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Comparison of the 7th and 8th editions of the TNM staging system and of 2009 and 2015 American Thyroid Association risk stratification system in terms of predicting recurrent/persistent disease in a consecutive prospective series of 451 patients with differentiated thyroid cancer. Proposal of a nomogram to predict recurrent/persistent disease

TESI DI DOTTORATO DI RICERCA IN BIOMEDICINA TRASLAZIONALE (XXXIII ciclo)

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INTRODUCTION

Epidemiology

Thyroid cancer (TC) is the most common endocrine malignancy, representing about 90% of cases.

In the literature there are considerable differences in the TC incidence and survival between the registries of different countries since it is difficult to check the completeness of data of these registers.

TC is the most rapidly increasing cancer in the United States, where its incidence increased by 211% in the years 1975-2013 (1).

According to the Surveillance Epidemiology and End-Results Cancer Registry, TC represents 2.9% of all new cancer cases in the USA, with an incidence of 8.1/100.000 inhabitants in males and 23.1/100.00 in females and mean age at diagnosis of 51 years old (2). It's incidence has rapidly grown in the last decades ranking the 4th most frequent cancer in females today while it was 14th 20 years ago(3, 4). In Italy it approximately doubled (+ 115% in females and + 84% in males) in the years 1991-2005. It is more common in women, with a 3:1 female-to-male ratio in most geographic regions and demographic groups (5).

This increase in TC incidence has been driven largely by increases in papillary thyroid cancer (PTC), the most common and least aggressive histologic type, from 58% to 85.9%; in the same years anaplastic TC incidence reduced from 5.7% to 2.1%.

Very recently the very fast incidence rate seems to slow in men and stabilized in women during 2012-2016, likely due in part to the adoption of more conservative diagnostic criteria by clinicians (1).

The mortality from TC is very low and the death rate increased slightly during 2008 to 2017 (0.6% per year) in spite of earlier diagnosis and better treatment. In recent years it appears to have stabilized (1). In 2020, in the USA, the estimated new TC cases are 52.890 and the estimated deaths are 2.180 (2). Moreover, TC mortality varies in relation to the size and age of the patient being very low for small papillary carcinoma localized to the thyroid and up to 20% in elderly patients who often have larger, locally advanced tumors with lymph node and/or distant metastases at the time of diagnosis.

The mean age at death is 73 years old, increasing from 17.6% in 55-64 years old, to 26.3% in 65.74 years old group, to 27.5% in 75-84 years old group.

Ten years mortality also changes in relation to the histotype: 10-40% for some aggressive variants of papillary carcinoma, for poorly differentiated or angio-invasive or massively invasive follicular tumors (6). For anaplastic cancer, mortality is very high as it is often locally invasive and with distant metastases at diagnosis; it is often rapidly lethal at 6-12 months and does not benefit from current therapeutic strategies.

Differentiated thyroid cancer (DTC) is generally associated with an excellent prognosis: the 5-year survival rate is near 100% for localized disease, 98% for regional disease and 55% for metastatic disease (2).

There has been remarkable debate about whether the increase in PTC represents a true increase in incidence or whether it is attributable to increased detection and “overdiagnosis” of small and “indolent” PTCs (that would never otherwise cause symptoms or require treatment) as a result of increased use of imaging techniques and diagnostic needle aspiration of nodules.

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A recent retrospective work showed that the diagnosis of TC was due in 39% of cases to the use of imaging techniques, in 15% of cases to incidental histological findings and in 46% of cases to clinical examination of the neck (7).

However, many evidences indicate that a true increase, probably due to environmental factors, has also occurred (3, 8).

A recent study of Lim et al (8) analyzing the Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1980-2005, showed a substantial increases in the incidence not only of small and indolent cancer but also of advanced-stage PTCs and PTCs greater than 5 cm in diameter;

The rates of increase for the largest (> 5cm) and the smallest PTCs (≤1 cm) were similar among white women, a group considered to be susceptible to overdiagnosis (9) .

Furthermore, the increased incidence of PTC may also be related to other causes, such as the spread of iodo-prophylaxis which has reduced the percentage of aggressive or undifferentiated follicular carcinomas in favor of papillary carcinomas and the reclassification of many follicular carcinomas as papillary (follicular variant or other variants).

Moreover, despite TC mortality rates seems to be stable over time, as it is much lower relative to incidence (3, 10-12), its rates have increased significantly since the late 1980s, probably due to temporal changes in the prevalence of some risk factors, including obesity and noncurrent smoking (13) .

Accumulating evidence supports, therefore, a true increase in both the incidence and mortality of TC are not only due to the improvements in diagnosis. In a 2015 analysis of some high-income countries, improvements in diagnostic capabilities were estimated to account for the detection of 60% or more of the total TC cases in France, Italy, the USA, Australia and South Korea between 2003 and 2007 (14).

Having TC in most cases a favorable prognosis, overtreatment is a relevant possibility.

A major issue, therefore is to find characteristics and criteria to identify cases having aggressive behaviour and poor prognosis. Moreover, it is necessary to better examine other associated causes and risk factors, including environmental factors (15-18), as the chemical pollutants (pesticides, phthalates, bisphenol A, metals etc.) or the volcanic environment including Mt. Etna in Sicily (15).

Risk factors

As for most solid neoplasms, also TC etiology seems to be multifactorial resulting from the interaction between environmental risk factors (previous neck irradiation, iodine intake, geographical area of residence) and related risk factors to the patient (positive family history for thyroid neoplasia, pre-existing benign thyroid disease, gender and hormonal factors).

Radiation

One of the most important and well documented risk factors for the development of cancer is a history of exposure to radiation, especially for thyroid gland due to its position in the neck and its ability to concentrate iodine (the use of iodinated contrast medium increases the absorbed dose of the thyroid by about 35% (19). Moreover the risk is higher during childhood and adolescence, phases in which the thyroid gland exhibits greater radiosensitivity (20).

The latency period between exposure and the onset of TC is very long ranging from 5 to 20 years.

TC risk is related to the dose (relative risk 7.7 for a dose of 1 Gy) and inversely related to age.

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Potential sources of radiation exposure include: a) medical applications such as for treatment of neoplasms such as lymphomas and leukemias, especially during childhood (21) and diagnostic procedures (in the USA the individual radiation dose has doubled in the last 25 years); b) environmental exposure to atomic weapons (Nagasaki and Hiroshima in Japan) or accidents at nuclear power plants (such as Chernobyl).

Moreover the exposure to ionizing radiation affects histopathological and clinical characteristics. After the accident at the Chernobyl nuclear reactor, in fact, there was not only a rapid increase in the TC incidence but also of tumors in advanced stage (with lymph node and lung metastases) at the time of diagnosis with a more aggressive biological behaviour (22).

Iodine intake

Iodine intake influences thyroid-stimulating hormone (TSH) level, a major grown factor for thyroid follicular cells. Therefore, iodine deficiency could have a role in TC onset; however it is shown in animal experiments and not in human. Iodine intake, instead, influences the TC histotype distribution: more follicular tumors in iodine-deficient areas and vice versa (23, 24). After the introduction of iodine prophylaxis, papillary/follicular ratio increases and also the frequency of BRAF mutation, typical for papillary histotype.

Area of residence

Comparing different global region, there is a substantial variability in incidence, due probably to different diagnostic procedures, environmental exposures, individual personal factors, differences in access to care, health-care system and national registries.

Some European countries such as Denmark, Holland and Slovakia have a low TC incidence and other countries as Japan, France and some volcanic areas such as Iceland, Hawaii, the Philippines that have a high incidence (25).

The published data of the Sicilian Registry showed as in the area adjacent to the Etna volcano there is an annual incidence rate of TC more than double compared to the rest of Sicily: 31.7 in women and 6.4 in men against 14.1 and 3.0 respectively per 100,000 inhabitants in the remaining areas of Sicily (15). The increased incidence is due to the increase in the papillary histotype, micro and macrocarcinoma. Other studies [17] showed the role of environmental factors; in fact in the water coming from volcanic aquifers and in the urine of the inhabitants in these areas there is a higher concentration of environmental pollutants, especially heavy metals (26, 27).

Familial influences

A family history of TC or benign thyroid disease is a risk factors for the development of TC (28). 3-10% of patients have a positive family history of TC (29).

Familial tumors of follicular cells are called familial nonmedullary thyroid cancers (NMTC) that account 3-9% of all TC cases with a dominant type with incomplete transmission. These tumors have a greater aggressiveness (multifocality and relapses). Having 3 or more family members have TC, there is a 94% chance that it is an inherited familial syndrome (30). Moreover, TC is common in several familial syndromes, such as familial polyposis, Carney complex, multiple endocrine neoplasia type 2 (MEN2), Werner syndrome or Cowden syndrome in which the risk of a nodule being malignant increases (31).

Pre-existing benign thyroid disease

A history of thyroid disease, such as nodular goiter or Graves' disease, appears to increase the risk of TC; however, in some studies there may be selection errors as patients with known disease carry out more controls. In Graves' disease the incidence of malignant nodules ranges from 0.4 to 9.8% (32); often in these patients TC seems to have a more aggressive clinical course (33). Hashimoto's chronic autoimmune thyroiditis is associated with nodular thyroid disease but there are conflicting data regarding thyroiditis as a risk factor (34, 35).

Gender and hormonal factors

The incidence of thyroid cancer is similar in male and female before puberty and after menopause (female: male ratio 1.5: 1) and much higher in female during childbearing age (female: male ratio approximately 2-4:1). Few relationships between TC and hormonal factors of reproductive age (as pluriparity, late menarche, age at first pregnancy and surgical menopause) have been identified as significant (36).

Obesity, nutrition and lifestyle

Increased BMI and percentage of fat mass are associated with an increased risk of papillary carcinoma, especially in women (37, 38). The relative risk, compared to normal weight subjects, is 1.7 for overweight and 4.2 for obesity. In obese patients, the involved mechanisms are inflammation, higher TSH values, interaction between TSH and insulin-like-growth factor 1 in the activation of MAP kinase and PI3K signaling pathways.

Some studies showed a positive significant associations for pork consumption, butter, the abuse of smoked fish and negative one for tomatoes, lemons, pasta, fruits, vegetables (39).

Histopathological classification

The World Health Organization (WHO) in 2017 updated the histopathological classification of tumors of thyroid gland (40):

A) tumors deriving from the follicular epithelium

- Follicular adenoma
- Hyalinizing trabecular tumour
- Other encapsulated follicular patterned thyroid tumours
- Follicular tumours of uncertain malignant potential
- Well differentiated tumour of uncertain malignant potential
- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT)
- Papillary thyroid carcinoma
    - Papillary carcinoma
    - Follicular variant
    - Encapsulated variant
    - Papillary microcarcinoma
    - Diffuse sclerosing variant
    - Columnar cell variant
    - Oncocytic variant
- Follicular thyroid carcinoma (FTC)
    - FTC, minimally invasive
    - FTC encapsulated angioinvasive
    - FTC, widely invasive

- Hürthle (oncocytic) cell tumours
    - Hurtle cell adenoma
    - Hürthle cell carcinoma
- Poorly differentiated thyroid carcinoma
- Anaplastic thyroid carcinoma
- Squamous cell carcinoma

B) C cell tumors

- Medullary thyroid carcinoma

C) tumors with mixed histogenesis

- Mixed medullary and follicular thyroid carcinoma

Differentiated thyroid carcinomas (papillary and follicular) represent about 90% of cases (41) and papillary carcinoma is the most frequent (60-80%). Medullary carcinoma, which originates from parafollicular C cells, accounts for 3-5% of cases, while anaplastic thyroid cancer is very rare (less than 2% of all TC) (42).

Non-invasive capsulated follicular variant (NIFTP)

This is a noninvasive thyroid follicular cell tumor exhibiting a follicular growth pattern and nuclear characteristics of PTC. It should not be considered a carcinoma but a benign lesion (43). It represents approximately 25% of all PTC or 20% of all thyroid cancer. It has an excellent prognosis: no patients out of 109 of a retrospective study had evidence of disease after a follow-up of 13 years (44).

Papillary carcinoma

In addition to conventional (classic, common or usual) type PTC, 14 variants were listed in the new WHO classification of thyroid tumors.

Classic variant: PTC accounts for more than 80% of thyroid carcinomas in sufficient iodine areas with a peak of incidence between the 3rd and 5th decade (average age 45 years) (45) and mainly affects female (60-80% of cases). The classic variant of PTC consists of the classic papillary structures and fibrovascular central axis often with ramifications that can be associated with follicular structures (46). On ultrasound, the malignant characteristics most frequently associated with PTC are: hypoechogenicity, irregular margins, development in depth (higher than wide), microcalcifications and nodular increase in vascularity (this characteristic is less relevant). Extrathyroid microscopic extension (mETE) is present in 10-30% of cases; vascular invasion is present in about 5-10% of cases. Lymph node metastases to the neck compartments (most frequently paratracheal, mid-jugular, supraclavicular and subdigastric) are identified in 20-50% of cases at diagnosis (47). At diagnosis, distant metastases are infrequent (less than 5% of cases), localized mostly to the lung or bone (more rarely to the brain, kidney, liver or adrenal glands).

