Therapeutic options in locally advanced thyroid carcinoma

Our experience

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INTRODUCTIONS: *Thyroid cancer is the most common endocrine malignancy with an incidence equal to 1% of all malignant tumors. Prognostic factors affecting survival are manifold, including in several classifications (AMES, AGES, CORN and TNM). In this sense, the invasion of adjacent structures is one of the most important variables. The authors describe the experience of a single center in surgical treatment of advanced thyroid cancer.*
MATERIALS AND METHODS: *Between 1986 and 2010 , 1565 patients were undergoing surgery with thyroid cancer. In particular, 1403 interventions were made for differentiated cancer, 97 for medullary carcinoma, 25 for insular carcinoma, 29 for anaplastic carcinoma, 2 for plasmacytoma, and 7 for lymphoma and 2 for angiosarcoma. Among these 896 showed invasion of adjacent structures and / or distant metastases.*
RESULTS: *There were no perioperative deaths or major complications. Surgical procedures consisted of: 13 loboistmectomy, 519 total thyroidectomy (TT), 325 TT with lymphadenectomy of the central compartment, 7 TT with radical lymphectomy, 621 TT with functional lymphectomy, 6 TT with breast lumpectomy, 5 TT with with video-assisted lung metastasectomy, 16-TT with resection and tracheal anastomosis, 6 TT with laryngotracheal resection, 3 TT with laryngectomy, 4 TT with trachetomy, 28 TT with respiratory stent placement, 12 tracheotomy. At present, 1328 patients were free of disease, while 104 showed recurrence. Total of 133 deaths were recorded, all linked to disease relapse.*
DISCUSSION: *The role of surgery in the treatment of advanced thyroid cancer is still undeniable. In the presence of extracapsular trespassing, in fact, the adoption of interventions demolition permits long-term survival, given the lack of aggressiveness of the tumor differentiated representing the majority of cases. The aim of surgical radicalization addition, even in the presence of distant metastases, it is justified by the possibilities offered by the therapeutic radioiodine treatment, which is not feasible in the presence of significant amounts of thyroid tissue which picks. In the presence of undifferentiated tumors, finally, endoscopic or surgical treatment may be indicated by simple purpose of palliation of respiratory symptoms.*

KEY WORDS: Advanced thyroid carcinoma, Combined treatment, Local invasion.

Introduction

Thyroid cancer is the most frequent endocrine neoplasm, accounting for 0.7-1% of all malignancies [1]. In Italy incidence reaches 4.3 x 100,000 in males and 12,5 x 100,000 in females.
Ninetyfour percent of all thyroid malignancies are differentiated carcinomas (DTC), 5% are medullary carcinomas (MC) while 1% are anaplastic carcinoma (AC) [2]. Long term survival is 94% at 5 years (DTC), against only 5.6-11.4% for AC [3]. Prognostic factors affecting survival are patient-related (age, gender), tumor-related (size, multicentricity, histologic type, grading, extension to adjacent structures, lymph node spread, blood-borne metastasis), and procedure-related (complete/incomplete

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resection). The above mentioned variables are included in the most widely used classification systems: AMES (Age, Metastasis, Extension, Size), AGES (Age, Grade, Extension, Size), MACIS (Metastasis, Age, Completeness, Invasion, Size), and TNM. Recurrence rate (RR) and overall survival (OS) are high-risk indicators influenced by age >45 years, M+ stage, T3-4, histology (tall cell, columnar cell, diffuse sclerosing, widely invasive follicular carcinoma, poorly differentiated "insular" follicular carcinoma).
Invasion of adjacent structures is one of the principal prognostic factors in DTC [5-9], In such clinical setting surgery plays a central role regarding extent of thyroid resection, of lymphectomy, and resection of adjacent structures involved by the neoplasm.
In the present paper the Authors report the own experience in the management of both locally invasive thyroid tumors and local tumor recurrence.

