Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for persistent/recurrent and metastatic differentiated thyroid cancer 2018 (English version)

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1. Diagnosis and dynamic assessment of persistent/recurrent and metastatic differentiated thyroid cancer (prmDTC)

Differentiated thyroid cancer (DTC), including papillary, follicular and Hürthle cell types, accounts for nearly 95% of all thyroid carcinomas. The concept of DTC recurrence or persistence after surgery is still difficult to define due to its indolent nature. The recurrent or persistent tumors in this guideline refer to new lesions or residual tumors found during the follow-up after initial treatments.

1.1 Basic principles of diagnosis

The role of multidisciplinary team (MDT) should be emphasized during the diagnosis of prmDTC. A task force of specialists with complementary expertise (endocrinology, surgery, nuclear medicine, radiology, pathology, oncology, molecular diagnostics, and epidemiology) should be included in the MDT management of prmDTC. The diagnosis or further managements of prmDTC which may include surgical managment, radiiodine-131 (¹³¹I) therapy, thyroid stimulating hormone (TSH) suppressive therapy, as well as molecular targeted therapy (or being enrolled in certain clinical trial) or radiation therapy, etc., should be tailored according to comprehensive consideration of MDT.

1.2 Diagnostic methods

Laboratory tests, imaging studies and pathological examinations are recommended in the diagnosis of prmDTC (Table 1).

1.3 Ongoing assessment of response to therapy (Table 2)

As the risk of recurrence and cancer-related death in prmDTC may change over time, life long follow-up and periodical surveillance including laboratory and imaging evaluation are needed. Ongoing assessment of response to therapy should be used to guide the long-term surveillance and therapeutic management decision. In this guideline, we adopted the system of response to therapy which was put forward by 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.

Multiple factors including clinical, biochemical, imaging (structural and functional) and cytopathology findings were taken into comprehensive consideration in this response system to assess the individual response to therapy during follow-up. It has been verified as an objective ongoing evaluation system to reflect the clinical outcomes from...
Table 1 Diagnostic methods of prmDTC

| Methods                        | Level I recommendation                                                                 | Level II recommendation                     |
|--------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------|
| Laboratory diagnosis          | Serum Tg\(^a\) and TgAb\(^b\) (2A)                                                  | Tg washout determination (2A)               |
| Imaging diagnosis             | Various image detections are as follows:                                               |                                             |
| Suspected local lesions       | Neck ultrasound\(^c\)−\(^e\) (2A), contrast CT or contrast MRI\(^f\) (2A)             | Ultrasound-guided fine needle aspiration cytology (2A), \(^{131}\)I-WBS + SPECT/CT\(^g\) (2A), \(^{18}\)F-FDG PET/CT (2A) |
| Suspected distant metastasis  | CT\(^h\) (2A), \(^{131}\)I-WBS + SPECT/CT (2A), MRI\(^i\) (suspected nervous system involvement) (2A), bone scan\(^j\) (suspected bone involvement) (2A) | MRI (when organs other than the nervous system are involved) (2A), \(^{18}\)F-FDG PET/CT\(^k\) (2A) |
| Pathological diagnosis        | Previous pathology results                                                             | Review previous tissue specimens            |
|                               | Confirmation of previous primary lesions                                              | Immunohistochemistry\(^n\), molecular pathology\(^o\) (2A) |
|                               | General inspection\(^l\), microscopic examination\(^m\) of biopsy specimens          |                                             |

\(^a\) Thyroglobulin (Tg) monitoring facilitates postoperative assessment and risk stratification. Low serum Tg level has a high negative predictive value in the absence of thyroglobulin antibody (TgAb) interference after initial treatment (1). Thyroglobulinemia out of proportion to what is seen on \(^{131}\)I-whole body scan (WBS) indicates the presence of distant metastasis (1-3). Tg also holds value in predicting the response or resistance to \(^{131}\)I therapy (4,5).

\(^b\) Simultaneous monitoring of Tg and TgAb levels is needed. The presence of TgAb will falsely lower serum Tg determinations in immunoassays, and in this clinical setting, the serial monitoring of TgAb level may serve as a surrogate prognostic marker (6,7).

\(^c\) Ultrasound (US) is considered the first-line imaging study for assessing locoregional lesions of persistent/recurrent and metastatic differentiated thyroid cancer (prmDTC), and experienced radiologists may enhance the diagnostic credibility in the management of such patients (1,8-11).

\(^d\) The assessment of cervical ultrasonography includes cervical lymph nodes, thyroid beds, soft tissue, blood vessels, trachea and esophagus. Sonographic features of prmDTC are as follows (Figure 1).

\(^e\) Frequently, it is not easy to distinguish thyroid bed recurrence from benign nodules. Interpretation of neck US should take into account clinical and biological data.

\(^f\) Cross-sectional imaging studies, computed tomography (CT) or magnetic resonance imaging (MRI) with intravenous (IV) contrast, are recommended for suspicious prmDTC (12,13).

\(^g\) \(^{131}\)I-WBS and single photon emission computed tomography (SPECT)/CT can be used to locate the iodine-avid foci, which is helpful in tailoring the subsequent \(^{131}\)I therapy (14,15).

\(^h\) CT is routinely recommended for assessing patients with pulmonary metastases, \(^{131}\)I-WBS may play a complementary role in some patients with micrometastatic lesions which may be missed by chest CT (16,17).

