Hemithyroidectomy versus total thyroidectomy in the intermediate-risk differentiated thyroid cancer: the Italian Societies of Endocrine Surgeons and Surgical Oncology Multicentric Study

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Abstract

The surgical treatment of the intermediate-risk DTC (1–4 cm) remains still controversial. We analyzed the current practice in Italy regarding the surgical management of intermediate-risk unilateral DTC to evaluate risk factors for recurrence and to identify a group of patients to whom propose a total thyroidectomy (TT) vs. hemithyroidectomy (HT). Among 1896 patients operated for thyroid cancer between January 2017 and December 2019, we evaluated 564 (29.7%) patients with unilateral intermediate-risk DTC (1–4 cm) without contralateral nodular lesions on the preoperative exams, chronic autoimmune thyroiditis, familiarity or radiance exposure. Data were collected retrospectively from the clinical register from 16 referral centers. The patients were followed for at least 14 months (median time 29.21 months). In our cohort 499 patients (88.4%) underwent total thyroidectomy whereas 65 patients (11.6%) underwent hemithyroidectomy. 151 (26.8%) patients had a multifocal DTC of whom 57 (10.1%) were bilateral. 21/66 (32.3%) patients were reoperated within 2 months from the first intervention (completion thyroidectomy). Three patients (3/564) developed regional lymph node recurrence 2 years after surgery and required a lymph nodal neck dissection. The single factor related to the risk of reoperation was the histological diameter (HR = 1.05 (1.00–1-09), $p = 0.026$). Risk stratification is the key to differentiating treatment options and achieving better outcomes. According to the present study, tumor diameter is a strong predictive risk factor to proper choose initial surgical management for intermediate-risk DTC.

Keywords Differentiated thyroid carcinoma · Surgery · Thyroid · Intermediate-risk differentiated thyroid cancer · Hemithyroidectomy · Risk stratification

Abbreviations

DTC	Differentiated thyroid cancer
TT	Total thyroidectomy
HT	Hemityroidectomy
ATA	American Thyroid Association
US	Ultrasonography
FNA	Fine-needle aspiration
CND	Central neck dissection
LND	Lateral neck dissection
Tg	Thyroglobulin
RAI	Radioactive iodine
SIUEC	Unitary Italian Society of Endocrinology
SICO	Italian Society of Oncological Surgery
pts	Patients

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Introduction

Thyroid cancer is the fifth most common cancer in women in the USA and its incidence continues to rise worldwide [1–6]. Differentiated thyroid cancer (DTC) is considered to be low risk because of the excellent patient outcomes, with a 10-year disease-specific survival of > 80–90% [6]. Due to the concern for over-treatment, surgical management of thyroid cancer has evolved. The intermediate-risk thyroid cancer includes tumors with different degrees of aggression.

The American Thyroid Association Revised Guidelines defines intermediate-risk DTC as having one or more of the following features: (i) age > 45 years, (ii) vascular invasion, (iii) microscopic extrathyroidal extension (T3), (iv) the presence of cervical lymph node metastases (pN1), (v) aggressive histological variants [7].

Although the condition of most patients with DTC improves when properly treated, a proportion of them (14–23%) experience disease recurrence or do not respond to conventional therapies. To improve the effectiveness of treatment, the management of DTC should be individualized. For this purpose, the ATA guidelines suggest that patients should be staged after surgery to assess the risk of recurrence and persistence of the disease in addition to the risk of mortality [7].

While in well-differentiated thyroid microcarcinomas (tumors with a diameter < 1 cm) there is consensus on performing a hemithyroidectomy (HT), in the absence of other risk factors and/or additional nodules in the thyroid contralateral lobe [8–11], for intermediate-risk tumors (1–4 cm) the recommendations for the surgical treatment remains controversial especially in patients who have a tumor diameter of 3–4 cm. Several Authors advocate HT to minimize perioperative morbidity. Studies have shown that patients with low and intermediate-risk DTC may benefit from a more conservative treatment, eg. HT followed by careful follow-up [12–14]. Nevertheless, there is no consensus yet about the extent of surgery ensuring oncologic completeness and a low risk of complications.

Aim of the study

The purpose of the present study was to determine an effective treatment strategy for patients with unilateral well-differentiated T1–2 N0 thyroid cancer and estimate the prevalence of total thyroidectomy (TT) in patients with unilateral intermediate-risk DTC (1–4 cm in diameter) without contralateral nodular lesions, absence of chronic autoimmune thyroiditis, absence of lymph node involvement at the preoperative US, and absence of familiarity; based on a retrospective evaluation of a register of activities of the 16 referral centers in Thyroid Surgery in Italy.

Methods

Principal investigator setting

UOC Clinica Chirurgica—Department of Medical and Surgical Sciences, Cattinara Hospital, Università degli Studi di Trieste, Italy.

Time frame

DTC operated between January 2017 and December 2019.

Type of study

Multicentric national retrospective observational study.

Regulations and ethics

Study endorsed by the Italian Society of Endocrine Surgeons and the Italian Society of Surgical Oncology. The study received approval from the Institutional Research Ethics Committee (Protocol #3264-001_2020H). Participants provided written informed consent.

Patient recruitment

Italian Endocrine Surgery Units received an invitation to participate in the study.

Data collection was carried out on a database (Excel database) distributed to all participating centers. There was no minimum or maximum number of patients per single Center. Outcomes were diagnosed and reported by the study sites and were confirmed by a central medical review of supporting documentation. Patient and Unit data remained anonymous. Only patients with preoperatively predicted localized unilateral disease were included. The patients enrolled were identified by the co-researchers of all the participating Centers, among all the patients that had a diagnosis of intermediate-risk DTC and underwent a TT or HT between January 1st 2017 and December 31st 2019. The patients were then followed up for a median time of 29.21 months.

