Surgical management of thyroid cancer

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Thyroid cancer is the most common endocrine neoplasm; however, it only accounts for less than 1% of all human malignances. Thyroid cancers are divided into well differentiated and non-well differentiated cancers, according to their histology and behavior. The surgical management options of well-differentiated thyroid cancer include total or near-total thyroidectomy, subtotal thyroidectomy and lobectomy plus isthmusectomy. The extent of surgery for thyroid cancer continues to be an area of controversy. Complications associated with thyroid surgery are directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the operating surgeon. They occur less frequently with good surgical technique and better understanding of surgical anatomy, and include wound healing and infections (seroma, hematoma and wound infection), nerve injury, hypoparathyroidism, hypothyroidism, postoperative hemorrhage and respiratory obstruction.

Thyroid cancer is the most common endocrine neoplasm; however, it only accounts for fewer than 1% of all human malignances [1]. Thyroid cancers develop in tissues deriving from follicular cells. They are classified as well-differentiated thyroid cancer (DTC) and non-well-differentiated cancers, according to their histology and behavior. DTCs include papillary thyroid cancer (PTC), which is the most common follicular thyroid cancer (FTC), Hurthle cell and mixed tumors, containing both papillary and follicular cells. Non-well-differentiated or poorly differentiated tumors commonly refer to insular or anaplastic cancers (AC). Medullary thyroid cancers (MTCs) derive from parafollicular (C cell) tissue and show a biological behavior completely different from that of DTC.

Uncommon tumors, such as lymphoma, sarcoma, squamous cell carcinoma and metastatic tumors mainly arising from epithelial neoplasias (breast, colon, kidney, ovary and lung), can develop in the thyroid gland [2].

The incidence of thyroid cancer is rapidly increasing in the USA [5]. In recent years, it has represented 1.5% of all new cancers diagnosed in the USA and has been increasing at a rate of more than 4% every year for the past 20 years, according to a report of the American Cancer Society [2]. Approximately 24,000 new patients with thyroid cancer are diagnosed in the USA annually.

The Italian Cancer registry reports 5.2 new thyroid cancers per 100,000 males and 14.5 per 100,000 women every year, with an overall figure of 675 new thyroid cancers diagnosed among males and 2579 among females. Regarding mortality, there were 189 deaths due to thyroid cancer among males and 356 among females in the year 2002 [6]. The Italian network of cancer registries analyzed 5101 cases of thyroid carcinoma, showing a mortality rate reduction of 4% per year [7].

In the UK, there is an annual incidence of 1000 new cases per year, with 220 reported deaths [8]. The rate of thyroid cancer in Hong Kong in 1998–1999 was 2.5 per 100,000 for men and 6.5 per 100,000 for women [9,10]. On the other hand, mortality has not increased in the last 20 years and the 10-year survival is strictly related to histology, being up to 99% for
Surgical management
Surgical options for thyroid carcinoma include the following:
- Conservative surgery: hemithyroidectomy plus isthmectomy
- Conservative surgery plus central neck dissection
- Radical surgery: total thyroidectomy with or without lymphadenectomy

Surgery for thyroid cancer should be performed by experienced surgeons in trained teams employing a multidisciplinary approach. Surgeons should be thoroughly familiar with the natural history of the different thyroid malignancies and the surgical techniques, including both thyroidectomy and neck dissection. Various studies have shown that the surgeon's experience in thyroidectomy is significantly associated with lower complication rates and length of stay [13-15].

