

Surgery of thyroid cancer: twelve years' personal experience

Il trattamento del carcinoma tiroideo: esperienza clinica di 12 anni

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Parole chiave

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Summary

Diagnosis and treatment of thyroid carcinoma require a multidisciplinary approach. The close and long-standing collaboration between the Otorhinolaryngology, Pathological Anatomy and Nuclear Medicine Departments of Legnano Hospital has led to a precise diagnostic and therapeutic protocol in thyroid patients. In the 1990-2002 period, 131 patients underwent total thyroidectomy after diagnosis of thyroid cancer at the Otorhinolaryngology – Head and Neck Surgery Department. Patients submitted to lobectomy for differentiated thyroid cancer were excluded from the present study. The patient population is composed of 96 females (73%) and 36 males (27%) aged between 22 and 85 years. Of the 131 patients, 115 (87%) presented papillary carcinoma, 13 (10%) follicular carcinoma, 2 (2%) medullary carcinoma and one (1%) undifferentiated carcinoma. Two patients (2%) suffered from a preoperative monolateral recurrent nerve palsy. Total thyroidectomy was performed in all 131 patients. Selective neck dissection was performed only in patients with positive lymph nodes for papillary (37/115, 32%) and follicular carcinoma histotype (2/13, 15%) and, in both patients with medullary carcinoma (100%). Of the 131 patients, 15 (11%) did not undergo routine follow-up and were, therefore, excluded from the study, the remainder completed a mean follow-up of 47 months. During follow-up, the incidence of the two most frequent complications of thyroid surgery were evaluated: recurrent nerve paralysis and permanent hypoparathyroidism (exceeding the postoperative 6 months). Results of treatment have been evaluated considering the incidence of local and/or distant recurrences and patient survival rate. As far as concerns papillary and follicular histotype, we have considered as healed (absence of signs suggesting loco regional and distant recurrence) only those patients presenting both negligible levels of plasma thyroglobulin and a negative total-body ¹³¹I scintigraphy. Briefly, in 3 cases (3%), all papillary carcinomas, local recurrence occurred; 9 (8%), all with papillary carcinoma, developed lateral neck recurrence; 6 (5%), 5 with papillary carcinoma and one with follicular carcinoma, developed distant metastases, of which 3 pulmonary, 2 bone and 1 hepatic. Serum thyroglobulin values were considered during the last control visit in 95/113 patients (84%). Of these, 86 (91%) with negligible thyroglobulin levels and negative ¹³¹I scintigraphy, were considered healed. All 113

Riassunto

La diagnosi e la terapia dei carcinomi della tiroide prevedono un approccio multidisciplinare. La stretta e pluriennale collaborazione tra la nostra Unità Operativa, il Servizio di Anatomia Patologica e l'Unità di Medicina Nucleare dello stesso Ospedale ha permesso di mettere a punto un preciso iter diagnostico e terapeutico nei pazienti con patologia tiroidea. Nell'Unità Operativa di ORL dell'Ospedale Civile di Legnano dal 1990 al 2002 sono stati operati di tiroidectomia totale 131 pazienti affetti da carcinoma della tiroide. Sono stati esclusi da questo lavoro i pazienti affetti da tumore differenziato della tiroide operati di emitiroidectomia. La casistica è composta da 96 donne (73%) e 36 uomini (27%) di età compresa fra i 22 e gli 85 anni. Dei 131 pazienti, 115 erano affetti da carcinoma papillare (87%), 13 da carcinoma follicolare (10%), 2 da carcinoma midollare (2%) ed 1 da carcinoma indifferenziato (1%). Due pazienti (2%) presentavano una paralisi ricorrente monolaterale preoperatoria. In tutti i casi (131/131, 100%) è stata eseguita una tiroidectomia totale. Lo svuotamento linfonodale è stato eseguito solo in presenza di linfonodi positivi per gli istotipi papillare (37/115, 32%) e follicolare (2/13, 15%) e nei due casi di carcinoma midollare (100%). Dei 131 pazienti operati, 15 (11%) sono stati esclusi per mancanza di follow-up ed i restanti 116 hanno un follow-up medio di 43 mesi. Abbiamo quindi valutato la prevalenza delle due più frequenti complicanze della chirurgia tiroidea, la paralisi ricorrente e l'ipoparatiroidismo definitivo (considerato tale se persistente oltre i 6 mesi dall'intervento). Il risultato della terapia è stato valutato analizzando l'incidenza di recidive locali o a distanza e la sopravvivenza. Relativamente agli istotipi papillare e follicolare, abbiamo considerato guariti (assenza di segni di recidiva loco-regionale e a distanza) i pazienti che all'ultimo follow-up presentavano tireoglobulina sierica non più dosabile e scintigrafia total-body con ¹³¹I negativa. In 3 casi (3%), tutti carcinomi papillari, si è avuta una recidiva locale della patologia. Nove pazienti (8%), tutti affetti da carcinoma papillare, hanno sviluppato una recidiva linfonodale laterocervicale, mentre 6 pazienti (5%), 5 affetti da carcinoma papillare ed uno da carcinoma follicolare, hanno sviluppato metastasi a distanza, in 3 casi polmonari, in 2 ossee ed in uno epatica. Sono stati raccolti i dati relativi ai valori di tireoglobulina sierica presentati all'ultimo controllo di 95 dei 113 pazienti (84%) affetti da carcinoma differenziato della tiroide. Di questi, 86 (91%) che presentavano valori indosabili di tireoglobulina e scintigrafia con ¹³¹I negativa sono stati definiti

