The Current Surgical Approach to Non-Medullary Thyroid Cancer

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5.1 Introduction

About 150 years ago, thyroid surgery was performed only in life-threatening situations. The main reason for this restrictive approach was the high mortality of up to 40%, the cause of death being usually either uncontrollable bleeding or infection. Against this background, Theodor E. Kocher and Theodor Billroth set out to improve surgery on the thyroid gland and reported their results. The "Kocher incision," a transverse, slightly curved incision about 2 cm above the sternoclavicular joints, is well known to all thyroid surgeons.

Other complications were then identified, in particular hoarseness. It was soon found that preservation of the recurrent laryngeal nerve was important in order to prevent this complication. The pathophysiology of hypoparathyroidism and tetany were not understood at that time. Kocher had a very precise operating technique. He also worked in a relatively bloodless field. These are probably the reasons why he had only a few problems with postoperative tetany. In addition, his technique enabled him to decrease the mortality from 14% in 1884 to 2.4% in 1889 and 0.18% in 1898. By 1874, Kocher had noticed symptoms of hypothyroidism in patients who successfully underwent removal of the thyroid gland. The patients became very tired, showed decreased initiative, and became cretinoid. Even though Kocher misinterpreted these findings as a result of tracheal injury, he made the correct decision in trying to avoid removal of the whole thyroid gland. After the condition of myxedema had been described, transplantation and injection of extracts of thyroid tissue were tried, and in 1892 oral therapy was introduced.

With this knowledge about the physiology, pathology, and surgery on the thyroid gland, for which Kocher received the Nobel Prize in 1909, surgery was extended to treat malignant disorders of the thyroid. Since then, surgery has been the treatment of choice for thyroid cancer. However, new therapeutic tools are required for effective treatment of thyroid cancer extending beyond the thyroid gland. Since the efficiency of the available tools (e.g., radioiodine) is limited and new tools are yet to be found, thyroid surgery will continue to play an important role in the therapy of thyroid cancer in the twenty-first century.

5.2 Prognostic Factors

Therapeutic strategies and the extent of surgery depend on factors that influence the prognosis of thyroid cancer. A variety of factors (e.g., histological type and subtype, tumor grade, tumor stage, capsular and vascular invasion, age, and sex) have been analyzed, but the data are not uniform in all studies. Histological type, size of the primary tumor, extrathyroidal tumor extension, and distant metastases are generally reported to correlate with outcome [5, 7, 20]. In contrast, while lymph node metastases have been repeatedly shown to correlate with tumor recurrence [22, 26], their significance on survival has only been reported in some studies [15].

Three histologically defined thyroid cancers derived from follicular thyroid cells comprise more than 95% of all nonmedullary thyroid malignancies (see Chaps. 1 and 2): papillary, follicular, and undifferentiated thyroid carcinoma.

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer (up to 80%) in iodine-sufficient regions. PTCs are generally slow-growing. Despite the fact that they have a tendency to be multifocal and tend to metastasize early via the lymph nodes (about 50% at the time of diagnosis), the prognosis is considered to be good, with 10-year survival rates of 80–95% [23].

Follicular thyroid carcinoma (FTC) is more common in iodine-deficient regions but is rarely more frequent than PTC. FTC is much less often multifocal but metastasizes hematogenously rather than lymphogenously [39, 43]. Patients with FTC have 10-year survival rates of 70–95% [1, 23]. Malignant thyroid tumors that histologically show mainly the features of FTCs but also show papillary structures are classified as PTCs (see Chap. 2).

FTC and PTC have also been classified as differentiated thyroid carcinomas (DTC). Undifferentiated thyroid carcinoma (UTC) is one of the most aggressive human malignancies. Almost all patients present with a thyroid mass, which rapidly enlarges within a few weeks or months. Most patients die within a year after diagnosis due to distant metastases (often occult at the time of diagnosis) if local tumor control can be achieved [7, 24]. Clinical observation and molecular findings support the hypothesis that UTC can develop from FTC [51]. It is also well known that PTC can dedifferentiate in such a manner that it behaves like UTC [35]. The development of UTC has also been seen in patients with longstanding goiter. Whether UTCs derive directly from „normal“ follicular thyroid cells, however, is not known.

