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original article

Total thyroidectomy and central lymph node dissection. Experience of a referral centre for endocrine surgery

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SUMMARY: **Total thyroidectomy and central lymph node dissection. Experience of a referral centre for endocrine surgery.**

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Aim. *Thyroid cancer prognosis is determined by several variables, even with extremely elevated survival rate. The most debated issues are the type of thyroidectomy and extension of lymphadenectomy. Aim of the study is the analysis of benefits of level VI lymphadenectomy associated to total thyroidectomy in the treatment of thyroid cancer.*

Patients and methods. *316 total thyroidectomy with central node dissection were carried out in the Unit of Endocrine Surgery, University of Perugia. Direct parathyroid auto-implantation was carried out if damage or accidental excision occurred. High risk patients received radioiodine treatment.*

Results. *Lymph node metastases in the VI level were observed in 42% of cases with a significant difference (p 0.0042) of positive lymph node in level VI comparing tumor larger than 1 cm vs smaller than 1 cm. No significant differences were observed when considering difference of sex, and age. Significant difference (p 0.005) was shown when considering over 45 years old male patients with tumor larger than 1 cm vs smaller ones. The 78% of patients underwent iodine ablation after surgery. Recurrence rate in these patients was 3.2%, with no significant difference compared to not treated patients. Bilateral temporary recurrent nerves palsy were observed in 0.6% of cases, unilateral temporary recurrent nerves palsy in 3.4%, unilateral permanent palsy in 1.5%, temporary hypoparathyroidism in 17%, permanent hypoparathyroidism in 4.4%.*

Conclusions. *Total thyroidectomy combined to central node dissection, even in absence of risk factors and without clinical evident nodes, is the treatment of choice offering clear indications to radioiodine ablation.*

KEY WORDS: Cancer - Thyroidectomy - Level VI - Lymphadenectomy - Prognosis - Radioiodine treatment.

Introduction

Thyroid cancer is the most common endocrine neoplasia and consists in the 0.7-1% of all neoplasm and its incidence is continuously increasing with 8.7 cases every 100.000 inhabitants in the USA (1, 2). The incidence observed in Italy is 4.3/100.000 in male and 12.5/100.000 in female population. Specifically in Umbria Region is 5/100.000 in male and 15/100.000 in female (3).

Differentiated carcinomas (DC) are the 94% of all tumors and are divided in papillary carcinoma (80%), follicular carcinoma (11%), Hürtle cells carcinoma (3%). Medullary carcinoma and anaplastic carcinoma represent respectively 5% and 1% of cases. The 5-years survival rate is 94% and in case of anaplastic carcinoma it decreases to 5.6-11.4% (1). This percentage of survival is determined by several prognostic variable, related to the characteristics of patient (age, sex), of the tumor (size, multifocal tumoral foci, grading, histotype, extraglandular invasion, lymph node metastases), of the surgical procedure (radical resection or tumoral residual). These variables are indicated in the international more used classification systems, i.e. AMES (Age, Metastases, Extension, Size), AGES (Age, Grade, Estension, Size), MACIS (Metastasis, Age, Completeness, Invasion, Size) and TNM (4, 5). Although the survival rate is extremely elevated, the current most debated issues are the type of thyroidectomy and extension of lymphadenectomy.

Patients and methods

Since 2005 to 2009, 316 total thyroidectomy (TT) with central node dissection (CND) for papillary cancer (12% of all operations for thyroid pathology) were carried out in the Unit of Endocrine Surgery, S. Maria University Hospital, Terni, University of Perugia. The cases included 216 female

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(68%) and 100 males (32%), with a mean age of 42.32 ± 10.34 years.

All the surgical procedures were carried out in the endocrine surgery unit (AFOI, Area Funzionale Omogenea Interaziendale) of Umbria Region, by the same surgical team, with standard surgical technique. An ultrasonic scalpel, Harmonic Ace® (Ethicon Endosurgery) was used during the dissection in almost 50% of cases. The dissection was operated with preliminary superior and inferior laryngeal nerves identification, the inferior was followed completely till the larynx. If vascular damage or accidental excision of parathyroid glands was observed, their direct autoimplatation in the sternocleidomastoideus muscle was carried out. In all patients a Jackson Pratt drainage was used and removed in first post-operative day. Plasmatic Calcium level was tested twice in first post-operative day. In the 98% of cases, patients were discharged in second post-operative day.

