disease-related survival, and improving quality of life.
(2) Adjuvant therapy (AT): treatment of patients with postoperative suspicious biochemical remnants without imaging evidence, or ATA high-risk DTC patients, with the goal of reducing the risk of recurrence and tumor-related death.
(3) Remnant ablation (RA): removal of any thyroid remnant after total or subtotal thyroidectomy in order to achieve an excellent response (ER) as soon as possible, easier monitoring of disease progression with serum Tg or $^{131}$I WBS during follow-up, and DTC restaging.

*Therapy of persistent disease* Therapy of Persistent Disease (TPD) is the definite goal of $^{131}$I therapy, but treatment response varies between RAI-avid lesions and RAI-refractory lesions. $^{131}$I therapy could improve disease-free survival (DFS) and overall survival (OS) for patients with RAI-avid lesions while not for those with RAI-refractory lesions [125–127]. The study showed that the 10-year survival rate is significantly lower in patients with RAI-refractory (RAIR) DTC than those with good iodine intake (10% vs 60%) [127].

Remarkably, the order of remnant ablation, adjuvant therapy, and therapy of persistent disease is not progressive per se. For patients with recurrence, metastasis, or unresectable residual disease according to initial pretreatment assessment, TPD should be directly used instead of RA following TPD. Repeat $^{131}$I treatment should be performed based on a comprehensive evaluation, including the response to previous $^{131}$I therapy, RAI-avid lesions detected on diagnostic whole-body scan (DxWBS), and a favorable benefit/risk ratio [128, 129].

Recommendation 52: DTC patients with recurrence, metastasis, or suspicious residual disease according to initial pretreatment evaluation are recommended to receive TPD; repeat $^{131}$I therapy should be performed based on the response to previous treatment, DxWBS results, and a favorable benefit/risk ratio.

*Adjuvant therapy* Adjuvant therapy is mainly used in patients without confirmed imaging evidence, including those with (1) elevated postoperative serum Tg or indeterminate biochemical response mismatched with DxWBS suggesting thyroid remnants; and (2) clinically suspetecd postoperative residual disease without definitive imaging evidence [130]. The possibility of successful removal by upfront treatment (such as surgery) cannot be excluded.

For a biochemical indeterminate response (BIR), such as unexplained elevated serum Tg [ps-Tg > 10 μg/L]), the possibility of microcarcinomas or occult lesions that cannot be detected by current imaging techniques should be considered. At present, no optimal ps-Tg cut-off values have been established to guide decision-making for $^{131}$I therapy. For high-risk patients, $^{131}$I adjuvant therapy is routinely recommended because of the benefits on OS and DFS [131]. The benefit of 131I adjuvant therapy is still controversial for intermediate-risk patients, and no significant benefit on OS or DFS for low-risk patients [131–133].

Recommendation 53: Adjuvant therapy could be selectively used for patients with BIR or as prophylactic therapy for high-risk patients. The patients should be informed the risks and benefits of adjuvant therapy in advance.

*Remnant ablation* Remnant ablation is helpful to the stratification of serum Tg and disease monitoring after thyroidectomy [134], and improve the sensitivity of DxWBS in diagnosing DTC metastases, assisting in staging [1]. Studies demonstrated that remnant ablation did not improve disease-specific survival (DSS) or DFS [131–133]. When using the response to therapy classification to measure the prognosis and benefits, it's reported that patients could achieve ER earlier after remnant ablation [135].

$^{131}$I therapy is not recommended for remnant ablation in children with DTC.

Recommendation 54: Remnant ablation is helpful for accurate staging and disease monitoring with Tg and DxWBS; it's also helpful for low to intermediate-risk patients to achieve ER as soon as possible, reducing the frequency of follow-up.

#### 3.5.2 Pretreatment preparation

*Low iodine preparation* The response to $^{131}$I therapy depends on the dose of $^{131}$I that uptaked by thyroid remnant and DTC tissue. To increase $^{131}$I uptake and improve the therapy response, the patients should maintain a low iodine status (iodine intake < 50 μg/d) for 2 to 4 weeks before $^{131}$I therapy, including low-iodine diet, avoiding amiodarone and other drugs that affect iodine intake or metabolism, avoiding skin disinfection using iodophor, avoiding iodine-containing contrast agents or performing $^{131}$I therapy after 1–2 months [136]. Considering the individual condition and metabolism, the timing of $^{131}$I therapy should be based on the measurement of urinary iodine.

*TSH elevation* Generally, a pre-treatment TSH of > 30 mIU/L has been required in preparation for $^{131}$I therapy. Two modalities of TSH elevation were usually adopted: (1) levothyroxine (L-$T_4$) withdrawal for 2–4 weeks to increase the secretion of endogenous TSH; (2) exogenous TSH administration [recombinant human TSH (rhTSH) 0.9 mg qd im for two days].

*Routine tests* In addition to the aforementioned items for real-time ongoing evaluation, examinations including routine blood and urine, liver and kidney function, parathyroid hormone, electrolytes, electrocardiogram (ECG), and serum human chorionic gonadotropin (for women with childbearing age) should also be performed to rule out contraindications for radionuclide therapy such as renal failure and pregnancy.

DxWBS can identify postoperative remnants and suspicious recurrent/metastatic lesions before $^{131}$I therapy. Meanwhile, it could intuitively detect the systemic RAI-avid lesions, iodine uptake capacity, and tumor burden, to predict the response to RAI therapy. The distribution of radioactivity in vital organs reflected on DxWBS suggests the potential side effects of $^{131}$I therapy. All the above would affect the decision-making of 131I therapy and clinical management [137, 138].

*Physician–patient communication, patient education, and informed consent* Patients and their families should be informed about the purpose, procedures, and potential adverse reactions of RAI treatment; receive education on radiological safety protection; and sign the informed consent form for $^{131}$I therapy.

Recommendation 55: Patients should maintain low-iodine status (iodine intake < 50 μg/day) for 2–4 weeks before $^{131}$I therapy, and avoid using drugs that affect iodine intake or metabolism.

Recommendation 56: Serum TSH > 30 mU/L was required through L-$T_4$ withdrawal or rhTSH administration before $^{131}$I therapy.

Recommendation 57: Before $^{131}$I therapy, patients and their families should receive education on radiological safety protection, and women with childbearing age must have a negative pregnancy test.

#### 3.5.3 Dosing decision for $^{131}$I therapy

*$^{131}$I dose for remnant ablation* The recommended dose for remnant ablation is 30 mCi (1.11 GBq) [139, 140]. The dose may be increased in the case of a large amount of thyroid remnant, high Tg level, and the presence of other risk factors (such as age ≥ 55).

Recommendation 58: The recommended $^{131}$I dose for remnant ablation is 30–50 mCi. A higher personalized dose (100 mCi) may be given in the case of a large amount of thyroid remnant and other factors.

*$^{131}I$ dose for adjuvant therapy* There is not enough evidence available to support the recommended dose of $^{131}I$ for adjuvant therapy. It is generally 1.35–5.55 GBq (50–150 mCi), and the specific dose should be determined combining with the risk factors [1, 141].

Recommendation 59: The recommended $^{131}I$ dose for adjuvant therapy is 50–150 mCi, and a personalized dose is encouraged based on the pretreatment evaluation.

*$^{131}I$ dose for treatment of persistent disease* The optimal dose of $^{131}I$ for treatment of local or distant metastases has not been determined. Empirical fixed dose, the maximum tolerated radiation absorbed dose, or a calculated dose based on foci absorption can be selected as appropriate. Ultimately, the response to $^{131}I$ treatment of persistent disease depends on the lesion's dose absorption (Gy) and its sensitivity to ionizing radiation. Patients with lymph node and pulmonary micrometastases could achieve complete remission with administered RAI activities of > 80–100 Gy but do not respond with an activity of < 20 Gy [142–144].

The specific $^{131}I$ activity range is 3.70–5.55 GBq (100–150 mCi) for cervical lymph node metastases, 5.55–7.40 GBq (150–200 mCi) for lung metastases, 5.55–7.40 GBq (150–200 mCi) for bone metastases, and 3.7–7.4 GBq (100–200 mCi) for brain metastasis (just as adjuvant therapy after surgery or radiotherapy) [145, 146]. For patients over 70 years of age, the maximum tolerated radiation absorbed dose should be noted, which generally should not exceed 5.55 GBq (150 mCi) [1]. The RAI activity for adjuvant therapy and treatment of persistent disease should be 5/6 of the adult dose for children and adolescents aged 15 years, 1/2 of the adult dose for those aged 10 years, and 1/3 of the adult dose for those aged 5 years [147].

Recommend 60: The recommended $^{131}I$ dose for treatment of persistent disease is 100–200 mCi, and a personalized dose is encouraged based on the pretreatment evaluation and foci absorption dose.

#### 3.5.4 Short-term and long-term adverse reactions of $^{131}I$ therapy

Short-term adverse reactions: Common adverse reactions include mild, transient neck pain and swelling that improves over time, occasional salivary gland damage [148, 149], taste change, oral mucositis, lacrimal gland damage, etc. [150]. Most adverse reactions always occur within 1–5 days and resolve without special treatment or only require symptomatic care. Some patients with extensive lung metastases may develop radiation pneumonitis and pulmonary fibrosis after repeated $^{131}I$ therapy [151].

Long-term adverse reactions: $^{131}I$ therapy does not increase the risk of infertility, miscarriage, congenital malformations, or congenital dysplasia [152, 153]. The risk of secondary malignancy is low after $^{131}I$ therapy for DTC [154].

#### 3.5.5 Timing and dose of repeat $^{131}I$ therapy

As with initial therapy, pretreatment evaluation for repeat $^{131}I$ therapy is a process of evidence-based decision-making.

