UNIVERSITÀ DEGLI STUDI DI GENOVA

DOTTORATO DI RICERCA IN
EMATO ONCOLOGIA E MEDICINA INTERNA CLINICO-TRASLAZIONALE –
CURRICULUM FISIOPATOLOGIA E CLINICA DELLE MALATTIE ENDOCRINO-METABOLICHE (XXXV CICLO)

TESI DI DOTTORATO

"The role of multidisciplinary approach in the clinical management of differentiated thyroid cancer"

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SUMMARY

This thesis has been elaborated on the basis of the following research papers, which are currently published or in phase of review:

- Baldi D. Papillary thyroid microcarcinoma: prevalence and evaluation of recurrence risk predictors. A retrospective analysis of real-life data. Thesis of graduation in Medicine and Surgery. Discussant: Albertelli M., Co-discussant: Gay S. 2022.

- Patti L, Gay S, Musso L, Maltese C, Spina B, Minuto M, Morbelli S, Vera L, Boschetti M, Ferone D, Albertelli M. Impact of microscopic extrathyroidal extension on differentiated thyroid cancer post-surgical risk of recurrence: a retrospective analysis. Journal of Endocrinological Investigation. 2022. Article under review

- Maltese C. Low dose radiometabolic treatment in differentiated thyroid cancer. Clinical experience of a third level center and comparison with the past. Thesis of graduation in Medicine and Surgery. Discussant: Albertelli M., Co-discussant: Gay S. 2021

- Beretta G. Tolerability profile of radioiodine therapy in differentiated thyroid cancer: comparison between high and low doses one year after the administration. Thesis of graduation in Medicine and Surgery. Discussant: Albertelli M., Co-discussant: Gay S. 2022

- Gay S, Comina M, Teliti M, Monti E, Albertelli M, Porto I, Rosa G M, Bottiglieri L, Giusti M, Ferone D. The role of cardiovascular assessment in low risk thyroid neoplasm patients: results from a tertiary care center experience. Int J Sci Rep. 2021; 7(2): 71-79

- Gay S, Raffa S, De'Luca di Pietralata A, Bauckneht M, Vera L, Miceli A, Albertelli M, Morbelli S, Giusti M, Ferone D. 2-[18F]FDG PET in the Management of Radioiodine Refractory Differentiated Thyroid Cancer in the Era of Thyrosin-Kinases Inhibitors: A Real-Life Retrospective Study. Diagnostics (Basel). 2022; 12(2):506

Introduction

Differentiated thyroid cancer (DTC) represent the most common endocrine malignancy, affecting about 10.1 per 100 000 women and 3.1 per 100 000 men per year worldwide. Despite this, its mortality remains extremely low (1). This is partially due to the indolent course of the disease, however also to the efficacy of diagnostic procedures and treatments (2), so that mortality in DTC patients is usually related to other clinical conditions (3).

The low aggressiveness of the disease and the long-term survival after primary treatments raised the need of targeted approaches, aimed at minimizing the extent and side effects of therapies, while maintaining their high quality and efficacy (4). In this context, the evolving knowledge in each of the field related to the thyroid cancer management necessitates a close and continuous contact among the involved professional figures, mostly endocrinologists, pathologists, endocrine and INT surgeons and nuclear medicine physicians (4,5).

Besides that, another issue concerns the long term follow up of DTC patients, who are often kept at supraphysiological dosage of thyroid hormones in the early phase after primary treatments and, in in most cases, require a lifelong total thyroid hormone replacement therapy. A continuous balance between the risk of DTC recurrence and the side effects of TSH suppression is, therefore, mandatory. The long-term effects of thyroid hormones, with specific regard to the cardiovascular system and the bone metabolism, cannot be neglected, as well (6,7). For this reason, a comprehensive approach and a multidisciplinary interaction should be aimed at identifying a therapeutic regimen which considers the whole aspects of physical health, as well as the optimal quality of life.

This last point, on the other hand, represents an important matter also in patients affected by advanced and metastatic disease. The impressive advantages, in terms of progression free survival and overall survival, provided by the introduction of novel target therapies, namely the thyrosin-kinases inhibitors (TKIs), need to be

accompanied by a carefully attention to their side effects, which are still a matter of investigation and a great challenge for physicians. For this reason, such clinical settings often require the involvement of other specialists, in order to optimize the treatment and maintain its dosage, when possible (8,9).

In the field of advanced disease, as well as in the early stage of diagnostic process and in defining the prognosis, the role of a complete and exhaustive anatomo-pathological characterization of the neoplasm has raised its importance, again in the perspective of a tailored and personalized approach (10, 11). Furthermore, the availability of a molecular phenotyping already changed the approach to DTCs in several aspects of their management: from the initial surgical choices to the selection of the systemic treatments in the advanced stages of the disease. Nevertheless, it still seems it could carry new advantages and further modify the current diagnostic and therapeutic algorithms (12, 13).

Based on the abovementioned issues, a multidisciplinary approach seems increasingly essential in the clinical approach to DTCs. In these regards, the recent historical and social happenings, namely the Sars-Cov2 pandemic, on the one hand initially hindered the possibility of interaction between physician and the discussion of cases, but on the other they brought to the improvement of digital and technological tools aimed at facilitating people interaction, even avoiding physical meetings. This led to an empowerment of digital networks, most of which were already present before the pandemic, and which allow the connection not only among physicians within the single structure or hospital, but also among different healthcare centres at national and international levels.

As a conclusion of the course, the thesis aimed at reporting some of the topics of the clinical research carried out last years in our centre, in the perspective of the multidisciplinary approach to the DTC patient treatment after the diagnosis, throughout surgery, the choice of radio-iodine therapy and the long term follow-up, with a particular focus on some aspects and challenges regarding the advanced disease.

A targeted surgical approach

Surgery has historically been considered as the first line therapy after the diagnosis, or even in case of high suspicion of DTC, with the goal of removing macroscopic disease and prevent tumour persistence or recurrence (PRD) (5,14). Nevertheless, even in high specialized centres, surgery might be burdened by the risk of side effects, which are mainly represented by hypocalcaemia, due to parathyroid damage, as well as recurrent nerve palsy, due to its impairment during the procedure (15). These eventualities, although transient in most cases, and strongly related to the surgeon's experience in the field, have to be weighted against the aggressiveness of the disease and its risk of PRD after the operation.

The increased capacity of predicting tumour behaviour, led to a reduction of the extent of surgery, which in many cases prevents the onset of the abovementioned conditions (16). In particular, the possibility of performing only a lobectomy in cases with nodules characterized by indeterminate cytology, smaller than 4 cm (without extrathyroidal extension and clinical evidence of lymph node metastasis), low-risk papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), obviously excludes the possibility of damage to the contralateral structures and, consequently, the eventuality of complete permanent hypoparathyroidism or vocal cords palsy.

This kind of approach, however, excludes the possibility of a subsequent radioiodine (RAI) therapy and strongly reduces the reliability of thyroglobulin (Tg) measurement during the follow-up. Therefore, it requires a close discussion between the surgeon and the endocrinologist, or the radiologist, as concerns the preoperative neck ultrasound evaluation, as well as with the pathologist in order to identify histological variables and/or the presence of somatic mutations (i.e. BRAF V 600E mutation), which could contraindicate lobectomy and suggest the need of a more extensive surgery (16).

In addition to that, a particular focus is required by the forms of PTC which do not exceed 1 cm of maximum diameter, namely the papillary microcarcinomas (mPTCs).

In this context, recent research provided the evidence not only of a very low rate of PRD after surgical treatments (17), but also an extremely indolent course even if the disease remains untreated and the patient kept in follow-up (18).

On these basis, innovative clinical approaches to mPTC have been proposed, such as the radiofrequency ablation, and proved their safety and efficacy, summed to the advantages of a mini-invasive technique (19).

Moreover, in selected cases and when a close follow-up is available, the possibility of mPTC surveillance without any therapeutic strategy has been considered, and the results reported to date describe an important gain in term of costs and side effects, with a limited amount of disease progression after a considerable follow-up time. Moreover, in any case, no differences in terms of complete remission and overall survival, even in those patients who experienced a progression and were pointed to surgery (20,21). Nevertheless, this kind of approach also must be carefully balanced and discussed by a multidisciplinary team, taking into account all the clinical-pathological features of the thyroid nodule, the age and the general clinical condition of the patient and, not last, his preference and confidence with a wait-and-see strategy (21).

Papillary thyroid microcarcinoma: prevalence and evaluation of recurrence risk predictors. A retrospective analysis of real-life data.

As concerns the experience of our centre, we performed a revision of the files related to all patients diagnosed with DTC from 2000 to 2020 who had clinical data recorded at our Clinic, in order to identify the amount of those who were diagnosed with mPTC, and, among them, the occurrence of PRD during the follow-up. Furthermore, we tried to analyse clinical, biochemical, and histological features which could be correlated to PRD.

Overall, we considered 780 patients, out of which 231 (29,6%) had a diagnosis of mPTC. Of them, 76 were excluded due to the lack of at least 1 year of follow-up: therefore, 155 patients were included in our analysis.

For each patient, we collected personal data (sex, ethnicity and age at diagnosis), the duration of follow-up, the cause and type of surgery, the histology report including the degree of differentiation, the stage and the size of the neoplastic lesion, the presence of multifocality and eventually the number of thyroid lesions, the number of invaded lymph nodes when present, the presence or absence of a capsule of the mPTC and the neoplastic invasion of the thyroid capsule. We also recorded information about RAI administration and the administered dosage, Tg values at 40 days after surgery, as well as Tg, TSH, fT3 and fT4 values at 1 year after surgery. We correlated all the above-mentioned variables to the occurrence of PRD.

The impact of each categorical variable on PRD was estimated using Kaplan Maier curves. The association of each continuous variable considered with the PRD was instead evaluated using the Cox Proportional Hazard Ratio or logistic regression. ROC curve analysis was used to determine the cut-off and its sensitivity and specificity in predicting the event.

Of the 155 patients included, 141 (91%) were female, mean age was 51.9 (±14.0), predominantly Caucasic (91%). Among them, 78.1% had been operated on for nodular thyroid disease, not related to the nodule which resulted mPTC, 14.8% operated on for toxic multinodular goiter, 3.2% for Basedow Disease and 3.9% for of a suggestive cytology (Thy3a/Thy4/Thy5) at the FNA performed on the nodule then diagnosed as mPTC.

The type of surgery performed was total thyroidectomy in 79.4% of cases, total thyroidectomy associated with lymphadenectomy of the central compartment of the neck in 16.1%, and lobectomy in 4.5% of cases.

The histological subtype resulted a classic variant in 92.3% of cases, a follicular variant in 7.1% and only in one case a tall cell variant was found (0.6%). The most represented histological grading was G1 (89%), while a G2 was found in 10.3% of the cases and a G3 in only 0.7%. According to the AJCC VIII classification, in 94% of the population the tumour was classified as stage I, in 6% stage II. The median size of the lesions was 5 mm (range 0.4-10 mm), multifocal lesions were found in 27.7% of cases (median number of lesions 2, range 2-6), and in 9.7% of the cases positive secondary lymph

nodes were described (median 1, range 1-11 lymph nodes involved). Out of them a localization in the central lymph node compartment (N1a) was reported in 78.6% of cases, and in the lateral compartment in 21.4%.

The tumour was totally encapsulated in 22.7% of cases, partially encapsulated in 16.7%, while in 60.6% it did not present a capsule at all. As concerns the invasion of the thyroid capsule, it was found in 14.6% of cases.

The median postoperative Tg was 0.55 (range 0.04-286.0 ng/mL). About half of the patients (47.7%) received RAI, at a median dose of 80 (30-376) mCi.

One year after primary treatments, the median TSH value was 0.3 mU/L (0.005-78.5 mU/L), while fT4 was 14.95 pg/mL (0.5-28.0 pg /mL), and fT3 2.97 pg/mL (0.70-5.61 pg/mL). At this evaluation, the median Tg value was 0.23 ng/mL (0.04-37.42 ng/mL).

The mean follow-up was 104.2 (±83.7) months. Disease recurrence was demonstrated in 5 patients (3.2%) after a median time since diagnosis of 36 (12-204) months. None of the patients in the study died due to the thyroid cancer.

All patients who relapsed had undergone surgery for nodular goiter or thyroid nodularity suspected, but different from the one which demonstrated malignant histology.

The type of surgery performed ($p=0.004$, Fig.1), the stage ($p=0.026$) and the presence of lymph node localizations at diagnosis ($p=0.017$, Fig.2) were associated with the onset of recurrence, with a prevalence in patients undergoing lobectomy or thyroidectomy and lymphadenectomy. Conversely, the association was not statistically significant with lesion multifocality ($p=0.859$), the age at diagnosis ($p=0.716$), the histological type ($p=0.745$), the grade ($p=0.931$), the size of the lesion ($p=0.207$), the presence of the capsule of the neoplastic node ($p=0.926$), the invasion of the thyroid capsule ($p=0.478$) and RAI administration ($p=0.151$). However, significant associations were found between the decision to deliver RAI therapy and lesion multifocality ($p<0.001$), the higher lesion size ($p<0.001$), and the thyroid capsule invasion ($p=0.021$).

