

German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors

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Ohne Schilddrüse leben e.V.

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Abstract

Introduction Over the past years, the incidence of thyroid cancer has surged not only in Germany but also in other countries of the Western hemisphere. This surge was first and foremost due to an increase of prognostically favorable (“low risk”) papillary thyroid microcarcinomas, for which limited surgical procedures are often sufficient without loss of oncological benefit. These developments called for an update of the previous practice guideline to detail the surgical treatment options that are available for the various disease entities and tumor stages.

Methods The present German Association of Endocrine Surgeons practice guideline was developed on the basis of clinical evidence considering current national and international treatment recommendations through a formal expert consensus process in collaboration with the German Societies of General and Visceral Surgery, Endocrinology, Nuclear Medicine, Pathology, Radiooncology, Oncological Hematology, and a German thyroid cancer patient support organization.

Results The practice guideline for the surgical management of malignant thyroid tumors includes recommendations regarding

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preoperative workup; classification of locoregional nodes and terminology of surgical procedures; frequency, clinical, and histopathological features of occult and clinically apparent papillary, follicular, poorly differentiated, undifferentiated, and sporadic and hereditary medullary thyroid cancers, thyroid lymphoma and thyroid metastases from primaries outside the thyroid gland; extent of thyroidectomy; extent of lymph node dissection; aerodigestive tract resection; postoperative follow-up and surgery for recurrence and distant metastases.

Conclusion These evidence-based recommendations for surgical therapy reflect various “treatment corridors” that are best discussed within multidisciplinary teams and the patient considering tumor type, stage, progression, and inherent surgical risk.

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Keywords Lymph node classification · Compartment-oriented surgery · Papillary, follicular, and medullary thyroid carcinoma · Poorly differentiated and undifferentiated carcinoma · Thyroid lymphoma · Thyroid metastases from renal cell, lung, and breast cancer

Preamble

Malignant thyroid tumors, accounting for 5,000 new cases in Germany every year, represent fewer than 2 % of all new cases of cancer [1]. This heterogenous group of tumors differs greatly in tumor biology and clinical outcome. Most tumors, producing and secreting thyroid hormones, are of follicular cell origin: papillary [PTC], follicular [FTC], poorly differentiated [PDTC], and undifferentiated (anaplastic) thyroid cancer [UTC]. Other tumors derive from the parafollicular C cells, which are dispersed across the thyroid gland (medullary thyroid cancer [MTC]), whereas a few tumors originate from the thyroidal mesenchyma (e.g., malignant lymphoma and sarcoma) [2].

Over the past years, the incidence of thyroid cancer has surged not only in Germany but also in other countries of the Western hemisphere [1, 3–6]. This surge was first and foremost due to an increase of prognostically favorable (‘low risk’) papillary thyroid microcarcinomas, for which limited surgical procedures are often sufficient without loss of oncological benefit. These developments called for an update of the previous practice guideline [7] to detail the surgical treatment options that are available for the various disease entities and tumor stages.

The present German Association of Endocrine Surgeons practice guideline was developed on the basis of clinical evidence considering current national and international treatment recommendations [8–15]. Because thyroid cancer is uncommon, most, if not all, clinical studies on thyroid cancer surgery are retrospective in nature [16]. The following recommendations for surgical therapy reflect various “treatment corridors” that are best discussed within multidisciplinary teams and the patient [17] considering tumor type [2], stage [18], progression, and inherent surgical risk.

Preoperative workup

History and physical examination

Taking a family history is important in that it can provide valuable clues as to a patient’s predisposition to thyroid cancer or hereditary tumor syndromes that include thyroid cancer as an integral component (e.g., multiple endocrine neoplasia type 2 (MEN2), familial nonmedullary thyroid cancer, Cowden’s disease, Carney complex, familial adenomatous polyposis) [19]. The patient’s personal history may reveal previous neck

radiation (neck, skull, mediastinum, thymus, whole body) [20], earlier malignancies (e.g., renal cell cancer; cf. “[Thyroid metastases of primaries from outside the thyroid gland](#)” section), or fast growth of a thyroid nodule, all of which may be indicative of malignant disease. Rapid growth of the thyroid nodule may point to poorly differentiated or undifferentiated thyroid cancers or malignant lymphoma, calling for cytological or histological confirmation via fine-needle aspiration cytology or biopsy.

Physical examination consists of palpation of the thyroid gland and a search for enlarged neck nodes. Firm consistency or reduced movement of a thyroid nodule on swallowing, palpable neck nodes, or new onset hoarseness as a result of recurrent laryngeal nerve palsy often signify thyroid cancer so that additional investigations are necessary.

Recommendation 1:

Family and personal histories support the identification of risk factors for thyroid malignancy. The clinical work-up of the neck needs to focus on suspicious findings, clarifying their relationship within the anatomy of the neck.

Ultrasonography

Neck ultrasonography forms an integral part of the clinical workup for thyroid disease, laying the foundation for the performance and the extent of surgery [21]. Ultrasonography provides information about the extension and structure of nodular and invasive thyroid disease. Moreover, it visualizes abnormal findings outside the thyroid gland such as enlarged lymph nodes [22].

Although ultrasonography is not suited to rule out malignancy definitively because of inherent limitations in the evaluation of tumor dignity, the totality of ultrasonographic evidence can strengthen the clinical suspicion of malignancy. The ultrasonographic finding of a circumscribed hypoechoic nodule with irregular margins, microcalcifications, and central hypervascularization can increase that nodule’s likelihood of malignancy by up to 80 % [23–26].

Recommendation 2:

Ultrasonography of the thyroid gland and neck nodes is an indispensable diagnostic tool for the preoperative work-up of thyroid nodules. Irregular margins, microcalcifications and central hypervascularization are ultrasonographic findings associated with an increased risk of malignancy.

Scintigraphy and positron emission tomography/computed tomography

For functional differentiation of nodules, ^{99m}Tc-pertechnetate scintigraphy is useful in particular when basal thyroid stimulating hormone (TSH) serum levels are low.

Increased concentration of the radiotracer by a hyperfunctioning nodule is almost inconsistent with malignancy [25]. Reduced or absent concentration of the radiotracer on the other hand is poorly predictive of malignancy because the majority of thyroid nodules are hypofunctioning (‘cold’) in regions where multinodular goiter is endemic [26]. Metaiodobenzylguanidine (MIBG) scintigraphy and fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) are rarely helpful in the subdifferentiation of cold nodules [27–30], limiting their use to special circumstances.

Recommendation 3:

Preoperative scintigraphy is useful for the functional mapping of thyroid nodules, informing decisions on the extent of thyroid resection.

Extended imaging and endoscopic workup

Upon evidence of extrathyroidal extension, retrosternal growth, and clinically or sonographically widespread lymph node metastases, extended imaging is advised to define the required extent of thyroid resection and dissection in the neck. For this purpose, magnetic resonance imaging (MRI) is the method of choice because contrast-enhanced CT interferes with postoperative radioiodine therapy.

Laryngoscopy

Vocal cord dysfunctions have a tremendous impact on treatment plans, especially when thyroid surgery is an option and surgical procedures need to be planned. Preoperative laryngoscopy is recommended to exclude or verify preexisting vocal cord palsy, even in the face of an intact-appearing voice [31, 32]. Before reoperation in the neck and when the voice is abnormal, preoperative laryngoscopy is imperative and may necessitate further diagnostic investigations.

Recommendation 4:

Because vocal cord dysfunctions influence treatment decisions greatly, especially when thyroid surgery is an option and surgical procedures need to be planned, preoperative laryngoscopy is generally recommended. It is imperative after previous neck surgery and when the voice is abnormal.

Calcium

Preoperative determination of serum calcium levels is necessary for exclusion or confirmation of concomitant primary hyperparathyroidism. A preoperative diagnosis of primary hyperparathyroidism has immediate consequences for the surgical treatment plan, which also needs to consider the possibility of MEN2 (coexistence with medullary thyroid cancer and pheochromocytoma).

The presence of asymptomatic hypoparathyroidism as a result of previous thyroid surgery is associated with an increased risk of permanent hypoparathyroidism after reoperation.

Recommendation 5:

Preoperative determination of calcium serum levels is needed for exclusion of concomitant primary hyperparathyroidism. If calcium levels are elevated, the presence of MEN type 2 (medullary thyroid cancer, pheochromocytoma) should be considered. In patients with preexisting hypocalcemia after previous neck surgery, there is an increased risk of postoperative permanent hypoparathyroidism.

Calcitonin

Increased serum levels of calcitonin are very sensitive for medullary thyroid cancer [33–36]. Because early diagnosis of medullary thyroid cancer is thought to improve survival [36] and ultrasonography and fine-needle aspiration cytology cannot rule out medullary microcarcinomas reliably, the preoperative measurement of serum calcitonin is recommended before thyroid surgery (cf. “[Medullary thyroid cancer](#)” section).

If basal calcitonin serum levels are elevated, a calcitonin stimulation test with pentagastrin or calcium [37, 38] should be carried out for distinction between C cell hyperplasia and medullary thyroid cancer [39–42]. Pentagastrin-stimulated levels ≤ 100 pg/mL do not rule out medullary thyroid cancer, whereas stimulated levels >100 pg/mL increase the likelihood of its presence. Medullary thyroid cancer is almost always found when stimulated calcitonin levels are higher than 500 pg/mL.

Commercially available calcitonin assays, differing in their normal limits, may also vary by patient age and gender [41]. To interpret these calcitonin measurements correctly, clinical conditions (e.g., chronic renal failure) and drug interactions raising serum calcitonin levels must be taken into account.

Recommendation 6:

Basal calcitonin serum levels should be determined for early diagnosis of medullary thyroid cancer before thyroid surgery. If calcitonin levels are elevated, a calcitonin stimulation test with pentagastrin or calcium is recommended.

Thyroglobulin

Measuring serum thyroglobulin levels is helpful for the workup of recurrent differentiated thyroid cancers after total thyroidectomy [43, 44]. Because these levels may be elevated in benign thyroid disease [45], measurements of serum thyroglobulin levels have no role in the workup of newly diagnosed differentiated thyroid cancers.

