2 General Preoperative Workup, Informed Consent, Antibiotic Prophylaxis, and Anesthesia in Thyroid Surgery

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2.1 General Preoperative Workup

Patients with thyroid disease (TD) requiring surgery must be properly evaluated by obtaining their medical history; physical examination, laboratory testing, and imaging studies aim to define and confirm the diagnostic hypothesis and facilitate the choice of the most appropriate surgical approach and the extension of the surgical procedure [1].

2.1.1 History and Clinical Characteristics

Medical history includes the search for exposure to previous neck or whole-body irradiation or ionizing radiation. The radiation-related risk factors are dose, age at exposure, latency period, female gender, and degree of iodine deficiency at exposure [2].

First-degree relatives suffering from syndromes that include thyroid cancer (TC) (Cowden syndrome, familial polyposis, Carney complex, MEN 2, Werner syndrome, etc.) must be identified. For instance, the presence of a familial RET mutation (MEN 2) may impact the extent of initial thyroid surgery (TS) or the decision to perform prophylactic TS [3].

The patient should be asked about how and when the condition was identified, and the rapidity of growth or change in thyroid nodules (TN); a history of autoimmune thyroiditis, hypothyroidism, or Grave's disease should also be obtained [3].

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Non-thyroid malignancies must be investigated, as the gland could be the site of metachronous metastasis (renal cell, lung, colon, breast, melanoma, ovarian primaries) with a presentation similar to a primary TN [4].

The search for compressive symptoms includes solids dysphagia that suggests a mechanical obstruction [5]. Swallowing symptoms are reported by up to 50% of patients [3]. Dyspnea is frequent in goiter and should be differentiated from cardiac and pulmonary dysfunction while its rapid progression can be associated with an aggressive malignancy.

Symptoms related to TD may include fatigue, palpitations, anxiety, insomnia, weight fluctuations, and heat intolerance in the case of hyperthyroidism, whereas hypothyroidism may cause cold intolerance, constipation, dry skin, slowed thinking, and edema [3].

Comorbidities that increase operative risk are [3]:

- personal or family history of anesthetic complications (malignant hyperthermia, difficult intubation);
- prior neck surgery;
- possible or diagnosed bleeding or clotting disorder; use of antithrombotic or antiplatelet medications;
- celiac sprue, inflammatory bowel disease, Roux-en-Y gastric bypass, any condition of chronic diarrhea.

2.1.2 Physical Examination

Physical examination findings should suggest hyperthyroidism if elevated heart rate, hypertension, and exophthalmos are present; signs of hypothyroidism should be a slow heart rate and slowed Achilles heel reflex time.

Neck examination may identify palpable nodules (at least 1 cm in size); immobile nodules and lymphadenopathy are concerning for malignant disease. Goiter may be graded by World Health Organization criteria from Grade 0 (nonpalpable/nonvisible) to Grade 3 (visible at a distance) [6].

Substernal goiter (SG) is diagnosed when the full extent of an enlarged thyroid cannot be palpated with the patient's neck extended, even with deglutition or supine positioning. Obesity, a short thick neck, or kyphosis, need further imaging to fully appreciate a SG.

Voice assessment is part of the physical examination and voice abnormalities may change the indication or the extent of TS or delay the operation. Mirror examination and flexible laryngoscopy are the most commonly used methods and are routinely recommended [7].

2.1.3 Laboratory Tests

- Serum TSH level [1, 3].
- Calcitonin dosage to screen for medullary thyroid cancer is controversial in routine assessment. Current American guidelines do not recommend screening basal serum calcitonin levels in the evaluation of TN, but only targeted screenings in at-risk individuals [1, 3].
- Secondary level tests are: serum calcium to screen for primary hyperparathyroidism, followed by, serum phosphate and PTH assays if serum calcium is high; anti-TPO and anti-Tg if autoimmune disease is suspected; TSH-receptor antibody for diagnosis of Grave's disease.

2.1.4 Imaging Studies

Thyroid ultrasound (US) with color flow Doppler scanning is the crucial imaging study in all patients with a clinical suspicion of TN and nodular goiter (CT or MRI of the neck, thyroidal uptake on ^{18}FDG-PET scan, etc.). US allows an accurate anatomical evaluation of the thyroid and adjacent regional lymph nodes (LN), by giving relevant information on:

– location, size (possibly total gland volume);
– presence, number, size, and structure (solid, cystic, mixed) of the TN;
– vascular pattern of the TN on color Doppler;
– status of the contralateral lobe in the case of unilateral disease;
– nodular features indicative of malignancy (hypoechogenicity, microcalcifications, absence of halo, irregular margins, chaotic intranodular vascularity, round shape);
– condition of the trachea (midline, displaced, compressed);
– status of regional LN (reactive or suspicious).

The 2020 guidelines of the American Association of Endocrine Surgeons summarized the US features predictive of TC, reconsidering the specificity of nodule hypoechogenicity and focusing on microcalcification, irregular margins, and tall shape to guide the need for fine needle aspiration cytology (FNAC) for TN [3].