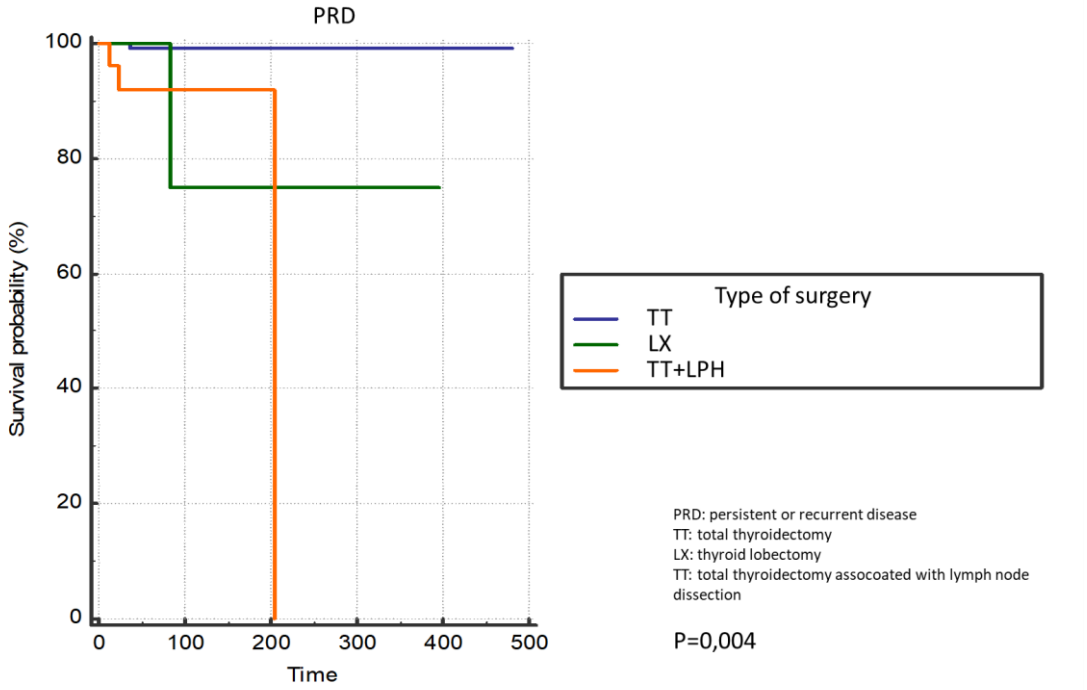


Figure1. Kaplan-Meier curves describing the incidence of PRD with respect to the type of surgery performed

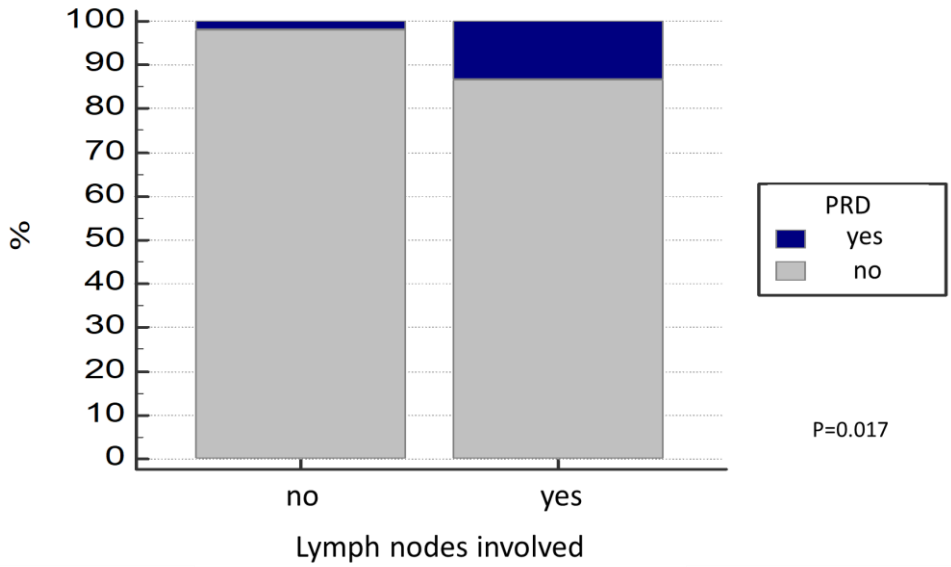


Figure 2. Distribution of PRD between patient who presented with vs without lymph node involvement at diagnosis

Logistic regression also showed an association between postoperative Tg levels and the occurrence of PRD (p=0.013). This test showed a sensitivity of 100% albeit with a specificity of 71% in predicting recurrence (cut-off >1.8 ng/mL, p<0.001, Fig 3).

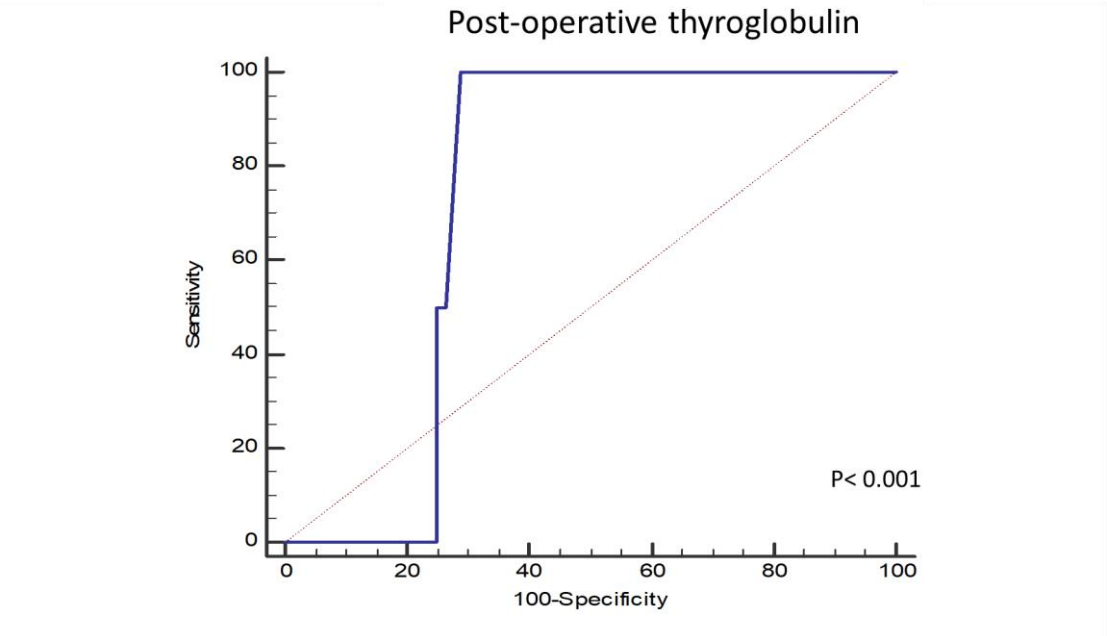


Figure 3. ROC curve describing the sensitivity and specificity of post-operative Tg levels in predicting PRD.

Regarding the data recorded one year after the primary treatments, the Tg value maintained its prognostic value on the risk of recurrence (p=0.019).
On the other hand, the value of TSH (p=0.100), fT4 (p=0.197) and fT3 (p=0.069) were not associated with disease recurrence (22).

In summary, our data resulted in line with those reported in literature and confirmed the great proportion of mPTC among the diagnoses of DTC, and the very low, but not absent, despite extensive treatments, incidence of PRD. On these bases, a less extensive surgical approach appears advisable, when performed after a carefully comprehensive evaluation and considering histological, radiological, clinical and biochemical features of the disease, as well as of the patient.

The choice of radioiodine treatment

In the same way as surgery, nuclear medicine management of DTC radically changed over the last decades (4,5,14). Specifically, the 'one size fits all' principle, namely a standard dose of radioiodine to be administered to every patient who had undergone surgery with a diagnosis of DTC, has gradually been replaced by a much more customized approach, characterized by the early definition of the target of the treatment (23).

After the diagnosis and the surgical removal of the thyroid cancer, indeed, a further assessment is necessary in order to discriminate patients who should have already been cured by the surgical treatment itself, from those cases in which the persistence of any amount, even microscopic, of pathological tissue might bring to the tumour recurrence in the subsequent years, and from cases where the presence of metastatic, or even advanced disease, is known but cannot be solved by the surgeon. Each of these settings deserve a different clinical management with respect to RAI therapy, and, in the former instances, the possibility of the administration of a reduced amount of radioiodine must be considered, as well as the decision to avoid the treatment at all (14, 24).

The risk of DTC recurrence, mainly assessed through the comprehensive classification proposed by 2015 American Thyroid Association (ATA) Guidelines, might drive this choice (5), but it must be integrated and personalized with regards to patients age, his general prognosis, eventually related to other clinical conditions and, in those cases when more than one option is feasible, it has to be extensively discussed with the patient himself (25).

As mentioned above, histopathological and molecular data are essential to assess the risk of recurrence and, consequently, in defining the need and the regimen of RAI. On the other hand, the improvements in the post-operative characterization of DTCs and the recent data concerning the correlation between the histological features and prognosis led to several significant updates, which were included into the VIII edition of the American Joint Committee on Cancer (AJCC) Staging System compared to its

previous version. One of the main changes introduced by the new AJCC classification is the microscopic extrathyroidal extension of the tumour (mETE), which is considered in the same way as intrathyroidal lesions (26).

It is worthy to note that TNM staging aims to predict the prognosis and specifically the disease-specific overall survival related to the DTC, which is different from the assessment of the risk of recurrence (5,27)

Dealing with this topic, we collected data from a cohort of patients followed by our Clinic in the medium-long term, to address the effect of the new assessment of mETE with respect to the prediction of recurrences.

Impact of microscopic extrathyroidal extension on differentiated thyroid cancer post-surgical risk of recurrence: a retrospective analysis

Introduction

Differentiated thyroid cancers are the most common endocrine neoplasms, with a maximum incidence between 30 and 50 years of age and a higher prevalence in women, with a female-to-male ratio close to 3:1 (29,30). They are generally associated with a very low disease specific mortality and an excellent overall survival (31]). The diagnosis is mainly based on clinical examination, thyroid ultrasonography (US) and fine needle aspiration biopsy, while surgical approach is the first-choice treatment, possibly followed by radioiodine (131-I) administration in selected cases (5). Similarly with other types of malignancies, postoperative staging of thyroid cancer is crucial to provide prognostic information, with the aim to achieve an adequate disease surveillance and optimize therapeutic strategies (5,32). An accurate staging is based on risk stratification data, which can be obtained as part of preoperative testing, during surgery, or in the postoperative evaluation (5). Over the years, multiple staging systems have been developed to predict the risk of mortality or recurrence in patients with DTC (33). The TNM staging proposed by the AJCC, in particular, is aimed at estimating the risk of disease related mortality (34). In 2017, the AJCC updated its staging system, when publishing the 8th edition, to improve the

survival predictive value. One of the main changes introduced by the new version focuses on the mETE, which is considered in the same way as an intrathyroidal disease, with respect to the assessment of T (35). The mETE, indeed, is defined as a microscopically detected invasion of perithyroidal tissues and is not considered to have an impact on the clinical behaviour and prognosis of the disease (36). Several studies confirmed the improvement brought by this last classification, in terms of mortality risk stratification, compared to the previous one (35,37,38). On the other hand, the ATA proposed a system which, to predict the risk of recurrence, includes the evaluation of T, together with molecular analysis (e.g., BRAF and TERT mutation) and histological features [i.e., the histological variant, the number and size of lymph-nodes involved]. This system allows to classify patients in a three-tiered stratification system (5,39,40).

The aim of the present study is to evaluate the impact of the updated assessment of T, following the new parameter of mETE, when applied to the post-operative risk stratification system for disease recurrence (DR) proposed by the ATA.

Materials and methods

- Study subjects and data collection

Among patients who underwent thyroidectomy between 2000 and 2015 and followed by the Thyroid Cancer multidisciplinary group of the IRCCS Policlinico San Martino University Hospital in Genoa (Italy), one hundred patients were randomly selected and retrospectively enrolled in this study. The inclusion criteria of the present study were the following: patients with histologically confirmed DTC [papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) or their variants, Hurthle cell carcinoma], age ≥ 18 years, follow-up longer than 24 months and at least one evaluation per year for the whole follow-up period. Medical and histological reports of all patients were reviewed, and the following data acquired: age at diagnosis, gender, histological subtype, extent of surgery (thyroidectomy or lobectomy), neck lymph node dissection (central and/or lateral), post-surgical radioiodine ablation therapy (RAI), cumulative RAI dose, biochemical data [TSH, fT4,

thyroglobulin antibodies, post-surgical basal (psTg) and stimulated (stTg) thyroglobulin levels], imaging reports [US neck and whole body scan (WBS)].

- Study design

The post-surgical risk of recurrence was re-assessed for each patient, by reviewing all the histological reports, according to ATA 2015 Guidelines. Persistent disease and DR were considered as the final outcome. Subsequently, a modified stratification of the risk of recurrence was attributed to each patient, introducing the downstaging given by the microscopic ETE in the definition of T. The updated classification was defined as ATA modified risk of recurrence (ATAm-RR). PsTg, stTg, neck US and post ablative 131-I WBS reports at baseline were also considered. After the initial assessment, each patient underwent morphological and biochemical re-evaluations, performed every six months for follow-up: all these data were reviewed to detect the persistence or recurrence of the disease. The rise > 1 ng/mL of a previously undetectable basal Tg levels, stTg >10 ng/ml, neck US reports suggestive of malignancy and tracer uptake of WBS are the parameters, that were used to define the persistence or recurrence of the disease. All findings suspicious for structural recurrences were confirmed by CT and/or cytology. The predictive performance for DR was calculated for each single parameter, as well as for the whole parameters together. Data collection and statistical analysis were performed in compliance with the Helsinki Declaration, 1964 and informed consent was obtained from all patients.

- Laboratory evaluations

Serum Tg was assayed through immuno-chemiluminescence (Roche Diagnostics, Mannheim, Germany). Functional sensitivity of the method was ≤ 0,5 ng/mL. TSH and fT4 were measured by mean of ultrasensitive immuno-chemiluminescence methods (Roche Diagnostics). Normality ranges were 0,3–4,2 mIU/l for TSH, 9,3 – 17,0 ng/L for fT4. Anti-Tg antibodies were determined through commercial assays (DiaSorin, Saluggia, Italy).

- Imaging

US neck examinations were performed by means of a conventional high-resolution device with a Echocolor-Doppler module equipped with a ML 4-13 linear probe working at 7.5 MHz (MyLab Five, Esaote Biomedica, Genoa, Italy). The finding of hypoechogenic round lymph-nodes or the presence of measurable hypo- or iso-echogenic tissue in the thyroid bed were considered as characteristics of suspicion for disease persistence/recurrence. FNA was performed in every such cases, to confirm the presence of recurrent/persistent disease.

- Statistical Methods

Parametric distribution of the data was assessed through Kolmogorov-Smirnov test. Data are reported in the text as “median, range” if non-parametric, as “mean ± standard deviation” when parametric. Chi-squared test was used to evaluate the association among non-quantitative variables and recurrences, whereas logistic regression was used to correlate these last with quantitative parameters. Cut-off values for the best sensitivity and specificity were calculated by mean of ROC curves. Afterward, the multiparametric score, comprehensive of the variables, which resulted related to the risk of recurrence, was calculated attributing one point for each variable that exceeded the cut-off value previously calculated, and ROC curves were used to assess the sensitivity and specificity of this score as well. The association between quantitative non-parametric data and the ATA-RR class was assessed by mean of Kruskal-Wallis test. Statistical analyses were carried out by mean of MedCalc Portable Launcher software, version 2.2.0.0; the same program was used to create all figures and graphs.

Results

Of the 100 patients enrolled, 79 were female. The characteristics of patients included in our analysis are summarized in Table 1. The mean age of the study population was 52.4 (±14.1). Two patients underwent total lobectomy, 98 patients total thyroidectomy alone, a lymph-node dissection of the central compartment of the neck (level VI) was associated to total thyroidectomy in 21 cases, and a central and

lateral neck compartment dissections (levels II-III-IV and Va) were performed in 10 patients. Final histology revealed a PTC in 93 patients: 84 were classic variant (25 mPTC) and 9 follicular variant (2 microcarcinomas). A follicular thyroid cancer was diagnosed in 5 patients. Two patients displayed both a PTC and an FTC. Seventy-eight patients underwent ^{131}I treatment after surgery, and the median dose administered was 80 mCi (range 30-120 mCi).

