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Which surgery needs to be used in the Differentiated Thyroid Carcinoma?

Antonella Pino, Ettore Caruso, Antonina Catalfamo, Fausto Famà, Francesca Pia Pergolizzi, Alessandro Pontin, Gianlorenzo Dionigi

Division for Endocrine and Minimally Invasive SurgeryDepartment of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy,

Abstract

Surgery for thyroid carcinoma involves a complex decision-making process and technical skills, both related to the experience of the endocrinologist and surgeon. Based on a stratified risk approach for the management of differentiated thyroid carcinoma, therapeutic decisions can now be divided into active surveillance or immediate surgery, e.g. hemithyroidectomy with isthmectomy, total thyroidectomy, or thyroidectomy and locoregional lymphadenectomy. Total thyroidectomy is a surgery associated with high rates of healing and has been considered the gold standard for years. However, thyroid lobectomy, in selected cases, is now recognized as equally oncologically effective and is associated with decreased morbidity in appropriately selected patients. The morbidity of the prophylactic lymphadenectomy of the central compartment is significant in terms of transient and permanent hypocalcaemia. This led to a less aggressive prophylactic surgical approach in the recent guidelines of the American Thyroid Association of 2015. Re-operations in the central or lateral compartment can be difficult and lead to an increased risk to the patient. Therefore, it is important to perform an optimal initial operation in every patient with thyroid cancer. Consideration should be given to addressing patients with high-risk characteristics (N1 clinical disease, locally invasive disease) to experienced surgeons, both for oncologic completeness and for significant impact on clinical outcomes and complication rates.

Keywords **Thyroid; thyroid cancer; differentiated thyroid carcinoma; papillary carcinoma; follicular carcinoma; surgery; endoscopic surgery; recurrence; pediatric surgery**

Introducing Member: Gianlorenzo Dionigi
Corresponding AuthorGianlorenzoDionigigdionigi@unime.it; https://orcid.org/0000-0003-0864-6087

Introduction

The incidence of the malignant tumor of the thyroid gland is increasing (1). In women, thyroid cancer has increased faster than that of any other cancer (2). According to the US database of the National Cancer Institute Surveillance, Epidemiology and Results, in 2013 there were 60,220 thyroid cancers and 1,850 deaths due to endocrine disease (2).

Papillary thyroid carcinoma is the most common histotype (3). In 1990, the annual incidence rate of papillary carcinoma was 5.50 out of 100,000 people per year; in 2010, the annual incidence reached 13.83 out of 100,000 people per year (3-6). Incidence rates of the other histological subtypes of thyroid carcinoma (follicular carcinoma, medullary carcinoma and anaplastic carcinoma) have increased modestly in the last four decades (3, 4). This heterogeneous group of tumors differs greatly in terms of biology and clinical outcomes (5).

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Although much of the increasing incidence of papillary carcinoma is determined by an increase in the detection rate of asymptomatic thyroid microcarcinoma (defined as tumor with diameter <10mm), prognostically favorable ("low risk"), related to medical surveillance and other studies sensitive diagnostics, in particular ultrasound, there is also evidence that the increased incidence of papillary carcinoma can not be wholly dependent on the early diagnosis alone, but also on the increase in advanced malignancies, the increase in mortality rates , exposure to new carcinogens (6-8) (Table 1). Although the extent of thyroid cancer surgery remains controversial, patients with thyroid cancer usually require more extensive resections than patients with benign thyroid disease. A study of 5,860 thyroidectomies showed that, when thyroid cancer is operated by high-volume surgeons, they showed complication rates of at least two-thirds lower than those of low-volume surgeons, reduced hospital stays and significantly lower hospital costs (9,10).

The surgeon must constantly interact with Endocrinologists, translate the data emerging from research and apply new technologies in a standardized manner for optimal care (Figure 1).

Table 1. Are thyroid cancers actually increasing? Incidence rates of thyroid cancer have increased, but the reason for this is not clear.Both the increasing use of diagnostic technologies that allow the detection of asymptomatic thyroid cancer and a true increase in the incidence of thyroid cancer have been proposed.Despite improvements in early detection and diagnosis of thyroid cancer, rates of disease mortality are increasing over time rather than remaining stable *

Increase of microcarcinoma
- Wide availability of advanced medical procedures (ultrasound and fine needle aspiration biopsy) - Increased detection of "accidental" microcarcinomas - In course of thyroidectomy for benign lesions - More detailed histo-pathological examinations - Incidental discovery of nodules on diagnostic examination for other diseases (laryngectomy) - Feedback during autopsy
Increase of thyroid carcinoma
- Updated tumor classifications - Improved accuracy of tumor registers
Increase in the incidence of patients diagnosed with advanced papillary tumor
- The papillary histotype has increased in advanced stages of disease and tumor size (+ 3.5% per year, period 1994-2013).The increase was observed regardless of gender and age at diagnosis
Increase mortality rates
- Mortality for the papillary histotype increased by + 1.7% per year, period 1994-2013 - Mortality for the advanced stage papillary histotype + 2.9%

Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA. 2017;317(13):1338–1348. doi:10.1001/jama.2017.2719

*Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013;2013:965212. doi: 10.1155/2013/965212. Epub 2013 May 7. PubMed PMID: 23737785; PubMed Central PMCID: PMC3664492.