Hürthle cells (also known as oxyphilic cells or oncocytic cells) are most often found in follicular thyroid adenoma and carcinoma, but they have also been described in papillary and medullary thyroid carcinoma. They are not specific for malignant thyroid diseases. However, if they are observed in a thyroid carcinoma, they are believed to be associated with a poorer prognosis [30]. One reason might be that these tumors are less likely to take up radioiodine.

Also of particular interest are tumors with insular growth pattern. Insular growth pattern may be seen in nonneoplastic thyroid lesions [49] but is most often seen in papillary and, less often, follicular thyroid carcinoma. Insular thyroid carcinoma has been described in both adults and adolescents. Even

though the presence of insular growth does not unequivocally qualify a given tumor as a poorly differentiated thyroid carcinoma, a low overall survival rate has been reported in comparison with well-differentiated thyroid carcinoma [40]. In some studies, insular thyroid carcinoma is more often associated with extrathyroidal tumor extension and metastatic spread. Interestingly, despite a lower degree of differentiation, insular thyroid carcinoma may still be capable of taking up radioiodine, which may be used as a therapeutic option if surgery is not feasible [27].

Sarcomas, lymphomas, and other rare cancers comprise about 5% of all non-medullary thyroid malignancies. Their prognosis is generally worse than DTC but often better that UTC. Because of their rareness, therapeutic recommendations are generally based on experiences analyzing small numbers of patients [2].

A variety of prognostic scoring systems (e.g., AGES, AMES, DAMES, MACIS, age-related pTNM, EORTC prognostic index [5, 19, 20, 25, 36, 46]) have been developed. Unfortunately, none of them are widely used, making comparison of studies extremely difficult if not impossible.

5.3 Surgical Treatment

5.3.1 Technique

A precise surgical technique and bloodless operation should be aimed for to provide the best treatment possible in terms of tumor removal, morbidity, and long-term outcome. Magnifying glasses, bipolar coagulation forceps, and neuromonitoring of the recurrent laryngeal nerve have proven helpful. They facilitate the identification, preparation, and preservation of important structures (e.g., parathyroid glands, recurrent laryngeal nerve) [10].

5.3.2 Primary Therapy

5.3.2.1 Thyroid gland

5.3.2.1.1 Differentiated thyroid carcinoma

The extent of thyroid gland resection has been an issue of controversy. The arguments in favor of total thyroidectomy are:

1. Thyroid cancer is often multifocal. This is particularly true for PTC [9].
2. Small intraglandular tumor remnants may dedifferentiate further and/or be the source of metastatic disease [32].

3. The rate of local recurrences is increased after less than total thyroidectomy [26].
4. In the hands of an experienced endocrine surgeon, minimal or no long-term complications can be expected [6].
5. Reoperation due to tumor remnant is associated with a higher morbidity [21, 50].
6. Thyroglobulin can be used as a marker for persistent/recurrent tumor during follow-up [3, 12].
7. Application of radioiodine application is feasible for diagnostic and/or therapeutic purposes [42].

Factors in support of less than total thyroidectomy are:

1. The rate of clinically significant recurrent thyroid cancer within the thyroid remnant is lower than the reported incidence of microscopic tumor within the thyroid remnant [17].
2. Differentiated thyroid carcinoma dedifferentiates in only a minority of patients [8].
3. Most studies have failed to demonstrate a statistically significant difference in survival rates between total thyroidectomy and less than total thyroidectomy [17].
4. In nonspecialized centers, the morbidity after less than total thyroidectomy is lower than after total thyroidectomy [45].
5. If necessary, ablation of small thyroid remnants can be achieved by application of radioiodine [28].
6. Scoring systems enable the identification of low-risk patients with a long-term disease-free and survival rate of over 90% [5, 19].