Well-differentiated thyroid cancer
The options for therapy include the following:
- Conservative surgery
- Conservative surgery plus central neck dissection
- Radical surgery for advanced or high-risk disease

The options for surgical management include total thyroidectomy or lobectomy plus isthmectomy [16]. The extent of surgery for thyroid cancer has always been controversial, due to the good prognosis of these tumors. There is a general consensus about the management of high-risk patients, defined by different prognostic factors such as age, metastases, extent and size (AM ES) [17]; age, grade, extent and size (AGES) [18]; and primary tumor, regional lymph nodes and distant metastasis (TNM) [19]. In these patients, the optimal treatment is total thyroidectomy [16,20]. On the other hand, the optimal extent of thyroidectomy in patients with low-risk disease remains a matter of debate [11]. A prospective, randomized, controlled trial to evaluate the potential benefits or risks of the hemithyroidectomy versus total thyroidectomy is difficult to perform, owing to the high number of patients required and the length of follow-up necessary to demonstrate a difference in outcome between the two surgical options [16].

Authors supporting total thyroidectomy in all patients with thyroid cancer underline the following advantages of this procedure [16,21-23]:
- Microscopic cancer foci may be present in the contralateral lobe, where recurrences develop in approximately 7% of patients following conservative surgery
- Reduced number of repeated surgical interventions, decreasing the risk of complications
- Radioactive iodine may be used to detect and treat residual tissue or metastases
- Serum thyroglobulin level, considered to be a more sensitive marker of persistent or recurrent disease, is more reliable after complete removal of the thyroid gland
- Prevention of dedifferentiation of residual thyroid tissue
- Therapy of thyroid hormone replacement is straightforward

Authors supporting conservative surgery [20,24,25] for patients at low risk suggest the following:
- Total thyroidectomy may be associated with a higher complication rate
- Possible local recurrences can be controlled with surgery
- Local recurrence rate in the thyroid bed is less than 5%
- Tumor multifocality has little clinical significance
- Extrathyroidal extension of the tumor gland modulates neuroendocrine functions
- If disease has a very good prognosis, demolitive surgery is unwarranted

Shaha divides patients into low risk, high risk and intermediate risk, including in the intermediate-risk group patients younger than 45 years with unfavorable prognostic factors or those older than 45 years with favorable prognostic factors [24]. He reports a 10-year survival in patients with DTC as high as 99% in low risk groups, 87% in intermediate-risk groups and 57% in high-risk groups. Shaha et al. studied a series of low-risk patients who underwent total versus less-than-total thyroidectomy and found no difference either in survival or in local control [25]. Based on these results, they suggest that decision-making in management of DTC should be based on both prognostic factors and individual risks (age, histological variants, previous radiation exposure, familial disease and others).

Lobectomy plus isthmectomy is satisfactory for the low-risk group; a total thyroidectomy is the best option for the high-risk group. Extent of thyroidectomy and possible additional treatment should be tailored according to prognosis factors in the intermediate-risk group [24].

The incidence of nodal metastases in patients with DTC is up to 50%, and the level VI is mainly involved (paratracheal) [2]. For this reason, several surgeons routinely perform a central neck dissection in patients with papillary carcinoma of the thyroid. Elective neck dissection (levels II-VI) is usually performed only in patients with clinically evident nodal disease [2].

There is no agreement regarding the utility of prophylactic node dissection in clinically negative patients. PTC tends to spread to regional lymph nodes in the early stages, increasing recurrence rates but not affecting cancer mortality. There are no randomized, prospective studies to prove that prophylactic lymphadenectomy is superior [26].

Thyroglobulin (Tg), which can be synthesized both by normal gland and tumor tissue, is a unique marker for benign and malignant thyroid follicle activity. Tg is a highly specific
and sensitive marker for DTC when autoantibodies are absent. Basal Tg level directly correlates with the quantity of functioning thyroid tissue [27].

A variety of different genetic alterations, such as rearrangements and point mutations, occur in the development of DTC. Targets include rearrangements in RET and TRK and point mutations in BRAF and RAS. Rearrangements have been linked with radiation exposure, while the origin of point mutations remains unknown [28].

Molecular markers of neoplastic progression include expression of vimentin, fibronectin, osteopontin, RUNX2 and down-regulation of E-cadherin. Expression of these genes is promoted by various growth factors with tyrosine kinase activity [29].

