

Cancer of the thyroid in patients over the age of fifty

Surgical and prognostic aspects

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Aim. The authors performed a retrospective investigation of patients over the age of 50, in order to detect any peculiarities of cancer of the thyroid possibly affecting surgical treatment and whether age itself represented an independent prognostic factor.

Methods. A total of 152 patients were examined at the Department of Surgical Science of "La Sapienza" University of Rome with a minimum follow-up of 10 years. The 152 subjects recruited were divided into 3 age groups: from 51 to 60 years, (74 patients); from 61 to 70 years, (57 patients); from 71 to 80 years, (21 patients). **Results.** Relating the different histologic types to age group, there was found to be a lower incidence of well-differentiated carcinoma and a relative increase in the epidermoid and undifferentiated forms in older patients. In the 51-60 age group 80% of the patients were at stages I and II, while in the 71-80 age group 56.2% of cases were at stages III and IV.

Conclusion. In the elderly patient undifferentiated, anaplastic or epidermoid forms and those with a higher biological aggressiveness are more frequently found. We believe that prompt diagnosis would present the surgeon with neoplasms at an early stage and with less aggressive histotypes, thus ensuring greater scope for radical surgical treatment and appreciably enhancing prognosis.

KEY WORDS: Thyroideal neoplasms - Thyroidectomy - Aged.

Interest in cancer of the thyroid affecting elderly patients stems from both the relative increase in its frequency and the fact that the disease is generally diagnosed at a later stage with a greater local extension and more frequent metastatic spread.

Nevertheless, postoperative prognosis is generally good and the operation does not present any specific risk factors, nor does it require any particular strategies to be adopted. Several different classifications are proposed for the purpose of identifying elements of use in ensuring correct diagnosis and treatment and for identifying subjects liable to recidivation. Numerous studies have shown that the histologic type, size of primary tumour, infiltration of neighbouring vessels, the presence of distant metastases and

Received May 22, 2003.

Accepted for publication November 26, 2003.

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regional lymph node involvement are prognostic factors of variable importance.

There are comparatively few reports in the literature on cancer of the thyroid in elderly patients. Although the unfavourable role played by age over 45 years is universally acknowledged, only a few authors have made a more analytical examination of this aspect.

We performed a retrospective investigation of patients over the age of 50, subdivided into different age groups, in order to detect any peculiarities of cancer of the thyroid in them possibly affecting surgical treatment and whether age itself represented an independent prognostic factor.

Materials and methods

A total of 9 124 patients with thyroid pathologies, 898 of whom (9.84%) with neoplastic pathologies, was observed at the Department of Surgical Science of "La Sapienza" University of Rome between 1970 and December 2001.

We restricted the investigation to patients admitted between 1 January 1983 and 31 December 1992 in order to obtain a group that was sufficiently homogeneous regarding diagnostic method, surgical procedure and allows a follow-up lasting at least 8 years.

During this period 192 patients over the age of 50 underwent surgery for cancer of the thyroid. Subsequently 40 patients were excluded from the investigation as they did not satisfy the recruitment criteria or because they could not be followed up.

The 152 subjects recruited were divided into 3 age groups: from 51 to 60 years, with 74 patients; from 61 to 70 years, with 57 patients; from 71 to 80 years, with 21 patients.

Factors considered were gender, duration of symptoms, ultrasonographic size of neoplasm, presence of lymph node or distant metastases, type of surgery. Histologically the neo-

TABLE I.—The different histologic types to age group there was found to be a lower incidence of well-differentiated carcinoma and an increase in the epidermoid and undifferentiated forms in older subjects.

Age (years)	Differentiated carcinoma	Insular carcinoma	Medullary carcinoma	Epidermoid undifferentiated forms
51-60	40.6%	0.52%	—	3.12%
61-70	30.2%	0.52%	1.04%	6.25%
71-80	8.3%	—	1.04%	8.41%

plasm were classified as follows: well-differentiated, insular, medullary, epidermoid and undifferentiated carcinoma. Neoplasm staging was performed in accordance with the UICC 2000 classification. Operative mortality included deaths occurring during the postoperative hospitalization period (4 days on average).

All the above parameters were evaluated as a function of the total number of case histories and in relation to the distribution by age group.

Results

Cancer of the thyroid accounted for 9.86% of the thyropathies included among our total case histories. This incidence increased gradually up to a level of 15.12% over the last 5 years.