Microcarcinoma: the percentage of microcarcinomas (tumor ≤1cm) has significantly increased, becoming one of the most common variants of PTC (about 50% of all PTC). It has an excellent prognosis and may not always require surgical intervention in selected patients but an active surveillance (48).

Tall cell variant: more aggressive variant, characterized by cancer cells (more than 30-50%) that are 2- to 3-times taller than wide It is more frequent in older patients, who often have more advanced cancer and with a poor response to radioactive treatment with ^{131}-

Iodine (49, 50). It is also associated with a higher risk of relapse and reduced survival compared to classic PTC.

Diffuse sclerosing variant: more frequent in young people, characterized by widespread involvement of the entire thyroid gland (or one lobe) with a lymphocytic infiltrate, massive squamous metaplasia, numerous psammomatous bodies and stromal fibrosis. Recent meta-analysis still considers diffuse sclerosing variant as a high-risk PTC because of a high incidence of extrathyroid invasion at surgery, advanced tumor stage at presentation (lung metastases in 10-15% at diagnosis) and bilaterality, however there is an obvious trend in the modern institutional series that diffuse sclerosing variant PTC has no adverse effect on survival (51-55).

Other variants: solid variant, columnar variant, hobnail variant, infiltrative follicular variant, Hurtle cell variant, Warthin-like variant, and cribiform variant.

Follicular Carcinoma

It accounts about 10% of all thyroid carcinomas with a peak incidence at 5th-6th decade and an higher frequency in iodine deficiency area. The percentage of follicular carcinoma has decreased over the years due to the different diagnostic criteria (follicular variant of papillary carcinoma) and the increased incidence of papillary carcinoma due to iodine supplementation.

It appears as a solitary nodule, often has a larger size than papillary carcinoma, ultrasonographically it often appears as an iso-hyperechoic lesion and has a dense and irregular halo and without microcalcifications. The main route of metastasis is blood and rarely by lymphatic route (5-14%).

FTC was traditionally divided into two prognostic subgroups according to the invasion pattern, minimally invasive or widely invasive. More recently, O'Neil et al. combined

the invasive pattern and angioinvasion, and classified FTC into three groups: (i) minimally invasive FTC, (ii) encapsulated angioinvasive FTC and (iii) widely invasive FTC. Disease-free survival rates at 40 months of the above three groups were 97%, 81% and 46%, respectively (56).

In the 2015 Armed Forces Institute of Pathology (AFIP) atlas (57), FTC was classified into four prognostic groups: (i) minimally invasive FTC with capsular invasion; (ii) minimally invasive FTC with limited (<4 vessels) vascular invasion; (iii) minimally invasive FTC with extensive (≥ 4 vessels) vascular invasion; and (iv) widely invasive FTC.

These two classifications highlighted the importance of vascular invasion in risk stratification of thyroid carcinomas.

In fact, the clinical evolution of patients depends to vascular invasion: excellent if absent and progressively worse in relation to the degree of involvement of the vessels (56, 58) with metastasis rates ranging from 8% to 80%.

Variants: Hurtle cell or oncocyte or oxyphilic (particularly aggressive variant with a morbidity and mortality about 10 times higher than the classic follicular form) and clear cell.

Poorly differentiated thyroid cancer

They are rare (1-5%) and in order to define a poorly differentiated tumor, the following 3 characteristics are necessary: 1) cell growth of a solid, trabecular or insular type 2) absence of the characteristics of papillary carcinoma, 3) tumor necrosis, 3 or more mitoses per field or convoluted nuclei. Tumors that show solid, trabecular or insular growth with no other features of poor differentiation should not be classified as poorly differentiated. They affect elderly patients (75% of the age at diagnosis is > 65 years).

They usually appear as a solid, fast-growing mass with early invasion of the perithyroid tissues and metastasize prematurely by lymphatic (25-80%) and distant blood (up to 75%). They have a worse clinical evolution with a 10-year survival of about 50% (59).

Initial therapy of differentiated thyroid cancer

The initial treatment of DTC includes surgical removal of the thyroid ± lymphnode dissection, radioiodine (^{131}I) therapy if indicated and the consequent administration of thyroid hormone (L-thyroxine). In specific cases, external neck radiotherapy is indicated as initial therapy.

Surgery

The extent of surgical treatment depends on a correct pre-operative assessment to quantify the extent of the disease (primary tumor and the presence of lymph node metastasis). Neck ultrasound is an excellent diagnostic tool for loco-regional staging; it allows to identify in particular the pathological lymph nodes of the latero-cervical compartment, needful to establish the extension of the lymphadenectomy; other cross-sectional imaging might be useful in selected, locally advanced cases.

Surgical therapy is the first and most important treatment for all DTC, however the extent of surgery is still debated, since surgical aggression should be related to the extent of the disease and prognostic factors. Many changes in the extent of surgery for DTC have been recently proposed. In the past (60), the surgical option of choice was total thyroidectomy for all DTC > 1 cm, regardless of other pathological features, based on several studies that showed lower recurrence rates in patients treated by total thyroidectomy compared to lobectomy (61-63). Conservative surgical approaches are currently considered first choice in certain patients given the high incidence of very low risk thyroid carcinomas

with excellent prognosis regardless of the surgical procedure (64) (65). Total thyroidectomy is the treatment of choice for most patients, however the ATA guidelines (66) suggest lobectomy as first choice in papillary microcarcinomas without evidence of extrathyroid extension or suspected lymph nodes and an option for patients with papillary or follicular intrathyroid carcinoma < 3-4 cm, without evidence of extrathyroid extension, without suspected cervical lymphadenopathy, no pathology of the contralateral lobe (Hashimoto's nodules or thyroiditis), no signs or symptoms of distant metastases and histological features such as high risk (data difficult to obtain from cytology) (67). For all DTC > 4 cm, or ≤ 4 cm with aggressive features, total thyroidectomy is usually recommended (66, 68).

Regarding lymph node dissection, the frequency of lymph node metastases is variable and depends on the tumor characteristics, in particular on the histotype and tumor extension. In papillary carcinoma, lymph node metastases are present in about 35-65% of patients at diagnosis and up to 80% in children (69); in follicular carcinomas their frequency is lower, about 20% of cases. The most frequently involved compartments (80-90% of cases) are the central compartment (level VI) and less frequently the laterocervical compartment (level II-IV) (70); other lymph node stations are rarely involved (level I, V).

If any lymph node metastases of the central or latero-cervical compartment are clinically or ultrasonographically evident, confirmed by needle biopsy of the lymph node and measurement of thyroglobulin (Tg) on the lymph node wash-out, an oriented therapeutic lymph node dissection is recommended (66, 71-75) because it is associated with lower recurrence (76) and disease-specific mortality rates (77, 78). Prophylactic dissection of loco-regional lymph nodes remains a still debated topic as this can increase surgical morbidity. In many studies, lymph node involvement is associated with a higher risk of

local and regional recurrence and distant metastasis. The relationship between lymph node metastases and survival is still controversial, but several studies have shown higher mortality in patients with large, extranodal, multiple, bilateral or mediastinal localized lymph node metastases or present in older patients (6). Prophylactic dissection of the central compartment should be considered in patients with PTC with advanced thyroid cancer (T3 or T4) or with latero-cervical lymph node metastases (CN1b), but not routinely recommended (66, 68).

Post-surgical assessment

Postoperative risk assessment is based on risk stratification system for predicting persistent/recurrent disease and TNM staging system for predicting mortality.

The details of the criteria used in the different risk stratification system (2009 and 2015) e in previous and current TNM (VII and VIII editions), object of this thesis, will be explained in detail in the next chapter.

Postoperative radiodine treatment with ^{131}I

Radiometabolic treatment with ^{131}-Iodine can be carried out with 3 main different purposes: 1) remnant ablation: to destroy the residual non-neoplastic thyroid tissue (to obtain undetectable levels of Tg); 2) adjiuvant treatment: to irradiate any potential residual neoplastic foci and thus reduce the risk of recurrence and 3) treatment of known disease: to treat the tumor residual disease in the case of advanced stage, both at local and distant level and to perform whole body scan (WBS) with ^{131}-I to identify residual local and/or distant disease.

Based on several studies carried out in the late 1970s that showed a reduction of the risk of relapse and an increase of survival in DTC patients after radiometabolic treatment (79),

the indication to ^{131}-I has grown significantly and almost all patients in the following decades were subjected to radiometabolic treatment.

In the last decade, however, several authors have shown that there is no benefit for low-risk patients and that the clinical evolution in these patients was favorable even without ablation (80). In recent years there has been a renewed interest in identifying and treating patients who can benefit from radiometabolic treatment, or those at a higher risk of relapse and mortality (73).

Therefore the patients should be selected on the basis of the initial risk stratification (low, intermediate, and high) (64, 66, 68) and in agreement with postoperative evaluation, too (66, 81-83).

In ATA guidelines, radiometabolic treatment is not recommended in low-risk patients because the cancer-specific mortality and the persistent/recurrent disease is negligible and therefore not improved by post-surgical radioiodine (RAI) (84-87), it is recommended in intermediate risk patients, according to risk factors (such as aggressive histotype, with lymph node metastases in patients > 45 years (86) (in patients < 45 years with lymph node metastases no benefit has been shown on mortality and relapse and it is recommended with high ^{131}-I activities in high-risk patients (stage III and IV) as it increases survival and the disease-free interval (86, 88).

The choice of ^{131}-I activity depends on the clinical and prognostic characteristics of the disease and the size of the residue. In many referral centers, empirical fixed activity of ^{131}-I are used (range between 30 and 150 mCi); in other centers, on the other hand, dosimetry is used to establish the correct activity to administer.

According to current legislation (directive 2013/59/Euratom) it is mandatory to administer the dose calculated to each patient by dosimetry.

Since the risk of adverse effects from metabolic radiotherapy increases with increasing administered activities, it is recommended to use doses of 30 mCi for the radioablation of low and intermediate risk patients and to use a higher dose (100-150 mCi) in patients with high-risk pathology (6).

To rise ^{131}-I uptake in thyroid cells (89) a thyroid stimulating hormone (TSH) > 30 mIU/L at the time of treatment was required. This value can be obtained by endogenous TSH stimulation (hormone withdrawal for 4 or more weeks) or exogenous with recombinant TSH (rhTSH 0.9 mg im 24 hours apart, two days prior to the administration of ^{131}-I).

To increase TSH levels (36), to rise ^{131}-I uptake in thyroid cells, RAI can be performed after thyroid hormone withdrawal (THW) or administration of recombinant human TSH (rhTSH).

Moreover it is also necessary to reduce food iodine intake for 1-2 weeks before treatment and the exclusion of possible interference caused by drugs, contrast media or products with a high iodine content.

In low- and intermediate-risk patients, two randomized noninferiority trials comparing low and high activities of radioiodine, each with either THW or rhTSH, showed a similar ablation rate in the four groups (90). Moreover, recurrence rates in low- (91) (92) and intermediate-risk patients (93) are similar in patients prepared with THW or rhTSH, Moreover, rhTSH has advantages in terms of quality of life (94) and exposure of non-pathological tissues to radioiodine, thanks to a faster renal clearance (95), while maintaining the efficacy of superimposable ablation (96).

Long-term follow-up

Long-term follow-up in disease free patients after the first treatment remains a debated topic. It is not clear whether this follow-up should be based only on the Tg measurement

under L-T4 therapy associated with the neck ultrasound or whether rhTSH stimulation testing should be performed in patients undergone to radiometabolic treatment 1 year after ^{131}I therapy. In recent years, due to the ultrasensitive measurement of Tg, rhTSH stimulation testing is required less frequently since the basal Tg measurement with the neck ultrasound are predictive of persistence / relapse of disease. The long-term follow-up of patients considered to be in remission includes annual control based on physical examination, ultrasound of the neck (biennial in some patients) and baseline Tg measurement. In the presence of suspicion of recurrence, further morphological investigations are indicated in order to identify the site of the disease.

Management of the patient with metastases

Metastases can be discovered at the time of initial staging or during the follow-up. If metastases occur after initial therapy, many patients can benefit, in terms of survival and/or improvement of associated symptoms, from targeted therapies on individual metastases (126, 127). The most frequent metastases occurred as local recurrences (mostly laterocervical lymph nodes) and pulmonary localizations; bone, central nervous system, skin and liver metastases are rare. ^{131}I treatments are generally successful in small metastases while it is less effective in macroscopic ones. The treatments of choice for metastatic disease depend on the site of the metastases; in general the order of possible treatments is: surgical excision of the locoregional disease (potentially curative), ^{131}I treatment in cases of disease responsive to this treatment, external radiotherapy or other targeted treatments and systemic therapy with tyrosine kinase inhibitors (for patients with ^{131}I refractory disease and with disease progression). Localized treatments such as thermal ablation (radiofrequency or cryoablation), ethanol ablation or chemoembolization may be useful in patients with single or few metastases at high risk of local complications;

such treatments should be performed before systemic therapies (66). In not symptomatic patients with stable metastatic disease, the choice of close clinical and morphological follow-up during suppressive therapy may be appropriate.

Prognosis

DTC patients have an excellent prognosis. About 80% of patients can be cured definitively after initial treatment and 95-97% of these patients are still alive after a follow-up of 30 years. Despite this good prognosis, some patients have a high risk of relapse and death; these patients could be identified at the time of diagnosis using well established prognostic factors which can be divided into personal, histopathological, biological, molecular and treatment-related factors.