Radioactive iodine ablation

Current indication to radioactive iodine (RAI) ablation is still debated although there is a general trend in reducing its use. Our surgical unit follows the guidelines of the Oncological Multidisciplinary Team of Umbria Region (Centro di Riferimento Oncologico Interaziendale, CRO).
The protocol of treatment includes:

- Very low risk patients: papillary unifocal carcinoma with size < 1 cm, without lymph node metastases, radical surgery and good prognosis histotype.
- Low risk patients: papillary unifocal carcinoma with size between 1 and 2 cm, without lymph node metastases, multifocal tumors or with size between 2 and 4 cm, limited to the thyroid, without systemic or lymph node metastases.
- Intermediate high risk patients: all T3-T4 differentiated carcinoma, all N1 and M1 tumors and high grade tumors.

According to this classification RAI treatment is indicated in intermediate high risk patients, whereas in low risk patients the treatment is indicated considering surgical radicality, histotype, age and all the risk factors.

In RAI treatment a proper level of TSH stimulation with concentration higher than 25-30 mU/ml is recommended. In low risk patients TSH increase is gained by suspension of Levo-tiroxine (L-T4) intake, as endogenic stimulation, or by rhTSH treatment as esogenic stimulation. In intermediate high risk patients the increased level of TSH might be preferably obtained by endogenic stimulation.

Follow-up

The CRO provides guidelines for follow-up
In patients affected by papillary carcinoma T1 with size ≤ 1 cm, N0M0, treated by total thyroidectomy: a neck ultrasound after 6 months and than every year and FT3, FT4, TSH, Tireoglobulin (Tg), Anti-Tg antibody dosage every 6 months and during endogenic and esogenic stimulation.

In patients treated by total thyroidectomy and radioiodine ablation:

- Low risk: after 3 months during TSH suppression, FT3, FT4, TSH, Tg, Anti-Tg antibody dosage and neck ultrasound. 8-12 months after rhTSH, Tg dosage and ultrasound. Every 6 months FT3, FT4, TSH, Tg, Anti-Tg antibody dosage during L-T4 treatment. Every 12 months ultrasound is recommended. Further rhTSH test is suggested only in patients with a positive Tg after rhTSH, associated to negative radiological imaging or clinical suspicion of recurrence not otherwise demonstrated.
- Intermediate high risk: Ultrasound FT3, FT4, TSH, Tg, Anti-Tg antibody after 3 months and during esogenic stimulation and after 6-8 months an ultrasound control are recommended. Further rhTSH test only in patients with a positive Tg after rh TSH, associated to negative radiological imaging or to clinical suspicion of recurrence not otherwise demonstrated.

Statistical analysis

The statistical comparison between groups was performed by using chi-squared test and Fisher's exact probability test.

P values were reported as the result of two-tailed testing and P values less than 0.05 were considered as statistically significant.

Results

An average volume of 30 cc was collected in the drainage. Lymph node metastases in level VI were observed in 42% of cases at the final histological examination. Results showed a significant difference (p 0.0042) of positive lymph nodes in level VI comparing tumor larger *vs* smaller than 1cm, respectively with a rate of lymph node metastases of 52,8% *vs* 26%. Female patients older than 45 years old presented a rate of positive lymph node of 38.9%, 57% when younger with no significant difference. Similar results were observed in males comparing patients older *vs* younger than 45 years old, with respectively 37% and 33% of involved lymph nodes. Not significant resulted the difference of positive lymph nodes comparing patient's gender (Table 1).

Furthermore when considering all the prognostic factors female older than 45 years, with tumor size larger than 1cm presented metastases in 48% of cases, when younger only in 13%, with no significant difference. Younger patients with tumor larger than 1cm, presented positive lymph nodes in the 62% of case, 50% in smaller cancer, even with no significant difference.

A significant difference (p 0.005) was observed when considering over 45 years old male patients with tumor larger than 1cm *vs* smaller ones, respectively with positive nodes in 48% of patients older than 45 years with tumor >1 cm, 0% in older than 45 years with tumor

TABLE 1 - POSITIVE VI LEVEL LYMPH NODES INVOLVEMENT CONSIDERING ONLY ONE PROGNOSTIC FACTOR: TUMOR SIZE, GENDER AND AGE.