Materials and methods

A series of 1565 patients (age range 18-89 years), underwent at surgical resection for thyroid carcinoma between 1986 and 2010, are analyzed retrospectively. Specifically, 1403 procedures were performed for DTC, 97 for MC, 25 for insular carcinoma (ITC), 29 for AC, 2 for plasmocitoma, 7 for lymphoma, and 2 for angiosarcoma.
Preoperative workup included:
– FT3, FT4, TSH;
– CEA, Calcitonin;
– anti-TPO, Anti-TGB;
– neck ultrasound;
– FNAB of the lesion;
– chest films;
– I131 Scinti scan;
– laryngo-tracheoscopy.

If local invasion was suspected the following procedures were added:
– rigid bronchoscopy;
– CT and/or MR scan.

Results

In 896 patients local and/or distant extension was detected (57.25% of operations performed for thyroid cancer). Direct neoplasm extension involved cricothyroid muscles in 43 cases (4.7%), strap muscles in 92 (10.2%), sternocleidomastoid muscle in 7 (0.7%), unilateral recurrent laringeal nerve (RLN)(3.3%), bilateral RLN in 6 (0.6%), laryngo-tracheal axis in 69 (7.7%), cervical esophagus in 7 (0.7%), vessels in 11 (1.2%), skin in 11 (1.2%), cervical sympathetic chain in 4 (0.4%), lymph nodes in 621 (69.3%). Lung secondaries were present in 31 cases (3.4%), bone in 12 (1.3%), breast involvement in 6 (0.6%). The surgical procedures are summarized in Table I. In 12 cases the occurrence of laterocervical lymphadenopathy led to the diagnosis of thyroid cancer. Of the 13 patients submitted to LI, in 11 cases microcarcinomas were occasionally detected in surgical specimen; in the remaining two the patients refused TT (dimension tumor < 1 cm.). The patients with resectable lung secondaries were managed as follows: TT first and, five days later, VATS lung metastasectomy. In the other 26 cases the lesions were too numerous to permit resection. In case of breast secondary, TT and breast quadrantectomy were performed simultaneously.

Table I

Loboisthmectomy (LI)	13
Total Thyroidectomy (TT)	519
TT + central compartment lymphectomy (MAS)	325
TT+ radical neck dissection (RND)	7
TT+ functional neck dissection (FND)	621
TT+ superoexternal quadrantectomy (SEQ)	6
TT + Videoassisted lung meastasectomy (VATS – MTS)	5
TT + tracheal resection (TTR)	16
TT+ laryngotracheal resection (TT-LTR)	6
TT+laryngectomy (LAG)	3
TT + tracheotomy (TCT)	4
TT+ tracheal stent	28
TCT alone	12

Table II - *Patients free of disease*

DTC	**1264**
LI	13
TT	459
TT+MAS	269
TT+FND	512
TT+TRR	9
TT+LTRR	2
MTC	**64**
TT + MAS	37
TT + FND	27

Table III - *Disease recurrence*

DTC	**73**
TT	4
TT+MAS	24
TT+FND	38
TT+LAG	2
TT+TRR	4
TT+MTS	1
MTC	**31**
TT+MAS	4
TT+FND	27

For DTC, lymphectomy was always performed in the central compartment, and when necessary in the II, III, IV level.
In the 69 cases of laryngotracheal axis involvement, 40 procedures were performed with palliative intent, due to histology (AC), multi-organs metastatic disease or poor general conditions. Such cases were managed by endoscopic airway stenting (Dumon/Ultraflex) or tracheotomy. Patients free of disease are 1328 (1264 DTC – 64 MTC) The results are summarized in Table II. Recurrence occurred in 104 patients (73 DTC, 31 MTC - Table III). Four ITC patients have bone secondaries. In the DTC group, 71 patients died (TT 3, TT+MAS 10, TT+FND 12, TT+TRR 3, stent 28, TCT 10, TT+TST 4, TT+MTS 1). Six MTC patients (TT+MAS 3, TT+FND 3), all patients with anaplastic carcinoma, insular carcinoma and angiosarcoma died .

