Papillary thyroid microcarcinoma: proposal of treatment based on histological prognostic factors evaluation.

Ann. Ital. Chir., 2014 85: 1-5
pii: S0003469X14022027

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BACKGROUND: *Papillary thyroid cancer accounts for approximately 80% of thyroid tumors and its incidence has increased over the past decades. Papillary thyroid microcarcinomas (PMCs), defined by the World Health Organization as less than 1.0 cm in size, are identified with greater frequency. The majority of patients with PMCs follows a benign clinical course, however a subgroup of these carcinomas is as aggressive as bigger tumors. Risk factors related with poor outcome have not been defined and the optimal treatment has not been proved. The authors investigated histologic prognostic factors predicting high risk patients considered for more aggressive treatment and propose reviewed therapeutic guidelines based on analysis of histopathologic features which determined the recurrence rate.*
STUDY DESIGN: *One hundred forty nine patients with PMC who underwent surgery were retrospectively analyzed. Clinical and histopathologic parameters potentially predicting patient outcome and recurrent disease were statistically investigated, after a minimum follow-up of 5 years.*
RESULTS: *After a median follow-up of 5.4 years 28 of 149 patients experienced recurrent disease. All of them were reoperated on and newly treated with radioiodine administration. The multivariate statistical analysis identified extrathyroidal invasion (Odds Ratio, OR, 58.54; P=0.013), the solid pattern (OR,25.77; P>0.001), the tumor multifocality (OR, 15.80; P= 0.005), and the absence of tumor capsule (OR, 9.74; P=0.015) as significant and indipendent risk factors for the appearance of PMCs recurrences. Of note, none of the PMC "incidentally" discovered at histopathological examination alone experienced recurrent disease during follow-up.*
CONCLUSIONS: *Although most PMC have favourable long-term prognosis, some patients (19% in our series) presented aggressive clinical course strongly correlated with some histopathologic features (extrathyroidal invasion, tumor multifocality, solid pattern and absence of capsule) who need to be investigated and for whom a radical therapeutic approach is recommended based on total thyroidectomy and regional lymphadenectomy followed by radioiodine administration.*

KEY WORDS: Neck dissection, Multifocality, Personalized Surgery, Prognostic factors, Tailored medicine, Thyroid surgery, Tumor invasion

Introduction

Thyroid carcinoma is the most common endocrine tumor, however it represents only 1% of all malignancies. Its incidence in the overall population varies between 0.5 and 10 new cases each year every population of 100.000 [1].
Papillary thyroid carcinoma (PTC) is the most frequent histological type accounting for 80 per cent of cases [2],

Pervenuto in Redazione Settembre 2013. Accettato per la pubblicazione Ottobre 2013
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and it is considered a curable neoplasm. Overall, clinical outcomes for patients with PTC are excellent, with a mortality rate of 3-11% and a 10-year survival rate of approximately 95% [3-6].

To date there has been a considerable number of registries which have reported that the incidence of papillary thyroid cancer is increasing [7]. The U.S. incidence of PTCs overall has increased over the past several decades and data obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, report that in the period 1973-2002, the incidence of thyroid cancer increased from 3.6 per 100.000 in 1973 to 8.7 per 100.000 in 2002: a 2.4 fold increase. This 5.1 per 100.000 increase in the incidence of thyroid cancer is virtually entirely due to an increase in papillary cancer [8]. The same data are obtained from registries, as National Cancers Institute of Bethesda and Associazione Italiana Registri Tumori [9].

The bulk of this incidence is the result of increased detection of small cancers and particularly of the lesion called "microcarcinoma" a variant of PTC which is defined, according to World Health Organization (WHO), as a malignant thyroid cancer 1.0 cm or less in greatest dimension [10].

Three circumstances may lead to the diagnosis of Papillary microcarcinoma (PMC): 1) surgery for benign thyroid disease, (incidental PMC), 2) preoperative FNAB of thyroid nodule (not incidental PMC), 3) preoperative FNAB of enlarged neck lymph-node (not incidental PMC) [11,12].

PMC, as a specific subgroup of PTC, is not correlated with any thyroid pathology, is present equally in both sexes, is not related to exposure to radiation and rarely progresses to clinically apparent thyroid cancer with advancing age.

PMC is being found in an increasing proportion representing up to 30 per cent of all papillary cancers seen in a thyroid surgeon's practice and deserves attention for conflicting reports on treatment modalities for this subgroup of patients.

Several studies, based on multivariate analyses, have shown that the vast majority of PMCs have favorable long term prognosis and the life expectancy does not differ much from that of the normal population [13]. Nonetheless, on rare occasions, a PMC behaves aggressively and metastasizes early, presenting with clinically evident loco-regional recurrences and distant metastases [14-16].

To date multivariate analysis does not reveal any prognostic factors affecting morbidity or mortality [17].