Based on these data [20,24,25], we may conclude that conservative surgery represents a safe technique. TABLE 1 shows the European Institute of Oncology (EIO) therapeutic guidelines since 2003.

DTCs include both papillary and follicular cancer; follicular cancer is the more aggressive and should be included in the intermediate-risk group when planning treatment.

**Table 1. European Institute of Oncology therapeutic protocol.**

<table>
<thead>
<tr>
<th>TNM</th>
<th>Age</th>
<th>Surgery</th>
<th>Pharmacoprevention</th>
<th>131I ±</th>
<th>0.05 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
<td>All</td>
<td>EH + CND</td>
<td>No if &lt;1cm</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>&lt;45 years</td>
<td>EH + CND</td>
<td>L-thyroxin suppressive therapy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>&gt;45 years</td>
<td>TT + CND</td>
<td>L-thyroxin suppressive therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T3-T4N0M0</td>
<td>All</td>
<td>TT + CND</td>
<td>L-thyroxin suppressive therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Any T-N1M0M1</td>
<td>All</td>
<td>TT + CND/ND</td>
<td>L-thyroxin suppressive therapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CND: Central nodal dissection; EH: Enlarged hemithyroidectomy with isthmusectomy; ND: Nodal dissection; TNM: Tumor–node–metastasis; TT: Total thyroidectomy.
Medullary carcinoma

Options for medullary carcinoma therapy include radical surgery plus lymphadenectomy (discussed extent of lymphadenectomy).

MTC accounts for approximately 3–10% of all thyroid cancers and 13–15% of all thyroid cancer-related deaths [11,60,61]. MTC was recognized as a disease different from papillary and follicular carcinoma by Hazard, Hawk and Crile in 1959 [62]. MTC originates from C cells derived from the neural crest and, for this reason, MTC are classified as neuroendocrine neoplasms [63], biologically and pathologically different from the follicular-derived tumors (PTC, FTC) of the thyroid. No exogenous etiological factors have been identified as yet.

MTC can occur both as a sporadic or familial tumor. The familial type accounts for more than 25% of cases and may present as a single tumor or be associated in a syndromic disease, multiple endocrine neoplasia type II (MEN 2) (TABLE 3) [63]. All ages may be affected by this neoplasm, obviously with earlier presentation for familial disease. The mean diagnosis age is 49 years for the sporadic type and 30 years for the familial type [64].

MTC generally presents as a painless nodule in the thyroid gland. Only in advanced disease does the patient complain of pain, dysphagia or hoarseness.

Neuroendocrine symptoms, such as rash and diarrhea, secondary to the release of calcitonin, adrenocorticotrophin, vasoactive intestinal polypeptide or serotonin, are rarely early signs of the tumor, but are often present as associated symptoms in patients with metastatic or locally advanced disease [65,66]. Germ-line mutations in the RET proto-oncogene are responsible for MEN 2A, MEN 2B and FMTC. Most patients with MEN 2A have mutations in the extracellular domain of RET in exons 10 or 11 (codons 609, 610, 611, 618, 620 and 634). Patients with MEN 2B usually have a RET mutation involving codon 918 in exon 16 (seen in 95% of cases); however, other mutations have also been described (codons 804, 806, 883 and 922) [67] and in patients with sporadic disease, 40–60% of cases have somatic RET mutations of codon 918 [68].

Metastatic dissemination to both central and laterocervical lymph nodes occurs at similar high frequencies; lymph node metastases are found in 20–30% of patients with an MTC of less than 1 cm in diameter, in 50% of patients with a tumor 1–4 cm in diameter and in up to 90% of patients with a tumor greater than 4 cm in diameter [69]. Distant metastases may arise in the liver, lungs, bones and, less frequently, in the brain and skin. They are usually diffuse and multiple in involved organs, and generally affect multiple organs.

