Clinically unpredictable prognostic factors in the outcome of medullary thyroid cancer

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Abstract

Total thyroidectomy and central neck dissection are the procedures of choice in patients affected with medullary thyroid cancer. It is known that a medullary thyroid cancer with node metastases can be rarely cured, and therefore the utility of a modified radical neck dissection in the absence of suspicious node metastases still needs further evidence. The study aims to verify whether other epidemiological and pathological parameters could affect the prognosis of medullary thyroid cancer patients. We prospectively studied 70 medullary thyroid cancer patients consecutively operated on (from 2000 to 2004) at the same institution and analysed by the same pathologists. All patients underwent total thyroidectomy and central lymphadenectomy. In 27 cases, the ipsilateral (n=19) or bilateral (n=8) modified radical neck dissection was performed in the presence of suspicious lateral neck node metastases. After surgical treatment, basal and stimulated serum calcitonins (Cts) were measured in all patients. Follow-up ranged between 1 and 4 years. Patients were considered 'cured' when stimulated Ct was undetectable. Age, sex, tumour size, tumour capsule, multicentricity, nodes in the central neck and mean number of positive nodes were analysed in 'cured' and 'not-cured' patients. The presence of node metastases in the central compartment was significantly correlated with the outcome of the patients, being present in 9 and 72% of cured and not-cured patients respectively (P<0.000001). Tumour size was also significantly correlated with the outcome of the disease (P<0.000006). The presence of the tumour capsule correlated with better prognosis (P=0.0005) and absence of node metastases (P=0.0080). By multivariate analysis, the presence of node metastasis remained the most significant variable affecting the outcome of the disease (P=0.000014). Our results show that the outcome of encapsulated cancer is significantly better regardless of tumour size and node metastases. Although the early diagnosis and the extensive surgical treatment may favour the good outcome of medullary thyroid cancer, they do not always guarantee the definitive cure of the disease, being the capsular infiltration an independent bad prognostic factor.

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Introduction

Total thyroidectomy associated with central neck dissection is considered the surgical option in patients affected with medullary thyroid cancer (MTC). According to the American Association of Clinical Endocrinology and the Society of Surgical Oncology guidelines, a modified radical neck dissection of the ipsilateral and contralateral compartment is indicated only when there is evidence of suspicious or metastatic nodes at preoperative imaging or cytology (AACE. Clinical practice guidelines for the diagnosis and management of thyroid nodules 1996, Mazzaferrri 1999, Kebebew & Clark 2000).

Still, some authors advocate the necessity of modified radical neck dissections (ipsilateral or bilateral) associated with the initial operation in patients without any evidence of suspicious lymph nodes (Scollo et al. 2003, Yen et al. 2003). This more aggressive approach, which significantly raises the morbidity of the operation even in experienced centres (Roh et al. 2007), is justified by the early lymphatic spreading of the tumour, leading to a high incidence of node metastases in all compartments of the neck.

It is well known that the presence of node metastases is a negative prognostic factor, so that an early diagnosis, performed before the involvement of the nodes,
represents the only tool to reach a cure for MTC patients. Routine serum calcitonin (Ct) measurement in thyroid nodular diseases has proven to be the most effective diagnostic procedure to perform an early diagnosis of this tumour, thus positively affecting the patients’ outcome (Pacini et al. 1994, Elisei et al. 2004, Machens et al. 2005, Vierhapper et al. 2005).

Despite the general observation that the tumour size is significantly correlated with the lymphatic spreading of MTC, there are clinical hints that other unknown parameters might play a role in facilitating the extrathyroidal metastatic dissemination. In this paper, we analysed several pre- and post-operative features of a series of MTC diagnosed, operated on and followed up at the same institution from 2000 to 2005, aiming to find further parameters that may predict the outcome of MTC patients.

**Materials and methods**

**Patients**

Among 350 patients actively followed for MTC, we selected 70 consecutive patients (43 females and 27 males, mean age 53.4 years) operated on between January 2000 and December 2004 at our institution, a tertiary care surgical centre for endocrine diseases. The inclusion criteria were: first time surgery, disease confined to the neck, pre-operative diagnosis performed or confirmed in our institution and a follow-up of at least 12 months.