The recommendations regarding surgical extent in the presence of small, unifocal, and intrathyroidal (pT1a) PTC tumors (hemithyroidectomy or subtotal thyroidectomy) and extrathyroidal (pT4) DTC tumors (total thyroidectomy including lymphadenectomy of the cervicocentral and, if necessary, cervicolateral compartment) are uniform in Europe and the USA. However, the extent of surgery in all other stages of DTC is controversial. Epidemiological data indicate the existence of a regional and intercontinental difference with regard to tumor biology [48]. While studies from the USA have not been able to show an advantage of total thyroidectomy and cervicocentral lymphadenectomy over less extensive procedures in pT2/3-DTC [29, 41], studies from Europe have demonstrated improved survival rates when lymphadenectomy is performed in addition to total thyroidectomy [15]. Since it has been shown that morbidity correlates with surgeons‘ experience [45], these extended procedures should only be performed in specialized centers. In this regard, the conduction of prospective long-term studies would be desirable; although the feasibility is questionable.

5.3.2.1.2 Undifferentiated thyroid carcinoma

UTC occurs typically in older patients (>60 years), however, it has also been reported to occur in patients younger than 50 years.

If possible, complete surgical resection of the tumor is indicated. However, these tumors tend to grow in a rapid and invasive fashion so that complete surgical removal is often not possible. Debulking of the tumor is often all that can be achieved. In addition, adjuvant or neoadjuvant radiochemotherapy is often applied to facilitate local tumor control [33, 37]. Radioactive iodine therapy has no role in the management of UTC (see Chap. 6).

5.3.2.1.3 Rare types of thyroid cancer

Lymphomas are susceptible to radiochemotherapy, and long-term survival rates of more than 50% have been reported in patients with local disease [44, 47]. Whether total thyroidectomy can further improve patient's outcome has not yet been proved. Other rare types of thyroid cancer (e.g., sarcoma, carcinosarcoma, squamous cell carcinoma) are very aggressive and may behave like UTC.

5.3.2.2 Extrathyroidal tumor extension

If thyroid carcinoma extends beyond the thyroid capsule (pT4-tumor; not to be mistaken with infiltration of the tumor capsule) the tumor can infiltrate the trachea and/or the esophagus. The infiltration of these structures by DTC is a rare but surgically challenging situation. Massive hemorrhage and airway obstruction due to uncontrolled local tumor are found to be the cause of death in almost 30% of patients who die from thyroid cancer [24]. Hence, most experienced surgeons recommend the removal of as much tumor mass as possible, while preserving function; however, the exact surgical method to best approach this situation is controversial.

If tumor mass adheres to tracheal and/or laryngeal cartilage, a mere shaving procedure might be sufficient. Should tracheal and/or laryngeal cartilage be transmurally invaded, more radical procedures such as circumferential tracheal resection or total laryngectomy may be required [11, 13]. Involvement of the esophagus may require esophagectomy with interposition of free colon, stomach, or, preferably, small intestine autografts. If distant metastases are present, stent implantation is an alternative therapeutic option to prevent airway obstruction and hemorrhage.

It also should be considered that preservation of the laryngeal nerve might be worthwhile in order to maintain its function if infiltrated by differentiated thyroid carcinoma. It has been shown that this strategy neither increases the incidence of local recurrences nor affects survival [34].

Tracheal and/or esophageal invasion is more often found in patients with UTC than patients with DTC. The aggressiveness of this tumor and the likelihood that these patients will die within 1 year do not justify surgical procedures with a high morbidity rate and the patients would require long-term hospitalization.