Size	Tumor > 1 cm (n=110/208) 52.8%			Tumor < 1 cm (n=28/108) 26%		p 0.0042
Gender	Female (n=102/216) 47.2%			Male (n=36/100) 36%		p 0.28
Age	> 45 years (n=46/118) 38.9%	<45 years (n=56/98) 57%	p 0.14	> 45 years (n=26/70) 37%	<45 years (n=10/30) 33.3%	p 0.96

TABLE 2 - POSITIVE VI LEVEL LYMPH NODES INVOLVEMENT CONSIDERING COMBINATION OF PROGNOSTIC FACTORS (TUMOR SIZE, GENDER AND AGE).

	Female			Male		
	Tumor > 1cm	Tumor < 1 cm		Tumor >1 cm	Tumor < 1 cm	
> 45 years	(n=42/86) 48%	(n=4/32) 13%	p 0.76	(n=26/54) 48%	(n=0/16) 0%	p 0.005
< 45 years	(n=36/58) 62%	(n=20/40) 50%	p 0.65	(n=6/10) 60%	(n=4/20) 20%	p 0.15

< 1 cm, 60% in younger than 45 years old with tumor > 1 cm and 20% in younger than 45 years old with tumor < 1cm (Table 2).

The 78% of patients underwent RAI after surgery. Recurrence rate in these patients was 3.2% (8 patients out of 247), in not treated patients after thyroidectomy 4.3% (3 patients out of 69), with not significant difference. Complications observed were 2 bilateral temporary recurrent nerves palsy (0.6%), 11 cases of unilateral temporary recurrent nerves palsy (3.4%), 5 cases of unilateral permanent palsy (1.5%), 54 cases of temporary hypoparathyroidism (17%), 14 cases of permanent hypoparathyroidism (4.4%).

Discussion

Survival in patients affected by papillary thyroid carcinoma is related to different factors including age, tumor size, stage and surgical radicality.

In the present study all patients affected by papillary thyroid carcinoma underwent TT and CND, level VI. Although general consent is registered regarding the extension of TT, different authors report controversial experiences about lymphadenectomy of level VI of the neck. The American Thyroid Association (ATA) guidelines recommend the level VI lymphadenectomy in high risk patients but it is not considered mandatory in patients with T1 tumors (6).

Conzo et al. (7) evaluated the importance of clinical nodal status considering 221 patients affected by DTC, classified as cN0 and treated by TT alone. They excluded from the study 211 patients classified as cN1 who had clinically suspicious lymph node findings by preoperative ultrasound or intraoperative inspection and who underwent lymphadenectomy. As a matter of fact Conzo considers central nodal dissection therapeutic rather than prophylactic in case of clinical pathological lymph nodes.

As opposite experience, Clark (8) due to the lack of evidence recommends lymphadenectomy, till relevant results coming from clinical studies will be obtained. Other authors suggest more conservative approach indicating lymphadenectomy only for high risk patients (9) or limiting it to ipsilateral lymph nodes (10).

Chisholm (11) performs a prophylactic dissection in all high risk patients while other authors (12) report that it decreases local recurrence and increases the rate of post-operative undetectable levels of Tg . Shen (13) showed a 10-15% of lymph node recurrence in patients who did not undergo a level VI lymphadenectomy, although an high rate of complication in those patients treated by prophylactic bilateral lymph node dissection.

Benefit of CND when clinically positive nodes are detected is widely accepted. Differently, in absence of definitive evidence regarding oncologic benefit from dissecting clinically negative lymph nodes, the significance of microscopic nodal disease is widely questioned (14).

Randolph et al. (15) deeply investigated the role of nodal metastases highlighting the differences in recurrence risk in node-positive patients based on nodal characteristics. Specifically, cN0 patients who have pN1, low volume microscopic central nodal metastases, without extranodal extension in neck dissection specimens, still have very low recurrence risk, similar to the recurrence risk in cN0/pN0 patients who didn't undergo nodes dissection. Whereas cN1 patients present a 22 % of recurrence. Both, microscopic cN0/ pN1 and cN1/pN1 are staged by TNM classification as N1, although they present a significant difference in recurrence, confirming the importance of identification of clinically positive nodes before and during surgery in order

to perform a justified lymph node dissection. Another important issue is related to the use of RAI treatment. In the experience reported by Conzo (7), considering the long retrospective observation time, there is a wide use of RAI which is nowadays debated especially for low risk patients in order to minimize morbidity or overtreatment which are present especially if the ablation is not necessary for reducing recurrence rate and improving survival.

