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DELAYED 131-I FIRST TREATMENT AFTER SURGERY HAS NO IMPACT ON THE MEDIAN TERM OUTCOME OF PATIENTS WITH INTERMEDIATE RISK DIFFERENTIATED THYROID CANCER.

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Running title: Timing to perform the first 131-I

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Abstract

Objective: In intermediate risk DTC (IR-DTC) patients, selective use of radioiodine (131-I) for remnant ablation and/or as adjuvant therapy (RRA) is advocated. The recently suggested post-operative evaluation could delay the RRA. The aim of this study was to evaluate if a delayed RRA, can worsen the clinical outcome of IR-DTC patients.

Patients and methods: 414 consecutive IR-DTC patients were divided according to the time elapsed from surgery to RRA, < 6 months (Group A - 186/414 [44.9%]) or ≥ 6 months (Group B - 228/414 [55.1%]). Clinical and biochemical data were collected, and clinical outcome was analyzed at the first evaluation after RRA (first-EV) and after a median of 6 years of follow-up (last-EV).

Results: No difference in the clinical outcome of Group A and B was found. Since a different activity of 131-I could have an impact on the outcome, we separately analyzed the groups according to the 131-I activity [low-activity group:1,110MBq/30 mCi (n=320) and high-activity group: 3,700MBq/100 mCi (n=94)], further subdivided according to the time elapsed from surgery to RRA. No major differences were found in both low and high activity-groups when comparing the features of their subgroups A and B as far as in their clinical outcome.

Conclusions: The time elapsed between surgery and the first 131-I treatment does not influence the clinical outcome of IR-DTC patients. This finding allows a more relaxed attitude in the decision making to perform or not the RRA in those IR-DTC cases in which a selective use of 131-I is recommended.

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Introduction

The radioiodine (131-I) treatment after total thyroidectomy is part of the initial treatment in selected cases of well differentiated thyroid cancer (DTC) patients (1, 2). According to the recent joint statement performed by delegates of the American Thyroid Association (ATA), European Association of Nuclear Medicine (EANM), Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Thyroid Association (ETA), the first 131-I treatment should be differently named on the basis of its final purpose (3). It should be named "ablation" when it is given to eliminate any residual thyroid tissue/cells that can produce "normal" thyroglobulin (Tg), thus making the measurement of serum Tg more specific for the presence of metastatic tissue; "adjuvant treatment" when it is given to destroy any subclinical tumor thyroid tissue/cells leftover the surgery that could theoretically develop as recurrence or metastases over the years; "therapeutic treatment" when it is given to treat the tumor residual disease especially when a well known advanced stage, both at local or distant site, make the surgery ineffective to definitively cure the patient. While the administration of 131-I for therapeutic purpose is confirmed in all DTC cases defined at high risk (HR) of recurrence, the first 131-I administration for remnant ablation and/or adjuvant treatment, which are indeed very difficult to be distinguished and that, for practical reasons, we will consider together in the present paper as RRA, is limited to selected cases with an intermediate risk (IR), and not recommended anymore in those with a low risk (LR) of recurrence (4).

In the last years, many evidences have demonstrated that, the post-operative biochemical evaluation and neck ultrasound (US) evaluation performed 3-4 months after surgery, can play an important role in the decision making to administer or not the first 131-I treatment in some cases of IR-DTC for which a "selective" use of 131-I is indicated (5-7). Whenever the decision to administer 131-I would be based on this post-operative control, this procedure could determine a delay of at least few months. Despite the few previously reported data (8, 9), it is still unclear if a 6 months postponed first 131-I treatment can affect the outcome of DTC patients with particular regard to IR-DTC.

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On the basis of these considerations, we decided to perform this retrospective study with the aim to evaluate the clinical impact of a different timing of administering the first 131-I treatment in a group of IR-DTC patients, followed for a median time of 6 years (mean 64.1±23.7; range 6 to 104; median 71 months).

Patients and Methods

We evaluated the epidemiological, clinical and pathological data of 414 consecutive IR-DTC patients who arrived at the Endocrine Unit of the University Hospital of Pisa in the years 2010 and 2011 to perform their first 131-I treatment. Data were collected until the data lock of this study (July 2018). Then, they were divided in two groups according to the time elapsed from surgery to the first 131-I treatment that could vary from one month up to two years. The study was approved by the Internal Review Board and, for policy of the University Hospital, all patients signed an informed consent to the use of their clinical data for scientific research.

For the purpose of this study, we focused our attention on cases defined as IR-DTC according to the ATA 2009 classification (10) that took into consideration only the presence of one or more histological features such as: 1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery (i.e., T3 at that time, according to the 7th TNM classification); 2) presence of cervical lymph node metastases (N1, either N1a or N1b); 3) tumor with aggressive histology (i.e. tall cell, hobnail variant, columnar cell carcinoma and others) or vascular invasion.

Up to 2015, surgical treatment for DTC in our institution, consisted of total thyroidectomy. Lymph node dissection of the central and/or latero-cervical compartment was performed only in case of a suspected metastatic nature of the lymph nodes at neck US and confirmed by fine needle aspiration cytology.

Most patients included in the present study (92.5%), have been surgically treated at the Endocrine Surgery Unit of the same University Hospital. All of them, had a histological diagnosis of DTC and when surgery was performed elsewhere the histological diagnosis was confirmed by our pathologists (L.T. and F.B.) with a new examination of the histological slides. Furthermore, TNM classification has been revised according to the Cancer 8th Edition T Staging System for Differentiated Thyroid Carcinoma (11).

According to the 2009 ATA Guidelines (10), that were followed at the time of the study initiation, 131-I was routinely performed in all IR-DTC patients, for either remnant ablation, adjuvant or therapeutic purposes.

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Patients were treated with 1,100 MBq (30 mCi) or 3,700 MBq (100 mCi) of 131-I, mainly according to the level of histological aggressiveness: as general rule, the 131-I activity was lower when a remnant ablation should be performed and higher when a therapeutic purpose should be reached. To obtain an appropriate TSH level to increase the 131-I uptake, either rhTSH administration (im injection of 0.9 mg of rhTSH for 2 consecutive days - Thyrogen, Genzyme Corp., Cambridge, MA), or a 30 days of L-thyroxine withdrawal were used. It is worth to note that the time elapsed from surgery to the first 131-I treatment was not fixed, but conditioned by the doctors judgment of the severity of the case and by the waiting list. Nevertheless, and with only few exceptions, the 131-I administration was hardly ever performed later than 12 months from surgery (mean 5.6±2.8; range 1 to 27; median 6 months).