Fine-needle aspiration and cytology

Fine-needle aspiration cytology gained from a suspicious thyroid nodule helps define nodule type and risk of malignancy [46, 47]. Cytological results should be reported using a therapy-stratifying classification system [48–52]. Fine-needle aspiration entails a low risk of nerve injury and local hemorrhage, which may be relevant to patients susceptible to spontaneous bleeding. Needle tract metastases from thyroid cancers are exceedingly rare, and in all likelihood do not affect clinical outcome [53].

The validity of fine-needle aspiration cytology is operator-dependent and conditioned by the size and position of the target lesion. Cytology alone rarely allows decisions on whether to operate or not to operate. A target lesion should be evaluated using fine-needle aspiration cytology if it is:

- A suspicious thyroid nodule, clinically or on imaging
- An enlarged neck node suggestive of tumor
- A large or rapidly growing tumor
- A locally invasive tumor

The cytological diagnosis of ‘follicular neoplasia’ cannot distinguish follicular adenoma, follicular thyroid cancer, and the follicular variant of PTC, requiring histopathological clarification. If malignant lymphoma is suspected, additional immunocytochemical investigations are necessary (cf. “[Lymphoma](#)” section). Molecular genetic investigations (e.g., BRAF) may augment the validity of fine-needle aspiration cytology, and, if positive, may also be predictive of clinical outcome [54–56].

Recommendation 7:

Nodules that are suspicious of malignancy clinically or on imaging should prompt fine-needle aspiration. If the cytological result comes back negative (*‘benign’*), clinical and imaging results must determine the need for thyroid surgery. Histological evaluation of a lesion is always needed for a cytological diagnosis of *‘follicular neoplasia’*, suspicion of malignancy, BRAF-positive tumors, or an apparent malignancy.

Biopsy

Biopsies (punch biopsy, open thyroid or nodal biopsy, or endoscopic tracheal or esophageal biopsy) should be taken when fine-needle aspiration cytology is indeterminate, but the tumor’s clinical presentation is demanding an operation, the required extent of which is unclear. Typical examples include:

- Large or locally invasive, potentially unresectable tumor
- Suspected lymphoma
- Lymph node enlargement without a known primary

Table 1 Classification of locoregional nodes used in thyroid cancer

Compartment classification (Dralle et al. 1994 [59])	American Head and Neck Society classification (Robbins et al. 2008 [60])	UICC classification (Wittekind et al. 2003 [62])	Japanese classification (Qubain et al. 2002 [63])
Compartment 1 (1a cervicocentral right, 1b cervicocentral left)	Without side identifier: level 1 (submental, submandibular), level 6 (central), level 7 (lower central)	Without side identifier: nodal groups 1 and 2 (submental, submandibular) and 8 (central)	Without side identifier: regional nodal groups 1–4
Compartment 2, cervicolateral right; Compartment 3, cervicolateral left	Without side identifier: level 2A, 2B (upper jugular), level 3 (mid-jugular), level 4 (lower jugular), level 5A, 5B (lateral jugular)	Without side identifier: nodal groups 2, 3 (upper jugular), 4 (mid-jugular), 5 (lower jugular), 6 (posterior-lateral), and 7 (lateral-supraclavicular)	Without side identifier: regional nodal groups 5–7
Compartment 4 (upper infrabrachiocephic mediastinum: 4a right, 4b left)	–	–	–

Recommendation 8:

In patients with potentially unresectable tumor, suspected lymphoma, or lymph node enlargement without a known primary, biopsies affording a tissue diagnosis are necessary to clarify the need for, and the extent of surgery after fine-needle aspiration cytology returned an indeterminate cytological result.

Classification of locoregional nodes and terminology of surgical procedures

Classification of locoregional nodes

Based on anatomical–clinical investigations, the locoregional lymph nodes are grouped into four compartments: a central, an ipsilateral lateral and a contralateral lateral neck compartment, and an infrabrachiocephalic mediastinal compartment [57–59]. Internationally, four classifications of locoregional lymph nodes are used for reporting nodal involvement in thyroid cancer (Table 1) [57, 59–63]. These classification systems differ mainly in how nodal subgroups are divided, whether the side of the nodal group (right versus left) forms an integral part of lymph node terminology, and whether the infrabrachiocephalic upper mediastinum is included.

Because correct side identification is so important for tumor staging and adequate surgical treatment, the compartment classification (Fig. 1) will be used in this practice guideline.

Central compartment

The central compartment (C1a, cervicocentral right; C1b, cervicocentral left; Fig. 1a) comprises, from an anatomical–surgical perspective, the entire soft tissue and lymph node space confined by the common carotid arteries laterally and the hyoid bone superiorly. Its inferior border is marked on the right by the brachiocephalic trunk and on the left by the V-shaped departure of the left common carotid artery from the aortic arch. The traverse left brachiocephalic vein divides the neck from the mediastinal nodal space so that the suprabrachiocephalic part of the upper mediastinum belongs to the cervicocentral compartment.

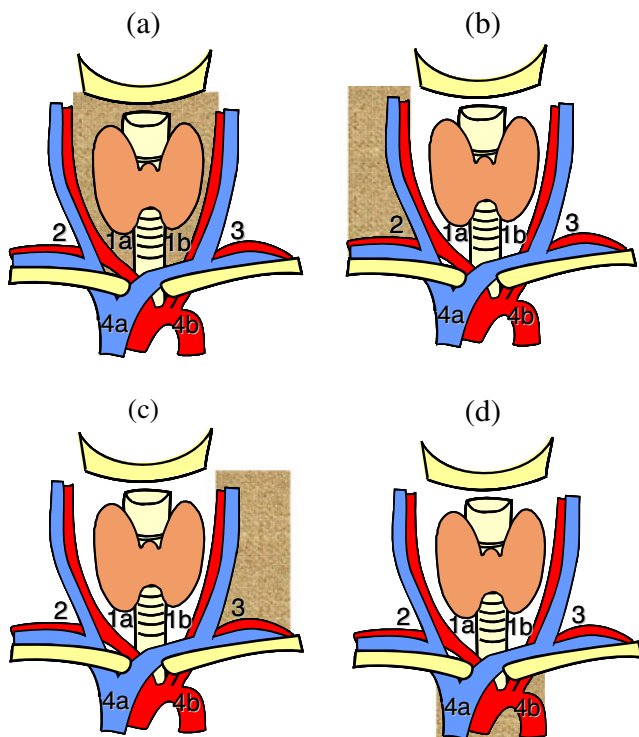


Fig. 1 Compartment classification of locoregional nodes. **a** Cervicocentral (C1a, right; C1b, left); **b** right cervicolateral (C2); **c** left cervicolateral (C3); and **d** infrabrachiocephalic upper mediastinal compartment (C4a, right; C4b, left) [55–60]

The median trachea, lacking anatomical borders comparable to the lateral fascial limitation at the carotid artery, splits the central compartment into a right and left portion. The recurrent laryngeal nerve subdivides the right and left central compartment into an anterior ('anteneural') (level 6) and posterior ('retroneural') part (level 7). The third part of the central compartment includes the superior pretracheal ('Delphi') nodes.

Recommendation 9:

The central compartment is bordered laterally by the common carotid arteries, superiorly by the hyoid bone, and inferiorly by the left brachiocephalic vein. It is split by the median trachea into a right (C1a) and left portion (C1b). The recurrent laryngeal nerve subdivides the central compartment into an anterior (anteneural) and a posterior (retroneural) part.

Lateral compartment

The lateral compartment (C2, cervicolateral right; C3, cervicolateral left; Fig. 1b, c) extends on either side of the common carotid artery laterally to the trapezius muscle, superiorly to the hypoglossal nerve, and inferiorly to the subclavian vein. Posteriorly, it is confined by the dorsal cervical fascia below which courses the phrenic nerve. Conversely, the fascicles of the cervical–brachial plexus and the accessory nerve run through the lateral compartment, leaving them vulnerable to injury during lateral lymph node dissection. The thyroid lobes and the central compartment connect to the lateral compartment through lymph ducts that follow the thyroid veins anterior and posterior to the carotid sheath [64, 65].

Recommendation 10:

The lateral compartment (C2 right, C3 left) extends from the common carotid artery to the trapezius muscle laterally. It is confined superiorly by the hypoglossal nerve, inferiorly by the subclavian vein, and posteriorly by the posterior cervical fascia.

Mediastinal compartment

The mediastinal compartment (C4a, right; C4b left; Fig. 1d), uninterrupted by fascial boundaries, continues seamlessly from the left brachiocephalic vein superiorly in two directions inferiorly. Bordered laterally by the mediastinal pleura, it takes an anterior route to the thymus and preaortic nodes down to the pericardium, and a posterior route to the paratracheoesophageal nodes down to the tracheal bifurcation.

A transsternal approach is required for dissection of the infrabrachiocephalic mediastinum. When the central neck and the mediastinal compartment need to be cleared in one session, the soft tissues with all the nodes, preserving vascular and neural structures, can be removed as one contiguous central–mediastinal specimen because of the lack of anatomical barriers.

Recommendation 11:

The mediastinal compartment (C4a right, C4b left), bordered laterally by the mediastinal pleura, extends from the left brachiocephalic vein superiorly in two directions inferiorly, taking an anterior route to the thymus and the preaortic nodes, and a posterior route to the paratracheoesophageal nodes down to the tracheal bifurcation.

Terminology of surgical procedures

A number of technical terms have been used in the international literature to denote different forms of resection and dissection [60, 61]. Many terminologies combine in various ways the extent of lymph node dissection with the extent of resection of muscles, nerves, and vessels (e.g., radical or modified radical neck dissection). These terminologies do not seem to be appropriate for thyroid cancer surgery because they refer to surgical techniques often applied to squamous cell cancers of the head and neck, aggressive malignancies that differ greatly from thyroid cancer. To better reflect the biological behavior of thyroid cancer, the surgical terminology used in this practice guideline makes reference to the compartment classification ("Classification of locoregional nodes" section).