For patients with structural incomplete response (SIR) to TPD, repeat $^{131}I$ therapy may be considered in the case of unresectable, RAI-avid lesions that respond to previous $^{131}I$ therapy. However, the timing of repeat $^{131}I$ therapy is still controversial. For patients with RAI-avid lung micrometastases, repeated $^{131}I$ treatment could be considered in 6–12 months [1]. For patients with macrometastases and declining Tg/TgAb, closely monitoring is needed, and re-evaluation should be performed until Tg/TgAb stop decreasing. Repeat $^{131}I$ therapy may be considered when pretreatment DxWBS indicates RAI-avid lesions. If no significant improvement is observed in serology and imaging assessment after $^{131}I$ therapy, additional treatment should be considered carefully, and further management should be chosen by MDT to HIM.

Recommendation 61: For patients with lung micrometastases respond to $^{131}I$ therapy, repeat $^{131}I$ treatment could be considered in 6–12 months.

Recommendation 62: For patients with macrometastases and declining serum Tg/TgAb after $^{131}I$ therapy, closely monitoring is needed, and re-evaluation should be performed until Tg/TgAb stop decreasing. Repeat $^{131}I$ therapy may be considered when pretreatment DxWBS indicates RAI-avid lesions.

#### 3.5.6 Indication and timing of repeat $^{131}I$ therapy for patients with prmDTC evaluated as SIR

The response to previous $^{131}I$ therapy should be evaluated based on RAI uptake capacity, size, and serum Tg/TgAb changes. Repeat $^{131}I$ therapy should be performed based on serological and imaging benefits, or terminated until the lesions no longer respond to $^{131}I$ therapy, known as RAIR.

The timing of repeat $^{131}I$ therapy remains controversial. For responders (declining Tg and/or TgAb, shrinking lesions with RAI uptake), repeat $^{131}I$ therapy could be performed every 6–12 months and then less frequently after 2 years [155]. For those with low absorbed RAI activities after repeated treatments (< 20 Gy) [156], the

risks and benefits should be carefully considered to discern any benefits of repeat $^{131}$I therapy.

Recommend 63: Objective evaluation of serological (Tg/TgAb) and imaging responses to $^{131}$I therapy should form the basis for repeat $^{131}$I therapy.

#### *3.5.7 Diagnosis of RAIR-DTC*

Approximately 5–25% of DTC patients developed distant metastasis, of whom approximately one-third experienced dedifferentiation of tumor cell morphology and function, and loss of the ability to concentrate iodine during the natural course of disease or treatment, which ultimately developed to RAIR-DTC [157]. The definition of RAIR-DTC requires a comprehensive evaluation from nuclear medicine, imaging, oncology, endocrinology, and other disciplines. In the absence of exogenous iodine interference, RAIR-DTC is defined (not absolute criteria) if any of the following criteria is met (with TSH stimulation), indicating little benefit of additional $^{131}$I therapy: (1) the first Rx-WBS indicates the metastatic lesions do not concentrate RAI; (2) the tumor tissue gradually loses the ability to concentrate RAI after previous evidence of RAI-avid disease; (3) RAI is concentrated in some lesions but not in others; or (4) metastatic disease progresses despite significant concentration of RAI [1].

Structural or functional imaging examinations is helpful to further identify the location, size, number, and extent of invasion of RAIR-DTC lesions [1, 158–164], providing the evidence for appropriate treatment strategies [165, 166]. In addition, ongoing Tg monitoring not only contributes to evaluate the response to $^{131}$I therapy, but also has a certain value in predicting RAIR-DTC [167].

Recommendation 64: The diagnosis of RAIR-DTC may be affected by many factors, such as RAI uptake capacity, response to treatment, dynamic changes in response, etc.

#### *3.5.8 Treatment strategy for RAIR-DTC*

Patients with RAIR-DTC are unlikely to benefit from $^{131}$I therapy alone, therefore the strategy of $^{131}$I therapy alone should be terminated to prevent unnecessary radiation damage. The treatment strategy for RAIR-DTC should be considered based on tumor burden, accompanying symptoms, Eastern Cooperative Oncology Group (ECOG) score, Response Evaluation Criteria in Solid Tumors (RECIST), patient preference, social support and so on, weighing the benefits and risks individually. The natural course of RAIR-DTC is heterogeneous, with the median time to progression ranges from 1.31 to 1.63 years [168, 169]. For RAIR-DTC patients with stable disease and without apparent tumor-related symptoms, starting targeted therapy early may seriously lower the quality of life due to treatment-related adverse reactions. For patients with tumor-related symptoms or rapidly progressive disease, surgery, radiotherapy, and seed implantation may be considered to alleviate local symptoms based on a comprehensive evaluation. For patients with multiple metastases, unresectable lesions, rapidly progressive disease, and a high tumor burden, molecular targeted therapy may be considered.

Recommendation 65: A diagnosis of RAIR-DTC indicates that the patient is unlikely to benefit from $^{131}$I therapy alone and should be closely monitored and followed up under TSH suppression therapy.

#### *3.5.9 Follow-up of RAIR-DTC*

The follow-up of RAIR-DTC is aimed to monitor disease condition. The monitoring contents mainly include serum TSH, Tg, TgAb, and imaging examinations according to the location of metastases, such as CT (to monitor lung nodules), enhanced CT (to examine the relationship between tumor and surrounding tissues), enhanced MRI (to identify brain metastases), and, if necessary, $^{18}$F-FDG PET/CT (to determine systemic tumor burden). Disease progression must be confirmed with imaging examinations according to RECIST v1.1 [170]. The patients should be followed up every 3–6 months.

Recommendation 66: Regular serological and imaging follow-up should be performed for patients with RAIR-DTC to determine the disease condition and decide further treatments.

### 3.6 Postoperative endocrine therapy

#### *3.6.1 The main contents of postoperative endocrine therapy for thyroid cancer*

For thyroid cancer, postoperative endocrine therapy includes three components: TSH suppression therapy for DTC; thyroid hormone replacement therapy for PDTC, MTC, and ATC; and postoperative treatment for hypoparathyroidism.

#### *3.6.2 The goal of TSH suppression therapy for DTC*

The goals of postoperative TSH suppression therapy are to treat thyroid hormone deficiency caused by surgery [171] and inhibit the growth of DTC cells [172].

Stratification of TSH suppression target based on initial risk of recurrence has been recommended since 2012 [173, 174]. Evidence suggests that for high-risk DTC patients, postoperative suppression of TSH to < 0.1 mU/L significantly reduces the risk of recurrence and metastasis and improves DFS, but suppression of TSH to < 0.03 mU/L confers no additional benefits [175]; for intermediate- to low-risk patients, a postoperative TSH at 0.1 mU/L to the lower limit of normal (LLN) significantly improves overall prognosis, but TSH < 0.1 mU/L may induce adverse events associated with TSH

suppression therapy, with no advantages in reducing recurrence risk [131, 175–178]. Recent studies suggest that TSH suppression therapy showed a limited benefit in low-risk DTC patients [179–182], indicating that long-term, excessive TSH suppression therapy is not necessary for these patients [57, 173].

Dynamic risk assessment has been recommended for a patient-tailored TSH suppression approach, which indicates performing risk stratification that incorporates the initial risk of recurrence, the risk of adverse effects from suppression therapy, and patient responses to therapy during the postoperative follow-up period (> 1 year after surgery ± RAI therapy) (Tables 7 and 8). "Relative suppression" to keep TSH below the LLN (< 2.0 mU/L) is advised for low-risk DTC patients with excellent responses.

Recommendation 67: DTC patients are recommended to receive TSH suppression therapy after surgery and have a personalized TSH target based on the initial risk of recurrence, risk of adverse effects from TSH suppression therapy, and treatment responses.

Recommendation 68: In low-risk DTC patients with excellent responses, considerations should be given to receive "relative suppression" therapy after surgery to keep TSH below the LLN (< 2.0 mU/L) and switch to thyroid hormone replacement therapy after 5–10 years of follow-up.

#### *3.6.3 Medications and dosing of postoperative TSH suppression therapy for DTC*

DTC patients who have undergone subtotal thyroidectomy (especially low-risk patients after lobectomy) do not require exogenous thyroid hormone if the remnant thyroid tissue is sufficient to maintain the TSH suppression target [1, 179].

For patients requiring exogenous thyroid hormone to reach a target TSH level, oral levothyroxine (L-T4) is primarily indicated for TSH suppression therapy. Desiccated thyroid extracts (DTE) is not recommended for long-term suppression therapy, because the dose of thyroid hormone and the triiodothyronine to thyroxine (T3/T4) ratio can vary between batches, and the T3/T4 ration in DTE fails to mimic a physiological ratio in humans. Nonetheless, some DTC patients who have undergone total thyroidectomy and $^{131}$I remnant ablation may have a lower serum T3 level and T3/T4 ratio than healthy individuals after L-T4 monotherapy, or experience persistent symptoms such as fatigue and cognitive decline even after achieving the biochemical targets. In these cases, the substitution of DTE (60 mg DTE is approximately equivalent to 88 μg of L-T4) [183] or liothyronine (LT3, not yet approved in China) for L-T4 partially can be considered.