Before surgery, all patients underwent basal and pentagastrin (Pg)-stimulated (Peptavlon, Newcastle, UK, 0.5 μg/kg) serum Ct measurement, neck ultrasound, fine needle aspiration citology (FNAC) of suspicious thyroid nodules and/or neck nodes and chest X-ray (and computed tomography when requested). Serum Ct was measured using a solid-phase two-site IRMA (ELSA-hCT, CIS, Gif-Sur-Yvette, France) with a functional sensitivity of 14 pg/ml.

According to the diagnostic protocol for MTC, abdominal ultrasound and the measurement of serum and urinary epinephrine and nor-epinephrine as well as parathyroid hormone and calcium were also performed. All subjects underwent rearranged during transfection (RET) genetic screening before undergoing surgery.

According to the guidelines of the American Association of Clinical Endocrinologists, all patients underwent total thyroidectomy and central neck dissection (TT), along with ipsilateral or bilateral modified radical neck dissection only when suspicious lymph node metastases were found at pre-operative clinical examination.

All patients were evaluated 3 months after surgery with neck ultrasound and basal Ct measurement. Six months after surgery, a Pg test was performed in all basal Ct-negative patients. A Pg test was repeated once a year in negative cases. Patients with elevated basal and/or stimulated Ct underwent further imaging studies (i.e. computed tomography, abdominal ultrasound, RMN) to localise the disease. According to their clinical status at the last evaluation, patients were classified in two groups: a) ‘cured’ as defined by a negative postoperative basal and Pg-stimulated Ct and b) ‘non-cured’ as defined by a positive postoperative basal or Pg-stimulated Ct with or without radiological evidence of disease (negative neck ultrasound, computerised tomography or bone scintigraphy).

All patients signed an informed consent for the clinical, biochemical and genetic analysis and for the surgical procedure.

**Histology**

Thyroids, after formalin fixation, were serially sectioned perpendicular to the long axis of each lobe from the superior to the inferior pole and then embedded in paraffin. Lymph nodes were sampled and processed separately.

Haematoxylin and eosin staining and Ct, chromogranin A, carcinoembriogenic antigen (CEA) and thyroglobulin immunohistochemistry (Ventana Medical System, Tucson, AZ, USA) were performed on the tumour samples. The diagnosis of medullary carcinoma was based on the WHO classification of the tumours (De Lellis et al. 2004). The size of the primary tumour, the multifocality and the bilaterality of the tumour, the presence of a complete tumour capsule and the extrathyroidal extension were described. C-cell hyperplasia was diagnosed when the immunohistochemistry for Ct and chromogranin A reveals an increased number of C-cells, at least more than 50 C-cells per low-power field in areas of high C-cell concentration (Albores-Saavedra & Krueger 2001).

Node metastases were counted and confirmed by immunohistochemistry with Ct, chromogranin A and thyroglobulin antibody (Ventana Medical System). Negative nodes were also evaluated by immunohistochemistry with the same antibodies for the presence of micrometastases.

**Statistical analysis**

Statistical analysis was performed with univariate tests ($\chi^2$, Mann–Whitney U test). Regression models were utilised to examine those factors identified as significant in univariate tests. Values of $P < 0.05$ were
considered statistically significant. The software used was STATISTICA 6.0 (Statsoft, Tulsa, OK, USA).

Results

According to the enrolment criteria, all patients underwent a total thyroidectomy associated with central lymphadenectomy as previously described. Nineteen and eight patients also underwent ipsilateral and bilateral modified radical neck dissection respectively. Out of 70 patients, 5 (7.1%) demonstrated permanent hypoparathyroidism and 1 (1.4%) demonstrated permanent monolateral vocal chord palsy after the operation.

Mean and median preoperative Ct levels were respectively 1110 and 213 pg/ml (range <14–13910). Nineteen and eight MTC patients showed a clinical suspicion of ipsilateral and contralateral node metastases respectively. No patients had signs of pheochromocytoma and or hyperparathyroidism. Eight patients were positive for a germ line RET mutation.

At final histology, all patients demonstrated an MTC (100% positivity for Ct, chromogranin A and CEA at immunohistochemistry); in six patients a papillary microcarcinoma was also found. As shown in Table 1, mean and median size of the MTC were respectively 1.6 and 1.2 cm (range: 0.2–4.8). The tumour demonstrated a complete capsule in 18 cases and it was not encapsulated in 52 cases. Multifocality was present in 11 out of 70 (15.7%) cases, 7 of whom showed the tumour foci in the two lobes. The coexistence of C-cell hyperplasia and/or chronic thyroiditis was demonstrated in 20 out of 70 (28.6%) and 12 out of 70 (17.1%) MTC patients respectively.

