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RECOMMANDATIONS

French ENT Society (SFORL) practice guidelines for lymph-node management in adult differentiated thyroid carcinoma[☆]

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[☆] The full text of these recommendations will be published in French language in <http://www.orldfrance.org/download.php?id=159>.

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Introduction

Cervical and mediastinal lymph-node management differentiated thyroid carcinoma of the follicular epithelium (DTC) remains controversial. Depending on the situation, pre-operative staging and indications for and extent of lymph-node dissection are still matters of debate, even in case of palpable nodes found on primary surgery. Procedural indications for adenectomy, selective neck dissection,

and anatomic regional extension of dissection are not clearly defined. Attitudes in suspected recurrence during follow-up need to be laid down.

The principles of DTC management in France are founded on the French Endocrinology Society (*Société Française d'Endocrinologie*) 2007 guidelines for the management of DTC of vesicular origin [1] (consensus guidelines), the 2006 and 2009 American Thyroid Association guidelines [2,3] (consensus guidelines), and the good practice guide for cervical ultrasound scan and echo-guided techniques in treating differentiated thyroid cancer of vesicular origin [4] (consensus guidelines). To formalize the rules for management of lymph-node involvement in DTC, the French ENT & Head Neck Surgery Society (*Société Française d'Oto-Rhino-Laryngologie et de Chirurgie de la Face et du Cou: SFORL*) called upon contributions from lymph-node specialist teams to a joint set of guidelines drawn up with the French Societies of Nuclear Medicine and Molecular Imaging (*Société Française de Médecine Nucléaire et d'Imagerie Moléculaire*), Radiology (*Société Française de Radiologie*) and Pathology (*Société Française de Pathologie*)¹.

The present guidelines are a logical formalization of concepts and practices regarding lymph-node management strategies in DTC. They are intended for surgeons specialized in thyroid pathology, but also for physicians managing DTC patients.

The full text, including rationale and extended reference list, is available on-line on the SFORL website (<http://www.orlfrance.org/download.php?id=159>).

Method

SFORL-member experts were appointed by the guidelines steering committee. Each of the participating societies asked its expert members to take part in a work group, which met several times during the process of drawing up the guidelines. A review group, independent of the work group, read over the draft guidelines. The final version was agreed upon at an editorial meeting.

Level of evidence and recommendations grade

The literature analysis used levels of evidence, according to the French Health Authority (HAS) 2000 guidelines. The various recommendations were graded on a modified version of the Sackett Score (Table 1).

Questions raised in the guidelines

The steering committee drew up a list of questions for the work group to address in their guidelines.

The questions concerning lymph-node involvement prognosis are as follows:

- what is lymph-node involvement in DTC?
- what information can anatomopathologic lymph-node examination provide?
- what is the prognostic value of lymph-node invasion: for recurrence, and for survival?

The question concerning complementary examinations and assessment in primary management are:

- what baseline assessment is required ahead of treatment of papillary thyroid carcinoma to assess possible lymph-node involvement?
 - in morphologic imaging,
 - in cytology,
 - in isotopic imaging.

The questions concerning neck dissection are:

- what are the principles of lymph-node surgery? Central and lateral dissection, and dissection extended to the mediastinum;
- what is the iatrogenesis in cN0 and cN+ neck?
- what is the impact of central and lateral neck dissection on recurrence, survival, secondary treatment and surveillance in cN0 and cN+ ?
- in cN0 patients, when neck dissection is considered, what lymph-node regions should be indicated?
- in IIA invasion, what should be the attitude regarding IIB?
- when should neck dissection be bilateral, electively and mandatorily?
- what is the role of the sentinel node (SN) technique?
- what role is there for extensive cervico-mediastinal dissection?

What is the role of ¹³¹I in primary treatment of adenopathy?

The questions concerning particular situations are:

- When a papillary microcarcinoma is discovered, what should be the attitude, per-operatively and postoperatively, toward the lymph-nodes areas?
- are some histologic forms of papillary cancer more aggressive than others, and therefore requiring more extensive first-line neck dissection?
- in case of recurrence or of refractory cancer:
 - what is the role of Positron emission tomography with 18-fluoro-2-deoxyglucose (PET-CT) imaging?
 - what are the indications for morphologic imaging?
 - what is the role of fine-needle aspiration cytology?
 - what surgical procedure should be performed?
 - with what precautions?
 - what risks are involved?
 - what are the other aspects of treatment?