\(^i\) MRI is routinely recommended for assessing cerebral metastases (1).

\(^j\) Bone scan is recommended for assessing suspicious bone metastases (18).

\(^k\) \(^{18}\)-fluorodeoxyglucose (\(^{18}\)FDG) PET/CT is recommended in patients with elevated Tg (generally >10 ng/mL) or TgAb, especially in patients with non-radiiodine-avid foci (1,19-22). It may also be considered as a part of initial staging in poorly or invasive DTC and serve as a prognostic tool in prmDTC, especially in predicting those who are unlikely to benefit from \(^{131}\)I therapy (1).

\(^l\) The gross examination should include the following: specimen type, tumor location, tumor size, gross morphology, relationship between the tumor and adjacent tissue structures, number of lymph nodes detected, size, and group.

\(^m\) Microscopic examination should include the following: morphological variants, tumor size, dissemination, invasion range, resection margin, vascular invasion, nerve invasion, lymph node metastasis and total number, and TNM staging. For cases with morphological PTC, if possible, the possible histologic subtypes that may indicate poor prognosis, such as tall cell variant, columnar cell variant, diffuse sclerosing variant and hobnail variant, should be further reported (23).

\(^n\) Commonly used immunohistochemical markers for determining the origin include CK, Tg, TTF-1, TTF-2, PAX-8, Syn, CgA, Calcitonin and CEA (24). Commonly used immunohistochemical markers for distinguishing malignancy from benign lesion include galectin-3, HBME-1, CK19, CD56, E-cadherin, p27, cyclinD1, p53, Ki-67 index, etc. (24).

\(^o\) Common molecular markers used to indicate malignancy or benign lesion include BRAF\(^V600E\), NRAS 61 codon, HRAS 61 codon and KRAS 12/13 codon mutations, RET/PTC and PAX8/PPAR\(_y\) rearrangements, etc. (25).

both the risk of recurrence and mortality (1). Four categories including excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR) and structural incomplete response (SIR) are used to describe clinical outcomes at any time after initial treatment (1).
Figure 1 Sonographic features of persistent/recurrent and metastatic differentiated thyroid cancers (prmDTCs). (A, B) Local recurrence of thyroid bed (among cursors and arrows); (C–E) Suspicious metastatic lymph nodes; (F, G) Recurrence in soft tissue (among cursors); (H) Venous tumor thrombus; (I) Tracheal invasion (arrow point). M, mass; IJV, internal jugular vein; CCA, common carotid artery.

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Table 2  Stratification of ongoing assessment of response to therapy

| Stratification                      | Definition (serology and imaging meet simultaneously) | Level I recommendation                                                                 |
|------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------|
| **Excellent response**<sup>a</sup> (ER) | Suppressive Tg <0.2 ng/mL or stimulated Tg <1 ng/mL | Decrease of the intensity and frequency of follow-up and the degree of TSH suppression (1A) |
| Indeterminate response<sup>b</sup> (IDR) | Non-stimulated Tg detectable, but less than 1 ng/mL. Stimulated Tg detectable, but less than 10 ng/mL. Or Tg antibodies stable or declining in the absence of structural or functional disease | Continuing observation with appropriate serial imaging of the non-specific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy (1A) |
| Biochemical incomplete response<sup>c</sup> (BIR) | Suppressed Tg >1 ng/mL. Stimulated Tg >10 ng/mL. Or rising TgAb levels | Those with stable or decreasing serum Tg levels may continue TSH suppression therapy and follow-up; patients with elevated serum Tg or TgAb should prompt additional investigations and potentially additional therapies (1A) |
| Structural incomplete response<sup>d</sup> (SIR) | Serum Tg or TgAb at any level | Additional treatments or ongoing observation depending on multiple clinicopathologic factors including the size, location, rate of growth, RAI avidity, 18F-FDG avidity, and specific pathology of the structural lesions (1A) |

Tg, thyroglobulin; TgAb, thyroglobulin antibody; TSH, thyroid stimulating hormone; FDG, fluorodeoxyglucose.

<sup>a</sup> The risk of recurrence ranged from 1% to 4% over 5–10 years among ER patients.

<sup>b</sup> 15%–20% of IDR patients are reclassified as persistent/recurrent disease over approximately 10 years.

<sup>c</sup> 8%–17% of BIR patients developing structurally identifiable disease over 5–10 years.

<sup>d</sup> Death from disease was seen in 11% of patients with a loco-SIR and in 57% of patients with distant SIR.

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2. Multidisciplinary treatment of prmDTC

2.1 Basic principles of treatment

Treatment options for prmDTCs usually include surgical resection, $^{131}$I therapy of lesions that can uptake $^{131}$I, external beam radiation therapy, active follow-up under L-T4 suppression therapy and other options (e.g., targeted medicines, radiofrequency or ethanol ablation). Among them, surgery should be the first choice for resectable lesions with surgical indications.

2.2 Surgical management

PrmDTCs are commonly seen in clinical practice, approximately 95% of which occur in the neck (1). Since the difficulty and risk of reoperation increase significantly, the risks and benefits of surgery must always be balanced when selecting reoperation. Surgery should be performed by experienced specialists, and frequently even under multidisciplinary collaboration.