5.3.2.3 Lymph nodes

At the time of diagnosis, lymph node metastases are a common (35–50%) finding in patients with PTC. Micrometastases are even found in up to 60–90%. The prognostic significance of these micrometastases is difficult to predict. In adults, about 15% of micrometastases are believed to become clinically significant [7]. In contrast, micrometastases in children may become clinically significant in more then 50% [18]. Only a few studies have shown a significant influence on survival [15]. It is, however, generally accepted that lymph node metastases correlate with tumor recurrence [18, 22, 31]. No scoring system clearly enables high-risk patients to be distinguished from low-risk patients. It has been shown that lymphadenectomy, in addition to thyroidectomy, does not increase the morbidity as compared to thyroidectomy alone. In contrast, the increased morbidity after reoperation is very well described [21, 50]. Therefore, in patients with PTC, a cervicocentral lymphadenectomy is justified. Of note, the ipsilateral (regarding the site of the primary tumor) cervicolateral compartment (C2 or C3) contains lymph node metastases almost as frequently as the cervicocentral compartment (C1) [16]. Lymph node metastases can even be found in the cervicolateral compartment without lymph nodes in the cervicocentral compartment [16]. However, routine dissection of the ipsilateral cervicolateral compartment is not recommended, since no survival benefit has been shown and surgery at the time lateral lymph node metastases are found is not associated with an increased morbidity.

In contrast, patients with FTC rarely (10–20%) present with lymph node metastases. It seems that they are less common in Europe [10] and more common in the USA [23, 28]. In a study published by the National Cancer Institute, lymph node metastases in FTC correlates with a decreased survival rate [14]. Whether dissection of the lymph node is able to improve survival has not yet been demonstrated. Distant metastases are more often found in patients with FTC. They may be adequately treated with radioiodine (see Chap. 6), but only if radioiodine uptake is sufficient. One prerequisite is the absence of other thyroid tissue that takes up radioiodine. In addition to total thyroidectomy, dissection of involved lymph node compartments is thus recommended [10].

Because of the tendency of UTC to grow very large, cervical adenopathy may be difficult to appreciate. Whether removal of the lymph nodes influences survival in any way is not known. It is generally recommended that lymph nodes within the cervicocentral compartment be removed, accompanied by those in the cervicolateral compartments if complications are suspected [37].

5.3.2.4 Distant metastases

Distant metastases of nonmedullary thyroid malignancies are most often reported to be present in lung and bone but may also be found in brain, liver, and even heart [24]. They are found in more than 75% of patients who die from

thyroid carcinoma, and lung metastases themselves account for almost 50% of tumor-related deaths [24]. Whenever technically feasible, the treatment of choice for distant metastases is surgical resection. In the case of isolated metastases, the surgical removal may be curative and, hence, a more aggressive approach may be justified. If surgery is only indicated to alleviate symptoms, a more restricted approach should be followed. A combination therapy consisting of surgery, radioiodine, and/or external radiation may be beneficial [4].

5.3.3 Completion Thyroidectomy

About 5% of thyroid nodules are believed to be malignant [38]. Pre- and intraoperative diagnostic techniques do not always allow a clear decision whether a nodule is benign or malignant. Thus, histopathological analysis may reveal the diagnosis „thyroid cancer" postoperatively. Usually, the extent of thyroid gland resection in these cases is less than total thyroidectomy. The indications for not performing a completion thyroidectomy equal those that justify performing less than total thyroidectomy (see above). In other words, if the definitive histopathological diagnosis is thyroid cancer a completion thyroidectomy is indicated if one of the following applies:

1. Tumor remnant is proved.
2. Histology shows tumor multifocality or multifocal disease is very likely (e.g., history of external radiation).
3. Primary tumor is larger than 1 cm in diameter (>pT1), at least in pT4.
4. The presence of lymph node (N1) and/or distant metastases (M1).

5.3.4 Recurrent Disease

Patients with thyroid cancer have to be followed up for the rest of their lives. Tumor can recur even more than 20 year after primary operation. Recurrent thyroid cancer occurs most frequently in the cervical lymph nodes. Even though the complication rate of surgical therapy in patients with recurrent thyroid cancer is higher than the complication rate at primary therapy, surgery is treatment of choice if feasible.

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Part II

Differentiated Thyroid Cancer II