After the initial treatment (i.e., surgery plus 131-I), we evaluated the clinical response at both the time of the first evaluation (first-EV), commonly performed 6 months after the first 131-I treatment, and at the last evaluation (last-EV) of the patient's follow-up. To define the response to treatment, we followed the criteria indicated in the 2015 ATA guidelines (4). In our series, to characterize the clinical outcome, Tg and Tg-autoantibodies (TgAb) values, neck US and other imaging procedures if necessary (CT scan, MRI, 18^{fdg}-PET, etc.), were considered. Tg values, have been taken into consideration to delineate the clinical response, only in the absence of interfering TgAb, and on LT4 therapy. Conversely, in the presence of interfering TgAb, their values and changes during the follow up were considered to define the response to therapy (12, 13).

Thyroglobulin (Tg) and Thyroglobulin Antibodies (TgAb)

Serum Tg was measured by a highly sensitive chemiluminescent assay (Beckman Coulter, Fullerton, CA, with a functional sensitivity of 0.1 ng/mL). Serum TgAb were measured using a Fluorescence Enzyme Immuno Assay (AIA-Pack 2000; Tosoh Corporation, Tokyo, Japan). The cut-off to identify thyroid autoimmune disease with thyroid gland in situ was 30 IU/ml. The functional sensitivity was 8 IU/ml and the cut-off interfering with Tg measurement was 9.3 (14).

Neck ultrasound

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Neck US was used to monitor the central and bilateral neck lymph node compartments and the superior mediastinum. Neck US was performed using a color Doppler apparatus (MyLab 50, Esaote Biomedica, Firenze, Italy) with a 7.5-12 MHz linear transducer. Suspicious lesions were evaluated by US guided fine-needle aspiration cytology (FNAC), and measurement of Tg in washing fluid.

Whole Body Scan (WBS)

For 131-I imaging, we used a 1-head gamma camera (Aspex SPX 4000, Elscint Italy) with a high-energy collimator and a sensitivity of 160 cpm/mCi. The scan speed was 10 cm/min with total counts of at least 140.000 cpm. We defined the ptWBS results negative, if the presence of 131-I uptake was exclusively present in the thyroid bed due to the presence of a post-operative thyroid remnant or positive, for the presence of uptake due to lymph nodes and/or distant metastases.

Statistical Analysis

Data are presented as mean±SD or as frequency (percentage), as appropriate. The independent samples t-test was used to evaluate differences between groups for continuous variables with a Gaussian distribution, while the Chi-squared test was used to assess difference between categorical variables. Linear logistic regression analysis was used to assess the association between each clinical parameter and the outcome. Analyses were performed in the whole cohort and then stratifying by the two activity groups. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed in SPSS (version 21.0, Armonk, NY: IBM Corp.).

Results

Outcome of patients according to the time elapsed from surgery to the first 131-I treatment.

According to the time elapsed from surgery to the first 131-I treatment, two groups of patients were identified: Group A (< 6 months from surgery to 131-I; 186/414 [44.9%] patients) and Group B (≥ 6 months from surgery to 131-I; 228/414 [55.1%] patients).

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As shown in Table 1, most of the epidemiological, clinical and pathological data were similar in the two groups, with the exception of the presence of lymph node metastases at histology that were more frequent (51.1% vs 33.8%, $p<0.01$) in group A than in group B. Moreover, they were also more numerous (49.5% vs 27.3% when considering cases with more than 5 lymph nodes, $p<0.01$) and more frequently present in the latero-cervical compartment (N1b) (29.6% vs 15.8%, $p<0.01$) in group A. The other differences observed in the two groups (Table 1) were: a) a significant higher prevalence of cases with interfering serum TgAb in group A than in group B (40.3% vs 23.2%, $p<0.01$); b) a significant larger number of cases treated with higher activities (i.e, 3,700MBq/100mCi) of 131-I in group A than in group B (41.4% vs 7.5%, $p<0.01$); c) a larger number of cases prepared for 131-I administration by withdrawing the LT4 therapy in group A than in group B (21% vs 3.9%, $p<0.01$).

Despite these differences, as shown in Fig 1, the patients' outcome, evaluated as prevalence of excellent, biochemical, structural or indeterminate response to the initial treatment, was similar in group A and B, both at the first-EV (mean 7.9 ± 2.9; median 7 months) (panel a) and at last-EV (mean 64 ± 23.7; median 71 months) (panel b).

Moreover, as shown in Table 2, when considering the further treatments performed during the follow up, the two groups, that were evaluated with the same interval of time from RRA to first-EV as well as from first-EV to last-EV, did not differ for both the number of 131-I courses and surgical re-interventions for lymph node metastases.

Because of the several differences observed between Group A and Group B, we also analyzed all the epidemiological, pathological and clinical parameters, including the different time elapsed from the surgery and the RRA (< 6 months *vs* $\geq$ 6 months) that could have influenced the outcome, both at the first-EV and at the last-EV, in the entire group of patients (Supplemental Table 1). While several factors were significantly associated with the outcome, both at univariate and multivariate analyses, the time elapsed from the surgery and the RRA was confirmed to do not play any role.

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Outcome of patients according to both the activity of 131-I administered and the time elapsed from surgery to 131-I treatment.

As reported in the patients and methods section, the activity of 131-I was varying from 1,100MBq/30mCi to 3,700 MBq/100 mCi and usually it was higher when there was a higher level of histological aggressiveness. It is intuitive that the group of patients treated with higher activities represented a group with a higher risk of recurrence. Taking into consideration this difference, we decided to separately analyze the group of patients treated with low activities of 131-I (i.e., 1,110 MBq/30 mCi), identified as low-activity group (n=320), and the group treated with high activities of 131-I (i.e., 3,700 MBq/100 mCi), identified as high-activity group (n=94). Then, we analyzed each group according to the time elapsed between surgery and 131-I treatment (<6 [subgroup A] and ≥ 6 months [subgroup B]).

As shown in Table 3, patients belonging to either low-activity or high-activity group showed very similar epidemiological, clinical and pathological features when they were divided according to the time elapsed from surgery to 131-I treatment (i.e., subgroups A and B, respectively). Only minor differences were found in the low-activity group (Table 3), likely not playing any role in the outcome of the patients.

As shown in Fig 2, the outcome of the low-activity group was similar independently from the time elapsed from surgery to 131-I, both at the first-EV (panel a) and at last-EV (panel b). The same pattern of results, although with a difference in the prevalence of the different types of responses respect to the low-activity group, was observed in the high-activity group patients both at first-EV (Fig 3, panel a) and the last-EV (Fig 3, panel b). Finally, as shown in Table 4, when considering the further treatments during the follow up, the number of 131-I courses and the surgical re-interventions for lymph node metastases were independent from the time elapsed from surgery to 131-I (subgroup A vs subgroup B) both in low-activity and high-activity groups.