¹ The French Society of Endocrinology (*Société Française d'Endocrinologie*) and French-speaking Association of Endocrine Surgery (*Association Francophone de Chirurgie Endocrinienne*) took part in the editing process.

Table 1 Levels of evidence and recommendation grades.

Level of evidence according to the literature	Recommendation grade
Level 1 High-power randomized comparative trials Meta-analysis of randomized comparative trials Decision analysis based on well-conducted studies	Grade A Established scientific proof
Level 2 Low-power randomized comparative trial Non-randomized well-conducted studies Cohort studies	Grade B Scientific presumption
Level 3 Case-control studies Retrospective comparative studies	Grade C Low level of evidence
Level 4 Comparative studies with serious bias Retrospective studies Case series Descriptive (transversal, longitudinal) epidemiological studies	
<i>Other publication (case report, expert opinion, etc.)</i> <i>No publication</i>	<i>Consensus guidelines^a</i>

Correspondence between literature assessment and recommendation grades (adapted from Sackett Score) according to the HAS Literature Analysis and Recommendation Grading Guide/January2000: www.has-sante.fr/portail/upload/docs/application/pdf/analiterat.pdf.

^a Unless otherwise stated, recommendations here correspond to consensus guidelines.

Guidelines

Questions concerning lymph-node involvement prognosis

What is lymph-node involvement in differentiated thyroid carcinoma?

Prognosis of lymph-node involvement in follicular DTC is controversial.

The following definitions are to be borne in mind:

- clinical stage N0 (cN0): no (clinical or radiological) pre-operative lymph-node involvement;
- lymph-node metastasis (pN1 or +): 200 μm-2 mm intranodal tumor tissue, micrometastasis; more than 2 mm, macrometastasis; less than 200 μm, isolated tumor cells (of no known prognostic value) [5];
- occult lymph-node metastasis (cN0-pN+). This term is ambiguous, covering lymph-node metastases not diagnosed on pre- or per-operative assessment, but of greatly varying sizes and whatever the type or value of the assessment.

Micrometastasis is not detected in routine practice, as it requires a large number of cross-sections per node and immunostaining (e.g., the SN technique) [6] (level of evidence, 4) [7] (level of evidence, 2).

Metastatic lymph-node involvement is very frequent in DTC, but often underestimated, both in clinical practice and in the literature. Histopathologically, the rate of pN+ varies from 15% to 60% [8] (level of evidence, 4) and may reach

80% [9] (level of evidence, 4), depending on the degree of precision of lymph-node work-up.

What factors are relevant to prognosis?

Lymph-node invasion impacts both locoregional recurrence and survival. The relative risk of mortality in DTC associated with lymph-node metastasis is 1.9 [10] (level of evidence, 2). pN+ disease was associated with elevated rates of recurrence and of mortality in 30-year follow-up studies [11] (level of evidence, 4).

Diagnosis of lymph-node metastasis reclassifies DTC patients over the age of 45 years from AJCC stage I to stage III [12] (level of evidence, 4). Thus, in case of pN+ in T1N0 cancer, iodine 131 (¹³¹I) is recommended in 30% of patients [13] (level of evidence, 4) [1] (consensus guidelines).

Recommendation 1

Infraclinical lymph-node involvement should be taken into account in micro- and macro-metastasis, as a pathological condition worsening prognosis and indicating a curative attitude. Treatment consequently does not fall under the definition of "prophylaxis" (grade B).

Pre-operative lymph-node staging

Doppler ultrasound (US) is the reference imaging examination in pre-operative assessment and surveillance of DTC [14] (level of evidence, 4), [2] [1,4] (consensus guidelines),

Table 2 Ultrasound signs of malignancy.

A single major criterion is sufficient

- Microcalcification
- Cystic area
- Hyper-echogenicity
- Exclusive or mixed peripheral vascularization (unless infection)

Minor criteria are not decisive alone

- Short axis ≥ 8 mm
- Long/short axis < 2
- No visible hilum

[15] (level of evidence, 1), with regard to detection, diagnosis, exploration for signs of malignancy and surveillance of cervical lymph nodes. The US data and interpretation of this examination are detailed in the French good practice guide [4] (consensus guidelines).

Table 2 presents the ultrasound signs of malignancy [16] (consensus guidelines) [17] (level of evidence, 4).

Lymph-node fine-needle aspiration cytology is recommended in suspect nodes discovered on pre-operative assessment or during surveillance examination, with wash-out liquid thyroglobulin (Tg) assay as required [4] (consensus guidelines).