Indications

Surgery for thyroid cancer is usually performed for one of the following reasons: (a) diagnostic resection of a thyroid lobe containing a suspicious nodule for neoplasia; (b) treatment of a known thyroid carcinoma; (c) prophylaxis in patients positive for a genetic mutation that puts them at high risk of developing thyroid cancer; (d) for the treatment of recurrent thyroid carcinoma (Table 3) (11).

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Tabella 2. New TNM classification of thyroid differentiated tumor (VIII Edition AJCC / TNM, 2017), valid from 1 January 2018 *.All categories can be subdivided: (s) solitary tumor and (m) multifocal tumor.The larger tumor determines the classification.The TNM 2017 classifies thyroid carcinomas limited to the gland or macroscopically infiltrated carcinomas in defined anatomical structures.The "minimal extrathyroid diffusion" in perithyroidal soft tissue no longer appears as a classification parameter in the new TNM.

T- Primary tumor (for papillary, follicular, poorly differentiated, Hurtle cell, medullary and anaplastic thyroid carcinomas)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary
T1	Tumor diameter 2 cm or smaller, limited to the thyroid
T1a	Tumor diameter 1cm or smaller
T1b	Tumor diameter > 1 cm but < 2 cm
T2	Tumor diameter 2 cm to 4 cm
T3	Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
T3a	Tumor > 4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscle (sternohyoid) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneus soft tissue, larynx, trachea, esophagus, or reccurent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size

N- Locoregionalnodes

Nx	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0 a	One or more cytologic or histologically confirmed benign lymph node
N0 b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regionalnodes
N1 a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1 b	Metastasis to unilateral, bilateral or controlateral neck lymph nodea (levels I, II, III, IV or V) or retropharyngeal lymph nodes

N- Locoregional nodes

M0	No distant metastasis
M1	Distant metastasis

Stage grouping					
Age at diagnosis	T	N	M	Stage	10-years survival rate
< 55 years old	Any T	Any N	M0	I	98-100%
< 55 years old	Any T	Any N	M1	II	85-95%
>55 years old	T1	N0/Nx	M0	I	98-100%

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>55 years old	T1	N1	M0	II	85-95%
>55 years old	T2	N0/Nx	M0	I	
>55 years old	T2	N1	M0	II	85-95%
>55 years old	T3a/T3b	Any N	M0	II	85-95%
>55 years old	T4a	Any N	M0	III	60-70%
>55 years old	T4b	Any N	M0	IVA	<50%
>55 years old	Any T	Any N	M1	IVB	

Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. 2017. New York: Springer.

Table 3. Surgery for thyroid cancer is usaully performed for one of the following reasons:

- **(a) Diagnostic resection of a thyroid lobe conteining a possible neoplastic nodule;**
- **(b) Treatment of a known thyroid carcinoma;**
- **(c) Prophylatic resection in patients with a gene mutation implying a high risk of thyroid cancer;**
- **(d) Treatment of relapses**

Thyroid cancer typically presents itself as a solitary nodule discovered due to compressive symptoms, palpable nodule, or as a result of radiological imaging performed for another reason. The cytology obtained from a suspected thyroid nodule helps to define the risk of neoplasia (12). Cytological results should be reported using a classification system (13, 14).

According to the American Thyroid Association guidelines published in 2015, fine needle aspiration biopsy is recommended for the thyroid nodule greater than or equal to 1 cm, unless theechographic appearance is completely characteristic of benignity (eg, a pure cystic nodule). FineNeedle aspiration biopsy should also be considered for subcentimetric thyroid nodules with suspicious ultrasound appearance (eg, solid, hypoechoic, with calcifications) and for those patients with a greater risk of thyroid cancer due to a positive family history or previous exposure radiation (12).

In recent years the systems of cytopathological classification were published: Bethesda in 2017; Italian Society of Endocrinology (AIT, AME and SIE) and of Pathological Anatomy and Cytology (SIAPEC-IAP) in 2014 (Table 3a, b) (13, 14).

These systems require that the experts assign the thyroid cytology to a category based on the adequacy

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of the sample, the risk of malignancy and the consequent clinical action suggested (Table 4a, b).

This standardized approach greatly removes the variability of opinion that used to exist among cytopathologists. This information helps physicians determine the appropriate management of the nodule. However, it is important that the Centers do not rely exclusively on published category neoplasia rates, but rather, analyze their own. For example, rates of malignancy published in the diagnostic category "suspected for papillary carcinoma" vary from 50% to 90%, suggesting that diagnostic thyroid lobectomy may be an appropriate initial management (13, 14). In those Institutes, where this category is associated with papillary carcinoma in more than 90%, a formal oncological operation is usually selected as the first one.

Pre-operation evaluation

Laryngoscopy and computerized axial tomography (CT) or magnetic resonance imaging (MRI) are II level examinations aimed at deepening the preoperative evaluation of the patient candidate for surgery for thyroid neoplasia(15-18). Vocal cord dysfunctions have a huge impact on surgical strategy, especially when thyroid surgery is bilateral and surgical procedures must be planned and discussed with the patient. Routine preoperative laryngoscopy is recommended to exclude or verify pre-existing paralysis of the vocal cords, even in the presence of an apparently normal voice. For the prevention of bilateral paralysis therefore the preoperative control of the cordal motility with a flexible fibroscope is mandatory, in all patients who are candidates forthyroidectomy to identify the subjects at risk, namely the carriers of a monolateral recurrent paralysis misunderstood and clinically undetectable by compensation of the rope contralateral vocal.