The median age of the group studied was 62.5 years (range 51-79); the female:male ratio was 5:3.

Of the total number of 192 patients, 85 patients (44.24%) were in the 51-60 year range, 73 patients (38.01%) in the 61-70 year range and 34 patients (17.75%) in the 71-80 year range.

Well-differentiated carcinoma accounted for 79.21% of cases (152 patients), insular carcinoma for 1.04% (2 patients), medullary carcinoma 2.08% (4 patients) and the epidermoid and undifferentiated forms 17.67% (34 patients).

On relating the different histologic types to age group there was found to be a lower incidence of well-differentiated carcinoma and an increase in the epidermoid and undifferentiated forms in older subjects (Table I).

All the patients included in the investigation underwent total thyroidectomy, except 4 cases in which complete exeresis of the gland was not possible owing to the extent of local infiltration by the neoplasm and in which cervicotomy was performed to determine histologic type or else a cytoreduc-

tive procedure performed on the tumour mass, leaving *in situ* relatively small quantities of the neoplastic tissue that had infiltrated the noble structures. After the operation the patients were referred to the oncologist for suitable radioiodine therapy.

As a function of the size of the tumour to be removed (pT), 64.58% of cases were accounted for by pT1 or pT2 (124 patients), 9.37% by pT3 (18 patients), 26.05% by pT4 (50 patients). In the 51-60 age group the initial stages accounted for 72 patients (82.75%), while in the 71-80 age group the pT4 age group alone accounted for 75% of the cases (24 patients), (Table II).

As a function of staging, 27.6% (41 patients) belonged to stage I, 46% to stage II (70 patients), 21.7% (34 patients) to stage III and 4.7% (7 patients) to stage IV.

In the 51-60 age group over 80% of patients (60 patients) were in stages I and II, while in the 71-80 age group stage I was not represented and 56.2% (12 patients) of the cases were at stages III and IV ($p=0.01$), (Table III).

In the differentiated tumours lymph node repetitions were present in 9.9% of cases (15 patients), with an incidence of 5.4% (4 patients) in the 51-60 age group and of 19.4% (4 patients) in the 71-80 group ($p=0.01$). Distant metastases were observed in a total of 4.6% of cases (7 patients), increasing from 2.7% in the younger subjects to 14.28% in older subjects ($p=0.01$), (Table IV).

Postoperative complications took the form of haemorrhage (0.5%), permanent hypocalcemia associated with lymphectomy of the neck (1.04%) and lymphectomy of the anterior-superior mediastinal (MAS) (10.4%). Temporary paralysis of the inferior laryngeal nerve was observed in 1.04% of cases, permanent paralysis in 0.5% while in 1.04% of cases it proved necessary to proceed to nerve resection. Paresis of the accessory spinal nerve displayed an incidence of 0.52%; no cases of paralysis of the brachial plexus were observed, while the incidence of lesions of the cervical sympathetic nerve was 0.5% (Table V).

Global survival of the 152 patients with at least 8 years follow-up was 90.8%, with 95% of patients in the 51-60 age group and 68.7% for those in the 71-80 age group.

Discussion and conclusions

Thyropathies in the elderly are particularly insidious because of their slow evolution, their often atypical symptoms, which may lead to confusion between endocrine-related events and physiological ageing, as well the behaviour of the elderly subject, who often tends to neglect his disorders and put off consulting a physician.

TABLE II.—The size of the tumour as a function of age and the different histologic types: group of 152 patients.

Histologic type	51-60 years		61-70 years		71-80 years	
	Staging	%	Staging	%	Staging	%
Differentiated carcinoma	pT ₁ T ₂	89.7%	pT ₁ T ₂	81.0%	pT ₂	25.0%
	pT ₃	5.15%	pT ₃	12.1%	pT ₃	25.0%
	pT ₄	5.15%	pT ₄	6.9%	pT ₄	50.0%
Insular carcinoma	pT ₃	100%	pT ₄	100%	—	—
Medullary carcinoma	pT ₂	100%	pT ₂	50%	—	—
			pT ₃	100%	—	—
Epidermoid undifferentiated forms	pT ₄	100%	pT ₃	8.3%	pT ₄	100%
			pT ₄	91.7%		

TABLE III.—Age as a function of staging: group of 152 patients.