Because of the several differences observed between the two groups of patients treated with low or high activities of 131-I, we also analyzed all the epidemiological, pathological and clinical parameters, including the different time elapsed from the surgery and the RRA (< 6 months *vs* ≥ 6 months) that could have influenced the outcome, both at the first-EV and at the last-EV, separately in the two groups of patients (Supplemental

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Table 2). While some parameters resulted to be significantly associated with the outcome, both at univariate and multivariate analyses, the time elapsed from the surgery and the RRA was confirmed to do not play any role.

Discussion

After the publication of the most recent ATA guidelines (4), the decision making to perform or not 131-I for RRA in the IR-DTC represents a very important challenge for the clinicians. If, in case of LR and HR-DTC, the scientific evidences are enough to decide to not administer or to administer 131-I respectively, in case of IR-DTC a selective use for RRA is recommended (4). Several studies have been recently reported to better clarify the clinical relevance of the 131-I treatment for RRA in IR-DTC some of which demonstrated that the use of 131-I for RRA was associated with a reduction in mortality rate, while others did not show any benefit from this treatment (15-17). Moreover, although randomized prospective trials confirmed the non-inferiority of different activities of 131-I administered at the time of RRA, for either LR (18, 19) or IR-DTC (20), some other recent reports showed that in IR-DTC low activities (1,100 MBq/30 mCi) of 131-I were strongly associated with a biochemical incomplete and structural incomplete response, when compared with high activities (3,700-5,550 MBq/100-150 mCi), after 10 years of follow up (21). These issues are still so controversial that they were faced in the joint statement of 4 important scientific societies (3) that ultimately concluded that the RRA needs and modalities should be better defined on an individual basis and in a multidisciplinary team.

So far, scanty data are available regarding the impact of timing of the first 131-I treatment, both for RRA or therapeutic purposes, on the clinical outcome of IR-DTC patients (9, 22). Despite the fact that this is becoming a relevant issue, if we want to include the results of serum Tg and neck US after surgery in the 131-I decision making (4), we have to consider that the treatment will be delayed. Unfortunately, not even the above mentioned very recent joint statement report any useful indication about when it could be better to perform the first 131-I treatment (3).

In the present study, we tried to give an answer to this question by evaluating a large group of IR-DTC patients (n=414) followed at a single tertiary referral center for a median follow up time of 6 years. Patients were

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divided into group A (< 6 months) and B (≥ 6 months) based on the time elapsed between surgery and 131-I treatment, performed for either therapeutic purpose or RRA. No differences in the short (first-EV) and median term (last-EV) outcome was found between these two groups. However, although these two groups were very similar in the majority of features, they differed for the presence of lymph node metastases, not only in terms of numbers, but also for the localization. Since this is a retrospective and not randomized study, it is conceivable that in the real life, IR-DTC with a greater number of lymph node metastases, would be treated quicker (within 6 months) and with higher activities at the time of first 131-I treatment. However, not only the short and median term outcome were similar, but also the number of subsequent 131-I treatments and/or surgical procedures, thus demonstrating that the time elapsed from surgery to the first 131-I treatment did not play any role in the disease course. Moreover, the absence of interference of the time elapsed from surgery to the first 131-I treatment on the outcome of patients was conformed when we performed both the univariate and the multivariate analysis of the entire group.

The same type of results was obtained when we divided the cases into 2 groups according to the higher or lower activities of 131-I . Indeed, as well as in the entire group, the time elapsed between the surgery and 131-I treatment did not play any impact in the outcome of these two groups either.

Our results are apparently in contrast with those of a Japanese study (22) that showed that in patients younger than 45 years and with distant metastatic disease a delayed 131-I could significantly affects their overall survival. However, the mean time elapsed from surgery to 131-I treatment was 2.59±4.77 years that is significantly longer than that of our study population (i.e., 5.6±2.8 months). Moreover, while they analyzed HR-DTC patients, our patients were all IR-DTC and in our series the related death would be an unexpected and infrequent event.

At variance, our results were somehow comparable to that of Tsirona et al. (8) who did not find any difference in the clinical outcome when patients were divided according with the timing of RRA (≤ 4.7 vs > 4.7 months). However, at variance from our study, their patients were all LR-DTC patients likely even overtreated since they used a mean of 72 mCi of 131-I for RRA. It is conceivable that in this LR-DTC population, that *per se*, has a good outcome it is difficult to observe a difference in their ultimately good outcome.

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More recently, Li et al. (22) retrospectively evaluated 235 LR- to IR-DTC patients. In this paper, the authors evaluated the clinical response in a short term follow up and patients were divided in two groups, < 3 or ≥ 3 months elapsed from surgery to RRA. They found that a delayed RRA (≥ 3 months) was significantly associated with an incomplete response, either biochemical or structural. Although the data reported in this study are very clear we can argue that the significantly shorter follow up (median: 2.1 years) compared to ours (median: 6 years) did not allow the authors to observe the impact of other procedures on a longer term outcome as we could do. However, our patients had a similar follow up also when analyzed at first-EV performed 6 months after the initial treatment and this difference can be explained only by the observation that Li et al. had a higher number of advanced cases in both groups (i.e., T3 and N1), respect to us and this difference can justify the high prevalence of not cured patients after the initial treatment.

More similar to our study is the study of Scheffel et al. (9), in which the authors retrospectively evaluated a large group of patients half of whom (n=245) were IR-DTC, like ours. Also, in this paper, patients who performed RRA were divided in those submitted to the first 131-I treatment before or after 6 months from surgery. Accordingly with our study, they did not find any difference between the 2 groups when they analyzed their outcome after both 1 and 6 yrs of follow up.

As all retrospective studies, also our study suffers from this limitation and certainly a prospective study could definitively answer the question of whether a delayed first 131-I treatment can affect the outcome of IR-DTC patients. However, it is also true that there are no scientific evidences that an early treatment with 131-I improves the outcome of the not metastatic DTC patients. The only reason for performing this treatment immediately or almost immediately after the surgery was related to the practical reason to do not unnecessarily prolong the post surgical hypothyroidism. Today, this is not more an issue since patients are treated with L-T4 therapy immediately after the surgery and then stimulated with rhTSH, if 131-I treatment is necessary for RRA purposes (23).

In conclusion, we demonstrated that in IR-DTC patients, the time elapsed between surgery and RRA does not influence the clinical outcome neither in the entire group of IR patients nor when we divided them according to the activity of RRA administered, that can be a mirror of a higher aggressiveness of the disease. This finding

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is in favor of a more relaxed attitude in the decision making to perform or not the RRA in those IR-DTC cases for which a selective use of 131-I is recommended (4). Taking into consideration our results, physicians can take time to re-evaluate patients 3-4 months after surgery and then decide to perform or not RRA, looking at the patients' clinical benefit.