Figure 1. The advantages of a team multidisciplinary approach include: (a) for those patients suffering from thyroid cancer: increasing in survival for those patients followed by the multidisciplinary team; decreasing diagnosis-treatment time; more possibilities of assistance according to clinical practice guidelines, including psychological support; more accessibility to information; better satisfaction with

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treatment and care. (b) for healthcare professional: improvement of care and patients' results through the development of an agreed treatment plan; simplified treatment pathways and reduction in the duplication of services; better coordination of care; educational opportunities for healthcare professionals.

Table 4a. **The Bethesda System of Reporting Thyroid Cytopathology *. Surgery is indicated for categories IV, V, VI.**

	Diagnosticcategory	**Risk of malignancy (%)**	**Usualmanagment**
I	**Non-diagnostic or unsatisfactory** Cyst fluid only Virtuallyacellular specimen Other	1-4%	Repeat FNA with ultrasound guidance
II	**Benign** Begnin follicular nodule Lymphocytic (Hashimoto's) thyroiditis in the proper clinical context Granulomatous (subacute) thyroiditis Altro	0-3%	ClinicalFollow up
III	**Atypia of undetermined significance or follicular lesion of undetermined significance**	5-15%	Repeat FNA
IV	**Follicular neoplasm or suspicious for a follicular neoplasm** Specify if Hurtle cell (onocytic) type	15-30%	SurgicalLobectomy
V	**Suspicious for malignancy** Sospicious for papillary carcinoma Sospicious for medullary carcinoma Sospicious for metastatic carcinoma Sospicious for lymphoma Other	60-75%	Surgical Lobectomy or Near-total thyroidectomy
VI	**Malignant**	97-99%	Near-total thyroidectomy

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	Papillary carcinoma Poorly differentiated carcinoma Medullary carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin'slymphoma, other		

*****Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017 Nov;27(11):1341-1346. doi: 10.1089/thy.2017. 0500. PubMed PMID: 29091573.*

Recurrent paralysis may already be present (a) due to infiltration of the nerve by a malignant thyroid tumor; (b) in patients previously undergoing cervical intervention (partial thyroidectomy, esophagectomy, carotid TEA, cervical spine surgery) or mediastinum (cardiac surgery on the aortic arch) (c) or prior treatment of nodules by alcoholization or radiofrequency (15, 16) . Preoperative recurrent laryngeal nerve paralysis is an important indicator for locally invasivethyroid neoplasia, present in 70% of patients with invasive disease and only 0.3% of patients with non-invasive disease (15). Vocal cord paralysis is associated with voice changes in only one third of patients (16). Preoperative computed tomography was positive for paralysis of the vocal cords in only 25% of patients (17). Symptomatic speech evaluation and radiographic evaluation are insufficient (15-17). Laryngoscopic examination is recommended for all patients undergoing thyroid surgery (15-17) because of the prevalence of invasive disease of the thyroid, of the importance of preoperative diagnosis of invasive disease in operational planning and counseling of the patient, and the importance of functional analysis of the vocal cords in the algorithms of management of laryngeal nerves recurrent for the nerves found infiltrators at the time of surgery.

Table 4b. Italian classification of thyroid cytology *. Surgery is proposed for the diagnostic categories TIR3B, TIR4 and TIR5.

Group	Diagnostic category	Risk of malignancy rate (%)	Clinical managment
TIR1	Non-diagnostic	Undetermined	Repeat FNA
TIR1C	Non-diagnostic cystic	Low risk	Clinical evaluation Repeat FNA
TIR2	Non-malign/ benign	< 3	Follow up
TIR3A	Low risk undetermined lesion	< 10	Repeat FNA/ follow up
TIR3B	High risk undetermined lesion	15-30	Surgery
TIR4	Suspicious for malignancy	60-80	Surgery with intraoperative exam
TIR5	Malignant	95	Surgery Diagnostic investigation

* ***Nardi F, Basolo F, Crescenzi A, Fadda G, Frasoldati A, Palombini L, Orlandi F, Papini E, Zini M, Pontecorvi A, Vitti P (2014) Italian Consensus for the classification and reporting of thyroid cytology. J EndocrinolInvest DOI 10.1007/s40618-014-0062-0.***

Preoperative use of imaging studies (CT and MRI) is recommended for patients with clinical suspicion of advanced disease. Following evidence of extrathyroid extension, retrosternal growth,

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recurrent laryngeal nerve palsy and clinically or echographically diffuse lymph node metastasis, it is recommended that extended imaging be performed to define the required extent of resection and dissection in the neck. One study showed that preoperative evaluation combined with neck ultrasound and CT scan is superior to neck ultrasound alone in the preoperative detection of lymph node disease, especially in the middle group of cervical nodes. (18, 19).

Neck-mediastinal CT scan is useful for defining the extent to which mediastinal structures are involved in cases with significant caudal diffusion. TAC findings can influence management by indicating the need for sternotomy and / or tracheal or laryngeal, vascular resection / reconstruction, which would require the organization of additional resources and staff in preparation for surgery (18, 19).