Recommendation 2

A. In thyroid ultrasound examination, especially when pre-operative, all cervical lymph-node areas should be analyzed (grade A).

B. In proven or suspected thyroid cancer, complete pre-operative US mapping of all cervical lymph-node areas is recommended (grade A).

Recommendation 3

A. In case of non-characteristic radio-clinical presentation on initial assessment, fine-needle aspiration cytology associated to in situ wash-out liquid Tg assay is highly contributive (Expert opinion).

B. In post-treatment follow-up of thyroid cancer, fine-needle aspiration cytology is recommended:

in case of any major US malignancy criterion: microcalcification, cystic area, hyperechogenicity, or exclusive or mixed peripheral vascularization (except when associated with infection);

or in case of at least two minor criteria: short axis more or equal to 8 mm, long/short axis ratio less than 2, absence of visible hilum.

C. In lateral compartment nodes, fine-needle aspiration cytology should be completed by nodal biopsy liquid Tg assay (grade B).

Recommendation 4

In case of risk of mediastinal lymph-node extension, cervico-thoracic contrast-enhanced radiology exam should be performed (grade B).

Iodized contrast medium injection for CT precludes radio-iodine therapy for 6–8 weeks.

Postoperative and post-treatment ^{131}I scintigraphy is a whole-body planar imaging technique. Interpretation is significantly improved by hybrid SPECT-CT (single proton emission computed tomography–computed tomography) [18].

Recommendation 5

In case of radio-iodine therapy, SPECT-CT is recommended, as the optimal imaging technique for lymph-node staging, especially during the first 3 postoperative months, in preference to ultrasound. Staging influences subsequent management (grade B).

PET-CT should be reserved for suspected recurrence or persistent disease, in which cases it affects treatment decision-making in 30–40% of cases [19] (level of evidence, 3).

Recommendation 6

During postoperative follow-up, PET-CT is recommended in case of elevated serum Tg with or without suppressive treatment, unaccounted for by US and/or iodine scintigraphy (grade A).

What are the aims and principles of lymph-node surgery? Concepts of central and lateral dissection

The literature classically contrasts prophylactic dissection in cervical cN0 (“elective neck dissection”) and therapeutic dissection in clinical cervical adenopathy (“modified radical neck dissection”). However, infraclinical lymph-node metastasis (cN0-pN+) is of poor prognosis, and dissection is therefore more therapeutic than prophylactic. We therefore advise the terms “elective dissection” in cervical cN0 and “mandatory dissection” in clinical cervical adenopathy; this semantic distinction is important in order to avoid certain mistakes of management in cervical cN0.

Recommendation 7

In clinical central adenopathy, node picking (resecting just the clinical adenopathy) is not recommended but rather, if conditions permit, full-scale dissection (grade A).

Recommendation 8

In cN0, surgical exploration of the central compartment is of little diagnostic use. Two strategies are recommended: full-scale dissection of one or several lymph-node levels, or abstention from any lymph-node surgery (grade B).

Recommendation 9

Extemporaneous analysis of a lymph node can establish only a positive result, but cannot rule out lymph-node metastasis (grade A).

The central compartment thus corresponds to Robbins' level VI [20] (level of evidence, 4). It contains bilateral prelaryngeal, pretracheal and paratracheal nodes. Dissection is unilateral when it spares the paratracheal nodes contralateral to the tumor.

Recommendation 10

"Unilateral" central compartment dissection consists in complete dissection of prelaryngeal, pretracheal and paratracheal nodes on a single side, whether right or left.

"Bilateral" central compartment dissection consists in complete dissection of prelaryngeal, pretracheal and paratracheal nodes on both sides.

These terms should be used for procedural descriptions (grade B).

Recommendation 11

Surgical specimens should be sent to the anatomic pathology laboratory labelled according to the Robbins classification (grade A).

It should be borne in mind that oncologic and functional results are operator-dependent [21] (level of evidence, 4).

Lateral dissection concerns lymph-node levels I to V. Its extent and whether it is to be uni- or bi-lateral and the various surgical approaches vary from team to team and according to clinical situation. MacFee's staged incision gives very good cosmetic results [22] (Fig. 1).

Recommendation 12

In primary surgery, central dissection must precede any lateral dissection (expert opinion).