Individual prognostic factors

Age: Advanced age at diagnosis represents a negative prognostic factor for both relapse and mortality and the risk of relapse and death increases proportionally with age (45, 97). Often elderly patients have locally invasive tumors at presentation, a higher incidence of distant metastases at diagnosis and more frequently tumors with aggressive histological variants, less differentiated with a significantly lower uptake of ^{131}I and, therefore, a lower efficacy of the ^{131}I therapy.

On the other hand, children and adolescents, despite frequently presenting a disease locally extended at diagnosis, have an excellent long-term prognosis (98).

Gender: TC in men have often a more aggressive clinical presentation and a double probability of death.

Histopathological prognostic factors:

The prognosis of papillary carcinoma is better than that of follicular carcinoma. The less favorable prognosis of follicular carcinoma is closely related to the advanced age of the patients and the extent of the tumor at the time of diagnosis, rather than to the histology. The survival rate of patients with PTC and FTC is similar in patients with similar age at diagnosis and the same stage of disease (97). Furthermore, within these two histological entities, the prognosis may differ due to their different variants.

Tumor necrosis, vascular invasion and advanced histological grade (G3-G4): unfavorable indicators in both papillary and follicular carcinoma.

Tumor size: It's shown by several paper a gradual increase in the risk of tumor-specific recurrence and mortality with the increase in the size of the primary tumor (especially > 4 cm) (45, 97), mostly for papillary tumors.

Multifocal: multifocal papillary carcinoma is more frequently associated with lymph node metastases and evidence of persistent local disease, regional recurrence and distant metastasis. Controversial data have been reported on mortality (97).

Biological prognostic factors

Extra-thyroid invasion: it is considered an independent predictor of a worse prognosis in both PTC and FTC. It is associated with a higher rate of local recurrence, distant metastasis and tumor-related death (45, 97). It can be microscopic or macroscopic with involvement of other organs in the neck, in which the prognosis is worse.

Lymph node metastases: many authors have shown that regional lymph node metastases are associated with a higher rate of tumor recurrence and tumor specific mortality (97, 99), while others found no significant differences in survival (45).

In addition to the presence or absence of lymph node metastases, the site, size, number and extralinfonodal extension have an impact on prognosis.

Distant metastases: the presence of distant metastases at the time of diagnosis represents the worst prognostic factor in patients with both papillary and follicular thyroid cancer. Tumor-specific mortality in patients with distant metastases ranges from 36% to 47% at five years and increases up to 70% at 15 years (100, 101). In the case of distant metastases, the younger age, the well differentiated histological type, the location in the lung rather than in the bone, the presence of small lesions and the uptake of ^{131}-I are all factors associated with a better prognosis. The best clinical evolution is shown in younger patients with micronodular metastases responsive to radio-iodine therapy not detected on standard radiography.

Molecular prognostic factors

Worse clinical evolution is associated with the loss of differentiation of specific thyroid expression genes, such as the TSH receptor, the Na + / I transporter, Tg and thyroperoxidase genes, as demonstrated by the reduced expression of these genes in poorly differentiated tumors. and their absence in undifferentiated tumors (102). Among the oncogenes involved with the pathogenesis of PTC, only BRAFV600E has been shown to have a negative impact on clinical evolution (103), while this has not been shown for RET / PTC rearrangements (104). Similarly, the overexpression of the p21 protein, which is encoded by the RAS oncogene, has been associated with more aggressive forms of TC.

INTRODUCTION TO THE THESIS

The more appropriate clinical-therapeutic management of Thyroid Cancer (TC) includes:

1) Post-surgical assessment (in order to optimize initial staging) based on:

- Risk Stratification System: predicting the risk of persistent / recurrent disease
- TNM Staging System: predicting survival

2) Short and long-term follow-up based on the "Ongoing risk stratification" through Thyroglobulin, thyroglobulin antibodies (TgAb), neck ultrasound, post-^{131}I WBS, other imaging

More individualized and accurate assessments of the risk of persistent or recurrent disease and of dying from TC have a significant impact on initial therapeutic decision (extension of thyroid and/or lymph node surgery, need for radioactive iodine ablation/therapy, need for TSH suppressive therapy) and appropriate management strategies during short and long-term follow-up.

Risk stratification and staging of differentiated thyroid carcinoma

Post-operative evaluation (risk stratification and staging) for DTC, as for other cancer type, has several purposes: 1) allows to defines prognostic informations for each patient; 2) allows to evaluate the need of additional post-operative therapies, in order to estimate the patient's risk of disease recurrence and mortality; 3) provides information on follow-up, and 4) to enable an universal risk-stratified description of patients to communicate among health care professionals, monitoring by cancer registries and research purposes.

Risk stratification

Initial risk assessment could be used to choose the initial therapy (extent of surgery, radiometabolic treatment, degree of TSH suppression) and short-term follow-up (frequency of neck ultrasound or other diagnostic techniques such as CT, MRI or FDG-PET). During the follow-up, patients should be re-evaluated and reclassified into the new risk category based on their response to initial therapy and therefore their Tg levels, TgAb positivity, evidence of structural disease.

The 2015 American guidelines (66) introduced a new risk stratification system for differentiated thyroid cancer (DTC), adding to the previous one (2009) other prognostic variables, such as lymph node status (the number of involved nodes, their size and the presence of extranodal extension), mutational status and the degree of vascular invasion in follicular thyroid cancer.

However, “the incremental benefit of adding these specific prognostic variables to the 2009 initial risk stratification system has not been established” (ATA guidelines, RECOMMENDATION 48, page 41), because their efficacy has never been validated since the required histopathological data have not been collected, even in qualified institutions.

2009 American risk stratification for DTC:

Low-risk patients: 1) no local or distant metastases; 2) all macroscopic tumor has been resected; 3) there is no tumor invasion of locoregional tissues or structures; 4) the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion; 5) and, if ^{131}I is given, there is no ^{131}I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan (RxWBS).
Intermediate-risk patients 1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; or 2) cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation; or 3) tumor with aggressive histology or vascular invasion.
High-risk patients: 1) macroscopic tumor invasion, 2) incomplete tumor resection, 3) distant metastases, and possibly 4) thyroglobulinemia out of proportion to what is seen on the posttreatment scan.

Proposed modifications in 2015 ATA guidelines

Not present in the original 2009 initial risk stratification system (additional criteria than previous risk categories):

Low-risk patients: Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (< 4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)
Intermediate-risk patients Clinical N1 or >5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension Multifocal papillary microcarcinoma with mETE and BRAFV600E mutated (if known)
High-risk patients: Pathologic N1 with any metastatic lymph node ≥ 3 cm in largest dimension Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

Legend: mETE= Extrathyroid microscopic extension; N1= lymph node metastases

Staging

In the past years, different thyroid cancer staging systems have been developed to classify each tumor within the risk categories associated with a low, intermediate or high risk of relapse and mortality (TNM, AMES, MACIS, AGES, MSKCC etc ...) but no one has proved superior to the others. The AJCC/UICC TNM and MACIS staging systems have shown the highest proportions of variance explained (PVE), i.e. a statistical measure that quantifies how a staging system predicts clinical evolution in a large cohort of patients.

The AJCC/UICC (American Committee on Cancer/International Union against Cancer) classification for papillary, follicular, poorly differentiated cancer is based on pTNM parameters (Tumor, Node, Metastasis) and age.

TNM VII edition

Definition of primary tumor (T)

T category	T criteria
T1	Tumor diameter 2 cm or smaller
T2	Primary tumor diameter > 2 to 4 cm
T3	Primary tumor diameter > 4cm limited to the thyroid or with minimal extrathyroidal extension
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel
Tx	Primary tumor size unknown, but without extrathyroidal invasion

Definition of regional lymph node metastases (N)

N category	N criteria
N0	No metastatic nodes
N1a	Metastases to level VI (pretracheal, paratracheal and prelaryngeal/delphian lymph node)
N1b	Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal nodes
Nx	Nodes not assessed at surgery

Definition of distant metastases (M)

M CATEGORY	M CRITERIA
M0	No distant metastases
M1	Distant metastases
MX	Distant metastases not assessed

TNM VIII edition

(underlined the differences between the VII and the VIII editions)

Definition of primary tumor (T)

T category	T criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3a	Tumor > 4 greatest dimension limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscle (sterno-hyoid, sterno-thyroid, thyro-hyoid, or omo-hyoid muscles) from a tumor of any size
T4a	Gross extrathyroidal invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal invading prevertebral fascia or encasing carotid artery or mediastinal vessel from a tumor of any size

Definition of regional lymph node metastases (N)

N category	N criteria
Nx	Regional lymph nodes cannot be assessed
N0a	One or more cytological or histologically confirmed benign lymph node
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1a	Metastases to level VI or VII (pretracheal, paratracheal and prelaryngeal/delphian lymph node or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastases to unilateral, bilateral, contralateral lateral neck lymph nodes (Level I, II, III, IV or V) or retropharyngeal lymph nodes

INTRODUCTION TO THE THESIS

Definition of distant metastases (M) hasn't changed in VIII vs VII edition

Figure 1 shows the distribution of regional lymph nodes:

- Level I: submental and submandibular lymph nodes
- Level II: upper jugular lymph nodes
- Level III: middle jugular lymph nodes
- Level IV: lower jugular lymph nodes
- Level V: spinal and transverse cervical lymph nodes
- Level VI: prelaryngeal, pretracheal and paratracheal lymph nodes
- Level VII: upper mediastinal

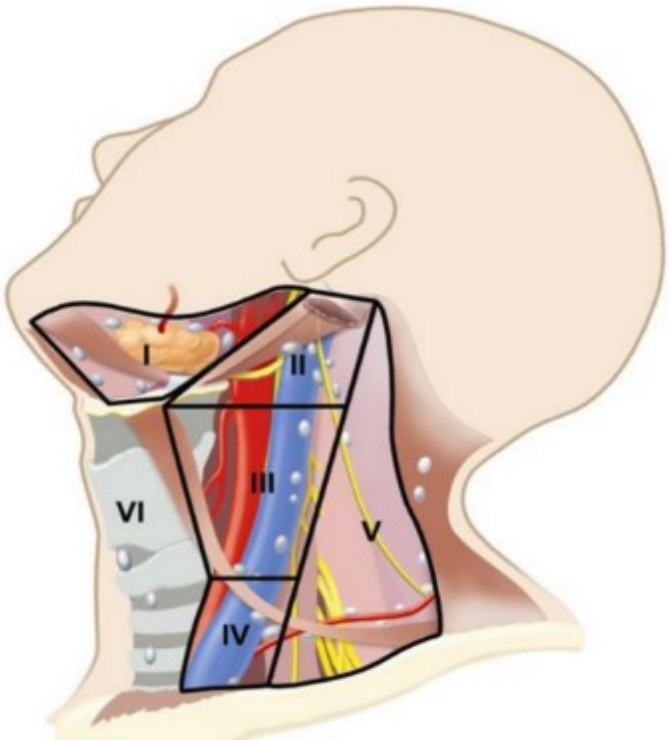

Figure 1: Neck lymph node levels

Staging

	VII edition TNM	**VIII edition TNM**
	<45 years old	<55 years old
Stage I	Any T, Any N, M0	Any T, Any N, M0
Stage II	Any T, Any N, M1	Any T, Any N, M1
	≥ 45 years old	≥ 55 years old
Stage I	T1, N0, M0	T1-T2, N0, M0
Stage II	T2, N0, M0	T3, N0, M0 T1-T3, N1, M0
Stage III	T3, N0, M0 T1-T3, N1a, M0	T4a, Any N, M0
Stage IVA	T4a, N0-N1a, M0 T1-T4a, N1b, M0	T4b, Any N, M0
Stage IVB	T4b, Any N, M0	Any T, Any N, M1
Stage IVC	Any T, Any N, M1	Removed

The major changes in the TNM VIII edition are:

- Minor histological extrathyroidal extension was removed from the T3 classification
- T3 was subgrouped into T3a (tumor size > 4 cm) and T3b (gross extrathyroidal extension)
- Upper mediastinal compartment (Level VII) nodal involvment was reclassified to N1a from previous N1b
- N0 was subgrouped into N0a (one or more cytological or histologically confirmed benign lymph node) and N0b (no radiologic or clinical evidence of locoregional lymph node metastasis)
- The age-at-diagnosis cut-off used for staging increased from 45 to 55 years
- For patients older than 55 years each category includes different histopathological features (except stage I which remained unchanged)

Ongoing risk stratification

In the last decade, the risk stratification of DTC has undergone substantial changes: from an initial static evaluation at the time of diagnosis to a dynamic risk stratification, called "ongoing", introduced in ATA 2015 guidelines, that assesses the risk over time based on the response to initial therapy not only of mortality but above all of persistent disease or biochemical or structural recurrence (66). This dynamic risk stratification is useful to guide disease long-term surveillance (the frequency of visits, the degree of suppression of TSH, the need to resort to other diagnostic techniques or therapies) and therapeutic management, assuming that the risk can evolve over time (after 6-18 months) based on the patient response to treatment.