The surgical removal of muscles, nerves and vessels, and the respective surgical approach (cervical, transsternal) should also be reflected in the surgical terminology. If a compartment is not cleared in total, i.e., when only single nodes or certain nodal groups are removed ("berry picking," "focused approach"), this should be noted as well (e.g., selective lymph node dissection in compartment 1, 2, 3, and/or 4).

The prophylactic clearance of a compartment indicates a systematic lymph node dissection in the absence of clinical lymph node metastases, whereas a therapeutic dissection of a compartment signifies a lymph node dissection for lymph node metastases that are clinically apparent, visible on imaging, and/or have been confirmed cytologically or histopathologically.

As is customary practice in surgical oncology, the histopathological examination of surgical specimens should specify the number of examined and involved nodes per compartment. The central and mediastinal compartments

include means of ten nodes (five on each side), whereas lateral compartments encompass means of 20 nodes [58, 62, 66].

Recommendation 12:

The terminology of surgical procedures for thyroid cancer is based on the compartment classification. It is to be completed as needed by additions regarding surgical indication (prophylactic vs. therapeutic), surgical approach (e. g. cervical vs. transsternal), resected adjacent structures (e.g., muscles, nerves and vessels), and surgical technique (compartment-oriented vs. selective).

Papillary thyroid cancer

Frequency, clinical and histopathological features

Papillary thyroid cancer (PTC), accounting for 60–80 % of all thyroid cancers and featuring survival rates of 90 %, is the most common and prognostically most favorable tumor entity [67]. In infancy and adulthood, PTC is encountered almost exclusively. In adults, the female-to-male ratio approximates 4:1. Although women as a group develop less aggressive cancers, both women and men end up having an equal share of more aggressive thyroid cancers. PTC is characterized by a high prevalence of papillary thyroid microcarcinoma (defined as PTC measuring 10 mm or less in greatest dimension) and a propensity to lymphatic dissemination.

Histopathologically, PTC is defined as a malignant epithelial thyroid tumor of follicular cell origin revealing a unique nuclear morphology (“ground-glass nuclei”) [2]. Papillae-like structures are common but absent in the follicular variant of PTC. Additional subtypes include the oncocytic, clear-cell, diffuse-sclerosing, tall-cell, columnar-cell, solid, and cribriform variants of PTC [2, 68]. Some variants are associated with worse clinical outcomes than the classic form of PTC [69].

To keep the risk of local and distant recurrence at a minimum, the thyroid primary and all involved locoregional nodes have to be removed [70–73]. For node-positive PTC, total thyroidectomy with clearance of the central compartment during the same session is the method of choice, providing an optimal setting for postoperative follow-up investigations (serial thyroglobulin measurements, diagnostic, and therapeutic radioiodine scans).

Nonmetastatic papillary thyroid microcarcinoma (≤10 mm, PTMC)

Thyroidectomy

Numerous studies have shown that patients with papillary thyroid microcarcinomas (PTMC) confined to the

thyroid gland (implying node-negative primary tumors ≤10 mm without distant metastases) have excellent clinical outcomes [74–76]. Given this large body of evidence, there is universal consensus that these non-metastatic PTMC do not require total thyroidectomy on oncological grounds [7, 8, 10–12]. This implies no need for completion total thyroidectomy or postoperative radioiodine therapy on histopathological demonstration of PTMC when there is no clinical evidence of residual tumor [13, 77–79].

Although a size threshold of 10 mm is well founded [73, 74], oncologically it reflects a biologic continuum [80]. This continuum, especially when the diagnosis is made after thyroid resection, provides for a treatment corridor of alternative therapies that is to be customized to the individual patient in an interdisciplinary effort.

The same principles governing these treatment corridors also apply to multifocal [81–88], postradiation [89], and minimally extrathyroidal [90–95] classic PTMC and the special variants of PTMC. The latter micrometastases, measuring no more than 10 mm, perhaps entail an incremental risk of recurrence that may be too small for total thyroidectomy to be clinically useful.

Recommendation 13:

Papillary thyroid microcarcinomas confined to the thyroid gland (implying node-negative tumors ≤ 10mm without distant metastases) do not require routine total thyroidectomy. Because the 10-mm size threshold, delimiting microcarcinomas, represents a biologic continuum, decisions regarding completion thyroidectomy and/or postoperative radioiodine therapy should be made by an interdisciplinary board, notably for minimally extrathyroidal, multifocal, and non-classic incidental PTMC.

Lymph node dissection

Whatever the extent of thyroidectomy, prophylactic dissection of the central lymph node compartment is generally unwarranted in clinically nonmetastatic PTMC confined to the thyroid gland with no involvement of the thyroid capsule [7, 8, 10–12, 83, 88, 96]. The rationale behind this consensus is the lack of proven benefit as to long-term clinical outcome and the risk of surgical complications attendant to central lymph node dissection, i.e., recurrent laryngeal nerve palsy and specifically hypoparathyroidism [96–100].

One third of patients harboring PTMC who undergo neck surgery reveal subclinical lymph node metastases on histopathological examination that were difficult, if not impossible, to spot on ultrasonography before the operation [101, 102]. In this setting, treatment corridors exist

not only regarding the extent of total thyroidectomy but also regarding the need for prophylactic central lymph node dissection. Because none of these procedures yielded demonstrable oncological benefits, individual treatment decisions need to be made within these corridors, focusing first and foremost on the patient's risk of surgical complications, i.e., recurrent laryngeal nerve palsy and hypoparathyroidism. Prophylactic clearance of the central compartment is not recommended for completion of an earlier thyroidectomy unless there is evidence of residual tumor in the neck.

Recommendation 14:

If a clinically nonmetastatic PTMC is confirmed before or during the operation that was confined to the thyroid gland and did not involve the thyroid capsule, the unproved oncological benefit of total thyroidectomy and central lymph node dissection should be weighed against the surgical risk of recurrent laryngeal nerve palsy and hypoparathyroidism.

Recommendation 15:

For patients without a postoperative diagnosis of clinically node-negative PTMC and without evidence of residual tumor, prophylactic completion thyroidectomy and/or lymph node dissection is not recommended.

PTC larger than 10 mm and metastatic PTC of any size

Thyroidectomy

Total thyroidectomy is generally warranted for PTC >10 mm and for metastatic or grossly invasive PTC of any size [7, 8, 10–12]. Key arguments supporting this recommendation include the high rate of tumor multifocality, the risk of intraglandular and extraglandular dissemination, and facilitation of radioiodine therapy and diagnostic scintiscans on follow-up [78]. It has been demonstrated that total, as opposed to subtotal, thyroidectomy for PTC >10 mm lowered the risk of locoregional recurrence while improving survival [74, 75].

Recommendation 16:

Total thyroidectomy is warranted for PTC >10 mm and for metastatic or grossly invasive PTC of any size.

Lymph node dissection

Central compartment dissection If lymph node metastases are clinically apparent (cN1), dissection of the central compartment is needed, whatever the size of the thyroid primary, to reduce the rate of locoregional recurrence and improve

survival [70], avoid reoperation for recurrent tumor at incremental surgical morbidity, and perhaps to save radioiodine activity that otherwise would be required for ablation of undissected lymph node metastases [8, 10, 11]. The total number of involved lymph node metastases is of prognostic relevance [103–105]. It remains to be shown whether it is oncologically sound to restrict the compartment dissection to the clinically affected side [100] so that the normal-appearing opposite side of the neck can be spared [106, 107].

Without clinical evidence of lymph node metastases (cN0), the overall benefit of prophylactic lymph node dissection, a lower locoregional recurrence rate and improved survival, is uncertain [85, 96, 98, 99, 108–114]. Arguments in favor of prophylactic clearance of the central compartment include more accurate histopathological staging [85], the high frequency of occult lymph node metastases [108], and the higher rates of postoperative normalization of the tumor marker thyroglobulin [98, 115]. Counterarguments are the lack of proven oncological benefit [109, 110, 114] and the greater risk of complications, in particular transient and permanent hypoparathyroidism [98–100]. On balance, and subject to the availability of adequate surgical expertise, the pendulum is currently swinging towards prophylactic central compartment dissection for PTC >10 mm [8]. Based on the data available, there is a treatment corridor for clinically node-negative PTC regarding central compartment dissection, within which surgical decisions need to be individualized according to patient-related factors such as age, surgical risk, and perhaps molecular factors, such as BRAF mutations [116–120].

Recommendation 17:

The clinical benefit regarding locoregional recurrence and survival after prophylactic compartment dissection for clinically node-negative PTC >10mm is unproven although occult lymph node metastases are common in this setting. To prevent the risk of surgical complications from outweighing a conceivable oncological benefit, prophylactic lymph node dissection is not advised unless the requisite surgical expertise is available.

Recommendation 18:

For clinically node-positive PTC, whatever the size of the thyroid primary, central compartment dissection should be combined with total thyroidectomy to diminish the risk of locoregional recurrence and improve survival.

Recommendation 19:

If the diagnosis of clinically node-negative PTC is made after thyroidectomy, prophylactic central compartment dissection is not warranted for completion in the absence of residual tumor.

Lateral compartment dissection Lymph node metastases in the lateral neck are present in 25 % of patients with PTC [121, 122]. In 20 % of patients with node-positive PTC, skip metastases (implying involvement of the lateral but not the central neck compartment) are found [123]. This pattern of lymphatic dissemination is seen predominantly in thyroid primaries of the upper thyroid pole [124, 125].

If lateral neck metastases are suspected or identified by clinical palpation, ultrasonography and/or biopsy before, or by visual inspection and/or frozen section during the operation, it is recommended to dissect the involved lateral compartment during the same session [8, 10, 103, 126, 127]. Whether this dissection can be safely restricted to certain regions of the lateral neck [128, 129] is to be clarified. For the time being, it may be more prudent to clear the entire lateral compartment. Numerous central lymph node metastases (i.e., >5 involved nodes) increase the risk that the lateral compartment is involved on either side of the neck to more than 70 % [103]. In this setting, it is worthwhile to dissect the lateral compartment on one or each side of the neck to minimize the risk of locoregional recurrence and avoid reoperations. Alternatively, lymph node dissection may be held off until diagnostic or therapeutic scintiscans or other imaging localize residual lymph node metastases in the lateral neck.

