

Treatment of "locally advanced" well-differentiated thyroid carcinomas.

Original article



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Introduction

Well-differentiated tumors are the most common form of thyroid cancer. Their prognosis is generally favourable, with 12 year survival rates in excess of 90%. Local relapse of the disease is observed in 20%-30% of cases, with latero-cervical metastases or distant metastases. Several risk factors have been identified that influence the prognosis, such as age, presence of distant metastases at the time of diagnosis, extrathyroid extension (ETE), diameter and tumor grade (1-5).

The locally advanced well-differentiated tumor of the thyroid is a tumor with interruption and invasion of the capsula sometimes involving the surrounding cellulomuscular tissue and possibly the surrounding structures, such as the trachea, esophagus, veins; it accounts for between 4% and 16% of cases and is accompanied by an increase in percentage relapse and mortality rate (6-8); in particular, invasion of the thyroid capsule is considered a very important risk factor in the onset of distant metastases (5).

Invasion of the esophagus and trachea is reported in the literature as having an incidence varying from 1% to 6.5% (5, 6).

The treatment of locally advanced thyroid carcinomas is still being debated in the literature. In the case of the more advanced forms some authors claim that the best treatment consists in the removal of the entire neoplasm,

Riassunto

IL TRATTATO DEI CARCINOMI DIFFERENZIATI DELLA TIROIDE "LOCALMENTE AVANZATI". ARTICOLO ORIGINALE

Obiettivo: *Analisi dei carcinomi della tiroide con estensione extra tiroidea allo scopo di individuare i fattori prognostici più importanti e delineare una efficace strategia terapeutica.*

Materiale di studio: *Abbiamo selezionato un campione di 160 pazienti con carcinoma differenziato della tiroide "localmente avanzato" (T4), sottoposti ad intervento chirurgico nel Dipartimento di Scienze Chirurgiche dell'Università degli Studi di Roma "La Sapienza", suddividendo il campione in tre gruppi: microcarcinomi T4, T4 I di tipo limitato, T4 II di tipo estensivo.*

Risultati: *Nei T4 microcarcinomi abbiamo avuto ottimi risultati, soprattutto nei pazienti con età inferiore ai 45 anni, con sopravvivenza pari al 94.5% versus l'88% nei pazienti con età superiore ai 45 anni. Nei T4 di tipo I limitato abbiamo riscontrato una sopravvivenza del 79.5% nei pazienti con età superiore ai 45 anni. Nei T4 di tipo II estensivo abbiamo avuto valori di sopravvivenza pari al 29.4% nei pazienti con età superiore ai 45 anni.*

Discussione: *L'età e una variante istologica aggressiva (ca. papillifero in sclerosi e ca. papillifero a cellule alte) rappresentano fattori prognostici importanti. La radicalità dell'exeresi chirurgica è considerata un fattore prognostico importante, anche se in letteratura sono riportati risultati contraddittori.*

Conclusioni: *Una chirurgia aggressiva può rendere liberi da malattia un'alta percentuale di pazienti oltre il 50° anno d'età anche con T4. Riteniamo fondamentale eseguire una tiroidectomia totale in tutte le neoplasie avanzate della tiroide e, estendere l'exeresi della neoplasia ai tessuti adiacenti, sino ad interventi demolitivi giustificati.*

Parole chiave: Carcinomi differenziati della tiroide, Carcinoma della tiroide con estensione extra-capsulare, Chirurgia della tiroide.

Abstract

Purpose: *To analyse thyroid carcinomas having an extra-thyroid extension in order to identify the principal prognostic factors and outline an effective therapeutic strategy.*

Methods: *We selected a sample of 160 patients suffering from locally advanced "well differentiated thyroid carcinoma"*

ma (T4) who had undergone surgery at the Department of Surgery of University of Rome "La Sapienza". The sample was subdivided into three groups: T4, limited type I, and extensive type II, T4 microcarcinomas.