Characteristics	No. of patients/value
Gender	
Female	79
Male	21
Age at diagnosis	
Mean	52.4 (± 14.1)
Histology	
PTC (classic/follicular variant)	93 (84/9)
Follicular thyroid carcinoma	5
PTC + FTC	2
Extent of surgery	
Total thyroidectomy	98
Lobectomy	2
Lymph node dissection	
No	79
Central compartment neck dissection	11
Central + lateral compartment neck dissection	10
Stage	
I	70
II	26
III	4
ATA 2015 risk stratification system	
Low risk	60
Intermediate risk	27
High risk	13
ATA modified risk stratification system	
Low risk	79
Intermediate risk	8
High risk	13

Table 1. Table reporting the distribution of demographic, histopathological data and the risk of mortality and recurrence at the time of primary treatment in the study population

According to 2015 ATA Guidelines, post-surgical risk of recurrence (2015 ATA-RR) was low (LR) in 60, intermediate (IR) in 27 and high (HR) in 13 cases. In the ATAm-RR, the proportions changed as follows: 79 patients resulted in LR class, 8 in IR and 13 in HR

class. Therefore, 19% of patients were downgraded, all of them switching from the intermediate to the low-risk class (Fig. 4). In particular, 70,4% of the IR patients in our cohort were down staged to the lower category.

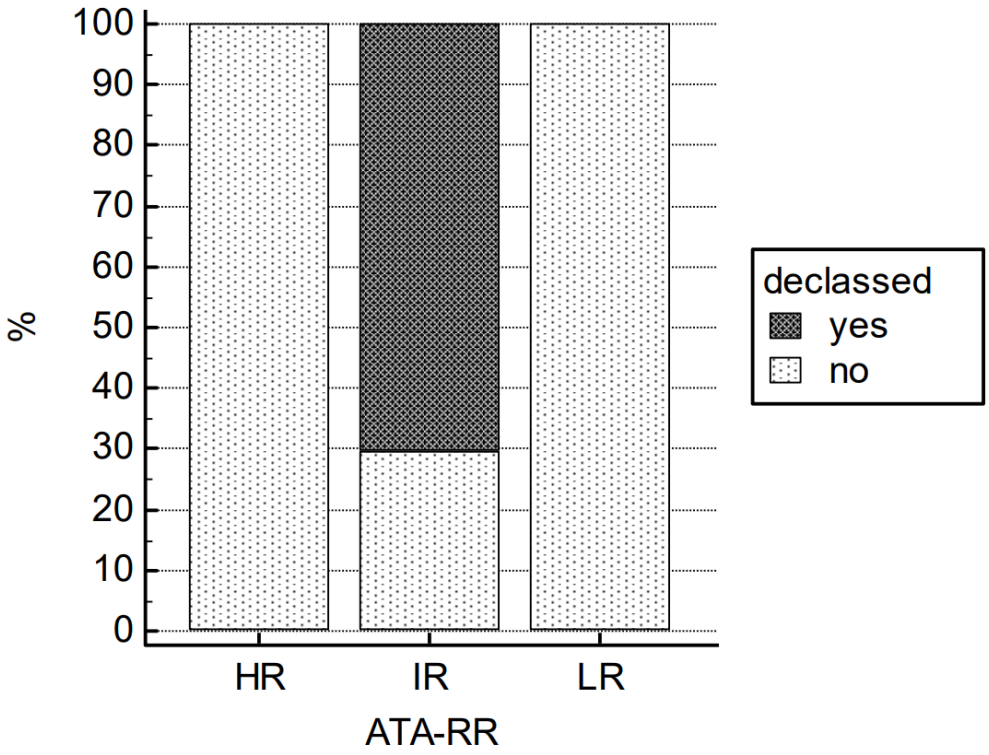


Figure 4. The graphic shows, for each ATA-RR class, the percentage of cases which changed their class after the updated assessment of T with respect to mETE.

Median psTg value was 0.48 ng/mL (0.04-48.00 ng/mL), while stTg was 2.90 ng/mL (0.04-140.00 ng/mL). Ninety-seven patients underwent post-surgical neck US examination. No patient showed gross persistent disease at the US examination. The post-dose whole body scan (rxWBS) showed an uptake outside the thyroid bed in 6 patients. Both 2015 ATA-RR and ATAm-RR class were significantly associated with psTg (p=0.029 and p=0.032, respectively), but not with stTg (p=0.110 and p=0.104). The 2015 ATA-RR and ATAm-RR did not show any association with post-surgical US findings (p=0.960 and p=0.967). A correlation between 2015 ATA-RR classification and rxWBS findings, as well as between rxWBS and ATAm-RR (p=0.002), were demonstrated (p=0.003). The average duration of the follow-up was 127.6 (± 52.7) months. During that period, a morphological thyroid cancer recurrence occurred in

eight patients. No statistically significant relationship was found between recurrence and age (p=0.651), gender (p=0.871), or histology (p=0.505), while the correlation with the type of surgery performed approached statistical significance (p=0.059). The 2015 ATA-RR showed a significant predictive performance for recurrences (sensitivity 75.0%, specificity 63.0%, p=0.023), but ATAm-RR performed slightly better due to an increased specificity (sensitivity 75.0%, specificity 83.7%, p<0.001). Post-surgical neck US findings (p=0.873) and the rxWBS (p=0.871) were not predictive of recurrence. On the other hand, stTg seemed to perform better than basal psTg, at least in this setting (p=0.004 vs p=0.043). Nevertheless, the best predictive performance was obtained when all the above-mentioned variables were considered (2015 ATA-RR, pathological or suspicious US findings, basal psTg≥1 ng/mL, stTg≥10 ng/mL): in this scenario, the adoption of ATAm-RR slightly improved the specificity of the assessment (ATAm-RR sensitivity 87.5%, specificity 80.4%, p<0.001 versus sensitivity 87.5%, specificity 72,8%, p<0.001 considering 2015 ATA-RR) (Figure 5)

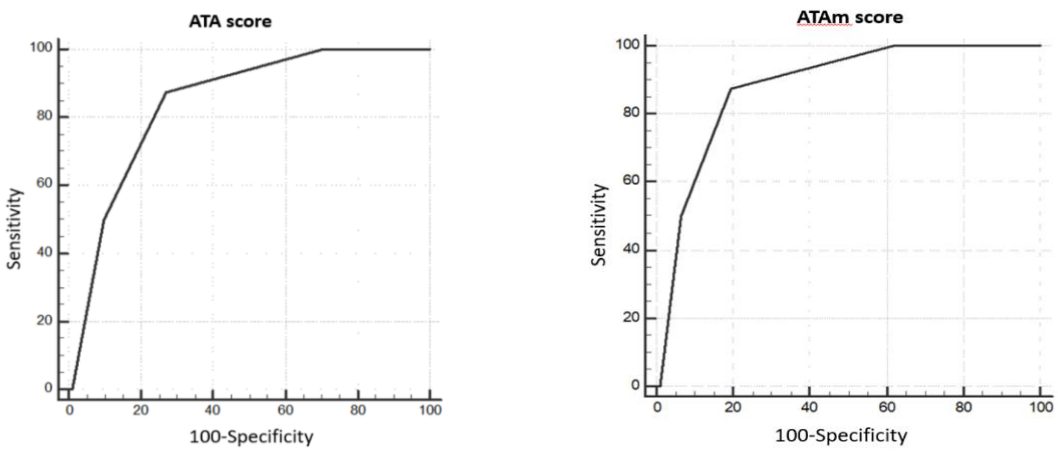


Figure 5

ROC curves representing the predictive performance for DR of the cumulative score calculated through all the parameters considered (pathological or suspicious US findings, basal psTg≥1 ng/mL, stTg≥10 ng/mL) together with 2015 ATA-RR (on the left) or ATAm-RR (on the right)

Discussion

The present study was specifically designed to evaluate the impact of mETE downgrading on post-operative ATA 2015 risk stratification. To the best of our knowledge, very few studies addressed this issue to date, and our results were able to provide new evidence about a better predictive performance for recurrences. Historically, ETE has been recognized as a potential negative prognostic factor in DTCs (41), and it has often been included in thyroid cancer staging systems, i.e. MACIS (metastasis, age, completeness of resection, invasion, and size) (42), AMES (age, distant metastasis, extent and size of primary cancer) and GAMES (tumour grade, age, metastases, extent, and size) (43). On the other side, the impact of a mETE has been questioned, and recent investigations have showed its negligible effect on relapse-free survival rates (44,45). Thus, the 8th last edition of the AJCC staging system for DTC has removed it from the definition of pT3 disease (46). In line with this evidence, our results suggest that the downgrading of T in DTCs having mETE, applied to the post-operative ATA risk of recurrence, provides a better predictive performance for recurrences, due to an increased specificity ($p<0.001$). Therefore, tumours with mETE might be assimilated, in term of prognosis, to intrathyroidal cancers. According to this concept, several studies (47-49) have previously showed that mETE is not associated with higher rate of recurrence compared with those without ETE. In particular, Ito et al. and Woo et al. have reported that the presence or absence of mETE did not significantly influence recurrence-free survival among patients with solitary PTC or microcarcinoma. On the other hand, two studies from Tran et al. and Park et al. suggest that mETE is a parameter that might negatively affect the prognosis of thyroid cancer (50,51), but no multivariate analysis was carried out to support this evidence. As a matter of fact, in the clinical practice, the initial estimation of the risk of recurrence is routinely and dynamically re-assessed during the follow-up, as well as treatment response, mainly through psTg and stTg levels, neck US and post ablative ^{131}I WBS (5,52). Regarding Tg, several studies appear to corroborate our findings and emphasised that a low psTg level could be considered as a favourable prognostic factor for patients with DTC (53-55). In line with these

results, a meta-analysis conducted by Giovanella et al. in 2014 confirmed psTg testing as a readily available and reliable tool, with a high negative predictive value (NPV) toward cancer recurrences (56). Furthermore, psTg level might be an independent postoperative assessment factor and provide ongoing serologic evidence for the recurrence risk stratification system (57). Conversely, our results suggest that both post-surgical RxWBS and/or neck US, when taken alone, showed no correlation with the risk of recurrence, and this is in accordance with Klain et al. who found that RxWBS findings had no significant incremental value in the identification of patients at higher risk of recurrence in low-risk cohort of patients (58). Although US reports are reliable and relevant methods for the early diagnosis and follow-up, they seem not to provide sufficient information to ascertain the risk of thyroid cancer recurrence in the neck region (59). In this study, there was no association between recurrences and age or gender ($p=0.651$ and $p=0.871$, respectively), and this was consistent with other studies (60). Nevertheless, it is well recognized that an older age is associated with a poorer prognosis: for this reason, the 8th edition of the TNM system, raised the cut-off for an increased risk of death from 45 to 55 years (61). This update was supported by a large retrospective study from 10 American institutions (62). On the other hand, gender has not been considered a prognostic factor in the commonly used staging systems, and this study, as well as other reports, showed that the overall survival is not affected by the gender at birth (63,64). Nevertheless, this topic is still matter of debate, as other studies reported a higher risk of DTC recurrence in men than in women (65,66). The retrospective design and the relatively small sample size represent a limitation of the present study. However, the availability of a long and accurate follow-up, with multiple annual evaluations performed and registered within the same centre counterbalance the relatively small cohort evaluated, reducing the intra-observer biases, and improving data reliability.

Conclusions

The present findings suggest that the adoption of ATAm-RR, compared to 2015 ATA-RR, can improve the predictive performance of DR due to an increased specificity. Furthermore, most patients classified as IR in our study population was declassed

using ATAm. The best predictive performance was obtained when considering the whole abovementioned variables (2015 ATAm-RR, pathological or suspicious US findings, basal Tg ≥ 1 ng/mL, stTg ≥ 10 ng/mL) together.

The update introduced by the 8th edition of AJCC confirms to be a significant step forward in initial risk stratification for patients with DTC and represents an important tool to improve the personalized treatment of thyroid cancer. Prospective studies performed on extended cohorts of patients might be advisable to provide more solid data on this intriguing topic.

A tertiary care real-life experience of low versus dose versus standard regimen of radio-iodine therapy in the treatment of differentiated thyroid cancers: focus on clinical side effects

As mentioned above, the rationale of a precise and comprehensive definition of the risk of recurrence of DTCs after surgery is critical in the decision making for further treatments.

A specific aspect concerning this issue is the possibility of the administration of a restricted amount of RAI (low doses RAI, LDRAI), when performed with an ablative purpose, in low-intermediate risk of recurrence DTCs (24).

In this setting, we retrospectively collected the experience of our centre describing a limited cohort of 200 patients randomly selected among those treated for DTC and followed in our Clinic between 2000 and 2020. Among these, we identified those who had follow-up data available for at least one year after diagnosis with the purpose of assessing the efficacy of the different RAI regimens with respect to the post-surgical RR.

For each of the patients, we collected personal data (sex, age at diagnosis), the type of surgery performed, the histological report, the post-surgical staging (reassessed according to TNM AJCC 8), post-operative US reports (within 3 months after surgery), pre-RAI basal and stimulated Tg, RAI dosage, post-RAI RxWBS, subsequent scintigraphy reports (when present) and duration of the follow-up. Hence, we

assigned a RR class in accordance with the classification proposed by the ATA Guidelines (2015). We also considered both Tg and US data performed one year after primary treatments, as well as the PRD occurred during the patients' follow-up, defined through the US finding and subsequent cytological confirmation of pathological tissue, or a new or persistent uptake at subsequent WBS, or basal Tg levels > 1 ng/mL or stimulated Tg levels > 10 ng/mL. Based on these parameters, we compared the performance of RAI regimens, for all the risk classes.

The Wilcoxon test was used to compare data between the assessments (pre-RAI and one-year after the treatment). To compare the trend of Tg between LDRAI and the standard dose RAI (SDRAI) group, the ratio between the values measured at one year and before the RAI was calculated, and the medians of this ratio compared in the two groups using the Mann Whitney test. The same test was used for the comparison between the pre-RAI Tg of patients who had and those who did not present disease recurrence in each group. The Chi-Squared test was used to assess the distribution of RAI treatment modalities according to ATA2015-RR, as well as to define the relationship between the RAI regimen administered and the onset of recurrences, and between the latter and the ATA2015-RR class. The analysis of the ROC curves allowed to determine the sensitivity and specificity of the ATA2015-RR classification. Statistical analyses were carried out using MedCalc Portable Launcher software, version 2.2.0.0; The same software was used for the creation of the graphs related to the study data. Data collection and processing were carried out in accordance with the Helsinki Declaration of 1964.