2.2.1 Preoperative clinical assessment

Preoperative clinical assessment includes the review of previous treatments, current status of the disease and vital organ function, which are the basis for the decision regarding intervention and extent of revision surgery. Structural lesions are required as a target for a surgical revision approach, therefore, imaging evaluation is of the utmost importance to surgeons to identify and localize the structural lesions (Table 3).

2.2.2 Principles of surgical treatment for prmDTC

The timing and extent of surgery are the most important issues which should be considered when the surgical management of prmDTC is decided. In general, the goal of revision surgery should be to try to cure or control the disease, improve survival, and preserve the function of the vital organs as far as possible (Table 4).

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| Table 3 Recommendations of preoperative clinical assessment |
|-----------------------------------------------------------|
| **Evaluation content** | **Level I** | | **Level II** | | **Level III** |
| | **recommendation** | | **recommendation** | | **recommendation** |
| **Clinical data** | | | | | |
| Preoperative and pathological record review | | | | |
| Complications of previous surgery, such as hematoma, infection, etc. | | | |
| Physical exam, esp. special signs for recurrent metastases. | | | |
| **Laboratory tests** | | | | |
| Serum Tg, TgAb, see 1.2 Diagnostic methods (2A) | | | |
| Parathyroid function evaluation: serum calcium and PTH levels | | | |
| **Routine examination** | | | | |
| Neck ultrasound (2A) | | | CT angiogram or MR angiogram (MRA) when suspected of vascular involvement |
| Contrast neck CT or MRI, chest CT, etc. See 1.2 Diagnostic methods (2A) | | | $^{131}$I-WBS + SPECT/CT and $^{18}$F-FDG PET/CT if necessary, see 1.2 Diagnostic methods (2A) |
| Assessment of vocal cords movement and recurrent laryngeal nerve function assessment | | | |
| Laryngoscopy, when trachea involvement is suspected. | | | |
| Esophagoscopy, when esophagus involvement is suspected. | | | |

PTH, parathyroid hormone; CT, computed tomography; MRI, magnetic resonance imaging; WBS, whole body scan; SPECT, single photon emission computed tomography; FDG, fluorodeoxyglucose.

*Thyroglobulin (Tg), Tg antibody (TgAb) and imaging examinations can be used to evaluate the current state of disease. Neck ultrasonography is the most important technique to detect structural lesions (2,3).*
Table 4 Recommendations of surgical treatment principles

| Lesions                                                                 | Level I recommendation                          | Level II recommendation                           | Level III recommendation                           |
|------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Cervical lesions without invasion to surrounding vital structures^a    | Preservation in situ or autotransplantation of parathyroid glands^b (2A) | Active follow-up: lesion <8 mm in the smallest dimension (2A) Consider reoperation: lesion ≥8 mm in the smallest dimension (2A) Preoperative FNA (2A) Completion of thyroidectomy and standardized central compartment neck dissection (2A) Intraoperative Neuromonitoring (IONM) of the recurrent laryngeal nerve^c (2A) Active follow-up: lesion <10 mm in the smallest dimension (2A) Consider reoperation: lesion ≥10 mm in the smallest dimension (2A) Preoperative FNA (2A) Therapeutic modified radical neck dissection and preservation of vital structures for previously undissected compartments (2A) Limited neck dissection (generally includes levels II, III, IV, or 1-2 levels of them) for previously managed compartments, due to extensive scar and unclear anatomy (2A) | Ipsilateral central neck dissection in patient without bilateral central compartment involvement (2B) |
| Central compartment                                                     | —                                                | —                                                | —                                                |
| Lateral compartment                                                     | —                                                | —                                                | —                                                |
| Cervical lesions with invasion to surrounding vital structures^c        | Shave the tumor off as much as possible and preserve the nerve in patient without vocal cord paralysis (2A) Remove lesions and the affected nerve in patient with preoperative vocal cord paralysis or intraoperative finding of complete tumor encapsulation of the nerve (2A) | Nerve reinnervation simultaneously at surgery after resection or injury of the nerve, if feasible (2A) Second-look operation with nerve repair for postoperative identification of recurrent laryngeal nerve injury (2A) | —                                                |
| Recurrent laryngeal nerve involvement^d                                | —                                                | —                                                | —                                                |
| Airway/digestive tract (larynx trachea/ esophagus) involvement^e        | —                                                | —                                                | —                                                |

Table 4 (continued)
remove metastatic lesions, but also relieve life-threatening intracranial complications (36). Intracranial metastases may be preferred for surgical treatment, which can not only control local recurrence of tumor and prolong the survival of patients (24).

Cervical vascular involvement ($^f$)

| Lesions                      | Level I recommendation | Level II recommendation                                                                 | Level III recommendation |
|------------------------------|------------------------|-----------------------------------------------------------------------------------------|--------------------------|
| Cervical vascular involvement $^f$ | —                      | Sacrifice of the unilateral internal jugular vein without reconstruction if it is significantly involved (2A) | —                       |
|                              |                         | Reconstruction of at least one side with autologous vein graft after resection of the bilateral involved internal jugular veins (2A) | —                       |
|                              |                         | Reconstruction of the common carotid artery after resection for its local involvement (2A) | —                       |

Distant metastatic lesions $^g$

| Lesions                      | Level I recommendation | Level II recommendation                                                                 | Level III recommendation   |
|------------------------------|------------------------|-----------------------------------------------------------------------------------------|----------------------------|
| Lung metastases              | —                      | Consider surgery for solitary lesion (2A)                                               | —                          |
| Bone metastases              | —                      | Consider surgery (2A)                                                                     | —                          |
| Brain metastases             | —                      | Surgery (2A)                                                                             | —                          |
| Other rare site metastases   | —                      |                                                                                         | Consider surgery for solitary lesion (2B) |
| (liver, pancreas, etc.)      | —                      |                                                                                         |                            |