Results: We obtained excellent results with the T4 microcarcinomas, above all in patients under the age of 45, with a 94.5% survival rate, compared with 88% in patients aged over 45. In the extensive type II T4 carcinoma we obtained a survival rate of 29.4% in patients aged over 45 years.

Conclusions: Age, combined with an aggressive histological variant (Sclerosing and tall-cell papillary carcinoma), is an important factor in prognosis. The radicality of surgical excision is considered an important prognostic factor, although the results reported in the literature are contradictory. Aggressive surgery can free from the disease a high percentage of patients over the age of 50 even with T4. We deem it fundamental to perform total thyroidectomy in all advanced cases of thyroid neoplasm and to extend neoplasm excision to the adjacent tissues, even involving justified surgical demolition.

Key words: Differentiated thyroid carcinoma, thyroid carcinoma, extracapsular extension differentiated thyroid carcinoma, surgery thyroid carcinoma

safeguarding functionality wherever possible (9, 10); other authors propose a more conservative treatment (11).

In choosing the treatment to follow it is necessary to take into account the different histologic variants, the more aggressive forms (high degree of differentiation), and the different prognostic factors, in order to identify high risk patients (12).

In the present study we analysed well-differentiated tumors of the thyroid that definitive histologic analysis showed to be locally advanced (T4). The tumors were evaluated on the basis of the histologic variants, mode of presentation, age, size, presence or absence of latero-cervical lymph node pathology, for the purpose of determining the best therapeutic strategy to adopt in such cases.

Materials and Methods

Between 1970 and December 2001 some 9124 patients with thyroid pathologies were examined at the Department of Surgery of "La Sapienza" University of Rome; 965 of these patients were found to be affected by neoplastic pathologies.

In the present study we examined patients that definitive histologic examination showed to be suffering from locally advanced *well-differentiated thyroid carcinoma* (ETE) who had undergone surgery between 1970 and December 2001; we selected a group that was comparatively homogeneous for diagnostic method, surgical procedure adopted and that had been subjected to at least six years' follow-up; the group comprised 160 patients with "locally advanced" well-differentiated T4

carcinoma of the thyroid who had undergone surgical treatment. In accordance with U.I.C.C.I.V edition classification we define locally advanced well-differentiated thyroid carcinoma as "a tumor of any size that extends beyond the thyroid capsule (pT4)". T4 may be subdivided into: T4 *microcarcinomas* (carcinoma with a diameter of less than 1.0 cm); *limited type I T4* (invasion of prethyroid muscles, recurrent nerves, large neck vessels and the surface of the tracheal cartilage); *extensive type II T4* (involvement of pharynx, esophagus, larynx and intraluminal trachea).

The sample was made up of the following microcarcinomas: T4 (45 cases), limited type I T4 (97 cases), extensive type II T4 (18 cases).

Factors taken into consideration were sex, mode of pathology onset, tumor diameter, histologic type, histologic variant, presence of lymph node metastases at the time of surgery (also depending on the various histologic variants) and type of surgery.

Histologically, the neoplasms were classified as pure papillary carcinoma, sclerosing papillary carcinoma, follicular carcinoma, insular carcinoma, tall-cell carcinoma, oxyphil cell carcinoma.

Post-operative staging was performed in accordance with the criteria approved by the American Joint Commission on Cancer.

Prognosis was evaluated exclusively in the case of patients having completed follow-up.

Operative mortality included deaths occurring during the post-operative hospitalization period (4 days on average). During follow-up patients underwent assay of thyroid hormones, thyroglobulin and antibody anti-thyroglobulin, neck ultrasound, total-body scintigraphy, bone scintigraphy, liver ultrasound, thorax X-ray and, whenever deemed necessary, also radioiodine therapy and radiotherapy.

Results

Patients with locally advanced thyroid carcinoma (T4) accounted for 16.5% of all cases.

T4 microcarcinomas totalled 45 (28.1%), 19 males and 26 females, limited type I T4 totalled 97 (60.6%), 29 males and 68 females, and extensive type II T4 18 (11.25%), with a slight preference for males in a ratio of 5:4.

