

ONCOLOGY

Role of surgery in treatment of advanced differentiated thyroid carcinomas

Il ruolo della chirurgia nel trattamento dei casi avanzati di carcinoma differenziato della tiroide

F. MATTAVELLI, E. BOMBARDIERI¹, P. COLLINI², L. COSTA, N. PIZZI, D. FALLAHADAR, E. PENNACCHIOLI³, S. SANTAMARIA⁴, N. CASCINELLI⁵

Otorhinolaryngology Unit, ¹ Nuclear Medicine Unit, ² Dept. of Pathology, ³ Dept. of Surgery, Istituto Nazionale dei Tumori, Milan; ⁴ Maxillo-Facial Surgery Unit, Policlinico Universitario di Messina; ⁵ Scientific Director, Istituto Nazionale dei Tumori, Milan; Thyroid Cancer Study Group of Istituto Nazionale dei Tumori, Milan, Italy

SUMMARY

Well-differentiated thyroid carcinomas are characterized by a long natural history. The evolution of the reconstructive techniques and the improvement of the peri-operative anaesthesiologist management of the patient have contributed, over the last few years, to a progressive widening of demolitive surgery. The aims of enlarged surgical treatment in differentiated advanced thyroid carcinomas are to guarantee respiratory and alimentary functions as well as symptomatic benefits, to obtain local control of the disease and the recovery of adjuvant therapeutic options, such as metabolic and conventional radiation. In the present study, 27 patients who underwent enlarged surgery for differentiated thyroid carcinoma involving the superior digestive-aerial ways (SDAW) were treated between January 1992 and December 2002. The following results were achieved: Group 1 (7 patients): partial resection of the trachea and larynx: 57% of patients are Not Evidence Disease (NED) at a mean follow-up of 7 years; the other 43% are Alive With Disease (AWD). Group 2 (4 patients): total laryngectomy associated with emi-pharyngectomy or oesophagectomy of whom 50% are NED at a mean follow-up of 6 years. Group 3 (4 patients): mediastinum dissection in sternotomy of whom 3 patients NED at 7, 8 and 12 years of follow-up, respectively (75%). Group 4 (12 patients): latero-cervical, retro-clavear and subclavear dissection, of whom 75% of cases are NED at a mean follow-up of 5.1 years. Enlarged surgery is justified by the long natural history of the differentiated histotypes and the advantages it offers to adjuvant therapies. An essential principle, in the case of enlarged thyroid resections, is the modularity. With respect to the loco-regional spread of the disease, the surgeon has to study a treatment plan with a surgical procedure that involves the various elective districts of spreading, planning each surgical step with the entity of demolition and reconstruction being modulated according to the demand.

KEY WORDS: Thyroid • Differentiated carcinomas • Surgical treatment • Radiometabolic therapy

RIASSUNTO

I carcinomi differenziati della tiroide sono caratterizzati da una storia naturale molto lunga. L'anatomia topografica della loggia tiroidea e del mediastino antero-superiore comporta frequentemente il coinvolgimento per compressione, dislocazione o infiltrazione delle vie aeree digestive superiori (VADS), sia all'insorgenza della malattia, sia in caso di recidiva. L'evoluzione delle tecniche ricostruttive, nonché il miglioramento del management anestesiológico perioperatorio del paziente hanno consentito, negli ultimi anni, un progressivo ampliamento delle possibilità demolitive, conferendo nuove potenzialità e ridefinendo il ruolo della chirurgia allargata. Gli obiettivi della chirurgia nei casi avanzati di carcinomi differenziati della tiroide sono: garantire la funzione respiratoria e alimentare, ottenere un controllo locale della malattia e il recupero della praticabilità di altri presidi terapeutici, quali radioterapia metabolica e convenzionale. Sono stati analizzati retrospettivamente 27 pazienti sottoposti a chirurgia allargata per il trattamento di carcinomi differenziati tiroidei coinvolgenti le VADS dal gennaio 1992 al dicembre 2002. Tutti i pazienti sono stati trattati presso l'Istituto Nazionale Tumori di Milano. A seconda del tipo di estrinsecazione extra-tiroidea e del coinvolgimento linfonodale sono stati distinti quattro gruppi di opzioni chirurgiche: 1) resezioni parziali della trachea e della laringe, 2) laringectomia totale associata ad emifaringectomia e/o esofagectomia: 4 casi, 3) svuotamento mediastinico in sternotomia: 4 casi, 4) svuotamento latero-cervicale e succlavio: 12 casi. Gruppo 1: resezioni parziali della trachea e della laringe: 7 casi. 57% dei pazienti NED ad un follow-up medio di 7 anni. 43% dei pazienti AWD. Gruppo 2: laringectomia totale associata ad emifaringectomia e/o esofagectomia: 50% dei pazienti NED a un follow-up medio di 6 anni. Gruppo 3: svuotamento mediastinico in sternotomia: tre pazienti (75%) NED a rispettivamente 7, 8 e 12 anni di follow-up. Gruppo 4: svuotamento latero-cervicale e succlavio: 75% dei pazienti NED a un follow-up medio di 5,1 anni. Il controllo loco-regionale della malattia è l'obiettivo oncologico primario della chirurgia allargata, unitamente al sicuro beneficio sintomatico. La negativizzazione oncologica loco-regionale o anche semplicemente un "debulking" della neoplasia, consentono il recupero della possibilità terapeutica con radioterapia metabolica per eventuali residui o metastasi captanti e con radioterapia convenzionale dall'esterno per la sterilizzazione oncologica loco-regionale. Principio essenziale nella pratica in caso di resezioni tiroidee allargate è la modularità.