patients with differentiated thyroid carcinoma were alive at the last control visit. Both patients with medullary carcinoma are alive with no sign of illness at the last follow-up control. The patient presenting undifferentiated carcinoma died 2 months after surgery. In conclusion, at the last follow-up control, 1 (1%) patient has died, 5 patients (4%) are alive with disease (2 of whom suffered from multiple recurrences) and the remaining 110 (95%) patients are alive without evidence of disease. As far as concerns complications of surgery, iatrogenic recurrent palsy and permanent hypoparathyroidism are present in 2 (2%) and 10 patients (8%), respectively.

Introduction

Malignancies of the thyroid gland are rare neoplasms with an incidence of 1.2-2.6 per 100,000/year in males and 2-3.8 per 100,000/year in females. Diagnosis and treatment of thyroid carcinomas require a multidisciplinary approach. The close and long-standing collaboration between the Otorhinolaryngology, Pathological Anatomy and Nuclear Medicine Departments of the Legnano Hospital has led to the development of a precise diagnostic and therapeutic protocol in thyroid patients that is periodically updated according to personal experience and the world literature ¹.

Diagnostic protocol

A thyroid node is to be considered clinically suspicious when > 1 cm in diameter, and if associated with: age < 15 or > 60 years, previous head and neck radiotherapy, > 4 cm diameter, male sex, thyroid carcinoma familiarity, anamnestic positivity to pheochromocytoma, hyperparathyroidism, Gardner's syndrome. Suspicious nodes are evaluated by means of thyroid-stimulating hormone (TSH) dosage, thyroid scintigraphy and fine-needle aspiration biopsy (FNAB). Cytological examination is the only method producing a high-level of accuracy in the preoperative diagnosis.

Therapy

The key point of thyroid carcinoma treatment is surgical removal. If a cytological or histological (previous lobectomy) diagnosis is available, indicating thyroid gland carcinoma, the minimum procedure to be performed is total thyroidectomy. This can be associated, in the case of differentiated neoplasms, with a selective recurrential neck dissection which can be

guariti dalla patologia. Tutti i 113 pazienti affetti da carcinoma differenziato della tiroide sono vivi all'ultimo controllo. I due pazienti affetti da carcinoma midollare sono vivi senza segni clinici di patologia all'ultimo follow-up. Il paziente affetto da carcinoma indifferenziato è deceduto due mesi dopo l'intervento. Complessivamente, quindi, all'ultimo follow-up, 1 paziente è deceduto (1%), 5 pazienti (4%) sono vivi con malattia (2 non presentano più recidive della patologia) ed i restanti 110 (95%) sono vivi senza malattia. Relativamente alle complicanze della chirurgia, la paralisi ricorrentiale ex-novo e l'ipoparatiroidismo definitivi si sono riscontrati rispettivamente in 2 (2%) e 10 pazienti (8%).

extended to other lymph node sites if recurrent nodes are found to be pathological. Exception is made for follicular encapsulated carcinomas 1 to 4 cm in diameter, in which the extent of thyroidectomy is evaluated individually and in papillary incidentalomas < 1 cm in diameter, completely resected and in the absence of contralateral disease. As far as concerns medullary carcinoma, total thyroidectomy is always associated with selective recurrential or with monolateral/bilateral functional neck dissection.

