Surgical treatment of differentiated thyroid carcinoma: a retrospective study


SUMMARY: Surgical treatment of differentiated thyroid carcinoma: a retrospective study.

Patients and methods. Patient population consisted of 432 cases, operated from 1978 to 2003. We carried out 285 operations of total thyroidectomy of which 39 associated to some kind of lymphadenectomy, 66 totalization (21 pts had been operated in other institutes), 60 subtotal thyroidectomies and 21 lobo-isthmectomies. Survival and mortality curves have been calculated. Kaplan-Meyer statistical elaboration for disease-free interval and Mann-Whitney test for the comparison of different clinical and pathological data have been employed.

Results. The statistical analysis puts in evidence that on 432 cases examined, with a follow-up from 1 to 25 ys (median = 6.33 ys) and with a drop-out of 60 cases (13.8%), total mortality for cancer has been of 24 cases (6.4%), with a median interval free by disease of 4.2 ys (range 5 months to 25 ys), and a probability to stay free by disease at 12 and 24 months respectively of 95.1% and 91.6%. The median survival is resulted of 5.8 ys (range 1 to 25 ys) with a probability of survival at 24 and 48 months respectively of 97.5% and 94.3%. The multivariate analysis evidences the most important variables, i.e. age > 45 ys, tumor of intermediate malignancy, with size 1.5 cm, operative M+, significantly condition the prognosis, noticeably getting worse it, independently by the kind of intervent. Conclusion. Our present therapeutic choices are: 1. total thyroidectomy in the treatment of the apparently benign pathology when bi-

Riassunto: Trattamento chirurgico del cancro differenziato della tiroide: studio retrospettivo.

Introduzione. Viene riportata un’analisi retrospettiva della nostra esperienza nel trattamento del cancro differenziato della tiroide, per definire al meglio i fattori prognostici (età, sesso, tipo istologico, stadio) e proporre una procedura standard, dove possibile, per il trattamento chirurgico.

Pazienti e metodi. Trattasi di 432 casi operati tra il 1978 ed il 2003; presentiamo 285 tiroidectomie totali, di cui 39 associate a linfadenectomie, 66 totalizzazioni (21 pazienti sono stati operati in altri istituti), 60 tiroidectomie subtotali, 21 loboistmectomie. Le curve di sopravvivenza e mortalità sono state calcolate in base a età, sesso, tipo istologico, grading e stadio: sono stati utilizzati l’elaborazione statistica di Kaplan-Meyer per l’intervallo libero di malattia e il test Mann-Whitney per comparare i differenti dati clinici e patologici.

Risultati. L’analisi statistica mette in evidenza che su 432 casi esaminati, con un follow-up da 1 a 25 anni (media = 6.33 anni) e con un drop-out di 60 casi (13.8%), la mortalità totale per cancro è stata di 24 casi (6.4%) con un intervallo medio libero da malattia di 4,2 anni (range 5 mesi-25 anni) e una probabilità di essere liberi da malattia tra 12 a 24 mesi rispettivamente del 95,1% e del 91,6%. La sopravvivenza media è risultata di 5,8 anni (range 1-25), con una probabilità di sopravvivenza a 24 e 48 mesi rispettivamente del 97,5% e del 94,3%. L’analisi multivariata evidenzia le più importanti variabili, ovvero età > 45 anni, grado di malignità intermedia, dimensione maggiore di 1,5 cm, presenza di metastasi all’atto dell’intervento, condizionanti significativamente la prognosi, che peggiora notevolmente, indipendentemente dal tipo di intervento effettuato.

Conclusioni. Le nostre attuali scelte terapeutiche sono: 1) tiroidectomia totale nel trattamento della patologia apparentemente benigna, con estensione bilaterale; il rilievo all’esame istologico di un cancro inci...
Introduction

Differentiated Thyroid Cancer (DTC) represents the most frequent thyroid cancer, originating from the follicular epithelium and accounting for 90% of all thyroid carcinoma (1). Part of these tumors occurs in low-risk patients that may benefit of less aggressive management strategies. However, the characterization of low-risk patient is still confusing and we lack adequate markers to tell apart patients that may present a troublesome progression of the disease (2).

Different score staging systems (AGES, AMES, MACIS, TNM, etc.) attempted to define reliable prognostic factors, with encouraging results, but no conclusive data have emerged, able to guide the choice of treatment, also because some essential elements for the score are obtainable only at surgery (e.g., histology, T stage) (3-5).