The long-term outcome can be reliably predicted at 6-18 months after initial treatment by the serum Tireoglobulin (Tg) levels and neck ultrasound (64, 105, 106).

Also the relevance of this “ongoing” risk evaluation is poorly studied and little published data are available.

For patients with DTC undergone to total thyroidectomy or to lobectomy, the response to treatment can be divided into four classes:

Dynamic Risk Stratification ATA 2016

	Excellent Response	Biochemical Incomplete Response	Structural Incomplete Response	Indeterminate Response
Lobectomy	stable basal serum Tg levels related to the presence of a contralateral thyroid lobe and negative neck US;	basal serum Tg not related to the presence of a contralateral thyroid lobe, or increasing basal serum Tg levels without evidence of structural disease	evidence of structural disease;	non-specific findings on neck US and doubtful trends of Tg.
TTx alone	basal Tg <0.2 ng/mL and/or stimulated Tg 2 ng/mL plus undetectable TgAb and negative imaging	basal Tg >5 ng/mL and/or stimulated Tg ≥10 ng/mL or rising TgAb levels plus negative imaging	Structural or functional evidence of disease regardless of Tg or TgAb.	Not stimulated Tg 0.2–5 ng/mL and/or stimulated Tg 2-10 ng/mL and TgAb levels stable or declining, in the absence of structural or functional disease or nonspecific findings on imaging studies or faint uptake in thyroid bed on RAI scanning
TTX+^{131}-I	basal Tg <0.2 ng/mL and/or stimulated Tg <1 plus undetectable TgAb and negative imaging	basal Tg ≥1 ng/mL and/or stimulated Tg ≥10 ng/mL or rising TgAb levels plus negative imaging	Structural or functional evidence of disease regardless of Tg or TgAb.	Not stimulated Tg 0.2-1 ng/mL and/or stimulated Tg 1-10 ng/mL and TgAb levels stable or declining, in the absence of structural or functional disease or nonspecific findings on imaging studies or faint uptake in thyroid bed on RAI scanning

AIM OF THE THESIS

Because of the very low mortality and the long overall survival of DTC patients, overdiagnosis and overtreatment is a relevant possibility and the few cases of DTC-related death are considered an acceptable risk and a less aggressive management has been recently suggested for most PTC patients (66). However, because of the high and increasing prevalence of TC, the number of deaths cannot be overlooked: it is estimated that 56,870 new cases of TC will occur in the US in 2017 with 2,010 deaths (107).

ATA guidelines changed risk categories and the indications to radioiodine treatment and new TNM has been published trying to identify patients who deserve more careful management and to avoid overtreating patients with low risk of relapse and mortality.

A major issue, therefore is to find characteristics and criteria identifying cases having aggressive behaviour and poor prognosis.

Regarding the 2015 American guidelines' risk stratification, the addition of the new prognostic variables made the categorization, from a histopathological point of view, more accurate and it allows to tailor the management. The studies from which the risk factors have been identified are all retrospective and therefore no studies were available analyzing all prognostic factors together.

Moreover not all pathological reports, even from qualified institutions, provide data required to correctly categorize the patient and on which the clinicians establish the decision of a consequent treatment with radioiodine (activity and modality).

Evaluating the changed criteria of TNM and staging, the net effect of all the changes from VII to VIII TNM editions is to downstage a significant number of patients into lower stages that more accurately reflect their low risk of dying from TC.

Using the new TNM 8th edition, nearly 30% of patients were down-staged from stages III-IV to stages I-II and the proportion of intermediate/high ATA risk patients in stage I-II increased considerably, underestimating the risk of aggressive disease in some patients. The new staging system, therefore, will be particularly useful for identifying patients with advanced cancer and/or end-stage cancer with a very high short-term mortality, not so useful in most DTC patients who have a long life expectancy. So the new TNM-VIII staging system would seem to better discriminate mortality but the significant downstaging should not underestimate the severity of disease in many patients.

For example, one of the most important change is the prognostic role of metastatic lymph node location (N1a, central compartment vs N1b, latero-cervical compartments) that was judged controversial in the past (ATA, recommendation #48, [B20]). Instead, in the new staging system the metastasized node location is considered to have no impact on the prognosis of patients older than 55 years and it doesn't influence risk stratification (both N1a and N1b patients are classified in stage II).

In our newly published studies (99) (108), we showed how lymph node (LN) metastases, particularly latero-cervical LN, should be considered an important risk factor, not only for recurrent/persistent disease, distant metastases but also for mortality.

Long-term, prospective studies are needed to evaluate the impact of the new risk stratification and TNM. This novel system still needs to be validated by additional studies.

Lastly, regarding the risk of TC due to the area of residence, some volcanic areas such as Iceland, Hawaii, the Philippines and the area near Mt. Etna in Sicily have a high incidence of TC. In previous papers the authors showed that the increased incidence is due to the

increase in the papillary histotype, micro and microcarcinoma and they postulated a possible role of volcanic environment in the pathogenesis of TC. Whether this environment also influence the outcome is not known.

The Aims of this thesis are:

- To evaluate the clinical and histopathological characteristic of a consecutive series of 451 DTC patients with a minimum follow-up of 6 months at Endocrinology Thyroid Clinic, Garibaldi-Nesima Medical Center in Catania
- To stage these patients according to VII and VIII TNM staging system and to stratify DTC patients according to the ATA 2009 and 2015 risk stratification system
- To evaluate the response to the initial therapy after 12-18 months, "ongoing" risk stratification, in all patients, according to ATA risk categories, to VII vs VIII TNM editions and to the post-operative treatment (RAI administration or not) and to assess the structural disease at 12-18 months after initial treatment according to VII and VIII TNM staging
- To identify the risk factors of disease (biochemical and structural) at the 12-18 months assessment after primary treatment in all patients and only in intermediate risk category and to investigate whether DTC, in patients resident in the volcanic area, has a worse short-term staging and not only higher incidence as already demonstrated
- To assess the power of persistent/recurrent disease prediction between the different ATA risk categories (2009 vs 2015) and therefore the incremental benefit of additional prognostic variables added to the 2009 risk stratification system and to estimate the incremental benefit of the new TNM staging (VIII vs VII) at short-term re-evaluation 12-18 after the first treatment

- To construct a Nomogram, according to significant factors in multivariable logistic regression, with a risk score for predicting the probability of persistent and recurrent disease.

PATIENTS AND METHODS

A consecutive series of 451 DTC patients, all followed up at the Endocrinology Thyroid Clinic, Garibaldi-Nesima Medical Center in Catania, Sicily, undergone to thyroidectomy ± lymph node dissection, from October 2017 to February 2020, was analyzed. The median follow-up was 20.5 (IQR 14.7-27.4) months.

Traditional and new histopatological variables (size, histotype and histopathologic variants of TC, grading, status of resection margin, presence of vascular invasion with the number of invaded vessels in FTC, extrathyroid extension, number of lymph nodes examined and number of metastatic including their size and location site and the presence/absence of extranodal extension of lymph node metastases) have been examined.

In our series, the criteria for LN dissection were: a) central compartment node excision in all patients having a pre-surgery cytologic diagnosis of TIR4 or TIR5; b) pre-surgery evidence of neck LN involvement either clinical or at ultrasound examination, confirmed cytologically; c) intra-surgery suspicion of metastatic LN.

Tumors were staged according to the 7^{th} and 8^{th} TNM edition: T (the maximum extent of the primary tumor) and N (regional LN metastases) were assessed at pathological examination. The N status was indicated as N0 when all excised nodes were negative, N1a when positive nodes were only in the central compartment (levels VI and VII) and N1b when latero-cervical nodes (levels I–V) were involved. M (distant metastases) was assessed according to the first post-surgical ^{131}I-whole body scan (WBS) and/or additional diagnostic imaging examinations.

At initial evaluation, patients were subdivided into three different risk categories: low, intermediate and high risk according to ATA risk stratification published in 2009 and 2015.

Post-surgical radioiodine (RAI) treatment was given to patients with one or more of the following characteristics: gross tumor extension, lymph node metastases (according to the number, location and size), postoperative evidence of large thyroid remnant and/or high postoperative thyroglobulin (Tg) levels (postoperative Tg value >5–10 ng/mL); in other cases as tumor size > 2.0 cm, tumor extension to soft tissues adjacent to the thyroid gland (pT3 in VII TNM edition), <5 central nodal micrometastases (N1a), and also in presence of host risk factors (familial thyroid cancer, previous neck external beam radiotherapy) ,RAI treatment was evaluated case by case.

Post-surgery RAI therapy (30-100 mCi or 1110 – 3700 MBq), ablative or adjuvant, was administered to 277 (61.4%) patients.

All patients were followed up periodically with serum Thyroglobulin and anti-Tg antibodies measurements and neck ultrasound during levothyroxine (L-T4) therapy.

After 12-18 months from the first evaluation, the response to initial therapy (surgery ± ^{131}I treatment) was assessed with neck ultrasound and both serum Tg and TgAb measurements, either basal or TSH stimulated (with L-thyroxine, L-T4, withdrawal or rhTSH administration) in RAI treated patients. According to their response to the initial therapy (“ongoing” stratification) patients were re-classified in excellent, indeterminate, biochemical incomplete or structural incomplete response, as described in the introduction of this thesis.

Subsequent follow-up intensity was modulated on the basis of the initial risk evaluation and the response to first treatment.

PATIENTS AND METHODS

The TSH-suppression level was decided according to the same parameters: no suppression but substitutive LT4 therapy in low risk patients with no evidence of disease; mild TSH suppression (TSH 0.1-0.4 mcU/ml) in patients with intermediate risk or biochemical disease; complete suppression (TSH <0.1 mcU/ml) in patients at high risk of recurrence and/or with structural disease.

All patients presenting persistent/recurrent disease during follow-up underwent additional morphological examinations such as computed tomography, magnetic resonance imaging, bone scan and positron emission tomography. When patients were not cured, further treatments (RAI therapy, repeated surgery or other therapies) were carried out.

Risk factors of persistent/recurrent disease have been evaluated in all patients and after subdividing the cases according to the areas of residence (volcanic vs non-volcanic).

STATISTICAL ANALYSIS

Categorical variables were expressed as frequencies and percentages (%). Quantitative normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). The normality of quantitative variables was tested by the Kolmogorov-Smirnov test. Categorical variables were analyzed using the Chi-square test with Yates's correction or Fisher's test.

Multivariate analysis was carried out using logistic regression including only variables identified as being significant for recurrent/persistent disease at univariate analysis.

Power of persistent/recurrent disease prediction was estimated using Harrell's C concordance index (C-index). A nomogram was implemented based on the parameters that resulted significantly associated with the risk of recurrent / persistent disease at the multivariate logistic regression analysis. A p-value <0.05 was considered statistically significant for all analyses. Data analysis was performed using the Stata software version 16 (StataCorp, College Station, TX, USA).

RESULTS

Clinical and Histopathological characteristic of DTC patients

The clinical characteristics of these 451 DTC patients are shown in Table 1.

Most patients were females (324, 71.8%) with a F/M ratio of 2.6/1.0. Median age at diagnosis was 47.5 yrs (IQR 36.9-57.8).

Previous radiation exposure was present in 2 (0.4%) patients, family history of benign thyroid disease in 122 (27.1%) patients and of TC in 65 (14.4%) patients.

Seventy-five (16.6%) of patients had risk factors for TC (family history, Graves' disease, previous radio or chemo-therapy).

Twenty-nine (6.4%) patients were diabetic and 37 (8.2%) had cancer diagnosis before TC or during the follow-up.

Total thyroidectomy was performed in almost all patients (448, 99.3%) and lobectomy alone in 3 (0.7%).

Lymph node surgery was performed in 307 patients: 245 (54.3%) central compartment dissections and 62 (13.7%) central and lateral compartment dissections.

Among these patients, 433 (96.0%) had papillary and 12 (2.7%) follicular histotype, 4 (0.9%) papillary-follicular and 2 (0.4%) poorly differentiated. 64 (14.2%) had an aggressive PTC variant (tall cell, diffuse sclerosing, columnar and insular).

Minimal extrathyroidal extension was present in 97 (21.5%) patients and multifocality in 176 (39.0%). 11 patients (2.4%) had distant metastases at diagnosis or after short follow-up (10 lung metastases and 1 with lung and bone metastases).

Six (1.3%) patients required another surgical treatment in the neck and 6 (1.3%) patients underwent to a second ^{131}I treatment after about 12 months from the first.

Table 1 Clinical and histopathological characteristics of the 451 DTC patients

	n.	(%)
Patients (n.)	451	
Follow-up median (IQR) (months)*	20.5 (14.7-27.4)	
Age median (IQR) (y)	47.5 (36.9-57.8)	
Gender		
F/M (ratio)	324/127 (2.6/1)	
Histotypes		
Papillary	433	96.0
Follicular	12	2.7
Papillary-follicular	4	0.9
Poorly differentiated	2	0.4
M1	11	2.4
Minimal extrathyroid extension (ETE)	97	21.5
Multifocality	176	39.0

* Follow-up minimum 6 months

Distribution of patients by residence

According to the province residence distribution we observed: 304 from Catania, 32 from Caltanissetta, 34 from Siracusa, 24 from Ragusa, 23 from Enna, 23 from Agrigento, 8 from Messina, 1 from Palermo and 2 from Calabria.