Post-surgical treatment

All patients receive hormone treatment with L-thyroxine at TSH-suppressive doses. Regarding the definitive histological examination and results of instrumental analyses, patients can be divided into two main risk categories ²:

- high risk patients: distant metastases, incomplete excision of tumour, age < 15 or > 45 years, high cells, cylindrical cells or diffusely sclerotic papillary carcinoma, highly invasive follicular carcinoma, diameter > 4 cm, extra thyroid extension or massive lymph node metastases (multiple or bilateral);
- low-medium risk patients.

Recognition of risk factors is of fundamental importance since it permits stratification of thyroid carcinomas considering the risk of recurrence and mortality and, consequently, the selection of therapeutic and adjuvant approaches to the condition. In fact, patients in the high-risk group undergo routine ablative ¹³¹I therapy (approximately 100 mCi), whereas patients belonging to the low-medium-risk group undergo ablative radiometabolic therapy only in the case of positive "whole-body" ¹³¹I scintigraphy. Adjuvant radiotherapy has a limited impact and is adopted exclusively in non-I-captant tumours or not amenable to surgery.

Treatment of recurrence or persistence of the disease

Elective therapy, in the case of persistent or recurrent disease, is surgical excision. Loco-regional recurrences are not amenable to surgical excision and are treated with ^{131}I (radiometabolic therapy) or radiotherapy (in the case of I-resistance). Chemotherapy is limited to disseminated non-I-captant disease. Radiotherapy and chemotherapy are eligible in cases of persistent or recurrent medullary carcinoma, in loco-regional and in disseminated disease, respectively.

Materials and methods

In the 1990-2002 period, a total of 131 patients underwent total thyroidectomy following diagnosis of thyroid cancer at the Otorhinolaryngology – Head and Neck Surgery Department of the Legnano Hospital. Patients with differentiated thyroid cancer submitted to hemithyroidectomy were excluded from the present study. The patient population comprised 96 females (73%) and 36 males (27%), aged between 22 and 85 years. Of the 131 patients, 115 were suffering from papillary carcinoma (87%), 13 (10%) from follicular carcinoma, 2 patients (2%) presented

medullary carcinoma while 1 patient (1%) was affected by undifferentiated carcinoma. In 102 patients (78%), in whom FNAB was positive for thyroid carcinoma, total thyroidectomy was performed, in 29 patients (22%), isthmo-lobectomy was performed which was followed, after histological examination, by removal of the remnant lobe. In those cases, histotypes were of follicular invasive carcinomas, follicular encapsulated carcinomas > 4 cm in diameter or papillary incidentalomas > 1 cm in diameter, positive margins of resection, or echography demonstrating contralateral disease. Of the 13 patients presenting follicular carcinoma, 5 (38%) had an invasive carcinoma while the other 8 patients (62%) presented the encapsulated histotype. Two patients (2%) suffered from preoperative monolateral recurrent nerve palsy. Functional neck dissection has been performed (Table I) only when histological positivity for papillary (38/115, 33%) and follicular (2/13, 15%) carcinomas has been revealed in recurrent lymph nodes and in both patients with medullary carcinoma. Total thyroidectomy was performed in the patient with undifferentiated histotype thyroid carcinoma due to its high-grade aggressiveness and patient's advanced age (85 years).

Primitive tumour dimensions are classified according to the TNM classification (IV edition) (Table II). Of

Table I. Neck treatment.

Clinic N+	Papillary 38/115 (33%)	Follicular 2/13 (15%)	Medullary 2/2 (100%)
Area VI mono-/ bilateral dissection	15/38 (39%)	0	0
Functional dissection mono/bilateral, areas II-VI	23/38 (61%)	2/2 (100%)	2/2 (100%)

Table II. pT classification.

	T1			T2			T3			T4		
	a	b	tot	a	b	tot	a	b	tot	a	b	tot
Papillary	18	10	28 (24%)	44	11	55 (48%)	4	3	7 (6%)	13	12	25 (22%)
Follicular	0	0	0	6	1	7 (54%)	4	0	4 (31%)	2	0	2 (15%)
Medullary	1	0	1 (50%)	1	0	1 (50%)	0	0	0	0	0	0
Undifferentiated	0	0	0	0	0	0	0	0	0	0	1	1 (100%)

the 131 patients submitted to surgery, 15 (11%), of whom 13 presented papillary and 2 follicular carcinomas, have been excluded from this study on account of lack of follow-up. The remaining 116 patients, of whom 102 (88%) with papillary carcinoma, 11 (9%) follicular, 2 (2%) medullary and 1 undifferentiated carcinoma were observed at a mean follow-up of 47 months (median 39 months). Moreover, 22 (20%) had a follow-up of < 12 months, 18 (15%) of 12-24 months, while 76 patients (65%) had a longer follow-up (> 24 months).