$^a$, The most important and difficult decision for these patients is the timing of the operation. At present, it is commonly accepted that the patient can be closely followed up when the lesion is less than 8 mm in the central compartment and <10 mm in the lateral compartment, otherwise, reoperation should be considered (1-10). Preoperative fine needle aspiration (FNA) diagnosis is an important step in preoperative evaluation to avoid unnecessary reoperations. The threshold of 8 mm (central) and 10 mm (lateral) in the smallest dimension signifies disease sufficiently macroscopic to be potentially dangerous if it were to grow, and amenable to FNA as well as surgical localization if it were to be targeted for excision (1-4,9,10). In the decision-making of surgery, the following factors should also be considered (1,2,8,9): location of the lesion (whether it is adjacent to the important structures), doubling time of Tg (11), whether a positive result is shown on $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) imaging, the extent of previous operation, complications, and whether the primary lesion is a highly malignant subtype. For revision surgery, it may be a standardized lymph node dissection (1-5,9,10) or a limited operation (2,12,13).

$^b$, The incidence of temporary and permanent recurrent laryngeal nerve injury during reoperation is 1.5%–22.2% and 0.3%–6.4%, respectively (14-16), and the incidence of temporary and permanent hypoparathyroidism during reoperation is 6.5%–46.3% and 9.5%, respectively (15-17). The recurrent laryngeal nerve monitoring in such operations plays an important role in reducing nerve injury and improving the safety of the operation (18-21). The time of nerve repair may be different between patients (21-23). Parathyroid glands should be carefully identified, rescued and preserved in situ or auto-transplanted into other locations, such as the sternocleidomastoid (1-5).

$^c$, The extent of surgical resection for such lesions has been controversial, but the removal of visible tumors is very important to control local recurrence of tumor and prolong the survival of patients (24).

$^d$, 33%–61% of thyroid cancers that invade the surrounding vital structures have recurrent laryngeal nerve invasion (24-27). Studies have shown that recurrent laryngeal nerve involvement is not an independent risk factor for survival (25), residual trace lesions do not increase the local recurrence rate and reduce the survival rate (26,27). Therefore, the nerve should be preserved as far as possible (1,4,28), and if not, the affected nerve should be removed and reconstructed (1,4,28,29). Of course, when determining the surgical approach, the contralateral recurrent laryngeal nerve function and distant metastases status should also be considered in order to balance the risks and benefits of surgery.

$^e$, Airway/digestive tract (laryngeal trachea/esophageal) involvement is more serious situation, and over half of disease-specific deaths are related to airway obstruction and bleeding (28). For such patients, there are different options in surgery (1,2,28,30), when partial esophageal/tracheal/laryngectomy can be carried out, it can not only ensure adequate resection margins, but also avoid serious complications caused by more extensive resection, however, postoperative adjuvant therapies such as RAI treatment and radiotherapy are generally needed (1,28).

$^f$, Reconstruction may be required in the treatment of cervical vascular involvement (28), although severe invasions to the major blood vessels of the neck by differentiated thyroid cancers (DTCs) are rare (31). The involvement of internal jugular veins by metastatic lesions is the most common (32). Obstruction of bilateral internal jugular veins can cause at least 2% of patients to die (33).

$^g$, Common distant metastatic sites of DTC include lung, bone, and brain. In general, surgery is feasible for solitary lesion and lesions that cause complications (34,35). Intracranial metastases may be preferred for surgical treatment, which can not only remove metastatic lesions, but also relieve life-threatening intracranial complications (36).
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2.3 131I therapy

131I therapy is one of the important adjuvant postoperative treatment modalities for prmDTC patients. It can reduce the risks of tumor recurrence, metastasis and death in high risk population (1,2), and significantly improve the 5- and 10-year survival for high-risk DTC patients with iodine-avid lesions (3-9).

131I therapy is recommended in patients with iodine-avid prmDTC lesions, and should be repeated at an interval of 6−12 months as long as the lesions continue to concentrate radioiodine and respond clinically. In addition, cumulative radioiodine activities, balance between benefits and risks, and patient preferences, are relevant to 131I therapy decision-making. Patients with TSH stimulation and iodine preparation, whose lesions no longer concentrate 131I or respond to 131I therapy, are identified as radioactive iodine refractory DTC (RAIR-DTC) in four basic ways: 1) the malignant metastatic lesion does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic WBS); 2) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination); 3) RAI is concentrated in some lesions but not in others; and 4) disease progresses despite significant concentration of RAI (10).