Several scoring systems have been proposed to establish the indication for FNAC and avoid unnecessary diagnostic TS [3, 8]. Among them is the Thyroid Imaging Reporting and Data System (TI-RADS), which uses US features to assign a predictive score from TR1 to TR5, related to the rate histological malignancy [9].

FNAC indications depend on the US features, but also the size of the TN is considered. Nodules <1 cm are usually not biopsied, because of the indolent behavior of TC of this size, unless they are suspicious for metastases or local invasion [10]. Other indications, regardless of nodule size, are the risk factors for malignancy identified during medical history or clinically suspicious findings (hoarseness, fixed nodule, laryngeal nerve dysfunction).

Cytology reports have been standardized using the Bethesda System for Reporting Thyroid Cytopathology, published in 2008 and updated in 2017, which provides six categories from I to VI, ranging from benign lesions to suspected malignancy or malignant lesions. In 2012 in Italy, a panel of experts introduced a subcategory of Tir 3 to reduce the number of nodules with intermediate cytology to be subjected to surgery (Tir 3a, low-risk indeterminate lesion; Tir 3b, high-risk indeterminate lesion). Washout fluid testing for thyroglobulin (TG) and calcitonin are not routinely performed; they may be useful to distinguish if the biopsied lesion is a LN or parathyroid and to identify metastatic node cancer in doubtful cases [1].

CT/MRI are needed only as second-level examinations for the assessment of large, rapidly growing lesions, or SG, or in the presence of invasive TC to define the involvement of extrathyroidal tissues.

Thyroid scintigraphy with radioactive iodine uptake test is not useful in euthyroid patients. Indications are limited to subclinical or overt hyperthyroidism, recurrent goiter, and suspicion of forgotten or ectopic goiter.

PET/CT (^{18}FDG-PET) is not recommended for routine preoperative evaluation but may be worthwhile when aggressive histology is suggested as in poorly differentiated or anaplastic TC; 30–40% of accidentally discovered ^{18}FDG-PET-positive nodules may be malignant. Nonetheless, such nodules should be evaluated by US and FNAC at the same time. As regards the detection of cervical LN metastases, CT and MRI show higher sensitivity, while PET can identify inflammatory LNs [11].

Finally, the preadmission workup includes a complete preoperative assessment with blood chemistry, blood cell count and coagulation tests, electrocardiography and, depending on the patient's age and comorbidities, chest X-ray [1].

2.2 Informed Consent

The patient's right to informed consent is discussed in the European Chapter of Patients' Rights which establishes that each patient has the right to choose between various treatments based on appropriate information [12].

The patient should be informed about the results of the preoperative workup, the extent of TS, and the reasons for suggesting one procedure rather than others. A two-step surgery must be discussed in the case of a pre- or perioperative difficult diagnosis or higher risk of iatrogenic damage (TS, inflammation, previous irradiation of the neck, re-operation) [13].

The risks and benefits of the TS proposed should be analyzed. The information should be based on the literature data, the patient's situation, and the surgeon's experience, in particular distinguishing between the generic risks of TS and the specific risks related to the patient's characteristics. In detail, the patient should be informed about:

– postoperative hematoma and bleeding requiring re-intervention;
– unilateral or bilateral laryngeal palsy, temporary or definitive;

– transient and definitive hyperparathyroidism, increasing with central compartment LN resection, Graves-Basedow disease, needing temporary or permanent medication;
– rare complications such as surgical site infection, tracheal necrosis, minor swallowing disorders, pathological scar healing, as well as general nonspecific complications [3].

Patient information should include anesthesia and the possibility of extemporaneous anatomopathological examination.

Patients must be informed that the use of intraoperative neuromonitoring (IONM) does not completely avoid the risk of recurrent laryngeal nerve (RLN) dysfunction, especially in supposed difficult procedures. According to the International Neural Monitoring Study Group consensus statement of 2021, the patient should be told the purpose of IONM use (RLN identification, function prognostication, and intraoperative decision-making) [14].

Alternative treatment to TS and the consequences of refusing the proposed treatment should be discussed.

Hormone replacement therapy, with subsequent monitoring of thyroid function should be stressed [12].

Once correct verbal information has been provided in clear and simple terms to the patient himself and to a designated trusted person, a written document should be signed by the patient and the surgeon and attached to patient's chart [3].

2.3 Anesthesia in Thyroid Surgery

The real target for anesthesia in TS is to pay attention to the patient's various comorbidities, allowing for adequate monitoring while maintaining adequate anesthesia.

There are currently two types of anesthesia employed in clinical practice during TS: the most used are general anesthesia (GA) with tracheal intubation, and the cervical plexus nerve block.

TS under regional anesthesia is anecdotal, as reported in the literature, and remains limited in clinical practice especially to patients with underlying medical comorbidities that preclude GA [15]. By contrast, GA and tracheal intubation represent the methods of choice for TS. The complications generated by tracheal intubation and by TD with induction of anesthesia must be considered and avoided. Indeed, preoperative identification of TD and its implications is important for optimal patient management. The patient should be subjected to GA and TS in the case of a preoperative euthyroid state and only emergency procedures should be performed without euthyroidism. In the event of preoperative hypothyroidism, the clinician should pay attention to an increased tendency to depression of myocardial function, decreased spontaneous ventilation, abnormal baroreceptor function, reduced plasma volume, anemia, hypoglycemia, hyponatremia, and impaired hepatic drug metabolism. Conversely, in the event of a preoperative hyperthyroid state, thyroid crisis must be excluded. This could be triggered by surgery, trauma, or

infection and it must be managed with hydration, cooling, inotropes, steroids, beta-blockade, and antithyroid drugs as the first-line treatment.