Recommendation 20:

If lateral lymph node metastases are clinically suspected or histopathologically confirmed, lateral compartment dissection is recommended on the involved side, and perhaps also on the clinically uninvolved side, notably if numerous central lymph node metastases are present. Alternatively, a two-stage approach may be a viable option.

In view of the attendant surgical morbidity (e.g., lymphatic leakage and shoulder-arm syndrome) [130–135], the data available do not provide sufficient evidence to warrant prophylactic lateral compartment dissection [136] if no lateral lymph node metastases are clinically apparent and no or only a few central nodes are involved.

Recommendation 21:

In the absence of lateral lymph node metastases, prophylactic lateral compartment dissection is not generally recommended. Possible exceptions include PTC that originate from the upper thyroid pole or are associated with numerous central lymph node metastases.

Transsternal mediastinal compartment dissection Mediastinal lymph node metastases, which are rare in PTC (<5 %) [137], can be surgically cleared with curative intent in the absence of distant metastases [138]. If clinical imaging

studies or surgical exploration of the mediastinum reveal infrabrachiocephalic lymph node metastases underneath the sternum, transsternal dissection of the mediastinal compartment should be considered, taking into account the patient's physical shape and overall tumor burden. There is no need for prophylactic transsternal mediastinal dissection because of the related incremental morbidity.

Recommendation 22:

Transsternal mediastinal lymph node dissection is generally warranted when infrabrachiocephalic mediastinal lymph nodes are involved, especially when the patient is in reasonably good shape and distant metastases are absent. Owing to the incremental surgical risk of the transsternal approach, prophylactic mediastinal lymph node dissection is discouraged.

Aerodigestive tract resection for grossly invasive PTC

Grossly invasive PTC, unlike minimally extrathyroidal PTC [95, 135, 139, 140], has a high risk of distant and locoregional metastases and recurrence [91–94]. Invasion of the aerodigestive tract is seen in no more than 5–7 % of all patients with PTC. Clearance of grossly invasive thyroid primaries should be attempted to circumvent, or surgically treat, tumor-related aerodigestive complications unless the patient is in poor shape and there are progressive distant metastases. The successful performance of aerodigestive resections is dependent on the availability of the requisite surgical expertise and adequate postoperative care [141–146]. Alternatives to segmental or window resections of the trachea include tracheal shaving (implying removal of the invasive tumor leaving behind the invaded tracheal wall) or nonoperative palliative procedures in conjunction with adjuvant therapies (e.g., radioiodine therapy, external radiation, chemotherapy). Shaving is not advised for transmural tumor invasion.

Recommendation 23:

If certain preconditions are met (reasonable physical shape, absence of progressive distant metastases, resectable tumor, requisite surgical expertise and adequate postoperative care), surgical clearance of aerodigestive tumor invasion should be attempted. Alternatively, nonoperative palliative therapies are an option.

Completion surgery for incidental PTC

Reoperations for PTC are required for completion when the extent of the initial operation was less extensive than recommended for a comparable thyroid primary, or when clearance of the thyroid primary was incomplete. Rare exceptions include irresectable tumors and minimal tumor extensions into

the trachea or around the recurrent laryngeal nerve that are amenable to radioiodine therapy [79]. The treatment plan needs to reconcile tumor-, treatment-, and patient-related factors, which is best accomplished through interdisciplinary evaluation.

If a small thyroid remnant has been left behind without evidence of residual disease, thyroid ablation with radioiodine is a viable alternative to completion thyroidectomy, in particular when the recurrent laryngeal nerve on the side of completion is the sole functional recurrent laryngeal nerve [147–149]. The equivalence of these two alternatives has not been established so that an interdisciplinary consensus should be sought.

After complete thyroidectomy, there is no need for prophylactic dissection of locoregional nodes for completion. If laboratory tests (e.g., thyroglobulin) or imaging studies suggest residual disease in the thyroid bed or nodes, these foci should be excised first to decrease the total dose of radioactivity needed for tumor ablation and follow-up scintiscans.

If a reoperation is needed for completion, it should be scheduled preferably within 4 days of, or more than 3 months after the initial operation [79, 150] to circumvent the complication-rich period between these time limits [150]. As a matter of fact, there is no difference in the level of oncological risk between very early and delayed reoperations for completion provided that the thyroid primary was removed initially [150–152]. Minimization of surgical morbidity is of greater concern in this setting than early reoperation. After an incomplete resection of a thyroid primary, completion surgery should be carried out as soon as possible.

Recommendation 24:

Reoperation for incidental PTC is necessary for completion when the extent of the initial operation was less extensive than recommended for a comparable thyroid primary, or tumor removal was incomplete, with exceptions including irresectable tumors or limited tumor extensions into the trachea or around the recurrent laryngeal nerve that are amenable to radioiodine therapy. The best time for surgical completion is within 4 days of, or more than 3 months after the initial operation. In the absence of residual tumor, a 3-month wait does not involve a higher level of oncological risk.

Special variants of PTC

Oncocytic PTC

Please refer to “[Oncocytic FTC](#)” section.

Familial PTC

An estimated 5 % of PTC are hereditary, being an integral element of a hereditary tumor syndrome or not [19, 153]. For the majority of nonsyndromic “familial” PTC, the precise molecular genetic basis remains to be elucidated. In the

absence of a hereditary syndrome (e.g., Gardner’s syndrome or Cowden syndrome), a minimum of three affected family members are necessary to be 95 % sure that the disease is truly hereditary [154]. If three or more kindreds are affected, total thyroidectomy may be considered when the thyroid gland is morphologically abnormal [19, 155]. Whether familial, as opposed to sporadic PTC per se has a more aggressive tumor biology requiring extended surgery or adjuvant therapy remains uncertain [19].

Postradiation PTC

After previous exposure to radiation, the risk of developing thyroid nodules and multifocal PTC is significantly increased, reflecting the total dose of radiation and the patient’s age at the time of external radiation or incorporation of unsealed radioactive materials [156]. The latency between the patient’s exposure to radiation and the clinical manifestation of PTC, peaking 15 years after the exposure, is rarely shorter than 5 years. The rate of PTC continues to be increased even 40 years after the exposure and beyond [157].

If a thyroid nodule is noted after previous neck irradiation or exposure to ionizing radiation, total thyroidectomy is generally warranted because of the increased risk of multifocal PTC. The need for, and extent of additional lymph node dissection, are the same as for nonradiogenic PTC.

Pediatric and adolescent PTC

Although pediatric and adolescent PTC are associated with lower rates of cancer-specific morbidity and mortality than adult PTC, these tumors more often give rise to lymph node and distant metastases [158–160]. There is evidence to suggest that the pattern of lymphatic tumor dissemination does not differ between children and adolescents with PTC [161].

Of note, the staging criteria of the UICC/AJCC tumor–node–metastases classification system derive mainly from adult thyroid cancer, implying adult ratios of primary tumor size and thyroid volume [162]. Consequentially, the adoption of thyroid tumor size at face value (i.e., unadjusted for by patient age) to determine the extent of surgery for children and adolescents is bound to systematically underestimate the risk of tumor spread and recurrence. Owing to their greater prevalence of central and lateral lymph node metastases, children and adolescents require a meticulous preoperative workup of, and a diligent intraoperative search for, suspicious locoregional nodes to define the adequate extent of neck surgery.

Pediatric and adolescent thyroid cancer should preferably be managed at dedicated cancer centers because the clinical workup and therapy of these patients require special expertise in surgical management, histopathological analysis, and postoperative care.

*PTC originating from outside the thyroid gland
(thyroglossal duct PTC, struma ovarii)*

Thyroglossal duct PTC and struma ovarii are exceedingly rare. Local tumor eradication should be pursued as a minimum. For thyroid tumor deposits and/or local and distant tumor spread, total thyroidectomy and lymph node dissection are recommended with subsequent diagnostic scintigraphy and radioiodine therapy [163–165].

Postoperative follow-up and surgery for recurrence and distant metastasis

The need for postoperative radioiodine therapy by endogenous or exogenous TSH stimulation is to be discussed with the patient and should be coordinated well ahead of time. This is even more important when the diagnosis of PTC was made only after an operation for benign thyroid disease, bringing up the issue of reoperation for completion.

Locally resectable recurrent or persistent PTC should be removed surgically. Depending on the histopathological findings and the extent of the initial operation, a focused approach to take out a target lesion or a systematic compartment dissection for completion may be appropriate. In the presence of distant metastasis, identification of the driver of disease (“pacemaker”) is critical so that potentially life-threatening lesions in the neck and mediastinum can be surgically cleared or at least controlled as far as technically feasible. Because the tumor’s intrinsic radiosensitivity is limited, external radiation to the neck is advised only if the residual tumor cannot be removed surgically. The use of prophylactic adjuvant external radiation is discouraged.

When multiple distant metastases are present, it may become necessary exceptionally to resect tumor deposits from distant sites. Examples include the need to eliminate a locally progressive metastasis or to facilitate adjuvant therapy. These decisions should be made by an interdisciplinary panel. A surgical benefit regarding clinical outcome has been confirmed mainly for bone and brain metastases [166–169].

Follicular thyroid cancer

Frequency, clinical, and histopathological features

Follicular thyroid cancer (FTC), making up 10–15 % of all thyroid cancers in Germany [170], is less frequent than PTC. Its incidence is higher in iodine-deficient than iodine-sufficient regions. FTC emerges much later in life than PTC, peaking around the age of 50 years and affecting women five times more often than men.