Stage	51-60 age	61-70 age	71-80 age
I	33.3%	27.6%	—
II	47.4%	46.5%	43.8%
III	16.7%	22.4%	43.7%
IV	2.6%	3.5%	12.5%

TABLE IV.—Lymph node repetitions and distant metastases: group of 152 patients.

	51-60 age	61-70 age	71-80 age
N	5.4%	12.3%	19.4%
M	2.7%	3.5%	14.28%

In our clinical cases the incidence of cancer of the thyroid has gradually increased and, over the past 5 years has accounted for 15.12% of all thyropathies. During the same period, the undifferentiated forms have decreased in number from 9% to 2.8%.

This may be the result of earlier diagnosis of the differentiated neoplastic forms in the younger age groups. This is less significant in the older patients, who are more frequently affected by highly malignant forms. Among our clinical cases over the past 5 years undifferentiated carcinoma was found exclusively in patients over the age of 60.

Carcinoma of the thyroid is more frequent among women even in the elderly, with a female: male ratio of 5:3. This ratio tends to decrease with increasing age, perhaps because of the relative increase in epidermoid and undifferentiated forms, which are not gender-related.

In the elderly the neoplasms tend to be more aggressive both in their biological behaviour and owing to the higher incidence of comparatively undifferentiated or actual anaplastic forms.

A strong correlation was recently found between the nuclear DNA content of tumour cells and the age of patients with cancer of the thyroid: higher age apparently corresponds to a frequent aneuploidy and a poorer prognosis.¹

In subjects aged less than 50 years papillary carcinoma accounts for over 60% of the neoplasms, while in those over the age of 50 it may attain a percentage of 30%, with early lymph node and distant metastases. Follicular carcinoma has an incidence similar to that of the papillary form, with a tendency to appear at more advanced stages. In our experience, medullary carcinoma, which accounts for 5-7% of malignant cancers of the thyroid, was present in 2.08% of cases and was characterized by distant metastization and capsular extrinsecation at the time of diagnosis. Anaplastic carcinoma is a rare neoplasm (4-5% of all primary cancers of the thyroid), typical of more advanced age, with its greatest incidence around the 7th decade of life, with no gender preference.²

Current immunohistochemical techniques have allowed many anaplastic carcinomas to be reassessed and reclassified. The coexistence of well-differentiated carcinoma foci has been documented in 8.5-10% of them. In the elderly patient there is a possibility of anaplastic carcinoma being

TABLE V.—Postoperative complications.

Mortality	0
Complications	
— Haemorrhage	0.5%
— Permanent hypocalcemia	
TT+lymphectomy neck	1.04%
TT+lymphectomy MAS	10.4%
Paralysis of the inferior laryngeal nerve	
— Temporary	1.04%
— Permanent	0.5%
— Nerve resection	1.04%
Paresis of the accessory spinal nerve (postlymphectomy)	0.5%
Paralysis of the brachial plexus (postlymphectomy)	0
Lesions of the cervical sympathetic nerve	0.5%

TT: total thyroidectomy. MAS: anterior-superior mediastinal.

the product of evolution towards the dedifferentiation of a well-differentiated carcinoma or of a long-standing benign thyroidopathy.²

Lastly, poorly differentiated carcinomas (insular, tall cell) are situated mid way between well-differentiated and anaplastic carcinomas. Unlike the anaplastic form, these neoplasms cannot be considered a typical carcinoma of the elderly, because they reach their highest incidence between the ages of 40 and 70 years. Histologically they present an architecture comprising large foci of (insular) tumoural thyrocytes that are well delimited by the stroma, or else scirrhous or trabecular type cells which may often coexist with a papillary or follicular component.³⁻⁶

As in young subjects, also in the elderly patient surgery remains the elective treatment wherever the general conditions allow.

Old age does not lead to a higher operative mortality *per se*. Indeed no postoperative mortality at all was found in our series.