Out of 70 patients, 21 (30%) showed node metastases in the central compartment (CC). Out of 27 cases, 18 (66.6%) selected for ipsilateral neck dissection were also positive for node metastases. Among them, 13 out of 18 cases were positive for both central and ipsilateral compartments. Out of the eight cases undergoing bilateral neck dissection, seven did not demonstrate node metastases in the lateral compartment opposite to the tumour; therefore, only one case demonstrated metastases in all three compartments.

At the end of the follow-up, 42 patients (60%) were cured. In particular, among the 28 non-cured patients, 10 cases demonstrated a negative postoperative basal Ct but an elevated stimulated Ct. In this latter group, the mean and median stimulated Ct were 43.4 and 29 respectively (range: 23–108 pg/ml). Eighteen patients showed elevated postoperative basal Ct (mean and median basal Ct: 309 pg/ml, 75 pg/ml respectively).

Demographic, biochemical and pathological features of ‘cured’ and ‘non-cured’ patients are reported and compared in Table 2. In accordance with other studies, in our series, both preoperative Ct and tumour size were significantly related to the outcome of the disease. No correlation was demonstrated for any demographic feature, for the number of tumour foci or for the presence of desmoplastic stromal reaction.

Nevertheless, the results obtained from this analysis demonstrate that the infiltration of the tumour capsule was significantly more frequent in patients of the ‘non-cured’ group ($P<0.0001$).

In patients belonging to the ‘cured group’, the presence of node metastases in the CC was significantly less frequent than in patients belonging to the ‘non-cured group’ (9% vs 72%, $P<0.0001$). This difference was also statistically significant when considering metastatic nodes from the ipsilateral compartment ($P=0.0014$). Finally, the presence of a metastasis in any compartment of the neck is significantly related to the ‘non-cured’ group ($P<0.0005$).

Since the presence of node metastasis is confirmed to represent one of the most important prognostic factor in MTC patients, we decided to compare the clinical and pathological features of patients with and without node metastases (N+ and N0 groups respectively). As shown in Table 3, higher preoperative

Table 1 Demographic, biochemical and clinical profile of 70 patients affected with MTC

<table>
<thead>
<tr>
<th>Demographic profile</th>
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<tbody>
<tr>
<td>Mean age</td>
<td>53.4 years</td>
</tr>
<tr>
<td>Females/males</td>
<td>43/27</td>
</tr>
<tr>
<td>Familial/sporadic</td>
<td>8/62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical profile</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Ct: mean, median and range (pg/ml)</td>
<td>1110/213 (&lt;14–13 910)</td>
</tr>
<tr>
<td>Stimulated Ct: mean and median and range (pg/ml)</td>
<td>3904/493 (31–54 784)</td>
</tr>
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<table>
<thead>
<tr>
<th>Characteristics of T</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean and median diameter (cm)</td>
<td>1.6/1.2</td>
</tr>
<tr>
<td>Single focus</td>
<td>59</td>
</tr>
<tr>
<td>Multifocal</td>
<td>11</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7</td>
</tr>
<tr>
<td>Tumour capsule (yes/no)</td>
<td>18/52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N+ in the central compartment</td>
<td>21/70</td>
</tr>
<tr>
<td>N+ in the ipsilateral compartment</td>
<td>18/27</td>
</tr>
<tr>
<td>N+ in the contralateral compartment</td>
<td>1/8</td>
</tr>
<tr>
<td>Mean number of N removed in the central, ipsilateral and contralateral compartment</td>
<td>6.5/18.1/13</td>
</tr>
</tbody>
</table>

Ct, calcitonin; T, primary tumour; N, node; N+, metastatic node.
basal Ct, greater tumour size, infiltration of tumour capsule and extrathyroidal tumoral extension were significantly correlated with lymphatic spreading (N^C). The presence of a tumour capsular infiltration (not necessarily associated with extrathyroidal extension) was significantly associated with the presence of node metastases in any compartment of the neck (P<0.008). The multivariate regression analysis showed that both bigger tumour size and tumour capsule invasion, but not preoperative serum Ct, were statistically significant for the presence of lymph node metastases in any compartment of the neck.