Histopathologically, FTC is an epithelial malignancy of follicular cell origin lacking the nuclear features that are pathognomonic of PTC [2]. In terms of presentation, clinical outcome and surgical strategy, minimally invasive FTC is to be set apart from widely invasive FTC, reflecting the tumors’ disparate biologies [2, 57]. FTC ≤ 1 cm, unlike PTMC, is so unusual [171] that a diagnosis of FTC given to a thyroid microcarcinoma should be verified by an expert in thyroid cancer pathology.

Minimally invasive follicular thyroid cancer

Almost two thirds of all FTC are minimally invasive (MIFTC) [172]. The delimitation of MIFTC from follicular adenoma and the follicular variant of PTC usually cannot be made cytologically or by frozen section, requiring histopathological examination of paraffin-embedded tissue. The diagnosis of MIFTC hinges on nuclear morphological criteria and histopathological demonstration of minimal invasion of the tumor capsule and/or vascular invasion [68, 173–176].

It remains to be shown whether Rosai’s categorization of the intensity of histopathological vascular invasion, this is four or more vs. one to three sites of invasion [173], can discriminate between minimally invasive and widely invasive FTC. The best indicator of vascular invasion that is clinically relevant is histopathological evidence of tumor cells inside the vascular wall in connection with a thrombus adherent to the intravascular tumor [177]. If the distinction between minimally and widely invasive FTC cannot be made, an expert in thyroid cancer pathology should be consulted given the dissimilar therapeutic ramifications of these histopathological subtypes [178].

Clinical outcome studies confirmed the excellent long-term prognosis of MIFTC [57]. Lymph node metastases were present in fewer than 10 % of MIFTC, but in 33 % of widely invasive FTC [172], and only in the presence of distant metastasis at first diagnosis or vascular invasion on histopathological analysis [179–181].

Thyroidectomy

Minimally invasive FTC typically presents as a solitary thyroid nodule that is scintigraphically cold or in concert with multinodular goiter. The initial extent of resection depends on the presence of one or more than one thyroid nodules. Frozen section performed to clarify a cytological diagnosis of “follicular neoplasia” rarely is able to yield positive proof of MIFTC [182–185] but may be useful to confirm or rule out other tumor entities within a suspicious thyroid nodule [183, 186, 187].

After a solitary thyroid nodule was given a cytological diagnosis of follicular neoplasia, the possible extent of neck surgery, depending on the tumor entity at hand, should be discussed with the patient in detail. Particular emphasis should be placed on the limited capability of frozen section to differentiate MIFTC from

widely invasive FTC and the follicular variant of PTC [188]. Because fewer than 30 % of thyroid lesions that cytologically appear as follicular are genuine cancers [48], total thyroidectomy is not mandatory for solitary nodules unless there is a strong suspicion of malignancy. The pathologist nevertheless is to be informed of the urgent need for definitive tissue diagnosis so that completion thyroidectomy can be carried out within 4 days of the initial operation should vascular invasion be present on histopathological analysis [150].

Histopathological vascular invasion, signifying a greater risk of distant metastasis in patients with MIFTC, should prompt total thyroidectomy for completion followed by radioiodine therapy for ablation of residual disease. In the absence of vascular invasion, minimal histopathological invasion of the thyroid capsule alone is insufficient to warrant completion thyroidectomy in patients with MIFTC because of the very small risk of metastasis.

Recommendation 25:

When vascular invasion is absent on final histopathology, patients with solitary MIFTC do not require total thyroidectomy. If vascular invasion is noted, total thyroidectomy and postoperative radioiodine therapy are recommended regardless of the number of histopathological invasions.

Lymph node dissection

Lymph node metastases are not encountered in conjunction with MIFTC, whether it is associated with vascular invasion or not [172]. There is no need for prophylactic lymph node dissection in this setting even if total thyroidectomy should be necessary for completion.

Recommendation 26:

In the absence of clinical evidence for lymph node metastasis, patients with MIFTC do not require prophylactic lymph node dissection.

Widely invasive follicular thyroid cancer

Widely invasive follicular thyroid cancers (WIFTC), characterized by grossly diffuse tumor margins with broad-based protrusions into the neighboring thyroid tissue, can be diagnosed on frozen section most of the time. WIFTC, which is associated with larger thyroid primaries and advanced patient age [189, 190], has a worse clinical outcome than MIFTC because distant metastases are present in as many as one third of patients [172]. WIFTC, spreading easily to distant organs via the bloodstream, often present with distant metastases before the thyroid primary manifests itself.

Thyroidectomy

Because vascular invasion is a typical feature of WIFTC, total thyroidectomy should be complemented by postoperative radioiodine therapy as a matter of principle, especially in the presence of distant metastases [7, 8, 10–15, 57, 58, 78]. This implies performance of total thyroidectomy for completion. For the timing of completion thyroidectomy and radioiodine ablation of a small thyroid remnant, please refer to “[Completion surgery for incidental PTC](#)” section.

Recommendation 27:

Total thyroidectomy, initially and for completion, and postoperative radioiodine treatment are recommended for WIFTC as a matter of principle, especially in the presence of distant metastases.

Lymph node dissection

Lymph node metastases, involving some 20 % of patients with WIFTC, are frequently associated with distant metastases [172, 179, 191]. Clearance of neck compartments is generally warranted upon evidence of lymph node metastases before or during the operation. The extent of dissection needs to be attuned to the extent of tumor spread.

Recommendation 28:

Because lymph node metastases in WIFTC often arise concomitantly with distant metastases, there is no need for prophylactic lymph node dissection.

Aerodigestive tract resection for grossly invasive FTC

The therapeutic approach to aerodigestive invasion is the same for FTC and PTC (please refer to section on “[Aerodigestive tract resection for grossly invasive PTC](#).”)

Special variants of FTC

Oncocytic FTC

Oncocytic thyroid cancer, also referred to as oxyphilic or Hürthle cell cancer, is a rare (<5 %) variant of differentiated thyroid cancer found most often in FTC and only infrequently in PTC. To make the diagnosis, more than 75 % of tumor cells must be oncocytic [2]. Oncocytic cancers are not only unique in their morphological appearance (“mahogany-colored”) and cytology (eosinophilic cytoplasm as a result of mitochondrial hyperplasia) but also may be biologically more aggressive and may have lower radioiodine avidity [192–198].

Thyroidectomy Because oncocytic thyroid cancers have a more adverse biology than their non-oncocytic counterparts, total thyroidectomy should be carried out, initially or for completion, in patients with oncocytic thyroid cancer, whatever the size of the thyroid primary.

Recommendation 29:

For oncocytic thyroid cancer of any size, total thyroidectomy is generally recommended as initial surgical therapy or for completion, which should be complemented by radioiodine therapy.

Lymph node dissection Owing to the rareness of oncocytic thyroid cancer, there are no adequately powered studies available on the clinical benefit of prophylactic compartment dissection. Because lymph node metastases are common and radioiodine uptake may be limited, dissection of the central compartment is advised at least in patients in whom the diagnosis of oncocytic cancer was made before or during thyroidectomy. If the initial thyroidectomy was complete as evidenced by negative surgical margins, prophylactic central lymph node dissection is not recommended for completion unless postoperative thyroglobulin levels fail to normalize or lymph node metastases surface on imaging.

Recommendation 30:

When oncocytic thyroid cancer is diagnosed before or during thyroid resection, central compartment dissection is generally required in addition to total thyroidectomy. If the diagnosis is made only after the operation, the dissection should be held off until thyroglobulin serum levels fail to normalize or lymph node metastases become clinically apparent.

Postoperative follow-up and surgery for recurrence and distant metastasis

The therapeutic approach is the same as for PTC (cf. “Special variants of PTC” and “Postoperative follow-up and surgery for recurrence and distant metastasis” sections).

Poorly differentiated thyroid cancer

Frequency, clinical and histopathological features

Poorly differentiated thyroid cancer (PDTC) carries a much worse prognosis than well-differentiated PTC or FTC [199, 200]. It was not before 2004 that the WHO recognized PDTC as a cancer entity in its own right, ranging between differentiated and undifferentiated cancer [2]. Because PDTC is not easy to distinguish from differentiated and undifferentiated thyroid cancer, its diagnosis is not straightforward. Because of this fact,

the incidence of these tumors, accounting for some 5 % of all manifest thyroid cancers [2], cannot be determined reliably.

The World Health Organization, relying on the Turin criteria, defines PDTC as a thyrocytic neoplasia of limited follicular-cell differentiation, falling morphologically and clinically between PTC and FTC on one hand and undifferentiated (anaplastic) thyroid cancer on the other. PDTC is characterized by a solid/trabecular/insular growth, necrosis, and an increased mitotic rate [201–204]. To make the diagnosis, 10 % or more of the tumor must exhibit the morphological features of PDTC [205, 206].

At the time of presentation, PDTC is rarely smaller than 3 cm, often displays locally invasive growth, and has spread to lymph nodes (64 %) and frequently to distant organs (50 %) including lung, liver and bone [207–216]. The radioiodine uptake of these tumors is often scarce.

Thyroidectomy

The more aggressive biological behavior of PDTC as compared with PTC and FTC, and the loss of radioiodine uptake in 20 % of tumors warrant initial and completion thyroidectomy. PDTC should be surgically removed as completely as possible, even in the presence of distant metastases, to exploit the potential of postoperative radioiodine to the fullest [200, 215, 216]. No survival benefit was demonstrated for adjuvant radiotherapy [210].

Recommendation 31:

If PDTC is resectable, total thyroidectomy with complete removal of the tumor and postoperative radioiodine therapy should be performed, even in the presence of distant metastases.

Lymph node dissection

Because PDTC is commonly associated with lymph node metastases, there is a need for dissection of the involved compartments. Studies on prophylactic lymph node dissection in PDTC have not been forthcoming. If the diagnosis is made before or during the operation, dissection of at least the central neck compartment is recommended because of the high risk of concomitant lymph node metastases.

Recommendation 32:

If PDTC is resectable, dissection of the involved compartments with locally curative intent is advocated.