L-T4 should be taken on an empty stomach at 60 min before breakfast. If this is not possible under certain situations, patients are advised to take L-T4 before bedtime [184, 185]. Patients who miss a dose of L-T4 should take a double dose should the next day. Some patients may need to adjust the dose of L-T4 based on the seasonal fluctuation of TSH level (increased in winter, decreased in summer). Certain foods (such as dietary fiber additives, soy protein, grapefruit juice, and coffee) and supplements (such as calcium and iron) may affect the absorption of L-T4, so they should be avoided within 4 h of an L-T4 dose. If this is not possible, a proper time interval should be

**Table 8** TSH suppression target during the postoperative follow-up period (> 1 year after surgery ± $^{131}$I therapy) for DTC patients

| TSH suppression target* | | Treatment response (ongoing risk assessment) | | | |
|---|---|---|---|---|---|
| | | ER*** | IDR | BIR | SIR |
| Risk of TSH Suppression** | None or unknown | 0.5–2 | 0.1–0.5 | < 0.1 | < 0.1 |
| | Low | 0.5–2 | 0.1–0.5 | 0.1–0.5 | < 0.1 |
| | Moderate | 0.5–2 | 0.5–2 | 0.1–0.5 | < 0.1 |
| | High | 0.5–2 | 0.5–2 | 0.5–2 | 0.1–0.5 |

* 0.5 (mU/L) represents the lower TSH reference limit, which can be 0.3–0.5 (mU/L) depending on the specific assay

** Risk of TSH suppression: low risk: menopause, tachycardia, osteopenia; moderate risk: age > 60, osteoporosis; high risk: atrial fibrillation. For patients at high risk of adverse effects, the degree of TSH suppression should be adjusted to achieve or be close to the TSH target on the basis of a tolerated dose

*** For low-risk DTC patients with ER, it is reasonable to initiate thyroid hormone replacement therapy to maintain serum TSH levels below the upper limit of normal after 5–10 years of TSH suppression therapy; for high-risk DTC patients with ER, considerations should be given to keep TSH 0.1–0.5 mU/L for 5 years, after which the suppression target should be adjusted based on this table

**Table 7** TSH suppression targets during the initial postoperative stage (1 year after surgery ± $^{131}$I therapy) for DTC patients

| TSH suppression target (mU/L) | Initial risk of recurrence | | | | |
|---|---|---|---|---|---|
| | High | Intermediate | Low | | |
| | | | Low serum Tg levels | Undetectable serum Tg levels | Lobectomy |
| Risk of adverse effects from TSH suppression is not included in risk stratification | < 0.1 | 0.1–0.5 | 0.1–0.5 | 0.5–2 | 0.5–2 |

maintained between intake of L-T4 and the above food and supplements [186, 187].

Recommendation 69: Oral levothyroxine (**L**-T4) is primarily recommended for postoperative TSH suppression therapy for DTC. It should be taken on an empty stomach 60 min before breakfast. Foods and supplements that may interfere with the absorption and action of **L**-T4 should be avoided within 4 h of an **L**-T4 dose.

#### *3.6.4 L-T4 dosing and monitoring as postoperative TSH suppressive therapy for DTC*

The usual suppressive dose of L-T4 is 1.5–2.5 μg/kg/d, higher than replacement doses. The initial dose and the time to reach the full replacement dose vary with age, weight, comorbidities, and concomitant medications. For DTC patients aged < 50 who have undergone total thyroidectomy without a history of heart disease, TSH suppression can be started on the target dose directly. For patients aged > 50 with coronary heart disease or other high-risk factors, the initial dose should be 12.5–25 μg/d, with gradual increases to avoid inducing or exacerbating heart disease.

Thyroid function should be monitored every 4–6 weeks during initial treatment for L-T4 dose adjustment. Once the TSH target has been reached, serum TSH should be measured every 2–3 months in 1 year, every 3–6 months in 2 years, and every 6–12 months in 5 years to keep a TSH level within the target range.

#### *3.6.5 Adverse effects and risk management during TSH suppression therapy*

Major risk factors for adverse events associated with TSH suppression therapy include advanced age, the extent and duration of TSH suppression therapy, and comorbidities [188]. Long term suppression of TSH to below the LLN (i.e., exogeneous subclinical hyperthyroidism), especially when TSH levels < 0.1 mU/L, may lead to significantly increased risk of multiple adverse events, including cardiovascular disease, atrial fibrillation, osteoporosis (OP), and fractures. These negative effects are most pronounced in the elderly and postmenopausal women [173, 189–193].

Proper risk management to prevent or reduce adverse effects of TSH suppressive therapy is necessary. Risks of adverse effects from TSH suppression should be incorporated in considerations of TSH target, and an inappropriately suppressed TSH level ignoring potential risk should be avoided.

Recommendation 70: The risk of adverse effects should be managed in DTC patients receiving postoperative TSH suppression therapy. For patients requiring TSH suppression to below the lower reference range for a long term (especially the elderly and postmenopausal women), cardiac functions and bone mineralization should be evaluated before treatment, and long-term monitoring, prevention and early treatment of adverse effects is recommended.

#### *3.6.6 TSH suppression therapy in DTC patients during pregnancy and the postpartum*

For female DTC patients of childbearing age, thyroid function evaluation and dose adjustment should be performed as soon as pregnancy is confirmed. Medication should not be stopped without proper withdrawal procedures. Recruiting DTC patients diagnosed and treated before pregnancy to investigate the association between the degree of TSH suppression and prognosis is impractical for ethical considerations. Therefore, a personalized, preconception TSH suppression target can be maintained during pregnancy [1]. There is no evidence suggesting that lowering serum TSH can improve the outcomes of patients diagnosed with DTC during pregnancy who have deferred the surgery. However, based on real-world evidence on postoperative TSH suppression therapy in DTC patients [184] and the trimester-specific reference range of TSH [194] (such as TSH > 2.0 mU/L), thyroid hormone treatment with a TSH target at 0.3–2.0 mU/L can be considered for these patients.

For pregnant DTC patients, thyroid function should be monitored every 2 to 4 weeks based on TSH and T4, and the dose adjustment until gestational week 20. Once a stable serum TSH level is achieved, the time interval can be adjusted to 4–6 week. TSH suppression therapy should continue during the postpartum period, with the same target as before or during pregnancy [194].

Recommendation 71: For DTC patients, postoperative TSH suppression therapy should continue during and after pregnancy. DTC patients diagnosed and treated before pregnancy should maintain the same TSH target as determined postoperatively during gestation and postpartum period.

Recommendation 72: For patients with DTC diagnosed during pregnancy who have deferred the surgery, thyroid hormone therapy to keep a TSH level at 0.3–2.0 mU/L should be considered if the patient's serum TSH is > 2.0 mU/L.

Recommendation 73: For pregnant DTC patients, thyroid function should be tested 6 weeks after delivery for TSH assessment. The frequency of thyroid monitoring within 1 year post partum depends on patient

characteristics such as the size of remnant tissue, the level of thyroid autoantibodies, and the clinical manifestations.

#### 3.6.7 Postoperative thyroid hormone therapy for PDTC, MTC, and ATC

The growth of PDTC, MTC, and ATC cells is TSH-independent due to the absent expression of TSHR. These patients do not require postoperative TSH suppression therapy because a suppressed TSH level show no benefits in slowing disease progression [195]. Thyroid hormone replacement therapy is only necessary in patients with hypothyroidism after surgery. The preferred drug and dosing are the same as in TSH suppression therapy for DTC, and the goal is to keep TSH within the normal range.

Recommendation 74: PDTC, MTC, and ATC patients with postoperative hypothyroidism should receive thyroid hormone replacement therapy to keep TSH within the normal range.

#### 3.6.8 Treatment of postoperative hypoparathyroidism

Postoperative hypoparathyroidism may be asymptomatic or present as symptoms of neuromuscular excitability (tingling of fingertips and toes, numbness around the mouth, muscle twitching, tetany, and laryngospasm), depending on the progression, severity, and individual tolerance to hypocalcemia. Hypoparathyroidism is indicated if postoperative laboratory test shows a low albumin-corrected serum calcium while parathyroid hormone (PTH) is decreased or below normal, with or without hyperphosphatemia and hypomagnesemia [196]. Hypoparathyroidism may be transient or permanent, depending on the recovery of parathyroid function within 6 months postoperatively [196]. Incidences of transient and permanent postoperative hypoparathyroidism are 14–60% and 4–11%, respectively [1, 57, 179, 180, 197–201].

Prevention of postoperative hypoparathyroidism is more important than treatment. Hypocalcemia should be detected and corrected before surgery, preoperative detection and treatment of vitamin D deficiency should also be performed if possible. During thyroidectomy, appropriate measures should be taken to protect the parathyroid glands [201]. After surgery, albumin-corrected serum calcium should be monitored. Prophylactic supplementation and medication for hypoparathyroidism may be prescribed depending on clinical symptoms and serum calcium (Table 9) [196].

Permanent hypoparathyroidism should be managed in accordance with relevant guidelines [202, 203]. The main goal of treatment is to keep serum calcium at a level that does not induce symptomatic hypocalcemia, while preventing complications such as hypercalciuria (> 300 mg/d), kidney stones, renal dysfunction, and ectopic calcification in other soft tissues. At present, the long-term treatment for hypoparathyroidism consists of oral calcium supplements, active vitamin D (calcitriol, 0.25–2 μg/d) or its analogue (alfacalcidol, 0.5–3 μg/d), and high-dose vitamin D (10,000–200,000 IU/d). Patients with hypercalciuria may take thiazide diuretics (such as hydrochlorothiazide 12.5–50 mg/day po) to enhance the reabsorption of calcium in renal distal tubules and reduce the excretion of urinary calcium [204], while blood pressure, urine output, and serum potassium should be monitored. Recombinant human PTH is an alternative option for permanent hypoparathyroidism [205, 206], but it is expensive and only available in a few countries. Moreover, further research is needed to validate its efficacy and long-term safety.

Patients with permanent hypoparathyroidism should receive long-term follow-up and be monitored for potential end-stage organ damage and complications. Renal imaging should be performed in the case of symptomatic kidney stones or elevated serum creatinine [202, 203].

Recommendation 75: Prevention is more important than treatment for postoperative hypoparathyroidism.

Recommendation 76: For permanent hypoparathyroidism, the main treatment goal is to keep serum calcium at a level that does not induce symptomatic hypocalcemia, while preventing complications. Long-term treatments include oral calcium and active vitamin D or its analogs.