Of the 200 patients selected, 167 met the study inclusion criteria and were considered for statistical analysis. Surgery was performed in all the cases: 164 had a total thyroidectomy, 33 of these underwent to lymph-nodes dissection of the neck central compartment as well, while 17 had both central and lateral compartment lymphadenectomy. A thyroid lobectomy was performed in only 3 cases. Histological reports described a prevalence of papillary thyroid cancer (PTC), which was demonstrated in 136 cases (37 mPTC), in 3 cases a concomitance of PTC and FTC was reported, and in 17 a follicular variant of PTC (fvPTC). Four patients had a diagnosis of follicular thyroid cancer (FTC), while data of the remaining 2 histological reports were not available. Radioiodine therapy was administered to 142 patients, of which

66 treated with LDRAI (median 30 mCi, range 30-50 mCi) and 76 with SDRAI (median 80 mCi, range 80-120 mCi); the remaining 25 patients had not undergone RAI.

A significant reduction in both baseline and stimulated Tg at the one-year-evaluation was observed in those administered SDRAI (median 0.1 vs 0.5 ng / mL, $p < 0.001$ and 0.13 vs 2.65 ng / mL, $p < 0.001$, respectively), as well as in those treated with LDRAI (median 0.04, range 0.04-3.20 ng / mL vs 0.04, range 0.04-0.54 ng / mL, $p = 0.002$ and 0.04 vs 0.06 ng / mL, $p = 0.001$, respectively). However, a greater reduction was reported in the former compared to the latter ($p = 0.004$ and $p < 0.001$).

A PRD was reported in 10 patients, all treated with high-dose RAI as the first treatment ($p = 0.006$). At the ATA2015-RR, 4 of them were classified in the high risk (HR), 4 as intermediate risk (IR) and 2 as low risk (LR) class. In particular, regarding patients classified as LR or IR, a significantly higher baseline and stimulated Tg pre-RAI was found in those who relapsed than in the others (0.97 vs 0.17 ng / mL, $p = 0.008$ and 12.65 vs 0.4 ng / mL, $p < 0.001$, respectively). Of the whole study group, 102 patients underwent RAI before 2015. In that subgroup, 62 would be classified as LR according to ATA2015 -RR: of these, 21 did not receive RAI, 4 received a low dose and 37 a high dose, and among the latter 2 relapsed (Tg 0.48 and 34.00 ng / mL, respectively). Of the 65 patients treated since 2015, 40 were classified as LR, 38 of them received low-dose treatment and 2 did not receive it; 24 were classified as IR, 23 of them received low-dose and one high-dose treatment. The only patient showing recurrent disease in this subgroup was classified as HR and had received high-dose treatment.

From this retrospective analysis we concluded that, although both LDRAI and SDRAI regimens appeared effective in treating post-surgical residual, high doses remained more effective in reducing Tg levels and, therefore, in treating thyroid residual. As regards the choice of the RAI dosage to be administered, a multiparametric assessment, including imaging and laboratory tests, appeared necessary, in addition to the identification of the ATA risk category. In summary, if well stratified, patients undergoing LDRAI did not appear to be at increased risk of relapse compared to those undergoing SDRAI (67).

A further analysis we performed was aimed at evaluating the safety profile of the abovementioned regimens. We, therefore, collected out of the 167 patients' files considered in the previous analysis, data concerning the occurrence of clinical symptoms related to RAI (xerostomia, xerophthalmia and dysgeusia) during the first year after treatment, as well as full blood count reports (at the post-operative evaluation and one year after primary treatments) in order to assess the bone marrow status. Hence, we compared these data between LDRAI and SDRAI group.

Overall, clinical side effects (CAE) occurred in 18 individuals, of whom 16 had undergone SDRAI while only 2 had undergone LDRAI. Overall, 13 cases of dysgeusia, 3 of xerophthalmia and 4 of xerostomia have been reported. In the SDRAI group, 5.26% of patients developed xerostomia, 2.63% xerophthalmia and 15.78% developed dysgeusia. In the LDRAI group, only 1.51% of patients developed xerophthalmia and 1.51% of patients developed xerophthalmia, while none developed xerostomia (Table 2).

	SDRAI	LDRAI	Duration (months)*
CAE	21.05%	3.03%	5 (2-60)
Xerostomia	5.26%	1.51%	3.5 (2-60)
Dysgeusia	15.78%	0%	5 (2-24)
Xerophthalmia	2.63%	1.51%	4 (3-13)

Table 2

Clinical adverse events (CAE) distribution in standard dose RAI (SDRAI) and low-dose RAI (LDRAI) groups and their duration.

** described as median (range)*

Xerostomia had a median duration of 3.5 months (range 2 – 60 months), while xerophthalmia lasted for a median of 4 months (range 3 – 12 months) and dysgeusia for 5 months (range 2 – 24 months).

Overall, a significantly higher incidence of clinical side events was reported in the SDRAI group compared to LDRAI (p=0.002, Figure 6).

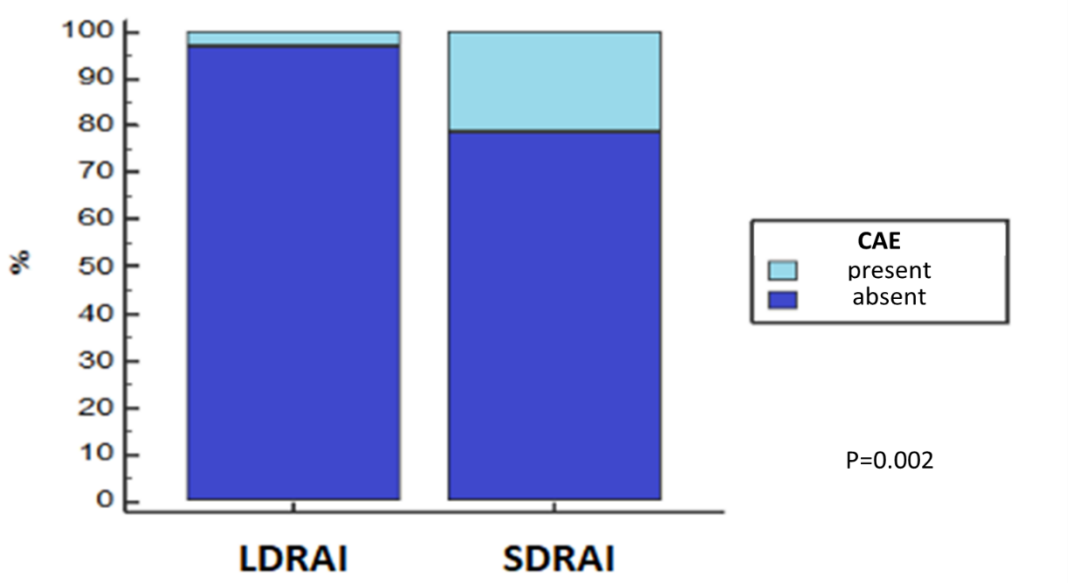


Figure 6. Distribution of the clinical adverse events (CAE) related to the RAI treatment in the LDRAI and SDRAI groups. An increased incidence was reported in the latter

No significant correlation was shown between the occurrence of side effects and age (p=0.130), sex (p=0.667), histology (p=0.504) and type of surgery performed (p=0.598). A significant correlation was shown, instead, with the stage of disease (p = 0.002).

The threshold of RAI dosage associated with an increased occurrence of side effects in our series resulted 77 mCi, with a sensitivity of 88.89% and specificity of 53.66% (P< 0.001). Interestingly, this value is very close to that used in discriminating LDRAI from SDRAI (80 mCi).

The mean haemoglobin (Hb) value prior to RAI was 13.74 (±1.53) g/dl. In particular, in patients who received LDRAI, it was 13.61 (± 1.37) g/dl, while in SDRAI group 13.94 (±1.66) g/dl (p=0.236). Median pre-RAI red blood cells (RBC) value was 4.7 (3.0-6.1) x 10^6/µl: 4.6 (3.9-6.1) x 10^6/µl and 4.8 (3.0-5.8) x 10^6/µl in LDRAI and SDRAI group, respectively (p=0,045). Overall, median white blood cells (WBC) value was 6.4 (3.0-11.0) x 10^6/µl: 6.1 (3.2-10.9) x 10^6/µl in LDRAI and 7.0 (3.4-11-0) x 10^6/µl in SDRAI patients (p=0,031). The median platelets (PLT) count before interventions was 253 (120-603) x 10^3/µl; 250 (120-441) x 10^3/µl and 255 (139-453) x 10^3/µl in the LDRAI and SDAI subgroup, respectively (p=0,556).

Data concerning the full blood count at the evaluation performed one year after primary treatments are reported in Table 3.

	LDRAI group	SDRAI group	P
	mean±SD	mean±SD	
Hb (g/dL)	13.42 (±1.11)	13.54 (±1.27)	0.592
	median (range)	median (range)	
RBC (x 10^9/µl)	4.6 (3.7-5.6)	4.7 (3.7-8.4)	0.130
WBC (x 10^6/µl)	6.4 (4.3-14.0)	5.8 (2.3-12.0)	0.069
PLT (x 10^3/µl)	243 (144-495)	238 (127-425)	0.230

Table 3. Blood tests counts at the one-year-evaluation compared between LDRAI and SDRAI group.

As regards the variation of Hb values during the first year of follow-up, a slightly but significantly greater reduction was observed in the group of subjects treated with SDRAI compared to those treated with LDRAI (-2.2% vs +0.8%, p=0.027).

A significant reduction was found in WBC in the SDRAI group (-21.6%) compared to LDRAI (+7.0) (p<0.001). Similarly, RBC (-3.1% vs -0%, p=0.025) and PLT (-9.5% vs +1.6%, p=0.007) in the SDRAI group also showed a significant reduction compared to the LDRAI group (Fig. 7).

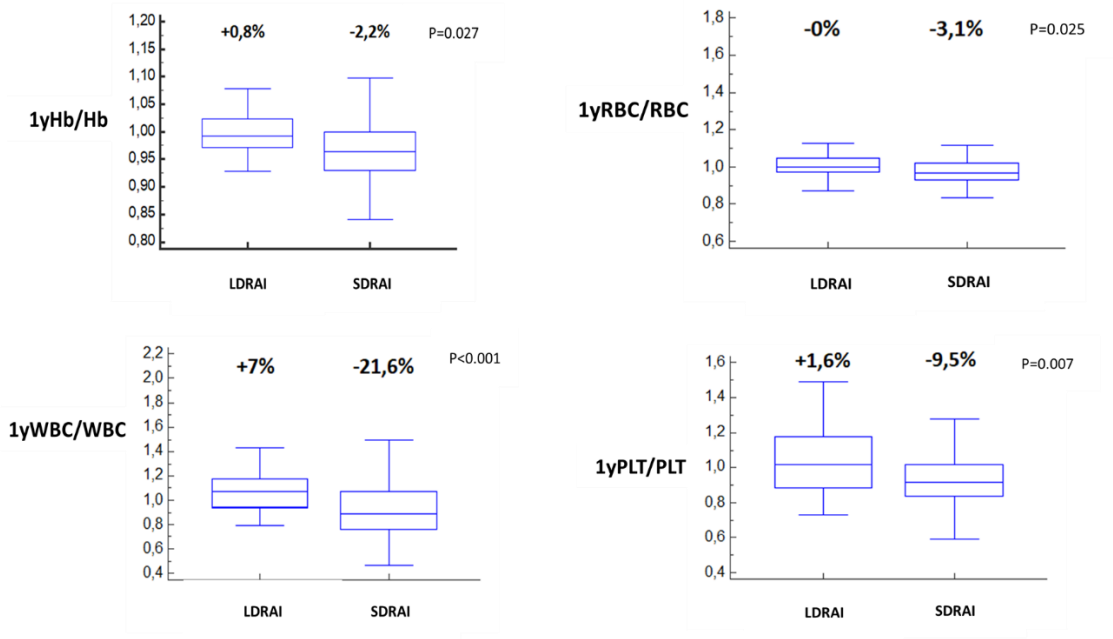


Figure 7. Mann-Whitney tests comparing the variation, between the pre-RAI evaluation and the one 1 year after primary treatments, of haemoglobin (Hb), red blood cells (RBC), white blood cells (WBC) and platelets (PLT).

No correlation was found between the changes in blood counts and age at diagnosis (p=0.953 for Hb, p=0.664 for RBC, p=0.869 for WBC, p=0.149 for PLT), sex (p=0.537 for Hb, p=0.531 for RBC, p=0.497 for WBC, p=0.595 for PLT), the type of surgery (p=0.346 for Hb, p=0,966 for RBC, p=0,994 for WBC, p=0,900 for PLT), the histology (p=0.888 for Hb, p=0.892 for RBC, p=0.965 for WBC, p=0.240 for PLT) nor for disease stage (p=0.273 for Hb, p=0.226 for RBC, p=0.264 for WBC, p=0.178 for PLT) (68).

In conclusion, our data confirm the optimal performance of LDRAI in the treatment of DTC, provided an adequate and multiparametric stratification of patients. On the other hand, our data suggest LDRAI protocol to be associated with a lower incidence of adverse events in terms of xerostomia, xerophthalmia and dysgeusia, without any significant impact on survival. Moreover, although the effect of RAI on the bone marrow appeared clinically neglectable in both SDRAI and LDRAI group, a slightly more evident variation was reported in the former than in the latter.

A comprehensive approach to the long term follow-up

As previously mentioned, in the vast majority of DTC patients a complete remission is achieved after primary treatments, and their prognosis *quoad vitam* in subsequent years will not be related to the thyroid cancer itself (69).

Nevertheless, even in very low recurrence risk cases, a history of DTC might influence patients' clinical history, mainly due to the long-term effects of primary treatments and to the need of a permanent thyroid hormone replacement therapy (70,71). TSH suppression, in particular, represent one of the mainstays of DTC management in order to prevent recurrences; on the other hand, the benefits of such approach have to be carefully balanced with the potential risks, mainly concerning cardiovascular and skeletal disorder which could be promoted by the levothyroxine excess. This aspect, in the same way as those described so far, deserve a multidisciplinary approach in order to focus on all the different clinical needs which might emerge in the long-term follow-up on DTC survivors (72).

In this perspective, we revised the experience of our centre to investigate the incidence of cardiovascular diseases in a cohort of DTC patients in a medium-long term follow-up, their relationship with thyroid function and with the oncological outcome.