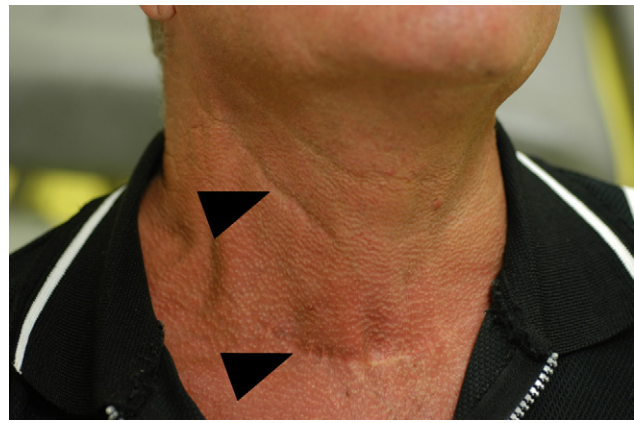


Figure 1 MacFee incision scar: enlarged lower cervicotomy of thyroidectomy (lower arrow-head) and mid-cervical contra-incision (upper arrow-head), according to Uchino et al. [22] (level of evidence, 4). Courtesy of Dr Cartier.

Recommendation 13

A. The scar left by lateral dissection is a problem for both surgeon and patient. There are no data in the literature recommending one incision rather than another (grade B).

B. In cervical cN0, MacFee's staged incision provides sufficient operative exposure, with a very good cosmetic result (expert opinion).

Recommendation 14

Radical neck dissection is not advised in thyroid cancer, other than in case of exceptionally large adenopathy, massive capsule rupture or invasion of neighboring structures seen on pre-operative imaging (expert opinion).

The levels affected in lateral cervical cN0 are IIa, III and IV, which should therefore be included in elective dissection [23–25] (level of evidence, 4).

Recommendation 15

In elective lateral compartment dissection – i.e., in clinically negative lateral compartments—levels IIa, III and IV should be dissected. Extension to levels IIb and V is recommended only when their involvement has been demonstrated histologically (grade C).

The SN technique has been validated in DTC [7] (level of evidence, 2) [26,27] (level of evidence, 4). It is applicable only in cN0 neck [7] (level of evidence, 2). It consists in intrathyroid radiotracer injection, lymphoscintigraphic imaging, selective dissection guided by handled detection probe, and definitive anatomopathologic analysis of serial step sections with immunostaining [7] (level of evidence, 2). There are, however, no reports of oncologic or functional

results in DTC for treatment strategies founded on SN analysis.

Recommendation 16

The SN technique is feasible in lymph-node treatment in DTC (grade A).

Recommendation 17

The technique should include intrathyroid radio-colloid injection, SN adenectomy and definitive pathological analysis using serial step sections with immunostaining (grade A).

Recommendation 18

The SN technique should not be applied in cN+ (grade A).

The pN stage can be determined by neck dissection and the SN technique; this results in the patient's status being changed and treatment strategy being readjusted in 30% of patients [13] (level of evidence, 4).

Recommendation 19

The nodal stage pSN based on the SN technique is more precise than the clinical nodal stage cN (grade B).

Recommendation 20

There are no data on the therapeutic impact of the SN technique; it should be implemented in formalized clinical studies (grade C).

Regarding indications, mandatory central dissection leaves no room for discussion.

Recommendation 21

Bilateral central dissection is indicated in clinical cN+ adenopathy, at whatever site, and represents "mandatory" dissection. Ideally, it should be performed in the same surgical step as total thyroidectomy (grade A).

Elective dissection (cN0) was accepted in recent consensus documents [2], with the following benefit: prevention of locoregional recurrence, improved survival, reduced morbidity associated with surgical revision, and facilitation of

subsequent treatment and follow-up [28,29] (level of evidence, 4).

Recommendation 22

Uni- or bi-lateral elective central neck dissection is strongly recommended in T3 or T4cN0 tumor (grade B).

Recommendation 23

If it is decided to totalize thyroidectomy in a cancer discovered on definitive histology (cN0), there is no recommendation for ipsilateral latero-tracheal dissection, due to elevated inferior laryngeal nerve palsy and parathyroid gland risk and the lack of sufficient evidence for improved initial control (expert opinion).

In central clinical involvement cN1a without lateral signs, lateral dissection on the lesional side is strongly recommended, as reducing the risk of lymph-node recurrence, even in low-risk tumor [30] (level of evidence, 3) [31] (level of evidence, 4).

Aggressiveness criteria such as stage T3 or T4 tumor, capsule rupture, age more than 55 years or presence of an aggressive variant are associated with increased risk of lateral involvement [32] (level of evidence, 4).