In the literature, TS is also associated with difficult endotracheal intubation (DEI) because of the possibility of large goiter or TC infiltration, with a reported rate of 5.3–24.6% higher than the general population. An adequate airway assessment is therefore mandatory to detect and avoid potential difficult intubation [16]. Among factors linked to DEI, the presence of cancerous goiter causing tracheal infiltration and fibrosis which may reduce the mobility of laryngeal structure are considered major predictors of DEI. In these cases, with a higher risk of DEI and airway loss, if GA is induced, awake fiberoptic intubation could be indicated [17].

GA induces intubation through the injection of small doses of nondepolarizing muscle relaxants, including rocuronium bromide. IONM during TS and parathyroid surgery (PTS) has gained widespread acceptance as an adjunct to the gold standard of visual RLN identification but, at the same time, its routine application in surgical practice has modified the type of GA. The success of GA and airway control in TS is now related not only to correct tracheal intubation but also to correct positioning of the endotracheal electromyography tube necessary for precise IONM [18].

Starting from the evidence that quantitative neurophysiological evaluation of the RLN is based on the recording of evoked potential at the vocalis muscle, the unrestricted use of a neuromuscular blocking agent (NMBA) in GA for TS has been widely discussed. The neuromuscular blockade, indeed, may interfere with IONM of the RLN by reducing the signal to varying degrees, and generating confusion in the interpretation of IONM. To address this issue, some strategies have been proposed:

- *Tracheal intubation without muscle relaxant*. Although clinical experience and some studies have proposed tracheal intubation without muscle relaxant in the induction of GA, this requires deep anesthesia and is associated with a higher risk of airway injury, and is therefore now considered only if performed by experienced hands [19].
- *Succinylcholine*. Thanks to the rapid onset and short duration of muscular relaxation, succinylcholine was initially considered for TS with IONM. However, it is now avoided because of the association with a variety of adverse effects from minor to catastrophic, such as cardiac dysrhythmia, hyperkalemia, and malignant hyperthermia as a result of its membrane depolarizing effect and release of potassium [20].
- *Alternative nondepolarizing NMBA at different posology*. The current literature proposes an alternative of nondepolarizing NMBA with short onset and offset of neuromuscular block to replace succinylcholine for IONM. A single dose of rocuronium and atracurium at 0.5 mg/kg was considered adequate for tracheal intubation allowing for spontaneous gradual recovery of neuromuscular transmission and positive electromyography signals [21]. Moreover, a single reduced dose of rocuronium was proposed as a possible alternative [22].
- *Introduction of selective relaxant binding agents (SRBAs)*. SRBAs have the potential to overcome the limitations of cholinesterase inhibitors, acting as a

selective relaxant binding agent for rapid neuromuscular blockade reversal. The first SRBA to be introduced is sugammadex with the function of rapidly restoring neuromuscular function suppressed by rocuronium [22].

The degree of neuromuscular blockade could be intraoperatively monitored by the train of four (TOF) count and ratio derived from the adductor pollicis muscle. Furthermore, anesthetic depth could be assessed by using the response entropy or bispectrality index [23].

2.4 Antibiotics in Thyroid Surgery

Postoperative infections in patients undergoing TS are uncommon. The absence of contact with the upper aerodigestive tract and the type of surgery, normally considered a clean procedure, justify the low rate of surgical site infection (SSI). Indeed, the incidence of SSI after TS and PTS ranges from 0.09% to 2.9% [24].

In the literature, a significant divergence appears to exist between guideline recommendations and clinical practice with regard to the use of antibiotic prophylaxis (AP). AP seems to be commonly used, often on an open basis, depending on the clinical practice and the behaviors of each center. In contrast, the international guidelines do not routinely recommend AP, since unnecessary courses are often associated with pathogen resistance and superinfection, potential toxicity, increased cost and hospital stay. The 2020 guidelines of the American Association of Endocrine Surgeons suggest avoiding AP in most cases of standard transcervical TS for the management of TD in adults because of the low risk of SSI, whereas no mention of AP is made in the guidelines of the American Thyroid Association [3, 14].

A recent metanalysis of postoperative SSI analyzed the outcomes of nine studies (4 RCTs and 5 non-RCTs) showing that there are no significant differences between the SSI rate in patients undergoing TS and PTS with or without AP [25].

Nevertheless, a few studies report some risk factors for the development of SSI such as diabetes, cardiopulmonary comorbidity, ASA score and older age (above 65 or above 80 years), disease factors such as the presence of malignancy, and procedure-related factors such as prolonged operating time and lymphadenectomy [26, 27]. This evidence does not therefore justify the routine use of antibiotics in clean neck surgery but only a limited use if specific preconditions are present.

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