Total thyroidectomy is widely justified as the elective surgery in the case of thyroid carcinoma in the elderly patient, also in view of the later stage reached by the neoplasm.^{7, 8}

Furthermore, numerous studies have shown that the bilaterality of the lesion fluctuates between 30% and 85%, and that in 30% of cases contralateral lesions are present that may be evaluated only microscopically. Lastly, neoplastic recidivation in the remaining lobe is affected by a high morbidity as the patient returns to the surgeon with lymph node recidivation. Furthermore, total thyroidectomy guarantees a more complete radiometabolic therapy.⁹⁻¹¹

It must not be overlooked that in the elderly patient neoplasms are often treated at an advanced stage: a decrease has been observed in the percentage of patients with intrathyroid cancer. Authors¹² point out that in the elderly, compared with young patients, intrathyroid cancer is less frequent (papillary 34% vs 39%, follicular 38% vs 51%, medullary 16% vs 44%), lymph node metastases are more frequent (papillary 43% vs 47%, follicular 16% vs 23%, medullary 16% vs 44%), there is a higher incidence of invasive tumours (papillary 31% vs 13%, follicular 22% vs 23%, medullary 75% vs 38%, anaplastic 83% vs 54%) as well as of distant metastases (papillary 23% vs 13%, follicular 45% vs 26%).

Nevertheless several authors consider that total thyrroi-

dectomy does not ensure increased survival, that the development of carcinoma in the residual tissue is a real, but wholly negligible, possibility and that conservative surgery actually involves a smaller number of complications such as lesions of the recurrent nerve and removal of the parathyroid glands.¹³

Other authors, although agreeing that total thyroidectomy is the best way to treat differentiated tumours, suggest a more conservative treatment (lobectomy plus isthmectomy), in papillary carcinomas less than 1 cm in size.¹⁴

Several authors recently proposed modulating surgical action according to whether the risk of recidivation was "low", "intermediate" or "high", pointing out that total thyroidectomy offered no advantage over less invasive action.^{15, 16} Conversely, Loh pointed out that patients with more extensive tumours than T1N0M0 or associated with risk factors (age, size and extension of tumour, lymph node and distant metastases), if treated with conservative surgery (lobectomy or subtotal thyroidectomy), display a recidivation frequency 250% greater than patients treated with total thyroidectomy.¹⁷

Other authors claim that hemithyroidectomy or total thyroidectomy without radioiodine treatment is to be preferred for stage T1-T3 of papillary carcinoma and in minimally invasive follicular carcinomas, in the absence of lymph node metastases, regardless of age.¹⁸

In elderly subjects subjected to total thyroidectomy for differentiated carcinoma, this incidence of temporary or persistent hypoparathyroidism (0.6-17%) and of recurrent nerve damage (0.5-3%) does not differ from that of young subjects.

Nevertheless persistent hypoparathyroidism represents a serious problem for such patients, in view of the bone demineralization that typically occurs in elderly subjects.

These complications increase (by over 20%) when the total thyroidectomy operation needs to be extended because of the invasiveness of the neoplasm, a situation that occurs in most cases in the 6th-7th decade of life.⁷

Invasion of the thyroid owing to contiguity of the carcinoma is a rare event, which becomes more frequent in the case of undifferentiated carcinoma. Considering the high incidence of undifferentiated carcinoma in the elderly subject, surgical treatment must be determined not only according to the age of the patients and their general conditions, but also to the degree of local-regional infiltration, considering that extended operations are liable to the risk of serious complications without having a significant effect on prognosis.⁸

Moreover, total thyroidectomy may be practiced in 20-60% of subjects in 50% of whom neoplastic residues nevertheless remain.^{19, 20}

Surgery associated with complementary therapy sometimes achieves better results than extended operations and leads to fewer complications. Also the neoplasm stage affects surgical strategy. At stage IV it is inoperable in 20-40% of cases, (large size tumour, invasiveness of extrathyroid structures), as a result of which an abstentionist attitude is adopted or else simple biopsy is performed, associated with tracheostomy if required.

Cervical lymphatic metastases are deemed to be more frequent in patients under the age of 45 years (45% vs 34%), while they are found to be associated with distant metastases in patients aged over 45 years (33% vs 10.4%).

Lymph node involvement does not seem to be related *per se* with any reduction in time of survival, while it is believed to represent a predictive indicator of recidivation.

Conversely, Sellers *et al.*²¹ showed that the long-term mortality index of patients with positive lymph nodes is directly proportional to their age. Also Noguchi *et al.*²² deems that lymph node involvement is prognostically significant only in patients over the age of 50. Other authors²³ consider that stages N0-N1-N2 have the same prognostic significance, while stage N3 is considered to be associated with higher mortality. Chen *et al.*²⁴ investigated the protein p53 as well as the epidermal growth factor receptor (EGFR), observing a close relationship with the presence of lymph node metastases but no relationship with the patient's age.