Patients with MEN 2A and FMTC have a better long-term outcome than patients with MEN 2B or sporadic tumors [70,71]. Outcome of MTC patients is not strictly related to nodal status and stage of the tumor, and even patients with positive lymph nodes or distant metastases may survive for many years with their disease [72]. Symptoms of flushing and diarrhea, associated with high calcitonin levels, are considered poor prognostic factors. Age over 40 years, presence of

### Table 2. Unfavorable prognostic factors.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Author</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;45 years</td>
<td>Strate SM, Cady B, Tsuchiya A</td>
<td>[117–119]</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>Cady B, Yamamoto Y</td>
<td>[118,120]</td>
</tr>
<tr>
<td>Unencapsulated tumor</td>
<td>Appetecchia M</td>
<td>[121]</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>Pellegriti G</td>
<td>[122]</td>
</tr>
<tr>
<td>Increased cyclin D1 overexpression, p27 underexpression, expression of transforming growth factor B3</td>
<td>Santoro M, Khoo ML, Sugitani I</td>
<td>[123–125]</td>
</tr>
<tr>
<td>Increased expression of p53, bcl2, c-erbB-2 and p21</td>
<td>Brown DC, Soda G</td>
<td>[126,127]</td>
</tr>
</tbody>
</table>

### Table 3. Clinical features of medullary thyroid cancer.

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Clinical features</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Palpable unilateral and solitary mass in 70% of patients, bilateral or multifocal in 30%. Respiratory complaints, hoarseness and dysphagia are seen in approximately 15% of patients and a majority of them have metastatic lymph nodes at the time of diagnosis; they are not associated with other endocrinopathies</td>
<td>[128]</td>
</tr>
<tr>
<td>Familial non-MEN (FMTC)</td>
<td>Recurrent cases within a single family in the absence of pheochromocytoma or parathyroid adenoma; least aggressive form</td>
<td></td>
</tr>
<tr>
<td>MEN 2A</td>
<td>Autosomal dominant inheritance pattern: bilateral medullary thyroid cancer, pheochromocytoma and hyperparathyroidism accounting for approximately 90% of MEN 2 patients</td>
<td></td>
</tr>
<tr>
<td>MEN 2B</td>
<td>Autosomal dominant inheritance: medullary thyroid cancer, pheochromocytoma, ganglioneuromatosis, marfanoid features and muscular and skeletal abnormalities; worst prognosis</td>
<td>[129,130]</td>
</tr>
</tbody>
</table>

FMTC: Familial medullary thyroid cancer; MEN: Multiple endocrine neoplasia.
Debulking surgery or nothing

Radical surgery

Anaplastic cancer
Survival [73,74]. Surgical excision all contributed to a poorer prognosis and regional or distant metastases and an inadequate primary surgical excision all contributed to a poorer prognosis and survival [73,74].

Calcitonin, the primary secretory product of MTC, is a reliable marker being used as the first diagnostic test of MTC. This test is widely available, accurate, reproducible and cost effective. Basal- or pentagastrin-stimulated plasma calcitonin levels are elevated in virtually all patients with MTC. Basal concentrations are correlated with tumor mass; elevated plasma levels after surgery are consistent with persistent or recurrent disease.

There is general agreement that total thyroidectomy central neck dissection (levels VI and VII) and neck dissection is the appropriate treatment for the primary (whatever T, C N 0); most authors also suggest a bilateral or homolateral neck dissection in C N 0 (levels II–V). The goal of this operation is to remove all the thyroid tissue and the nodes reached by the lymphatic stream from the thyroid gland. Parathyroid glands should be identified during thyroidectomy; however, controversy exists regarding how these glands should be preserved in order to maintain function. Some authors preserve the parathyroids in situ [75] or perform total parathyroidectomy with autotransplantation [76]. Preferred sites for autotransplantation are the muscle of the nondominant forearm (in most patients with MEN 2A) or sternocleidomastoid muscle (in most patients with MEN 2B).