**Table 9** Management of postoperative hypoparathyroidism

| | Oral calcium | Calcitriol | Intravenous calcium |
|---|---|---|---|
| Prophylactic treatment[a] | Calcium carbonate or calcium citrate with an equivalent amount of elemental calcium, 0.5–1.25 g, bid or tid | 0.25–0.5 μg, bid | Unnecessary |
| Mild to moderate hypoparathyroidism[b] | Elemental calcium, 1–3 g/day, po in 2–3 doses | 0.25–0.5 μg, bid | Unnecessary |
| Severe/symptomatic hypoparathyroidism[c] | Elemental calcium, 3–4 g/day, po in 2–3 doses | 0.25–1 μg, bid | 1–2 g calcium gluconate bolus followed by IV drip |

[a] Correction of vitamin D deficiency and hypomagnesemia;

[b] Serum calcium < 8.5 mg/dL (2.12 mmol/L), new-onset symptoms of hypocalcemia;

[c] Serum calcium < 7 mg/dL (1.75 mmol/L), persistent/severe symptoms after treatment; Q-T prolongation ruled out by ECG

### 3.7 Radiotherapy

#### 3.7.1 The application of radiotherapy to thyroid cancer without distant metastasis

Thyroid cancer patients without distant metastasis but at risk for local relapse may receive radiotherapy after subtotal surgery in order to improve their treatment outcomes. In particular, for patients with postoperative remnants, lymph node metastasis, or extrathyroid invasion, postoperative radiotherapy significantly reduces the risk of local relapse in the case of iodine-refractory lesions, remnants after $^{131}$I therapy, or no response to other treatments; radiotherapy has no significant effect on OS or distant metastasis-free survival [207–211].

Recommendation 77: External radiotherapy is recommended for patients with unresectable local lesions that are iodine-refractory or do not respond to iodine therapy.

#### 3.7.2 The application of radiotherapy to thyroid cancer with distant metastasis

For patients with thyroid cancer, distant metastases include bone metastasis, brain metastasis, and lung metastasis. Palliative radiotherapy also has some effects. For patients with bone metastasis, external radiation effectively relieves pain symptoms and reduces and delays pathological fractures and other events [212–215]. $^{131}$I therapy may cause edema of the surrounding tissues, so external radiation and surgery are the main treatments for brain metastasis. With the advancement of radiotherapy technology, stereotactic radiosurgery is achieving similar outcomes as those of surgery [197, 198]. For oligometastatic lesions in the lung ($\leq 5$ metastases), stereotactic radiosurgery is clinically effective while ensuring an adequate biological dose [216].

Recommendation 78: Palliative radiotherapy relieves symptoms and delays disease progression in thyroid cancer patients with distant metastases, such as bone metastasis, brain metastasis, and lung metastasis.

#### 3.7.3 Radiotherapy technique and dose

Radiotherapy techniques include two-dimensional conventional radiotherapy, beam intensity–modulated radiotherapy (IMRT), and stereotactic radiosurgery (SRS) [217]. Depending on the patient's condition, the target area of radiotherapy may include the thyroid tumor bed and/or the lymphatic drainage area. The median dose of postoperative radiotherapy is generally 60 Gy (54–70 Gy; 1.8–2 Gy per fraction per day) [218]. Moreover, a palliative external radiation dose of $>50$ Gy helps improve the disease control rate of distant metastases [219, 220].

Recommendation 79: IMRT is recommended for radical radiotherapy, with a median dose of 60 Gy and conventional fractionation. For palliative radiotherapy of distant metastases, SRS may be used for hypofractionated, short-course therapy.

#### 3.7.4 Application of radiotherapy to ATC

For ATC patients with R0, R1 (near-R0), or R2 resection, postoperative radiotherapy is significantly beneficial to the prognosis [214, 215, 221–224]. A radiation dose of $\geq 60$ Gy improves local progression-free survival (PFS) and OS [214, 225, 226]. Kwon J et al. [224] conducted a retrospective analysis of 1147 ATC patients and found that for ATC patients in stage IVa and IVb, surgery plus postoperative radiotherapy was superior to surgery alone.

Recommendation 80: For ATC without distant metastasis, conventional fractionated IMRT with or without concurrent systemic therapy is recommended.

Recommendation 81: For ATC with distant metastasis, systemic therapy combined with IMRT with conventional fractionation for the primary tumor is recommended.

Radiotherapy regimen (timing, target volume, dose, fractionation):

> ATC grows rapidly, so postoperative radiotherapy should start as soon as possible. Target area of radiotherapy: tumor area + lymph node drainage area (cervical II-VI + upper mediastinal lymph nodes). Optimal dose: $\geq 65$ Gy in the tumor area; $\geq 60$ Gy in high-risk areas, including the thyroid area, the surrounding lymph node drainage area, and all lymph node-positive areas; and $\geq 54$ Gy in low-risk areas, including negative but potentially metastatic cervical II-VI + upper mediastinal lymph nodes.
>
> Compared with two-dimensional and conformal radiotherapy, IMRT yields a superior dose distribution [227, 228].
>
> Hyperfractionation, accelerated hyperfractionation, and hypofractionation significantly increase the risk of radiotherapy-related side effects, without significant benefits to survival or the local control rate [229–231].

Recommendation 82: For ATC, the target area includes the tumor area + lymph node drainage area (cervical II-VI + upper mediastinal lymph nodes), and IMRT with conventional fractionation should be used.

Radiotherapy for metastases:

Surgery helps treat brain metastasis, spinal cord compression, and pathological fractures. Postoperative radiotherapy may also be used. Bone metastasis and lung metastasis may be treated with palliative radiotherapy. Hypofractionation or conventional fractionation is indicated.

Recommendation 83: For metastases, palliative radiotherapy is recommended. For brain metastasis, radiotherapy or postoperative radiotherapy is recommended. Postoperative radiotherapy is recommended for spinal cord compression and pathological fractures.

### 3.8 Nonsurgical treatment

The main nonsurgical treatments for primary and metastatic thyroid cancer are thermal ablation and percutaneous alcohol injection. No large, prospective, randomized, controlled studies have been conducted on this topic, so nonsurgical treatments are only used as an adjunct therapy in some cases, such as patients at risk for anesthesia or surgery and those who refuse surgery. The indications for nonsurgical treatments should be carefully evaluated and followed.

#### *3.8.1 The application of thermal ablation as the initial treatment for PTMC*

Imaging-guided thermal ablation (including radiofrequency, microwave, laser treatment) is minimally invasive, cosmetic, and repeatable. In recent years, it is mainly used to treat benign thyroid nodules, as well as low-risk PTMC.

Thermal ablation of PTMC is still widely controversial [232–236]. Thermal ablation is a local treatment and thus cannot guarantee radical removal of PTMC and violates the principle of minimum treatment unit (unilateral lobe). Moreover, it cannot treat potential occult central lymph node metastasis. High-quality randomized controlled studies are lacking, and further research is needed to evaluate the long-term efficacy of thermal ablation. At present, thermal ablation is not recommended as a routine treatment of PTMC [237].

Informed, eligible PTMC patients may be enrolled in prospective clinical studies to investigate the effectiveness and safety of thermal ablation and to clarify the indications of thermal ablation and whether it can become an option for thyroid cancer. Inclusion criteria include as follows: (1) nonpathological high-risk thyroid cancer; (2) maximum tumor diameter $\leq 5$ mm ($\leq 1$ cm if the tumor does not involve the capsule), and the nodule is $> 2$ mm from the medial posterior capsule; (3) no capsule or surrounding tissue invasion; (4) nonisthmus cancer; (5) single lesion; (6) no family history of thyroid cancer; (7) no history of cervical radiation exposure in adolescents or childhood; (8) no evidence of lymph node or distant metastasis [233, 237]; (9) the patient is fully informed but still refuses surgery and follow-up [238].

Recommendation 84: Thermal ablation is not recommended as a routine treatment for PTMC.

### 3.9 Systemic therapy

#### *3.9.1 Comprehensive considerations of targeted therapy for RAIR-DTC*

Targeted drug therapy is an effective treatment for populations resistant to conventional treatment regimens and can effectively prolong PFS. The following factors should be considered before targeted drug therapy: (1) Targeted therapy is not a radical treatment. Some clinical studies show certain PFS benefits, but the evidence is not strong enough to support OS benefits. (2) Targeted therapy has a high incidence of side effects, which is likely to affect the quality of life during treatment. (3) Some RAIR-DTC patients may have stable disease for months or years without targeted therapy. Factors such as patient wishes, clinical manifestations, social support, and economic status should be taken into account in the decision-making. A MDT should be consulted, the patient should be informed about the pros and cons before treatment, the risks and benefits of treatment should be carefully weighed, and the timing of targeted therapy should be carefully selected.

*Indications and contraindications of targeted therapy for RAIR-DTC* Tyrosine kinase inhibitor (TKI) therapy should be considered for patients with metastatic, rapidly progressive, symptomatic and/or immediate life-threatening DTC, as in the following cases: (1) rapidly progressing disease that is expected to require intervention within 6 months or may be life-threatening (e.g., lung or lymph node metastases may rapidly invade the airway, resulting in dyspnea or bronchial obstruction); (2) symptomatic disease that cannot be adequately resolved with local treatment (e.g., exercise-induced dyspnea, unresectable painful lesions); (3) disseminated progression rather than focal progression (e.g., progression of multiple lung metastases rather than slow progression of local lesions).

Relative/absolute contraindications to TKI therapy: (1) pregnant or nursing women (absolute contraindication); (2) severe hepatic and renal insufficiency; (3) patients at risk for severe active bleeding or massive hemoptysis after treatment with anti-angiogenic drugs with vascular endothelial growth factor receptors (VEGFRs) as the main target (absolute contraindication); (4) active or recent bowel disease (e.g., diverticulitis, inflammatory bowel disease, recent bowel resection); (5) recent cardiovascular incidents; (6) recent tracheal radiotherapy (radiotherapy and kinase inhibitor therapy increase the risk of airway-gastrointestinal fistula); (7) cachexia, low body weight, malnutrition, uncontrolled hypertension, corrected QT (QTc) prolongation, marked acute arrhythmias (including ventricular and chronic arrhythmias); (8)

untreated brain metastases (controversial); (9) patients with recent suicidal ideation (suicides have been reported in depressed patients on TKIs).