The problem rises when these methods concern daily routine; here in fact, also where there is a refined pre-operating diagnostics, less than half of cancers reaches the treatment with a diagnosis of cancer, and it means that the 10-15% has doubtful cytological diagnosis and that nearly 40% reaches the treatment under the apparent spoils of a multinodular goitre. We have to consider that FNAB (Fine-Needle Ago-Biopsy), even if carried out by expert hands, points out on important results, a checking of false-negative from 1.7% to 4% and of false-positive from 0.5% to 2% (6); ultrasound guide offers some possibilities of improvement of the methodology, as well color power-Doppler for vascular intralesional signal (7, 8) and from nuclear medicine for determination of hyper-seeding lesions to positive sesta-MIBI tracer (9).

Total thyroidectomy (TT) is the technique of choice for several reasons, above all an easier and more efficient follow-up, with acceptable surgical morbidity if the procedure is performed in qualified Centers (10-12). At the time of surgery only 50% of cancers has been diagnosed, despite the improvements in diagnostic workup (ultrasonography, nuclear medicine, pathology). In 10-15% of cases there is diagnostic uncertainty, and in the remaining 30-40% cancer is found within a multinodular goiter (6).

Aim of this study was to highlight the most reliable prognostic factors through a retrospective analysis of our experience, and possibly identify the optimal surgical strategy for such disease. Two basic questions are open:

a) in which cases lobo-isthmectomy (LHY) or subtotal thyroidectomy (STT), followed by opotherapic treatment, can be judged a definitive cure?

b) is it correct to consider as appropriate treatments only LHY or TT?

We retrospectively examined our surgical experience aiming to partially address these important questions that remain unanswered and need to be addressed by the current generation of thyroid-dealing physicians.

Patients and methods

A total of 432 cases of DTC (117 male, 315 female) was operated on by our groups in the period 1978-2003 (Tab. 1). Procedures are summarized in Table 2. We carried out 306 total thyroidectomies, 39 of them associated with laterocervical lymphadenectomy; 21 totalizations in patients who underwent previous surgery elsewhere, 12 of them associated with lymphadenectomy, 60 subtotal thyroidectomies and 66 loboisthmectomies; about these latter patients, 36 of them have accepted totalization, 9 have been totalised with laterocervical lymphadenectomy, 9 have refused the operation and in 12 of them loboisthmectomy has been deliberately considered radical surgical treatment.

Concerning the prognostic variables taken into consideration data were searched for

Age

It’s enough evident the effect of the age on survival and it’s known for a long time that DTC discovered over 40 years olds have worse prognosis than DTC discovered in younger patient (13-15) and that the pejorative effect increases years by years after

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>432</th>
</tr>
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<tbody>
<tr>
<td>Follow-up</td>
<td>1 – 25 years (median 6.3 years)</td>
</tr>
<tr>
<td>Drop out, n (%), patients lost to the follow-up</td>
<td>60 cases (13.8%)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>24 cases (6.45%)</td>
</tr>
<tr>
<td>Overall survival at 24 and 48 months</td>
<td>97.5% and 91.6%</td>
</tr>
<tr>
<td>Median survival</td>
<td>5.8 ys (range 1-25)</td>
</tr>
<tr>
<td>Median disease-free interval</td>
<td>4.2 ys (range 10 months-25 ys)</td>
</tr>
</tbody>
</table>

TABLE 2 - SURGICAL PROCEDURES.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Case (n)</th>
<th>Lymphadenectomy (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy</td>
<td>306</td>
<td>39</td>
</tr>
<tr>
<td>&quot;D'emblèe&quot;</td>
<td>219</td>
<td>11</td>
</tr>
<tr>
<td>Totalization our patients</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Totalization patients treated somewhere else</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Lobo-isthmectomy</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Not accepted</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Deliberated</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

these registry limit, both about resumption and as cause of death (16-18). DTC in patients over 40 years old seems to have a worse outlook than in younger subjects, such phenomenon increasing decade after decade. In agreement with the UICC 1997 Statement, we accepted the age limit of 45 years staging discriminant.

Gender

A variable that apparently has a weaker prognostic significance than age. Females apparently fare better than their male counterpart (16).

Histological type and grading

Classification of the neoplasm as papillary or follicular entails different prognosis, with the best outlook for papillary lesions (80-90% survival at 10 years) compared to follicular neoplasms (65-75% survival at 10 years) (19). However such differences disappear if groups of patients are matched for age and stage, indicating that follicular tumors are usually diagnosed in a more advanced stage of disease (20, 21). We applied the classification of Carcangiu and Rosai, based on morphological data, that divides the lesions of the follicular epithelium basically into three groups:

1. low malignancy (78%), including all typical forms of papillary carcinoma, the follicular varieties of papillary carcinoma, the differentiated variety of Hürthle's cell tumor;
2. intermediate malignancy (15.2% of cases), including all solid cancers, trabecular cancer, widespread sclerosing forms, high-columnar cell type, insular forms, less-differentiated Hürthle's cell variety, differentiated lesions with areas of de-differentiation;
3. high malignancy (6.8% of cases), including all forms of anaplastic carcinoma.