The role of cardiovascular assessment in low risk thyroid neoplasm patients: results from a tertiary care center experience

Introduction

After surgery, therapeutic approach to DTC involves an accurate evaluation of the risk of persistence or recurrence of the disease based on histological, clinical and radiological parameters in order to establish the most appropriate subsequent approach. In particular, the necessity and the entity of TSH suppression are issues to

be carefully considered (5, 73-75). Due to the very low mortality related to these cancers, especially for those with a low stage of disease at diagnosis, every therapeutic decision should result from a balance between the benefit in preventing recurrences and the related risks, particularly in terms of cardiovascular disease (76). In these patients, in fact, the incidence of cardiovascular events is increased, particularly in those with a suppressed TSH (77). On the other hand, the effects of thyroid hormones on cardiovascular system are well known: the relationship between hyperthyroidism and atrial fibrillation (AF) has widely been studied both from the pathophysiological point of view and from the epidemiological one. Even subclinical hyperthyroidism proved association with an increased risk of arrhythmias (78,79). Exogenous TSH suppression also affects many cardiac function parameters, such as heart rate, blood pression, maximum heart rate, work-load and different kinds of ultrasound findings (80). Other data suggest the influence of thyroid axis on coagulation processes, by increasing pro-coagulant factors such as Von Willebrand factor, fibrinogen and factor VIII, and reducing anti-coagulant activity of other proteins such as ADAMTS13 (81,82). Moreover, atherosclerosis seems to be affected by the excess of thyroid hormones (83). On these basis, the aim of the present study was to investigate the clinical and echocardiographic features of a cohort of low risk thyroid neoplasm women and their evolution in time, and to assess the utility of a complete cardiovascular examination at baseline, as well as during the subsequent follow-up. A second goal was to identify clinical, biochemical or ultrasound parameters associated with cardiovascular events, in order to prevent, or at least to detect them earlier, so optimizing the care plan for these patients.

Subjects and methods

Patients enrolled in this study were female aged over 18 years at the beginning of the study period, who had undergone total thyroidectomy for a nodular thyroid disease, with an available histological report describing a follicular derived, differentiated thyroid neoplasm and with a tumour stage lower than 2, and with at least 5 years of follow-up. A first examination (V1) at the end of the primary treatments (surgery and, when necessary, a first dose of radio-iodine therapy), a five years follow-up period

and a second examination (V2) at the end of it were retrospectively analysed. V1 had to be performed within 6 months from primary treatments, and a subsequent 5 years follow-up had to be available, unless death due to cardiovascular events. A written informed consent to join the research was subscribed by all patients before data collection. From every patient, familial and personal cardiovascular anamnesis, menopausal and smoking status, as well as the therapeutic scheme administered were investigated. In each examination, body mass index (BMI), blood pressure and heart rate were measured. A blood examination, including the thyroid axis (TSH, fT4), thyroglobulin (Tg), anti-thyroperoxidase antibodies (TPO-Ab), the lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) and the glycaemic one (glycemia, insulin, insulin sensitivity index HOMA and glycosylated haemoglobin) were evaluated. The administered dosage of levothyroxine pro kilogram of body weight (LT4) was annotated. When available, echocardiographic parameters of left ventricular mass indexed to body surface area (LVMI), interventricular septal thickness at end diastole (IVSd), left atrial diameter at end systole (LAs) and left ventricular ejection fraction (LVEF) were collected. Subsequent follow-up consisted in clinical, biochemical and ultrasound evaluations performed every six months in our clinic. During the five years considered, the degree of TSH suppression was assessed dividing the study population in three subgroups: those with no suppression (S0, TSH ≥0.5 mU/l), moderate suppression (S1, 0.1 mU/l <TSH <0.5 mU/l) and severe suppression (S2, TSH < 0.1 mU/l). Lastly, new cardiovascular events or cardiovascular deaths and the initiation of anti-hypertensive, anti-arrhythmic, anti-platelets or lipid-lowering therapies were recorded. Thyroid neoplasm stage was assigned after a reclassification of the histologic report according to the AJCC/TNM classification, 8th edition, approved since January 1st, 2018 (84). Biochemical persistent diseases (defined as Tg permanently above 1 ng/mL after primary treatments) or recurrent diseases (morphological or biochemical) were also recorded.

- Biochemical blood tests

Serum thyroglobulin was assayed through immuno-chemiluminescence (Roche Diagnostics, Mannheim, Germany). Functional sensitivity of the method was ≤0.5 µg/l. TSH and fT4 were measured by mean of a ultrasensitive immuno-

chemiluminescence methods (Roche Diagnostics). Normality ranges were 0.3-4.2 mIU/l for TSH, 15.4-28.3 pmol/l for fT4. Anti-thyroglobulin antibodies were determined through commercial assays (DiaSorin, Saluggia, Italia).

Automated Roche Modular Analytics E170 were used for serum creatinine (normality range 0.51-0.95 mg/dl), glycemia (65-110 mg/dl), total cholesterol (130-200 mg/dl), HDL-cholesterol (39-60 mg/dl) and triglycerides (40-170 mg/dl) dosage. LDL-cholesterol was calculated by mean of Friedenwald formula (85). Glycosylated haemoglobin (HbA1c) was dosed by mean of high-performance liquid chromatography with TSK gel G7 Variant Hiscolumn (Tosoh Co. Tokyo, Japan), and results were reported in percentage with normality range 4.3–5.8%. Insulin was determined through micro-particle immunoassay (Abbot, Abbot Park, IL, USA): normality range for our laboratory was 2.0–25.0 mU/l.

- Echocardiographic exams

Transthoracic echocardiography was performed by means of a Vivid E80 ultrasound machine (GE Healthcare) equipped with a Phased Array probe set at 3.5 mHz. Standard images were obtained with the patient in the lateral decubitus position. LV end-diastolic diameter (LVEDD), posterior wall thickness at end diastole (PWd) and LAs were measured in the parasternal long axis view. LVMI was calculated through the following formula: LV Mass (g)=0.8{1.04 [(LVEDD+IVSd+PWd)3–(LVEDD)3]} +0.6 using a dedicated online software (www.csecho.ca).

- Statistical analysis

Chi-squared test was used to evaluate the association among non-quantitative or semi-quantitative variables. Quantitative data were correlated by mean of Spearman rank correlation. Multiple regression test was used for multivariate analysis, considering all variables which had resulted associated at the linear correlation tests. Correlation between non-quantitative and quantitative variables was assessed through logistic regression and cut-off values for the best sensitivity and specificity calculated by mean of ROC curves. The entity of the variation of each parameter between V1 and V2 was evaluated through Wilcoxon test. The distribution of the variables depending on TSH suppression class was studied through ANOVA.

Kolmogorov-Smirnov test was used to assess data normality. They are reported in the text as “median, range” if nonparametric, as “mean ± standard deviation” if parametric. Statistical analyses were carried out by mean of MedCalc Portable Launcher software, version 2.2.0.0; the same program was used to create all figures and graphs. Data collection and subsequent analysis were performed in compliance with the Helsinki Declaration, 1964.

Results

- Study population

One-hundred-eight patients were enrolled, the mean age at the time of surgery was 52.7 ±14.7. Out of the 108 patients enrolled, eleven (10.1%) had had a previous CV event in their personal history, 35 (32.4%) in familiar anamnesis. Nineteen (17.6%) were active smokers at the time of the first visit, and 13 (12.0%) had stopped smoking since at least one year before. Seven patients (6.5%) had a diagnosis of diabetes mellitus, 10 (9.3%) were hyperlipidaemic. At the first examination, 36 (33.3%) were in treatment with antihypertensive drugs (ACE inhibitors, angiotensin-receptor blockers, beta-blockers, calcium antagonists or diuretics), 12 (11.1%) with lipid-lowering drugs (statins, k-monacolin), 13 (12.0%) with anti-platelets drugs and 12 (11.1%) with estro-progestin therapy.

- Oncological condition

The most represented histology was PTC (88 patients, out of which 80 classical variant and 8 a follicular variant, FvPTC), 4 FTC, in one patient both PTC and FTC were found. Fifteen (13.9%) had a diagnosis of thyroid adenoma. Seventy-seven patients had a stage I, 16 a stage II disease. Seventy-seven patients had been treated with radioiodine therapy (RAI), out of which 53 in stage I, 14 in stage II. A significant association was found between histological type and both RAI delivery ($p<0.001$) and RAI dosage ($p=0.007$). A summary of the main population characteristics is reported in Table 4.

- V1: relations among thyroid function tests, echocardiographic and metabolic parameters

At the first examination, administered LT4 dosage, besides the relations with TSH (p=0.002) and fT4 (p<0.001), proved a negative correlation with age (p=0.007), BMI (p<0.001), total cholesterol levels (p=0.045), LDL (p=0.048) and mean blood pressure (p=0.001). It was also positively related to IVSd (p=0.042) and LAs (p=0.005). Only this last association and the one with BMI, however, remained significant at the multivariate analysis (p=0.033 e p=0.005, respectively).

Total subjects	108
Age (years)	52,7±14,7
Menopause (y/n)	63/45
Active smokers (y/n)	19/89
Diabetes mellitus (y/n)	7/101
Dyslipidaemia (y/n)	10/98
Previous cv event (y/n)	11/97
Familiarity for heart disease (y/n)	35/73
Anti-hypertensive drug (y/n)	36/72
Lipid-lowering drugs (y/n)	12/96
Anti-platelets drugs (y/n)	13/95
Estro-progestinic drugs (y/n)	12/96
Histology (PTC / FVPTC / FTC / PTC+FTC / FA)	80 / 8 / 4 / 1 / 15
Stage (i / ii)	77/16
Rai (y/n)	77/31
Estro-progestinic drugs (y/n)	12/96

Table 4. Summary of study population's main demographic and clinical characteristics.

LVMI proved associated with age (p=0.005) and LAs (p=0.001). IVSd was correlated positively with BMI (p=0.011), LAs (p=0.012) and age (p<0.001) and negatively with fT4 (p=0.040) and LT4 (p=0.042). LAs, furthermore, was positively related to age (p=0.015).

None of the considered factors correlated with LVEF, and no significant association was found with the initiation of anti-arrhythmic, anti-hypertensive, lipidlowering or anti-platelet therapy. At multivariate analysis, the only significant correlations were between LVMI and age and between LAs and LT4.

- Recurrent and persistent disease

The percentage of PRD (morphological or biochemical) was 6.5%. It was associated with histological type (p=0.007), and with an administered RAI dosage superior to 110 mCi (sensitivity 100%, specificity 100%, p<0.001). Tg levels at V1 correlated with the risk of recurrence (p=0.024), although the low sensitivity and specificity at ROC analysis made impossible to define a useful predictive cut-off (cut-off >0.29, sensitivity 100%, specificity 42%, p=0.087).

- Incidence of cardiovascular events.

Eight cardiovascular events were recorded (7.4%) during the study period, 3 of which were arrhythmic (one atrial tachycardia treated by flecainide, a new onset AF and a AF recurrence), and 5 ischaemic (2 acute myocardial infarction, 2 transient ischaemic attacks and one death due to cardiovascular arrest). We found as predictive elements of total CV and ischaemic events, respectively, the presence of a previous event in personal anamnesis (p=0.001 and p=0.003), the diagnosis of diabetes mellitus (p=0.049 and p=0.012), the use of lipid-lowering (p=0.002 and p=0.004) and anti-platelets drugs (p=0.027 and p=0.007). A significant important association was also proven with age (p=0.032 and p=0.005) (Figure 8). TSH value at V1 was higher in patients who would develop an ischaemic event (cut-off >0.76 mU/l, sensitivity 100%, specificity 60.2%, p<0.001). In those patients, conversely, administered LT4 dosage was lower LT4 (cut-off ≤1.73 µg/kg/day, sensitivity 100%, specificity 46.9%, p=0.040). Among echocardiographic parameters, only a IVSd > 11 mm proved associated with ischaemic events (sensitivity 66.6%, specificity 91.1%, p<0.001). As regards the metabolic profile, a BMI > 26 kg/m2 and triglycerides > 135 mg/dl showed the same association (sensitivity 100%, specificity 55.1%, p<0.001 and sensitivity 80%, specificity 77.2%, p<0.001, respectively). Out of 8 cardiovascular events, 3 were recorded in the S0 group (2 acute myocardial infarction and a TIA), all the others in the group with severe suppression, S2. TSH suppression class was, therefore, statistically associated with the incidence of arrhythmic events (p=0.035), although with a very low specificity and positive predictive value (VPN 100%, VPP 6.2%, sensitivity 100%, specificity 52.9%, p<0.001). Limiting this last analysis to those subjects who had not a previous cardiovascular event in their anamnesis, we found

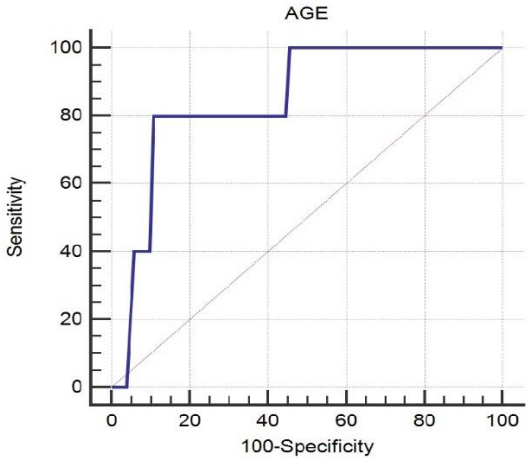
that a TSH-suppression ≤ 0,1 mU/l was associated also with cardiovascular events in toto (NPV 100%, PPV 15.2%, sensitivity 100%, specificity 55.6%, p<0.001). On the other hand, TSH-suppression class was not statistically associated with the initiation of anti-arrhythmic drugs (p=0.656), anti-hypertensive (p=0.582), lipid-lowering (p=0.902) or anti-platelets drugs (p=0.543)

No statistical difference was found between cancer patients and those with a benign pathology report in the incidence of total (p=0.447), ischaemic (p=0.663) and arrhythmic (p=0.906) CV events. LVMI, LVEF, IVSd and LAs variations from V1 to V2 were not different between the two subgroups, either (p=0.308, p=0.915, p=0.446 and p=0.424, respectively).

- Parameters variation between V1 and V2 and the incidence of cardiovascular events

Out of all the variables considered, the only ones that showed a significant difference between the first and the second examination were TSH, fT4 and LT4, which decreased (0.22 vs 0.51 mU/l, p<0.001; 15.3 vs 16.5 pg/ml, p=0.006 and 1.61 vs 1.68 µg/kg/die, p=0.017, respectively), while Tg, TgAb and BMI increased (0.37 vs 0.1 ng/mL, p=0.006; 33 vs 21 U/ml, p<0.001, 26.9 vs 25.4 kg/m2, p=0.014, respectively). At the ROC curve analysis, a significant association was found between the incidence of ischaemic events and TSH ratio (V2/V1) (cut-off ≤ 0.13 mU/l, sensitivity 80%, specificity 75%, p=0.001), LT4 ratio >0.98 (sensitivity 100%, specificity 58.9%, p<0.001) and fT4 ratio ≥1.06 (sensitivity 100%, specificity 73.4%, p<0.001), while an fT4 ratio ≤0.94 was associated with arrhythmic events (sensitivity 100%, specificity 53 %, p=0.035). Among echocardiographic parameters, LVMI ratio between V2 and V1 was associated with total cardiovascular events (cut-off >1.089, sensitivity 100%, specificity 77%, p=0.001). At ANOVA analysis, LVMI ratio proved different depending on TSH-suppression class (p=0.012, Figure 9). None of the other parameters' variation showed association with TSH-suppression class.