Diagnosis of T4 microcarcinomas was made in 10 cases (22.2%) after onset of latero-cervical lymph node adenopathy, in 9 cases (20%) after fine needle aspiration, in 26 cases (57.7%) during surgery for plurinodular thyroid pathologies; in the limited type I T4 forms diagnosis was made in 51 cases (52.5%) after total thyroidectomy for plurinodular thyropathy surgery, in 27 cases (27.8%) after FNA, in 16 cases (16.5%) after latero-cervical lymph node pathology, in 2 cases (2.1%) after primary hyperparathyroidism and in 1 case (1%) after removal of papillary carcinoma on the thyroglossal duct. In the extensive type II

T4 forms diagnosis was made in 10 cases (55.5%) of late-rocervical lymph node adenopathy and in 8 cases (44.5%) of the onset of dysphonia and dysphagia.

In the case of T4 microcarcinomas total thyroidectomy was performed, combined with resections limited to the soft tissues and radioiodine treatment; limited type I T4 total thyroidectomy was performed, combined with any necessary resections, radioiodine treatment and, wherever required, external radiotherapy; in extensive type II T4 "justified" demolition surgery was performed (resection of up to 4/5 tracheal rings, "minimal" laryngo-esophageal resection, "necessary" hemilaryngectomy), two cycles of radioiodine therapy and external radiotherapy. The patients were subjected to a follow-up of at least 6 years. No cases of peri-operative mortality were observed.

At the histological level we found that, despite the prevalence of the pure form of papillary carcinoma (56.4% of total case histories), in the locally advanced forms the sclerosing and tall-cell papillary carcinomas predominated (Tab. I).

As far as neoplasm size is concerned, it may be said that, regardless of the histologic variant involved, the neoplasms were found to have a mean diameter of between 1.5 and 2 cm, and only follicular carcinoma had a diameter of 5.5 cm (Tab. II).

One significant fact is the observed increase in the incidence of locally advanced tumors as a function of age. Observing our case histories, the more advanced forms may be said to account for 50% of well-differentiated neoplasms in patients over the age of 70, while they account for only 5.1% in patients aged between 45 and 60 years (Tab. III).

Patients' survival was evaluated as a function of age group (over or under 45 years of age); excellent results were obtained for T4 microcarcinomas, particularly in patients under the age of 45, with a survival rate of 94.5% compared with 88% in patients aged over 45 years. In the limited type I T4 form we found a 79.5% survival rate in patients aged over 45. In the extensive type II T4 form a survival rate of 29.4% was found in patients over the age of 45 (Tab. IV).

Tab. I – INCIDENCE OF LOCALLY ADVANCED TUMORS AS A FUNCTION OF HISTOLOGIC VARIANTS

Histologic Type	Total	Microcarcinomas Case (%)	T4 (%)
Pure pap. ca.	56.4	65.4	31.9
Sclerosing pap. ca.	14.1	12.4	33.1
Tall-cell ca.	5.1	2.2	11.2
Insular ca.	1.3	2.2	3.7
Follicular ca.	17.9	13.4	13.3
Oxyphil ca.	2.6	2.2	1.2
Medullary ca.	2.6	2.2	5.6

ca. = carcinoma
pap. ca. = papillary carcinoma

Tab. II – MEAN SIZE AS A FUNCTION OF HISTOLOGIC VARIANTS IN LIMITED TYPE LOCALLY ADVANCED CARCINOMAS (T4I)

Histologic Type	n. Cases	multifocal	mean neoplasm diameter
Pure pap. ca.	36	9	1.63
Sclerosing pap. ca.	29	5	1.86
Insular ca.	3	-	2
Tall-cell ca.	10	-	1.74
Follicular ca.	13	-	3.9
Oxyphil ca.	1	-	5.5
Medullary ca.	5	-	1.54

ca. = carcinoma.
pap. ca. = papillary carcinoma.