Inclusion and exclusion criteria

Eligible patients had to be older than 18 years, with ultrasonography (US) tumor diameter between 1 and 4 cm, proven intermediate-risk DTC, pre-operative cytological diagnoses of TIR3A or TIR3B.

mutated (BRAF, NRAS, KRAS, HRAS, PIK3CA), TIR4, and TIR5 (2017 SIAPEC classification) [15, 16]. Exclusion criteria were previous thyroid surgery, familiar history of thyroid cancer, previous neck or upper mediastinum radiation, US and/or biochemical evidence of thyroiditis, bilateral multinodular goiter, and bilateral cancer. Patients with preoperative evidence of lymph node disease, those with extrathyroidal extension at clinical and/or ultrasonography (US), and tumors larger than 4 cm were not included in the analysis (Table 1).

Definitions and procedures

Preoperative work-up consisted of full clinical examination, neck US, and fine-needle aspiration (FNA) cytology. Intermediate-risk DTC is defined by 2015 ATA revised Guidelines. Total thyroidectomy is the surgical removal of the whole thyroid gland. Hemithyroidectomy removes one of the thyroid lobes, leaving the other intact. Patients who received HT presenting a capsular invasion and/or perithyroid tissue infiltration at the definitive histological examination underwent completion thyroidectomy with or without lymph node dissection. When nodal metastases were identified at the time of the surgical procedure or during follow-up, the patients underwent either unilateral or bilateral central neck dissection (CND) or lateral neck dissection (LND) [7]. Patients were followed every 6 months after the operation for the first year. Follow-up visit consisted of clinical examination, imaging, thyroid function test including thyroglobulin (Tg) and Tg antibodies. Recurrence was defined by the presence of thyroid carcinoma within the neck, regional lymph nodes metastases or distant metastases. Radioactive iodine ablation therapy (RAI) was administered based on the stage and prognostic risk factors [7, 8, 17–20]. Patients received radioactive iodine (RAI) treatment after TT or completion of thyroidectomy in case of aggressive histological subtypes (i.e. tall cells, columnar cells, or diffuse sclerosant variants), multifocality, extrathyroid invasion, and lymph node metastases. Successful tRAI was defined by the disappearance of any visible area of uptake in the thyroid bed ($\leq 1\%$), and undetectable serum Tg levels of levothyroxine (TSH > 30μUI/mL).

Data collection

A systematic search was performed to assess the effect of TT with or without radioactive iodine (RAI) treatment versus HT on recurrence and overall morbidity in patients with differentiated (papillary or follicular) T1–2 N0 thyroid cancer. The groups were compared on the following variables: gender, age, tumor size, cytological characteristics, lymph node metastasis, mutational status (panel) on FNA, histological analysis, TNM stage, clinical outcomes (complication rates, local recurrence, reoperation rate: HT followed by completion thyroidectomy ± cervical lymphadenectomy). Patients were further stratified into two groups, based on the size of the tumor nodule: group 1 with tumor diameter < 2 cm and group 2 tumor diameter 3–4 cm. The hypothesis of further dividing patients into two subgroups resulted in a "covariate" variable [< 2 cm vs > 2 cm] to further stratify patients' risk. We collected the presence of unexpected lesions in the contralateral lobe. Histopathologic data (I.e. multifocality, aggressive features, extracapsular invasion, lymph node metastases) were recorded for all patients and analyzed to determine whether completion thyroidectomy or TT were appropriate or should have been considered as an overtreatment.

Primary outcomes

- Estimate the prevalence of TT surgical treatment in patients with intermediate-risk DTC (1–4 cm in diameter).

Secondary outcomes

- Estimate the incidence of reoperation in the hemithyroidectomy group within one year of primary surgery
- Evaluate the incidence of occult contralateral carcinoma in patients undergoing TT
- Compare morbidity rate of thyroidectomy vs hemithyroidectomy and of any reoperation (completion thyroidectomy or lymph node dissection due to recurrence)

Table 1 Inclusion and exclusion criteria for the study cohort

Total patients 1896	1332 pts (70.2%) excluded	564 pts (29.8%) included
	– Previous thyroid surgery: 57 patients (3%) – Familiar history of thyroid cancer: 38 pts (2%) – Previous neck or upper mediastinum radiation: 19 pts (1%) – US and/or biochemical evidence of thyroiditis,: 512 pts (27%) – Bilateral multinodular goiter, bilateral cancer: 474 pts (25%) – Preoperative evidence of lymph node disease: 151 pts (8%) – Presence of extrathyroidal extension at clinical and/or ultrasonography (US): 57 pts (3%) – Tumors < 1 cm o > 4 cm: 588 pts (31%)	– Tumor diameter between 1 and 4 cm (TIR 4-TIR 5), proven intermediate-risk DTC – Pre-operative cytological diagnoses of TIR3A or TIR3B mutated – Pre-operative cytological diagnoses of TIR3A or TIR3B without mutations panel, but with US signs of malignancy: EU-TIRADS 4–5

- Identify patients who would have benefited best from total thyroidectomy early vs. hemithyroidectomy.
- Identify the specific risk factors to identify a group of patients to whom propose total thyroidectomy (age, sex, tumor diameter, extrathyroid extension, multifocal, lymph node involvement

Statistical analysis

Data were collected in an XLS Database (Microsoft office 2016; Microsoft Corporation, Redmond, WA, USA) and subsequently imported into software R (version 4.0.2, 2020). The close-out for data collection was February 5, 2021. Descriptive statistics summarized data using the mean and standard deviation or median and range (minimum–maximum), as appropriate based on the variable distribution (verified through Shapiro–Wilk normality test), or even frequencies for dichotomic variables; consequently, comparisons between HT and TT groups were made by parametric (t test for two independent samples) or no parametric tests (Mann–Whitney test) for a continuous variable, while chi-square tests for dichotomic variables (of Fisher Exact test when appropriate). Univariate logistic regression was performed, and variables significantly associated were included in a multivariate logistic regression model. Results were reported as Odds Ratio (OR) and 95% confidence intervals (95%CI).

To describe the likelihood of no reintervention (for relapse or reoperation), we used the standard Kaplan–Meier method and a log-rank test was used to compare the two different groups. Univariate Cox proportional regression model was used to identify prognostic factors related to reintervention and results reported as Hazard Ratios and 95% confidence intervals (HR, 95%CI).