The 91 (81%) patients who presented differentiated carcinomas (papillary and follicular) have been treated with adjuvant ablative radiometabolic therapy on the thyroid remnant (range of activity: 80-300 mCi, median 100 mCi). Both cases of medullary carcinoma have undergone radiotherapy on T and on N, in one case, after surgery as adjuvant therapy while, in the other, due to persistence of high CEA and CT values, one year after surgery. We, therefore, analysed the patient's clinical history regarding surgical treatment and follow-up and observed the most common complications of thyroid surgery: recurrent nerve paralysis and permanent hypoparathyroidism (for > 6 months after surgery). The results of treatment have been evaluated taking into consideration the incidence of local and/or distant recurrences and the patient's survival rate. As far as concerns the papillary and follicular carcinoma, we have considered as healed (absence of signs of loco-regional and distant recurrence) only those patients presenting both negligible levels of plasma thyroglobulin and a negative total-body ¹³¹I scintigraphy.

Results

A total of 91 patients (81%) underwent ablative radiometabolic therapy on the thyroid remnant, in 2 cases (2%) the treatment has been repeated due to persistence of the thyroid remnant. In 3 cases (3%), all of which papillary carcinomas, a loco-regional recurrence was observed; in 2 of these 3 cases, radiometabolic therapy was then performed (one 110 mCi session), while in one patient, no treatment was given. Nine patients (8%), all suffering from papillary carcinoma, developed latero-cervical recurrence.

In 4 cases, functional neck dissection was performed, in 2 cases – radiometabolic therapy (one session of 120 mCi) and in 1 patient combined treatment (functional neck dissection plus radiometabolic therapy) was carried out. Again, in 2 cases, no treatment of the latero-cervical recurrence has been performed. Furthermore, 6 patients (5%) of whom 5 presenting papillary carcinoma and 1 follicular carcinoma, developed distant metastases, pulmonary in 3 cases, bone in 2 cases, and hepatic in 1 case. In one patient with a bone metastasis (humerus), surgical resection was performed. In the remaining 5 cases, no treatment has been carried out (Table III). Serum thyroglobulin values, during the last control visit, in 95 out of the 113 patients (84%) were taken into consideration. Of these, 86 patients (91%) presenting negligible thyroglobulin levels and negative ¹³¹I scintigraphy, were considered healed. Of the remaining 9 patients with measurable plasma thyroglobulin levels, 2 presented neoplastic papillary carcinoma recurrences on ¹³¹I scintigraphy.

All 113 patients suffering from differentiated thyroid carcinoma were alive at the last control visit. The two patients affected by medullary carcinoma are both alive with no sign of the disease at the last follow-up control. The patient with undifferentiated carcinoma died 2 months after surgery.

In conclusion, at the last follow-up control, one (1%) patient has died, 5 patients (4%) are alive with persistent disease (2 of whom suffered from multiple recurrences) and the remaining 110 (95%) patients are alive without disease. As far as concerns complications following surgery, iatrogenic recurrent nerve paralysis and permanent hypoparathyroidism are present in 2 (2%) and 10 patients (8%), respectively.

Discussion

The most appropriate treatment for thyroid carcinoma is surgery. Nevertheless, due to the important differences in clinical behaviour and treatment of the various histotypes of thyroid malignancies, distinction between differentiated neoplasms, medullary carcinoma and anaplastic tumour, is mandatory. As far as concerns differentiated neoplasias, the treatment of choice is total thyroidectomy.

Table III. Loco-regional and distant recurrences.