Surgery for differentiated tumor

Thyroidectomy extension

Surgery is the main treatment of patients with differentiated thyroid carcinoma (20-23). The specific goals of initial therapy are summarized in Table 5: (a) Removing the primary tumor, the tumor disease that has spread beyond the thyroid capsule and clinically detectable lymph node metastases. The completeness of the surgical resection is an important determinant for the prognosis, while the residual metastatic lymph nodes represent the most common site of persistence / recurrence of the disease (20, 25). (b) Minimizing the risk of disease recurrence and metastatic spread. Appropriate surgery is the most important variable affecting prognosis, whereas radioiodine treatment, TSH suppression and other treatments each perform additional roles in some patients (20, 26). (c) Facilitating postoperative treatment with radioiodine. For patients subjected to residual ablation, or radioiodine treatment of the presumed disease (adjuvant therapy) or known or residual metastatic (therapy), removal of all thyroid tissue is an important element of initial surgery (20, 27, 28). (d) Allowing accurate staging and stratification of disease risk. Since disease staging and risk stratification are used to guide the initial prognosis, disease management and follow-up strategies. Careful assessment and assignment to a risk class is an important element in the management of patients with differentiated thyroid cancer (20, 29). (e) Facilitating an accurate long-term surveillance. (f) Minimizing the morbidity related to surgical treatment. Surgical extension and the surgeon's experience both play important roles in determining the risk of surgical complications (20, 30, 31).

The optimal extension of thyroidectomy in patients with papillary and follicular carcinomas is still controversial. For patients with thyroid carcinoma with size> 4cm, or with extra-thyroid

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macroscopic extension (clinical T4), or with clinically apparent metastatic disease to lymph nodes (clinical N1) or distant (clinical M1), guidelines propose that the initial surgical procedure should include total thyroidectomy (20). For patients with thyroid carcinoma> 1cm and <4cm, without extrathyroid extension and without clinical evidence of lymph node metastasis (cN0), the initial surgical procedure may be a bilateral procedure (total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy may be a sufficient initial treatment for low-risk papillary and follicular carcinomas; however, total thyroidectomy is chosen to favor radioiodine therapy and / or to improve follow-up based on disease characteristics and / or patient preferences (20). Total thyroidectomy allows postoperative use of scintigraphy and serum thyroglobulin as sensitive tumor markers to detect disease recovery (20).

If surgery is chosen for patients with thyroid carcinoma <1 cm without extrathyroidalextention and cN0 extension, the proposed initial surgical procedure is a thyroid lobectomy unless there are clear indications to remove the contralateral lobe (multifocality, associated hyperthyroidism, multinodularity). Thyroid lobectomy alone is a sufficient treatment for small, unifocal, intrathyroidal<1cm carcinomas, in the absence of prior radiation to the head, neck, thorax and mediastinum, familiarity or clinically detectable cervical lymphatic metastases.

In a study of 50,000 patients, total thyroidectomy reduced recurrence and improved survival in patients with papillary carcinoma greater than 1 cm (20, 32). However, for patients with single, small, inferior or equal to 1 cm tumors (microcarcinomas), thyroid lobectomy can be considered (20, 32). Due to the excellent overall prognosis of patients with microcarcinomas, most studies do not show an increase in survival rates after total thyroidectomy compared to thyroid lobectomy (33, 34).

Table 5. Surgery objectives for differentiated thyroid carcinoma

(a)	**Removing locoregional disease (primitive tumor and involved locoregional nodes)**
(b)	**Accurate staging**
(c)	**Minimizing risks of relapses and locoregional metastasis**
(d)	**Reducingmorbidity**
(e)	**Facilitating post-surgery radioiodine treatment, when appropriate**
(f)	**Providing accurate long-term surveillance to avoid recurrence**

Lymph node dissection

The role of the dissection of the prophylactic middle group cervical nodes in papillary carcinoma is still controversial. The therapeutic lymph node dissection should be performed for the middle gruoup or lateral group of cervical nodes when involved (Figures 2 and 3). The dissection of the central therapeutic middle group (level VI and VII) for patients with clinically involved central compartment lymph nodes should always accompany total thyroidectomy to provide clearance of tumor disease (20). Prophylactic dissection of the central (ipsilateral or bilateral) compartment should be considered in patients with papillary thyroid carcinoma with central neck lymph nodes clinically uninvolved (cN0) but with advanced tumor stage (T3 or T4), or in the presence of clinically involved laterocervical lymph

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nodes (cN1b), or if information on the lymph node stage.

Table 6. Arguments for and against the dissection of the central compartment of the neck, prophylactic for papillary thyroid carcinoma

Pro	Cons
It can lead to lower rates of relapse and mortality	**No level 1 data of evidence and recommendation A that recurrence and mortality rates are lower ***
It can be performed essentially with the same morbidity of thyroidectomy but only by experts	**Most thyroidectomies are not performed by a high volume surgeon**
Postoperativethyroglobulinlevelsdecrease	**It can lead to higher rates of hypoparathyroidism and recurrent and permanent laryngeal nerve injuries**
Preoperative and intraoperative detection of central neck lymph node metastases is not reliable	
Itfavoursstaging (N)	
The need for reoperation in the central compartment of the neck decreases	