Due to the small sample size of events, multivariate analysis was not indicated. *P* values less than 0.05 were considered significant.

Results

Participants

16 Endocrine Surgical Centers participated. Among 1′896 DCT operated, 564 (29.7%) unilateral intermediate-risk DTC (papillary o follicular) T1-T2N0 were identified. The Cohort's characteristics are summarized in Table 2. Group TT consisted of 499 patients (88.4%), 362 women and 137 men, mean age 48.1 years. Group HT consisted of 65 patients (11.6%), 52 women and 13 men, mean age 45 years. The statistical analysis of the two groups is depicted in Table 3.

In summary, the patients treated with TT compared to patients treated with HT, had a preoperative diagnosis with FNAC TIR4-TIR5, presented a larger preoperative and histological tumor diameter and had a higher percentage of lymph nodes neck dissection and lymph node metastases (N1). These patients also had higher morbidity, a greater number of lymph nodes removed, longer hospital stay, and the percentage of plurifocal carcinomas at the definitive histological examination was higher. On the other hand, they had a lower rate of re-operations.

All of these differences were statistically significant (Table 3).

Histophatology

397 patients (70.4%) were operated on because of TIR4 or TIR5 lesions. 167 patients (29%) presented TIR3 lesions. In our cohort of 167 TIR3 lesions, 37 were TIR3A and 105 were TIR3B. In 25 cases the information was not available. Multifocality was found in 8 patients in Group HT (12.3%) and in 143 patients in Group TT (28.6%) (Table 3). Four (6.1%) presented a bilateral involvement in Group HT and 53 (10.6%) in Group TT ($p = 0.03$). We found a statistically significant different in preoperative diameter tumor in the two groups: 12 mm (10–40 mm) in Group HT and 15 mm in Group TT (10–40 mm) ($p = < 0.001$).

Morbidity and follow-up

Median hospital stay was 2 days (1–5) in Group HT and 3 days (1–12) in Group TT ($p = < 0.001$). Complete follow-up data were available in 358 patients (63.5%). Median time follow-up was 29.21 months (21.2 – 39.6). TT patients had a lower reoperation rate, 3 patients in the Group TT (0.6%) vs. 17 patients in the Group HT (26.2%) ($p = < 0.001$). All of the reoperations of the Group HT were a completion thyroidectomy after initial surgery on the basis of definitive histology.

The reasons for completion thyroidectomy (19 patients) were: 3 cases of tumors with capsular infiltration, 3 extraglandular extension, 5 for large diameter and patient preference, 2 patients for multifocality and patient preference, 4 patients with aggressive subtype (1 diffuse sclerosing variant of papillary thyroid carcinoma and 3 "tall cell" variants) one of which with lymph node metastases, and 1 patient with papillary cancer with extraglandular extension and lymph node metastases. The mean tumor size was 20,9 mm (range 10 -40 mm).

Complication rates were significantly different: 17.8% in Group TT vs. 7.7% in Group HT ($p = 0.04$). No significant difference was found between the two groups in

Table 2 Cohort's characteristics

Variable	Cohort ($N=564$)
Age	
Mean (SD)	48 (14)
Median (Range)	48 (16–87)
Sex (*N* %)	
Female	414 (73.4)
Male	150 (26.6)
Preoperative FNAC (*N* %)	
TIR3	167 (29.6)
TIR4	187 (33.2)
TIR5	210 (37.2)
Preoperative diameter (mm)	
Median (Range)	15 (10–40)
Surgery (*N* %)	
Hemithyroidectomy (HT)	65 (11.5)
Total thyroidectomy (TT)	499 (88.5)
Dissection (*N* %)	
Yes	246 (43.6)
Type of dissection (*N* %)	
Sampling	55/246 (22.3)
Sampling unilateral and bilateral central neck dissection	6/246 (2.4)
Bilateral central neck dissection	90/246 (36.6)
Unilateral central neck dissection	95/246 (38.6)
Complications (*N* %)	
Yes	94 (16.7)
Type of complications (*N* %)	
laryngeal nerve palsy	24 (4.3)
Transient	7/24 (29.2)
Definitive	17/24 (70.8)
Haemorrhage (*N* %)	5 (0.9)
Hypocalcemia POD 1* (*N* %)	70 (12.4: 1 HT, 69 TT)
Biochemical transient hypocalcemia	61/70 (87.1)
Symptomatic transient hypocalcemia	8/70 (11.4)
Definitive hypoparathyroidism	1/70(1.4)
Others	5 (0.9)
Histological diameter (mm)	
Median (min–max)	14 (0–45)
pT (*N* %)	
T0/NIFPT	11 (2.0)
T1a	170 (30.1)
T1b	273 (48.4)
T2	93 (16.5)
T3	17 (3.0)
pN (*N* %)	
Nx	329 (58.3)
N0	152 (27.0)
N1	83 (14.7)
Stage (*N* %)	
0	7 (1.3)
I	493 (88.2)
II	59 (10.5)
Missing	3 (0.5)

Table 2 (continued)

Variable	Cohort ($N=564$)
Number of lymph nodes (*N* %)	
0	326 (57.8)
1–4	100 (17.7)
>4	104 (18.4)
Missing	34 (6.0)
Number of positive lymph nodes (*N* %)	
0	460 (81.6)
1	30 (5.3)
2–3	23 (4.1)
>3	25 (4.4)
Missing	26 (4.6)
Focal thyroiditis at the definitive histology (*N* %)	
Yes	67 (11.9)
Multifocality (*N* %)	
Yes	151 (26.8)
Monolateral	94 (16.7)
Bilateral	57 (10.1)
Infiltration (*N* %)	
Yes	19 (3.4)
Margin	7 (1.2)
Capsular invasion	12 (2.1)
Length of hospital stay (days)	
Median (Min.–Max.)	3 (1–12)
Reoperation (including relapse) (*N* %)	
Yes	24 (4.3)
Type of reoperation (*N* %)	
Completion thyroidectomy	19 (3.4)
Bilateral central neck dissection	5 (0.9)
Recurrence rate (*N* %)	
Yes	3 (0.5)

*POD1 (first postoperative day)

terms of recurrence rates ($p=1.00$). Three patients in Group TT (0.6%) developed regional lymph node recurrence respectively 22, 25 and 27 months after surgery and required respectively a bilateral CND, CND with bilateral neck dissection, CND with monolateral neck dissection.