Now, although the anaplastic carcinoma is not, as it's right, to be included in the DTC, the simple identification of a form with it's characteristic automatically assigns it to the worse prognostics class.

About the first two groups, instead, it seems suggestive proposing a perspective study to verify if inclusion between the forms of the first or the second group really signs a prognostic destiny, different for the same age and classification staging, accepted by us to include them between the malign with low aggressiveness neoplasias, with survivals nearby the 100% (22). All this can be even more censured in the more and more diffused choice to limit to a lobo-isthmectomy the therapy of an incidental differentiated thyroid cancer which is T1N0M0, independently by age, sex, familiarity, histology; if this choice can appear daring, the conjecture of modulating the surgical strategy in relation to one or more variables is not so singular, in particular if we consider factors like dimensions, grading and histology.

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2. intermediate malignancy (15.2% of cases), including all solid cancers, trabecular cancer, widespread sclerosing forms, high-columnar cell type, insular forms, less-differe-
of metastases at the time of primary treatment (9 cases), or with their occurrence during follow-up (12 cases), and to local aggressiveness of the tumor (acute respiratory distress from massive tracheal invasion) – in 6 cases, with unfavourable histological type (extensive undifferentiated areas). Lymph node metastases, on the other hand, doesn’t seem to significantly alter the prognosis.

Standing to the resumption of disease look interesting the 3 cases, where the long surviving time seems independent from the primary treatment (lobo-isthmoectomy) and not conditioned by the evidence after years of loco-regional lymph node metastasis. Must, anyway, to be considered the importance of the secondary treatment with the totalization and the lymphadenectomy to ensure an easier follow up. Only the histologic type (intermediate malignancy) suggests some more careful consideration. Absolutely particular look 3 cases, where the primary treatment seems adequate, also if requires after 6 months to 2 years a latero-cervical lymphadenectomy on the same side and on the opposite side, confirming that doesn’t exist an ideal “d’emblée” lymphectomy in the treatment of DTC.

Standing to the mortality, must be considered that 6 cases belong to the histologic type group with intermediate malignancy (Carcangiu-Rosai) and that 3 of them arrived to the primary treatment already with cerebral metastasis; the aggressiveness is confirmed by the low grading, the high T and the type of metastasis that ensures a fast and unfavourable prognostic evolution. It’s not casual, overall, that the most unfavourable cases are male and >45 ys old.

Concerning the single prognostic variables, from our data the following considerations can be drawn.

**Age**

In our experience, the variable age showed correlation with variables sex and T, making difficult the interpretation of results that anyway seems to evidence a suggestive link with surviving and resumption of disease. As regards the age, the mortality for cancer is prerogative of >45 ys old patients (pts) and the resumption of disease of >30 ys old pts. We find, on 372 patients screened, from 180 pts <45 ys old, only 9 resumptions of disease (all of them lymph nodal, 5%); 6 had received a partial primary treatment, so had to be completed by totalization and lymphadenectomy after 6 to 9 ys, while the only 3 patients who had already received a total thyroidectomy, underwent to a locoregional lymphadenectomy after maximum 1 year. All of them are alive and free from disease (follow up range 2-20 ys). From the 192 pts > 45 ys old we have 27 recurrence (14%), 9 were lymphnodal associated to tracheal invasion and 15 were associated to distal metastasis; unfortunately of 27, 24 are deceased and only 3 are still alive (M+ after some ys, treated by radioiodine therapy).

**Gender**

In our revision, there is the difference between male and female gender, although the statistical interpretation of the phenomenon is doubtful, because of then remarkable level of dependence. The prognostic weight of the gender seems to negatively modulate, for male pts, the influence of other variables (histologic type, stage and age). In a group of 267 female patients we find only 18 recoveries (6,7%) with 9 dead patients, 9 still living and with disease-free interval included between 2 and 17 ys; in the group of 105 male pts, we find 18 resumption of disease (17,1%), of which 15 pts deceased and only 3 alive.

**Histology and grading**

Another particular significant data seems to be the histologic type and the grading that, although in correlation with T, results statistically independent by variables like age, sex, and familiarity; in fact the group of cancers with intermediate malignancy presents more deaths and recoveries. In the group with low malignancy (243 cases), we have examined 12 resumptions (4,9%): 9 patients actually living with an interval free by disease from a minimum of 4 to a maximum of 17 ys and 3 deceased after 8-10 ys. In the group with intermediate malignancy (129 cases) instead 24 resumptions (18,6%), with 18 dead patients and 6 still living and with a free-disease-interval included between 5 months and 6 ys.