Genetic diagnosis has changed the way in which MTC is managed. Prophylactic surgery for patients carrying a positive RET proto-oncogene has proved to be highly effective in treating those likely to experience the development of MTC [77]. One new approach for prophylactic surgery for patients carrying a positive RET proto-oncogene is video-assisted central compartment lymphadenectomy. This is effective and safe but a greater number of cases with a long follow-up is needed [78].

Anaplastic cancer

The options for therapy for AC include the following:

- Radical surgery
- Debunking surgery or nothing
- Chemotherapy and radiotherapy
- Palliative therapy

AC of the thyroid gland is one of the more aggressive human cancers, but it is rare, with an adjusted annual incidence of two cases per million per year [79] and it accounts for approximately 1.6% of all thyroid cancers, having a greater incidence in areas of endemic goiter (twice as common). In recent years, a decreasing trend has been noted in industrialized countries, and improvements in socio-economic status have been shown to be associated with a reduction in incidence [80] probably due to removal of DTC before anaplastic dedifferentiation. Most patients affected are elderly, with peak incidence between 60–70 years of age; 55–77% of cases are female [81,82].

The real incidence has to be re-evaluated because several cases of AC have been reclassified as lymphomas or undifferentiated medullary cancer by application of immunohistochemistry [81,83,84]. Many authors have suggested a biological progression from follicular adenoma to DTC to AC (Figure 1) [81,85–88].

Most anaplastic cells are unable to express specific thyroid genes, and neither produce thyroglobulin nor express receptors for thyrotropin and transport of iodine. The habitual clinical sequence commences with the existence of a thyroid tumor of long evolution, in which anaplastic changes occur [201].

Most patients present with large neck masses with rapid growth [81,82]. They soon develop local compressive symptoms that include dysphagia, dysphonia, stridor, dyspnea and often neck pain [89]. Invasion of adjacent organs (trachea, esophagus, vessels and muscles) is frequently observed (90%). Cervical nodes are metastatic in approximately 40% of patients and 30% show vocal cord paralysis [82]. Half of the patients with AC present distant metastases at the time of the diagnosis, the lung (86%) being the most common, followed by bones (6–15%) and the brain (5–13%) [81,82,88,90,91].

ACs are solid masses, generally hypofunctioning; thyroglobulin concentrations may be highly out of range or normal and carcinomaembryonic antigen concentrations may be high or normal. Fine-needle aspiration of the thyroid mass or lymph node metastases is accurate in 90% of cases, and open biopsy of these tumors is rarely needed [79,81]. Inadequate fine-needle aspiration may occur because of tumor necrosis, hemorrhage, leukocytic infiltration or fibrosis and, in these cases, the diagnosis should be confirmed by surgical biopsy or at surgery [201].

Microscopically, there are three recognized histological patterns: spindle (53%), giant-cell (50%), and squamoid (19%) [92], but they have no prognostic significance. Keratin is the most useful epithelial marker and is present in 40–100% of ACs [82]. DTCs with small-undifferentiated foci are called insular cancers and should be considered a variant of ACs.
The role of surgery in AC remains controversial. The Mayo Clinic reported its 50-year experience with AC in 134 patients and found that neither the extent of operation nor the completeness of resection achieved had a significant impact on survival [90]. Recently published consensus has suggested that total thyroidectomy is justified only if possible cervical and mediastinal disease can be resected with low morbidity. Tracheostomy could, when possible, be performed as a palliative procedure in patients with compressive AC.

Different studies have shown that age, size of tumor, resectability, extent of disease, distant metastases, presence of acute symptoms and duration of symptoms influences survival [81,82,93–95]. The treatment is multidisciplinary [81,91,96–99], including surgery before or after chemotherapy (the most effective single cytotoxic agent being doxorubicin) and hyperfractionated radiotherapy. Median survival is 2–6 months and only a few patients have survived beyond 12 months.