Recent literature (16) indicates that RAI ablation did not significantly impact survival/recurrence rate in low-risk patients and the equivalence of low and high dose for successful postoperative ablation in low-risk patients, considering possible avoidance of RAI in low-risk patients.

Differently Conzo et al. (7) observe that for cN0 patients in whom the decision to give RAI is made preoperatively, prophylactic central lymphadenectomy adds no benefit. Although routine prophylactic CND is not yet supported by recurrence/survival benefit, it offers more accurate staging which can correctly indicate post-operative RAI (17).

Sywak et al. (18) reported lower TG levels in patients treated by prophylactic central dissection before RAI ablation and 6 months after compared with a control group undergoing total thyroidectomy alone followed by RAI ablation. Bonnet et al. (19) reported that patients with T1 tumors undergoing prophylactic neck dissection, were excluded from RAI in 15 % of cases who would have otherwise received RAI without documentation of pN0 status.

Goddard and Steward (14) commenting results presented by Conzo (7) present the protocol adopted in their institution which favors potential avoidance of RAI therapy. They currently offer ipsilateral central nodal dissection to cN0 patients with T1 or T2 tumors. The information obtained from the nodal status is used to evaluate indication to iodine treatment, specifically avoiding RAI in patients who are pN0 without negative prognostic factors. Potential surgical morbidity in the form of transient hypocalcemia and laryngeal nerve lesion, is justified by potential avoidance of morbidity associated with not necessary RAI, although in these patients, this treatment could lead to upstaging and potential overtreatment of some patients. The authors underline that a prospective randomized controlled trial regarding prophylactic neck dissection was deemed to be infeasible by the ATA in 2012 due to statistical reason (15).

Our experience as a referral centre for Endocrine Surgery shows that the only prognostic factor significantly affecting the rate of lymph node involvement is the tumor size with significant difference in male patients using a cut-off of 1cm, whereas gender and age, when considered, didn't show any significant difference in relation to positive lymph nodes. Nevertheless incidence of lymph nodes involved resulted elevated in all groups examined, having metastases in about the 50% of patients, as previously shown by literature (2, 20) especially when patients are older than 45 years old with tumor larger than 1cm.

According to the classification of risk for patients affected by DTC adopted by the Multidisciplinary Team, University of Perugia, RAI treatment is indicated in intermediate-high risk patients, whereas in low risk patients the treatment is indicated considering surgical radicality, histotype, age and all the risk factors.

In our series RAI ablation seems not affecting significantly the incidence of recurrence after TT with lymphadenectomy, comparing treated *vs* not treated patients. For this reason we consider TT associated with routine level VI lymphadenectomy for thyroid cancer a reasonable treatment, at the light of current knowledge, in order to properly stage tumors and refer patients to RAI treatment only in cases selected by histological confirmation of nodal involvement, minimizing morbidity and overtreatment with acceptable complication rate due to CND. Although not already proven by randomized trial, this trend is clearly supported by literature (21).

The complication's rate we reported, in term of temporary and permanent hypoparathyroidism and inferior laringeal nerve palsy, might be considered acceptable in a referral centre for thyroid surgery compared to those presented in the main experiences reported in literature, especially when considering the higher risk of complications if reoperation is required (up to 9% of laryngeal nerves injury and 14% of hypoparathyroidism) (22-28). We report a recurrence rate in RAI treated patients of 3.2%, in not treated of 4.3%, with not significant difference. Conzo (7) observed analogous rate of loco-regional recurrence, with positive cervical lymph nodes, of 3.16 % in treated patients. Comparing complications we report a rate of 1.5% of unilateral permanent palsy, 4.4% of permanent hypoparathyroidism, Conzo (7) observed an incidence of permanent vocal chords paralysis and permanent hypoparathyroidism (iPTH <10 pg/ml), both of 0.91 %.

We agree that further studies concerning TT plus CND are required to better define the risk class and proper indication to RAI. This results should be related to a property in follow-up procedures and to the use of RAI which considers different protocols in case of lymph node metastasis (N+) independently from others risk factors.

Nevertheless TT combined to CND even in absence of risk factors and without clinical evident nodes, might be considered the best option in order to achieve a proper cure and a clear identification of prognostic factor and indication to RAI treatment.

Conclusions

In our experience lymph node involvement at level VI is observed in an high rate. In presence or less of risk factors we observed that this evidence might itself represent the criteria to indicate extension of lymphadenectomy in absence of clinical detectable lymph nodes.

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