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Table 1 – Epidemiological, clinical and pathological features of the entire IR-DTC study group, and divided in Group A [< 6 months from surgery to RRA (mean 3.4±1.3; median 4 months)] and Group B [≥ 6 months from surgery to RRA (mean 7.4±2.4; median 7 months)]

		Tot (414) n (%)	***Group A (186) n (%)***	***Group B (228) n (%)***	***p***
Gender	**Male**	128 (30.9)	51 (27.4)	77 (33.8)	0.16
	Female	286 (69.1)	135 (72.6)	151 (66.2)	
Age at surgery	**≤55**	310 (74.9)	146 (78.5)	164 (71.9)	0.13

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	>55	104 (25.1)	40 (21.5)	64 (28.1)	
Tumor size	*Mean ± SD*	2.1±1.6	2.2±1.6	2±1.6	0.17
	Median Value	1.6	1.75	1.5	
	≤4 cm	359 (86.7)	159 (85.5)	200 (87.7)	0.50
	>4 cm	55 (13.3)	27 (14.5)	28 (12.3)	
Histology	**CV-PTC**	195 (47.1)	95 (51.1)	100 (43.9)	0.23
	FV-PTC	44 (10.6)	14 (7.5)	30 (13.2)	
	FTC	17 (4.1)	7 (3.8)	10 (4.4)	
	AV-PTC	158 (38.2)	70 (37.6)	88 (38.6)	
Multifocality	**No**	200 (48.3)	84 (45.2)	116 (50.9)	0.25
	Yes	214 (51.7)	102 (54.8)	112 (49.1)	
Bilaterality	**No**	60 (28)	30 (29.4)	30 (26.8)	0.67
	Yes	154 (72)	72 (70.6)	82 (73.2)	
Histological Thyroiditis	**Absent**	273 (65.9)	113 (60.8)	160 (70.2)	0.05
	Present	141 (34.1)	73 (39.2)	68 (29.8)	
T classification (pTNM 8th edition)	**T1a**	115 (27.8)	49 (26.3)	66 (28.9)	0.29
	T1b	146 (35.3)	59 (31.7)	87 (38.2)	
	T2	96 (23.2)	49 (26.3)	47 (20.6)	
	T3	57 (13.8)	29 (15.6)	28 (12.3)	
Lymph Node	**No**	242 (58.5)	91 (48.9)	151 (66.2)	**<0.01**

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Mets	**Yes**	172 (41.5)	95 (51.1)	77 (33.8)	
N Classification	**Nx**	230 (55.6)	81 (43.5)	149 (65.4)	**<0.01**
	N1a	81 (19.6)	40 (21.5)	41 (18)	
	N1b	91 (22)	55 (29.6)	36 (15.8)	
	N0	12 (2.9)	10 (5.4)	2 (0.9)	
Number of Lymph Node Mets	**≤ 5**	104 (60.5)	48 (50.5)	56 (72.7)	**<0.01**
	>5	68 (39.5)	47 (49.5)	21 (27.3)	
Thyroid Capsule	**No Invasion**	93 (22.5)	39 (21)	54 (23.7)	0.15
	Invasion	50 (12.1)	17 (9.1)	33 (14.5)	
	mETE	271 (65.5)	130 (69.9)	141 (61.8)	
Interfering TgAb	**No**	286 (69.1)	111 (59.7)	175 (76.8)	**<0.01**
	Yes	128 (30.9)	75 (40.3)	53 (23.2)	
Post-operative Neck US	**Negative**	387 (93.5)	173 (93)	214 (93.9)	0.73
	Lymph Node Mets	27 (6.5)	13 (7)	14 (6.1)	
^{131}I activity	**1100 MBq/30 mCi**	320 (77.3)	109 (58.6)	211 (92.5)	**<0.01**
	3700 MBq/100 mCi	94 (22.7)	77 (41.4)	17 (7.5)	
Increasing ^{131}I Uptake	**rhTSH**	366 (88.4)	147 (79%)	219 (96.1)	**<0.01**
	LT4-Withdrawal	48 (11.6)	39 (21)	9 (3.9)	
ptWBS results	**Remnant**	393 (94.9)	177 (95.2)	216 (94.7)	0.98

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	Lymph Node Mets	14 (3.4)	6 (3.2)	8 (3.5)	
	Distant Mets	7 (1.7)	3 (1.6)	4 (1.8)	

CV-PTC: Classic Variant of Papillary Thyroid Carcinoma; FV-PTC: Follicular Variant of Papillary Thyroid Carcinoma; FTC: Follicular Thyroid Carcinoma; AV-PTC: Aggressive Variant of Papillary Thyroid Carcinoma; mETE: Minimal Extrathyroidal Extension; rhTSH: recombinant human TSH; ptWBS: post therapeutic Whole Body Scan

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Table 2 – Follow up data of the entire IR-DTC study group, and divided in Group A (< 6 months from surgery to RRA) and Group B (≥ 6 months from surgery to RRA)

		Tot (414) n (%)	***Group A (181) n (%)***	***Group B (226) n (%)***	***p***
Time elapsed from RRA to first-EV *(months)*	*Mean ± SD*	7.9±2.9	7.7±2.9	8.1±3	0.14
	Median Value	7	7	7	
Time elapsed from first-EV to last-EV *(months)******	*Mean ± SD*	64±23.7	63.2±24.6	64.8±23.1	0.52
	Median Value	71	70	71	
Number of ^{131}I treatments during follow up*	**RRA alone**	310 (76.2)	130 (71.8)	180 (79.6)	0.08
	RRA + one ^{131}I treatment	57 (14)	33 (18.2)	24 (10.6)	
	RRA + two or more ^{131}I treatments	40 (9.8)	18 (9.9)	22 (9.7)	
Surgical treatments for Lymph Node Mets during follow up*	**No**	396 (97.3)	173 (95.6)	223 (98.7)	0.06
	Yes	11 (2.7)	8 (4.4)	3 (1.3)	

* 7/414 (1.7%) patients were lost at follow up and data are available for 407/414 (98.3%) pts

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Table 3 – Comparison between epidemiological, clinical and pathological features of low-activity group (1,100 MBq/30 mCi) and high-activity group (3,700 MBq/100 mCi), subdivided based on the time elapsed from surgery to RRA in Subgroup A - < 6 months and Subgroup B - ≥ 6 months