When considering the different surgical compartments, we observed that in five cases the node metastasis skipped the CC and was present in the ipsilateral compartment. In contrast, no metastases in the contralateral neck compartment skipped both the central and the ipsilateral neck compartments. It is noteworthy that among eight cases of patients submitted to bilateral modified radical neck dissection, only one patient demonstrated a node metastasis in the contralateral compartment and this patient belonged to the 'non-cured' group. The post-operative biochemical and clinical profile of those eight patients is summarised in Table 4.

### Discussion

The definitive cure of MTC, as defined by undetectable basal and stimulated levels of serum Ct, is possible only if an early diagnosis of the tumour is performed (Gimm et al. 1998, Weber et al. 2001, Elisei et al. 2004). The question of whether the primary surgical treatment should consist of a total thyroidectomy, central neck dissection and ipsilateral and/or bilateral lymph node dissection independently of the clinical evidence of lymph node involvement is still debated (Franc et al. 2001, Scollo et al. 2003, Machens et al. 2006). Since such an extensive surgical treatment leads to a higher morbidity than total thyroidectomy alone, as demonstrated by the relative high rate of complications demonstrated in our series, one should consider whether it can really improve the prognosis of the patient. In the present study, we analysed the influence of several clinical and pathological parameters on the outcome of a series of 70 MTC patients all treated and histologically analysed at the same hospital in a quite...
short period of time. In agreement with other series (Modigliani et al. 1998, Machens et al. 2000, 2006), we found that the presence of lymph node metastases was the most important adverse prognostic factor for the definitive cure of the disease. It is noteworthy that in our series, the presence of node metastasis per se, with the exception of four cured cases, was the main factor in determining the biochemical persistence of MTC, regardless of the site of the involved lymph nodes. It could therefore be of practical usefulness to identify a clinical or pathological MTC feature able to predict the presence of metastatic neck nodes. Among all variants analysed, we found that tumour size significantly correlates with the presence of node metastases, as already demonstrated in other series (Tamagnini et al. 2005). Moreover, the absence of tumour capsule is also significantly related to the lymphatic spreading of the disease. This result may lead to reconsider the extension of the first operation on the basis of the presence of parenchymal tumoral infiltration that may be intraoperatively revealed by a thorough frozen section analysis. The indication to perform an intraoperative frozen section analysis in cases of MTC is also supported by a recent paper showing a positive relationship between desmoplasia and metastatic lymph nodes in patients with MTC (Scheuba et al. 2006). The intraoperative examination can be based on gross observation at first. If the tumour presents the typical infiltrative appearance, the intraoperative analysis could be limited to one capsular section. On the other hand, if the nodule presents a continue capsule at gross examination, the intraoperative analysis could be performed on two to five capsular sections. Nevertheless, in cases in which this analysis is not sufficient for a definite diagnosis, we suggest to follow the standard surgical attitude described above.

At present, our attitude is that ipsilateral neck dissection should only be performed at the first operation when there is evidence of suspicious node metastases at preoperative imaging. Although the neck ultrasound is able to identify nodes of millimetric diameters and fine needle aspiration can confirm their metastatic nature, at this stage the clinical outcome is already defined, and the biochemical cure of the disease is reached only in few cases (Modigliani et al. 1998). Also in our series, only 4 out of 28 (14%) MTC patients with node metastases reached surgical cure of the disease after the first operation. This observation supports the hypothesis that other parameters, such as infiltration of the thyroid parenchyma, should be taken into account to identify those MTC tumours prone to develop node metastases. These patients must be followed for the possibility to develop nodes metastases and immediately re-operated on before they become locally invasive or quite large. Although not definitively effective in terms of biochemical cure, this procedure proved to be useful in improving the overall survival (Tisel et al. 1986, Moley et al. 1997).

When analysing the pathway of lymphatic spreading of the tumour, in our series, 5 out of 19 (26.3%) cases with node metastases in the same lateral compartment of the neoplasia did not show any node involvement in the central neck. This finding might lead to reconsideration of the necessity of performing CC dissection at any first surgery. On the contrary, since the infiltration of the thyroid parenchyma has a negative predictive value of 100% and a positive predictive value of 50%, it could represent a better indicator for the choice of the extension of the operation.