**Complications of thyroidectomy**

Complications associated with thyroid surgery are directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the surgeon. The complications from thyroidectomy occur less frequently with good surgical technique and better understanding of surgical anatomy. They include wound healing and infections (seroma, hematoma and wound infection), nerve injury, hypoparathyroidism, hypothyroidism, postoperative hemorrhage and respiratory obstruction. Other complications may occur related to neck dissection, such as a spinal accessory nerve injury and chylous fistula (TABLE 4).

**Wound complications**

Thyroidectomy is associated with a low risk of wound infections; routine prophylactic antibiotics are not indicated. Different studies have reported wound infections of 0.5% [100]. Antibiotics, incision and drainage are the appropriate treatment. Seroma, hematoma and necrosis of skin flaps are relatively uncommon.

Intraoperative and postoperative bleeding may be venous or arterial; these occur in 1.2–1.6% of patients and may lead to fatal consequences due to tracheal compression and hypoxia [100,101]. Most postoperative bleeding occurs in the first 6 h, but 25% can occur between 6 and 24 h postoperatively. Drains do not reduce the risk from this complication. Treatment is reoperation and evacuation of the hematoma.

**Airway obstruction**

Airway obstruction is a major complication of thyroid surgery and can lead to death. The reasons include bilateral recurrent nerve injury, tracheal malacia, subglottic edema and postoperative hemorrhage or hematoma [102].

**Nerve injury**

Superior laryngeal nerve

Injury to the external branch of the superior laryngeal nerve leads to voice changes, including slight huskiness, poor volume, voice fatigue and the inability to sing high notes [101]. These injuries may lead to subtle voice changes if one fails to recognize the importance of this nerve. Prevention of this injury can be achieved by clearly identifying the superior thyroid artery before ligation or with superior artery branches ligated separately close to the thyroid gland without identification of the external laryngeal nerve [103].

**Recurrent laryngeal nerve**

This represents the most serious complication of thyroidectomy. The incidence of injury can vary from as low as 0.3% to as high as 17%, depending on the skill and experience of the surgeon [104,105]. There is a higher incidence in second thyroid operations. Factors that can have an influence on the incidence of injury include the type of surgical procedure, failure to identify the nerve and the histologic features.

In order to avoid the injury, meticulous techniques must be employed to identify this nerve, since there is considerable anatomic variation in its location. Anatomic variations may take place on either side of the neck. This is why the thoracic inlet is one of three potential sites where the nerve is at high risk.

**Complications of thyroidectomy**

<table>
<thead>
<tr>
<th>Intraoperative</th>
<th>Postoperative</th>
<th>Metabolic</th>
<th>Associated form neck dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>Hemorrhage</td>
<td>Hypocalcemia</td>
<td>Neural injuries</td>
</tr>
<tr>
<td>Superior laryngeal nerve injury</td>
<td>Airway obstruction</td>
<td></td>
<td>Chyle leak</td>
</tr>
<tr>
<td>Combinations of nerve injuries</td>
<td>Wound complications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BOX 1. METHODS OF SENTINEL NODE BIOPSY**

- **Vital dye**
  - Risk of disruption of the lymphatic channels from the nodule
  - Need to identify the parathyroid glands prior to injection
  - Not always easy
  - Requires experience

- **Lymphoscintigraphy**
  - Excellent for visualizing the lymphatic pathways
  - Eliminates lymphatic disruption during operation
  - There is no uptake in the parathyroid glands

**Table 4. Complications of thyroidectomy.**

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Intraoperative</th>
<th>Postoperative</th>
<th>Metabolic</th>
<th>Associated form neck dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>Hemorrhage</td>
<td>Hypocalcemia</td>
<td>Neural injuries</td>
<td></td>
</tr>
<tr>
<td>Superior laryngeal nerve injury</td>
<td>Airway obstruction</td>
<td></td>
<td>Chyle leak</td>
<td></td>
</tr>
<tr>
<td>Combinations of nerve injuries</td>
<td>Wound complications</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
risk. The other two areas where the nerve is at highest risk are at the point of ligation of the branches of the inferior thyroid arteries and at the ligament of Berry [106].