Discussion

Aero-digestive tract involvement, by the thyroid neoplasm growth, can occur in different manners: compression, dislocation or infiltration (incidence ranging between 5 and 34%) [10]. Symptoms include dyspnea (33%), dysphagia (25%), hemoptysis (25%), hoarseness (18%) [11].
Extrathyroid extension involves neck muscles in 8.1% of cases, trachea in 7.7%, esophagus in 3%, larynx in 2.2%, sternum in 3% [12].
Two studies [13,14] report the following incidences: RLN 47-61%, trachea 55-60%, larynx 34%, neck muscles 43-78%, jugular vein 13-45%, carotid artery 6%, vagus nerve 4-13%, skin 4%, esophageal wall 17-29%, full-thickness esophageal invasion 6%.
At present, extension of surgical resection is matter of debate. The main surgical goal is complete ablation of the tumor, resection of the infiltrated structures and regional lymph-nodes if positive, with minimal morbidity, enabling disease staging. With such basis, adjuvant therapy and follow-up can be established.
In case of locally invasive tumors, the breathing and alimentary functions need to be preserved, minimizing symptoms through local control of the disease.
Patient performance status, extension of disease and histology are the parameters upon which therapeutic decision is made, with a staged interventional philosophy [15].
According to AJCC, a locally advanced tumor is a T4a-T4b lesion extending beyond the thyroid capsule, to infiltrate subcutaneous tissue, laryngo-tracheal axis, esophagus, RLN, prevertebral fascia, carotid artery or mediastinal vessels. It is well-known that extrathyroid extension is a risk factor for recurrence, increasing mortality of DTC, both in papillary and follicular patterns [16, 17]. For such reason the surgical resection must be as complete as possible, considering that recurrence rate is about 1% for R0 resections vs about 25% for R1-2 procedures [18]. Similarly, metastatic spread and 5-year mortality, in the above mentioned settings, reach 46 and 27% vs 77 and 94%, respectively [19].
Muscle and Vessel Invasion. Infiltration of adjacent muscular structures is very frequent (43-78%); in our experience 63%. If the trachea is involved, incidence of muscular invasion is about 70%. Two aspects deserve consideration: 1) if only muscle infiltration is present, the outlook does not change, so a radical excision is warranted; 2) if muscles are involved by recurrence or metastatic spread, outlook worsens [20]. The internal jugular vein is invaded more frequently than the carotid artery: its resection en-bloc with the gland does not influence morbidity or mortality provided monolateral. Carotid artery invasion is surely more worrisome: in such case shave resection is generally performed. If intraluminal growth is present, both en-bloc resection and simple interruption of the vessel have been successfully applied, after evaluation of cerebral vascular reserve.
Esophageal Invasion. Dysphagia is present roughly in 25% of patients affected by locally advanced tumor, but only in few the esophageal wall is totally invaded. Mucosa infact acts as a barrier against disease infiltration.
Laryngotracheal Axis Invasion. The main symptoms of laryngotracheal axis involvement are hemoptysis (11%), dyspnea (5%), stridor (22%), due to the fact that dyspnea ensues for a lumen cross-sectional reduction of at least 50%. Five- and 10-year survival are in the range of 60-79% and 50-63%, respectively [21, 22]. Larynx and trachea can be infiltrated both by direct tumor invasion or by lymph node metastatic growth. Perichondrium acts as an efficient barrier against invasion; infact larynx infiltration occurs either laterally through the thyroid cartilage or anteriorly across the cricoid cartilage and cricothyroid membrane. Rarely the pyriform sinus is reached by upper pole neoplasms. Shin et al described 5 stages of neoplastic extension:
– stage 0: tumor limited to the gland;
– stage I: extension to the perichondrium, but no cartilage or soft tissue erosion or invasion;
– stage II: cartilage erosion, but no transmural extension;
– stage III: extension through the cartilage, but not beyond the mucosa;
– stage IV: disease extension beyond the mucosa, reaching the tracheal lumen.