2.3.1 Clinical assessment before 131I therapy

Clinical information, as well as the status exactly before 131I therapy should be considered for tailoring the management of prmDTC (Table 5). Further surgical consultation should be advised if a patient has lesions which might be amenable to surgery. While in terms of the clinical information, evaluation of the response to previous therapeutics is critical for subsequent 131I therapy of prmDTC, for instance, a previous 131I unresponsive patient would be unlikely to benefit from another repeated 131I therapy.

| Evaluation content                  | Level I recommendation                                                                 | Level II recommendation       | Level III recommendation |
|-------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|--------------------------|
| Clinical information                | Evaluate the response and adverse events to previous therapeutics, including surgery, 131I therapy, and TSH suppression, etc." | Serum/Urinary iodine measurement | —                        |
|                                     | Physical examination                                                                   |                               |                          |
| Laboratory tests                    | Thyroid hormones, TSH (2A)                                                              | Cardiac ultrasound or dynamic ECG | —                       |
|                                     | Tg, TgAb (2A)                                                                            |                               |                          |
|                                     | Complete blood count, hepatic and renal function test                                   |                               |                          |
| Routine examination                 | Electrocardiogram (ECG)                                                                 |                               |                          |
| Imaging examination                 | Diagnostic 131I WBS  | (2A) | Bone scan (2A) | MRI (2A) | 18F-FDG PET/CT (2A) | | |
| Pathological examination            | —                                                                                      | BRAFV600E mutation detection" | —                       |
|                                     |                                         |                               |                          |

prmDTC, persistent/recurrent and metastatic differentiated thyroid cancer; WBS, whole body scan; CT, computed tomography; MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; PET, positron emission tomography.

a, Serum TSH should be >30 mIU/L through L-T4 withdrawl before 131I therapy (11,12). Currently, thyrogen is not approved by CFDA.

b, Diagnostic WBS (Dx-WBS) can be used for identifying radioiodine-avid lesions, tailoring dosage of 131I, and predicting the efficacy of 131I therapy (1).

c, BRAFV600E mutation is the most common oncogenic mutation and related to aggressive disease, recurrence and mortality. BRAFV600E mutation in isolation or in combination with TERT mutation appears to be associated with more aggressive tumor behavior, and more likely to be refractory to 131I therapy (1,13,14).
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2.3.2 Management of 131I therapy for prmDTC

Indications and dose determination of 131I therapy for prmDTC are addressed in terms of the sites of metastases (Table 6).

**Table 6** Recommendations for 131I administration in prmDTC patients

| Items | Recommendation |
|-------|----------------|
| **Indications of 131I therapy for prmDTC** | | |
| Local lesions | — | 131I therapy (iodine-avid lesions) | — |
| Lung metastases | 131I therapy (iodine-avid lesions) | — | — |
| Bone metastases | — | 131I therapy (iodine-avid lesions) | — |
| Brain metastases | — | — | 131I therapy (iodine-avid lesions) |
| Tg(+),131I(−) | — | — | Empirical 131I therapy |
| **Preparation for 131I therapy** | | |
| TSH >30 mIU/L | Levothyroxine (L-T4) withdrawal for at least 2–4 weeks | Liothyronine (L-T3) may be substituted for L-T4 for at least 4 weeks, and then should be withdrawn for at least 2 weeks | — |
| Low iodine diet | Low iodine diet for at least 2 weeks | rhTSH | — |

Table 6 (continued)

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Management of prmDTC after $^{131}$I therapy

| Items                              | Level I | Level II | Level III |
|------------------------------------|---------|----------|-----------|
| Dose for $^{131}$I therapy         |         |          |           |
| Local lesions                      | 100–150 mCi $^{131}$I (1A) | -         | -         |
| Cervical lymph node metastases     | 100–200 mCi $^{131}$I (1A)| -         | -         |
| Lung metastases                    | 150–200 mCi $^{131}$I (1A)| -         | -         |
| Bone metastases                    | 150–200 mCi $^{131}$I (1A)| -         | -         |
| Brain metastases                   | -       | NA (2A)  | -         |
| $\text{Tg}(+)^{131}$I(−)            | -       | 100–200 mCi $^{131}$I (2B)| -         |

Management of $^{131}$I therapy

- **Post-therapy** $^{131}$I-WBS
  - Perform post-therapy $^{131}$I-WBS 2–10 days after $^{131}$I therapy
  
- **TSH suppression therapy**
  - Continue TSH suppression therapy within 3 days after $^{131}$I administration

- **$^{131}$I therapy after lymphadenectomy for DTC**
  - $^{131}$I therapy on iodine-avid local recurrent or metastatic tumor is of value (1,2), and $^{131}$I adjuvant therapy after lymphadenectomy for DTC relapse is associated with better progression-free survival (PFS) in patients with Tg-on ≥1 ng/mL (3).
  - $^{131}$I therapy may be repeated if benefits of structural or serum Tg/TgAb reduction have been observed, whereas complete remission is uncommon and the survival remains poor (2). It’s unclear whether the benefits of $^{131}$I therapy could be gained in patients with non-iodine-avid pulmonary metastases (9,10).

- Although $^{131}$I therapy is rarely curative, it can be recommended for patients with radioiodine-avid bone metastases, as some benefits may be obtained, such as stable disease, tumor reduction, and survival improvement (1,2,6,11). Other local therapies also should be considered for those unresectable bone metastases, including external beam radiotherapy, endovascular embolization, bisphosphonate therapy, and vertebroplasty.

- Surgical resection and external beam radiotherapy are the main therapeutic methods for brain metastases. For the radioiodine-avid brain metastases, $^{131}$I therapy can be considered. And if $^{131}$I therapy is employed, concomitant glucocorticoid therapy would be recommended to minimize the radioiodine-induced inflammatory response.