Injury to the recurrent nerve may result in symptoms of hoarseness, mild dysphagia and airway compromise, depending on the extent of the injury and whether or not both recurrent nerves are affected [101]. Most surgeons recommend identification of the recurrent laryngeal nerve, or its identification caudal to the inferior thyroid artery where its course is more consistent [107]. Some surgeons recommend intraoperative nerve monitoring for the identification of the recurrent laryngeal nerve, but this is no substitute for a thorough and methodical dissection by an experienced surgeon [101].

Hypoparathyroidism
Postoperative hypocalcemia may be caused by transient or permanent hypoparathyroidism. It frequently occurs in association with an extensive and invasive thyroid cancer and thyroidectomy with central and lateral neck dissection; when parathyroid tissue is removed and not reimplemented, gland infarcts arise from manipulation and the blood supply is disrupted [100]. The incidence varies and has been reported as ranging from 1.2 to 40% [102]. Most individuals have four parathyroid glands situated on the posterolateral capsule of the thyroid but the location is variable because they originate from the third and fourth pharyngeal pouch and then descend into the neck. When parathyroid glands cannot be dissected from the thyroid with a good vascular pedicle, it should be autografted into the sternocleidomastoid muscle or into the brachioradialis muscle of the nondominant forearm.

In 79 patients who underwent thyroidectomy during 2004 at the EIO, hypocalcemia was immediate in 21% of patients and increased 7% after 6 months, with an incidence of 18% in total thyroidectomy, 46% in thyroidectomy with central neck dissection and 20% in total thyroidectomy with neck dissection.

Conclusion
Thyroid carcinoma is an uncommon neoplasia, with several histologic variants from the differentiated tumors of very good prognosis to poorly differentiated tumors of worse prognosis. This disease should be managed in specialist cancer centers and by experienced surgeons to minimize the risk of complications. Opinion continues to diverge regarding the management of the differentiated cancers, with two clearly defined stances, from preservative to radical surgery. Each groups offers a definite approach, yet there is no clear evaluation of which is more effective. No randomized trials exist because of the great quantity of patients and long period of follow-up required. Microcarcinoma has the same divergence in the management as the differentiated cancer. Our own recommendation is conservative surgery. Treatment for MTC should be radical with a dissection of the bilateral neck, given its uncertain but aggressive behavior. AC continues to pose a challenge because of the few appropriate treatment approaches from the surgical and pharmacological point of view.

Expert commentary
Thyroid cancer is the most common endocrine neoplasm; the extent of surgery continues to be an area of controversy, but our own recommendation is conservative surgery for low-risk DTC and for microcarcinoma without unfavorable risk factors due to the good prognosis of these tumors. The great expectations for the management of thyroid cancer lie in the development of gene therapies and redifferentiating agents.

Five-year view
We believe that the development of the surgery and management of thyroid cancer in the next 5 years should be focused on advances in minimal access surgery, directed oriented nodal dissection and genetic therapy.

Table 5. Molecular targeted therapies in thyroid cancer.

<table>
<thead>
<tr>
<th>Acting at the plasmatic membrane (VEGFR, EGFR, RET pathway inhibitors)</th>
<th>Cytoplasm downstream effectors</th>
<th>Nuclear active</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZD6474</td>
<td>Sorafenib</td>
<td>Histone deacetylase inhibitors</td>
</tr>
<tr>
<td>AMG706</td>
<td>CI-1040</td>
<td>Vitamin-A derived retinoic acids</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>Imatinib mesylate</td>
<td>Peroxisome proliferator-activated receptor expression ligands</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEE788</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclooxygenase-2 inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EGFR: EGF receptor; VEGFR: VEGF receptor.
Minimal access surgery