*Indications for discontinuing targeted therapy for RAIR-DTC* TKI therapy should be promptly discontinued if the risks outweigh the benefits, such as if systemic disease rapidly progresses or there are serious adverse events during treatment. TKI therapy may continue if the patients experience marked benefits, they can tolerate the toxicity, and their disease is manageable, despite slow disease progression.

For locally progressive disease, local treatment (as indicated) may be in the patient's best interests in addition to systemic TKI therapy. For example, patients with shrinking lung metastases but progressive isolated bone metastases may receive systemic TKI therapy combined with radiotherapy for bone metastases.

Recommendation 85: For patients with metastatic, rapidly progressive, or symptomatic RAIR-DTC, TKI therapy should be started after MDT consultation, combined with careful consideration of patient condition, patient wishes, and risks and benefits. TKI therapy should be discontinued if the risks outweigh the benefits, such as with disease progression or serious adverse effects.

#### *3.9.2 Overview of targeted drug therapy*

*Targeted therapy for RAIR-DTC* **Pantargeted anti-angiogenic TKIs**

*Targeted drugs approved in China*

Sorafenib: small-molecule multitarget TKI with potent inhibitory effects on VEGFR2, VEGFR3, RET, and BRAF. In DECISION, a phase III randomized controlled clinical trial of RAIR-DTC patients with disease progression within 14 months, the overall response rate (ORR) is 12.3% in the sorafenib group, and PFS was significantly longer in the sorafenib group than in the placebo group (10.8 vs 5.8 months), but no significant difference in OS [239].

Lenvatinib: mainly targets epidermal growth factor receptor (EGFR) 1–3, fibroblast growth factor receptors (FGFR) 1–4, platelet-derived growth factor receptor alpha (PDGFRα), RET, and KIT. In SELECT, a phase III randomized controlled clinical trial, PFS was significantly longer in the lenvatinib group than in the placebo group [240].

*Other targeted drugs*

Apatinib: mainly targets VEGFR-2. In REALITY, a phase III randomized controlled clinical trial of RAIR-DTC patients with disease progression within 12 months before enrollment, ORR was 54.3% in the apatinib group, and PFS was significantly longer in the apatinib group than in the placebo group (22.21 vs 4.47 months). It showed survival benefits, as the median OS was significantly longer in the apatinib group than in the placebo group (NR vs 29.90 months) [241].

Anlotinib: mainly targets VEGFR-1, VEGFR-2, VEGFR-3, c-Kit, and PDGFRβ. In a phase II clinical study of progressive locally advanced or metastatic RAIR-DTC patients in China, the ORR was 59.21% in the anlotinib group, and the median PFS was significantly longer in the anlotinib group than in the placebo group (40.54 vs 8.38 months, hazard ratio (HR) = 0.21, $P < 0.0001$), suggesting anlotinib was effective in disease control in patients with progressive RAIR-DTC [242].

Surufatinib: mainly targets VEGFR1/2/3, FGFR1, and colony-stimulating factor 1 receptor (CSF-1R). In a multicenter phase II clinical study of 59 patients with locally advanced or metastatic DTC or MTC, the ORR of surufatinib was 21.7%, with a median PFS of 11.1 months in patients with locally advanced or metastatic RAIR-DTC ($n = 26$) [243].

**Target-specific TKIs**

Pralsetinib (BLU-667): specific RET inhibitor. Approximately 10–20% of PTC patients harbor a *RET* fusion gene. Pralsetinib has been approved by the United States Food and Drug Administration (FDA) for the treatment of advanced or metastatic MTC with *RET* mutation and advanced or metastatic RAIR-DTC with a *RET* fusion gene requiring systemic treatment [244].

Selpercatinib (LOXO-292): another highly selective RET inhibitor that was approved by the FDA in May 2020 for the treatment of advanced or metastatic MTC with *RET* mutation and advanced or metastatic RAIR-DTC with a *RET* fusion gene in adults and children 12 years or older [245].

Larotrectinib: broad-spectrum neurotrophin receptor tyrosine kinase (NTRK) inhibitor. Larotrectinib has been approved in the US for the treatment of advanced *NTRK*

fusion–positive solid tumors in adults or children that are refractory to standard treatment or have no standard treatment [246].

Recommendation 86: Targeted therapy prolongs the PFS of patients with progressive locally advanced or metastatic RAIR-DTC. Lenvatinib and sorafenib are recommended therapies. Patients with progressive, locally advanced, or metastatic RAIR-DTC may also receive apatinib and anlotinib therapy.

Recommendation 87: For patients with metastatic, rapidly progressive, symptomatic, and/or immediately life-threatening DTC, polygenic testing should be considered to identify genetic changes (including *RET* and *NTRK* fusion gene) and the total tumor gene mutation. That may guide treatment. Selpercatinib is recommended based on the characteristics of genetic variation.

Recommendation 88: Patients are encouraged to participate in clinical trials if systemic therapy is unavailable or inappropriate.

*Targeted therapy for MTC* **Multitarget TKIs**

Vandetanib: oral small-molecule multitarget TKI that mainly targets RET, EGFR, and VEGFR. Vandetanib was approved by the FDA in 2011 for the treatment of progressive, symptomatic, inoperable locally advanced, or metastatic MTC [247, 248].

Cabozantinib: another oral small-molecule multitarget TKI that mainly targets RET, MET, and VEGFR2. It has been approved by the FDA and European Medicines Agency for the treatment of advanced metastatic MTC [249].

Anlotinib: multitarget TKI independently developed in China. It mainly targets VEGFR2/3, FGFR1-4, and PDGFR. Anlotinib is currently approved for the treatment of inoperable locally advanced or metastatic MTC.

Surufatinib: targets VEGFR, FGFR-1, and colony-stimulating factor 1 receptors. In a multicenter phase II clinical study of 27 MTC patients in China, the ORR was 22.2%, and the median PFS was 11.1 months [243].

**Highly selective RET inhibitors**

RET is the main driver gene of MTC, and it is the most effective target for the treatment of MTC. Unlike multitarget TKIs, highly selective RET inhibitors have a high affinity for RET and are effective against tumors with *RET* fusion genes and point mutations. Two highly selective small-molecule RET inhibitors are available, pralsetinib (BLU-667) and selpercatinib (LOXO-292). Selpercatinib was given accelerated approval from the FDA for its excellent efficacy in phase I/II clinical trials [245].

Recommendation 89: For patients with symptomatic or progressive persistent/recurrent or metastatic MTC, multitarget TKI therapies such as vandetanib, cabozantinib, and anlotinib should be considered.

Recommended 90: For patients with symptomatic or progressive persistent/recurrent or metastatic MTC with *RET* mutation, pralsetinib (BLU-667) pralsetinib and selpercatinib (LOXO-292) are recommended.

*Targeted therapy for ATC* At present, targeted drugs for ATC are rare. In May 2018, the FDA approved tadalafil combined with trametinib or larotrectinib for the treatment of ATC harboring $BRAF^{V600E}$ mutation. Moreover, the FDA has approved larotrectinib and entrectinib for the treatment of NTRK fusion-positive tumors. In 2020, the FDA approved selpercatinib and pralsetinib, two specific RET inhibitors, as systemic treatment of *RET* fusion-positive iodine-refractory thyroid cancer, including ATC.

The current standard treatment is ineffective for ATC, so all patients, regardless of their surgical plans, should consider clinical trials.

Recommend 91: For unresectable locally advanced ATC lesions (IVa/IVb) with $BRAF^{V600E}$ mutation, molecular-targeted neoadjuvant therapy (tadalafil/trametinib) should be considered. For *RET* fusion-positive tumors, selpercatinib and pralsetinib should be considered; for NTRK fusion-positive tumors, larotrectinib and entrectinib should be considered; if RECIST assessment indicates disease progression, vandetanib, cabozantinib, selpercatinib (for *RET* mutation), and pralsetinib (for *RET* mutation) should be considered.

#### *3.9.3 Monitoring and management of adverse effects of targeted drugs*

TKIs are associated with a variety of side effects, including diarrhea, fatigue, induced hypertension, liver toxicity, skin changes, nausea, increased dose of levothyroxine, taste change, and weight loss.

Monitoring: Hypertension: daily blood pressure is measured, especially during the first 8 weeks of treatment. Calcium channel blockers may be most effective if antihypertensive treatment is required. Skin/mucosal toxicity: rash/mouth ulcers should be monitored; the

patients should be informed about the risk of sun exposure and sunburn. Liver toxicity: serum alanine transferase, alkaline phosphatase, and bilirubin should be monitored; the dose of TKI should be reduced in the case of liver toxicity. Cardiotoxicity: ECG and echocardiography should be monitored; TKI therapy should be discontinued (or not started) if QTc > 480 ms. Hypothyroidism: TSH should be monitored regularly to adjust the dose of levothyroxine. Renal toxicity: serum creatinine and urine protein should be monitored. Hematological toxicity: blood levels should be monitored. Pancreatitis: amylase should be monitored. Teratogenicity: pregnancy test and effective birth control are needed in men and women of childbearing age [1, 250–252].

Management principles: TKI therapy may continue, along with symptomatic and supportive care, in the case of grade I adverse events. TKI therapy should be discontinued in the case of recurrent grade 2 adverse events in a week. Once symptoms improve with symptomatic care, TKI therapy may resume at a lower dose and then at the original dose (if tolerated); TKI therapy should be discontinued in the case of grade 3 adverse events, which should receive active symptomatic care until symptoms improve to grade 1, before treatment resumption at a lower dose. TKI therapy should be terminated in the case of recurrent grade 3 adverse reactions [1, 250–252].