Recommendation 24

In case of central compartment lymph-node invasion (cN1a) without clinical signs of lateral compartment involvement, elective lateral dissection ipsilateral to the thyroid tumor is recommended, as the risk of lateral compartment involvement is elevated (grade B).

Recommendation 25

Complete lateral dissection is indicated in case of cytologic or histologic proof of involvement of any lateral compartment node (grade B).

Recommendation 26

Elective dissection of the lateral compartment contralateral to the thyroid tumor is indicated for pT4 tumor or more than 3 cm ipsilateral adenopathy (grade C).

Recommendation 27

Depending on the teams and practice, lateral neck dissection may or may not be performed in cN0 (expert opinion).

Recommendation 28

In locally aggressive tumor or cN0 aggressive variant, elective lateral dissection ipsilateral to the tumor is recommended (grade C).

Recommendation 29

To reduce hypoparathyroid risk during central neck dissection, hyperselective hemostasis is recommended after identification of the parathyroid glands (grade C).

Recommendation 30

If a parathyroid gland is resected during central neck dissection, it should be reimplanted, having checked that it is not a metastatic node: extemporaneous examination may be useful in case of doubt (grade C).

Recommendation 31

Neuromonitoring is recommended in case of scheduled extensive bilateral surgery and/or pre-operative unilateral palsy (grade C).

Recommendation 32

Ahead of any neck dissection, patients should be informed of the possible associated complications. Complications associated with central and with lateral dissection should be distinguished (grade B).

Recommendation 33

So-called ‘‘level VII’’ is defined above by the tracheal projection of the sternal manubrium, laterally by the brachiocephalic and left common carotid arteries, and below by the tracheal projection of the aortic arch and origin of the brachiocephalic artery (grade A) (Fig. 2).

Recommendation 34

In level VII lymph-node metastasis, it is essential to identify an at-risk group. Locally advanced DTC (>2 with extrathyroid invasion: T3–T4), uni- or bi-lateral clinical lymph-node metastasis, or level VI lymph-node metastasis raise suspicion of mediastinal lymph-node metastasis (grade B).

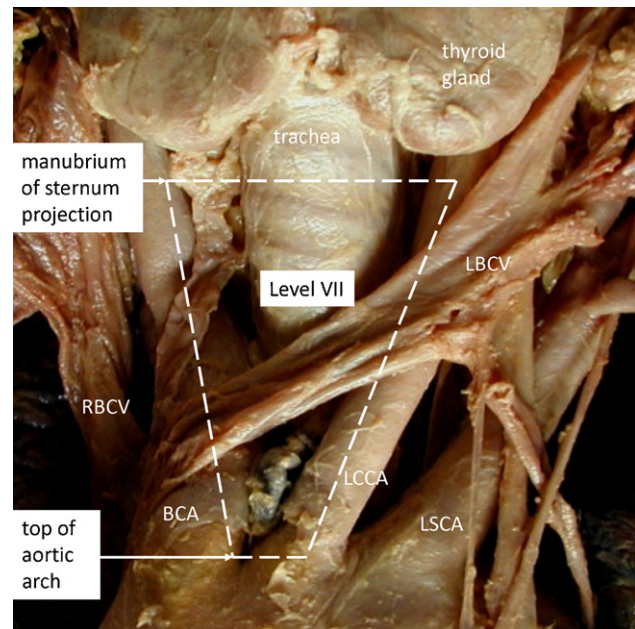


Figure 2 Cervico-mediastinal junction specimen, defined above by the thyroid body and below by the aortic arch. RBCV: right brachiocephalic vein; BCA: brachiocephalic artery; LCCA: left common carotid artery; LSCA: left subclavian artery; LBCV: left brachiocephalic vein.

Dissection by Dr Berthet.

Recommendation 35

Complete level VII (prevascular and peritracheal) cellulo-nodal dissection cannot be achieved by simple caudal extension of central cervical lymphadenectomy via the transverse cervicotomy. Optimal (en-bloc) and exhaustive level VII neck dissection (beyond the left brachiocephalic vein) requires manubriotomy extending into the third intercostal space; a multidisciplinary approach is recommended for this level (grade A).

Recommendation 36

The interest of combining video-mediastinoscopy in attempted mediastinal dissection via cervicotomy needs to be assessed (expert opinion).

Recommendation 37

A. Elective mediastinal dissection is not indicated except in case of adenopathy suspected on pre-operative examination, notably because overall survival is not improved (grade B).

B. In case of risk factors (see above), contrast-enhanced radiology exam should be systematic. According to thoracic oncologic malignancy criteria, any mediastinal adenopathy greater than 1 cm on the shortest axis is to be suspected of malignancy (grade C).