Dralle et al classified 6 types of laryngo-trachel resections, to be performed on the basis of site and extent of visceral invasion:
– type 1: limited area of invasion, often associated with homolateral RLN infiltration, with a longitudinal extension less than 2 cm and not greater than 1/3 of circumference. Possible reconstruction by sternomastoid muscle flap;
– type 2: similar to type 1, but more distal in the trachea. No laryngeal involvement;

– type 3: as type 1, but longitudinal extension >2cm or >1/3 of circumference. Laryngo-tracheal or tracheal resection-reconstruction;
– type 4: as type 3, but only tracheal;
– type 5: bilateral tumor growth in the laryngo-cricoid region. No esophageal involvement. Total laryngectomy with tracheotomy;
– type 6: pharyngo-esophageal involvement. Laryngo-pharyngectomy with cervical esophagectomy.

Extent of resection at present is still matter of debate. As far as technique is concerned, three options are available: shave resection, window resection and segmental resection with end-to-end reconstruction. Complete resection provides better 5-year survival compared to incomplete resection (R2 disease). Lipton et al [23] report survival rates of 90% and 35%, respectively, Ishihara [24] 78% and 44% respectively, Czaja [25] 85% and 50% respectively. Opinions diverge regarding conservative resections (R1 disease): R0-R1 5-year survival rates are 90% vs 75% according to Lipton, 85% in both settings according to Czaja, 84% in both settings for McCarty [26]. Apart from these Authors reporting similar survival values both for R0 and R1 resections, others do emphasize that R1 resections in the long term entail a strong risk of recurrence: McCarty (17%), Parck (25%), vs R0 resections: Nakao (6.5%), Gaissert (12.3%). The last Author also considers timing of surgery as an important prognostic factor, with 10- and 20-year disease-free survival (DFS) after early resection at 67% and 50%, against 7% and 0% respectively, for delayed resection. Finally, salvage procedures (*exenteratio*) achieving complete resection provide 74% and 61% survival at 5- and 10-years.
Sternal and Distant Metastases. Distant spread for DTC is rare, and mostly located in the lung and bones. Less than 1% of patients with papillary carcinoma and 3-4% of those with follicular carcinoma show distant metastases at the time of diagnosis. Outlook worsens with bone metastasis, alone or in other sites; bone resection is indicated only for solitary bone lesions, in order to maximize I131 action against other visceral sites [27]. Metastatic spread to the lung only is detected in 45-68% of cases who do recur, to the bone in 16-39%, to other sites (single or multiple) in 4% and 12-15%, respectively. Survival is related also to age (69% <45 years, 50% >45 years), site (lung or bone), histology (papillary vs follicular), I131 affinity [29,30].
Sternal invasion, mainly observed with follicular carcinoma, causes pain, ulceration, dyspnea. It may cause sudden death for superior vena cava obstruction [31]. In such case resection can be partial (<50%), subtotal (>50%) or total (100%).
Sternal substitutes are Marlex mesh, PTFE patch, myocutaneous flap, used alone or in combination. Literature contributions on this specific topic are few, but reported results are very good, with 5-year survival rates reaching 70% [32].

Conclusions

DTC shows very good long term survival. Such result significantly worsens in locally advanced cases (60-70% at 10 years). Local recurrence and distant spread require sound diagnostic workup and surgical planning aimed at gaining the best results with minimal morbidity and mortality. We agree with literature data indicating surgery as the treatment of choice for locally advanced DTC. Surgical results can be consolidated, when necessary, by application of adjuvant therapy, endoluminal laser therapy and stent placement, in order to improve quality of life.