Univariate and multivariate analysis

The univariate and multivariate analysis are shown in Table 4.

Predictors of total thyroidectomy

At univariate analysis, age, gender, lymph node involvement were not associated with the type of operation.

The multivariate analysis showed that patients with preoperative cytology TIR4-TIR5, with greater pre-operative diameter were more at risk of undergoing total thyroidectomy. Multifocality, significant to the univariate analysis, does not reach statistical significance when adjusted for the other factors.

Reintervention/recurrence

During the follow-up period, 21 patients underwent reoperation and 3 patients had a disease recurrence. 21 patients were reoperated within 2 months from the first intervention. Three patients were reoperated after 22 months (bilateral central neck dissection), 25 and 27 months respectively from the first intervention (bilateral central neck dissection with lateral neck dissection). Patients treated with TT showed a significantly higher rate of no re-intervention respectively to Group HT (1-year respectively 98.9%, 95%CI: 97.3–99.5% vs 75.0%, 95%CI: 62.4–83.9%,($p<0.001$), see Fig. 1).

Table 3 Comparison between TT and HT pts to identify specific risk factors

Variable	HT ($N=65$)	TT ($N=499$)	p value
Age			
Mean (SD)	45.0 (15.3)	48.1 (14.1)	0.11
Sex (*N* %)			
Female	52 (80.0)	362 (72.6)	0.20
Male	13 (20.0)	137 (27.4)	
Preoperative FNAC (*N* %)			
TIR3	34 (52.3)	133 (26.7)	
TIR4	16 (24.6)	171 (34.3)	< 0.001
TIR5	15 (23.1)	195 (39.1)	
Preoperative diameter (mm)			
Median (Range)	12 (10–40)	15 (10–40)	< 0.001
Dissection (*N* %)			
Yes	18 (27.7)	228 (45.7)	0.006
Complications (N %)			
Yes	5 (7.7)	89 (17.8)	0.04
Histological diameter			
Median (min–max)	11.5 (4–40)	15.0 (0–45)	0.008
pT (*N* %)			
T0/NIFPT	0 (0.0)	11 (2.2)	
T1a	25 (38.5)	145 (29.1)	0.37
T1b	28 (43.1)	245 (49.1)	
T2	9 (13.9)	84 (14.9)	
T3	3 (4.6)	14 (2.8)	
pN (*N* %)			
Nx	47 (72.3)	282 (56.5)	0.04
N0	13 (20.0)	139 (27.9)	
N1	5 (7.7)	78 (15.6)	
Stadio (*N* %)			
0	0 (0.0)	7 (1.4)	
I	56 (86.2)	439 (88.0)	
II	9 (13.8)	50 (10.0)	
Missing	0 (0.0)	3 (0.6)	0.42
Number of lymph nodes (*N* %)			
0	47 (72.3)	279 (55.9)	
1–4	14 (21.5)	86 (17.2)	0.007
> 4	2 (3.1)	102 (20.4)	
Missing	2 (3.1)	32 (6.4)	
Number of positive lymph nodes (*N* %)			
0	58 (88.5)	402 (80.6)	0.31
1	2 (3.1)	28 (5.6)	
2–3	3 (4.6)	20 (4.0)	
> 3	0 (0.0)	25 (5.0)	
Missing	2 (3.1)	24 (4.8)	
Thyroiditis (*N* %)			
Yes	6 (9.2)	61 (12.2)	0.48
Multifocality (*N* %)			
Yes	8 (12.3)	143 (28.6)	0.008
Monolateral	4 (6.1)	90 (18.0)	
Bilateral	4 (6.1)	53 (10.6)	
Infiltration (*N* %)			
Yes	2 (3.1)	17 (3.4)	

Table 3 (continued)

Variable	HT ($N=65$)	TT ($N=499$)	p value
Margin	2 (3.1)	5 (1.0)	0.99
Capsular invasion	0 (0.0)	12 (2.4)	
Days of hospitalization			
Median (Min.–Max.)	2 (1–5)	3 (1–12)	< 0.001
Reoperation (including recurrence)			
Yes	17 (26.2)	7 (1.4)	< 0.001
Only recurrence rate (N %)			
Yes	0 (0.0)	3 (0.6)	1.00

Table 4 Univariate and multivariate analysis of variables associate with total thyroidectomy (logistic regression models)

Variable	Univariate analysis OR (95%CI)	p value	Multivariate analysis OR (95%CI)	p value
Age	1.02 (0.99–1.03)	0.11		
Sex				
Female	1.00 (reference)	0.20		
Male	1.51 (0.80–2.87)			
Preoperative FNAC				
TIR3	1.00 (reference)		1.00 (reference)	
TIR4	2.73 (1.45–5.16)	0.002	3.02 (1.55–5.89)	0.001
TIR5	3.32 (1.74–6.34)	< 0.001	3.40 (1.73–6.65)	< 0.001
Preoperative diameter	1.05 (1.01–1.09)	0.02	1.06 (1.02–1.10)	< 0.001
Complications				
No	1.00 (reference)		1.00 (reference)	
Yes	2.60 (1.02–6.67)	0.04	2.04 (0.78–5.35)	0.15
pN				
Nx/N0	1.00 (reference)			
N1	2.22 (0.87–5.71)	0.09		
Multifocality				
No	1.00 (reference)		1.00 (reference)	
Yes	2.86 (1.33–6.15)	0.007	1.99 (0.90–4.39)	0.08

At univariate Cox regression model analysis, age, gender, multifocality, complications, lymph node involvement were not associated with reoperation or relapse.