Recommendation 92: Patients on TKI therapy should be closely monitored for adverse events. Any adverse events should be appropriately managed based on its severity.

#### *3.9.4 Chemotherapy for thyroid cancer*

DTC is insensitive to chemotherapy drugs [253]. Chemotherapy should only be used as palliative care, or experimental treatment when the patient does not respond to any other treatment.

For persistent or recurrent MTC, chemotherapy is only indicated for patients who do not respond to TKI therapy and who cannot participate in clinical trials. Small studies have shown that the ORR of dacarbazine-based combination regimens is 15–42%.

Chemotherapy is recommended for patients with metastatic ATC who lack other options, including clinical trials. The chemotherapy regimen for ATC consists of taxanes and/or anthracyclines, or taxanes with or without cisplatin or carboplatin.

Doxorubicin (adriamycin) is the only cytotoxic chemotherapeutic approved by the FDA for the treatment of ATC and metastatic DTC [254]. The recommended dose is 20 $mg/m^2$ weekly or 60–75 $mg/m^2$ every 3 weeks. Paclitaxel monotherapy may benefit some patients with newly diagnosed ATC; for weekly dosing, the recommended dose is 60–90 $mg/m^2$ per week.

Recommendation 93: Chemotherapy is not routinely recommended for DTC or MTC; chemotherapy is recommended for patients with metastatic ATC who have no other options.

#### *3.9.5 Immunotherapy for thyroid cancer*

Immunotherapy has developed rapidly in recent years, and several immune checkpoint inhibitors (ICIs) have been approved for the treatment of different solid and hematological tumors. For RAIR-DTC with therapeutic indications, several ongoing phase I/II clinical studies on immunotherapy show that ICIs have certain anti-tumor activity for progressive DTC.

Pilot studies on metastatic MTC have shown promising results for tumor vaccines and stimulated dendritic cell therapy.

Immunotherapy for ATC is being investigated, and no immunotherapy drug has been approved by the FDA for it [255]. Retrospective data show that targeted therapy combined with immunotherapy significantly improves the prognosis of ATC.

Recommendation 94: Immunotherapy is not routinely recommended for DTC or MTC. For ATC patients in stage IVc with high PD-L1 expression, ICIs may be used in the absence of other suitable targeted drugs.

### 3.10 Traditional Chinese medicine (TCM)

TCM is a component of the comprehensive treatment of thyroid cancer, especially for postoperative complications and adverse reactions to $^{131}I$ therapy and endocrine therapy. TCM may also be used to manage the side effects of radiotherapy, chemotherapy.

TCM is implemented according to TCM syndrome differentiation. TCM focuses on postoperative rehabilitation treatment. Attention should be paid to whether the disease is associated with iodine deficiency or iodine excess, as well as the use of herbs with high iodine content, such as kelp, seaweed, cuttlebone, and sea clam shells.

The following are common syndrome differentiations for postoperative recovery and adverse reactions of common treatments:

#### *3.10.1 Liver qi stagnation*

[Clinical manifestations] Neck fullness and discomfort, mental depression, irritability, chest tightness with deep sighs, fullness and discomfort in the rib-side, loss of appetite, stuffiness and abdominal congestion; pale tongue, with thin white coating, stringy pulse.

[Treatment] Soothing the liver and relieving stagnation, regulating qi and dispersing masses.

[Representative formula] Addition and subtraction of Xiaoyao San.

#### *3.10.2 Qi stagnation and blood stasis*

[Clinical manifestations] Neck swelling and tingling, dim complexion, irritability, chest oppression and shortness of breath with or without migratory pain; for women: menstrual arrest, dysmenorrhea, dark purple blood with clots; dark-purple tongue, with visible stasis macules, thin or sparse coating, stringy and astringent pulse.

[Treatment] Activating qi and invigorating blood, dispelling blood stasis and dispersing masses.

[Representative formula] Addition and subtraction of Xiaoyao San and Taohong Siwu Decoction.

#### *3.10.3 Qi stagnation and phlegm coagulation*

[Clinical manifestations] Neck mass or a hard scrofula on both sides of the neck, chest oppression and shortness of breath, irritability, shortness of breath with lazziness to speak, fatigue and limb weakness, loss of appetite; white greasy coating, stringy and slippery pulse. This syndrome is common in patients with advanced or relapsed/metastatic tumors.

[Treatment] Soothing the liver and regulating qi, resolving phlegm and dispersing masses.

[Representative formula] Addition and subtraction of Xiaoyao San and Beimu Gualou San.

#### *3.10.4 Liver depression transforming into fire*

[Clinical manifestations] Heat and pain in the neck, irritability, fullness of the chest and rib-side, dizziness, red eyes, dry mouth and bitter taste, vexing heat and sweating; red tongue, thin yellow coating, stringy and rapid pulse.

[Treatment] Soothing the liver and relieving fire, resolving toxins and dispersing masses. This syndrome may be observed in patients with hyperthyroidism.

[Representative formula] Addition and subtraction of Danzhi Xiaoyao San.

#### *3.10.5 Dampness heat in liver meridian*

[Clinical manifestations] Heat and pain in the neck, bitter taste and sticky sensation in mouth, bad breath, dizziness, red eyes, chest oppression and loss of appetite, dark yellow urine, dry stools; red tongue, yellow greasy coating, stringy and slippery pulse.

[Treatment] Clearing heat and removing dampness, resolving toxins and dispersing masses.

[Representative formula] Addition and subtraction of Longdan Xiegan Decoction.

#### *3.10.6 Intermingling of phlegm and stasis*

[Clinical manifestations] Mass in the front of the neck or a persistent hard scrofula on both sides of the neck, throat obstruction, thick and sticky phlegm, hoarseness, chest oppression, loss of appetite; dark-purple tongue or with stasis macules, greasy coating, stringy and slippery pulse. This syndrome is common in patients with advanced or relapsed/metastatic tumors.

[Treatment] Resolving phlegm and invigorating blood, dispelling blood stasis and dispersing masses.

[Representative formula] Addition and subtraction of Beimu Gualou San and Xiaoluo Pill.

#### *3.10.7 Yin deficiency with effulgent of fire*

[Clinical manifestations] Vexation and insomnia, irritability, dizziness, dry mouth and night sweats, vexing heat in the chest and palms and soles, soreness and weakness of the back and knees; red tongue with little saliva, little or no coating, thin and rapid pulse. This syndrome may be observed in patients with hyperthyroidism.

[Treatment] Nourishing yin and clearing heat, resolving toxins and, dispersing masses.

[Representative formula] Addition and subtraction of Zhibai Dihuang Pill.

#### *3.10.8 Spleen and kidney yang deficiency*

[Clinical manifestations] Facial edema or swollen limbs, cold body and cold limbs, pale face and listlessness, fatigue, loss of appetite, loose stools, dizziness, hair loss; pale and fat tongue, white slippery or greasy coating, with tooth marks on the margins of the tongue, deep, thin and weak pulse. This syndrome is common in patients with hypothyroidism.

[Treatment] Warming and tonifying the spleen and kidneys, inducing diuresis to alleviate edema.

[Representative formula] Addition and subtraction of Jinkui Shenqi Pill.

#### *3.10.9 Qi and Yin deficiency*

[Clinical manifestations] Dull pain of neck or with mass, weight loss and fatigue, dry mouth, palpitations, shortness of breath, spontaneous sweating and night sweats, vexing heat in chest and palms and soles, dizziness, tinnitus, soreness and weakness of the back and knees; light red tongue, little coating, thin or thin and rapid pulse. This syndrome is common in patients with advanced or relapsed/metastatic tumor or after surgery.

[Treatment] Supplementing qi and nourishing yin, resolving toxins and dispersing masses.

[Representative formula] Addition or subtraction of Sijunzi Decoction and Shashen Maidong Decoction.

These are basic syndromes. Addition or subtraction may be warranted based on clinical symptoms and syndromes. Common examples are as follows.

For neck pain, add kudzu root, hemlock parsley, and spatholobus stem. For dizziness and tinnitus, add rhizoma gastrodiae, cicada shell, and grass-leafed sweetflag. For dry mouth and throat, add root of straight ladybell, Rhizoma Anemarrhenae, and Radix Scrophulariae. For dry mouth and bitter taste, add felwort, Gardenia, and Scutellaria. For red face and red eyes, add Gardenia, Scutellaria, and chrysanthemum. For insomnia and excess dreams, add roasted jujube seed, caulis polygoni multiflori, and Flos Albiziae. For irritability, add Chinese thorowax, rhizoma cyperi, and radix curcumae. For loss of appetite, add Atractylis ovata, Poria from Yunnan, China, and charred triplet. For vexing heat in the chest and palms and soles, add Gardenia, yellow cypress, and dried rhizome of Rehmannia. For cold hands and feet, add processed Fuzi, cinnamon, and Morinda officinalis. For fatigue and weakness, add Astragalus root, radix codonopsidis, and sealwort. For spontaneous sweating and night sweats, add Chinese ephedra root, blighted wheat, and Radix Rehmanniae. For facial edema, add cortex mori radicis, ginger peel, and tangerine peel. For lower extremity edema, add Asiatic plantain seed, Alisma orientale, and umbellate pore furgus.

For thyroid cancer, TCM also focuses on daily care based on syndrome differentiation, which includes mental support, diet, sleep, lifestyle, and medication.

Recommendation 95: TCM treatment can significantly improve the clinical symptoms, improve the quality of life and improve the prognosis of patients with thyroid cancer. It is recommended to be used as routine adjuvant treatment. TCM treatment can significantly improve the postoperative complications of thyroid cancer and the adverse reactions caused by $^{131}$I treatment, endocrine therapy and other treatments. It is recommended that the above patients be used routinely.