Aerodigestive tract resection for grossly invasive PDTC

Owing to the infrequency of PDTC, no large-scale outcome studies have been put forward showing that the resection of

tumors invading the aerodigestive tract is clinically beneficial. In one series of 26 patients, 5-year survival was approximately 60 % after resection of grossly invasive PDTC [146]. Resection of grossly invasive tumor from the aerodigestive tract is rarely warranted in the context of advanced or progressive distant metastases, multiple nodular soft tissue infiltrates, or tumor extending beyond the carotid sheath or below the jugulum (cf. “[Aerodigestive tract resection for grossly invasive PTC](#)” section). In this situation, alternative multimodal treatment options have to be considered.

Recommendation 33:

Resection of grossly invasive PDTC from the aerodigestive tract is only advised with curative intent.

Postoperative follow-up and surgery for recurrence and distant metastasis

Given the rarity and the histological and biological variability of these tumors, no radiooncological standards exist at the moment for postoperative follow-up and treatment of tumor recurrence. For local tumor control, recurrences should be surgically excised unless these are irresectable. In that event, palliative radiotherapy and/or chemotherapy should be considered. Because PDTC may be, or subsequently become unresponsive to radioiodine therapy, FDG PET/CT is an important tool for identification of recurrent tumor and distant metastases [211–216].

Undifferentiated (anaplastic) thyroid cancer

Frequency, clinical and histopathological features

Undifferentiated thyroid cancer (UTC), representing fewer than 5 % of manifest thyroid cancer, takes the lion’s share (>90 %) of all thyroid cancer-specific mortality [2]. Pathologically, UTC is composed in part or in total of undifferentiated, spindle-shaped, pleomorphic, or large cells with high mitotic activity. Occasionally, smooth transitions occur from well or poorly differentiated to undifferentiated tumors, suggesting that dedifferentiation of preexistent follicular cell cancer underlies the causation of UTC if it did not arise de novo [2]. Immunohistochemical analysis is necessary to reliably differentiate UTC from poorly differentiated medullary thyroid cancer and non-epithelial tumors such as thyroid lymphoma (cf. “[Lymphoma](#)” section).

UTC is characterized by early invasive growth, lymph node metastases, and distant metastases [217–221]. If clinically suspected, cytological or histochemical confirmation of UTC by fine-needle aspiration cytology or tissue biopsy and clinical determination of local and systemic tumor spread are required for adequate treatment.

After the diagnosis was made and the clinical extent of disease is clear, different surgical and radiooncological therapies are available that can be employed within a neoadjuvant or additive/adjuvant treatment concept [215, 220]. Because most patients are older and present with more age-related comorbidities, a multidisciplinary consensus is needed regarding which therapeutic regimen is best suited for a given patient to achieve the goal of local and systemic tumor control.

Within the multidisciplinary treatment concept for UTC, the extent of surgery is to be attuned to the tumor stage on imaging:

1. Intrathyroidal UTC (T4a N0/1 M0/1)
2. Extrathyroidal UTC without invasion of the aerodigestive tract (T4b N0/1 M0/1)
3. Extrathyroidal UTC with invasion of the aerodigestive tract (T4b N0/1 M0/1)

Surgical therapy

Intrathyroidal UTC

In the rare event of intrathyroidal UTC, tumor resection with locally curative intent is the treatment of choice. In this setting, total thyroidectomy is needed only for tumor involving both lobes or tumor composed of partially differentiated cells amenable to radioiodine therapy. If the cancer contains undifferentiated tumor cells only, hemithyroidectomy on the side of the tumor with removal of enlarged lymph nodes is adequate. To decrease the risk of locoregional recurrence, external irradiation of the neck should be performed as quickly as possible after the operation. Survival rates are higher after curative than after palliative resections [220–224].

Recommendation 34:

In intrathyroidal UTC, surgical removal of all tumor with early postoperative external irradiation is recommended to reduce the risk of locoregional recurrence and improve survival. Total thyroidectomy is not mandatory if only one thyroid lobe is involved.

Extrathyroidal UTC without aerodigestive tract invasion

In extrathyroidal UTC without invasion of the aerodigestive tract, a locally curative tumor resection paves the way for radiotherapy and/or chemotherapy. Even if the tumor spares the aerodigestive tract, invasion of the carotid artery or the substernal space may occur that can be irresectable. In this event, it remains to be determined through careful multidisciplinary deliberations if a neoadjuvant approach with initial radiochemotherapy can improve conditions such that subsequent tumor

eradication becomes feasible. Palliative resections are not recommended because of the increased risk of surgical morbidity [218, 221, 222, 225–229].

Recommendation 35:

In the absence of aerodigestive tract invasion, complete resection of UTC with early postoperative radiotherapy, or alternatively a neoadjuvant approach with subsequent resection are warranted for local tumor control if the tumor spares the carotid artery and the substernal space. Palliative debulking resections are not recommended.

Extrathyroidal UTC with aerodigestive tract invasion

Barring exceptional circumstances [146], survival in UTC with invasion of the aerodigestive tract cannot be extended, not even through a hazardous multivisceral resection so that tumor eradication should not be embarked on.

Prophylactic construction of a tracheostomy ahead of radiotherapy, compromising an already reduced quality of life, is controversial [219, 225, 227]. If wound healing is impaired and tracheal necrosis ensues, the tracheostomy can delay radiotherapy to the effect that clinical outcome is diminished. As the sole intervention securing the airway, tracheostomy is often vital and may be unavoidable in a tumor obstructing the trachea because stenting of the proximal airway is mostly ineffective.

Recommendation 36:

UTC invading the aerodigestive tract should be treated radiooncologically with palliative intent. Debulking is discouraged. Prophylactic performance of tracheotomy should be abandoned.

Postoperative follow-up and surgery for recurrence and distant metastasis

Supportive measures take center stage in the postoperative follow-up of UTC after multimodal therapy. If the tumor recurs locally after the initial operation, reoperations should be refrained from in favor of nonoperative therapies. In UTC, there is no need to resect distant metastases.

Medullary thyroid cancer

Frequency, clinical and histopathological features

Medullary thyroid cancer (MTC) comprises 5–10 % of all thyroid cancers. It derives from the thyroid gland's parafollicular C cells that synthesize and secrete calcitonin and other peptides like carcinoembryonic antigen (CEA). Some 25–30 % of patients with MTC harbor causative germline mutations in the

rearranged during transfection (RET) protooncogene [230, 231]. These germline mutations give rise to familial MTC and other tumor manifestations, pheochromocytoma, and primary hyperparathyroidism, in a mutation-specific age-related manner.

The diagnosis of MTC, which is characterized by great morphological variability, is made on immunohistochemical evidence of calcitonin in the tumor cells. As a matter of fact, calcitonin-negative MTC is exceedingly rare, encompassing less than 1 % of sporadic MTC [232] so that increased calcitonin serum levels point to occult MTC.

MTC cells, lacking the sodium–iodine symporter, do not enrich iodine so that residual tumor in the neck or at distant sites cannot be treated with radioiodine unlike differentiated thyroid cancers. MTC, measuring no more than a few millimeters in greatest dimension, may spread via lymph ducts and the bloodstream [191, 233, 234]. Surgery for MTC is directed at removing the primary thyroid tumor along with all involved lymph node echelons.

Sporadic MTC

Patients with sporadic MTC, unlike those with hereditary MTC, do not harbor RET mutations in the germline. Yet patients with sporadic MTC may yield somatic RET mutations in the tumor tissue (mainly RET mutations in codon 918) that are associated with a bleaker prognosis [235–237]. Owing to rapid tumor spread and the inability of MTC to concentrate radioiodine, early diagnosis and therapy are essential for improving clinical outcome.

Calcitonin and CEA serum levels, paralleling total tumor mass, are valuable clinical biomarkers for early diagnosis of MTC and clinical follow-up of persistent C cell disease [238–243]. The routine use of calcitonin screening in patients with nodular thyroid disease and early thyroidectomy has been instrumental in lowering primary tumor diameters [244] and improving the prognosis of sporadic MTC appreciably [245–247]. Measurements of basal calcitonin and, if increased, also of pentagastrin- or calcium-stimulated calcitonin levels are warranted in patients with nodular thyroid disease to facilitate early diagnosis and therapy of sporadic MTC [38, 243, 248].

When basal calcitonin levels are elevated slightly, calcitonin stimulation affords better discrimination between C cell hyperplasia and MTC [34, 42], enhancing the test's validity in the grey area of moderately increased basal calcitonin serum levels. To be more informative regarding the need for, and the extent of surgery, the characteristics of the calcitonin assay [37, 249], the gender- [41] and age-dependency [250, 251], and exceptionally calcitonin-secreting extrathyroidal tumors [252–254] need to be

considered. If stimulated calcitonin serum levels are higher than 100 pg/mL (upper normal limit <10 pg/mL) in adults, total thyroidectomy is recommended because of the considerable risk of MTC, taking into account the gender-specific normal ranges [34].

Recommendation 37:

The clinical outcome of patients with sporadic MTC is much improved through routine measurements of calcitonin facilitating early surgical intervention. If basal serum calcitonin is increased slightly, stimulation with pentagastrin or calcium is helpful to enhance the test's validity. If stimulated calcitonin serum levels are higher than 100 pg/mL (upper normal limit < 10 pg/mL) in adults, the risk of MTC is substantial so that total thyroidectomy is generally warranted taking into account the gender-specific normal ranges.

When familial MTC with concomitant pheochromocytoma and/or primary hyperparathyroidism is suspected, the preoperative workup needs to cover the adrenal and parathyroid glands.

Recommendation 38:

If MEN2 is suspected, the preoperative work-up needs to include the adrenal and parathyroid glands to rule out or confirm pheochromocytoma and primary hyperparathyroidism, respectively.

Thyroidectomy

Upon clinical, biochemical, or cytological evidence of MTC, total thyroidectomy is warranted in the absence of effective nonsurgical therapies unless the tumor is irresectable or the patient is inoperable [9]. After due consideration of the differential diagnosis and the age- and gender-dependency of the calcitonin level, total thyroidectomy is recommended in patients with stimulated calcitonin levels of >100 pg/mL, even in the absence of an identifiable MTC. The rationale behind this recommendation is the observation that clinically apparent MTC already have spread to lymph nodes or distant organs, rendering these larger tumors harder to clear [234].