In addition to the type of intervention, the only factor related to the risk of reoperation was the histological diameter (HR = 1.05 (1.00–1–09), $p = 0.026$): as the diameter increases, there is a greater probability of reoperation. In summary, the total thyroidectomy and larger diameter on histology were independent risk factors related to the reoperation in the follow-up. Multivariate analysis was not performed due to the low number of events.

Correlation between tumor recurrence and reintervention/ relapse

Patients undergoing reoperation/ relapse had a significantly larger diameter on histological examination than patients who do not undergo reoperation (median respectively 19 mm (10–40) vs 14 mm (0–45), $p < 0.001$, see Fig. 2).

In particular, 7.3% (11 out of 150) of patients with tumor diameter > = 20 mm underwent reoperation compared to 3.1% (12/389) of patients with diameter < 20 mm ($p = 0.029$), see Table 5.

If we consider only the subgroup of patients who underwent HT ($n = 65$, for 1 patient histological diameter was not available) none of the possible factors (sex, age, lymph node status, multifocality) were associated with reoperation.

The histological diameter remains confirmed as a predictive factor: in particular,

9/52 patients with histological diameter < 20 mm, underwent reoperation (17.3%) while this percentage increased to 58.3% for patients with diameter > = 20 (7/12) (Odds ratio: 6.69, 95% CI:1.73- 25.9), $p = 0.006$). In summary, patients undergoing HT with a histological

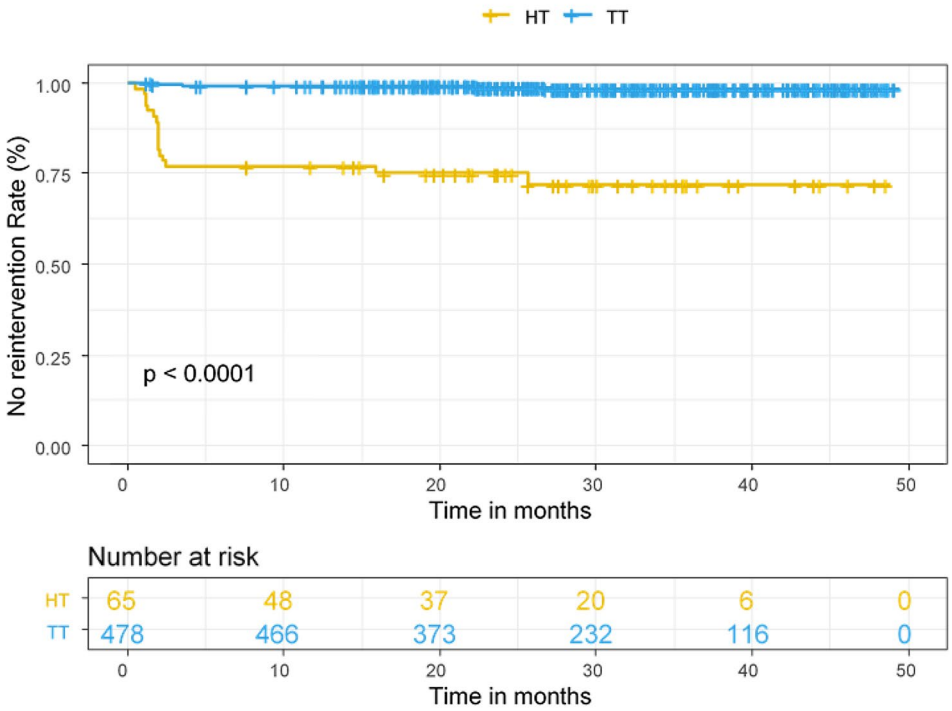

Fig. 1 Kaplan–Meier curves of No reintervention in the hemithyroidectomy and thyroidectomy groups (events: relapse o reoperation)

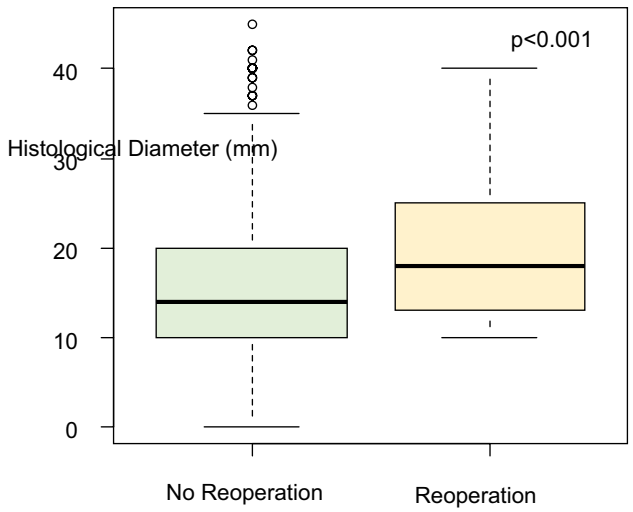

Fig. 2 correlation between diameter and reintervention / relapse. No reoperation: mean tumor diameter (mm): 14 (0–45). Reoperation: mean tumor diameter (mm): 19 (10–40). In three pts the histological exam found a benign thyroid adenoma, so the diameter was calculated: 0. The adjusted range for only malignant lesions was: (0.4–45)

diameter greater than 20 mm have a 6 time higher risk of undergoing reoperation than patients with a diameter < 20 mm. Since the number of re-operations in this group is only 17, it is not possible to perform a multivariate (Table 5).

Table 5 Patients' risk stratification in relation to reintervention. Results of two subgroups patients in a "covariate" variable [< 20 mm vs > 20 mm]

Diametro isto cat			
reint	< 20	> = 20	Total
0	377	139	516
	96.92	92.67	95.73
1	12	11	23
	3.08	7.33	4.27
Total	389	150	539
	100.00	100.00	100.00

Pr = 0.029

RAI treatment offered

151 out of 564 patients underwent post-surgery RAI therapy (26.8%). There were no differences with respect to surgery: RAI therapy in 27.4% of TT cases versus 23.4% of lobectomies with completion thyroidectomy patients ($p = 0.56$).

In two patients we found a recurrence after low-dose radioiodine ablation.