C. In massive mediastinal involvement with clear clinical or histological (aggressive variant) aggression criteria or in case of recurrence after initial treatment (surgery and radiation therapy), full-scale mediastinal dissection should be performed on the principles described above (grade B).

D. Mediastinal picking by caudal extension of central dissection is not recommended (grade B).

E. Suspected mediastinal adenomegaly on pre-operative assessment provides the only indication for full-scale level VII neck dissection on a direct manubriotomy approach. The procedure requires a multidisciplinary team, including a thoracic surgery team in particular (grade B).

First-line ¹³¹I radiation therapy

First-line ¹³¹I radiation therapy is indicated whenever tumor extension on the TNM classification and/or multifocality and/or aggressive histological type suggest residual disease, remote extension or risk of subsequent evolution [1,2] (consensus guidelines).

Recommendation 38

Lymph-node status is to be taken into account in indicating radio-iodine treatment, but is not the sole decision criterion (grade B).

Particular circumstances

In papillary microcarcinoma, what should be the per- and postoperative attitude toward the lymph-node areas?

Recommendation 39

A. In per-operatively confirmed T1-T2 cN0 cancer, at least unilateral central dissection is recommended. It should be performed by a trained surgeon. It determines pN staging (grade B).

B. Central dissection contralateral to the tumor is optional. It should be performed when inferior laryngeal nerve integrity is certain and a functional parathyroid has been conserved. Lymph-node surgery should begin ipsilaterally to the tumor (expert opinion).

Recommendation 40

If papillary microcarcinoma is discovered on definitive histology with no severity factors, no neck dissection is recommended (grade B).

Particularities relating to extension of histologic variants

Papillary thyroid cancer is generally associated with a good prognosis, but there exist certain "aggressive" variants: oncocyte, clear-cell, diffuse sclerosing, tall-cell, columnar cell, solid, cribriform morular, papillary with insular component, papillary with squamous or mucoepidermoid component, papillary with spindle or giant cell components, and composite papillary-medullary variants.

Vesicular carcinoma, on the other hand, is much less lymphophilic than papillary carcinoma, with a 0–10% rate of lymph-node involvement at presentation [33,34] (level of evidence, 4). Tumor multifocality and clearly invasive vesicular carcinoma are the two risk factors for initial lymph-node invasion [33] (level of evidence, 4).

Recommendation 41

A. If histology finds an aggressive papillary variant, a maximalist surgical attitude is recommended with respect to the lymph-node areas (expert opinion).

B. Vesicular carcinoma only rarely leads to lymph-node involvement, and lymph-node surgery is of little benefit. In multifocal and/or locally invasive forms, however, lymph-node surgery is recommended (grade C).

Management of lymph-node recurrence

In case of Tg elevation during follow-up, ultrasound and ¹³¹I scintigraphy should be performed with, in some cases, CT or MRI. Results will be negative in a quarter of cases. PET-CT is formally indicated in this situation [35] (level of evidence, 3).

Recommendation 42

In post-treatment follow-up of DTC, elevated Tg without target on complete imaging assessment is a contraindication for elective lymph-node surgery (grade B).

Recommendation 43

In lymph-node recurrence targeted on pre-operative assessment in the lateral cervical compartment, full-scale compartmental dissection including the target is recommended if no extra risk is associated with surgery (grade B).

Recommendation 44

A. Central compartment revision surgery for lymph-node recurrence should be targeted (grade B).

B. It requires optimal guidance, with at least conventional imaging and nuclear imaging with image fusion (grade C).

Most teams recommend neuromonitoring to facilitate inferior laryngeal nerve identification in such revision surgery [36–38] (level of evidence, 4).

Recommendation 45

Inferior laryngeal nerve neuromonitoring is recommended in central compartment lymph-node revision surgery (grade B).

Recommendation 46

A. Repeat ^{131}I treatment may be considered after surgical revision. If surgery is not indicated, radioiodine therapy should be performed.

B. In case of persistent fixation after a therapeutic dose of ^{131}I on scintigraphy, radioiodine therapy may be repeated.

Refractory tumor

DTC is considered refractory in the absence of ^{131}I fixation, in case of progression following radioiodine therapy or as of a cumulative dose of 22 GBq (600 mCi) [39] (consensus guidelines).

Recommendation 47

In refractory tumor with non-resectable adenopathy, treatment options are either external radiation therapy or participation in a therapeutic trial (grade B).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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