		Low-activity group (n=320)		***p***	***High-activity group (n=94)***		***p***
		Subgroup A n (%)	***Subgroup B n (%)***		***Subgroup A n (%)***	***Subgroup B n (%)***	
Gender	**Male**	22 (20.2)	69 (32.7)	**0.02**	29 (37.7)	8 (47.1)	0.48
	Female	87 (79.8)	142 (67.3)		48 (62.3)	9 (52.9)	
Age at surgery	**≤55**	83 (76.1)	150 (71.1)	0.34	63 (81.8)	14 (82.4)	0.96
	>55	26 (23.9)	61 (28.9)		14 (18.2)	3 (17.6)	
Tumor size	*Mean ± SD*	2.2±1.6	2±1.6	0.34	2.3±1.6	2.9±1.8	0.28
	Median	1.7	1.5		1.8	2.2	
	≤4 cm	93 (85.3)	187 (88.6)	0.4	66 (85.7)	13 (76.5)	0.35
	>4 cm	16 (14.7)	24 (11.4)		11 (14.3)	4 (23.5)	
Histology	**CV-PTC**	52 (47.7)	93 (44.1)	0.59	43 (55.8)	7 (41.2)	0.15
	FV-PTC	10 (9.2)	29 (13.7)		4 (5.2)	1 (5.9)	
	FTC	6 (5.5)	8 (3.8)		1 (1.3)	2 (11.8)	
	AV-PTC	41 (37.6)	81 (38.4)		29 (37.7)	7 (41.2)	
Multifocality	**No**	54 (49.5)	111 (52.6)	0.6	30 (39)	5 (29.4)	0.46

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	Yes	55 (50.5)	100 (47.4)		47 (61)	12 (70.6)	
Bilaterality	**No**	16 (29.1)	26 (26)	0.68	14 (29.8)	4 (33.3)	0.81
	Yes	39 (70.9)	74 (74)		33 (70.2)	8 (66.7)	
Histological Thyroiditis	**Absent**	70 (64.2)	147 (69.7)	0.32	43 (55.8)	13 (76.5)	0.12
	Present	39 (35.8)	64 (30.3)		34 (44.2)	4 (23.5)	
T classification (pTNM 8th edition)	**T1a**	35 (32.1)	65 (30.8)	0.15	14 (18.2)	1 (5.9)	0.51
	T1b	29 (26.6)	81 (38.4)		30 (39)	6 (35.3)	
	T2	27 (24.8)	41 (19.4)		22 (28.6)	6 (35.3)	
	T3	18 (16.5)	24 (11.4)		11 (14.3)	4 (23.5)	
Lymph Node Mets	**No**	81 (74.3)	147 (69.7)	0.38	10 (13)	4 (23.5)	0.27
	Yes	28 (25.7)	64 (30.3)		67 (87)	13 (76.5)	
N Classification	**Nx**	73 (67)	145 (68.7)	**0.01**	8 (10.4)	4 (23.5)	0.35
	N1a	18 (16.5)	35 (16.6)		22 (28.6)	6 (35.3)	
	N1b	10 (9.2)	29 (13.7)		45 (58.4)	7 (41.2)	
	N0	8 (7.3)	2 (0.9)		2 (2.6)	/	
Number of metastatic Lymph Nodes	**≤ 5**	20 (71.4)	50 (78.1)	0.49	28 (41.8)	6 (46.2)	0.18
	>5	8 (28.6)	14 (21.9)		39 (58.2)	7 (53.8)	
Thyroid Capsule	**No Invasion**	26 (23.9)	53 (25.1)	0.52	13 (16.9)	1 (5.9)	0.5
	Invasion	12 (11)	32 (15.2)		5 (6.5)	1 (5.9)	

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	mETE	71 (65.1)	126 (59.7)		59 (76.6)	15 (88.2)	
Interfering TgAb	**No**	70 (64.2)	162 (76.8)	**0.02**	41 (53.2)	13 (76.5)	0.08
	Yes	39 (35.8)	49 (23.2)		36 (46.8)	4 (23.5)	
Post-operative Neck US	**Negative**	103 (94.5)	200 (94.8)	0.91	70 (90.9)	14 (82.4)	0.3
	Lymph node Mets	6 (5.5)	11 (5.2)		7 (9.1)	3 (17.6)	
Increasing ^{131}I Uptake	**rhTSH**	107 (33.6)	211 (66.4)	0.05	38 (82.6)	8 (17.4)	0.86
	LT4-Withdrawal	2 (100)	/		39 (81.2)	9 (18.8)	
ptWBS results	**Remnant**	109 (100)	202 (95.7)	0.09	68 (88.3)	14 (82.4)	0.8
	Lymph Node Mets	/	6 (2.8)		6 (7.8)	2 (11.8)	
	Distant Mets	/	3 (1.4)		3 (3.9)	1 (5.9)	

CV-PTC – Classic Variant of Papillary Thyroid Carcinoma; FV-PTC – Follicular Variant of Papillary Thyroid Carcinoma; FTC – Follicular Thyroid Carcinoma; AV-PTC – Aggressive Variant of Papillary Thyroid Carcinoma; mETE – Minimal Extrathyroidal Extension; rhTSH – recombinant human TSH; ptWBS – post therapeutic Whole Body Scan

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Table 4 – Follow up data of the entire IR-DTC study group (n=407), splitted in low-activity group (1,100 MBq/30 mCi) and high-activity group (3,700 MBq/100 mCi), subdivided based on the time elapsed from surgery to RRA in Subgroup A - < 6 months and Subgroup B - ≥ 6 months

		Low-activity group (n=315)		***p***	***High-activity group (n=92)***		***p***
		Subgroup A n (%)	***Subgroup B n (%)***		***Subgroup A n (%)***	***Subgroup B n (%)***	
Time elapsed from RRA to first-EV *(months)*	*Mean ± SD*	7.6±2.4	8.1±3	0.64	7.7±3.6	7.8±2.5	0.92
	Median Value	7	7		7	8	
Time elapsed from first-EV to last-EV *(months)*	*Mean ± SD*	66.5±23.6	65.1±23.1	0.38	58.6±25.4	60.8±22.4	0.59
	Median Value	73	72		67	63	
Number of ^{131}I treatments during follow up*	**RRA alone**	86 (81.1)	171 (81.8)	0.54	44 (58.7)	9 (52.9)	0.91
	RRA + one ^{131}I treatment	13 (12.3)	19 (9.1)		20 (26.7)	5 (29.4)	
	RRA + two or more ^{131}I treatments	7 (6.6)	19 (9.1)		11 (14.7)	3 (17.6)	

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Surgical treatments for Lymph Node Mets during follow up*	**No**	102 (96.2)	207 (99)	0.08	71 (94.7)	16 (94.1)	0.93
	Yes	4 (3.8)	2 (1)		4 (5.3)	1 (5.9)	
* 7/414 (1.7%) patients were lost at follow up and data are available for 407/414 (98.3%) pts							

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Fig. 1 – Clinical outcome in patients of the study group (n=407), divided in Group A (RRA < 6 months from surgery – n=181) and Group B (RRA ≥ 6 months from surgery – n=226), at the time of first-EV (Panel a) and last-EV (Panel b)