- $\text{Tg}(+)^{131}$I(−) refers to the status in the absence of imaging evidence of structural lesions [anatomic imaging and $^{131}$I-whole body scan (WBS)], with significantly elevated serum Tg levels or rapidly rising serum Tg (2). So far, no survival advantages had been documented under the empiric $^{131}$I therapy in such cases.

- There are insufficient data to support the utilization of recombinant human thyroid stimulating hormone (rhTSH) in prmDTC patients. It may be considered as an alternative to thyroid hormone withdrawal in elder patients who could not withstand hypothyroidism, or mount an adequate endogenous TSH response (1,2,12).

- Avoiding iodine exposure, a low-iodine diet (<50 μg/d) before $^{131}$I administration is recommended (1,2,12).

- There are three approaches to determining the therapeutic doses of $^{131}$I: empiric fixed dosage, dosage determined by the upper limit of blood and body dosimetry, and quantitative lesional dosimetry. Currently, empiric dosimetric method is the most commonly used method (1,2,12,13).

- Empiric dosimetric methods are often reserved for patients with unusual situations, such as children, the elderly or renal insufficiency (1,2,12,13). Empirically administered $^{131}$I activities exceeding 150 mCi should be avoided in patients over age 70 years. $^{131}$I is a relatively safe treatment method. Currently, there is no recommendation for the upper limit of single or cumulative $^{131}$I doses based on prospective clinical studies. However, according to previous studies, the risk of radiation-related adverse events may be associated with the increasing cumulative $^{131}$I dose and the treatment times (13).

- There are few data to support the efficacy of $^{131}$I therapy for brain metastases, so no appropriate dosage could be recommended (1,2,14).

- Empiric (100–200 mCi) $^{131}$I therapy may be considered in patients with significantly elevated serum Tg levels (≥10 ng/mL), and undetectable structural disease which is unrevealed by anatomic imaging, $^{131}$I-WBS and/or 18FDG-PET/CT. Besides, the $^{131}$I therapy should be stopped when there is no benefit showed after the empiric therapy (2).

- For individualized TSH suppression, please refer to 2.4.
2.4 TSH suppression therapy

2.4.1 Strategy for TSH suppression therapy

For prmdTC that expresses TSH receptor, TSH suppression therapy is important in postoperative management of differentiated thyroid cancer. It has been realized the optimal degree of TSH suppression varies. An individually tailored approach to deciding TSH targets in prmdTC patients considering risk of side effects has been raised (Table 7).

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2.4.2 Management of adverse effects of TSH suppression therapy

When TSH has to be suppressed below the normal range (i.e. subclinical thyrotoxicosis) for a long period, especially below 0.1 mU/L, it may cause adverse effects (AEs) (Table 8).

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Table 7 Strategy for TSH suppression therapy

| Treatment period          | Level I recommendation                                                                 | Level II recommendation                 |
|---------------------------|----------------------------------------------------------------------------------------|------------------------------------------|
| Whole-course<sup>a</sup>  | Applicable patients: prmDTC expresses TSH receptor (category 1A)                       |                                          |
|                           | First-line medication: oral L-T4 agents (category 1A)                                   | Extend intervals of TSH monitor to 3–6 months once TSH reaches the goal (category 2A) |
|                           | Starting L-T4 dose: based on patient’s age and co-existing diseases                     |                                          |
|                           | Final L-T4 dose: titrated according to patient’s TSH goal and results of monitoring (category 1A) |                                          |
|                           | Check TSH every 4–6 weeks during the L-T4 dose adjustment (category 1A)                 |                                          |
| Initial period<sup>b</sup>| TSH target based on risks of TSH suppression therapy (category 1A)                     |                                          |
|                           | Low risk: <0.1 mU/L (category 2A)                                                      |                                          |
|                           | High risk: If tolerated, <0.1 mU/L to lower normal limit (category 2A)                  |                                          |
| Long-term follow-up period<sup>c</sup>| TSH target based on dynamic assessments (category 2A)                                  |                                          |
|                           | -ER: lower normal limit to 2.0 mU/L (category 2A)                                      |                                          |
|                           | -IDR: around the lower normal limit of TSH (category 2A)                               |                                          |
|                           | -BIR: 0.1 mU/L to lower normal limit; If risk of side effects of TSH suppression is low, <0.1 mU/L (category 2A) | Extend intervals of TSH monitor to 3–6 months once TSH reaches the goal (category 2A) |
|                           | -SIR: If tolerated, <0.1 mU/L (category 2A)                                            |                                          |

ER, excellent response; IDR, indeterminate response; BIR, biochemical incomplete response; SIR, structural incomplete response.

<sup>a</sup> If the tumor is poorly differentiated and no longer expresses thyroid stimulating hormone (TSH) receptor, only thyroid hormone replacement is needed (1,2).

<sup>b</sup> The initial treatment period refers to within one year after the persistent/recurrent and metastatic differentiated thyroid cancer (prmDTC) being treated with surgery and/or radioactive iodine (3,4).

<sup>c</sup> The long-term follow-up period refers to one year after the prmDTC being treated with surgery and/or radioactive iodine (3,4). TSH suppression goals may not be uniform and should be adjusted according to results of surveillance (5-8).

