Prophylactic central neck lymphadenectomy in high risk patients with T1 or T2 papillary thyroid carcinoma: is it useful?

Ann. Ital. Chir., 2014 85: 225-229
pii: S0003469X14022015

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INTRODUCTION: *The aim of this study was to evaluate the role of prophylactic central neck lymph node dissection in high risk patients with T1 or T2 papillary thyroid cancer.*
MATERIALS AND METHODS: *Seventy-three patients who had undergone total thyroidectomy for papillary thyroid cancer smaller than 4cm, without cervical lymphadenopathy and prophylactic central neck lymph node dissection were included. Patients were divided in two groups: low risk patients (group A) and high risk patients (group B). High risk patients were considered those with at least one of the followings: male sex, age ≥ 45 years, and extracapsular or extrathyroid disease. Statistical significant differences in persistent disease, recurrence and complications rates between the two groups were studied.*
RESULTS: *Persistence of the disease was observed in one case in group A (5.9%) and in three cases in group B (5.4%), while thyroid cancer recurrence was registered in zero and two (3.6%) cases respectively. One single case (5.9%) of transitory recurrent laryngeal nerve damage was reported in group A and none in group B, while transitory hypoparathyroidism was observed in 2 (3.6%) patients in group A, and 1 (1.8%) patient in group B. Permanent recurrent laryngeal nerve damage was observed in one patient in group A, while permanent hypoparathyroidism was registered in one case in group B. Logistic regression evidenced that multifocality was the only risk factor significantly related to persistence of disease and recurrence.*
CONCLUSIONS: *Our results suggests that prophylactic central neck lymph node dissection can be safely avoided in patients with T1 or T2 papillary thyroid cancer, except in those with multifocal disease.*

KEY WORDS: Cancer, Central neck, Cervical, Lymphadenectomy, Lymph nodes, Papillary carcinoma, Thyroid

Introduction

Prophylactic central neck lymph node dissection (CNLND) in patients with papillary thyroid cancer (PTC) is widely recommended by several scientific societies for patients with lesions larger than 4 cm [1-3]. For those with smaller lesions CNLND is generally recommended in presence of risk factors like age, sex and pathological findings of tumoral invasiveness [1-3]. Such recommendations are based on numerous institutional reports, but data from large perspective randomized clinical trials are not available. Furthermore, several Authors have found that prophylactic CNLND does not improve oncological outcomes in patients with T1 or T2 papillary malignancies and may lead to higher complication rates [4-6]. Consequently, the utility of CNLND in patients with T1 or T2 PTC is a matter of ongoing debate and needs to be better assessed.
The aim of this study was to evaluate the utility of prophylactic CNLND in high risk patients with T1 or T2 PTC and its benefits in terms of persistence of disease and local recurrences.

Pervenuto in Redazione Luglio 2013. Accettato per la pubblicazione Settembre 2013
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Materials and Methods