Fig. 2 – Clinical outcome in low-activity group patients (n=315) divided in Subgroup A (RRA < 6 months from surgery – n=106) and Subgroup B (RRA >= 6 months from surgery – n=209), at the time of first-EV (Panel a) and last-EV (Panel b)

Fig. 3 – Clinical outcome in high-activity group patients (n=92) divided in Subgroup A (RRA < 6 months from surgery – n=75) and Subgroup B (RRA >= 6 months from surgery – n=17), at the time of first-EV (Panel a) and last-EV (Panel b)

Fig 1

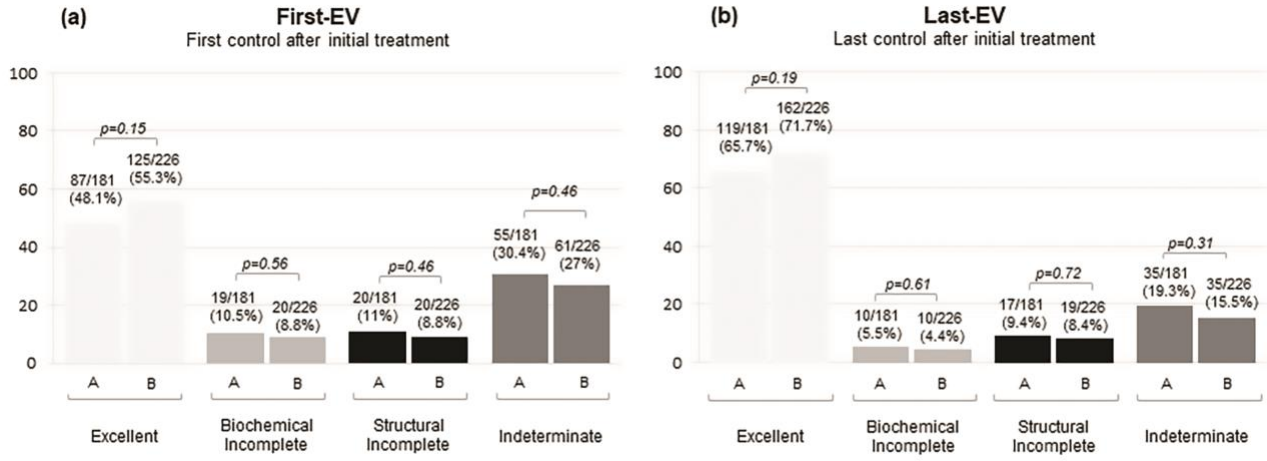

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Fig 2

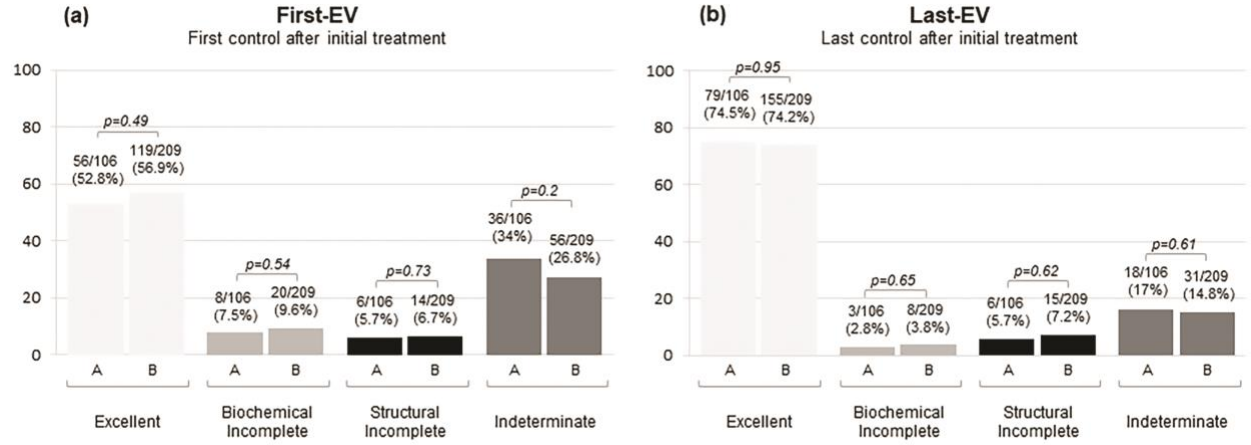
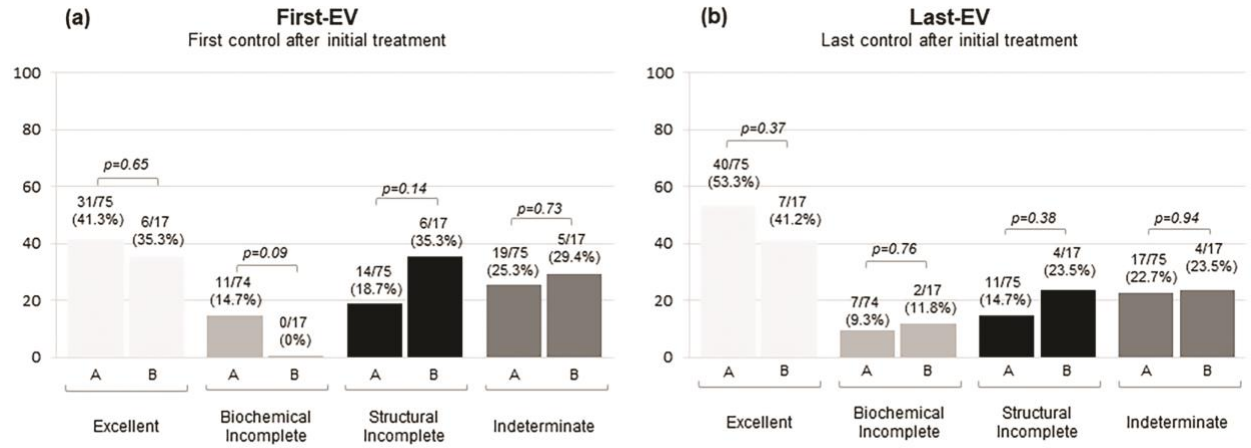


Fig 3



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Supplemental Table 1: Univariate analysis of the entire IR-DTC study, associated with clinical outcome at the time of First-EV and Last-EV.