Table 8 Management of adverse effects of TSH suppression therapy

| Adverse events (AE) | Level I recommendation                                                                 | Level II recommendation |
|---------------------|----------------------------------------------------------------------------------------|-------------------------|
| All AE<sup>a</sup>  | Set individualized TSH targets, monitor AEs and adjust L-T4 doses in a timely manner (1A) |                         |
| Cardiovascular AE<sup>b</sup> | Baseline cardiovascular assessment (2A), β blockers (2A)                        |                         |
| Skeletal system AE<sup>c</sup> | Baseline skeletal assessment (2A), primary prevention of osteoporosis (OP); anti-OP treatment (2A) |                         |

<sup>a</sup> When thyroid stimulating hormone (TSH) has to be suppressed below the normal range (i.e. subclinical thyrotoxicosis) for a long period, especially below 0.1 mU/L, it may cause AE, mainly involving cardiovascular system, as well as skeletal system in postmenopausal women (1-5).

<sup>b</sup> Patients with underlying heart diseases or high risk of cardiovascular events should be given appropriate treatments by specialists, and their TSH targets should be adjusted accordingly (6-9).

<sup>c</sup> Particular attention is warranted for female patients after menopause (10).

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2.5 External beam radiation therapy

External beam radiation therapy (EBRT) is an effective and safe local therapy with benefit to local control and palliative care for prmDTC. EBRT, stereotactic radiation therapy (SBRT) and other local therapies can be used for symptomatic, weight-bearing, key site metastasis, and oligo-metastasis (Table 9).

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2.6 Systemic therapy

Close follow-up is recommended in patients identified as RAIR-DTC. The degree of disease progression should be factored into treatment decisions. Systemic therapy, including chemotherapy and molecular targeted therapy, should be considered in RAIR-DTC patients with rapidly progressive and/or symptomatic disease. Potential benefits and risks of systemic therapy should be thoroughly balanced in the candidates (Table 10, 11).

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**Table 9 Recommendation of external beam radiation therapy for prmDTC**

| Lesions                | Level I recommendation                  | Level II recommendation                  | Level III recommendation |
|------------------------|----------------------------------------|------------------------------------------|--------------------------|
| Local recurrent lesions| —                                      | EBRT (unresectable local recurrent lesions) (2A) | —                        |
| Metastatic lesions     | —                                      | EBRT/SBRT (single or oligo-metastasis) (2A) | EBRT/SBRT (selective for multiple metastases) (2B) |
| Lung metastases        | —                                      | EBRT/SBRT (symptomatic or weight bearing bones) (2A) | —                        |
| Bone metastases        | EBRT/SBRT (single or oligo-metastasis) (2A) | EBRT/SBRT (multiple metastases) (2B) | —                        |
| Brain metastases       | EBRT/SBRT (non-iodine-avid disease, palliative relief of local symptoms) (2B) | —                        | —                        |

a, External beam radiation therapy (EBRT) and stereotactic radiation therapy (SBRT) can be considered for persistent/recurrent and metastatic differentiated thyroid cancer (prmDTC), such as local recurrence and distant metastases, especially for non-iodine-avid disease or RAI-refractory thyroid cancer (1,2).
b, The optimal target volume and dose for EBRT are still controversial (3,4). Conventional fractionation radiotherapy dose is: 1) Gross target volume (GTV, mainly including recurrent or residual tumor regions, metastasis): 60−70 Gy; and 2) Clinical target volume (CTV, mainly including subclinical area): 50−60 Gy (5). Precise radiotherapy technologies, such as intensity-modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT), are safe, effective, and less morbid (6,7).
c, In the case of DTC lung metastases, EBRT or SBRT mainly applies to: 1) Single or oligo-metastasis (the definition of oligo-metastasis is not uniformly standardized, and it is generally considered that the number of metastases is ≤3–4); and 2) Lung metastases that do not intake iodine (8).
d, EBRT or SBRT can be mainly considered for symptomatic skeletal metastases or those that are asymptomatic in weight-bearing sites. The main role is to relieve the pain symptoms, reduce the risk of pathological bone events, and improve the quality of life (9,10).
e, EBRT or SBRT is one of the main treatments for brain metastases regardless of the number and size of lesions, or the iodine intake status. Once brain metastases are diagnosed, disease-specific mortality is very high (67%), with median survival of 12.4 months. Survival can be significantly improved by neurosurgical resection. With the development of radiotherapy techniques, SBRT can achieve similar results to neurosurgery (11-13).
Table 10 Stratified recommendations for potential systemic therapy in RAI-refractory prmDTC patients

| Stratificationa | Level I recommendation | Level II recommendation | Level III recommendation |
|-----------------|------------------------|-------------------------|--------------------------|
| Asymptomatic, stable or slow progression | Regular follow-up (2A) | Participation in clinical trialsb (2A) | — |
| Symptomatic or rapid progression | Sorafenibbc (1) | Adriamycin* (2A); Participation in clinical trials (2A) | — |
| Termination of targeted therapy | Tumor response evaluated to be progressive disease (PD) according to RECIST (1A) Serious drug-related adverse reactions that cannot be tolerated for continued treatmentf (1A) | Tg continues to rise or fail to decrease without disease remission according to RECIST (2A) | — |

a, Patients with very indolent disease who are asymptomatic may not be appropriate for systemic therapy, and the follow-up strategy of every 3–6 months is recommended. Whereas patients with more rapidly progressive disease may benefit from systemic therapy (1,2).