77 patients out of /358 (20%) underwent radioiodine therapy. About of which 2 patients underwent reintervention. Particularly, the first patient was a female, 59 years old, who underwent total thyroidectomy for pT3Nx papillary thyroid carcinoma (diameter 15 mm) after 53 mci. The patient

underwent right functional laterocervical lymphadenectomy (level II—V) and central compartment lymphadenectomy (2 years later). Another patient, male, 46 years, after 150 mci, histology: pT2 Nx 23 mm, underwent bilateral central compartment dissection after two years.

Discussion

Differentiated thyroid carcinoma is increasing in incidence, partly due to increased detection determined by even more sensitive imaging techniques. Prognosis is generally excellent, with 10-year survival rates of 80–90% [1–6]. Despite several clinical studies performed around the world and different guidelines published for its treatment [4–11], there is still a debate as to which surgical approach is most appropriate for intermediate-risk (1–4 cm) DTC. The 2015 American Thyroid Association (ATA) Guidelines [7] suggest for < 1 cm differentiated thyroid carcinoma or clinical observation (active surveillance) or hemithyroidectomy, and for intermediate-risk tumors (1–4 cm) is suggested or hemithyroidectomy or total thyroidectomy, or completion thyroidectomy according to the different centers or according to various patients 'risk factors. In summary, the correct approach to treat intermediate-risk differentiated thyroid carcinoma (DTC) is still controversial in some issues, especially in patients who have a tumor diameter of 3–4 cm, for the lack of preoperative information or variables that allow predicting the level of aggressiveness of the tumor.

A strict patient selection based on risk stratification is the key to differentiating treatment options and achieving better outcomes. Stratifying and adopting the best surgical approach for each patient is essential for the development of the right treatment plan [19–22]. Whereas several Authors agree to perform a hemithyroidectomy and a strict follow-up in patients with well-differentiated thyroid tumors with diameter < 2, there is no consensus yet about the extent of surgery in tumors between 2–4 cm of diameter [1, 19–24].

The aim of this study was to describe the current practice of different Italian centers regarding the surgical management of intermediate-risk DTC and to determine risk factors to identify a group of patients to whom propose a total thyroidectomy vs. a hemithyroidectomy. We evaluated which surgical treatment is performed in 16 Italian Thyroid referral Centers.

From published studies [22–26], 67% of patients with DTC underwent total thyroidectomy, in our series the rate of TT was 88.5%. This data, in our opinion, reflects a difference in patient selection and in our National Health System.

In our series, the multivariate analysis demonstrated a strong correlation between the type of surgery (TT) and the results of preoperative cytology (TIR4-TIR5 candidates for TT). The tumor diameter (larger lesions in patients who underwent TT), higher morbidity (patients who underwent TT resulted more at risk of complications, $p = 0.04$, and multifocality ($p = 0.008$) at the limits of significance, represented two independent risk factors for choosing the best surgical therapy.

When we analyze the risk of relapse/reoperation, gender, multifocality, morbidity rate, and lymph node involvement were not associated with this outcome. The single factor related to the risk of reoperation was the histological diameter (HR = 1.05 (1.00–1-09), $p = 0.026$).

Recurrence rates following radioactive iodine ablation have previously been reported in observational studies. Two large randomized trials of patients with well-differentiated thyroid cancer reported in 2012 (HiLo and ESTIMABL1) found similar post-ablation success rates at 6–9 months between a low administered radioactive iodine (^{131}I) dose (1·1 GBq) and the standard high dose (3·7 GBq) [29].

The inclusion criteria were very restrictive and this meant that the number of patients included was 564, this point can be a limit of the study, however, it could also represent a strong point for the study as the patients are very strictly well selected.

We included the NIFTP and two benign tumors because our study was based on the pre-operative diagnosis of thyroid tumor (cytology and neck US).

The retrospective nature of the present study is a known potential bias. Obviously, it is important to differentiate patients diagnosed with DTC preoperatively from those diagnosed after initial hemithyroidectomy.

Another limitation of the present study is that certain risk factors, as histological features, vascular invasion, extrathyroidal extension, and spread to regional lymph nodes, are difficult to estimate preoperatively. But, in all patients, other potential risk factors, i.e. sex, age, familiarity, BRAF^{V600E} mutation status (when available), are evaluable preoperatively ant the extrathyroidal extension of the tumor and/or the presence of suspicious lymph nodes are evident in most cases at the time of surgery.

Total thyroidectomy is a more radical surgical procedure which allows for a complete removal of the tumor, especially for multifocal/bilateral disease, with lower local recurrence, a lower rate of re-operations, an accurate staging of the disease, and the possibility to detect and treat any local or distant recurrence by means of RAI and serum Tg levels. However, there is no definitive evidence in the literature regarding the improvement in both recurrence and survival rates in low-risk patients treated with more aggressive approaches other than HT.

In literature, conflicting data have been reported with regard to the extent of surgery to ensure oncologic completeness. In literature, conflicting data have been reported with regard to the extent of surgery to ensure oncologic completeness. Hemithyroidectomy generally presents lower

complication rates and determines a minimal impact on a patient's life, with earlier discharge, allowing for the preservation of thyroid functions by avoiding the need for substitutive hormonal therapy in about 30–40% of cases [27, 28]. However, hemithyroidectomy presents the risk for reoperation to the contralateral lobe after definitive histology and follow-up is usually limited because of the impossibility to perform radioiodine therapy and to check Tg levels.

In our series, only 15 patients with a preoperatively known diagnosis of cancer received HT. The data obtained surprised us because in fact 15 patients out of/438 (TIR 3A and B mutates, TIR 4, and TIR 5) (3.42%) represents a very small number of patients treated with HT but this data can be justified by several factors.

First of all, it must be considered that in Italy for many years the more important guidelines had always recommended the execution of total thyroidectomy in patients with thyroid cancer, for possible multifocality, to allow the patient an easier follow-up through the dosages of serum thyroglobulin levels and to allow the patient to undergo possible radioiodine therapy. Only in recent years, the National and International guidelines opened the possibility of performing an hemithyroidectomy also in case of malignancy. In addition, as already mentioned in the introduction of this article, the advantage of performing hemithyroidectomy in patients with a thyroid microcarcinoma is well established yet, on the contrary, the surgical choice changes if the tumor exceeds 1 cm in diameter.