## 4 Recovery and follow-up of patients with thyroid cancer

Recovery after thyroid cancer treatment mainly includes physical and mental recovery. After comprehensive treatment, most patients can return to their social life and resume normal work, without a significant impact on the overall immunity or spirit. In some cases, however, such as patients with locally advanced tumors who have undergone traumatic procedures of the trachea, larynx, and esophagus, attention should be paid to their nutritional support, mental support, and compassionate care after surgery to improve the patient's general condition.

Once the incision in the neck has healed, neck exercises, along with TCM, will help promote functional recovery. In addition, mental support also plays an active role in TC's treatment and follow-up.

### 4.1 Purposes of follow-up

For DTC patients, the purposes of long-term follow-up [256] include (1) early detection and treatment of relapse and metastasis; (2) observing disease progression and treatment response in DTC patients with relapse or remnants; (3) monitoring the effect of TSH suppression therapy to prevent undertreatment or overtreatment [195]; (4) for DTC patients with certain comorbidities (such as heart disease, other malignancies), closely monitoring their condition; (5) performing disease restaging and prognostic assessment (ongoing assessment) after treatment to determine what kind of treatment or follow-up is needed.

Recommendation 96: DTC patients should receive long-term follow-up and ongoing assessment.

### 4.2 Application of serological tests during the follow-up of thyroid cancer

#### *4.2.1 Application of serum Tg in long-term follow-up for DTC patients without remnants*

For DTC patients without remnants (after surgery and RAI ablation), serum Tg should be regularly monitored (with the same method) to detect any remnant or relapse. During follow-up of DTC patients, serum Tg tests include baseline Tg (with TSH suppression) and Tg after TSH stimulation. For accurate assessment, L-T4 may be discontinued, or rhTSH may be used to increase serum TSH to > 30 mU/L before Tg testing, which reflects the Tg level after TSH stimulation [257]. Both methods, L-T4 withdrawal and rhTSH administration, lead to similar Tg levels [258].

For serum Tg, long-term follow-up should start at 6 months after RAI ablation, at which time baseline Tg or serum Tg after TSH stimulation should be tested. Twelve months after RAI ablation, serum Tg after TSH stimulation should be tested [259], and baseline Tg (with TSH suppression) should be tested every 6–12 months thereafter. For low-risk DTC patients without any sign of remnant or relapse, the timing and necessity of Tg testing (after TSH stimulation) are not entirely clear [260]; for moderate-risk and high-risk patients, Tg (after TSH stimulation) should be monitored for 3 years after RAI ablation.

Recommendation 97: For DTC patients without remnants, serum Tg is an important indicator of any remnant or relapse.

Recommendation 98: During follow-up, serum Tg should be monitored with the same method, and TgAb should be also measured every time serum Tg is.

Recommended 99: At 6 months after RAI ($^{131}$I) ablation, baseline serum Tg (with TSH suppression) or serum Tg after TSH stimulation should be tested; at 12 months, serum Tg after TSH stimulation should be tested. Baseline serum Tg (with TSH suppression) should be monitored every 6–12 months thereafter. Moderate-risk and high-risk patients should have serum Tg monitored after TSH stimulation for 3 years after ablation.

#### *4.2.2 Application of serum Tg in DTC patients with normal thyroid residue*

For DTC patients with normal thyroid residue, the remnants are still a source of serum Tg. The cut-off value of Tg for normal tissue versus cancer tissue is still unknown. Therefore, to these patients, the sensitivity and specificity of serum Tg monitoring are both low for detecting DTC remnants or relapse, but it is still recommended to monitor serum Tg regularly (every 6 months) after surgery and monitor TgAb at the same time. DTC progression should be considered in patients with increasing serum Tg. Serum Tg after TSH stimulation is not required in such patients.

Recommendation 100: For DTC patients with normal thyroid residue, serum Tg (and TgAb) should be monitored every 6 months after surgery. DTC progression should be considered in patients with increasing serum Tg.

### 4.3 Imaging studies during the follow-up of thyroid cancer

#### *4.3.1 Application of cervical ultrasound during follow-up of DTC*

The purpose of ultrasound during follow-up is to assess the status of the thyroid bed and the central and lateral lymph nodes. Ultrasound is highly sensitive for early detection of cervical metastases in DTC patients and is thus an important component of the follow-up [248, 261, 262]. During follow-up, cervical ultrasound is generally performed every 3–6 months for 2 years after surgery or RAI ablation and then every 6–12 months in disease-free survivors. For long-term follow-up (> 5 years), cervical ultrasound is recommended to be performed every 1–2 years.

Biopsy may be performed on suspicious cervical lymph nodes with a minimum diameter of > 8–10 mm (8 mm in the central area, 10 mm in the lateral area). After biopsy, the Tg level in the rinsing solution from the biopsy needle can improve the sensitivity of detecting DTC metastases [263, 264]. Lymph nodes with a minimum diameter of < 8–10 mm may be followed up, and biopsy may be considered for signs suggesting malignancies, such as lymph node enlargement and invasion of the surrounding structures [68, 71, 72, 265].

Recommendation 101: Cervical ultrasound should be performed regularly (every 3–12 months) during the follow-up of DTC.

#### *4.3.2 Application of DxWBS during the follow-up of DTC*

DxWBS is not required in moderate-risk or low-risk DTC patients if they have no remnants after surgery and RAI ablation, their follow-up cervical ultrasound and baseline serum Tg (with TSH suppression) is normal [259, 266–268]. DxWBS may be considered in moderate-risk and high-risk patients 6–12 months after ablation [269].

Recommendation 102: For DTC patients without remnants, DxWBS may be selectively used in moderate-risk and high-risk DTC patients, especially those with suspiciously elevated Tg or TgAb during follow-up.

### 4.4 Monitoring and response assessment of $^{131}$I therapy

#### *4.4.1 Monitoring of $^{131}$I therapy*

Posttherapy whole-body scans (RxWBS) should be performed 2–10 days after taking iodine, including in $^{131}$I ablation, therapy for persistent disease, or adjuvant therapy, to assess the iodine uptake activity of the lesions and further clarify the disease stage and predict the treatment response [270]. RxWBS uses a higher dose of RAI than DxWBS. RxWBS can detect approximately 6–13% of the lesions undetectable by DxWBS, and 8.3% of patients will have a different tumor stage and thus a different treatment strategy due to newly detected lesions [271]. Single-photon-emission computed tomography combined with CT (SPECT/CT) is more accurate at locating the lesions, thereby improving the characterization, localization, and diagnosis of lymph node metastasis and distant metastasis by Rx-WBS, even resulting in a modified treatment plan for nearly 25% of patients [72, 272].

Recommendation 103: Imaging studies after $^{131}$I therapy assist in accurate tumor staging and response prediction.

#### *4.4.2 Response assessment*

After $^{131}$I therapy, the response is assessed based on a real-time ongoing risk stratification system, which combines current clinical data, biochemical indicators, and structural/functional imaging studies to clarify the current disease state and provide a basis for repeat $^{131}$I therapy and other treatments, while preventing overtreatment and undertreatment in a timely manner. Clinical outcomes vary with the treatment response, so clinicians should adjust the follow-up and treatment strategies on

**Table 10** Treatment response and corresponding follow-up strategy of DTC

| Treatment response | ER | Indeterminate response (IDR) | Biochemical incomplete response (BIR) | Structural incomplete response (SIR) |
|---|---|---|---|---|
| Clinical outcome | Relapse: 1% to 4%; disease-specific mortality: < 1% | Progressing to SIR during follow-up: 15–20%; other conditions are stable or improved; disease-specific mortality: < 1% | Spontaneous response: ≥ 30%; postintervention response: 20%; progressing to SIR: 20%; disease-specific mortality: < 1% | Persistent disease after late intervention: 50–85%; disease-specific mortality is up to 11% in patients with local metastasis and up to 50% in patients with distant metastasis |
| Management measures | Reduce follow-up frequency and the level of TSH suppression | Ongoing monitoring of imaging studies and serological indicators | Long-term follow-up with TSH suppression if Tg is stable or declining; $^{18}$F-FDG PET/CT should be performed if necessary to identify potential lesions in the case of increasing Tg/TgAb | Further treatment or follow-up strategy should be determined based on lesion size, location, growth, and iodine uptake |

an ongoing basis given the assessment results (Table 10) [270].

### 4.5 Follow-up methods

The methods and frequency of follow-up vary with tumor type, initial treatment, initial stratification of the risk of relapse, and real-time ongoing response assessment. Serological responses include changes in TSH, Tg, and TgAb. Imaging responses include cervical ultrasound, DxWBS, CT, MRI, whole-body bone scan, and PET/CT [273, 274].

#### *4.5.1 Serological indicators (Tg, TgAb)*

After successful ablation, serum Tg is a specific biomarker of DTC. The change in Tg level after treatment is a sensitive indicator of the change of lesion volume and the effect of treatment, which can be used to predict clinical outcome [275]. During follow-up, Tg tests should be performed in the same laboratory using the same method whenever possible [276]. TSH and TgAb should be tested at the same time, because Tg cannot be used as a reliable quantitative indicator in the presence of TgAb [277].

#### *4.5.2 Imaging indicators*

Cervical ultrasound is the most effective method for monitoring structural lesions. Its accuracy is close to 100% when combined with FNA and serum Tg [278, 279].

After treatment of persistent disease, DxWBS should be performed in 6–12 months for real-time evaluation of the iodine uptake capacity, which is the key molecular nuclear medicine evidence for repeat $^{131}$I therapy [280]. Both SPECT/CT and $^{124}$I-PET/CT are more sensitive than $^{131}$I-DxWBS at detecting remnants and/or metastatic DTC.

CT and MRI are not routine studies during the follow-up of DTC, but they can be used as supplementary studies if ultrasound is unsatisfactory or if the lesion has invaded local vital organs.

Recommendation 104: CT, MRI, and $^{18}$F-FDG PET are not recommended as routine studies during the follow-up of DTC.