Older age at presentation is a universally identified poor prognostic factor for patients with PTC, adversely it did not affect the outcome of patients with PMC [15, 18]. Hay et al. [19] in their report individualized 2 risk factors for loco-regional recurrences, namely, initial lymph node metastases and less radical thyroid surgery.

Baudin et al.[11] found that multifocality and extent of initial thyroid surgery influenced significantly PMC recurrence. Chow [15] confirmed that multifocality is predictive for loco-regional recurrence and found that multifocality is correlated with lymph-node metastasis at presentation, which also was noticed in an autopsy study by Sampson and al. [20].

Some studies demonstrated that capsule invasion was a significant prognostic factor [21, 22], while there is no agreement in the literature about the statistical significance of sex and tumor size as prognostic factors for PMC recurrence [15,17,18].

Other promising parameters related to immunohistochemistry and gene biomarkers as BRAF mutation, MIB1 expression, p27 expression are under investigation[23,24].

There is little discussion about whether surgery should be the primary treatment of PMCs, while yet, the extent of surgery continues to be debated, because most patients fare well regardless of the operation chosen. In 2009 the American Thyroid Association revised the guidelines for patients with thyroid nodules and differentiated thyroid cancer [25] and established that thyroid lobectomy alone may be sufficient treatment for small (1 cm), low-risk, unifocal, intrathyroidal papillary carcinoma in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases (recommendation 26, rating A). Similarly, the British Thyroid Association [26] and the European Thyroid Association [27] guidelines have previously stated that lobectomy may be proposed in a vast majority of low-risk patients (PMC N0M0). Conversely, other studies recommended total thyroidectomy or near-total thyroidectomy for preoperatively diagnosed PMC because it is not possible to discriminate patients with aggressive PMC from those with an indolent clinical course [15,17,29,31,32].

Controversies arise, also, on the use of RAI ablation, which does not improve the already excellent rates of outcome in patients with small PTC [4,17,33-36].

Patients and Methods

In our recently published study [37] we analyzed 149 patients with PMC. The management of patients with PMC consisted basically of primary surgery followed by evaluation for radioiodine (RAI) treatment.

In all patients with preoperative diagnosis of PMC the elective treatment was total thyroidectomy.

A therapeutic central neck dissection (CND) was performed in patients with evidence of central neck lymph node metastasis at the time of initial surgery, even if, we have considered, in selected cases, also the option of prophylactic CND.

A lateral neck dissection (LND) was performed only as a therapeutic procedure in patients with regional clinically involved nodes.

Total thyroidectomy was also performed in all cases of multinodular euthyroid goiters, multinodular toxic goiters and Graves' disease.

Lobo-isthmusectomy was indicated for single nodular disease with cytological diagnosis of "follicular neoplasm" accordingly to our operative protocol [38].
The criteria for RAI was age older than 45 years, extra thyroidal extension, multifocality, lymph node (LN) metastasis, postoperative residual disease in the neck and/or distant metastases (DM).
RAI was administered 3-5 months (mean 4.2 months) after surgery in hypothyroidism condition, obtained by withdrawing thyroid replacement, serum thyroid stimulating hormone (TSH) levels were above 30mUI/ml in all patients. The administered radioiodine activity was between 2.6 GBq. All patients were hospitalized during treatment according to the radioprotection Italian law (DLvo 187.00). To confirm the success of ablation, all patients underwent diagnostic 131I whole body scan (DxWBS , 185 MBq), 24 h 131I neck uptake test (RAIU), TSH, free T4 (FT4), free T3 (FT3), thyroglobulin autoantibodies (TgAb) and serum thyroglobulin (Tg) off L- thyroxine (L-T4) six-ten months after therapy. The criteria for successful thyroid ablation were defined as the disappearance of any visible area of uptake in the thyroid bed , a 24h RAIU below 1% and a serum Tg off L-T4 (TSH >30mUI/ml) below 2ng/ml in absence of Tg Ab.
Total thyroidectomy was performed in 135 patients, including 17 patients with associated node dissection (therapeutic central and lateral neck dissection in 8 patients and prophylactic central neck dissection in 9 patients considered clinically at high risk), whereas lobectomy plus isthmusectomy was preferred in the 14 cases of solitary thyroid nodule. Temporary symptomatic hypoparathyroidism was more common in the group of total thyroidectomy plus central neck and lateral neck dissection (8/17; 47%) than in the group of total thyroidectomy alone (25/118; 21%). Transient unilateral recurrent laryngeal nerve palsy was encountered in 22 patients (14.7%): 5 cases (29.4%) in the group of total thyroidectomy combined with neck dissection and 17 cases (14.4%) in the group of total thyroidectomy without neck dissection.
According to the histological analysis after thyroid surgery, the patients were subdivided in two groups on the basis of the potential different aggressiveness of PMC. In a subgroup of 49 patients with multiple unfavorable prognosis factors, radioiodine treatment was also considered.