PAROLE CHIAVE: Tiroide • Carcinomi differenziati • Trattamento chirurgico • Radioterapia metabolica

Introduction

Well-differentiated thyroid carcinomas are characterized by a long natural history, coherently with the degree of differentiation of the tumour.

The topographical anatomy of the thyroid and of the antero-superior mediastinum frequently implies the involvement, due to compression, infiltration or dislocation of the superior digestive-aerial ways (SDAW), at presentation of the disease, as well as at relapse. The incidence of this ill-fated event varies from 1% to 13% of all patients with thyroid carcinoma¹. The common sites of involvement are the muscles of the neck (8.1%), the trachea (7.7%), the oesophagus (3%) and the larynx (2.2%)².

The evolution of the reconstructive techniques, as well as the improvement in peri-operative anaesthesiologist management of the patient has led, in the last few years, to a progressive increase in the possibilities of demolitive procedures, offering new possibilities and redefining the role of enlarged surgery. Besides urgent provisions to guarantee respiratory and alimentary functions, the role of surgery must be estimated in the light of the oncologic therapeutic strategy in order to specify if and when wide demolitive surgical procedures (oncologic surgery and not only salvage surgery) are indicated³⁻⁵. In consideration of the anatomical localization of advanced thyroid tumours, planning of the surgical options is possible.

Clearly, careful pre-operative evaluation is essential with traditional imaging (ultrasonography (US), computed tomography (CT)-scan, magnetic resonance imaging (MRI)), together with endoscopic estimation of SDAW⁶. The parameters to consider for selection of patients are: 1) performance status of the patient; 2) local spread of the disease; 3) histology. Operability criteria must take into consideration the expectation and quality of life.

The aims of surgery in differentiated advanced thyroid carcinomas are as follows: to guarantee respiratory and alimentary functions, to confer symptomatic benefits, to obtain local control of the disease and, finally, the possibility to perform adjuvant therapeutic options, such as metabolic and conventional radiation.

Aim of this study is to define the role of enlarged surgery in the treatment of advanced differentiated carcinomas of the thyroid with impairment of the SDAW, in the light of data from the literature and personal experience.

Patients and methods

A retrospective analysis has been made of 27 patients who underwent enlarged surgery, at the National Cancer Institute (NCI) of Milan, for differentiated thyroid carcinomas involving the SDAW, from January 1992 to December 2002.

Of these patients, 12 had previously been treated, in other centres and referred to the NCI of Milan for advanced local relapse.

Of the other 15 patients, 12 underwent enlarged surgery as first treatment and the other 3 upon local relapse.

Past history, diagnostic examinations, clinical files referring to hospital stay and follow-up have been consulted in order to analyze the details of the pre-operative preparation, surgical treatment and outcome.

The standard surgical criteria used were: total thyroid-

Table I. Patients and disease characteristics.

Total no.	27	12 from other centers 15 1 st treatment in NCI
Age	Median 58 yrs	Range 40-73
Sex	Female: 18 Male: 9	
Previous treatment	12 in other centres 3 in NCI	
Enlarged surgery in NCI as 1 st procedure	12	
Stage T	13: T1a 1: T2 1: T3	
Stage N	15: N1b	
Histotype	24: PTC 3: FTC	Tall-cell and/or oxyphilic cell 2: oxyphilic cell 1: dedifferentiated

ectomy in follicular thyroid carcinoma (FTC) and hemithyroidectomy or total thyroidectomy in papillary thyroid carcinoma (PTC) according to the prognostic factors (age < 20 yrs and > 45 yrs, male sex, size > 3 cm, previous radiotherapy, clinical findings, palpable neck nodes, US evidence of vascularization and/or microcalcification). Neck dissection was performed in the event of evidence of metastatic nodes; recurrent nerve dissection was performed omolaterally despite macroscopic involvement.