Recommendation 105: For patients with suspicious relapse and metastasis, CT, MRI, or $^{18}$F-FDG PET may be selectively used to help determine the nature and extent of the disease.

### 4.6 Follow-up strategy

Initial evaluation is generally performed 6 months after treatment. All DTC patients should have cervical ultrasound and serum Tg (with TSH suppression or stimulation) and TgAb tests. DxWBS should be considered in high-risk patients with previous iodine metastases, abnormal Tg, and abnormal cervical ultrasound.

#### *4.6.1 Remnant ablation and adjuvant therapy:*

For moderate-risk and low-risk patients, serum Tg (with TSH suppression) and TgAb should be tested regularly (every 12–24 months) from 12 months after treatment if the initial evaluation indicates ER. The frequency of cervical ultrasound is determined as needed, and DxWBS is not required during future follow-ups. If the initial evaluation indicates IDR or BIR, serum Tg and TgAb tests and cervical ultrasound should be performed every 6–12 months [113, 281, 282]. Additional imaging studies are required in the case of increasing Tg or TgAb during follow-up [283].

For patients with high risk, poorly differentiated lesions, or extensive invasive lesions, serum Tg and TgAb should be monitored every 6–12 months if the initial evaluation indicates ER, IDR, or BIR.

#### *4.6.2 Therapy of persistent disease:*

- ER: No need for repeat $^{131}$I therapy. Initiate TSH suppression therapy, and follow up every 6-12 months.
- IDR: TSH suppression therapy + ongoing dynamic monitoring, and follow up every 3-6 months.
- BIR: If Tg/TgAb is stable or declining, TSH suppression therapy + ongoing dynamic monitoring should be performed, and follow-up is necenssary every 3-6 months; if Tg/TgAb is increasing, $^{18}$F-FDG PET/CT should be considered to identify potential iodine-refractory structural lesions.
- SIR: It is important to closely monitor any change in structural lesions since the last $^{131}$I session to determine the need for repeat $^{131}$I therapy or referral for local/systemic treatment [284].

Recommendation 106: Serological and imaging evaluations can assess the response to previous $^{131}$I therapy and provide a basis for subsequent treatments.

### 4.7 Follow-up monitoring of MTC

Ctn is the most sensitive and specific indicator for MTC, either measured before surgery or relapsed/metastatic after surgery. It has a long half-life, so early Ctn test after surgery may not be a reliable indicator of surgical response, especially if the patient has underlying liver or kidney disease or has elevated Ctn before surgery [285]. For patients with lymph node metastases and

preoperative Ctn > 1000 pg/mL, it takes an average of 57.7 days for Ctn to return to normal [286].

Patients with undetectable Ctn and normal CEA after surgery may have serological tests once a year. Imaging studies are indicated if Ctn is ≥ 150 pg/ml. Distant metastasis is indicated and imaging studies required if Ctn is > 1000 pg/ml in the absence of cervical and chest lesions. If imaging is negative or indeterminate, serum Ctn and CEA should be closely monitored.

Persistently elevated Ctn after surgery is not necessarily a sign of relapse, but progressively elevated Ctn is associated with relapse and metastasis [287].

Recommendation 107: Ctn and CEA tests should be performed 3 months after the initial surgery to evaluate the surgical response. Patients with undetectable tumor markers should be followed up every 6 to 12 months.

Recommendation 108: For patients with persistently elevated Ctn and CEA after surgery or elevated Ctn and CEA after they returned to normal once, the Ctn doubling time should be calculated (at least four tests at least 6 months apart). The patients should be followed up every 3–6 months.

Recommendation 109: Patients with elevated Ctn and CEA after surgery should undergo imaging studies to identify persistent or recurrent disease.

### 4.8 Response assessment after systemic treatment

For patients with advanced thyroid cancer who are receiving systemic treatment, treatment response is assessed in accordance with RECIST v1.1. Baseline lesions should be assessed before systemic treatment, and treatment response should be assessed regularly during the treatment. Moreover, the systemic treatment plan should be modified based on tumor progression, stable disease, or response.

Recommendation 110: Patients receiving systemic treatment should undergo regular response assessment.

### 4.9 The application of active surveillance (AS) in thyroid cancer

AS is also known as "delayed surgery", meaning that the patients will be followed up first after the diagnosis of DTC (rather than immediately undergoing surgery) and will undergo surgery in the case of tumor progression during monitoring [288, 289]. The indications for AS include (1) very low-risk papillary thyroid microcarcinoma (single lesion, the maximum diameter < 1 cm, no local invasion, no clinically suspected lymph node metastasis or distant metastasis, no cytological high-risk subtype); (2) the presence of comorbidities that require priority treatment (such as other malignancies, other medical conditions); and (3) a short life expectancy. Additionally, in some cases, inoperable advanced DTC may be stable for a long time without any sign of progression during follow-up, which is indicated for AS.

AS has been associated with many issues in clinical practice: (1) In most cases, microcarcinoma progresses slowly during AS, but some patients will have tumor progression, lymph node metastasis, and even distant metastasis, resulting in adverse consequences such as an expanded surgical scope. Younger age and pregnancy are potential risk factors for tumor progression [290–293]. AS has certain risks due to a lack of effective methods to identify true low-risk patients. (2) No standard operating procedures are available for AS, such as the AS criteria, follow-up time, TSH range, and the timing of surgery. The tumor size indicated for surgical intervention is still controversial [294]. (3) AS requires significant time and effort, so the overall cost may be higher than that of early surgery. In addition, AS causes greater mental stress to patients [288, 295]. (4) There are clinical challenges, including how to build patient confidence and grow the genuine acceptance of AS in China [296–300].

Recommendation 111: AS may be an option for some patients with low-risk thyroid microcarcinoma and patients with advanced DTC that is stable for a long time.

#### Abbreviations

AJCC: American Joint Committee on Cancer; AS: Active surveillance; AT: Adjuvant therapy; ATA: American Thyroid Association; ATC: Anaplastic thyroid carcinoma; AUS: Atypia of undetermined significance; BMI: Body mass index; BIR: Biochemical Indeterminate Response; CATO: Chinese Association of Thyroid Oncology; CCV: Columnar cell variant; CEA: Carcinoembryonic antigen; CT: Computed tomography; Ctn: Calcitonin; DFS: Disease-free survival; DSS: Disease-specific survival; DSV: Diffuse sclerosing variant; DTC: Differentiated thyroid cancers; DTE: Desiccated thyroid extracts; DxWBS: Diagnostic iodide whole-body scanning; EBSLN: External branch of the superior laryngeal nerve; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; ER: Excellent Response; ETS: Endoscopic thyroid surgery; FDA: Food and Drug Administration; FGFR: Fibroblast growth factor receptors; FLUS: Follicular lesion of undetermined significance; FN: Follicular neoplasm; FNA: Fine-needle aspiration; FGFR: Fibroblast growth factor receptors; FTC: Follicular thyroid carcinoma; FV: Follicular variant; GD: Grave's disease; IARC: International Agency for Research on Cancer; IDR: Indeterminate Response; IMRT: Intensity-modulated radiotherapy; IONM: Intraoperative neuromonitoring; LLN: Lower limit of normal; LT3: Liothyronine; L-T4: Levothyroxine; MDT: Multidisciplinary team/treatment; MEN2: Type 2 multiple endocrine neoplasia; MRI: Magnetic resonance imaging; MTC: Medullary thyroid carcinoma; NIFTP: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features; NTRK: Neurotrophin receptor tyrosine kinase; ORR: Overall response rate; OS: Overall survival; PDGFRα: Platelet-derived growth factor receptor alpha; PDTC: Poorly differentiated thyroid carcinoma; PET: Positron-emission tomography; PFS: Progression-free survival; prmDTC: Persistent/recurrent/metastatic differentiated thyroid cancers; PTC: Papillary thyroid carcinoma; PTH: Parathyroid hormone; PTMC: Papillary thyroid microcarcinoma; RA: Remnant ablation; RAI: Radioactive iodine; RAIR: RAI-refractory; RECIST: Response Evaluation Criteria in Solid Tumors; RLN: Recurrent laryngeal nerve; RxWBS: Posttherapy whole-body scans; SFN: Suspicious for a follicular neoplasm; SIR: Structural Indeterminate Response; SM: Suspicious for malignancy; SPECT/CT: Single-photon-emission computed tomography combined with CT; SRS: Stereotactic radiosurgery; SV: Solid variant; TA: Toxic adenoma; TBSRTC: The Bethesda System for Reporting Thyroid Cytopathology; TCM: Traditional Chinese medicine; TCV: Tall cell variant; Tg: Thyroglobulin;

TgAb: Anti-thyroglobulin antibodies; TKI: Tyrosine kinase inhibitor; TMNG: Toxic multinodular goiter; TNM: Tumor–node–metastases; TPD: Treatment of persistent disease; TRAb: Thyrotropin receptor antibody; TSH: Thyroid-stimulating hormone; T3/T4: Triiodothyronine to thyroxine; UD/UNS: Nondiagnostic or unsatisfactory; UICC: Union for International Cancer Control; VEGFR: Vascular endothelial growth factor receptors; WHO: World Health Organization.

**Acknowledgements**
This project was funded by the National Natural Science Foundation of China (81872170 [Minghua Ge]). We would like to give our thanks to Prof. Daiming Fan for valuable discussion and Chinese Association of Thyroid Oncology for the full academic support.

**Authors' contributions**
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CZ, HG, XZ, YW, SL and YL. MG, RC and XC revised material critically. The first draft of the manuscript was written by MG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding**
This work was funded by National Natural Science Foundation of China (81872170 [Minghua Ge]).

**Availability of data and materials**
Not applicable.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors have no relevant financial or non-financial interests to disclose.

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Received: 14 April 2022 Accepted: 8 October 2022
Published online: 08 November 2022

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