A)



B)

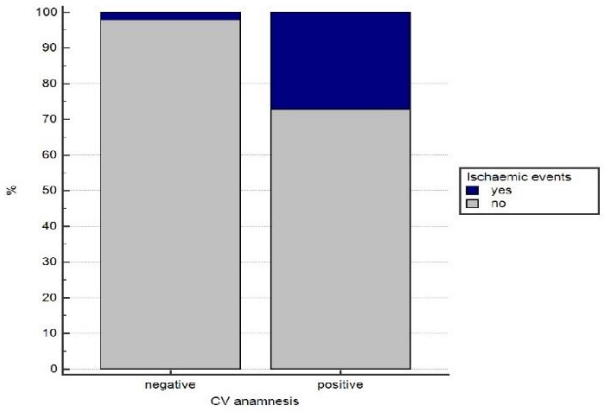


Figure 8. Study of ischaemic events' predictive factors.

A) ROC curve representing the association between age and the incidence of ischaemic events (cut-off >67 years, sensitivity 80%, specificity 89%, p<0.001)

B) percentage of ischaemic events among patients with positive or negative CV anamnesis: a prevalence of events was seen in the former (p=0.003).

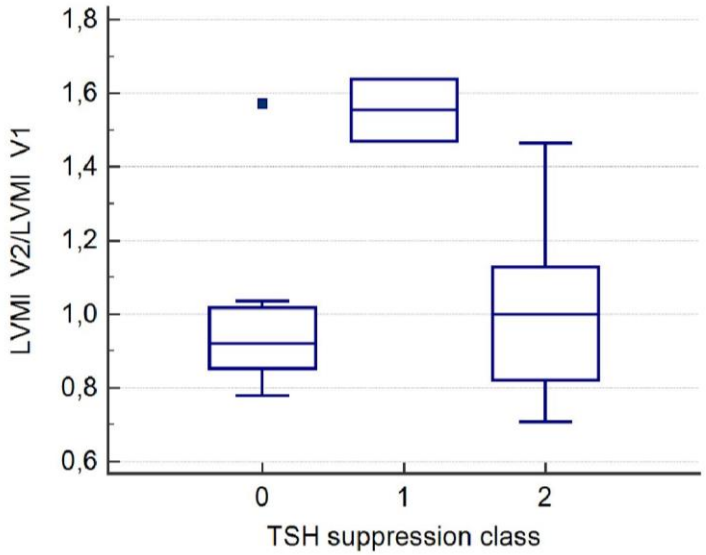


Figure 9. Stratification of LVMI V2/V1 ratio depending on TSH-suppression class during the study period. The largest increase was reported in class 1 (p=0.012).

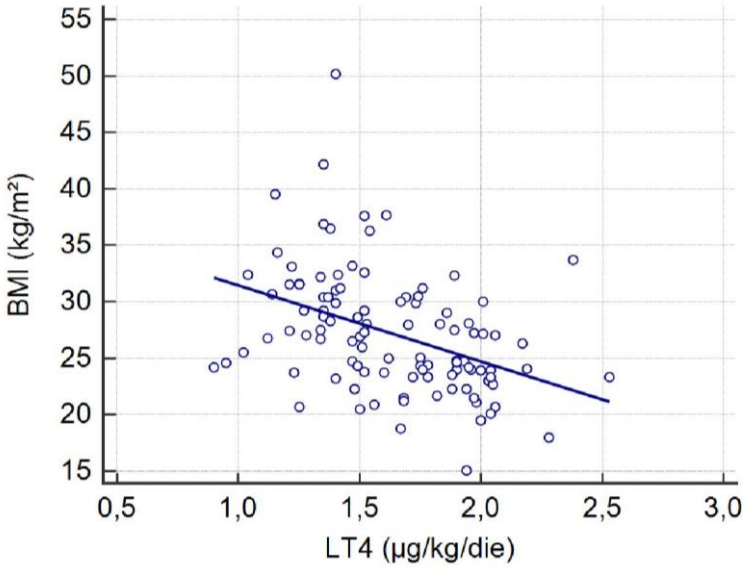


Figure 10. Linear correlation between LT4 dosage (µg pro kilo) and BMI (kg/m2) in V2 (p<0,001)

- V2: relations among thyroid function tests, echocardiographic parameters and metabolic profile

Among all the variables considered in V2, TSH levels were correlated not only with fT4 (p<0.001), but also with HOMA index (p=0.043) and negatively with Tg (p=0.040)

and TgAb (p=0.008) levels. FT4 was correlated with HOMA index (p=0.004), while LT4 dosage was negatively associated with BMI (p<0.001, Fig. 10), HbA1c (p<0.001) and triglycerides (p=0.019). A negative association was also found with LAs (p=0.002) and IVSd (p=0.035), a positive one with HDL (p=0.028).

Discussion

Patients in follow up after DTC show an increased risk of cardiovascular events compared to the population with same demographic characteristics but with no history of such disease (86-88). In the extensive analysis performed by Pajamaki et al. in 2017, a significant prevalence of cardiovascular disease was proven in cancer patients, both for the events in toto and for arrhythmic events. The different incidence between cases and controls was much more evident in the younger subgroups of population (<40, 40-60 yrs), that is those in which the "basal" cardiovascular risk was lower. The risk was also associated with the degree of TSH suppression and with RAI treatment, although it tended to increase again for TSH value above 0.5 mU/l (77). Similarly, in our study population the incidence of ischaemic events proved higher in unsuppressed TSH class than in the moderate-suppression one. This phenomenon is not surprising since in both cases the study was retrospective, and we also demonstrated the association between a positive cardiovascular anamnesis and the incidence of a new event: patients in secondary prevention, indeed, or those who presented an independently increased risk at the basal examination, did not receive high doses of LT4, also considering the low stage of the oncological disease.

The prediction of CV events in thyroid cancer patients with a negative cardiovascular anamnesis appears more difficult. A recent study conducted by Toulis et al., on the other hand, proved a higher mortality rate and a higher rate of cerebrovascular events even in those subjects (86). This study, even without any data about the degree of TSH suppression, seems consistent with the correlation that we observed between TSH suppression class and the incidence of arrhythmic events, even more significant if restricted to those subjects with no previous events. In an Israeli study performed on DTC patients compared to a control population matched for age and

sex, a significant difference was demonstrated also in the incidence of atherosclerotic events (87). Investigating which clinical parameters could predict cardiovascular events, Park et al. defined the 'classical' risk factors (age, sex, obesity, the presence of a previous event) as the most important predictive elements, and these data are consistent with the findings of our study. On the other hand, they also reported an association of cardiovascular outcomes with the stage of the disease, the presence of metastasis and the radioiodine ablation, which is not present in our data. In our study, on the other hand, we intentionally included only those subjects with a low stage of oncological disease and, therefore, a lower risk of recurrence: in these patients oncological treatments can be less aggressive and this allows a greater attention to medium-long term cardiovascular outcomes. A point of interest in the present study, is also the availability of a complete clinical examination of the patients, inclusive of physical parameters, anamnesis, biochemical blood tests and ultrasound assessments: this allowed to evaluate intermediate clinical outcomes besides proper cardiovascular events. Echocardiographic parameters modification, for example, can be considered as a cardiological outcome itself, which could precede and predispose to the event, and which can take less time to occur than the proper event. In this perspective, the five years follow up considered could suffice to assess cardiological consequences of thyroid neoplasm treatments and may allow to prevent the event itself. The prognostic role of echocardiographic parameters, indeed, is well established: LVMI proved highly predictive of CV events and death; IVSd and LAs correlate with the incidence of ischaemic and general CV events (89-92). With specific regard to patients treated for thyroid neoplasms, Wang et al. analysed clinical and echocardiographic parameters in 105 patients treated for DTC and classified according to TSH-suppression and the duration of such condition: in that study they proved significantly different LVEF, time to peak filling from end-systole and heart rate depending on both those elements (93) In addition, an increased left ventricular mass was proved in TSH-suppressed DTC patients (94).

Also in the literature review performed by Parker et al. an increased mortality, significant differences in terms of IVSd and an increased ventricular mass were described. Only one of those studies underlined a prevalent diastolic dysfunction in cases compared to the controls (95). This last, however, proved altered in other

studies, although performed on smaller cohorts of patients: Taillard et al. documented its occurrence even in the early phase of LT4 therapy, and such condition appears often spontaneously reversible once the normal TSH levels are reset (96,97). The finding of a negative correlation between LT4 dosage and IVSd is interesting and appears in contrast with data previously reported about thyroid axis and cardiac hypertrophy. Both these parameters, on the other hand, strictly correlate with both age and BMI: after statistical correction for those variables, their correlation was lost. Conversely, negative correlation between LAs and LT4 dosage persists even at the multivariate analysis, while it loses its significance in V2. A possible interpretation of this phenomenon could be the consideration of the negative effect of hypothyroidism, in this case iatrogenic, on cardiac function, which is reported even at the early stages of subclinical disease (98). A matter of discussion could be the larger increase, between V1 and V2, of LVMI in S1 patients than in S2 ones (Figure 2). Surely, we have to take into account that TSH-suppression is not the only determinant of LVMI variation, which is the result of many different processes. Furthermore, the low numerosity and the large variability in this subgroup contribute to this statistical finding. On the other hand, the incidence of ischaemic events during the study period proved associated to a higher increase of LVMI, and this confirms the prognostic importance of such parameter and its potential role in the follow-up of this kind of patients. The effect of LT4 therapy on metabolic profile is debated (99-106). In our findings, although negative correlations were found between LT4 dosage and total cholesterol, LDL and BMI, at the multivariate analysis only this last remains significant. In the study published by our group in 2008, lower HDL levels were found in cancer patients than in benign thyroid neoplasm group (99). Duntas and Brenta in 2012 reported lower LDL in hyperthyroid patients, Lee et al. also demonstrated a significant reduction of cholesterol levels in the two years after thyroidectomy (100,101). No impairment was found by Heemstra et al., instead, in glycaemic profile and BMI between TSH-suppressed subjects and the controls, and Parker et al. did not prove any difference in glycated haemoglobin and leptin levels between DTC patients and controls (102,103). On the other hand, some studies report a higher insulin resistance in hyperthyroid patients (104). The relation between thyroid function and body weight is instead well defined: the increase of basal metabolism, resting energy

expenditure and thermogenesis induced by thyroid hormones promote the weight loss (104-106). In our study, BMI was found to be negatively related to fT4 and LT4 in V1, and in V2 the relation with LT4 persisted even at the multivariate analysis. No relation between TSH-suppression class and BMI variation was demonstrated, but this last proved negatively related to fT4 and LT4 variations, in line with the findings in V1. On the other hand, a possible explanation of this correlation can be the lower LT4 requirement pro kilo in overweight or obese subjects, due to the lower percentage of lean body mass in these patients. For this reason, Ojomo et al. suggest that BMI should be taken into account, rather than the simple body weight, in defining LT4 therapy dosage (107). With regards to the persistence or recurrence of the disease, a selection bias could be speculated, since only patients affected by low stage of oncological disease were included. This selection was intentionally adopted in order to focus on a specific subgroup of patients in which oncological mortality is low. This kind of patients, furthermore, represent the majority of thyroid cancer patients. In these subjects, with a long disease related life expectancy, cardiovascular risk comes out as one of the major concerns. Made these premises, the absence of oncological disease related deaths is in line with literature data according to AJCC VIII for stage I and stage II diseases (108). Lastly, a matter of discussion could be the absence of a control group in the present study, that is because we focused on the effects of medium/long-term treatments, especially TSH suppression, regardless the histological report at diagnosis. Patients with less aggressive cancers and benign thyroid neoplasms were then considered together as the “less intensive therapy” subgroup, and compared with the others, more intensively treated. Nevertheless, for a major completeness of the analysis, we also performed a comparison between cancer patients and those with a benign neoplasm report at diagnosis assessing CV events incidence and LVMI, LVEF, IVSd and LAs variation between V1 and V2, and no significant differences were found.

In conclusion, in DTC patients, and particularly in low risk cases, cardiovascular morbidity and mortality exceed the ones due to their oncological condition. Cardiovascular risk, in these subjects, proved higher than in general population with same demographic characteristics and no history of thyroid neoplasm. This is due to

different and complex pathophysiological mechanism, mostly related to supra-physiological doses of LT4 therapy. A cardiovascular risk evaluation seems, therefore, necessary both at diagnosis and during the follow-up, and it could be scheduled through a complete baseline assessment. Particularly, patients presenting a previous cardiovascular event, diabetes mellitus or dyslipidaemia confirmed an increased ischaemic risk and deserve a stricter follow-up, independently from oncological treatments. On the other hand, TSH-suppressed patients show a higher risk of arrhythmic events. In this regards, echocardiographic parameters such as left ventricular mass index and inter ventricular wall thickness seems useful, easily manageable, and predictable of future events, and this make them advisable for baseline and follow-up examinations. TSH suppression could also play an important role in modifying some of these parameters, possibly predisposing to future events or just altering heart dynamic. Beside avoiding recurrent or persistent disease, we point out the role of the endocrinologist in preventing cardiovascular complications through a cautious and multidisciplinary follow-up.

Multidisciplinarity in the management of the advanced disease

In the panorama of the advanced differentiated or poorly differentiated thyroid cancer, multidisciplinarity is essential since the definition of advanced disease, which basically requires a comprehensive approach, considering the histopathological and above all the radiological and nuclear medicine assessment (4,5,24).

Subsequently, the decision concerning the clinical management of this condition is often a complex issue, which should be based on many different aspects of the disease itself, from the tumour burden to its evolution in time, as well as the possible impairment of other organs or vital functions, but also take into account patients' needs and preferences; furthermore, the efficacy of therapies always has to be balanced with their safety profile (109-111).

Surgery remains, when feasible, the first option even in these patients (5,110), and local therapies should always be considered when a limited number of foci is present (112,113).

The choice of a systemic therapy is limited to the cases of progressive radioiodine refractory disease, especially when a further progression might harm vital organs or systems (109). Thyrosin-kinases inhibitors (TKIs) are basically the only kind of drugs approved in this setting: particularly, lenvatinib and sorafenib showed a significant prolongation of the progression free survival (PFS) in the respective phase III studies (114,115). Nevertheless, their safety profile often requires a careful management and a prompt medical intervention at the onset of side-effects; a dose reduction is necessary in many of these patients as well, while the necessity of a permanent drug discontinuation is rare (116).

In the context of this evolving scenario and the possibility of new treatments of a disease which was hardly manageable until few years ago, another matter of debate is the way of monitoring the disease progression: computed tomography (CT) represents the gold standard in this regard, while Tg is not often a reliable marker when cellular differentiation is lost (113).

In this field, our research was aimed at evaluating the role of positron-emission tomography (PET) during the follow up of these patients and the insights which can

be provided by this technique concerning the prognosis and the response to treatments.