**** Feuerstein JD, Akbari M, Gifford AE, Hurley CM, Leffler DA, Sheth SG, Cheifetz AS. Systematic analysis underlying the quality of the scientific evidence and conflicts of interest in interventional medicine subspecialty guidelines. Mayo Clin Proc. 2014 Jan;89(1):16-24. doi: 10.1016/j.mayocp.2013.09.013. PubMed PMID: 24388018.***

can be useful for planning further treatment plans. Thyroidectomy without prophylactic dissection of the central compartment of the neck is appropriate for small tumors (T1 or T2), non-invasive tumors, with clinically negative lymph nodes (cN0) and for most follicular tumors (20). Therapeutic dissection of the lymph nodes of the lateral compartment should be performed for patients with metastatic lateral cervical lymphadenopathy proven by cytological, histological examination or thyroidoblobulin washout (20). The risks and benefits of prophylactic lymph node dissection of the central compartment in papillary thyroid carcinoma have recently been the subject of a prospective randomized study (35). The aim of this prospective randomized controlled trial was to evaluate the clinical advantages and disadvantages of the prophylactic dissection of central compartment (35). A total of 181 patients with papillary carcinoma without evidence of preoperative / intraoperative lymph node metastases (cN0) were randomly assigned to Group A (n = 88) and treated with total thyroidectomy or assigned to Group B (n = 93) and treated with thyroidectomy total + prophylactic dissection of lymph nodes. After 5 years of follow-up, no difference was observed in the outcome between the two study groups. However, a larger percentage of group A was treated with a greater doses and treatments of radioiodine (P = 0.002), while a higher prevalence of permanent hypoparathyroidism was observed in group B (P = 0.02) . No preoperative predictors of lymph node metastasis of the central compartment (N1a) were identified (35). Nearly 50% of patients with papillary carcinoma had lymph node micrometastases in the central compartment, but none of the pre-surgical

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features analyzed, including the BRAF mutation, were able to predict their presence (35).

The arguments in favor of the prophylactic lymphadenectomy of the central compartment include (Table 6): (a) the metastases to the lymph nodes of the central compartment of the neck can not be reliably detected pre-operatively or intra-operatively; (b) lymph node dissection of the central compartment of the neck improves staging accuracy, highlighting a substantial proportion of patients with Nx to N1a disease, which may be the only indication for RAI in a subset of patients; (c) the central dissection of the neck results in a decrease in postoperative thyroglobulin levels, allowing a greater sensitivity of thyroglobulin to detect recurrence in follow-up; (d) the dissection determines a reduction in recurrence rates (and possibly reduced mortality); (e) reduced relapse rates reduce the need for reoperation with associated morbidity; (f) in the hands of a high-volume endocrinosurgeon, the dissection of the central compartment can be performed essentially with the same morbidity as thyroidectomy alone (36, 37). Arguments against prophylactic lymphadenectomy of the central compartment include: (a) increased rates of hypoparathyroidism and / or temporary and permanent recurrent laryngeal nerve injury; (b) absence of data with levels of highlight 1 or recommendation A because the central dissection of the neck causes lower rates of recurrence and mortality; (c) most of the thyroidectomies (75%) are not performed by high-volume surgeons (36, 38, 39).

Table 7. Recommendations and guidelines for the treatment of low-risk thyroid papillary microcarcinoma

Country- Association	Year	Recommendation
American Thyroidassociation (20)	2015	hemithyroidectomy
BritishThyroidAssociation	2014	hemithyroidectomy
Japanese Society of Thyroid Surgeons/Japan Association of Endocrine Surgeons (21)	2010	Observation or surgery
German Society Surgery (20)	2012	hemithyroidectomy
Survey - Canadian otolaryngologist-head and neck surgeons (OHNS) and endocrinologists (32)	2014	Observation or surgery
Consensus - Chinese Association of Thyroid Oncology (31)	2017	hemithyroidectomy and isthmusectomy

Papillary Microcarcinoma: active surveillance vs. immediate surgery

Treatment of thyroid cancer can be adapted to the biological characteristics of the tumor and the

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characteristics of the patient, and active surveillance (AS) has recently been proposed to patients with low-risk tumors, particularly small tumors, as the first management step (40, 41). Low-grade papillary microcarcinomas rarely progress to clinical symptoms and carry a limited risk of death (42, 43). The introduction of AS programs for thyroid cancer brings with it new variables that require a more careful direct strategy (44-58). The long-term safety of an AS depends on the clinician's ability to promptly initiate interventions in those patients who need it and to avoid over-treatment in those who do not need it (45). Adherence to AS protocols is critical to ensuring that patients are well monitored and treated early when progression occurs (Table 7). As an increasing number of AS programs are proposed, it is important to understand whether the volume of cases could and should be incorporated into the design of quality indicators (46, 47).

The provision of optimal cancer care is a consolidated, coordinated, high quality multidisciplinary process based on specific experiences in endocrinology, pathology, radiology, surgery, nuclear medicine and ancillary services. In each of these areas, the opportunity for specialization within a specific AS program exists only with an increase in the volume of cases (48). Specific clinical pathways for diseases and treatment interventions can only be developed if supported by sufficient clinical volume (49, 50).

The specific rate of clinical progression and the need for treatment after active surveillance are still under investigation (Table 8). Because the low-risk papillary microcarcinoma presents a broad spectrum of biology, it is necessary to define the criteria that allow the patient and the clinician to propose and accept AS (51-54). Optimal selection criteria for AS still remain poorly defined (55).