		First-EV			Last-EV		
		NED n° (%)	Not Cured n° (%)	*p*	NED n° (%)	Not Cured n° (%)	*p*
Gender	M	64 (50.8)	62 (49.2)	0.73	81 (64.3)	45 (35.7)	0.17
	F	148 (52.7)	133 (47.3)		200 (71.2)	81 (28.8)	
Age at surgery (yrs)	≤ 55	155 (50.7)	151 (49.3)	0.32	206 (67.3)	100 (32.7)	0.19
	> 55	57 (56.4)	44 (43.6)		75 (74.3)	26 (25.7)	
Tumor size (cm)	≤ 4	181 (51.4)	171 (48.6)	0.5	242 (68.8)	110 (31.2)	0.75
	> 4	31 (56.4)	24 (43.6)		39 (70.9)	16 (29.1)	
Histology	CV-PTC	96 (50.3)	95 (49.7)	0.87	122 (63.9)	69 (36.1)	0.16
	FV-PTC	23 (52.3)	21 (47.7)		32 (72.7)	12 (27.3)	
	AV-PTC	83 (53.5)	72 (46.5)		113 (72.9)	42 (27.1)	
	FTC	10 (58.8)	7 (41.2)		14 (82.4)	3 (17.6)	
Multifocality	No	115 (58.7)	81 (41.3)	< 0.05	147 (75)	49 (25)	< 0.05
	Yes	97 (46)	114 (54)		134 (63.5)	77 (36.5)	
Bilaterality	No	27 (45)	33 (55)	0.86	37 (61.7)	23 (38.3)	0.73
	Yes	70 (46.4)	81 (53.6)		97 (64.2)	54 (35.8)	
Histological Thyroiditis	absent	151 (56.1)	118 (43.9)	< 0.05	186 (69.1)	83 (30.9)	0.95
	present	61 (44.2)	77 (55.8)		95 (68.8)	43 (31.2)	
T classification	T1a	64 (56.6)	49 (43.4)	0.15	82 (72.6)	31 (27.4)	0.08
	T1b	77 (53.5)	67 (46.5)		104 (72.2)	40 (27.8)	
	T2	39 (41.9)	54 (58.1)		54 (58.1)	39 (41.9)	
	T3	32 (56.1)	25 (43.9)		41 (71.9)	16 (38.1)	
Lymph Node Mets	No	142 (59.9)	95 (40.1)	< 0.01	183 (77.2)	54 (22.8)	< 0.01
	Yes	70 (41.2)	100 (58.8)		98 (57.6)	72 (42.4)	
N Classification	Nx	135 (59.5)	92 (40.5)	< 0.01	174 (76.7)	53 (23.3)	< 0.01
	N1a	38 (46.9)	43 (53.1)		54 (66.7)	27 (33.3)	
	N1b	32 (36)	57 (64)		44 (49.4)	45 (50.6)	
	N0	7 (70)	3 (30)		9 (90)	1 (10)	

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Number of Lymph Node Mets*°	≤5	54 (51.9)	50 (48.1)	< 0.01	73 (70.2)	31 (29.8)	< 0.01
	>5	16 (24.2)	50 (75.8)		25 (37.9)	41 (62.1)	
Thyroid capsule°	No invasion	54 (58.1)	39 (41.9)	0.32	76 (81.7)	17 (18.3)	< 0.01
	Invasion	27 (55.1)	22 (44.9)		36 (73.5)	13 (26.5)	
	mETE	131 (49.4)	134 (50.6)		169 (63.8)	96 (36.2)	
Interfering TgAb*	No	181 (64)	102 (36)	< 0.01	210 (74.2)	73 (25.8)	< 0.01
	Yes	31 (25)	93 (75)		71 (57.3)	53 (42.7)	
Post-operative Neck US*°	Negative	211 (55.4)	170 (44.6)	< 0.01	274 (71.9)	107 (28.1)	< 0.01
	Lymph node mets	1 (3.8)	25 (96.2)		7 (26.9)	19 (73.1)	
^{131}I Activity	1100 MBq/ 30 mCi	175 (55.6)	140 (44.4)	< 0.05	234 (74.3)	81 (25.7)	< 0.01
	3700 MBq/ 100 mCi	37 (40.2)	55 (59.8)		47 (51.1)	45 (48.9)	
Increasing ^{131}I Uptake	rhTSH	191 (53.5)	166 (46.5)	0.13	258 (72.3)	99 (27.7)	< 0.01
	LT4-with	21 (42)	29 (58)		23 (46)	27 (54)	
ptWBS result*	Remnant	211 (54.7)	175 (45.3)	< 0.01	267 (69.2)	119 (30.8)	0.92
	lymph node mets	1 (7.1)	13 (92.9)		9 (64.3)	5 (35.7)	
	Distant mets	/	7 (100)		5 (71.4)	2 (28.6)	
Time elapsed between surgery and ^{131}I (months)	< 6	87 (48.1)	94 (51.9)	0.15	119 (65.7)	62 (34.3)	0.2
	≥ 6	125 (55.3)	101 (44.7)		162 (71.7)	64 (28.3)	

NED: No Evidence of Disease; Not Cured (Biochemical Incomplete, Structural Incomplete and Indeterminate Response); Parameters confirmed to be relevant for the outcome of patients at the multivariate analyses at the First-EV (*) and Last-EV (°)

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Supplemental Table 2: Univariate analysis in the entire IR-DTC patients subdivided in Low-activity group and High-activity group, associated with clinical outcome at the time of First-EV and Last-EV.