Seventy-three consecutive patients who had undergone total thyroidectomy at our institution in the period 2001-2011 for PTC smaller than 4cm in diameter, without clinical evidence of cervical lymphadenopathy and without CNLND, were included in this study. Thirteen of them were males and 60 females (male-female ratio: 1/4.6). The mean age was 54.9 years (range 18-93).
Patients with previous neck radiation and history of disease associated with thyroid cancer (pheocromocytoma, MEN 2, familiar adenomatous polyposis, Cowden syndrome) were excluded, as well as patients with incomplete clinical and follow up data. Patients with concurrent retrosternal goiter were excluded because they generally need a peculiar clinical and surgical management, as we have previously reported [7,8]. Patients with follicular cancer and its Hurthle cell variant were not included [9]. Clinical examination and neck ultrasound were performed in all cases of known malignancy to rule out cervical lymphadenopathy.
In 17 (23.3%) patients diagnosis was obtained preoperatively by FNAB, while in 27 (37%) there was a high clinical, ultrasonographic or cytological suspicion for thyroid cancer, confirmed subsequently by final histopathological examination of the surgical specimen. In 29 (39.7%) cases one or more small carcinomas were casually discovered in patients who underwent thyroidectomy for multinodular goiter, which is endemic in Sardinia [10]. In these patients the absence of cervical nodal involvement was confirmed by postoperative ultrasound and radioiodine imaging.
Open total thyroidectomy was performed in all cases by a consultant surgeon or a registrar under consultant's supervision, after obtaining of a written informed consent. Visual and palpatory evaluation of the nodes of the central cervical compartment was performed in all cases without evidence of neoplastic involvement. No frozen section evaluation of the lymph nodes was employed in this series. After the operation 64 (87.7%) patients underwent radioactive iodine ablative treatment on the basis of pathology, postoperative thyroglobulin levels and evidence of residual thyroid tissue at postoperative imaging.
Patients were divided in two groups for statistical analysis: low risk patients (group A) and high risk patients (group B). High risk patients were considered, those with at least one of the followings: male sex, age ≥45 years, and extracapsular or extrathyroid tumoral spreading [1-3]. Follow up clinical and survival data on both groups were collected by outpatient clinical evaluation. The mean follow up time was 52 months (12-132) and 30% of the patients had a follow up time longer than 5 years.
Data were collected and processed by means of a dedicated statistical software (STATA 11.1, StataCorp LP, Texas, USA). Statistically significant differences in persistence of disease and recurrence rates, as well as in complication rates, between the two groups of patients were studied. Furthermore, a chi-square test was performed considering every single risk factor included in the current guidelines (male sex, age ≥45 years, and extracapsular or extrathyroid tumoral spreading) in order to assess its impact on residual disease and recurrence. In addition, two more risk factors were studied this way: multifocality and neoplastic vascular invasion. Factors found significant with chi-square test were further studied with logistic regression.

Results

Seventeen patients were assigned to group A and 56 to group B. The mean age was 35 years in group A and 61 years in group B. Sixteen (94.1%) of the patients in group A and 48 of those in group B (85.7%) had undergone radioidine treatment after surgery. The mean follow up time was 48.1 months in group A and 54.2 months in group B. No cases of reoperation or death were observed among patients in both groups. Persistence of the disease was observed in 1 case in group A (5.9%) and in 3 cases in group B (5.4%), while thyroid cancer recurrence was registered in 0 and 2 (3.6%) cases respectively. These differences were not statistically significant. As regards surgical complications, one single case (5.9%) of transitory recurrent laryngeal nerve damage was reported in group A and none in group B, while transitory hypoparathyroidism was observed in 2 (3.6%) patients from group A, and 1 (1.8%) patient from group B. Permanent recurrent laryngeal nerve damage was observed in one patient in group A and permanent hypoparathyroidism in one case in group B. No postoperative bleeding was observed in this cohort.
Table I depicts the results of the analysis of the impact on persistent disease and recurrences of each single risk factor mentioned before. Only cases with multifocal papillary tumors were found to be significantly related to persistence of disease and recurrence. This was further

TABLE I - *Impact of risk factors on disease persistence and recurrence in patients submitted to total thyroidectomy without central neck lymphadenectomy for papillary thyroid cancer.*

Risk Factor	Outcomes			
	Residual disease		Recurrence	
	χ^2 value	p value	χ^2 value	p value
Sex	0.0497	0.8235	0	1
Age	0.1728	0.6776	1.5168	0.2181
Extrathyroid	0.0621	0.8032	0.0310	0.8601
Extracapsular	0.2688	0.6041	0.1343	0.7140
Vascular invasion	0.2451	0.6206	0.1225	0.7264
Multifocaal	7.4140	0.0065	7.8640	0.0050

confirmed by logistic regression (*p values*: 0.01500 and 0.00325 respectively). Multifocality was not known preoperatively and was discovered after pathological examination of the surgical specimen in 12 patients among 16 globally diagnosed with multifocal papillary thyroid cancer.