2-[^{18}F]FDG PET in the Management of Radioiodine Refractory Differentiated Thyroid Cancer in the Era of Thyrosin-Kinases Inhibitors: A Real-Life Retrospective Study

Introduction

Advanced or metastatic radioiodine-refractory thyroid cancer (RR-TC) is a rare entity, and its definition is still evolving (24). To date, RR-TC is defined as a follicular-cell derived thyroid cancer no longer able to trap radioiodine or showing preserved radioiodine avidity only in some sites, or even displaying progression despite ^{131}I treatments (24,32). Its clinical management is, therefore, challenging, resulting in a poor prognosis (32,5,117,118]. The availability of tyrosine-kinases inhibitors (TKIs), in particular lenvatinib and sorafenib, radically changed the therapeutic approach to RR-TC, achieving in many cases the reduction of tumour burden and significantly improving the progression free survival (PFS) (114, 115,119). On the other hand, the efficacy of TKIs must be balanced with their side effects, which could lead to dose reductions or even temporary or permanent drug discontinuation in a significant number of patients (120,121).

On these basis, effective follow-up strategies and imaging techniques are needed to assess progression, response rate and duration, and to better define patients' management. Computed tomography (CT) scan represents the gold standard imaging technique both at the time of therapy initiation and during the follow-up [2,3,4,5], and tumour shrinkage assessed through RECIST 1.1 criteria is considered to measure the response to TKIs (122).

On the other hand, thyroglobulin (Tg) concentration and doubling time (Tg-DT) proved to have a prognostic value in RR-TC (123,124), and it is presently used as a complementary tool in monitoring drug response profile. Nevertheless, in some

cases, Tg could lose its reliability as a marker of disease, due to the possibility of cell dedifferentiation.

Of note, Tg variations are not always consistent with CT scans findings. In particular, after TKIs initiation, the drop of the Tg levels is not always consistent with the radiological response, and conversely a CT documented progressive disease might also not be associated with the raising Tg levels (125).

In this scenario, [^{18}F]-fluorodeoxyglucose positron emission tomography (2-[^{18}F]FDG-PET)/CT) could improve prognostic stratification of patients with RR-DTC, providing insights into tumour glucose consumption and aggressiveness (126). In the clinical practice, the report of 2-[^{18}F]FDG-PET is most often based on a visual/qualitative assessment and further supported by the use of SUVmax as a readily available semi-quantitative measure (126). However, other 2-[^{18}F]FDG-PET-derived parameters have been proposed to better capture the extent (metabolic volume of the tumour, MTV) and intensity (total lesion glycolysis, TLG) of the metabolically active disease burden. These variables have shown a potential additional value in several oncological diseases, even in those which are not characterized by high metabolic activity at disease onset, including DTCs (127). Ahmaddy et al. even suggested that 2-[^{18}F]FDG-PET/CT might outweigh the CT scan in the evaluation of the treatment response in patients with advanced RR-DTC undergoing TKI therapy. These authors claimed 2-[^{18}F]FDG-PET may play a role in the early assessment of the response to the treatment, identifying those patients who will most likely benefit from it (128). Similar findings were reported by Valerio et al., showing basal 2-[^{18}F]FDG-PET to be predictive of the response to TKIs and correlated with the OS (129).

Given these premises, we aimed to retrospectively evaluate the predictive value of a serial assessment of 2-[^{18}F]FDG-PET/CT parameters in a cohort of RR-TC patients, and their correlation with Tg and thyroid function tests.

Materials and Methods

All 2-[^{18}F]FDG-PET/CT performed in RR-TC patients between 2009 and 2019 in IRCCS Policlinico San Martino Hospital were evaluated. At the time of each examination, thyroid axis as well as Tg values were recorded, and the ongoing therapies were

reported, with specific regard to the levothyroxine (LT4) dosage and TKIs administration. Patients' clinical history and previous cancer treatments were also recorded, and data concerning the overall survival after the exam were subsequently registered.

All the patients signed a written informed consent before each examination. Data collection, as well as the subsequent analysis, were performed in compliance with the 1964 Helsinki Declaration. Regional Independent Ethical Committee (IRB) approved the study.

- 2-[^{18}F]FDG-PET/CT Acquisition

2-[^{18}F]FDG-PET/CT was performed according to the international guidelines (127) using a 16-slices PET/CT hybrid system (Biograph 16, Siemens Medical Solutions, Knoxville, TN, USA). Briefly, patients fasted overnight prior to the intravenous administration of 300–400 MBq of FDG, which was performed in a quiet room, with the patient lying in a recumbent position and instructed not to move. Blood glucose was measured before tracer injection, as to ensure blood glucose levels <160 mg/dL. To minimize artifacts caused by the urinary tract, patients were asked to drink 500 mL of water 1 h prior to image acquisition and to empty the bladder just before the acquisition start. Imaging started 60 ± 15 min after intravenous tracer administration. The technical parameters of the 16-detector row, helical CT scanner included a gantry rotation speed of 0.5 s and table speed of 24 mm per gantry rotation. The PET component of the combined imaging system had an axial view of 16.2 cm per bed position, with an interslice spacing of 3.75 mm. The trans-axial field of view and pixel size of the reconstructed PET images were 58.5 cm and 4.57 mm, respectively, with a matrix size of 128 × 128. Unenhanced low-dose CT was performed at 140 kV and 40 mA for attenuation correction of emissive data and anatomical localization of PET dataset. An emissive scan was performed in 3D mode, shortly after CT acquisition, with a 3-min acquisition per bed position. PET sinograms were reconstructed by means of ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (three iterations, eight subsets). A scan was performed starting from the orbital plane on to the mid-thigh, except for the cases where the clinical history demanded a whole body, vertex-to-toes scan.

- Image Analysis

2-[^{18}F]FDG-PET/CT images were interpreted in consensus by two expert nuclear medicine physicians blinded to biochemical and clinical results, as well as to the results of other imaging procedures. From the attenuation-corrected FDG PET images, the maximum standardized uptake value (SUVmax) of the hottest lesion was obtained in the transaxial view. Further, a volume of interest was drawn using an SUV-based automated contouring program (Syngo Siemens workstation, Siemens Medical Solutions, Princeton, NJ, USA) with a volumetric region of interest based on a 3D isocontour at 41% of the maximum pixel value (SUVmax), as previously recommended [16]. Total Metabolic Tumor Volume (MTV) was obtained by the sum of MTV values of all patients' lesions. Total Lesion Glycolysis (TLG) was computed as the sum of TLG of every lesion for each patient (thus corresponding for each patient, to the sum of the VOI average/mean SUV value for each lesion multiplied by corresponding MTV).

- Laboratory Tests

Serum Tg was assayed through immuno-chemiluminescence (Roche Diagnostics, Mannheim, Germany). Analytical sensitivity of the method was 0.04 ng/mL. TSH and fT4 were measured by means of ultrasensitive immuno-chemiluminescence methods (Roche Diagnostics). Normality ranges were 0.3–4.2 mIU/L for TSH and 9.3–17.0 pg/mL for fT4.

- Statistical Analysis

Statistical analysis was carried out by means of MedCalc Portable Launcher software, version 2.2.0.0; the same program was used to create all figures and graphs. Parametric distribution of the variables was assessed through the Kolmogorov–Smirnov test, and data were reported as mean ± standard deviation (95% CI of the mean) if parametric, or median (range, 95% CI of the median) if non-parametric.

The association among non-quantitative data were assessed through the Chi-squared test. Cox proportional hazard regression analysis was used to evaluate the association between each variable and the OS, and Kaplan–Meier curves to assess the difference

of OS among groups. The correlation among quantitative variables was assessed by means of Spearman rank correlation test, while linear regression test was used to investigate the relationship between thyroid function tests, LT4, Tg, and 2-[^{18}F]FDG-PET/CT parameters. As regards the TSH, it was considered as a continuous rather than a dicotomic variable (suppressed/unsuppressed); for this reason, patients with unsuppressed TSH were included in the analysis together with those who had it suppressed. In order to assess 2-[^{18}F]FDG-PET/CT parameters variation, the ratio between the values registered at the subsequent and the previous scan was considered; this parameter could not be assessed for patients who had a single 2-[^{18}F]FDG-PET/CT scan. Mann–Whitney test was used to compare 2-[^{18}F]FDG-PET/CT parameters variation in the periods in which TKI was administered to those in which no therapy was given. Lastly, sensitivity and specificity in predicting 1-year OS were calculated by means of ROC curves. p values < 0.05 were considered as statistically significant.

Results

Overall, out of 684 patients followed between 2009 and 2019, 46 2-[^{18}F]FDG-PET/CT scans were collected from 14 patients. Out of them, five were females, the mean age at diagnosis was 65.0 (±12.2, 95% CI 57.9 to 72.0), while at the time of the first scan it was 69.7 (±10.6, 95% CI 63.5 to 75.8). Surgery was performed in all but one patient: a total thyroidectomy in the majority of cases (64.3%), combined with central neck compartment lymphadenectomy in 7.1% or central and lateral neck compartment lymphadenectomy in 21.4%. In one elderly patient, surgery was not performed due to the local extension of the disease and the clinical status; therefore, only external radiotherapy was delivered.

The most prevalent histology was follicular thyroid cancer (eight patients), while a papillary carcinoma was reported in four patients, and poorly differentiated thyroid cancer and the combination of papillary and Hurtle cell thyroid cancer in one patient each.

Radioiodine therapy was performed in all surgically-treated patients, with an average cumulative dose of 386.4 mCi (±292.4, 95% CI 200.6 to 572.2 mCi).

- First 2-[^{18}F]FDG-PET Scan Assessment

At the time of the first scan, the median Tg was 1519.5 ng/mL (0.04 to 25,454.0, 95% CI 23.9 to 5788.6 ng/mL) and the mean administered LT4 dosage was 903.6 mcg/week (±298.7, 95% CI 731.1 to 1076.0 mcg/week). All but three subjects had suppressed TSH levels (median 0.093 mU/L, 0.005 to 4.700 mU/L, 95% CI 0.014 to 1.047 mU/L), and the mean fT4 was 17.46 pg/mL (±3.99, 95% CI 15.16 to 19.77 pg/mL).

The first 2-[^{18}F]FDG-PET was performed after a median of 29 months (range 3–416 months, 95% CI 5.13–104.37 months) from the diagnosis and LT4 therapy initiation. The distribution of the 2-[^{18}F]FDG-PET/CT exams among the study population is described in Table 5. As regards the initial assessment, median MTV at the first 2-[^{18}F]FDG-PET/CT scan was 18.90 cm3 (range 0.71–1197.3 cm3; 95% CI 3.52 to 58.87 cm3), while median TLG was 94.74 (5.33–10,632.20; 95% CI 23.71 to 644.75 SUV mean × cm3).

Patients	Age	Sex	Histology	TKI	TSH * (mU/L)	fT4 ** (pg/mL)	Tg ** (ng/mL)	LT4 (µg/Week)	MTV * (cm^3)	TLG*	OS (Months)	N° FDG-PET
1	63	F	FTC	-	0.89	14.2	2283.0	1050	1.56	6.88	35	6
2	77	M	PTC	L	0.03	22.2	1.1	900	126.67	700.48	53	4
3	79	M	FTC	-	0.01	22.4	20,583.2	1100	31.13	377.92	25	2
4	67	M	FTC	S	0.15	18.7	26.3	1050	25.00	314.17	39	5
5	71	M	PTC	S	0.06	18.8	2237.1	1125	3.27	-	-	4
6	70	F	FTC	L	0.02	22.1	2014.5	850	0.71	5.34	-	1
7	43	M	FTC	S	0.01	21.0	698.9	1400	7.25	45.96	41	5
8	76	M	PTC	S	0.17	15.1	532.4	1050	3.55	27.16	39	5
9	81	M	HC+PTC	S	2.44	12.3	1025.2	225	50.98	-	15	2
10	68	F	FTC	S	0.13	19.5	8853.3	650	4.04	22.99	14	2
11	53	M	FTC	-	4.70	10.5	5431.7	1050	1197.32	10,632.20	7	3
12	77	F	FTC	S	0.01	17.7	25,454.2	825	238.88	1748.60	8	1
13	76	F	PDTC	-	2.41	12.3	0.1	450	27.44	143.51	18	2
14	75	M	PTC	-	0.01	17.8	3.8	925	12.80	44.42	-	4

Table 5. Study population; clinical characteristics at baseline 2-[^{18}F]FDG-PET evaluation.

*(TKIs: tyrosine-kinases inhibitors; Tg: thyroglobulin; LT4: administered levothyroxine dosage per week; MTV: metabolic tumour volume; TLG: total lesion glycolysis; OS: overall survival); * approximated to two decimals; ** approximated to one decimal.*

- TKI Treatment

Lenvatinib was administered to 11 patients during the study period; among them, 8 had had a previous line of systemic therapy with sorafenib. At the time of the data collection, 11 patients had died due to thyroid cancer progression, 2 were still in treatment with lenvatinib, and 1 had withdrawn lenvatinib therapy due to adverse events. Overall, three patients received sorafenib as the only systemic therapy, three had only lenvatinib, and eight received both the drugs.

A representation of TKI administration schedule with respect to the study period is provided in Table 6.

	Before the Study Period	At the Time of the First ^{18}F-FDG PET Scan	During the Study Period
1	sorafenib	no	lenvatinib
2	sorafenib	lenvatinib	lenvatinib
3	sorafenib	no	lenvatinib
4	sorafenib	sorafenib	lenvatinib
5	sorafenib	sorafenib	lenvatinib
6	lenvatinib	lenvatinib	-
7	sorafenib	sorafenib	lenvatinib
8	sorafenib	sorafenib	lenvatinib
9	sorafenib	sorafenib	lenvatinib
10	sorafenib	sorafenib	no
11	no	no	sorafenib
12	sorafenib	sorafenib	-
13	no	no	lenvatinib
14	no	no	lenvatinib

Table 6. The distribution of TKIs therapies among the study population and with regards to the study period.

- Overall Survival

The median OS from the first 2-[^{18}F]FDG-PET/CT scan was 25 months (range 7–53, CI 95% 12.92 to 39.35 months), while the follow up of the patients who were still alive at the time of data collection was 45, 31, and 44 months, respectively.

No association was found between the OS and histology (p = 0.349), type of surgery (p = 0.586), and administered radioiodine dosage (p=0.545).

Conversely, Cox proportional hazards regression analysis showed a predictive role of TLG (p=0.027) and MTV (p=0.035), performed at baseline, on the OS, while Tg values nearly approached statistical significance (p=0.083). On the other hand, a negative correlation was found between basal Tg values at the first analysis and the OS (p=0.036).