Reliable clinical risk stratifications are known in predicting the prognosis of groups of patients with similar clinical and pathological characteristics, but there is residual uncertainty at the individual level (56). Prognostic tools are needed to guide clinical decision-making. For example, the papillary microcarcinoma propensity to be multifocal, the increase in TSH levels, the ultrasound site of the small thyroid tumor, the molecular support to determine the aggressiveness of the small tumor have all the potential to influence the clinical decision-making process (Figure 4).

The integration of information from imaging kinetics and biomarker technology will likely individualize future treatment decisions, while improving overall surveillance strategies (57-58). Further research is needed to define appropriate candidates for AS, taking into account patient preferences, how to follow them, when to treat them and what the clinical and pathological outcomes after late surgery after AS are (55).

Mortality due to thyroid-specific tumor is a challenging and ambitious endpoint to obtain estimates of the effect of treatment for a small thyroid tumor treated, even after AS. Numerous observations have accumulated over the years, indicating that the endpoint of thyroid cancer mortality is difficult

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to study and is confused by population heterogeneity, randomization, and the requirement of large cohorts of patients with sufficiently long follow-up due to the excellent prognosis of thyroid cancer (52, 53, 54). The median survival time after diagnosis for thyroid carcinoma is long (54).

As a result, it may be important to reconsider how to best measure the treatment of a small thyroid cancer. Recommendations against immediate surgery versus AS of thyroid cancer should be based on studies aimed at assessing treatment efficacy not only in a significant reduction in cancer mortality but also in other distinct endpoints (55). Therefore, it is also appropriate to evaluate the derivative endpoints that can reliably predict reductions in mortality. Derived endpoints may include the percentage of detected early stage tumors (the most treatable stage), the identification of small tumors, the decrease in the number of people developing metastatic disease, the increase in the possibility of conservative surgery and less extended (hemithyroidectomy), an optimized follow-up, administration of low-dose or absent RAI, and the complete evaluation of the histological piece. The guidelines suggest a conservative treatment for papillary carcinoma <1 cm (20, 48). Studies have confirmed that hemithyroidectomy is as effective as total thyroidectomy in patients with tumor <1 cm (20, 52). The rationale of hemithyroidectomy includes the elimination of the risk of bilateral damage of the recurrent laryngeal nerve, the permanent hypocalcemia (20).

Table 8. Review of the literature for active observation for papillary microcarcinomas

Author	Year	Number of Patients	Follow-up (months)	Unmodifiedmicrocarcinoma (%)	Tumor progression ≥3mm (%)	Surgery (%)	Lymphnodemetastasis (%)	Locoregionalrelapses (%)	Survival
Ito et al.(5)	2003	162	48,7	70%	11,1	34,6	12,3	-	100%
Ito et al. (11)	2014	1.235	75	-	8	16	38	1,1	100%
Kwon et al.(6)	2017	192	30,1	69%	14	13	29	-	100%
Tuttle et al. (7)	2017	291	25	87,6%	3,8	3,4§	0	0	100%
Kim HI et al (29)	2018	127	26	-	19,8	-	-	-	100%
Miyauchi A et al. (30)	2018	1.211	120	-	3,5-60**	-	-	-	-

Surgery for recurrence

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Disease recurrence occurs in 10-30% of patients with differentiated thyroid cancer after initial surgical treatment with curative intent (59). Approximately 80% of recurrences are loco-regional (thyroid site, central compartment lymph nodes or lateral neck lymph nodes) (60). Surgical resection in case of recurrence is associated with an increased risk of complications, such as hypoparathyroidism or recurrent laryngeal nerve injury (61). Although papillary carcinoma usually shows an indolent course, the combination of time-sensitive investigations such as ultrasound, increasingly sensitive doses for the detection of serum thyroglobulin, have led to the identification of recurrence of small thyroid carcinoma, with probable modest clinical significance (62). A study of 70 patients undergoing surgery for recurrent papillary carcinoma revealed that in about 10%, surgery failed to identify and remove disease recurrence and only 27% of patients showed undetectable postoperative thyroglobulin (60). Therefore, surgery should be performed by experienced surgeons or it may not be the ideal management strategy for all patients (60). Other recurrence options include radioiodine, percutaneous ethanol injection, and radiofrequency ablation (63, 64).

Endoscopic Surgery

The traditional cervical incision at the median level, anterior according to Kocher, is the predominant approach to remove the malignant pathology of the thyroid (20, 65). Many surgical procedures, including thyroidectomy, have become less invasive (65-67). Several approaches to the thyroid gland have been developed to search for a cosmetically better result than traditional surgery (66). In a skinny patient with a small volume thyroid gland, "open" conventional thyroidectomy is possible with a small, discreet, 3-4 cm surgical incision. Miccoli developed first the video-assisted endoscopic technique for thyroidectomy (MIVAT, "minimally invasive video assisted thyroidectomy"), which is performed through a 1.5 to 2 cm incision in the neck, and is the most minimally invasive technique widely adopted (65-67). MIVAT has demonstrated equivalent results to traditional surgery also in the field of oncology (65-67). Trans-axillary, trans-areolar and back-auric approaches have been proposed and applied by endoscopic and robotic techniques to avoid an incision on the neck (65-67). Minimally invasive techniques using extra-cervical, remote incisions seem to result in increased morbidity which is not present in conventional thyroid surgery (65-67) including lesions to the esophagus, trachea and brachial plexus, cutaneous necrosis and tumor spread along the surgical dissection (65-67).