		Low-activity group						**High-activity group**					
		First-EV			**Last-EV**			**First-EV**			**Last-EV**		
		NED n° (%)	Not Cured n° (%)	*p*	NED n° (%)	Not Cured n° (%)	*p*	NED n° (%)	Not Cured n° (%)	*p*	NED n° (%)	Not Cured n° (%)	*p*
Gender	M	51 (56)	40 (44)	0.91	65 (71.4)	26 (28.6)	0.46	13 (37.1)	22 (62.9)	0.64	16 (45.7)	19 (54.3)	0.42
	F	124 (55.4)	100 (44.6)		169 (75.4)	55 (24.6)		24 (42.1)	33 (57.9)		31 (54.4)	26 (45.6)	
Age at surgery (yrs)	≤ 55	125 (54.3)	105 (45.7)	0.48	166(72.2)	64 (27.8)	0.16	30 (39.5)	46 (60.5)	0.75	40 (52.6)	36 (47.4)	0.52
	> 55	50 (58.8)	35 (41.2)		68 (80)	17 (20)		7 (43.8)	9 (56.2)		7 (43.8)	9 (56.2)	
Tumor size (cm)	≤ 4	150 (54.5)	125 (45.5)	0.34	202(73.5)	73 (26.5)	0.38	31 (40.3)	46 (59.7)	0.99	40 (51.9)	37 (48.1)	0.71
	> 4	25 (62.5)	15 (37.5)		32 (80)	8 (20)		6 (40)	9 (60)		7 (46.7)	8 (53.3)	
Histology	CV-PTC	76 (53.5)	66 (46.5)	0.89	96 (67.6)	46 (32.4)	0.08	20 (40.8)	29 (59.2)	0.8	26 (53.1)	23 (46.9)	0.26
	FV-PTC	21 (53.8)	18 (46.2)		29 (74.4)	10 (25.6)		2 (40)	3 (60)		3 (60)	2 (40)	
	AV-PTC	70 (58.3)	50 (41.7)		98 (81.7)	22 (18.3)		13 (37.1)	22 (62.9)		15 (42.9)	20 (57.1)	
	FTC	8 (57.1)	6 (42.9)		11 (76.6)	3 (21.4)		2 (66.7)	1 (33.3)		3 (100)	/	
Multifocality	No	100 (61.7)	62 (38.3)	<0.05	130 (80.2)	32 (19.8)	<0.05	15 (44.1)	19 (55.9)	0.56	17 (50)	17 (50)	0.87
	Yes	75 (49)	78 (51)		104 (68)	49 (32)		22 (37.9)	36 (62.1)		30 (51.7)	28 (48.3)	
Bilaterality	No	19 (45.2)	23 (54.8)	0.57	26 (61.9)	16 (38.1)	0.32	8 (44.4)	10 (55.6)	0.49	11 (61.1)	7 (38.9)	0.34
	Yes	56 (50.5)	55 (49.5)		78 (70.3)	33 (29.7)		14 (35)	26 (65)		19 (47.5)	21 (52.5)	
Histological Thyroiditis	absent	129 (60.3)	85 (39.7)	<0.05	162 (75.7)	52 (24.3)	0.4	22 (40)	33 (60)	0.96	24 (43.6)	31 (56.4)	0.08
	present	46 (45.5)	55 (54.5)		72 (71.3)	29 (28.7)		15 (40.5)	22 (59.5)		23 (62.2)	14 (37.8)	
T classification	T1a	58 (59.2)	40 (40.8)	0.27	74 (75.5)	24 (24.5)	0.14	6 (40)	9 (60)	0.81	8 (53.3)	7 (46.7)	0.77
	T1b	61 (56)	48 (44)		84 (77.1)	25 (22.9)		16 (45.7)	19 (54.3)		20 (57.1)	15 (42.9)	
	T2	30 (45.5)	36 (54.5)		42 (63.6)	24 (36.4)		9 (33.3)	18 (66.7)		12 (44.4)	15 (55.6)	
	T3	26 (61.9)	16 (38.1)		34 (81)	8 (19)		6 (40)	9 (60)		7 (46.7)	8 (53.3)	
Lymph Node Mets	No	133 (59.4)	91 (40.6)	<0.05	173 (77.2)	51 (22.8)	0.06	9 (69.2)	4 (30.8)	<0.05	10 (76.9)	3 (23.1)	<0.05
	Yes	42 (46.2)	49 (53.8)		61 (67)	30 (33)		28 (35.4)	51 (64.6)		37 (46.8)	42 (53.2)	
N Classification	Nx	128 (59.3)	88 (40.7)	0.12	166 (76.9)	50 (23.1)	0.14	7 (63.6)	4 (36.4)	0.11	8 (72.7)	3 (27.3)	0.13
	N1a	27 (50.9)	26 (49.1)		38 (71.7)	15 (28.3)		11 (39.3)	17 (60.7)		16 (57.1)	12 (42.9)	

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	N1b	15 (39.5)	23 (60.5)		23 (60.5)	15 (39.5)		17 (33.3)	34 (66.7)		21 (41.2)	30 (58.8)	
	N0	5 (62.5)	3 (37.5)		7 (87.5)	1 (12.5)		2 (100)	/		2 (100)	/	
Number of Lymph Node Mets*°⊗	≤5	38 (54.3)	32 (45.7)	<0.01	52 (74.3)	18 (25.7)	<0.01	16 (47.1)	18 (52.9)	0.06	21 (61.8)	13 (38.2)	<0.05
	>5	4 (19)	17 (81)		9 (42.9)	12 (57.1)		12 (26.7)	33 (73.3)		16 (35.6)	29 (64.4)	
Thyroid capsule°	No invasion	50 (63.3)	29 (36.7)	0.21	67 (84.8)	12 (15.2)	<0.05	4 (28.6)	10 (71.4)	0.56	9 (64.3)	5 (35.7)	0.37
	Invasion	25 (58.1)	18 (41.9)		32 (74.4)	11 (25.6)		2 (33.3)	4 (66.7)		4 (66.7)	2 (33.3)	
	mETE	100 (51.8)	93 (48.2)		135 (69.9)	58 (30.1)		31 (43.1)	41 (56.9)		34 (47.2)	38 (52.8)	
Interfering TgAb	No	154 (67)	76 (33)	<0.01	180 (78.3)	50 (21.7)	<0.01	27 (50.9)	26 (49.1)	<0.05	30 (56.6)	23 (43.4)	0.22
	Yes	21 (24.7)	64 (75.3)		54 (63.5)	31 (36.5)		10 (25.6)	29 (74.4)		17 (43.6)	22 (56.4)	
Post-operative Neck US*#	Negative	174 (58.2)	125 (41.8)	<0.01	229 (76.6)	70 (23.4)	<0.01	37 (45.1)	45 (54.9)	<0.01	45 (54.9)	37 (45.1)	<0.05
	Lymph node mets	1 (6.2)	15 (93.8)		5 (31.2)	11 (68.8)		/	10 (100)		2 (20)	8 (80)	
Increasing ^{131}I Uptake	rhTSH	175 (55.9)	138 (44.1)	0.11	234 (74.8)	79 (25.2)	<0.05	16 (36.4)	28 (63.6)	0.47	24 (54.5)	20 (45.5)	0.53
	LT4-with	/	2 (100)		/	2 (100)		21 (43.8)	27 (56.2)		23 (47.9)	25 (56.1)	
ptWBS result	Remnant	175 (57.2)	131 (42.8)	<0.01	227 (74.2)	79 (25.8)	0.54	36 (45)	44 (55)	0.05	40 (50)	40 (50)	0.8
	Lymph node mets	/	6 (100)		4 (66.7)	2 (33.3)		1 (12.5)	7 (87.5)		5 (62.5)	3 (37.5)	
	Distant mets	/	3 (100)		3 (100)	/		/	4 (100)		2 (50)	2 (50)	
Time elapsed between surgery and ^{131}I (months)	< 6	56 (52.8)	50 (47.2)	0.49	79 (74.5)	27 (25.5)	0.94	31 (41.3)	44 (58.7)	0.65	40 (53.3)	35 (46.7)	0.37
	≥ 6	119 (56.9)	90 (43.1)		155 (74.2)	54 (25.8)		6 (35.3)	11 (64.7)		7 (41.2)	10 (58.8)	

NED: No Evidence of Disease; Not Cured (Biochemical Incomplete, Structural Incomplete and Indeterminate Response);

Parameters confirmed to be relevant for the outcome of patients at the multivariate analyses in the Low-activity group at the First-EV (*) and Last-EV (°), and in the High-activity group at the First-EV (#) and Last-EV (⊗)

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