TNM Staging System

TNM and staging (VII and VIII editions) are shown in Table 2.

Applying VII TNM staging system 271 (60.1%) tumors were T1a and T1b, 56 (12.4%) T2, 113 (25.1%) T3, 5 (1.1%) T4a and 6 (1.3%) Tx. Instead applying VIII TNM staging system more than 3/4 of the patients (349, 77.4%) had T1a and T1b tumors, 73 (16.2%) T2, 5 (1.1%) T3a, 13 (2.9%) T3b, 5 (1.1) T4a and 6 (1.3%) Tx. This different percentage depends on the removal of minimal extrathyroid extension from T3 classification.

Regarding the lymph node status, applying VII TNM staging 54 (12.0%) patients were N0, 121 (26.8%) were N1a, 62 (13.7%) were N1b and 214 (47.5%) were Nx. Instead applying VIII TNM staging almost 60% of cases were N0a or N0b (268, 59.4%), same cases of VII edition in N1a and N1b classes.

Six patients presented latero-cervical metastases without involvement of the central compartment (skip metastases).

Patients were also staged comparing VII vs VII TNM staging system (Figure 2): most patients fell into stage I using both classifications, respectively 324/451 (71.9%) vs 380/451 (86.5%); 23/451 (5.1%) vs 49/451 (10.8%) into stage II; 62/451 (13.7%) vs 5/451 (1.1%) into stage III and 57/451 (9.3%) vs 5/451 (1.6%) into stage IV. Therefore, using VIII TNM edition there was a significative downstaging in all categories (about 30%), mostly from stage III and IVA into stage I and II.

Table 2 TNM, staging (VII and VIII editions) and risk categories (2009 and 2015) of the 451 DTC patients

		n.	(%)			n.	(%)
TNM (VII ed.)				**TNM (VIII ed.)**			
T status (T)				**T status (T)**			
	T1a	166	36.8		T1a	206	45.7
	T1b	105	23.3		T1b	143	31.7
	T2	56	12.4		T2	73	16.2
	T3	113	25.1		T3a	5	1.1
	T4a	5	1.1		T3b	13	2.9
	Tx	6	1.3		T4a	5	1.1
					Tx	6	1.3
N status (N)				**N status (N)**			
	N0	54	12.0		N0a	70+54	27.5
	N1a	121	26.8		N0b	144	31.9
	N1b	62	13.7		N1a	121	26.8
	Nx	144+70	47.5		N1b	62	13.7
Staging (VII ed.)				**Staging (VIII ed.)**			
<45	I	202	44.8	<55	I	298	66.1
	II	4	0.9		II	10	2.2
≥45	I	122	27.1	≥55	I	92	20.4
	II	19	4.2		II	39	8.6
	III	62	13.7		III	5	1.1
	IVA	34	7.5		IVA	0	
	IVB	0			IVB	7	1.6
	IVC	8	1.8				
Risk categories at first evaluation 2009 guidelines				**Risk categories at first evaluation 2015 guidelines**			
	Low	193	42.8	Low		205	45.5
	Intermediate	247	54.8	Intermediate		231	51.2
	High	11	2.4	High		15	3.3

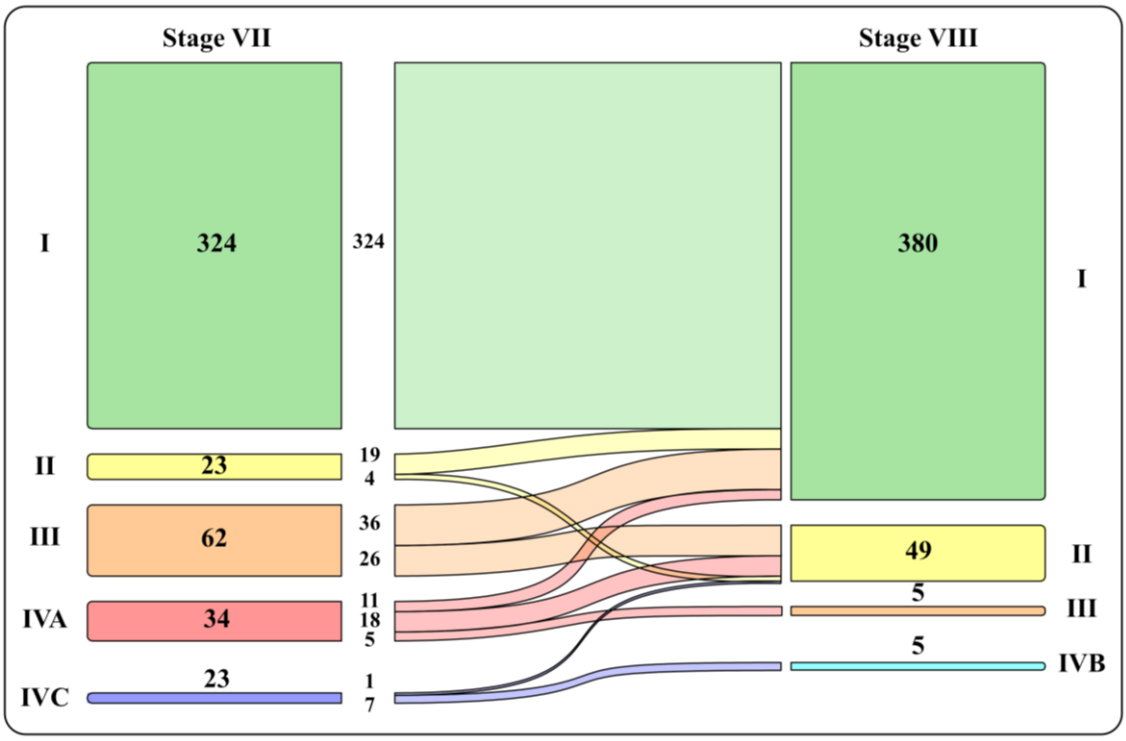

Figure 2: Graphic representation of patients' distribution into the four stages withVII vs VII TNM staging system

Risk Stratification System

Risk stratification classifications are shown in Table 2.

Evaluating the different risk categories published into ATA guidelines 2009 and 2015 in our cases there was only few variations in percentage due mainly to the lymph node number and size categorization. Using 2009 criteria 42.8%, 54.8% and 2.4% of patients were respectively into low, intermediate and high risk; with 2015 criteria, instead, the percentages were respectively 45.4%, 51.2% and 3.3%.

Postoperative RAI administration

Two hundred seventy-seven (61.4%) patients were treated with ^{131}I with different activities: 85 patients with 30 mCi, 186 patients with 100 mCi, 3 patients with 50 mCi, 1

patient with 70 mCi, 1 patient with 150 mCi e another 1 with 200 mCi. 156 patients were treated after L-T4 withdrawal and 121 after rhTSH administration.

Response to initial therapy, 12-18 months after initial treatment, in all patients

After initial treatment, 288/451 (63.9%) patients presented with excellent response. However 35 patients (not ablated) had basal Tg between 0.2 and 1 ng/mL, stable and compatible with small thyroid remnant.

At the evaluation 12-18 months after initial treatment, 163 (36.1%) patients were not cured.

In particular 82 patients presented an indeterminate response (68 patients had indeterminate Tg or TgAb and 14 patients non-specific finding at neck or TAC).

Five patients had biochemical incomplete response and 76 patients structural incomplete response (52 had lymph node metastases, almost all small in number and size; 10 had lung metastases; 1 only bone metastases and 5 lung and bone metastases, 5 lung and LN metastases, 2 lung, bone and local disease).

Outcome according to the post-operative treatment: RAI administration or not

Of 277 patients underwent to RAI treatment, 151 (54.5%) had an excellent response, 53 (19.1%) an indeterminate response, 5 (1.8%) a biochemical incomplete response and 68 (24.5%) a structural incomplete response.

Of 174 patients that didn’t undergone to RAI treatment, 137 (78.7%) had an excellent response, 29 (16.7%) an indeterminate response and 8 (4.6%) a structural incomplete response.

Province of residence: risk assessment and outcome in residents in Catania province vs residents in other areas

Of 304 inhabitants of Catania and his province, 141 (46.4%) had a low risk, 154 (50.7%) an intermediate risk and 9 (2.9%) a high risk of persistent/recurrent disease. At 12-18 months re-evaluation, 193 (63.5%) had excellent response, 61 (20.1%) indeterminate response, 1 (0.3%) biochemical incomplete response and 49 (16.1%) structural incomplete response.

Of 147 inhabitants of other areas, 64 (43.5%) had a low risk, 77 (52.4%) an intermediate risk and 6 (4.1%) a high risk of persistent/recurrent disease. At 12-18 months re-evaluation, 95 (64.6%) had excellent response, 21 (14.3%) indeterminate response, 4 (2.7%) biochemical incomplete response and 27 (18.4%) structural incomplete response.

Response to initial therapy according to ATA risk categories (Figure 3) and VII vs VIII TNM eds

VII ed

Of 193 low risk, 139 had an excellent response, 37 indeterminate response, 2 biochemical incomplete response and 15 structural incomplete response (2 cases with lung metastases).

Of 247 intermediate risk patients, 148 had an excellent response, 44 indeterminate response, 3 biochemical incomplete response and 52 structural incomplete response (14 cases with distant metastases).

Of 11 high risk patients, 3 had an excellent response, 1 indeterminate response and 9 structural incomplete response (8 cases with distant metastases).

VIII ed

Of 205 low risk patients, 147 had an excellent response, 40 indeterminate response, 2 biochemical incomplete response and 16 structural incomplete response (2 cases with lung metastases).

Of 231 intermediate risk patients, 138 had an excellent response, 40 indeterminate response, 3 biochemical incomplete response and 50 structural incomplete response (16 cases with distant metastases).

Of 15 high risk patients, 3 had an excellent response, 2 indeterminate response and 10 structural incomplete response (6 cases with distant metastases).

RESULTS

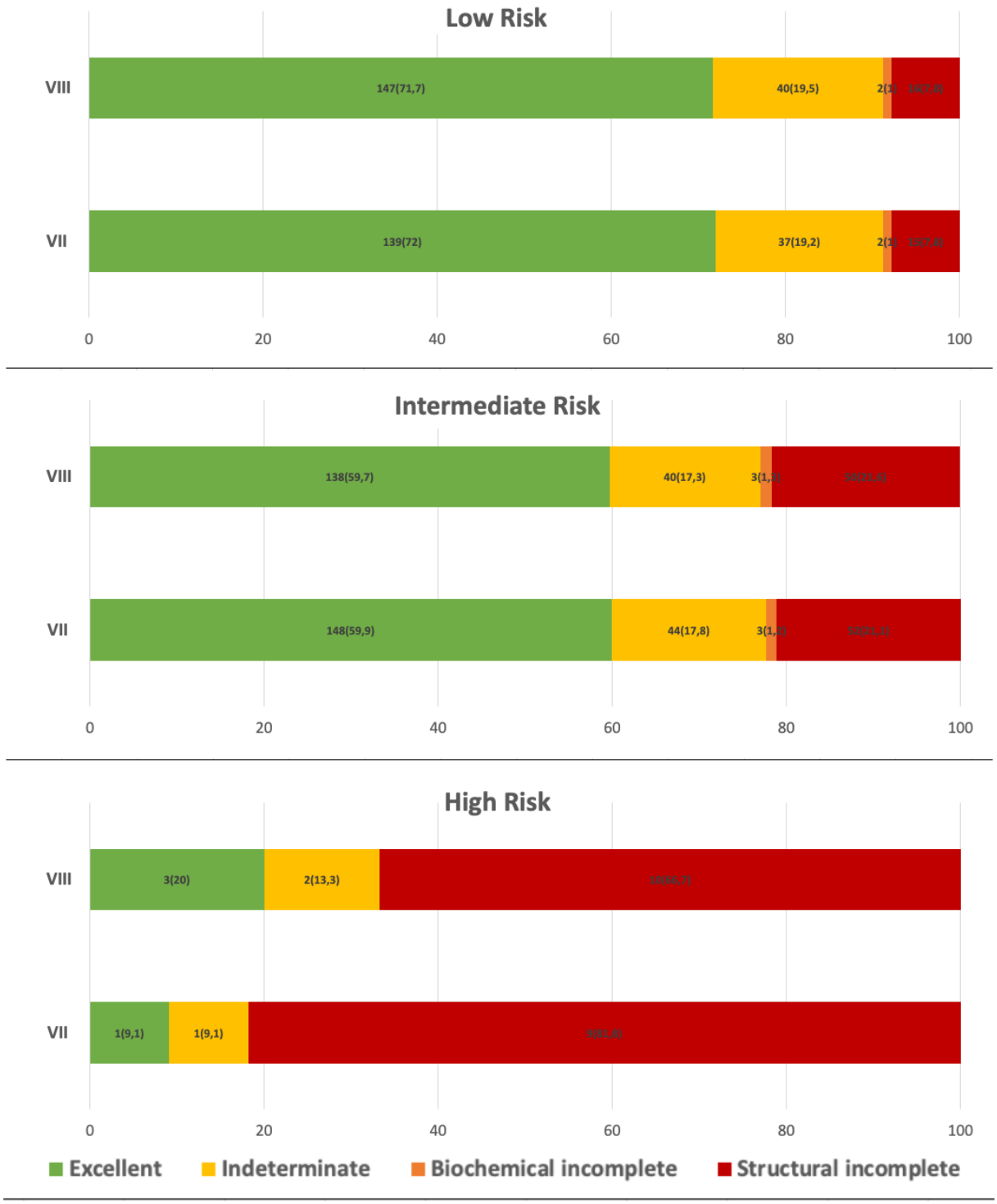

Figure 3: Response to initial therapy, 12-18 months after initial treatment, according to ATA risk categories

Structural disease after 12-18 months after initial treatment according to VII and VIII TNM staging (Figure 4)

Considering only patients with structural disease at last follow-up, a similar percentage of disease was observed in stage I (11.1% vs 12.8%) and II (34.8% vs 32.65%) both using VII or VIII TNM edition and a significant difference in stage III (20,9% vs 80%) and IV (45.2% vs 85.7%), respectively p=0.004 and p=0.04.