	Papillary	Follicular	Medullary
Local recurrence	3 pts (3%)	0	0
Regional recurrences	9 pts (8%)	0	0
Distant metastases	5 pts (4%)	1 pt (1%)	0

The advantages consist in removal of possible thyroid foci of the neoplasm, not detected pre-operatively, and in the possibility to use, at maximum accuracy levels, the tests which reveal possible recurrence of thyroid neoplasms (plasma thyroglobulin levels and ^{131}I scintigraphy). In accordance with the American Medical Association and National Cancer Institute guidelines ^{3,4}, exception is made in our protocol regarding the encapsulated follicular carcinomas of 1-4 cm in diameter in which total thyroidectomy is evaluated individually, and in papillary incidentalomas < 1 cm in diameter, completely resected and in the absence of contralateral involvement. Invasive follicular neoplasms always require total thyroidectomy ¹. Considerable controversy exists regarding the prophylactic treatment of lymph node in neck regions. This controversy is based on the fact that these tumours have an important tendency to regional lymph diffusion. Some 15-30% of thyroid neoplasms arise with a cervical lymph node metastasis ⁵, even if recent retrospective studies revealed that their presence does not significantly influence tumour prognosis ^{6,7}. This is to justify the extremely conservative treatment of lymph nodes in thyroid oncology. In our Department, in agreement with most Authors ^{8,9}, we do not perform prophylactic neck dissection in differentiated thyroid tumours; neck lymph node metastases are treated with efficacy by radiometabolic therapy. In N0 clinical cases the VI neck area is explored and node sampling is performed only in papillary carcinomas. In N+ cases, a central compartment neck dissection is carried out which can be associated with lateral neck dissection. In our study, indeed, lymph node dissection has been performed only in papillary (38/115, 33%) and follicular (2/13, 15%) neck metastases. Some Authors ¹⁰ routinely perform central compartment neck dissection in well-differentiated papillary carcinomas T3-T4 and in less differentiated histotypes of T1-T4 and carry out lymph node sampling in suspicious nodes at III-IV mono-/bilateral levels. The clinical behaviour and treatment of medullary carcinoma is completely different. This histotype is characterized by frequent node metastatization; medially 50% ¹¹ present node metastases in the central and/or lateral neck compartment (2/2, 100% in our study). Unlike differentiated carcinomas, however, the presence of neck metastases represents a critical prognostic factor both on account of loco-regional recurrence and patient survival ¹². Medullary carcinoma is neither amenable to radiometabolic therapy nor radiosensible, thus a radical surgical excision is necessary. That is the reason why most Authors consider total thyroidectomy and central compartment neck dissection, combined

with lateral neck dissection, in the presence of clinically or histologically diagnosed lymphatic metastases, the minimal intervention to perform in medullary carcinoma ^{13,14}. Some Authors perform prophylactic mono-/bilateral neck dissection of II-V levels in medullary carcinomas of T2-T4 ¹⁰. Anaplastic tumour is rarely amenable to total thyroidectomy with central and lateral functional or radical neck dissection which is the operation to be performed. Patient survival rarely reaches 2 months. The most common post-thyroidectomy complications are hypoparathyroidism and recurrent nerve paralysis. Post-operative hypocalcaemia is a relatively common but transient complication and regresses within a few weeks of the surgical treatment ¹⁵⁻¹⁷. Our study revealed permanent hypoparathyroidism in 10 patients (8%). Recurrent nerve damage depends on the histotype of the neoplasm and the type of surgery performed, being more frequent in the case of neck dissection and repeat surgery ¹⁸. Permanent recurrent nerve paralysis occurred in 2 (2%) of our patients. Furthermore, two patients (2%) suffered from preoperative monolateral recurrent nerve palsy. Data emerging from the present study are comparable to those reported in the literature ^{19,20}.

Conclusions

A multidisciplinary approach to the diagnosis and treatment of differentiated thyroid carcinomas leads to excellent oncological results. Surgery associated with hormone therapy and radiometabolic therapy, in high-risk patients, led to a 100% survival rate in our study population. Overall, 91% of the patients presented negligible plasma thyroglobulin levels and negative ^{131}I scintigraphy. Medullary carcinoma presents a worse prognosis than the differentiated neoplasms with a 60-75% patient survival rate after 10 years ¹. The 2 patients presenting medullary carcinoma are alive, with no clinical signs of the disease at the last control.

Over the last few years, genetics and molecular biology have allowed us not only to clarify some important pathogenetic aspects of these tumours but also to attempt to prevent the familial forms. Patients' relatives with a genetic anomaly should be submitted to prophylactic thyroidectomy. Recent studies have demonstrated the importance of performing this surgical procedure as early as possible: between 5 and 7 years in children with mutant RET ²¹. The prognosis of anaplastic tumour still remains extremely poor despite the very recent associated radio/chemotherapy protocols. Our only patient died 2 months after treatment.

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