No visible skin incision is required for transoral thyroidectomy with a vestibular approach (68). Unlike other remote access approaches, the vestibular endoscopic approach (trasoral endoscopic

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thyroidectomy vestibular approach "TOETVA") offers several advantages (68). In the first place, the incisions of the natural orifice are completely invisible, non-cutaneous, therefore the aesthetic result is optimal. Secondly, the median approach allows an excellent and safe central visualization of the recurrent laryngeal nerves, of the isthmus and both the thyroid lobes, the parathyroid glands and the central compartment (levels VI and VII) bilaterally. Thirdly, the distal identification of the recurrent laryngeal nerve when inserted into the larynx with the subsequent cranio-caudal dissection is familiar to the more experienced endocrine surgeons and provides a safe angle of dissection along the nerve, avoiding traction. Moreover, the required additional tissue dissection to approach the thyroid through this approach is relatively limited, close to the thyroid gland, and may lend itself to application in patients with a higher BMI (68).

Figure 2. Midline group of cervical nodes (Levels VI and VII). Level VI: It is the frontmost level, located between carotid arteries, hyoid bone superiorly and sternum inferiorly. It includes prelaryngeal, pretracheal, paratracheal and perithyroidal lymph nodes. Level VII: superior mediastinal lymph nodes.

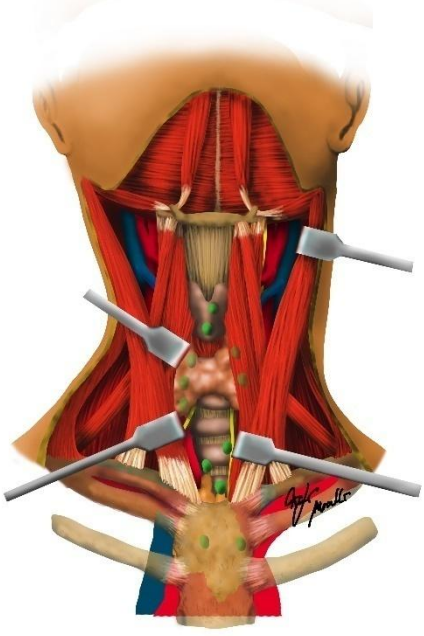
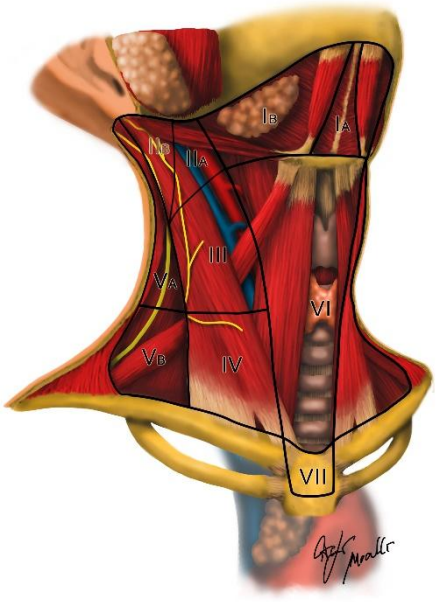


Figura 3. Lateral group of cervical nodes. As for thyroid surgery, it includes the following nodes: Level II: upper jugular nodes, close to jugular vein (as III and IV level nodes). They are anterior to the sternocleidomastoid muscle and posterior to the hyoid bone. They are bordered by skull base superiorly and stylohyoid muscle laterally. Level III: it is located below the level II, it includes middle perigiugular nodes and it is anterior to the sternocleidomastoid muscle and posterior to the hyoid bone and the thyroid cartilage. Level IV: it is located below the level III and it is bordered by the same elements; it includes the lower perigiugular nodes. Level V: it includes supraclavicular nodes and it is the most rear group of cervical nodes. It is located deep below to the sternocleidomastoid muscle and it is anterior to the trapezius muscle and above the clavicle. It is divided into level Va and Vb by the spinal accessory nerve.



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Pediatric Surgery

Pediatric Malignant thyroid tumors are rare but are diagnosed with increasing frequency and include about 2% of newly diagnosed thyroid cancer patients (69). The register of the National Cancer Institute Surveillance, Epidemiology and Results showed that the incidence of pediatric thyroid cancer increased to 1.1% per year between 1973 and 2004 (70). Studies in the UK have shown a 27.5% increase in males and a 68% increase in females aged 0-14 in the same period (71). Papillary carcinoma comprises about 80-85% of all pediatric thyroid tumors, 10% follicular carcinoma and 5% medullary carcinoma (72). Studies showed a wide variation in the prevalence of cancer in pediatric patients with thyroid nodules from 9% to 50%, with an average prevalence of 26% in 1,134 children, significantly higher than 10% of the prevalence of cancer in adult thyroid nodules (73). As in adults, fine needle aspiration biopsy is the gold standard for the diagnosis of thyroid nodules in the pediatric population. A meta-analysis of 12 pediatric studies on fine needle aspiration biopsy reported a sensitivity of 82% and a specificity of 91%, achieving a diagnostic accuracy of 83%, a positive predictive value of 55% and a negative predictive value of 98 % (74).