The follow-up was as follows: clinical examination and thyroglobulin marker every 6 months, Whole Body I-131 scan 6 months after metabolic radiation, latero-cervical US every 6 months, chest X-ray every 2 years.

As far as concerns extra-thyroid spread and nodal involvement, four groups of applied surgical options have been distinguished: 1) partial resections of the trachea and the larynx: 7 cases, 2) total laryngectomy associated with hemipharyngectomy or oesophagectomy: 4 cases, 3) mediastinum dissection in sternotomy: 4 cases, 4) latero-cervical and subclavian dissection: 12 cases.

The demographic analysis of the patients revealed a male/female ratio of 2/1, with a mean age, at time of surgical treatment, of 58 years (range 40-73).

The mean clinical-radiological follow-up, performed by the same multidisciplinary team, was 58.6 months (range 1-144).

Characteristics of the patients and the disease are outlined in Table I.

The study population, divided into 4 groups according to surgical treatment, is listed in Table II.

Results

Pathological diagnosis showed PTC in 24 cases and FTC in 3 cases.

The 24 cases of PTC showed the presence of high-risk, tall-cell and/or oxyphilic cell variants.

The 3 cases of FTC showed the presence of oxyphilic mor-

Table II. Study population considering the 4 groups of patients in relation to surgical procedure and follow-up.

Surgical procedure	PTS		Follow-up
Partial resection of trachea and larynx	7	4/7 NED at 5, 8, 8, 8 yrs follow-up	1/7 M+ lung at 4yrs 1/7 mediastinum relapse at 3 yrs 1/7 bone mets at 4 yrs → RT
Total laryngectomy ± emipharyngectomy ± oesophagectomy	4	2/4 NED at 4 and 8 yrs follow-up	1/4 M+ lung at 7 yrs 1/4 DOD at 30 months
Mediastinum dissection in sternotomy	4	3/4 NED at 7, 8, 12 yrs follow-up	1/4 dead within 1 month due to post-operative complications
Laterocervical and subclavicular dissection	12	9/12 NED Mean follow-up 4 yrs (range: 2-10 yrs)	1/12 M+ lung → metRT → AWD at 1 yr 1/12 bone mets → metRT+RT → AWD at 4 yrs 1/12 M+ lung → metRT → NED at 8 yrs

phology in 2 cases and dedifferentiated areas resembling a squamous cell carcinoma in the third case.

The pathologic stage of disease in those patients treated at NCI as first treatment has been re-evaluated according to the AJCC Staging System 2003 (VI edition): in 13 cases, the patients were staged as T4a, in 1 case T2 and in 1 T3. As far as concerns N, all patients were classified as N1b.

Results of the clinical-radiological follow-up of the 27 treated patients were as follows:

Group 1: partial resection of the trachea and larynx: 7 cases.

Four patients (57%) show no evidence of disease (NED), one patient at 5 years follow-up and the other 3 at 8 years. Three patients (43%) are alive with disease (AWD), one with lung metastases evident after 4 years of follow-up, one with a mediastinum relapse after 3 years of follow-up and the third with relapse at a cervical vertebra evident after 4 years of follow-up and treated with external radiation.

Group 2: total laryngectomy associated with hemi-pharyngectomy or oesophagectomy: 4 cases.

Two patients NED (50%): one at 4 years, and the other at 8 years of follow-up.

One patient AWD, with lung metastases after 7 years of follow-up (25%).

One patient died of disease (DOD) at 30 months of follow-up; this patient underwent total laryngo-esophagectomy and gastric pull-up reconstruction (25%).

Group 3: mediastinum dissection in sternotomy: 4 cases.

Three patients NED at 7, 8 and 12 years of follow-up respectively (75%).

One patient DOD at 1 month due to lung complications (25%).

Group 4: latero-cervical and subclavicular dissection: 12 cases.

Nine patients in this group are NED at a mean follow-up of 4.4 years (range 2-10) (75%).