Riassunto

INTRODUZIONE: Il cancro della tiroide è la più frequente neoplasia endocrina con una incidenza pari all'!% di tutti i tumori maligni. I fattori prognostici che influenzano la sopravvivenza sono molteplici, inclusi in numerose classificazioni (AMES, AGES, MAIS e TNM). In tal senso l'invasione di strutture adiacenti è tra le variabili di maggior importanza. Gli Autori descrivono l'esperienza di un singolo centro nel trattamento chirurgico dei tumori avanzati della tiroide.
MATERIALI E METODI: Tra il 1986 ed il 2010 sono stati sottoposti a chirurgia 1565 pazienti affetti da neoplasia tiroidea. Tra questi 896 presentavano invasione delle strutture contigue e/o metastasi a distanza. Le procedure chirurgiche sono consistite in: 13 loboistmectomie, 519 tiroidectomie totali (TT), 325 TT con linfoadenectomia del comparto centrale, 7 TT con linfectomia radicale, 621 TT con linfectomia funzionale, 6 TT con quadrantectomia mammaria, 5 TT con metastasectomia polmonare video assistita, 16 TT con resezione-anastomosi tracheale, 6 TT con resezione anastomosi laringo-tracheaòe, 3 TT con laringectomia, 4 TT con trachetomia, 28 TT con posizionamento di stent respiratorio, 12 tracheotomia.
RISULTATI: Non sono stati osservati decessi perioperatori, né complicanze maggiori. Al momento attuale 1328 pazienti sono liberi da malattia, mentre 104 mostrano recidiva. Sono stati complessivamente registrati 133 decessi, tutti legati a ripresa di malattia.
DISCUSSIONE: Il ruolo della chirurgia nel trattamento delle neoplasia tiroidee avanzate appare tuttora indiscutibile. In presenza di sconfinamenti extracapsulari, infatti, l'adozione di interventi demolitivi consente lunghe sopravvivenze, in considerazione della scarsa aggressività delle neoplasia differenziate che rappresentano la maggioranza dei casi. L'intento della radicalizzazione chirurgica inoltre, anche in presenza di metastasi a distanza, appare giustificato dalle possibilità terapeutiche offerte dal trattamento radiometabolico, non attuabile in presenza di significativa quantità di tessuto tiroideo captante. In presenza di neoplasie indifferenziate, infine, un tratta-

mento chirurgico od endoscopico può trovare indicazione con semplice finalità di palliazione della sintomatologia respiratoria.

References

1. Davies L, Welch HG: *Increasing incidence of thyroid cancer in the United States. 1973-2002*. JAMA, 2006; 295:2164-167.

2. Mazzaferri L: *Management of low-risk differentiated thyroid cancer.* Endocr Pract, 2007; 13:498-512.

3. Yu GP, Li JC, Branovan D, et al.: *Thyroid cancer incidence and survival in the national cancer institute surveillance, epidemiology, and end results race/ethnicity groups*. Thyroid, 2010; 20:465-73.

4. Rosaí J, Zampi G, Carcangiu ML: *Papillary carcinoma of the thyroid. A discussion of its several morphologic expressions, with particular enphasis on the follicular variant*. Am J Surg Pathol, 1983; 7:809-17.

5. Shaha AR: *Advances in management of Thyroid Cancer*. Int J Surg, 2005; 3:213-20.

6. Eustatia-Rutten CF, Corssmit EP, Biermasz NR et al: *Survival and death causes in differentiated thyroid carcinoma.* J Clin Endocrinol Metab, 2006; 91:313-19.

7. Mazzaferri EL, Jhiang SM: *Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer.* Am J Med, 1994; 97:418-28.

8. Lorentz TG, Lau PW, Lo CY, et al: *Multivariate analysis of risk factors influencing servivol in 110 ethnic chinese with papillary thyroid cancer*. Word J Surg, 1994; 18:547-50.

9. Lin HW, Bhattacharyya N: *Clinical behavior a follicular variant of papillary thyroid carcinoma: Presentation and survival.* Laryngoscope, 2010; 120:S163.

10. Datta D, Lahiri B: *Recurrent thyroid carcinoma presentino a san endotracheal nodule*. Conn Med, 2002; 66:585-87.

11. Segal K, Shpitzer T, Hazan A, et al: *Invasive Well-differentiated thyroid carcinoma: Effect of treatment modalities on autcome.* Otolaryngol Head Neck Surg, 2006; 134:819-22.

12. Hay ID, McConahey WM, Goellner JR: *Managing patients with papillary thyroid carcinoma: Insights gained from the Mayo Clinic's experience of treating 2512 consecutive patients during 1940 through 2000*. Trans Am Clin Climatol Assoc, 2005; 113:241-60.