Minimal access surgery was popularized after the introduction of laparoscopic cholecystectomy by Mouret [108]. These techniques have been applied in parathyroid and thyroid surgery. One of the more popular techniques is video-assisted minimal invasive thyroidectomy [109]. General indications for this technique include the following [110]:

- Thyroid nodules smaller than 30 mm at their largest diameter in thyroid glands with a volume less than 20 ml
- Graves' disease in glands smaller than volume of 20 ml
- No history of thyroiditis
- No previous neck surgery or irradiation
- Follicular tumor or low-risk papillary carcinoma
- RET gene mutation carriers with normal basal-stimulated calcitonin levels (still needs to be validated)

Indications for video-assisted thyroidectomy are still limited (only in 20% of patients who required thyroidectomy) and the learning curve is quite long [111,112].

Costs do not appear to be higher than those of open thyroidectomy, because the operating time is similar and the instruments are all reusable, offering potential advantages of better cosmesis and less postoperative distress [110].

This technique is becoming more widely available and indications for its use will increase as thyroid surgery develops in the coming years, but the actual role of minimal invasive surgery in cancer therapy is still being debated with the possibility of complete removal of tumor mass and effects of mass manipulation being the greatest concerns.

Sentinel node biopsy

Recently, for staging and surgery in DTC, sentinel node biopsy (SNL) has been applied, the concept of SNL is based on the fact that the first lymph node in a lymphatic chain (the sentinel node) will be the first affected by metastases and, if it can be shown to be negative, it is highly unlikely that other nodes are affected [113,114]. There are different methods of SNL biopsy in DTC (Box 1):

- Vital dye technique
- Preoperative lymphoscintigraphy and intraoperative detection with the γ probe technique
- The combination of a vital dye, lymphoscintigraphy and intraoperative γ probe

This technique offers advantages in DTC, primarily for small tumors:

- Better selection of patients for compartment-oriented nodal dissection
- More accurate staging
- Accurate selection of patients with metastatic disease optimized ablative 131I treatment
- Identification of lymph node metastases outside the central compartment

The main disadvantage of the SLN biopsy technique is the possibility that lymph node metastases can be found in non-SLN. It is prudent to perform larger multicenter studies before drawing conclusive judgments on the use of the SLN technique in DTC [115].

New therapies

Advances in molecular and cellular biology have made it possible to develop new therapeutic approaches to thyroid cancer (Table 5). Genes related to thyroid-specific functions are future targets for cancer therapy. Redifferentiating agents and gene therapy using thyroid-specific genes are currently being investigated and more well-designed clinical trials are warranted [116].

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Key issues

- Thyroid cancer is the most common endocrine neoplasm; but continues to be of low presentation (<1% of human malignances) and has a generally favorable prognosis.
- Surgery for thyroid cancer should be performed by experienced surgeons with trained multidisciplinary teams and with a large number of patients operated on annually.
- The surgical management options of papillary microcarcinoma include total or near-total thyroidectomy, subtotal thyroidectomy and lobectomy plus isthmusectomy.
- The extent of surgery for thyroid cancer continues to be an area of controversy.
- Central compartment dissection is a routine surgical procedure in patients with papillary carcinoma of the thyroid; lateral neck dissection is performed only if nodal metastasis is noted at the time of surgery or is clinically palpable.
- Conservative surgical therapy in well-differentiated thyroid cancer is a safe technique.
- Total thyroidectomy is the appropriate treatment for medullary thyroid cancer, accompanied by a central node neck (levels VI and VII) dissection and bilaterally (levels II–V) for removal of all thyroid and nodal tissue.
- There is an adenoma progression to well-differentiated carcinoma to anaplastic cancer.
- Treatment of anaplastic cancer is multimodal, including surgery before or after chemotherapy and hyperfractionated radiotherapy.
- Complications associated with thyroid surgery are directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the operating surgeon.
References


Website


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