Because sporadic MTC also grows multifocally in 10 % of patients [255], total thyroidectomy should be carried out on suspicion or evidence of MTC. Based on single case reports [256], the concept of hemithyroidectomy on the side of the tumor, relying on a negative RET gene analysis before the operation and disregarding

the inherent risk of tumor multifocality, has not been adopted widely.

Recommendation 39:

Because early diagnosis and therapy are critical to improve the clinical outcome of patients with sporadic MTC, total thyroidectomy should be carried out not only after the MTC has become apparent. In the presence of stimulated calcitonin levels >100 pg/mL (upper normal limit < 10 pg/mL), the risk of MTC is substantial. In this setting, total thyroidectomy is recommended in due regard of the differential diagnosis, the validity of the test, and the age- and gender-dependency of the calcitonin assay. In case of doubt, calcitonin measurements are to be repeated.

Lymph node dissection

Upon clinical, biochemical, or cytological evidence of lymph node metastases, there is a need to clear all involved lymph node compartments in view of the ineffectiveness of nonsurgical therapies. The use of selective, as opposed to systematic forms of lymph node dissection, diminishing the patient's chance of surgical cure [59, 257–262], may be justifiable under exceptional circumstances, e.g., in the setting of progressive distant metastases.

Because MTC is associated early on with occult lymph node metastases, the risk of occult disease over a patient's lifetime must outweigh the risk of surgical morbidity if prophylactic lymph node dissection is to be considered. Minimal residual disease signaled by slightly elevated calcitonin serum levels often does not affect clinical outcome in the long run [263]. For the individual patient, the tumor's growth dynamics, which usually cannot be anticipated at the time of surgery, are largely dependent on the primary tumor's size and the level of the patient's serum calcitonin before the operation [234, 242, 264]. There is also a quantitative relationship between the number of lymph node metastases and the development of distant metastases [265]. This observation suggests that the extent of lymph node dissection can affect outcome unless the clinical influence of distant metastases is overbearing.

As a matter of fact, the central compartment is free of tumor in patients with previously untreated MTC as long as basal calcitonin serum levels are 20 pg/mL or lower (upper normal limit <10 pg/mL), obviating the need for prophylactic central neck dissection [243]. With basal calcitonin levels on the rise up to a threshold of 200 pg/mL, paralleling primary tumor growth, the central and the ipsilateral lateral neck compartments are increasingly involved, requiring systematic lymph node dissection. When basal calcitonin levels exceed 200 but

not 500 pg/mL, primary tumors on average are larger than 10 mm, with involvement of the contralateral lateral neck in 14 % of patients. Above that threshold (>500 pg/mL), in the presence of even larger primary tumors, distant metastasis increasingly prevails. The issue of whether patients with basal calcitonin levels of >200 pg/mL should undergo prophylactic dissection of the contralateral lateral compartment in the absence of lymph node enlargement is to be discussed with the patient during the informed consent process, balancing the inherent benefits and risks of a one-stage versus a possible two-stage procedure [266].

Recommendation 40:

Sporadic MTC spreads to the central and ipsilateral lateral neck compartment early on. With basal calcitonin levels ranging between >20 and 200 pg/mL (upper normal limit >10 pg/mL), prophylactic dissection of the central and ipsilateral lateral neck compartments with curative intent is recommended even in the absence of enlarged lymph nodes. Above that threshold (>200 pg/mL), reflecting primary tumor growth, the risk of contralateral lateral neck involvement and distant metastases continues to rise gradually. The inherent benefits and risks of a one-stage versus a possible two-stage procedure, with or without initial inclusion of the contralateral lateral neck compartment, need to be discussed with the patient during the informed consent process.

Hereditary MTC

Hereditary MTC is caused by germline mutations in the RET protooncogene that are inherited in an autosomal dominant fashion. The development of MTC and the other MEN2-associated endocrine tumors is genetically encoded by the individual mutation in the RET protooncogene. These genotype–phenotype correlations are subject to the play of chance (i.e., the acquisition of somatic mutations by tumor cells) [9, 267–269].

Based on these genotype–phenotype relationships, the American Thyroid Association (ATA) classified the risk of disease into four levels, ranging from ATA group A, lowest risk, to ATA group D, highest risk [9]. Mutations in the following RET codons were assigned according to inherent risk. ATA group A: 321, 515, 531, 532, 533, 600, 603, 606, 635, 649, 666, 768, 777, 790, 791, 804, 819, 833, 844, 866, 891, 912; ATA group B: 609, 611, 618, 620, 630, 631, 633; ATA group C: 634; and ATA group D: 883, 918 [9]. The mutation in codon 634 (ATA group C) is the most common RET germline mutation worldwide, which is also most often associated with concurrent pheochromocytoma and primary hyperparathyroidism.

The mutation in codon 918 (ATA group D) is most aggressive, giving rise to MTC in early infancy and to pheochromocytoma frequently in adolescence and early adulthood but never to primary hyperparathyroidism.

Because a RET carrier's estimated life time risk of developing MTC may be greater than 90 %, preemption by way of prophylactic thyroidectomy is universally recommended [9, 270–272] since the causative mutations were first described in 1993 [230, 231].

Thyroidectomy

In contrast to resectable overt MTC in which no nonsurgical therapy is equally effective as total thyroidectomy, the decision regarding the timing of prophylactic thyroidectomy in asymptomatic carriers of ATA group A to C mutations is not easy given the impossibility of anticipating the time of tumor development individually [268, 273, 274]. Placing emphasis merely on age-specific timelines for prophylactic thyroidectomy is liable to result in both overtreatment and undertreatment [273].

In the presence of normal basal but not stimulated calcitonin serum levels, node-negative but not node-positive MTC was found in 20 % of patients [274]. These findings illustrate the importance of calcitonin serum levels for optimal timing of prophylactic thyroidectomy in RET carriers. The last possible moment for prophylactic thyroidectomy has arrived when stimulated calcitonin serum levels start turning abnormal [19, 273–275].

The combined DNA-based biochemical concept is superior in that it provides a temporal corridor within which RET carriers can decide on the time of thyroidectomy that is best for them individually, with no compromise on clinical outcome. Because the risk of surgical complications, notably with regard to postoperative hypoparathyroidism, is much increased in early childhood [276], it may be prudent to delay prophylactic thyroidectomy in asymptomatic carriers of ATA group A–C mutations with normal basal calcitonin levels into late childhood.

Contrary to the above, thyroidectomy should be performed as early as possible in carriers of RET mutations in codon 918, which predispose to MEN 2B. Remarkably, MTC in this setting appears in very early infancy and is solely curable within the first years of life [277, 278]. The majority of MEN 2B patients, harboring de novo germline mutations, yield uneventful family histories, thwarting family screening programs for the trait. This is why early diagnosis of carriers by instant recognition of the extrathyroidal

oidal signs and symptoms of MEN 2B (“crying without tears,” constipation) is pivotal [277, 278].

Recommendation 41:

Hereditary MTC features genotype-phenotype correlations. In asymptomatic carriers of ATA group A–C mutations, the moment of tumor development cannot be inferred from the underlying mutation alone so that determination of calcitonin serum levels is important for deciding on the optimal timing of prophylactic thyroidectomy. As long as basal calcitonin levels remain normal, the tumor has not spread beyond the confines of the thyroid gland. In carriers of ATA group A–C mutations, prophylactic thyroidectomy should be scheduled at the latest when stimulated calcitonin levels move into the abnormal range. In carriers of ATA group D mutations (MEN 2B), thyroidectomy should be carried out at the earliest convenience.

Lymph node dissection

Index and non-index patients with MTC whose basal calcitonin serum levels are increased should undergo systematic dissection of the central and lateral compartment on either side of the neck. When basal calcitonin levels are still within normal limits, prophylactic lymph node dissections should be refrained from because lymph node metastases have not been encountered in that setting [276].

Recommendation 42:

In RET carriers who reveal normal basal calcitonin levels, prophylactic compartment dissection should be refrained from. Index and non-index patients whose basal calcitonin serum levels are increased should undergo systematic dissection of the central and lateral compartment on either side of the neck.

Aerodigestive tract resection for grossly invasive sporadic and hereditary MTC

The therapeutic principles regarding the need for and the extent of resection are similar to those for extrathyroidal PTC (cf. “[Aerodigestive tract resection for grossly invasive PTC](#)” section) and FTC that invade the aerodigestive tract (cf. “[Aerodigestive tract resection for grossly invasive FTC](#)” section). However, as soon as minimal extrathyroidal invasion has occurred, the prognosis of MTC, owing to an increased risk of distant metastasis, is worse than the prognosis of a comparable differentiated thyroid cancer [143, 242, 243, 279]. As a consequence, the need for aerodigestive

resection of grossly invasive MTC must be deliberated carefully.

Recommendation 43:

The prognosis of an MTC with extrathyroidal invasion is worse than the prognosis of a comparable PTC or FTC owing to an increased risk of distant metastasis, rendering it important to determine the need for aerodigestive resection carefully.

Postoperative follow-up and surgery for recurrence and distant metastasis in sporadic and hereditary MTC

There is no need for completion thyroidectomy after an incidental finding of MTC if the postoperative stimulated calcitonin serum levels remain below the assay’s limit of detection and heredity has been excluded by RET screening [256, 280]. Despite an overall low risk of recurrence after biochemical cure [281], follow-up measurements of calcitonin and CEA serum levels are advised on a half-yearly basis.

Recommendation 44:

In RET-negative patients, there is no need for completion thyroidectomy after an incidental finding of MTC when the postoperative stimulated calcitonin serum levels fall below the assay’s limit of detection. Controls of calcitonin and CEA serum levels are recommended on a half-yearly basis.