Treatment of lymph node metastases has gone from extensive radical function lymphectomies of the neck 'on principle' to the present-day treatment 'according to need'. In low risk-patients, in the presence of positive lymph nodes, 'central compartmental' lymphectomies are performed, depending on tumour location. In high-risk patients, "central compartmental" lymphectomy is always performed and, in the case of positive lymph nodes, 'radical functional' lymphectomy. The so-called lymphadenectomy 'on demand', consisting of the removal of lymph nodes macroscopically affected by the neoplasm, is recommended only rarely today because of the high frequency of recidivation. The extension of lymphatic exeresis to the anterior-superior mediastinum is performed in principle only in cases of medullary carcinoma.²⁵

One controversial issue is that of the advisability of proceeding with lymphectomy in patients in whom lymph node metastases are not clearly demonstrable.²⁶

Lymphectomy in the case of highly lymphotropic tumours (medullary and papillary) is universally accepted for the purposes of staging and treatment in those cases in which metastases are clinically evident, while prophylactic lymphectomy is controversial, both owing to functional problems and to complications linked to the extension of dissection.

Prophylactic lymphectomy is recommended in principle in papillary carcinomas in patients over 45 years of age when accompanied by at least one other risk factor. This is in order to prevent evolution towards undifferentiated forms.²⁵ Furthermore, Noguchi *et al.*²² has demonstrated the presence of metastases in 82% of subjects undergoing elective lymphadenectomy for carcinoma.

Bone metastases are more frequent in patients over the age of 45 and are usually symptomatic and multicentric. Overall, survival is higher in the case of lesions that take up radioactive iodine and in those without metastases except for bone metastases.²⁷

Cancer of the thyroid in the elderly patient can take on peculiar features. Undifferentiated, anaplastic or epidermoid forms are more frequent, as well as those with greater biological aggressiveness. Diagnosis takes place at a later stage and there is thus a greater incidence of the more advanced stages (III-IV) as well as of larger sized neoplasms (pT4). The higher aggressiveness of the neoplasm manifests itself with a high percentage of lymph node involvement (25%), of distant metastases (14.3%) and of invasion by continuity.

Radical surgery is not always possible. Operative risk is higher due also to the presence of concomitant pathologies.

All these factors add up to a prognosis that is less favourable than for young subjects.

Conversely, we consider that, for equal staging, the possibility of radical surgery does not differ from that of the young subject and that the age factor alone (in the absence of any concomitant pathologies) does not affect the overall surgical risk. Consequently, a more thorough and timely diagnosis would bring to the surgeon's attention neoplasms at an earlier stage and with less aggressive histotypes, thus improving the chances of performing radical surgical treatment and appreciably enhancing prognosis.

Riassunto

Il carcinoma della tiroide nei pazienti con età superiore ai cinquanta anni. Trattamento chirurgico e valutazioni prognostiche

Obiettivo. Il cancro della tiroide nel paziente anziano si caratterizza per la maggiore estensione locale e la frequente diffusione metastatica. Gli Autori analizzano, retrospettivamente, pazienti con età superiore ai 50 anni, affetti da carcinoma della tiroide, allo scopo di valutare l'importanza prognostica dell'età avanzata.

Metodi. Nel Dipartimento di Scienze Chirurgiche dell'Università degli Studi «La Sapienza» di Roma, sono stati esaminati 152 soggetti con un follow-up minimo di 10 anni, suddivisi in 3 fasce d'età: 51-60 anni, 61-70 anni, 71-80 anni.

Risultati. Correlando i diversi tipi istologici alle fasce d'età, è emersa una minore incidenza del carcinoma differenziato e un aumento delle forme epidermoidali e indifferenziate nei soggetti più anziani. Nella fascia d'età di 51-60 anni oltre l'80% dei pazienti era allo stadio I e II, mentre nella fascia 71-80 il 56,2% dei casi era allo stadio III e IV.

Conclusioni. Nel paziente anziano sono più frequenti le forme indifferenziate, anaplastiche o epidermoidali e quelle a elevata aggressività biologica. Noi riteniamo che una diagnosi tempestiva può consentire al chirurgo di trattare neoplasie in fase precoce e con istotipi meno aggressivi, dando maggiore possibilità di poter effettuare un intervento chirurgico radicale, migliorando sensibilmente la prognosi.

PAROLE CHIAVE: Tiroide, neoplasie - Tiroidectomia - Età geriatrica.

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