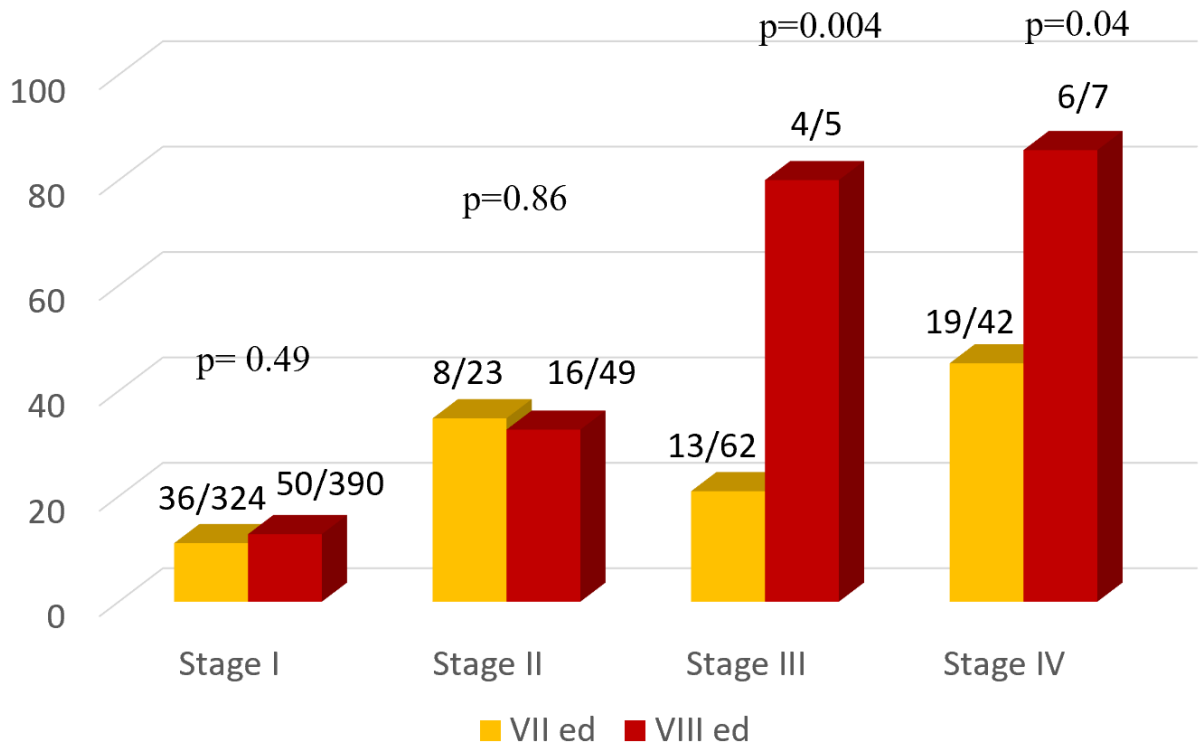

Figure 4: Comparison of the Number of Patients with structural disease according to the Seventh (yellow bars) and Eighth (red bars) TNM Editions

Predictors of persistent/recurrent disease at 12-18 months after first treatment

Risk factors of persistent disease (either morphologic or biochemical) at last disease assessment are presented in Table 3.

At univariate analysis, the factors associated to the presence of disease were: T status, the presence of lymph node metastasis, presence of more than five lymph node metastases, presence of lymph node metastases in the central compartment and in lateral compartments (N1a and N1b status), ATA risk intermediate or high and radioiodine treatment performed.

At multivariate analysis lateral lymph node metastasis had a high odd ratio.

Taking into account only SIR at univariate analysis, the factors associated to the presence of persistent disease are, beyond the same risk factors of above, male gender and multifocality. At multivariate analysis T status and lateral-lymph node were independent predictors of disease (Table 4).

Since the multivariate analysis showed that lymph node metastases have a significant impact to predict persistent/recurrent disease, LN characteristics (localization and number) have been investigated in detail.

The presence of positive LN (N1a + N1b vs N0/Nx), the number of nodal metastases and their location (N1b vs N1a) were relevant risk factors for persistent/recurrent disease persistence at 12-18 months after first treatment.

Persistent disease was significantly higher in N1 vs N0a/N0b patients (47% vs 28.7%, $p<0.001$).

Analyzing the number of nodal metastases, using the cut off of 5 positive nodes, the likelihood of persistent disease was higher for patients with > 5 vs ≤ 5 metastatic lymph

nodes or negative lymph node (respectively 64.6%, 40.8% and 28.7%) ($p<0.001$) (Table 3).

As for lymph node location (N1a or N1b), the frequency of disease at 12-18 months after first treatment progressively increased from 28.7% in N0a/N0b to 40.5% in N1a and to 59.7% in N1b ($p=0.02$ and <0.001 respectively).

Analyzing the number and location of nodal metastases, for 121 N1a patients, the probability of persistent disease was higher when more than 5 lymph nodes were involved (7 over 13 cases, 53.8%) compared with ≤5 lymph nodes involved (42 over 108, 38.9%); this difference was not statistically significant ($p=0.30$).

For 62 N1b patients, the probability of persistent disease was sensibly higher when more than 5 lymph nodes were involved (24/35, 68.5%) compared with ≤ 5 lymph nodes involved (13/27, 48.1%); also this difference was not statistically significant ($p=0.10$).

Table 3. Risk factors of disease (biochemical and structural) at the 12-18 months assessment after primary treatment

Variable	Biochemical and structural disease	Univariate analysis OR [95%CI]	p	Multivariate analysis OR [95%CI]	p
Age					
- < 55 years	105/308 (34.1)				
- ≥ 55 years	58/143 (40.6)	1.32 (0.88-1.99)	0,18		
Gender					
- Female	112/324 (34.6)				
- Male	51/127 (40.2)	1.27 (0.83-1.94)	0.27		
Lymph node surgery at primary treatment					
- Performed	117/307 (38.1)				
- Not performed	46/144 (31.9)	1.31 (0.86-2.0)	0.20		
Aggressive histology					
- No	139/387 (35.9)				
- Yes	24/64 (37.5)	1.07 (0.62-1.85)	0.80		
T status					
- T1a	61/206 (29.6)				
- T1b	49/143 (34.3)	1.24 (0.78-1.96)	0.36	0.99 (0.61-1.61)	0.98
- T2	38/73 (52.1)	2.58 (1.49-4.46)	<0.001	2.11 (1.19-3.74)	0.009
- T3a	0/5				
- T3b	8/13 (61.5)	3.80 (1.20-12.09)	0.01	2.54 (0.77-8.35)	0.12
- T4a	3/5 (60.0)	3.57 (0.58-21.88)	0.14	2.96 (0.48-18.46)	0.24
Multifocal					
- No	92/274 (33.6)				
- Yes	70/176 (39.8)	1.31 (0.88-1.93)	0.18		
Extra thyroidal invasion					
- No	123/355 (34.6)				
- minimal	40/96 (41.7)	1.35 (0.85-2.14)	0.20		
Lymph node metastases					
- Absent	77/268 (28.7)			Not included	
-Present	86/183 (47.0)	2.20 (1.48-3.26)	<0.0001		
Number of N1 at primary surgery					
- N0a/N0b	77/268 (28.7)			Not included	
- ≤5 N1	55/135 (40.7)	1.71 (1.10-2.65)	0.016		
- >5 N1	31/48 (64.6)	4.52 (2.37-8.65)	0.0000		
Location of N1 at primary surgery					
- N0a/N0b	77/268 (28.7)				
- N1a	49/121 (40.5)	(1.08-2.65)	0.02	1.40 (0.87-2.25)	0.16
- N1b	37/62 (59.7)	3.67 (2.07-6.51)	0.0000	3.07 (1.68-5.62)	<0.001
ATA risk stratification					
- Low	58/205 (28.3)			Not included	
- Intermediate	93/231 (40.3)	1.71 (1.14-2.55)	0.008		
- High	12/15 (80.0)	10.14 (2.76-37.24)	0.0000		
Radioiodine treatment					
- Not performed	37/174 (21.3)			Not included	
- Performed	126/277 (45.5)	3.09 (2.00-4.77)	0.0000		

Table 4. Risk factors of structural disease at the 12-18 months assessment after primary treatment					
Variable	**Structural disease n.76**	**Univariate analysis OR [95%CI]**	**p**	**Multivariate analysis OR [95%CI]**	**p**
Age					
- < 55 years	51/308 (16.6)				
- ≥ 55 years	25/143 (17.5)	1.07 (0.63-1.81)	0.80		
Gender					
- Female	46/324 (14.2)				
- Male	30/127 (23.6)	1.87 (1.12-3.13)	0.016	1.63 (0.92-2.90)	0.09
Lymph node surgery					
- Performed	57/307 (18.6)				
- Not performed	19/144 (13.2)	0.67 (0.38-1.17)	0.155		
Aggressive histology					
- No	63/387 (16.3)				
- Yes	13/64 (20.3)	1.31 (0.67-2.55)	0.42		
T status					
- T1a	23/206 (11.2)				
- T1b	21/143 (14.7)	1.37 (0.73-2.58)	0.33	1.12 (0.58-2.18)	0.73
- T2	21/73 (28.8)	3.21 (1.65-6.26)	<0.001	2.76 (1.37-5.56)	0.005
- T3a	0/5 (0.0)				
- T3b	5/13 (38.5)	4.97 (1.50-16.49)	0.004	3.18 (0.82-12.34)	0.09
- T4a	3/5 (60.0)	11.93 (1.89-75.22)	0.001	10.85 (1.60-73.52)	0.01
Multifocal					
- No	38/274 (13.9)				
- Yes	37/176 (21.0)	1.65 (1.00-2.72)	0.04	1.16 (0.66-2.04)	0.60
Extra thyroidal invasion					
- No	54/355 (15.2)				
- minimal	22/96 (22.9)	1.66 (0.95-2.89)	0.07		
Lymph node metastases					
- Absent	30/268 (11.2)			Not included	
- Present	46/183 (25.1)	2.66 (1.61-4.42)	<0.001		
Number of N1 at primary surgery					
- N0a/N0b	30/268 (11.2)			Not included	
- ≤5 N1	53/130 (40.8)	5.46 (3.26-9.15)	<0.001		
- >5 N1	31/48 (64.6)	14.47 (7.16-29.22)	<0.001		
Location of N1 at primary surgery					
- N0a/N0b	30/268 (11.2)				
- N1a	28/121 (23.1)	2.39 (1.35-4.22)	0.002	1.59 (0.84-3.03)	0.15
- N1b	16/62 (25.8)	2.76 (1.39-5.47)	0.002	4.04 (2.00-8.13)	<0.001
ATA risk stratification					
- Low	16/205 (7.8)				
- Intermediate	50/231 (21.6)	3.26 (1.79-5.94)	<0.001	Not included	
- High	10/15 (66.7)	23.63 (7.20-77.55)	<0.001		
Radioiodine treatment					
- Not performed	8/174 (4.6)				
- Performed	68/277 (24.5)	6.75 (3.16-14.44)	<0.001	Not included	

Analysis of intermediate risk patients

At univariate and multivariate analysis only of intermediate risk patients (n. 231) the same results of all patients were observed (Table 5), i.e. at univariate analysis, the factors associated to the presence of disease were T status, the presence of lymph node metastasis, presence of more than five lymph node metastases, presence of lymph node metastases in the central compartment and in lateral compartments (N1a and N1b status), ATA risk intermediate or high and radioiodine treatment performed. At multivariate analysis lateral lymph node metastasis had a high odd ratio.

Analysis of Catania area inhabitants

At univariate and multivariate analysis only of Catania area inhabitants (n.304) the same results of all patients were observed (Table 6), i.e. at univariate analysis, the factors associated to the presence of disease were T status, the presence of lymph node metastasis, presence of more than five lymph node metastases, presence of lymph node metastases in the lateral compartments and radioiodine treatment performed. At multivariate analysis lateral lymph node metastasis had a high odd ratio (OR 3.94).