Differently from Tg (p=0.145), TLG and MTV proved predictive of 1-year mortality (sensitivity 60%, specificity 100%, criterion > 817.8, AUC 0.812, p = 0.001; sensitivity 60%, specificity 96%, criterion > 126.7 cm3, p=0.001, AUC 0.815).

The results of Cox regression analysis are listed in Table 7, whereas the sensitivity and specificity of each parameter in predicting 1-year-mortality are reported in Table 8.

	Null Model-2 Log Likelihood	Full Model-2 Log Likelihood	Chi-Squared	DF	Significance Level
MTV	35.58	31.47	4.43	1	$p = 0.035$
TLG	30.78	25.92	4.86	1	$p = 0.027$
TSH	35.58	29.77	5.81	1	$p = 0.016$
fT4	35.58	31.59	3.99	1	$p = 0.046$
Tg	35.58	32.58	2.99	1	$p = 0.083$
RAI dosage	30.78	30.46	0.32	1	$p = 0.545$

Table 7. The results of Cox regression analysis of variables predicting the OS.

	AUC	Significance Level	Youden Index (J)	Associated Criterion	Sensitivity %	Specificity %
MTV	0.815	0.001	0.56	>126.67	60	96
TLG	0.812	0.001	0.60	>817.86	60	100
TSH	0.708	0.133	0.47	>0.47	67	81
fT4	0.763	0.010	0.54	≤17.68	100	54
Tg	0.675	0.145	0.48	>1253.0	75	73
RAI dosage	0.563	0.793	0.37	≤500	100	37

Table 8. The results of ROC curves analysis performed on all variables with respect to 1-year-survival. As regards the associated criterion, values are to be expressed in cm3 for the MTV, mU/L for the TSH, pg/mL for the fT4, ng/mL for the Tg, and mCi for the RAI dosage.

Data from the whole 46 evaluations showed a negative correlation of both TSH and Tg levels with the OS (p = 0.014 and p = 0.019.) A positive correlation was recorded, instead, between the OS and fT4 (p = 0.009, Figure 11).

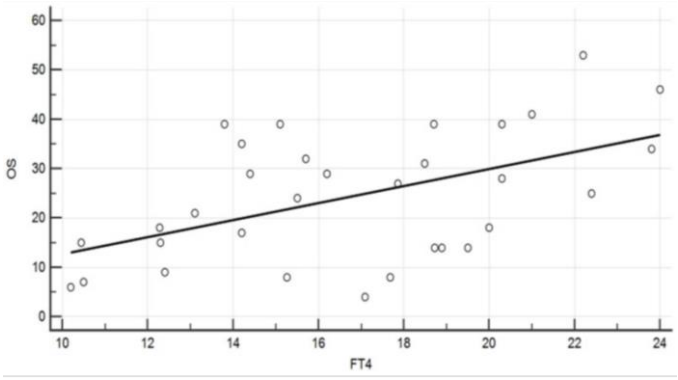


Figure 11. Diagram showing the association between fT4 levels (pg/mL) and the overall survival (months) (Spearman rank correlation, ρ = 0.457, p = 0.009).

An improved overall survival was found in the group of patients who underwent two lines of TKIs compared to those who received only one (p=0.005, Figure 12).

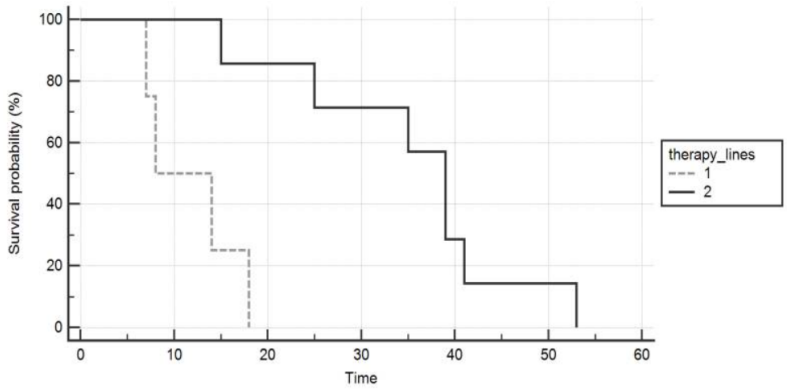


Figure 12. Kaplan–Meier curves comparing the overall survival (months) of patients who were treated with two lines of tyrosine-kinases inhibitors (continuous line) versus those who received only one (dashed line). A significant gain was proved in the formers.

- 2-[^{18}F]FDG-PET/CT Parameters Correlations

As regards 2-[^{18}F]FDG-PET/CT parameters, both TLG and MTV proved a negative correlation with the OS (p=0.015 and p=0.021, respectively).

Linear regression analysis showed an association between MTV values and TSH (R2=0.19, p=0.006) and between MTV and fT4 (R2=0.13, p=0.029). Conversely, Tg was not related to MTV (p=0.869). Also, TLG was associated to TSH and fT4 (R2=0.22, p=0.005 and R2=0.12, p=0.044, respectively).

No correlation was found between Tg and both MTV and TLG (p=0.807 and p=0.467, respectively). However, a significant correlation was found between Tg and MTV variation in time (p=0.011), while not between Tg and TLG variation (p=0.118).

A difference in terms of MTV variation was found between patients in treatment with TKIs and those who were not (median 0.88 vs. 2.73 cm3, p=0.045). Similar findings were recorded for TLG (median 0.65 vs. 4.01, p=0.013) and Tg variations (median 1.24 vs. 2.95, p=0.047) (Figure 13).

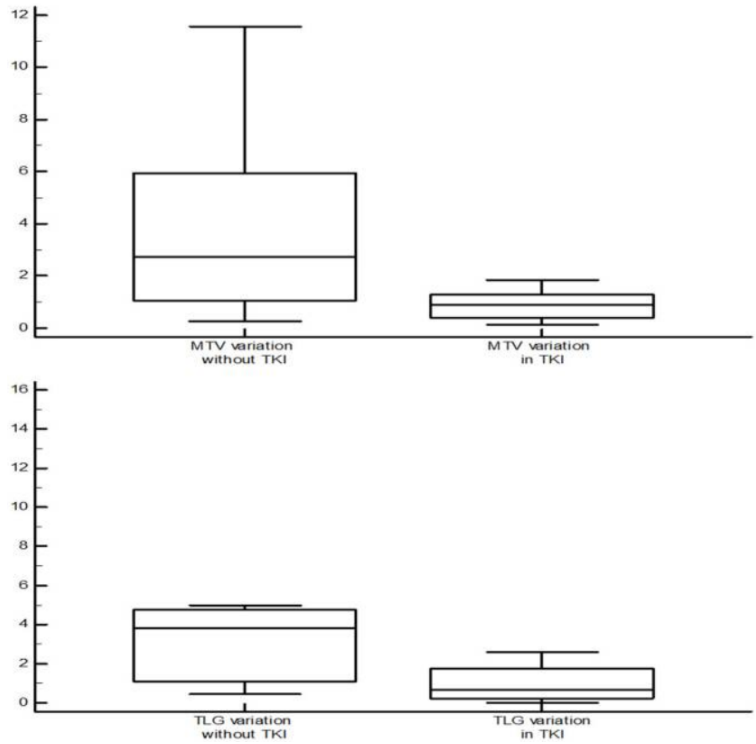


Figure 13. Comparison of MTV and TLG variation (value at the subsequent evaluation/value at the previous evaluation) between the scan performed during tyrosine-kinases inhibitors therapy and those without systemic therapy. In the first group, both MTV and TLG showed a trend of reduction, while in the second one it tended to increase (Mann–Whitney test, median 0.88 vs. 2.73 cm3, p = 0.045, for MTV; median 0.65 vs. 4.01, p = 0.013 for TLG).

Discussion

In our retrospective analysis, we evaluated the role of 2-[^{18}F]FDG-PET/CT in the management of RR-TC patients, in addition to Tg and CT scan assessment, which represent the gold standard tools for the follow-up of these patients (32,5). Interestingly, 2-[^{18}F]FDG-PET/CT seems to provide information about the clinical course of the disease through a first single scan. This may be due to the insights about the cellular biological activity besides the anatomical tumour burden (130). In this perspective, similar findings were obtained by Manohar et al. in their analysis, which included 62 RR-TC patients: MTV and TLG proved related to both the PFS and the OS, as well as Tg and Tg-DT (126).

On the other hand, differently from the abovementioned study, the present one was also aimed at investigating the performance of 2-[^{18}F]FDG-PET/CT during the follow-up, and even in this other setting the association with the OS was maintained.

A further intent of our analysis was to assess the impact on TKIs therapy on 2-[^{18}F]FDG PET/CT parameters. In this regard, our data suggest a completely opposite trend in the evolution of the 2-[^{18}F]FDG-PET/CT parameters when patients were treated with TKIs compared to the periods in which the same patients were not. Particularly, for both MTV and TLG, a trend in reduction seemed to be present in the former (median of the ratios 0.88 and 0.65, respectively), while an increase was recorded in the latter (2.73 and 4.01, respectively), confirming the effect of these drugs in hindering cancer cell biology.

Data recently published by Valerio et al. seems consistent with these findings, showing a metabolic response in most of the patients who started lenvatinib and an improved OS in this group compared to those who did not achieve a response. In that study, on the other hand, a concomitant shrinkage was registered in the tumoral lesions of 22 out of the 24 patients showing a metabolic response, and in 60.6% of patients this was correlated with the biochemical response (129).

Data concerning cancer cell activity and metabolism, indeed, may represent an important tool especially when biochemical and morphological data diverge [125, 131, 132). In most patients, a drop in Tg levels is observed after TKI initiation, but it is not always followed by a tumour size reduction at the CT scan (125,133). On these bases, a multiparametric approach, comprehensive of either morphological, biochemical, or metabolic data, could be advisable in evaluating tumour evolution in time. Moreover, while PET-determined non-responders proved lower PFS and disease-specific survival, only this last parameter resulted in association with the therapeutic failure according to RECIST (128).

Another aspect worth mentioning and which is still a matter of discussion, is the suitability of a further line of TKI after the failure of the first one. Our findings seem to support the use of TKIs in second line, according with the data reported by other authors on this topic (134,135).

A correlation between 2-[^{18}F]FDG-PET/CT parameters and Tg was mentioned by Chai et al. in 2017. These authors found higher stimulated Tg levels to be predictive of the

optimal diagnostic accuracy of the exam (132). Leboulleux et al. in 2009 reported similar findings and highlighted the role of recombinant TSH stimulation in improving diagnostic performance of 2-[^{18}F]FDG-PET/CT (136). On the other hand, data from other studies did not support the correlation between TSH levels and PET findings in RR-TC. In their recent prospective analysis, Almeida LS et al. failed to find a significant difference in SUVmax and in diagnostic accuracy of 2-[^{18}F]FDG-PET/CT performed during TSH stimulation in hormonal withdrawal compared to those in TSH-suppression. However, in this case, the study population was very small, and the correlation between TSH and SUVmax almost reached the statistical significance (p=0.064) (137). Furthermore, the previous meta-analysis published in 2010 by Ma et al. stated the role of TSH stimulation in improving diagnostic performance of 2-[^{18}F]FDG-PET in patients treated for a RR-DTC, with elevated Tg levels and a negative whole-body scintigraphy (WBS) scan (138).

On the other hand, the current evidence in literature suggests that a chronic TSH suppression might delay disease recurrence and improve the OS (5,139), and the hereby highlighted relationship between thyroid function tests and 2-[^{18}F]FDG-PET/CT parameters seems in keeping with that. However, the numerosity of the present sample prevents any clear conclusion on this issue.

Our data failed, instead, in demonstrating an association between Tg levels and 2-[^{18}F]FDG-PET/CT parameters, while a correlation was proved between Tg and MTV variation in time. This could be an important point to support the complementarity of the information provided by these tests. Tg represents, indeed, a prognostic factor in these patients, and in particular a short Tg-DT is correlated with a reduced OS (123,140). Furthermore, as previously mentioned, stimulated Tg levels should be considered in discriminating which patients may deserve an 2-[^{18}F]FDG-PET/CT or CT scan (132,140,141). On the other hand, the loss of cellular differentiation in thyroid cancer may lead to the dissociation between Tg levels and tumour progression (142,143).

The small number of patients enrolled is the main limitation of the present study. This is due to the rarity of the disease, beside the fact that these patients do not regularly undergo 2-[^{18}F]FDG-PET/CT. Nevertheless, the availability of a strict and

long-term follow-up, during which either clinical, biochemical, or radiological data are provided and recorded, strengthens the study. Interestingly, most male patients were included in the present study. In this framework, it should be noted that the female prevalence characterizing the well differentiated disease is not always maintained in the poor differentiated and/or more aggressive disease (144,145).

Conclusions

2-[^{18}F]FDG-PET/CT confirmed its prognostic role both in the initial assessment and during the follow-up of patients with RR-TC. MTV and TLG seem at least somehow independent from Tg values, while a relationship might be present with the thyroid axis parameters. TKIs confirmed their efficacy as systemic therapy even in second line. TKIs also seem to impact 2-[^{18}F]FDG-PET/CT parameters, limiting their evolution in time. Further studies might be carried out to investigate their effect even in the improvement of the OS. In this perspective, 2-[^{18}F]FDG-PET/CT should be considered an important tool during the follow-up, which could integrate the information provided by other morphological and biochemical tests.

Conclusions

In summary, we analysed some of the aspects concerning the management of DTCs which necessitate a close interaction among different medical figures, in order to reach the best outcome achievable for the patients, with respect to both the disease control and their expectancies, as well as their quality of life. As the knowledge and the technical skills in each part of the therapeutic path increase, indeed, the availability of multiple specialists dedicated to the single settings of care become mandatory. Particularly, in case of rare and advanced disease, the consultation between different centres of care might be advisable, in order to share the expertise at least at a national level, and in some complex cases the referral to a high-volume clinic should be considered. For these purposes, in the last few years, European Reference Networks (ERNs) have been built with the aim to facilitate the exchange of knowledge among the most experienced health-care providers (HCPs) in each country. Current communication tools allow a rapid and easy data exchange and interaction among physicians throughout Europe, and digital platforms are being implemented to discuss the single cases with panels of experts in each of the topic involved, so that in most cases the patient might receive the best standard of care without the need of traveling to the referral centre. Furthermore, exchange programs among the involved HCPs are now ongoing to train specialists in each field and to promote the improvement of the single centre. Additionally, the creation of international databases provides the possibility to data collection for research purposes, so that larger study populations could be built, and evidence shared to improve the clinical care even for rare diseases (146,147).

In conclusion, DTC patients' management deeply evolved throughout the recent years and rapid changes in several aspects of clinical approach to the disease are still ongoing. A comprehensive initial approach to the patient and the continuous interaction among the specialists involved is mandatory. Furthermore, the creation of ERNs is now a well-established and growing process, which allows the dialogue among specialists at a supranational level, aimed at improving the standard of care especially of rare disease patients and minimizing differences in clinical approach among the different countries.

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