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Table 4 Post-operative biochemical and clinical profile of the eight patients submitted to bilateral modified radical neck dissection (MRND)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Basal Ct</th>
<th>Stim Ct</th>
<th>Size (cm)</th>
<th>No of foci</th>
<th>Tumour capsule</th>
<th>CC</th>
<th>LC1</th>
<th>LC2</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neg</td>
<td>Neg</td>
<td>1.2</td>
<td>Bilat</td>
<td>No</td>
<td>0/9</td>
<td>0/14</td>
<td>0/10</td>
<td>T2</td>
</tr>
<tr>
<td>2</td>
<td>Neg</td>
<td>Neg</td>
<td>0.5</td>
<td>Single</td>
<td>Yes</td>
<td>0/7</td>
<td>0/13</td>
<td>0/16</td>
<td>T1</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>–</td>
<td>4</td>
<td>Single</td>
<td>Thyroid capsule infiltrated</td>
<td>6/6</td>
<td>5/7</td>
<td>2/7</td>
<td>T3a</td>
</tr>
<tr>
<td>4</td>
<td>Neg</td>
<td>Neg</td>
<td>0.7</td>
<td>Single</td>
<td>Yes</td>
<td>0/15</td>
<td>0/11</td>
<td>0/17</td>
<td>T1</td>
</tr>
<tr>
<td>5</td>
<td>Neg</td>
<td>Neg</td>
<td>1.5</td>
<td>Single</td>
<td>Yes</td>
<td>0/13</td>
<td>0/21</td>
<td>0/24</td>
<td>T1</td>
</tr>
<tr>
<td>6</td>
<td>Neg</td>
<td>25</td>
<td>1.6</td>
<td>Bilat</td>
<td>No</td>
<td>2/13</td>
<td>0/15</td>
<td>0/9</td>
<td>T1m</td>
</tr>
<tr>
<td>7</td>
<td>Neg</td>
<td>Neg</td>
<td>2.5</td>
<td>Single</td>
<td>No</td>
<td>0/9</td>
<td>0/20</td>
<td>0/12</td>
<td>T2</td>
</tr>
<tr>
<td>8</td>
<td>Neg</td>
<td>55</td>
<td>4</td>
<td>Single</td>
<td>NA</td>
<td>0/13</td>
<td>1/13</td>
<td>0/12</td>
<td>T2</td>
</tr>
</tbody>
</table>

CC, central compartment; LC1, lateral compartment ipsilateral to the primary tumour; LC2, lateral compartment contralateral to the primary tumour. Lymph nodes are expressed as: number of metastatic nodes out of number of total nodes (N+/N). TNM is expressed following the Vth Edition.

*aNeoplastic embolisation was demonstrated in this patient.*
Moreover, bilateral modified radical neck dissection has been indicated and performed in eight patients, and among them, only one case demonstrated the presence of a single node metastasis in the contralateral compartment. We can thereby assume that, as a consequence of an early diagnosis (Elisei et al. 2004), the lymphatic spreading of the tumour to the contralateral compartment is uncommon and may be easily predicted before the first operation. Furthermore, MTC patients with bilateral node involvement should be considered to have a systemic disease, and thus they are unlikely to be biochemically cured also after an extensive surgical operation (Machens et al. 2006).

In conclusion, the results of this study, obtained from a large series in a relatively small period of time, suggest that some tumoural patterns that might prove to be useful in avoiding unnecessary, time-consuming and morbid surgery. The extension of the neck dissection might therefore be limited to patients with the intraoperative evidence of thyroid parenchymal infiltration, a feature significantly correlated with the presence of node metastases. On the contrary, the integrity of the tumour capsule is a strong predictor of the absence of the lymphatic diffusion, allowing the prediction of surgical cure of the disease and maybe leading to reconsideration of the necessity of performing neck dissection at the first surgery in any patient. Nevertheless, we do not deny the possibility of repeated operations with the aim of reducing the tumour burden, thus allowing a prolonged survival to the patients affected with MTC.

Acknowledgements

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AACE 1996 Clinical practice guidelines for the diagnosis and management of thyroid nodules. Endocrine Practice 2 78–84.