Results

During the prolonged follow-up, PMC recurrence appeared in 28 patients (19% of cases), only in patients with preoperative diagnosis of PMC (not incidental PMC). This different behavior confirmed the existence of 2 distinct population of patients with PMC. The first one is represented by most PMC cases, typically disclosed incidentally and characterized by favorable prognosis, therefore, probably curable with limited surgery (lobectomy), without the support of RAI ablation, and follow-up alone.
The other one, a limited number of patients with PMC preoperatively diagnosed, conversely, should be considered at high risk, because characterized by aggressive behavior similar to that of a classical PTC and therefore independently from the size of the primary tumor

Discussion

The high rate of PMC with aggressive behavior found in our retrospective study allowed a significant analysis of the prognostic factors for PMC recurrence. According to the univariate statistical analysis, age, sex, and primary tumor size were not statistically significant risk factors for disease recurrence, whereas extrathyroid invasion, solid pattern, multifocality, presence of node metastases, and absence of tumor capsule resulted significant risk factors ($p<0.05$).
At multivariate analysis, the following 4 parameters were found to be significant and independent histological risk factors for recurrence disease after primary therapy: a) the extrathyroid invasion (Odds Ratio [OR], 58.54; $p=0.013$), b) the solid pattern (OR, 25.77; $p<0.001$), c) the tumor multifocality (OR, 15.80; $p=0.005$) and d) the absence of the tumor capsule (OR, 9.74; $p=0.015$). The other evaluated parameters did not result in statistical significance. This finding seemed foreseeable regarding the extension of primary surgery and the administration of radioiodine because all the patients from our series who experienced recurrent disease have received as initial treatment total thyroidectomy and all but one received radioiodine therapy.
To date, despite the number of published guidelines, there is no compelling evidence base for the management of PMC.
In patients diagnosed PMC before surgery total thyroidectomy results, in many surgical series, preferable to thyroid lobectomy [28,30-33]. If thyroid lobectomy should be considered, a completion thyroidectomy is recommended in all patients with multifocal disease, unfavorable histology, lymph node metastases or extrathyroidal extension[11, 39-41].
Routine therapeutic regional lymph node dissection at the time of thyroidectomy is warranted in patients with PMC with clinically involved central or lateral neck lymph nodes [26-29, 39].
Prophylactic central compartment neck dissection may be considered not appropriate for patients with non invasive and clinically node-negative PMCs [26,39].
Whether the application of RAI as ablation may improve patient outcome is a matter of debate, whereas as long as postoperative radioactive iodine ablation is planned, prophylactic central neck dissection is probably not essential[15, 39].

On the other hand prophylactic dissection of the central compartment of the neck is recommended in patients with multifocal tumor; administration of radioiodine may also be indicated for patients with multifocal PMC[11].

Conclusions

In conclusion PMC is being diagnosed with increasing frequency and considering the result of our series and in accordance with previous observations in literature, 2 well distinct population of PMC seem to exist. The identification of patients with aggressive PMC on the basis of the risk factors found in our recently published study is of great importance, because, in our opinion, they need a radical therapeutic approach, as classical PTC, as well as total thyroidectomy with central neck dissection, and radioiodine therapy.

Therefore, based on data of our recent surgical experience, we would propose our therapeutic strategies in the management of the PMCs.

In patients with incidentally PMC (discovered during surgery for benign thyroid disease) and in absence of histological prognostic factors predictors of aggressive outcome, we advocate neither adjuvant ^{131}I therapy nor completion thyroidectomy, if lobectomy has been chosen as surgical procedure.

We strongly agree that, in patients who have PMC diagnosed before surgery, total thyroidectomy should be the preferred treatment, given the difficulty to diagnose preoperatively an aggressive PMC type. We perform total thyroidectomy combined with central and lateral neck dissection only for patients with clinically involved central and/or lateral neck lymph-nodes. But we take in consideration prophylactic central neck dissection in patients with a history of radiation therapy to the head and neck or a first-degree member with differentiated thyroid cancer, or male older than 45 years and in patients preoperatively diagnosed multifocal PMC.

If the thyroid lobectomy has been chosen as the preferred treatment we recommend a completion thyroidectomy with central neck dissection and radioiodine therapy in those patients who present the referred histological prognostic factors predicting an aggressive PMC.

Riassunto

Il carcinoma papillifero della tiroide di dimensioni inferiori ad 1 cm, classificato microcarcinoma (MCT), viene considerato lesione a basso rischio e, pertanto, potrebbe richiedere un trattamento più conservativo rispetto alla lesione convenzionale. Tuttavia, in alcuni casi, il MTC può presentare un comportamento aggressivo con metastasi locali e a distanza con significativa morbilità e talvolta mortalità. Individuare questa categoria di pazienti con MTC aggressivo è di fondamentale importanza, poiché,in questi casi si rende necessario un approccio terapeutico più radicale che prenda in considerazione la tiroidectomia totale con la linfectomia del compartimento centrale e la terapia con radioiodio.

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