Discussion

Papillary carcinoma is the most common form of thyroid cancer, comprising approximately 80-90% of all the differentiated carcinomas of the thyroid gland [10,11]. Neoplastic involvement of the cervical lymph nodes in patients with PTC is frequent, representing 20-90% (including micrometastasis) of cases evaluated by pathological examination of surgical specimens [12]. It has been demonstrated that such involvement follows a predictable sequential pattern of tumour cell spreading, initially concerning the central compartment, then progressing to the lateral compartments on the side of the primitive tumour and finally to the opposite lateral and mediastinal lymph node compartments [11,13]. Nevertheless, a discontinuous lymphatic spread to the lateral compartments, without involvement of the central neck is also described, in percentages varying from 11.1% to 37.5% of cases with node-positive PTC [14]. The existence of a pattern of lymphatic spread has led some researchers to perform a sentinel lymph node biopsy with techniques borrowed from breast or melanoma surgery and with very interesting results in terms of sensitivity, specificity and diagnostic accuracy, as high as 100% in some reports [15,16].

The impact of cervical lymph node metastasis on survival of patients with PTC is not clear. Several studies have demonstrated increased mortality rates in patients with regional nodal metastasis, while others have found no differences in survival rates between patients with or without such condition [17-19]. There seems to be some agreement on the persistence and recurrence of the disease, which are higher in patients with cervical metastatic lymphadenopathy [20,21]. For this reason, the dissection of metastatic lymph nodes is recommended by the most important scientific societies [1-3].

The neoplastic involvement of the cervical lymph nodes may not be detectable with the preoperative imaging techniques routinely employed. High resolution ultrasonography of the neck can identify neoplastic lymphadenopathy in large part of patients with PTC, detecting nodes as small as 2-3 mm in greatest dimension, but with lower detection rates in the central cervical compartment [15]. CT scan is generally employed when lymph node involvement is confirmed, and is more useful for operative planning, especially in patients with mediastinal lymphadenopathy. It means that a considerable part of metastases remain undiagnosed preoperatively, leading to higher rates of persistent and recurrent disease as we mentioned before.

Reducing rates of persistent or recurrent disease and mortality represents the rationale of prophylactic CNLND. Unfortunately, such reduction was not confirmed in all studies. Initial evidences that mortality due to thyroid cancer was considerably reduced in patients who underwent CNLND, were not subsequently confirmed in other retrospective studies which showed a small difference or even no difference in mortality and recurrence rates, between these patients and those without CNLND [22,23]. Furthermore, the possibility of higher rates of postoperative complications represents an additional reason which leaded to reconsider the role of prophylactic CNLND. The most relevant complications of thyroid surgery are hypocalcaemia, recurrent laryngeal nerve damage and bleeding [24]. Some publications report higher incidences in transitory hypocalcaemia and recurrent nerve damage, but there seem to be no substantial differences in terms of permanent complications in comparison with total thyroidectomy alone [25]. On the other hand, such complications have a higher incidence when re-operations for CNLND are considered, due to the presence of scar tissue and distorted anatomy which makes the identification and preservation of the nerves and parathyroids challenging [26]. The incidence of chronic recurrent laryngeal nerve paralysis ranges from 1% to 12% for re-operative surgery and that of permanent hypoparathyroidism from 0% to 3.5% [25]. Nevertheless, some publications of experienced surgeons report lower and acceptable complication rates [27].

The supporters of CNLND advocate that the procedure is useful not only for the reduction of recurrences and mortality, but also for the adequate staging of the disease. This is very important for the appropriate planning of the global therapeutic strategy, especially in relation to the employment of radioiodine treatment and/or thyroxin suppression. These treatments may not be taken into consideration in patients in whom the nodal status was understaged. Furthermore, it is known that in patients who are 45 years old or more the responses to the radioiodine treatment are significantly lower than in younger individuals [28]. It has been speculated that there are neoplastic biological differences in PTC in older patients, which reduce radioactive iodine uptake and accelerate locoregional recurrences [29]. In these patients prophylactic CNLND may assume a therapeutic role, removing the clinically silent non-iodophilic metastatic lymph nodes. A recent study has demonstrated that CLND modifies the indication for radioidine treatment in 30% of patients initially staged as T1N0 [30].