There is no consensus on the optimal surgical management of well-differentiated thyroid carcinoma in the pediatric population, which reflects the absence of prospective randomized studies. Advocates of lobectomy cite a lack of survival benefit for total thyroidectomy and an increase in the complication rate with long-term hypocalcaemia reported in 2% of cases and permanent recurrent laryngeal nerve injury in 1% of pediatric patients (74). To counter this argument is the evidence of a lower recurrence rate after total thyroidectomy and the observation that at least 40% of the differentiated tumors in children are multifocal (75). In addition, total thyroidectomy facilitates postoperative radioiodine administration in cases of microscopic metastatic disease and the use of serum thyroglobulin measurement as a sensitive marker of recurrence (76). The role of prophylactic lymphadenectomy in the central compartment is also controversial in the pediatric population. Prophylactic lymphadenectomy of the bilateral central compartment is associated with a probability reduction of a second intervention from 20% to 7% (74-77).

Figure 4a, b, c, d, e, f, g, h. Graphicrepresentationof the anatomical relationship between papillary microcarcinoma of the thyroid gland, with tracheal wall, the recurrent laryngeal nerve (RLN) and pre-thyroid muscles in order to plan the therapy (active surveillance vs

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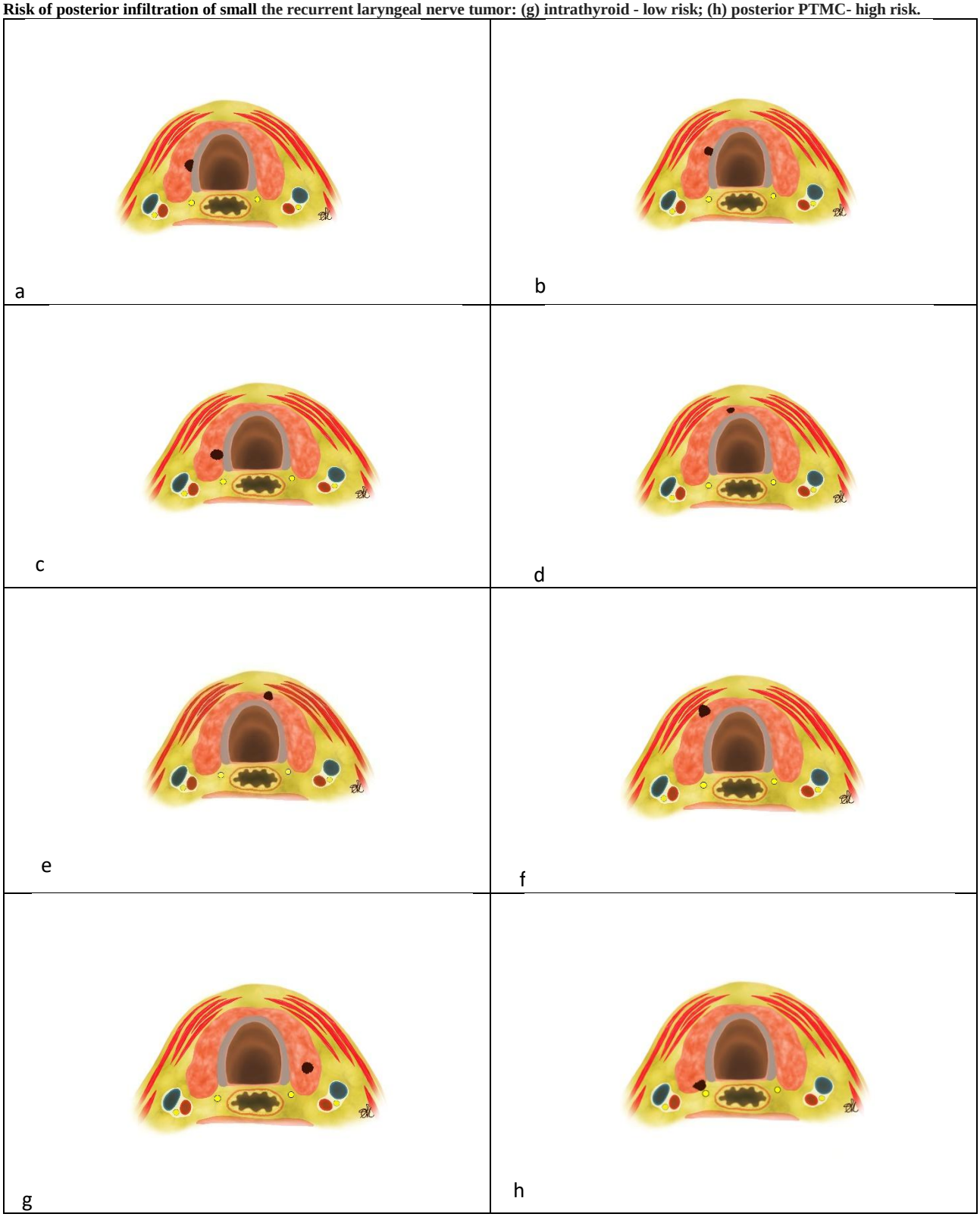
immediate surgery).
***Risk of tracheal infiltration by a papillary microcarcinoma:* (a) high risk angle; (b) almost right angle - medium risk; (c) round shape tumoral angle- low risk.**
***Risk of infiltration of soft tissues and muscles through papillary microcarcinoma: (*d) small tumor contained in the isthmus; (e) isthmus tumor spreading in front of the connective tissue; (f) small tumor spreading laterally to the connective tissue.**
Risk of posterior infiltration of small the recurrent laryngeal nerve tumor: (g) intrathyroid - low risk; (h) posterior PTMC- high risk.



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