Table 5. Risk factors of disease (biochemical and structural) at the 12-18 months assessment after primary treatment in intermediate risk category

Variable	Biochemical and structural disease	Univariate analysis OR [95%CI]	p	Multivariate analysis OR [95%CI]	p
Age					
- < 55 years	64/163 (39.3)				
- ≥ 55 years	29/68 (42.6)	1.15 (0.65-2.04)	0.63		
Gender					
- Female	61/157 (38.9)				
- Male	32/74 (43.2)	1.20 (0.68-2.10)	0.53		
Lymph node surgery at primary treatment	84/201 (41.8)				
- Performed	9/30 (30.0)	0.60 (0.26-1.37)	0.22		
- Not performed					
Aggressive histology	70/170 (41.2)				
- No	23/61 (37.7)	0.86 (0.47-1.58)	0.64		
- Yes					
T status					
- T1a	29/87 (33.3)				
- T1b	30/87 (34.5)	1.05 (0.56-1.97)	0.87	0.95 (0.49-1.83)	0.88
- T2	23/39 (59.0)	2.88 (1.32-6.26)	0.007	2.93 (1.29-6.67)	0.11
- T3a	0/2				
- T3b	4/9 (44.4)	1.60 (0.40-6.41)	0.50	4.24 (0.94-19.19)	0.06
- T4a	2/3 (66.7)	4.00 (0.35-45.96)	0.23	3.85 (0.33-45.03)	0.28
Multifocal					
- No	48/123 (32.5)				
- Yes	44/107 (41.1)	1.09 (0.64-1.85)	0.75		
Extra thyroidal invasion					
- No	55/139 (39.6)				
- minimal	38/92 (41.3)	1.07 (0.63-1.84)	0.79		
Lymph node metastases					
- Absent	17/68 (25.0)			Not included	
-Present	73/163 (44.8)	2.43 (1.30-4.57)	0.005		
Number of N1 at primary surgery					
- N0a/N0b	17/68 (25.0)			Not included	
- ≤5 N1	46/117 (39.3)	1.94 (1.00-3.77)	0.0047		
- >5 N1	30/46 (65.2)	5.63 (2.48-12.75)	<0.0001		
Location of N1 at primary surgery					
- N0a/N0b	17/68 (25.0)				
- N1a	44/108 (40.7)	2.06 (1.06-4.03)	0.03	2.01 (0.98-4.11)	0.058
- N1b	32/55 (58.2)	4.17 (1.94-8.99)	<0.001	4.72 (2.08-10.73)	<0.001
Radioiodine treatment					
- Not performed	6/33 (18.2)			Not included	
- Performed	84/194 (43.3)	3.44 (1.36-8.70)	0.006		

Table 6. Risk factors of disease (biochemical and structural) at the 12-18 months assessment after primary treatment in Catania Area

Variable	Biochemical and structural disease (n.304)	Univariate analysis OR [95%CI]	p	Multivariate analysis OR [95%CI]	p
Age					
- < 55 years	68/199 (34.2)				
- ≥ 55 years	43/105 (41.0)	1.34 (0.82-2.17)	0.24		
Gender					
- Female	75/222 (33.8)				
- Male	36/82 (43.9)	1.53 (0.91-2.57)	0.10		
Lymph node surgery at primary treatment					
- Performed	79/210 (37.6)				
- Not performed	32/94 (34.0)	0.86 (0.51-1.43)	0.55		
Aggressive histology					
- No	96/263 (36.5)				
- Yes	15/41 (36.6)	1.00 (0.51-1.99)	0.99		
T status					
- T1a	43/146 (29.5)				
- T1b	34/97 (35.1)	1.29 (0.75-2.24)	0.36	1.08 (0.61-1.91)	0.80
- T2	24/43 (55.8)	3.03 (1.50-6.09)	0.001	2.19 (1.06-4.51)	0.03
- T3a	0/3				
- T3b	4/7 (57.1)	3.19 (0.69-14.88)	0.12	1.53 (0.30-7.72)	0.61
- T4a	2/3 (66.7)	4.79 (0.42-54.24)	0.16	4.01 (0.35-46.06)	0.27
Multifocal					
- No	61/180 (33.9)				
- Yes	50/124 (40.3)	1.32 (0.82-2.12)	0.25		
Extra thyroidal invasion	82/236 (34.7)				
- No	29/68 (42.6)	1.40 (0.81-2.42)	0.23		
- minimal					
Lymph node metastases					
- Absent	52/181 (28.7)			Not included	
-Present	59/123 (48.0)	2.29 (1.42-3.69)	<0.001		
Number of N1 at primary surgery					
- N0a/N0b	52/181 (28.7)			Not included	
- ≤5 N1	35/86 (40.7)	1.70 (0.99-2.91)	0.005		
- >5 N1	24/37 (64.9)	4.58 (2.17-9.67)	<0.001		
Location of N1 at primary surgery					
- N0a/N0b	52/181 (28.7)				
- N1a	32/79 (40.5)	1.69 (0.97-2.94)	0.06	1.28 (0.72-2.29)	0.41
- N1b	27/44 (61.4)	3.94 (1.98-7.83)	<0.001	3.21 (1.53-6.74)	0.002
Radioiodine treatment	28/120 (23.3)			Not included	
- Not performed	82/184 (44.6)	2.64 (1.58-4.41)	<0.001		
- Performed					

C-Harrel test

To assess the power of persistent/recurrent disease prediction between the different ATA risk categories (2009 vs 2015) at short-term re-evaluation I performed the Harrell's C concordance index (C-index).

Considering biochemical and structural disease, the C-index indicated the power of 2009 and 2015 risk categories as essentially the same (C-index 2009 0.576 and C-index 2015 0.574).

Also with VII and VIII TNM staging system the C-index is low and similar (VII C-index 0.560 vs VIII C-index 0.570).

Subdividing intermediate class risk in two subgroups (N1a intermediate-low and N1b intermediate-high) the C-index was a little bit higher, i.e. 0.596.

Also considering only structural disease, the C-index indicated the power of 2009 and 2015 risk categories as the same (C-index 2009 0.656 and C-index 2015 0.657).

Also with VII and VIII TNM staging system the C-index is similar (VII C-index 0.644 vs VIII C-index 0.623).

Subdividing intermediate class risk in two subgroups (N1a intermediate-low and N1b intermediate-high) the C-index was a little bit higher, i.e. 0.685.

RESULTS

Development of a nomogram to predict persistent/recurrent disease

A nomogram incorporating all the significant parameters was constructed based on the multivariate logistic model identified in Table 3. For each parameter we obtained a corresponding prognostic points as shown in Figure 5. The point values for all predictor variables were summed to reach a total score. This value was plotted on the total score axis and a vertical line drawn from this axis straight up that indicates the patient's probability of persistent/recurrent disease at re-evaluation after the first therapy (Figure 6).

T status
T1a → 1.5 points
T1b → 3.1 points
T2 → 4.6 points
T3a → 6.1 points
T3b → 7.7 points
T4a → 9.2 points

N status
N0a/N0b → 3.3 points
N1a → 6.7 points
N1b → 10.0 points

Figure 5 significant parameters at multivariate and corresponding prognostic points

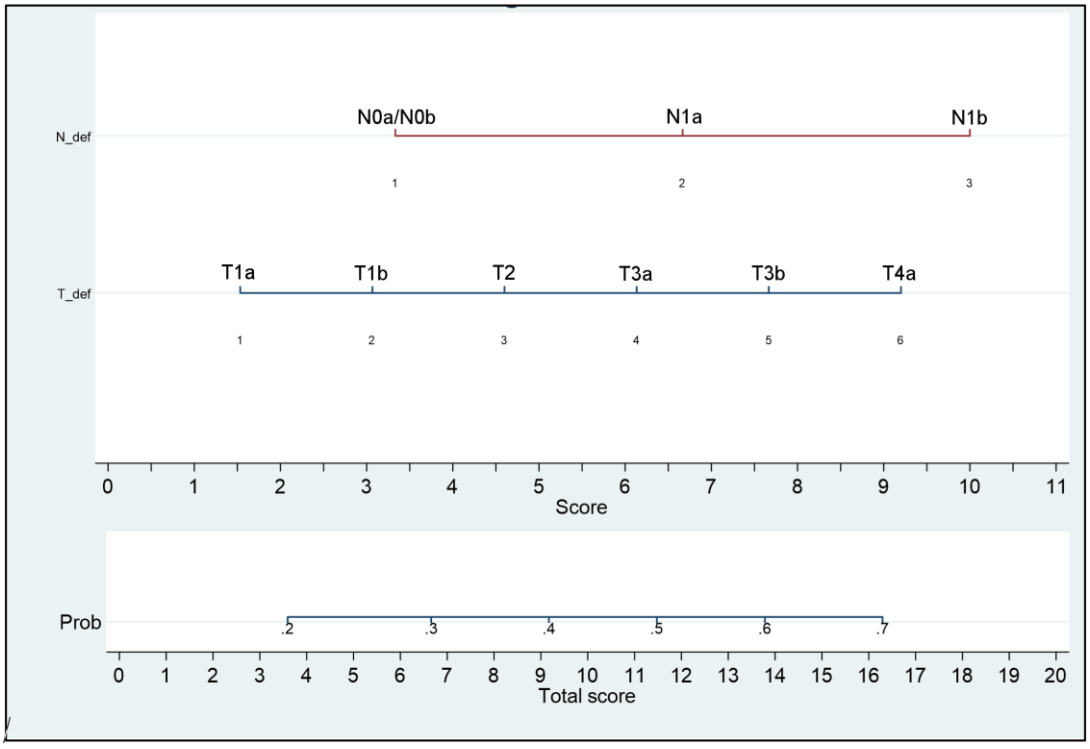

Figure 6: nomogram for the prediction of persistent/recurrent disease on the basis of clinical and histological characteristics.

DISCUSSION

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy (3) and over 85% of DTC cases have a papillary histotype (PTC). Its incidence, relatively stable until the early 1990s, has rapidly grown in recent decades, more than any other cancer (16), due mostly to an increase of low-risk thyroid cancer. Thyroid cancer is the most rapidly increasing cancer in the United States, where its incidence increased by 211% in the years 1975-2013 (1). However, the increase of about 7% per year during the 2000s has slowed to 2% per year in men and rates have stabilized in women during 2012 to 2016, likely due in part to the adoption of more conservative diagnostic criteria by clinicians (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf) (1).

DTC is generally associated with an excellent prognosis: the 5-year survival rate is near 100% for localized disease, 98% for regional disease and 56% for metastatic disease.

The death rate for TC increased slightly during 2008 to 2017 (0.6% per year) but appears to have stabilized in recent years.

In 2020, in the USA, the estimated new TC cases are 52.890 and the estimated deaths are 2.180 (2).

There has been remarkable debate about whether the increase in PTC represents a true increase in incidence or whether it is due to increased detection and “overdiagnosis” of small and “indolent” PTCs.

Moreover, despite TC mortality rates seems to be stable over time, as it is much lower relative to incidence (3, 10-12).

Accumulating evidence supports, therefore, a true increase in both the incidence and mortality of TC.

DISCUSSION

Although DTC has a good prognosis, in some patients tumor behavior is aggressive and associated with poor outcome. A major issue, therefore, is finding characteristics and criteria that identify these tumors for appropriate management.

Recently American guidelines (66) introduced a new risk stratification system with additional prognostic variables for tailored management. Moreover, the TNM (Tumor, Node, Metastasis) classification was changed in 2018 to better predict DTC survival. Most of the changes in the 8th edition (TNM-8) downstaged a significant number of patients into lower stages to more accurately reflect their low risk of dying, but probably underestimating the risk in some patients due to the fact that all young patients without distant metastases fall into stage I.

The changed American Thyroid Association (ATA) risk stratification and TNM staging have a significant impact on both the initial therapeutic decision and subsequent follow-up management. For this purpose, as recently suggested (109), molecular analysis data would be helpful in identifying the most aggressive DTC cases, thus influencing treatment decision making and subsequent follow-up.

Regarding the **clinical and pathological characteristics**, in the literature, the most frequent histotype is papillary thyroid cancer (about 85% of the cases), followed by follicular histology (about 12%), and by poorly differentiated tumors (<3%).

In our data we observed a higher percentage of papillary histotype (96% of the cases), followed by follicular cancer (about 3%). The majority of patients (71.8%) were female with a F/M ratio of 2.6/1. This finding is suchlike to the literature (F/M ratio=2.7) (110). Median age at diagnosis was 47.5 (36.9-57.8). These data are similar to those of literature (111).

The prevalence of the multifocality in the literature ranged from 32% to 39% in large series of PTC (111-113) similar percentage found in our data (39%).

One of the most important change applied by the new staging system (2018) concerns the minimal extrathyroid extension, whose incidence is reported in a wide range, from 5 to 30% (114, 115). Steinschneider et al. (111) showed a percentage of mETE of 20%, similar to our data (21.5%).

In our series lymph node metastases was present in 40.5%, higher than in other papers (20-30%) (111) and distant metastases in 11 patients (2.4%), similar to literature data (2-4%).

Concerning the **risk stratification**, DTC patients can be subdivided into three risk groups for recurrent/persistent disease (low, intermediate and high) allowing the identification of patients at risk of neck and/or distant disease and therefore helping to determine the extent of postoperative treatment decision. At the time of initial treatment our patients were classified mostly into low and intermediate risk and few into high risk, respectively 42.8%, 54.8% and 2.4% with 2009 ATA risk categories and 45.5%, 51.2% and 3.3% with 2015 risk categories.