Tab. III – T EVALUATION AS A FUNCTION OF AGE

Histologic type	45-60 yrs	61-70 yrs	71-80 yrs
Well-differentiated	pT1T2 89.7%	pT1T2 81.0%	pT2 25.0%
	pT3 5.1%	pT3 12.1%	pT3 25.0%
	pT4 5.1%	pT4 6.9%	pT4 50.0%
Insular	pT3 100%	pT4 100%	-
Medullary	pT2 100%	pT2 50%	-
		pT3 50%	
Undifferentiated	pT4 100%	pT3 8.3%	pT4 100%
		pT4 91.7%	

Tab. IV – SURVIVAL FOR LOCALLY ADVANCED WELL-DIFFERENTIATED THYROID CARCINOMA (12 YEARS)

	Survival <45 years	Survival >45 years
<u>T4 microcarcinoma</u> (45 patients)	94.4%	88%
TT + resections limited to soft tissues + radioiodine		
<u>limited T4</u> (97 patients)		79.5%
TT + necessary resections + radioiodine/radiotherapy		
<u>extensive T4</u> (18 patients)		29.4%
justified destructive surgery		
- resection up to 4-5 tracheal rings		
- "minimal" pharyngo-esophageal resections		
- "necessary" hemilaryngectomy		
+ radioiodine or radiotherapy		

Discussion

A well-differentiated tumor of the thyroid is defined as "locally advanced" (ETE) when it has an extracapsular extension, that is, when the primary tumor has infiltra-

ted and extended beyond the gland capsule and has involved the surrounding tissues (soft tissues and prethyroid muscles) or adjacent structures, such as the trachea, larynx, esophagus, muscles, recurrent nerve and vascular structures. As far as the extent of extracapsular invasion is concerned, locally advanced thyroid tumors may be further subdivided into three groups: locally advanced microcarcinomas, that is, tumors with a diameter of less than 1 cm, which account for 28.1% of cases among our case histories; limited extension type I T4 tumors, involving the prethyroid muscles, the recurrent nerve, the neck vessels, the superficial tracheal cartilage, account for 60.6% cases, extensive type II T4 tumors with involvement of the pharynx, esophagus, larynx and endoluminal trachea account for 1-5% of total thyroid neoplasms (2.1% in our experience) and 11.25% of locally advanced forms (11, 13, 14).

The spread of the tumor to the capsule and to the adjacent tissues or organs is considered by several authors to be the most important negative prognostic of the recurrence of the disease and in particular of the onset of distant metastases (1-3, 5, 7).

On the assumption that the radicality of the surgical treatment can represent an important factor in the prognosis of ETE patients, numerous studies were carried out to identify other prognostic factors influencing mortality and that determine the recurrence of pathology in these patients, with often contradictory results (5, 15). The prognostic factors subjected to multivariate analysis indicate that an age greater than 45 years, the non pure papillary histology of the tumor, the presence of distant metastases at the time of diagnosis, tumor size greater than 4 cm all have an unfavourable influence on prognosis. Analysis of the literature shows how all these prognostic factors affect prognosis as a function of the patient's age (7, 9, 16).

In our study we observed how locally advanced thyroid carcinomas are the most aggressive histological forms, characterized by a prevalence of sclerosing and tall cell papillary variants and of medullary carcinoma. In these forms a reversal of the normal ratio occurs in which pure papillary variants (which are present globally in 56% of cases) prevail, in favour of the more aggressive variants that account for 19% of the total, while in locally advanced forms they account for over 45% of cases.

Sclerosing papillary carcinoma represents a typical histologic variant, more frequently involving younger ages, with greater local and distant invasiveness, pulmonary metastases and a shorter time interval free of disease. Ortiz (5) demonstrated that the sclerosing papillary variant displays a lymph node relapse rate of 60% compared with 21% for pure papillary forms. Tall-cell papillary carcinoma displays a higher relapse frequency, estimated at around 35%, although relapses are found solely in the patient group aged over 50 years.