When calcitonin levels fail to normalize postoperatively, completion surgery is always warranted when the initial operation was inadequate for the extent of disease. For clearance of residual tumor that is resectable, reoperation is advised [282–286]. There is no need for radioiodine therapy because of the MTC cells’ inability to concentrate iodine. External radiation is recommended only for irresectable tumor or when the patient is inoperable. Biochemical cure is difficult to accomplish after reoperation, and almost out of reach for calcitonin levels in excess of 1,000 pg/mL [233, 287]. In the absence of a target lesion on high-resolution ultrasonography, CT, MRI or PET/CT, expectant observation is justified after previous dissection because the residual tumor is rarely identifiable on surgical exploration and biochemical cure is exceptional.

Recommendation 45:

When elevated calcitonin levels persist after an initial operation, compartment-oriented surgery is warranted when the initial thyroid resection was inadequate for the extent of disease or imaging pinpoints locoregional tumor deposits.

If imaging visualizes progressive distant disease, there is usually a need for radiooncological therapy with palliative

intent [288]. In the unusual event of solitary, locally dominant or symptomatic distant metastases (“pacemaker”) in the mediastinum, lung or liver, a number of options are available including a focused or regional interventional or surgical approach [289, 290].

Recommendation 46:

For symptomatic distant metastases, there may be a case for surgery with palliative intent after careful consideration of nonsurgical treatment options.

Patients with hereditary MTC should be worked up clinically for pheochromocytoma and primary hyperparathyroidism according to the carrier’s individual risk profile (RET mutation and age) [9, 267, 269, 291]. To confirm or rule out heredity, MTC patients with unknown genetic status should be offered RET gene analysis under informed consent.

Lymphoma

Frequency, clinical and histopathological features

Not uncommonly is the neck the site of first presentation of systemic Hodgkin’s and non-Hodgkin’s lymphomas. In classic Hodgkin’s lymphoma in particular, enlargement of neck nodes is the presenting symptom of this commonly juvenile lymphoproliferative disease. As a matter of principle, all neck “lymphomas” must be clinically worked up to arrive at the correct diagnosis.

Primary lymphoma of the thyroid gland is a rarity. With a female-to-male preponderance of 3–7:1, these tumors typically peak in patients older than 60 years of age [292–295]. The thyroid involvement of most patients corresponds to Ann Arbor classification stage 1E or 2E [296]. Especially Ann Arbor stage 2E is noteworthy for lymphoproliferative invasion of the juxtathyroidal soft tissues that may also involve the trachea and recurrent laryngeal nerve resulting in recurrent laryngeal nerve palsy. In Ann Arbor stages 3E and 4, involvement of cervical, juxtathyroidal, mediastinal, and abdominal nodes is common. Clinical outcome, reflected by Ann Arbor stage, is most favorable for mucosa-associated lymphoid tissue (MALT) lymphomas confined to the thyroid gland [292–296].

Histologically, most thyroid lymphomas represent non-Hodgkin B cell lymphomas, whereas Hodgkin’s lymphoma and T cell lymphoma are infrequent. MALT lymphoma accounts for some 30 % of B cell lymphomas. Virtually all thyroid lymphomas originate from within thyroid glands affected by chronic lymphocytic thyroiditis [2].

Differential diagnosis

In view of the limited surgical options for thyroid lymphoma, making the correct diagnosis is of utmost importance.

With the exception of MALT lymphoma confined to the thyroid gland, thyroid lymphomas featuring rapid tumor growth are barely distinguishable from undifferentiated and poorly differentiated thyroid cancers or metastases to the thyroid gland.

Therapeutic decisions on locally advanced and rapidly growing thyroid malignancies should be delayed until cytological or histopathological characterization has become available for the thyroid tumor. Although cytological techniques have been improved much [297], the accuracy of fine-needle aspiration cytology continues to remain observer-dependent so that a tissue biopsy in most cases is still necessary for histopathological diagnosis to decide on the subsequent course of action [292].

The histopathological analysis is directed at differentiating diffuse B cell lymphomas from MALT lymphoma, and even more importantly MALT lymphoma from Hashimoto’s thyroiditis. Immunocytologically, MALT lymphoma is negative for CD5, CD10 and CD23, whereas large-cell B cell lymphoma is positive for CD19, CD20, and CD45 most of the time [292, 297]. Once the diagnosis of lymphoma has been established histologically, clinical staging is next. FDG-PET/CT is helpful in spotting lymphoproliferative foci outside the neck [298].

Recommendation 47:

When locally advanced thyroid tumors appear, lymphoma should be ruled out or confirmed immunocytologically (via fine-needle aspiration) or histologically (via tissue biopsy) to determine the necessary course of action. If the diagnosis is confirmed, subtyping and clinical staging of the lymphoma are necessary to ensure adequate therapy.

The role of surgery

Surgery is important for the collection of tissue biopsies to clarify an indeterminate cytological result or when immunohistological subtyping of the lymphoma is needed to select the appropriate treatment, e.g., to distinguish MALT lymphoma from diffuse B-cell lymphomas.

No prospective studies are available to determine the need to surgically remove all tumor as opposed to tumor debulking, in particular regarding the impact of surgery (biopsy or debulking with subsequent radio-/chemotherapy) on clinical outcome for the various subtypes of thyroid lymphoma [292].

For the prognostically favorable MALT lymphomas confined to the thyroid gland, 83 % of which fall into Ann Arbor stage 1E, radiotherapy competes with thyroidectomy which may, or may not, be combined with subsequent chemotherapy or multimodal therapy. Which therapeutic regimen is superior to the other remains to be clarified [299–304]. Stand-alone radiotherapy and stand-alone thyroidectomy are widely believed to be

inadequate for MALT lymphomas that are beyond Ann Arbor stage 1E [304, 307].

For local control of lymphoproliferative tracheal involvement and related complications, debulking may be an option [305–307], even at the cost of incremental surgical morbidity [307]. Because of the greater effectiveness of newer drugs such as rituximab [308], primary radiochemotherapy remains the method of choice for tracheal involvement, supported by internal stenting [309] as the case may be.

Recommendation 48:

For MALT lymphomas confined to the thyroid gland (Ann Arbor stage 1E), thyroidectomy or radiotherapy alone represent adequate therapy.

Recommendation 49:

For diffuse or mixed-cell B-cell lymphomas, primary radiochemotherapy is recommended.

Recommendation 50:

For lymphoma with tracheal involvement, the best individual course of action is to be determined by an interdisciplinary panel.

Thyroid metastases of primaries from outside the thyroid gland

Frequency, clinical and histopathological features

Thyroid metastases of primaries originating from outside the thyroid gland are rare [310–313]. In autopsy series, metastases to the thyroid gland were found in approximately 1 % of unselected individuals [312] and in 4–25 % of patients with a personal history of metastatic disease [310, 314]. The clinical relevance of thyroid metastases, having become symptomatic in only 20 % of patients before postmortem [311, 315], is limited.

Most primaries spreading to the thyroid gland arise from the kidney (30–55 %), lung (15 %), breast (15 %), esophagus (10 %), and other solid organs like the skin, uterus, ovary, salivary glands, and the parathyroids [316, 317].

The mean latency between the first diagnosis of the metastatic primary and the manifestation of thyroid metastases varies by type and localization of the primary and follow-up strategy: 3.5 years for melanoma, 9 years for renal cell cancer, and 11 years for breast and endometrial cancer [313, 316, 318–322].

Metastases to the thyroid gland often appear as rapidly growing solitary nodules or nodules in the setting of multinodular goiter. Patients with primaries known to spread frequently to the thyroid gland (e.g., from the kidney, lung, breast) and cancer patients with new-onset thyroid nodules should undergo a thyroid workup [323].

Differential diagnosis

Suspicious nodules and space-occupying lesions in the neck should be worked up for malignancy using fine-needle aspiration cytology, especially in patients with known primaries outside the thyroid gland. The diagnosis is straightforward for thyroid metastases, which are cytologically unique [316, 320, 324]. The decision to remove, or not remove, the thyroid gland depends on the local extent of disease, necessitating locoregional and systemic staging.

Recommendation 51:

Suspicious nodules and space-occupying lesions in the neck should be worked up for malignancy using fine-needle aspiration cytology, especially in patients with known primaries outside the thyroid gland. Evidence of thyroid metastases requires locoregional and systemic tumor staging.

Recommendation 52:

The decision to remove, or not remove, the thyroid gland is made through interdisciplinary discussion. It is contingent on tumor stage, the prognosis of the metastatic primary, and the extent of local involvement of the thyroid gland and neck.

Thyroid metastases from renal cell cancer

Thyroid metastases from renal cell cancer, exhibiting variable time lags since the primary was first diagnosed, can appear in many ways [313, 316, 317, 319, 321, 325, 326].

Prognostic factors favoring thyroid resection include a long time lag since the first diagnosis and slow metastatic growth [319]. Adverse prognostic factors constitute extrathyroidal metastatic extension and invasion of the recurrent laryngeal nerve and other juxtathyroidal structures [327]. As a rule, total thyroidectomy is only required for bilateral nodules, and lymph node dissection only for apparent lymph node metastases [317]. In thyroid metastases invading the neck veins and soft tissues by continuity, extended cervical resections are oncologically sound if the metastatic disease is limited to the neck and clear surgical margins are achieved [327].

Recommendation 53:

In the absence of progressive systemic disease, surgical removal of the thyroid and neck metastases of renal cell cancer is a valuable therapeutic option provided the lesions are resectable.

Thyroid metastases from lung and breast cancer and other solid primaries

Metastases from lung and breast cancer and other solid primaries, rarely presenting as isolated thyroid metastases,

have a worse clinical outcome than renal cell cancer in which thyroid metastases often present in isolation [313, 316, 320, 328, 329]. Consequentially, caution should be exercised regarding the need for thyroid resection as only one component within a multidisciplinary approach unless these thyroid metastases give rise to complaints or threaten to cause local complications.

Recommendation 54:

Thyroid metastases from solid tumors other than renal cell cancer frequently herald a dismal prognosis. Neck surgery is generally unwarranted unless these metastases give rise to complaints or threaten to cause local complications.

Conflicts of interest None.

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