**T stage**

In our experience in cancer < 1,5 cm (129 cases), we have 3 resumptions (2,3%): the patients are alive after 9 to 18 ys from the primary treatment. With cancers of dimensions including between 1,6 cm and 2,5 cm (102 cases), we have 9 resumptions (8,8%), 6 deads at 1 year and 3 patients alive after 6 to 10 ys. With cancers of dimensions > 2,5 cm (135 cases), we have 24 resumptions (17,7%), 21 deads, 3 alive after 9 to 12 ys follow-up. Although this datum can look suggestive, the multivariated analysis has shown a remarkable level of correlation with the others variables (sex, age, family, and histology).

**N stage**

A doubtful data appears from the distribution of the survival in relation to the loco-regional lymph node metastasis: only 12 patients who have shown resumption N+ (36) are dead, 24 of them are still living.

**M stage**

As regards the resumption with distal metastases, the data reveals a reasonable prognostic weight; in fact,
between M+ patients there are 21 dead patients and only 3 still living. These last two dates, although they shown a good level of independence, are in correlation with variables like T and grading.

Discussion

The prognostic role of surgical treatment in the management of DTC is difficult to define: available studies are retrospective, biased by surgical habits, different technical aspects, non-standardized extent both on the gland and on the lymphatic line (36-38). Furthermore, in any case-population study, it is conceivable to expect over-treated or under-treated cases. Finally, sometimes a paradoxical effect may be observed, with tumors in advanced stage receiving under-treatment or vice-versa locally diffused low risk tumors receiving over-treatment (39, 40).

The statistical evaluation of our data allowed us to define the hypothetical portrait of a patient with unfavourable prognosis: male, age >45 years, affected by a tumor of >1.5 cm in diameter, histologically classified as intermediate malignancy; in our record of cases this group includes 57 cases with 18 resumptions (31.5%) with 15 dead patients and 3 still living, but with resumption within 1 year. What's the message for such class of patients? Aggressive initial treatment seems not to be sufficient, complementary therapies are needed, along with better knowledge of the biological and genetic mechanisms of disease. On the other hand, there is the group with the most favourable combination: female gender, age > 45 years, with a neoplasm <1.5 cm in diameter, histologically classified as low-grade malignancy; in our record of cases this group includes 123 pts with only 3 cases of resumption of disease, anyway still living.

Because of our prevalent option for total thyroidectomy in the treatment of the thyroid benign lesions, most of these often accidental cases have received this type of treatment independently by the definitive histological diagnosis and, even when the primary treatment has been a lobo-isthmectomy, our tendency has always been proceeding to a totalization of second resort, because we however consider preferable managing the follow-up of a patient without thyroid tissue at all. We however don't consider, about these cases, that lobo-isthmectomy is a under-treatment. The same speech, even more so, is valid for a typic adenomas, all of accidental importance, all treated in our experience with a total thyroidectomy of first resort, that particularly in the multiple focus forms, of a probable family origin, assumes a more preventive than curative meaning. For this reason we have never expected for these cases another post-operative therapy that is not a ophotherapy with substitutive dosages.

Other aspects may be of prognostic significance, such as local (extrathyroid) invasion, or multifocal neoplasia (such occurrence may be frequent if adequately searched on surgical specimens), or aneuploidy and DNA cellular content, and ultimately tumor angiogenesis index.

We stress the prognostic value of histological analyses of proliferative markers such as expression of 27 KII, Ki 67/mib1, and growth or cell cycle related factors (cyclin D1) (41, 42).

The identification of a familial form of papillary microcarcinoma (5.9% of carcinomas) has an unfavourable prognostic significance, in spite of the low T score (43). The role of other potential cell markers as useful tools in prognosis or management of DTC have turned out disappointing (laminine, collagenase, K1 antitrypsin) (44, 45).

The presence of peritumoral lymph cells infiltrates should have a doubtful meaning; irrelevant in the European experience, with protective meaning in United States and Japanese analyses.

At last, an interesting perspective may stem from integration of biomolecular studies and gene typing (46-49) with immunohistochemical determinations on FNAB. Surgical planning could be improved adding to morphologic studies on FNAB specimens biomolecular determinations based on real time quantitative reverse transcription for mRNA of the oncofetal-fibronectin-like marker of thyroid neoplastic differentiation (50). Anatomic and microscopic data could receive an additional insight on ultrastructural patterns, in order to improve surgical decision making.

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