These speculations based on contradictory data, along with the absence of well-designed perspective randomized clinical trials, do not allow clear, evidence-based conclusions on the quality of CNLND, especially in patients with early stage disease. This is perceivable even after consulting the current guidelines produced from the major scientific societies. The ATA guidelines published in 2006 recommended prophylactic lymphadenectomy in all patients with PTC; however in the last revision pub-

lished in 2009, recommendation yet exists for patients with advanced PTC (T3 or T4) as opposed to those with non-invasive T1 or T2 PTC [1,31]. Such modification reflects the tendency to restrict prophylactic central neck lymphadenectomy to a subset of patients who may have substantial advantages from the procedure and avoid overtreatment in those without any possible benefit. Also the last National Comprehensive Cancer Network guidelines and the second edition of the guidelines produced by the British Thyroid Association and the Royal College of Physicians substantially agree with the ATA advices [2,3]. Nevertheless, the quality of the scientific evidence and the strength of these recommendations are not high.

The BTA/RCP guidelines (excluding lesions >4cm) define *"high – risk patients*" those with the following characteristics: male sex, age >45 years, extracapsular or extrathyroidal disease. Controversy exists regarding the role of other risk factors like aggressive histological variant (tall cell, poorly differentiated, etc), history of neck radiation, multifocality or bilaterally, vascular invasion, and biological markers[32]. In presence of risk factors, prophylactic CNLND is recommended, even though some studies report no correlation between most of these factors and metastases to the central cervical compartment[11]. Our data suggest that prophylactic CNLND can be avoided in patients with T1 or T2 disease, except of those with multifocal disease. We used two different end points to assess this conclusion: persistence of disease and recurrence. Survival was judged not a good criterion because of the high rates of long term survival in patients with PTC. In fact, in both groups survival was 100%. Persistence and recurrence of disease rates are more reliable parameters in detecting advantages or disadvantages of prophylactic CNLND, as they become manifest earlier, clinically or radiologically. In our experience these rates were statistically similar in both patient groups, confirming that CNLND can be avoided in all patients with T1 or T2 PTC. Nevertheless, univariate analysis and logistic regression evidenced that neoplastic multifocality is a risk factor for disease persistence and recurrence. Unfortunately, multifocality is often discovered after surgery, as occurred in most cases in our series, and this limits the possibility to perform thyroidectomy and CNLND in one single stage. In these cases a thorough postoperative follow up is suggested, in order to early detect local recurrences. Conversely, in patients in whom multifocal papillary cancer is highly suspected or confirmed before or during surgery, CNLND is recommended. Multifocality was found to be a risk factor also in other than papillary thyroid cancer histotypes [33].

Our study presents some methodological limitations; the most important are its retrospective nature and the small number of patients included. Larger, prospective randomized trials are necessary to better investigate the role of prophylactic lymphadenectomy in patients with T1 and T2 papillary thyroid cancer.

Conclusions

Our results suggest that CNLND can be avoided in patients with T1 or T2 PTC, except those with multifocal disease. CNLND is recommended in patients with preoperatively or intraoperatively discovered multifocal papillary thyroid cancer, while in cases of post-surgical detection of multifocal disease a thorough postoperative follow up is suggested. Multifocality was the only risk factor influencing persistence of disease and recurrence rate. Such evidences should be further investigated through large perspective randomized clinical trials.

Riassunto

Lo scopo di questo studio è di valutare il ruolo della linfadenectomia profilattica del compartimento centrale del collo nei pazienti ad alto rischio affetti da carcinoma papillifero della tiroide in stadio T1 e T2. Settantatre pazienti sottoposti a tiroidectomia totale per carcinoma papillifero della tiroide, senza evidenza di linfadenopatia e senza linfadenectomia del compartimento centrale sono stati inclusi nello studio. I pazienti sono stati divisi in due gruppi. Nel primo gruppo sono stati inclusi quelli a basso rischio per persistenza di malattia o recidiva, e nel secondo gruppo quelli con i seguenti fattori di rischio: sesso maschile, età ≥45 anni, malattia extracapsulare o extratiroidea. I risultati in termini di persistenza di malattia, recidiva e complicanze sono stati analizzati, senza evidenziare differenze statisticamente significative tra i due gruppi. Inoltre, è stata effettuata una regressione logistica dei fattori di rischio più rilevanti, con evidenza di significatività solo per la malattia multifocale. Questi risultati suggeriscono che la linfadenectomia profilattica del compartimento centrale del collo può essere omessa nei pazienti con carcinoma papillifero della tiroide in stadio T1 o T2, ad eccezione dei pazienti con neoplasia multifocale.

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