Steinschneider et al (111)showed a different distribution of patients according to risk categories, approximately 70% low risk patients, 25% intermediate and 5.2% high risk patients.

Regarding the staging our data shows an **important downstaging** (about 30%) mostly from staging III and IVA to I, II and III. In particular the downstaging concerned 82.6% of stage II (into stage I), 100% of stage III (into stage II and II) and 100% of stage IV (into stage I, II and III).

Also in other papers (111, 116-119), a large proportion of patients staged according to the TNM 7th edition were down-staged in the 8th edition, including 64% of T3 patients, 6% of overall stage II patients, 99% of stage III patients, and 98% of stage IV patients. Stage migration depended mostly by the increasing of the age cut-off to 55 years, the down-classification of T3 disease, and the overall down-staging of N1 disease (120, 121).

Steinschneider et al revealed that while the TNM stage was unchanged in most patients, it was downstaged in 29.3% of them and when shifting to the 8th edition, 97.5% were in stage I-II, compared to 76.4% when using the 7th edition. They showed that despite the large proportion of shifted patients to stage I, there was a minimal impact on the expected 10-year disease-specific survival for this stage.

Kim et al (122) found that, among 493 patients, 41% were downstaged into lower stages and unavoidably more cases of recurrences and deaths were found in the lower stages. In particular, 17% of patients downstaged from stage III to stage II had recurrent disease, 25% died in the group downstaged from stage IV to III and 13.6% died in the group downstaged from stage IV to II. Thus, 18.4% of cases of death were found in the group downstaged from stage IV to stages III and II. The Kaplan-Meier plot for recurrence free survival showed a more significant *p* value using the TNM-8 staging system than the TNM-7 system; the Kaplan-Meier plot for overall survival showed a very significant value using both TNM-7 and TNM-8 but the value was higher for TNM-7.

Evaluating the different response at initial therapy, about 10 years ago Tuttle et al. (64) published a paper with the aim to validate the risk-of-recurrence staging system described in the ATA guidelines and to include a “response-to-therapy after 2 years” variable in an assessment to modify the initial estimates of risk. When using the ATA

classification system, an excellent response was found in 86% of low risk patients, in 57% of intermediate-risk patients and in 14% of the high-risk patients. Biochemical incomplete was found in 11% in the low-risk group, 22% in the intermediate-risk group, and 14% in the high-risk group and structural incomplete in 3% in the low-risk group, 21% in the intermediate-risk group, and 72% in the high-risk group.

Another paper evaluating 441 patients (111) showed that the proportion of intermediate/high-risk patients in stages I–II according to TNM-8 increased considerably compared to TNM-7 and that patients reclassified according to TNM-8 in stage II had more lymph node metastases, more intermediate and high recurrence risk, more reoperations, more persistency of disease and a non-significant increase in disease-specific mortality compared to TNM-7. They found that while rates of persistence/recurrence of disease in stage I was similar in VII and VIII editions, persistence/recurrence rates were significantly higher in stages II ($p = 0.05$) and III *(*$p = 0.03$) in VIII edition vs VII edition. Moreover they found a percentage of 25% of persistent disease at 1 year after first treatment. This study underlines that TNM-8 provides a more accurate system to discriminate mortality and persistence in DTC patients but that the severity of disease, especially in the 45–55-year age group and in stage II patients, should not be underestimated following the important down-staging of these patients.

In the present study, after initial treatment, 63.9% of patients presented with excellent response and 36.1% patients were not cured, of which half presented an indeterminate response, a little less cases structural incomplete response and few patients had biochemical incomplete response.

This rate depends mostly on the percentage of low- intermediate- and high risk categories.

DISCUSSION

Our data are different compared to previous data mostly for lower percentage of the excellent response in low risk patients (71.7%), for the higher number of patients with an indeterminate response (19.5% of low risk patients, 17.3% in intermediate-risk patients and in 13.3% of the high-risk patients) and very lower percentage of patients with biochemical incomplete response (1% in the low-risk group, 1.3% in the intermediate-risk group and 0% in the high-risk group); regarding the structural incomplete response the rate are similar to the other paper (in 7.8% in the low-risk group, 21.6% in the intermediate-risk group, and 66.7% in the high-risk group).

Moreover in our patients the rates of structural disease in stage I and II was similar in both editions and it was significantly higher in stages III ($p = 0.004$) and IV ($p = 0.04$) in VIII compared to VII edition.

Concerning the risk factors, most reports show that age, gender, aggressive variants, tumor size, lymph node metastases are the most important predictors of outcome (66).

In a very recent paper in 2020, Shin et al (123) found that in univariate analysis, tumour factors (including tumour size, multifocality, ETE, and lymphovascular invasion), nodal factors (including positive lymph node number, lymph node ratio and extranodal extension), and MACIS (metastases, age, completeness of resection, invasion, and size) scores were significantly associated with recurrence-free survival (RFS) outcomes ($P < 0.001$). In multivariate analysis, tumour size >4 cm, multifocality, Nodal factors and MACIS scores were the independent factors of RFS.

Kim et al (122)among the analyzed risk factors, found that multifocality, site of tumor and BRAF gene mutation had no significant difference in outcome for either age group (cut-off 45 or 55 years) whereas a statistical difference was found for mETE using both

age cut-offs. Male gender and larger tumors were predictors of the worst outcome using the 55-year cut-off.

In our data only tumor size and lymph node metastases independently predicted short term outcome, instead the other risk factors were not statistically significant.

In our series tumor size is an independent risk factors starting from T2 up to T4a (few patients in upper T categories) both for recurrent/persistent disease (biochemical and structural) and for only structural disease.

In a retrospective analysis of 574 patients with PTC, Tran et al(124) found that tumor size predicted recurrence-free survival on multivariate analysis.

A long-term study of 1.355 patients with DTC demonstrated that tumors smaller than 1.5 cm had lower 30-year recurrence and lower cancer mortality rates than tumors between 1.5 cm and 4.4 cm, and 4.5 cm or larger, respectively (97).

Another study using the SEER database found that the 10-year relative survival rates for tumors sized 1.5 cm or larger and tumors less than 1.5 cm were 95.4% and 99.8%, respectively (125).

Regarding lymph node metastases, in our series the positivity of lymph node metastases, the number (≤5 N1 or >5) and the location (N1a and N1b) are effective predictors of the outcome of the patients at 12-18 months after the first treatment, both for recurrent/persistent disease (biochemical and structural) and for only structural disease.

DISCUSSION

In a recent publication of our group(108), we found that latero-cervical metastatic LN may worsen prognosis and may be related to the appearance of distant metastases, which today represents the best surrogate indicator for cancer-specific death.

N1b status could be a marker of more aggressive PTCs, associated with other markers of cancer aggressiveness and/or a marker of more advanced disease at diagnosis.

The clinical relevance of LN metastases in PTC has been a matter of debate for decades (126, 127). At present, the impact of LN metastases at PTC presentation on the risk of recurrence is well documented in multiple series, including a recent study of our group (108, 128).

For many years, however, only neck node presence, with no other specified characteristic, was evaluated as a PTC prognostic factor.

The role of cervical LN metastases on PTC risk stratification was better defined in 2015 ATA guidelines, in which additional informations, as the number of metastatic nodes and the size and extranodal extension of the metastases, were included in the evaluation (66). These additional features have not been validated up to now and their relative importance in defining the risk of recurrence has yet to be quantified.

Data on the location of metastases in the central (N1a) or the latero-cervical (N1b) compartments were judged insufficient to include this information in the clinicopathologic features for the risk estimate in PTC (66) (recommendation #48, [B20], paragraph 1, line 16).

However, in our previous paper at the univariate and the multivariate analysis the metastases in the latero-cervical node compartment are an independent negative prognostic marker in PTC patients.

The number of positive LNs (>5) was also a significant negative prognostic factor, but only for N1a PTCs.

mETE is a controversial prognostic factor and several studies have evaluated its role on disease specific survival (DSS) and on overall survival (OS). Some authors (129-132) showed similar clinical outcomes independently of mETE. However, Castagna et al. (133) showed poorer outcome (persistent structural or recurrent disease and tumor-related death) in patients with mETE compared with tumors larger than 1.5 cm with negative margins (11.8% vs. 5.1%), concluding that only small mETE tumors should be low-risk tumors.

Recently an expansion of TNM-8 has been published (Telescoping) to collect additional data without altering the definitions of the current TNM categories in order to better classify each tumor category according to the presence or absence of mETE and to test the subcategories for prognosis and treatment planning considerations. In the next few years, more information on the importance of mETE for each tumor category will be available.

Comparing disease specific survival (DSS) between TNM VII vs VIII ed, Tam et al. (134) concluded that DSS in TNM-7 and TNM-8 is similar, although the 10-year DSS appears more appropriate between stages using the updated TNM-8 than TNM-7. The 10-year DSS for stages I–IV for TNM-7 ranged from 100% to 82.6% ($p < 0.001$) and for TNM-8 from 99.8% to 71.9% ($p < 0.001$). The 10-year OS for stages I–IV based on TNM-7 ranged from 95.8% to 59.7% and for TNM-8 from 94.3% to 34.6%.

In contrast, results from Chung et al. (116), analysing a large cohort of 3,176 DTC patients, and Jeon et al. (117), investigating the predictive capability of DSS of TNM-8 compared to TNM-7 in 1,613 DTC patients, suggested that TNM-8 has a higher ability to differentiate patients of different stages and therefore to predict DSS.

Although therefore TNM-8, on the one hand, suggests an improved allocation of patients at high risk of dying from DTC into more advanced stages of disease (135), on the other hand, induces a wrong belief of less aggressive disease. The boundaries between mortality and severity of disease overlap because the latter is strongly and independently related to the T, N, and M status. Indeed nearly half of the cancer-related deaths are now seen in stages I-II, compared to none in the previous edition (111). However it should be emphasized that the risk of death is not always related to the risk of recurrence in many patients.

Recently, several studies compared TNM-7 and TNM-8 and a better predictability in patients with DTC by TNM-8 has been suggested (111, 116, 118). When TNM-8 is applied, a significant number of patients with DTC are reclassified to lower stages and more accurate survival predictions are provided compared with TNM-7.

In our data, being the median follow-up of 20.5 months, mortality was not assessed so an analysis evaluating the presence of distant metastases, good surrogate for predicting mortality, was carried out. The C-Harrel test to evaluated the power to predict disease after short follow-up found no difference using VII and VIII TNM editions (both for biochemical and structural disease and also for structural disease).

Lastly, generally, cancer nomograms are prediction tools designed to assess risk based on specific characteristics of a patient and his disease and to predict the likely outcomes of treatment. The nomogram, therefore, has the ability to generate an individual numerical probability of a clinical event by integrating diverse prognostic and determinant variables, useful to improve disease prognostication and therefore a personalized follow-up.

In literature, recently, several nomograms for prediction the risk of death from thyroid cancer have been proposed (136, 137) and validated showing better predictive results compared to other staging systems included TNM staging system.

In 2016 Lang et al (138) validated a nomogram with an excellent discriminatory ability and accuracy in predicting 10-years-disease-specific death (factors included for the analysis: age at diagnosis, extrathyroidal invasion, tumor size, nodal status and distant metastases) and recurrence (factors included for the analysis: gender, age at diagnosis, extrathyroidal invasion, lymphvascular invasion, tumor size and nodal status) from PTC.

In 2017 Cai et al. (139) studied 1034 patients and proposed two nomograms, one for regional recurrence-free survival and one for distant recurrence-free survival prediction with a C-index of 0.72 and 0.83, respectively. They included family history, tumor diameter, capsular invasion and lymph node staging for regional recurrence-free survival and family history, histological variants, capsular invasion, perineuronal invasion and vascular invasion for distant recurrence-free survival.

Also the nomogram elaborated in this thesis could be useful to plan an individualized follow-up for each patient based on the score obtained from the risk calculation.

The limit of this system is that it needs a validation on both internal and external data. Moreover the nomogram assume that outcomes remain constant over time.

In last years, the concept of initial static evaluation at diagnosis has changed and in ATA 2015 guidelines a dynamic risk stratification, called "ongoing", was introduced.

Furthermore, another issue still to be validated is the timing of the re-evaluation. Based on our data, it seems that the restaging at 12-18 months could be too early as many patients with indeterminate response could change into excellent response (for example

for TgAb still positive but stable or declining). This hypothesis will be evaluated by extending the follow-up.

In conclusion, although the new TNM-8 in comparison to TNM-7 would seem to better discriminate mortality, the significant downstaging could underestimate the severity of disease in many patients and cause a non-negligible treatment burden, as for patients with latero-cervical metastases at diagnosis (99), especially when of large size and numerous (128). In fact the new TNM-VIII staging system don't discriminate the death rate in relation to the lymph node site differing from the previous staging system that included N1b patients in advanced risk categories and downgrade some cases (particularly N1b old patients) reducing the discriminating capacity for the few patients that will suffer a negative outcome, despite classified in stage II.

TNM-8 staging should have greater accuracy in identifying patients at higher risk of dying of TC, but careful follow-up is also needed for down-staged patients.

Further prospective studies are needed to better define the real effectiveness of the 2015 ATA risk stratification system and the VIII TNM staging system.

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