13. Breaux E, et al.: *Treatment of locally invasive carcinoma of the thyroid: how radical?* Am J Surg, 1980; 14:514-17.

14. Nakao K, Kurozumi K, Fukushima S, et al.: *Merits and demerits of operative procedure to the trachea in patients with differentiated thyroid cancer.* World J Surg, 2001; 25:723-27-1.

15. Mattavelli F, Bombardieri E, Collini P, et al.: *Role of Urgere in treatment of advanced differentiated thyroid carcinomas.* Acta Otorhinolaryngol Ital, 2007; 27:62-67.

16. Kebebew E, Clark OH: *Differentiated thyroid cancer "complete" rational approach*. World J Surg, 2000; 24:942-51.

17. György F, Lukács G, Nagy EV, et al.: *Differentiated thyroid carcinoma prognostic factors.* Magy Seb, 2001; 54:69-74.

18. Ito Y, Fukushima M, Yabuta T, et al.: *Prognosis of papillary thyroid carcinoma with minimal tracheal invasion.* Asian J Surg, 2009; 32:102-08.

19. Wada N, Nakayama H, Masudo Y, et al.: *Clinical outcome of differentiated modes of resection in papillary thyroid carcinomas with laringotracheal invasion*. Langenbecks Arch Surg, 2006; 391:545-49.

20. Nishida T, Nakao K, Hamaji M: *Differentiated thyroid carcinoma with airway invasion: indication for tracheal resection based on the extent of cancer invasion.* J Thorac Cardiovasc Surg, 1997; 114:84-92.

21. McCaffrey TV, Bergstralh EJ, Hay ID: *Locally invasive papillary thyroid carcinoma (1949-1990).* Head Neck, 1994; 16:165-72.

22. Andersen PE, Kinsella J, Loree TR, et al.: *Differentiated carcinoma of the thyroid with extrathyroidal extension.* Am J Surg, 1995; 170:467-70.

23. Lipton RJ, McCaffrey TV, van Heerden JA: *Surgical treatment of invasion of the upper aerodigestive tract by welldifferentiated thyroid carcinoma*. Am J Surg, 1987; 154:363-67.

24. Ishihara T, Kobayashi K, Kikuchi K, et al.: *Surgical treatment of advanced thyroid carcinoma invading the trachea*. J Thorac Cardiovasc Surg, 1991; 102:717-20.

25. Czaja JM, McCaffrey TV: *The surgical management of laryngotracheal invasion by well-differentiated papillary thyroid carcinoma*. Arch Otolaryngol Head Neck Surg, 1997; 123:484-90.

26. McCarty TM, Kuhn JA, Williams WL Jr, et al.: *Surgical management of thyroid cancer invading the airway*. Ann Surg Oncol, 1997; 4:403-08.

27. Eroglu A, Karaoglanoglu N, Bilen H, Gursan N: *Follicular thyroid carcinoma. Metastasis to the sternum, 13 years after total thyroidectomy.* Int J Clin Pract, 2006; 11:1506-08.

28. Lin JD, Huang MJ, Juang JH, et al.: *Factors related to the survival of papillary and follicular thyroid carcinoma patients with distant metastases*. Thyroid, 1999; 9:1227-235.

29. Lee J, Soh EY: *Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors.* Ann Surg, 2010; 251:114-19.

30. Sampson E, Brierley JD, Le LW, et al.: *Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastases at diagnosis*. Cancer, 2007; 110:1451-456.

31. Kitamura Y, Shimizu K, Nagahama M, et al.: *Immediate causes of death in thyroid carcinoma: Clinicopathological analysis of 161 fatal cases*. J Clin Endocrinol Metab, 1999; 84:4043-49.

32. Mssrouri R, Mohammadine E, Benamr S, et al.: *Sternal metastasis from differentated thyroid carcinoma:what management ?* J Chir (Paris), 2009; 146:48-52. 2009; 146:48-52.