Another point on which we must reflect is that, outside the guidelines, in each center, there is a different reality based on choices made by a multidisciplinary team that involves not only the surgeon but also the endocrinologist and the radiologist. Furthermore, we must consider that the choice of the type of intervention is also influenced by the patient's age and by his comorbidities.

The purpose of the study was to value, on the basis of the preoperative assessment (cytological examination, ultrasound, and discussion with the patient) whether to perform HT or TT.

Analyzing the data obtained from the study, the results show a clear preference in the execution of total thyroidectomy. The data show a tendency to perform total thyroidectomy especially in tumors larger than 2 cm in diameter. The Authors strongly recommend HT where is possible, when the.

tumor is unilateral, with diameter < to 2 cm, and when the tumor is in the thyroid central position/ intralobar and not in parahistmic position or in the pericapsular site. HT is also suggested, in the elderly who may benefit from a shorter operating time and in whom hemithyroidectomy may be sufficient even for larger tumors ($> 2 \leq 4$ cm). However, for the intraoperative detection of central compartment lymph node metastases (23%) or for the patient's preference most patients underwent total thyroidectomy.

Last but not least, we have to evaluate if the risk of tumor recurrence is increased after HT. There is more risk of tumor recurrence after HT because the patient has still developed a tumor and in 6–30% of cases you can have a spread to the contralateral lobe [30, 31] that is not visible on ultrasound (because it is punctiform) and because the surgeon does not explore the "healthy" lobe. However, it is a relative risk, because if the removal of the tumor is complete, the patient's risk of developing a recurrence/disease in the contralateral lobe is only linked to age and to histological variant (because in the other cases a complete thyroidectomy is done immediately). In our series, the risk factor that showed a greater risk of recurrence was the diameter of the tumor alone.

Conclusions

In conclusion, the results of the present study do not support the routine thyroid hemithyroidectomy in the treatment of indeterminate-risk DTC patients. The risk for the postoperative complication is significantly increased in TT patients, without clear evidence of a reduction in recurrence or added benefit survival. Probably the hemithyroidectomy, in patients with DTC with diameter < 2 cm without other specific risk factors could be safe. Although the best surgical approach for DTC has to be adequately tailored, a careful patient selection, based on risk stratification, is the key to differentiating treatment options and achieving better outcomes. More prospective studies with longer follow-up periods are needed to further clarify the extent of surgery for DTC and to recognize what risk factors are predictive of recurrence. The follow-up data 5 and particular after 10 years are of great interest and would give an important impact on future treatment strategies.

Author contributions DC, SN, GF and NdM: participated substantially in the conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript. RM, DCC, SL, DG, AGL, MM,VE, DG, SS, BM, PI, DPL, TM, GA, PA, PA, LS, CPG, GG, MA, DL, PD, RR, IM, IN, LCP: participated substantially in conception, design, and execution of the study; also participated substantially in the editing of the manuscript.

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Declarations

Conflict of interest Dobrinja C., Samardzic N., Giudici F., Raffaelli M., De Crea C., Sessa L, Docimo G, 4. Ansaldo G.L., Minuto M., Var-

aldo E., Dionigi G, Spiezia S, Boniardi M., Pauna I, De Pasquale L., Testini M, Gurrado A, Pasculli A, Pezzolla A, Lattarulo S, Calò P.G., Graceffa G., Massara A., Docimo L., Parmeggiani D., Ruggiero R, Iacobone M., Innaro N, Lombardi C.P., de Manzini N. declare that they have no conflict of interest related to this article. This study has been proposed by the Unitary Italian Society of Endocrinology (SIUEC) and to the Italian Society of Oncological Surgery (SICO), which accept it in all its parts and promote it to the associated structures. All authors declare that they have no conflict of interest.

Ethical approval This research involved only human participants and was in accordance with the 1964 Helsinki Declaration. This study was approved by the institutional Ethics Committee of the Cattinara Hospital ASUGI, (study ID 3264—001_2020H).

Research involving human participants and/or animals This article does not contain any studies on animals performed by any of the authors.

Informed consent Informed consent was obtained from all patients.