Three patients are AWD (25%): one patient known to present lung metastases at the time of surgery and treated with metabolic radiation is stable at 12 months; one patient

developed vertebral bone metastasis treated with metabolic and conventional RT and is stable at 4 years of follow-up; the third patient, who received metabolic RT for lung metastases, is currently NED at 8 years of follow-up.

The 3 patients with FTC received major surgery: total laryngectomy and oesophagectomy, total laryngectomy and hemi-pharyngo-laryngectomy, and had the worst outcome in our series.

Discussion

The role of surgery in the treatment of advanced cases of differentiated carcinoma of the thyroid is a topic of increasing interest thanks to the improvement, standardization and more widespread use of reconstructive surgery with microvascular flaps in the last two decades, and to the evolution of thoraco-vascular surgical techniques that have allowed greater demolitive possibilities, even total pharynx-larynx-oesophagectomy or resection of the major mediastinum vessels with prosthesis reconstruction⁷⁻⁹ (Table III).

The extra-thyroid spread, particularly to the SDAW, of differentiated thyroid carcinomas is an uncommon problem, with a difficult approach. No consensus exists in the literature concerning the role of enlarged surgery^{3 10-13}.

Nevertheless, from an analysis of the international literature, a tendency prevails on the indication to enlarged surgery, even if demolitive and mutilating^{4 10 14-20}.

On the other hand, surgical procedures, however invalidating, would be a matter of urgency on account of the evolution of the disease in order to guarantee vital functions.

Tracheal involvement, with superficial extension, is amenable to surgery, that comprises, besides total thyroidectomy, a "shaving resection" of the trachea; if the extension is greater, but still limited, surgical treatment comprises tracheal resection with subsequent sternocleido-periosteum reconstruction (sternocleidomastoid muscle, sternohyoid muscle). In the event of circular involvement, complete resection is necessary with a termino-terminal trachea-cricoid or trachea-trachea anastomosis^{1 16 21-23}.

If, instead, the thyroid tumour involves the larynx, resection

Table III. Surgical options.

Site	Tumour extent	Surgery	Reconstruction
Trachea	Superficial	Shave resection	Not required
	Limited	Window resection	Muscular rotating flap (sterno-cleidomastoid, sternohyoid)
	Circular	Circular resection	T-T anastomosis (tracheo-tracheo or tracheo-cricoid)
Larynx	Limited	Resection of thyroid or cricoid cartilage	Muscular rotating flaps (sterno-cleidomastoid, sternohyoid)
	Wide	Total laryngectomy	Standard mucosal suture
Pharynx	Wide	Hemipharyngo- total laryngectomy	Mucosal suture Pectoral major myo-cutaneous flap Free flap
	Circular	Total pharyngolaryngectomy	Gastric pull-up or Jejunum free flap
Oesophagus	Limited	Longitudinal resection	Direct suture
	Wide or Circular	Total pharyngo-laryngo-oesophagectomy	Gastric pull-up
Nodes	Latero-cervical	Selective neck dissection Radical neck dissection Modified radical neck d. Extended radical neck d.	Ev. Pectoralis major myo-cutaneous flap
	Subclavear or mediastinum	Subclavear and/or mediastinum dissection ± clavear disarticulation ± sternotomy	Ev. Pectoralis major myo-cutaneous flap

of the thyroid and cricoid cartilage or partial laryngectomy are the demolitive options of choice in the case of limited extension, making sure that satisfactory reconstructions are performed with the use of muscular flaps.

In the event of severe tracheal involvement, it is necessary to perform total laryngectomy with standard mucosal reconstruction of the pharynx.

Severe pharyngeal involvement requires total hemipharyngo-laryngectomy with various reconstructive op-

tions, related to the characteristics of the patient as well as the tumour, comprising standard mucosal reconstruction, a pectoral myo-cutaneous flap, or the use of microvascular flaps.

In the case of involvement of the oesophagus, a longitudinal resection with reconstruction becomes necessary by means of a direct suture of the oesophageal wall; in the event of a ring-like extended localization, total pharyngo-laryngo-oesophagectomy is necessary with subsequent reconstruction using gastric "pull up" or re-vascularized free flaps^{4,22-25} (Figs. 1, 2).