Age is a fundamental variable, also as far as tumor size is concerned. In a previous study, we found a percenta-

ge of 5.1% in patients aged between 51 and 60 years and of 50% in patients aged between 71 and 80 years. The importance of age with regard to prognosis was highlighted: in the case of locally advanced thyroid tumor, mortality was observed solely in patients over the age of 45 (17, 18).

In locally advanced microcarcinomas some authors suggest performing a lobectomy, obtaining percentage relapses practically identical with those of more aggressive surgery (19). Nevertheless, a study we carried out on microcarcinomas revealed the presence of extracapsular extension in 11.3% of cases and multifocality in 14.6% of cases. We also reiterate how total thyroidectomy carried out by skilled surgeons is characterized by a percentage complication rate that is practically identical to that of conservative action. Using this strategy, combined with radioiodine treatment wherever indicated, we obtained a survival rate of 94.4% in patients aged less than 45 years and of 88% in patients over the age of 45.

Prognosis in ETE patients seems to be influenced by aggressive surgery, which is of fundamental importance in a correct therapy and in order to achieve longer survival. Ishihara (9) reports 15 year survival rates for patients with well-differentiated thyroid tumor that has invaded the trachea that vary widely among patients subjected to complete resection compared with those having undergone incomplete resection (78% versus 24.3%). Other authors (10) report 15 year survival rates of 64% in patients with neoplasm extension to the trachea whenever surgical treatment led to the complete removal of the tumor mass. Fujimoto (8) reports an 83.3% survival rate in patients with tumor extension to the soft tissues, trachea and larynx treated with destructive surgery and radioiodine. In this case however follow-up was of less than five years duration. McCarty (20), in a group with similar characteristics, reports a survival rate of 10 years in 47.9% of patients. Breaux and Guillaumondegui (21) report a 10 year survival rate of 62% in patients with invasion of the larynx. Conversely, McCaffery and Gillenwater (11, 16) claim that, despite incomplete resection, the prognosis does not improve significantly in these patients. Moreover, in a study by Andersen (7) it is emphasized that incomplete excision of the neoplasm is an important predictor of local or regional recidivation, while only the factor of age greater than 45 years is predictive of the onset of distant metastases. In the forms that involve the laryngo-tracheal cartilage, McCarty (20) reports a 7 year survival rate of 71.4%. A study by Glanzmann (14) reports 100% survival in patients aged less than 38 years treated by surgery alone, while in patients aged over 38 years, radiotherapy significantly improves the prognosis, raising it from 60% to 89%.

In our experience, in limited type locally advanced carcinomas, we performed total thyroidectomy with necessary resection of the structures involved by the neopla-

sm followed by radioiodine therapy and possible radiotherapy. In these cases percentage survival was as high as 79.5%. In locally advanced cases of the extensive type we performed destructive surgery, involving the resection of as many as 4-5 tracheal rings, "minimal" pharyngo-esophageal resections and necessary hemilaryngectomy, followed by two cycles of radioiodine therapy and radiotherapy; these patients displayed a 12 year survival rate of 29.4%.

In conclusion, locally advanced thyroid tumors may be said to display an incidence related to increasing age and with the gradual onset of more aggressive histologic forms, such as sclerosing and tall-cell papillary variants. In agreement with Mazzaferri (18) it may be said that "the death rate due to well-differentiated thyroid carcinoma begins after the age of 40 and is rises dramatically, together with percentage relapse incidence after the age of 60 and is closely linked to T. Aggressive surgery can free from the disease a high percentage of patients aged more than 50 even with T4".

We consider it fundamental to perform total thyroidectomy in all advanced thyroid neoplasms and to extend excision to the adjacent tissues, even as far as justified destructive surgery: using an "aggressive" surgical strategy we achieved a 12 year survival rate of 29.4% in patients with extensive locally advanced thyroid tumor.

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