b, The following points should be taken into consideration when patients are tentatively regarded as candidates for molecular targeted therapy (3-7): 1) The benefit of molecular targeted therapy may primarily yield the prolongation of progression-free survival (PFS) rather than overall survival (OS); 2) Molecular targeted drugs may induce adverse effects and result in low quality of life (QoL); and 3) Despite radioactive iodine refractory (RAIR), the disease may remain stable for several months to several years.

c, Sorafenib is the first targeted drug applied in a completed randomized, double-blind, phase 3 trial for the treatment of locally advanced or metastatic RAIR-DTC (8). It was approved by China Food and Drug Administration (CFDA) in March 2017 for the treatment of progressive RAIR-DTC (9). Considering the balance of efficacy and side effects, 400 mg b.i.d. has been commonly utilized in most clinical trials (10-13); but the applications of low-dose sorafenib (200 mg b.i.d.) for treatment of RAIR-DTC could also achieve well efficacy with slight side effects, which may improve the compliance of patients and reduce medical costs (9,14).

d, The indications of clinical trials in this entity may include: 1) Locally advanced or metastatic RAIR-DTC patients with disease progression determined by Response Evaluation Criteria In Solid Tumors (RECIST); and 2) Patients with BRAF, PPARγ or other tumor-related gene mutations which could be targeted by molecular drugs.

e, Chemotherapy is only a palliative or experimental method for persistent/recurrent and metastatic differentiated thyroid cancer (prmDTC) with no response to other treatment. Adriamycin is the only chemotherapeutic drug approved by the US FDA (15,16).

f, Molecular targeted therapy-induced adverse effects are common, and may lead to dose reduction and drug discontinuation. Common adverse effects reported include skin toxicity, hypertension, gastrointestinal toxicity, proteinuria, fatigue, thyroid-stimulating hormone inhibitory disorders, and impaired thyroid function. Before treatment, comprehensive assessment of certain risk factors that may increase the risk of adverse effects and necessary intervention to control concomitant diseases are recommended. For adverse effects during treatment, multidisciplinary consultation should be considered to protect important organs, improve the quality of life, and maximize the effects of targeted drugs. If the degree of adverse reactions is low and the function of important organs is well, the sustained targeted therapy is recommended to obtain the maximum curative effect and survival benefit from targeted drugs; if grade 3–4 adverse effects or the damage of important organs occur, the dose reduction or drug discontinuation should be promptly adopted until the weakening or disappearance of adverse effects, and then the therapy should restart from a lower dose.

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Table 11: Efficacy of molecular targeted drugs for thyroid cancer therapeutics

| Medicines   | Pathological type | Experimental design | Number of cases | ORR        | Median PFS (month) | References                                                                 |
|-------------|-------------------|---------------------|-----------------|------------|-------------------|----------------------------------------------------------------------------|
| Sorafenib   | RAIR-DTC          | Phase III RCT vs. PLC | 207 SOR, 210 PLC | 12.2% vs. 0.5% | 10.8 vs. 5.8      | Lancet 2014; 384:319-28.                                                   |
| Lenvatinib* | RAIR-DTC          | Phase III RCT vs. PLC | 261 LEN, 131 PLC | 64.8% vs. 1.5% | 18.3 vs. 3.6       | New England journal of medicine 2015;372: 621-30.                         |
| Apatinibb   | RAIR-DTC          | Phase II            | 10              | 90%        | NR                | Oncotarget 2017;8:42252-61.                                               |
| Pazopanib   | RAIR-DTC          | Phase II            | 37              | 49%        | 11.7              | The Lancet Oncology 2010;11:962-72.                                       |
| Sunitinib   | RAIR-DTC          | Phase II            | 23              | 26%        | 8                 | European Journal of Endocrinology 2016;174:373-80.                       |
|             | RAIR-DTC/MTC      | Phase II            | 27 RAIR-DTC, 7 MTC | 31%        | NE                | Clinical cancer research 2010;16:5260-8.                                  |
| Axitinib    | RAIR-DTC/MTC      | Phase II            | 45 RAIR-DTC, 11 MTC | 30%        | 16.1              | Cancer 2014;120:2694-703.                                                |
|             | RAIR-DTC/MTC      | Phase II            | 45 RAIR-DTC, 6 MTC | 35%        | 15                | Cancer Chemotherapy and Pharmacology 2014;74:1261-70.                    |
| Vandetanib  | RAIR-DTC          | Phase I RCT vs. PLC | 72 VAN, 73 PLC  | 8% vs. 5%   | 11.1 vs. 5.9      | The Lancet Oncology 2012;13:897-905.                                     |
| Cabozantinib| RAIR-DTC          | Phase I             | 15              | 53%        | NE                | Thyroid 2014;24:1508-14.                                                 |

ORR, objective response rate; PFS, progression-free survival; RAIR-DTC, radioactive iodine refractory differentiated thyroid cancer; MTC, medullary thyroid carcinoma; RCT, randomized controlled clinical trial; PLC, placebo; SOR, sorafenib; LEN, lenvatinib; VAN, Vandetanib; NR, not reported; NE, not evaluated.

* The SELEC study showed that lenvatinib significantly prolonged PFS in RAIR-DTC compared with placebo (17). Lenvatinib mesylate has been approved by the European Commission for the treatment of invasive, locally advanced or metastatic DTCs.

b A single-arm prospective clinical trial had been conducted to evaluate the efficacy and safety of apatinib in the treatment of advanced RAIR-DTC, suggesting well tolerance with rapid-onset efficacy and high-rate of objective response in the first 8-week therapy (18).

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