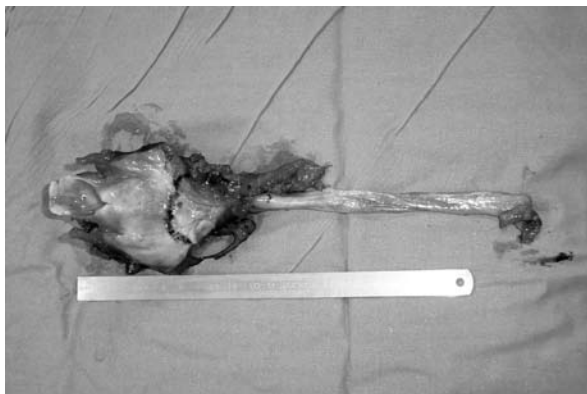


Fig. 1. Specimen from total laryngo-oesophagectomy. Black line shows margin of advanced relapse of thyroid carcinoma infiltrating laryngo-trachea structures and widening oesophagus with complete stenosis.



Fig. 2. Reconstruction with a gastric pull-up to replace oesophagus.



Fig. 3. Pre-operative CT scan: extent of nodal metastases shows lymphophily of PTC and anterior dislocation of left jugulo-carotid bundle shows drainage through lymphatic vessels accompanying the inferior thyroid artery, posteriorly to the carotid artery.



Fig. 4. Post-operative CT scan: no evidence of disease 6 years after left extended radical neck dissection.

Different considerations have to be taken into account in the presence of nodal involvement.

The presence of latero-cervical metastatic nodes requires selective neck dissection. In the case of latero-cervical metastases involving the soft tissues, radical neck dissection (RND) is necessary, while in cases of massive involvement of the soft tissues, an extended RND is mandatory with possible removal of the long muscu-

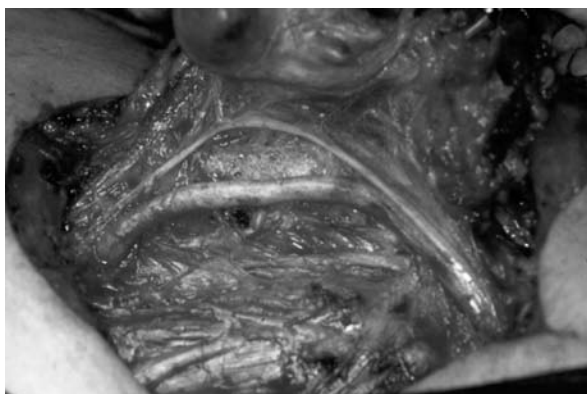


Fig. 5. Intra-operative image: bow drawn by carotid artery and vagus nerve shows adaptability of anatomic structures to tumour growth.



Fig. 6. Modularity. Census of anatomic structures offers possibility to modify of extent of surgery in relation to extent of tumour.

lature of the neck, the vagus nerve, the phrenic nerve as well as the chain of the cervical sympathetic nerves (Figs. 3-5). Moreover, in the presence of involvement of the supra or post-clavicular nodes, subclavicular dissection becomes necessary, possibly associated with clavicular disarticulation or sternotomy²⁶⁻²⁹.

In the event of mediastinum node progression, mediastinum dissection in sternotomy is required⁹. A dreaded complication of this surgical option is mediastinitis. In the case of a patient with a tracheostomy, the risk of infectious involvement of the mediastinum is very high. Prognosis, in the case of mediastinitis is very poor, with high mortality. The risk of mediastinitis can be limited by deferring the surgical time of the mediastinum from the cervical one or by reconstructing a cervico-mediastinum diaphragm with a pectoral myocutaneous flap or with re-vascularized flaps^{7,8,25}.

Conclusions

Local control of the disease is the most important oncologic objective of enlarged surgery, together with the symptomatic benefit. Regional eradication or also "debulking" of the tumour, resulting in macroscopically radical surgery or in minimal residual disease, allows other therapeutic options such as with metabolic radiation, especially for distant localizations, and conventional radiation for regional oncologic sterilization.

The essential principle, in the case of enlarged thyroid resections, is modularity (Fig. 6).

As far as concerns loco-regional spread of the disease, the surgeon has to study a surgical plan and to perform a surgical procedure involving the various elective districts of spreading, planning each surgical step, with extent of demolition and reconstruction being based upon the "demand".

Data emerging from the present analysis, despite the heterogeneity of the groups considered, revealed a large percentage of NED and AWD subjects after a mean follow-up of 4.1 years, with an optimal regional control of the disease.

In conclusion, enlarged surgery is justified by the long natural history of the differentiated histotypes and the advantages it brings to adjuvant therapies.

The indication to enlarged surgery must result from the evaluation of the performance status of the patient and compliance to major surgery; only thanks to correct management of these two variables, will it be possible to avoid useless over-treatment or guilty unforgivable omissions.

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