References

1. Davies LWH (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 295(18):2164–2167
2. Kent WDHS, Isotalo PA, Houlden RL, George RL, Groome PA (2007) Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ 177:1357–1361
3. Leenhardt LBM, Boin-Pineau MH, Conte Devolx B, Marechaud R, Niccoli-Sire P et al (2004) Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 150(2):33–39
4. Pellegriti G, Frasca F, Regalbuto C et al (2013) Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. https://doi.org/10.1155/2013/965212
5. Alvaro Sanabria, Luiz P Kowalski, Jatin P. Shah, Iain J. Nixon, Peter Angelos, Michelle D. Williams, Alessandra Rinaldo, Alfio Ferlito. (2019)Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis. Head Neck. Author manuscript; available in PMC
6. Wang TS, Sosa JA (2018) Thyroid surgery for differentiated thyroid cancer—recent advances and future directions. Nat Rev Endocrinol 14(11):670–683. https://doi.org/10.1038/s41574-018-0080-7
7. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26:1–133
8. Abdelgadir M, Adam J, Pura P, Goffredo MA, Dinan T, Hyslop SD, Reed RP, Scheri SA, Roman JAS (2015) Impact of extent of surgery on survival for papillary thyroid cancer patients younger than 45 years. J Clin Endocrinol Metab 100:115–121
9. K. Matsuzu, K. Sugino, K. Masudo, M. Nagahama, W. Kitagawa, H. Shibuya, K. Ohkuwa, T. Uruno, A. Suzuki, S. Magoshi, J. Akaishi, C. Masaki, M. Kawano, N. Suganuma, Y. Rino, M. Masuda, K. Kameyama, H. Takami, K.Ito (2014) Thyroid hemithyroidectomy for papillary thyroid cancer: long-term follow-up study of 1088 cases.
10. Dobrinja C, Pastoricchio M, Troian M, Da Canal F, Bernardi S, Fabris B, de Manzini N (2017) Partial thyroidectomy for papillary thyroid microcarcinoma: is completion total thyroidectomy indicated? Int J Surg 41(Suppl 1):S34–S39. https://doi.org/10.1016/j.ijsu.2017.02.012
11. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM (2006) American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 16(2):109–142. https://doi.org/10.1089/thy.2006.16.109
12. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epitelium. Eur J Endocrinol 154:787–803
13. Hegedus L (2004) Clinical practice. The thyroid nodule. N Engl J Med 351:1764–1771
14. Haymart MR, Esfandiari NH, Stang MT, Sosa JA (2017) Controversies in the management of low-risk differentiated thyroid cancer. Endocr Rev 38(4):351–378
15. Fadda G, Basolo F, Bondi A, Bussolati G, Crescenzi A, Nappi O, Nardi F, Papotti M, Taddei G, Palombini L (2010) SIAPEC-IAP Italian Consensus Working Group. Cytological classification of thyroid nodules. Proposal of the SIAPEC-IAP Italian Consensus Working Group. Pathologica 102(5):405–408
16. Nardi F, Basolo F, Crescenzi A, Fadda G, Frasoldati A, Orlandi F, Palombini L, Papini E, Zini M, Pontecorvi A, Vitti P (2014) Italian consensus for the classification and reporting of thyroid cytology. J Endocrinol Invest 37(6):593–599
17. Pacini F, Basolo F, Bellantone R, Boni G, Cannizzaro MA, De Palma M, Durante C, Elisei R, Fadda G, Frasoldati A, Fugazzola L, Guglielmi R, Lombardi CP, Miccoli P, Papini E, Pellegriti G, Pezzullo L, Pontecorvi A, Salvatori M, Seregni E, Vitti P (2018) Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. J Endocrinol Invest 41(7):849–876. https://doi.org/10.1007/s40618-018-0884-2 (**Epub 2018 May 4**)
18. Gharib H, Papini E, Paschke R (2010) Thyroid nodules: a review of current guidelines, practice and prospects. EJE 08:0135
19. Rosato L, De Crea C, Bellantone R, Brandi ML, De Toma G, Filetti S, Miccoli P, Pacini F, Pelizzo MR, Pontecorvi A, Avenia N, De Pasquale L, Chiofalo MG, Gurrado A, Innaro N, La Valle G, Lombardi CP, Marini PL, Mondini G, Mullineris B, Pezzullo L, Raffaelli M, Testini M, De Palma M (2016) Diagnostic, therapeutic and health-care management protocol in thyroid surgery: a position statement of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB). J Endocrinol Invest 39(8):939–935
20. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P (2016) AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules—2016 UPDATE. Endocr Pract 22(5):622–639
21. Davies L, Welch HG (2014) Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 140(4):317–322
22. Kluijfhout WP, Rotstein LE, Pasternak JD (2016) Well-differentiated thyroid cancer: thyroidectomy or hemithyroidectomy? CMAJ 188(17–18):E517–E520. https://doi.org/10.1503/cmaj.160336
23. Matsuzu K, Sugino K, Masudo K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Uruno T, Suzuki A, Magoshi S, Akaishi J, Masaki C, Kawano M, Suganuma N, Rino Y, Masuda M, Kameyama K, Takami H, Ito K (2014) Thyroid hemithyroidectomy for papillary thyroid cancer: long-term follow-up study of

1,088 cases. World J Surg 38(1):68–79. https://doi.org/10.1007/s00268-013-2224-1
24. Vargas-Pinto S, Romero Arenas MA (2019) Hemithyroidectomy compared to total thyroidectomy for low-risk papillary thyroid cancer: a systematic review. J Surg Res 242:244–251. https://doi.org/10.1016/j.jss.2019.04.036
25. Tsui KP et al (2019) Total vs Hemithyroidectomy for intermediate risk papillary thyroid cancer: a 23 year retrospective study in a tertiary center. Am J Otolaryngol 40(3):431–434
26. Donatini G, Castagnet M, Desurmont T, Rudolph N, Othman D, Kraimps JL (2016) Partial thyroidectomy for papillary thyroid microcarcinoma: is completion total thyroidectomy indicated? World J Surg 40(3):510–515. https://doi.org/10.1007/s00268-015-3327-7
27. Lee J, Park JH, Lee CR, Chung WY, Park CS (2013) Long-term outcomes of total thyroidectomy versus thyroid hemithyroidectomy for papillary thyroid microcarcinoma: comparative analysis after propensity score matching. Thyroid 23:1408–1415
28. Ito Y, Masuoka H, Fukushima M, Inoue H, Kihara M, Tomoda C et al (2010) Excellent prognosis of patients with solitary T1N0M0 papillary thyroid carcinoma who underwent thyroidectomy and elective lymph node dissection without radioiodine therapy. World J Surg 34:1285–1290
29. Dehbi HM, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A (2019) Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. Lancet Diabetes Endocrinol 7(1):44–51. https://doi.org/10.1016/S2213-8587(18)30306-1 (**Epub 2018 Nov 27**)
30. Hui Huang, MD, Shaoyan Liu, MD,∗ Zhengang Xu, MB, Song Ni, MD, Zongmin Zhang, MD, and Xiaolei Wang, MD Monitoring Editor: Eleonore Fröhlich (2019) Long-term outcome of thyroid lobectomy for unilateral multifocal papillary carcinoma. Medicine 96(27): e7461. Published online 2017 Jul 7. doi: https://doi.org/10.1097/MD.0000000000007461.
31. Genpeng L, Jianyong L, Jiaying Y, Ke J, Zhihui L, Rixiang G, Lihan Z, Jingqiang Z (2018) Independent predictors and lymph node metastasis characteristics of multifocal papillary thyroid cancer. Medicine 97(5):e9619. https://doi.org/10.1097/MD.0000000000009619

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