Differentiated thyroid cancer: feasibility of loboisthmectomy in an endemic region

P.G. CALÒ, E. ERDAS, F. MEDAS, L. GORDINI, A. LONGHEU, G. PISANO, A. NICOLOSI

SUMMARY: **Differentiated thyroid cancer: feasibility of loboisthmectomy in an endemic region.**

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Aim. *The aim of the present retrospective study was to assess the feasibility of loboisthmectomy for the treatment of differentiated thyroid cancer in a endemic area, evaluating the histopathological features and the results of a case series of 1154 patients.*

Patients and Methods. *The clinical records of 1154 patients submitted to total thyroidectomy in our Department were retrospectively reviewed to analyze the histopathological characters and the results.*

Results. *In 1044 cases (90.5%) a papillary cancer was observed, in 110 (9.5%) a follicular carcinoma; microcarcinomas were 399 (34.5%). Multifocality was present in 323 cases (28%), in 142*

unilateral (12.3%) and in 181 bilateral (15.7%). Thyroiditis coexisted in 472 patients (40.9%), multinodular goiter in 404 (35%), Graves' disease in 48 (4.1%), and multinodular toxic goiter in 38 (3.3%). Complications were: postoperative bleeding in 20 patients (1.7%), transient unilateral vocal cord paralysis in 20 (1.7%) definitive in 10 (0.86%), a transient bilateral paralysis in 1 (0.08%), a transient hypoparathyroidism in 351 (30.4%), and a definitive in 24 (2.07%). Nodal recurrence occurred in 25 patients (2.16%).*

Conclusions. *Total thyroidectomy remains the safest treatment in differentiated thyroid cancer, especially if performed in high volume centers in which complications can be minimized. Loboisthmectomy can be a viable and safe alternative in small (< 1 cm) unifocal tumors in patients at low risk. Loboisthmectomy is limited in endemic areas by the association with other thyroid diseases. A correct and detailed information of the patient is essential before planning surgery.*

KEY WORDS: Differentiated thyroid cancer - Thyroidectomy - Loboisthmectomy.

Introduction

Differentiated thyroid cancer (DTC) represents the most frequent thyroid cancer, originating from the follicular epithelium and accounting for 90% of all thyroid carcinomas (1-4). DTC is usually an indolent disease associated with a favorable prognosis for most patients. Some patients, however, exhibit local invasion or extensive metastases, and a small number of patients die of the disease (5-7).

Debate still exists with regard to the optimal surgical approach but trends toward a more conservative approach, such as loboisthmectomy (LI), are being more favored, especially in papillary thyroid cancer, of tumor sizes less than 4 cm, in the absence of other high-risk suggestive features (3, 8). In contrast to Western countries, LI has been the mainstay of primary surgery for DTC in Japan, and total thyroidectomy (TT) is reserved for advanced cases (9, 10).

American Thyroid Association (ATA) revised guidelines recommend TT for DTC > 1 cm, unless there are contraindications to this surgery (11); LI alone may be sufficient treatment for small (< 1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or by imaging or clinically involved cervical nodes metastases (8, 11, 12-14). The 2007 British Guidelines for the management of thyroid cancer mentioned that "patients with a papillary thyroid cancer more than 1 cm in diameter or with high-risk follicular thyroid cancer should undergo TT; patients with low-risk papillary thyroid cancer and even follicular thyroid cancer ≤ 1 cm in diameter may be treated with LI alone" (8).

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A recent study with 53,865 cases showed that for tumors< 1 cm the extent of surgery had no impact on recurrence or survival, while for tumors larger than 1 cm LI resulted in significantly higher risk of recurrence and death (8, 13, 15, 16). In another study involving 900 patients with papillary thyroid microcarcinoma (tumors < 1 cm) observed in a 60-year period , more extensive surgery did not reduce recurrence rates compared to LI (17).

Ito et al. (18) evaluated 2,638 solitary T1N0M0 papillary thyroid carcinoma and found LI without radioactive iodine (RAI) to be adequate for these patients with a 1% risk of recurrence to the remnant thyroid. This study included tumors ≤ 2.0 cm without massive extrathyroid extension, clinically apparent lymph node metastases or distant metastases at the diagnosis (18).

Nixon et al. (14) recently reported that patients with T1 (< 2.0 cm) T2 (2.0-4-0 cm) N0 DTC could be safely managed by LI alone, since no difference in recurrence was found between the group of patients treated either with LI or TT with a median follow-up of 99 months (14).

Multivariate analysis showed no survival difference between patients who underwent TT versus LI for all tumor sizes; increased age, increased tumor size, extrathyroidal extent, and positive nodal status displayed significantly worse disease specific survival and overall survival (8, 12).

Arguments in favor of TT are: bilateral cancers (30-85%), eliminates contralateral disease, central recurrence associated with substantial mortality, reduces recurrence in all risk groups, reduces mortality in patient at high risk, obviates remedial thyroid surgery, decreases risk of pulmonary metastases, morbidity is much the same as that with LI, enhances ability to use iodine-131, lower dose for ablation, enhances recurrence monitoring, and enhances use of thyroglobulin monitoring for recurrence (17, 19-24).

Arguments in favor of LI are: most patients have low-risk cancer and excellent prognosis, results are equally good with LI compared with TT, role of adjuvant treatment is not defined, complications rise with extent of surgery, prospective randomized trials are not feasible, absence of understanding of biology and low-risk nature of thyroid carcinoma, occult multicentric tumor is not clinically important, increased risk of complications with TT, recurrence in opposite lobe arises in less than 5% of patients, most local recurrences can be treated with surgery, and excellent long-term outcome with LI alone in low-risk patients (24-26).

The aim of this retrospective study was to assess the feasibility of LI for the treatment of DTC in a endemic area, evaluating the histopathological features and the results of a case series of 1154 patients.

Patients and methods

Between 2007 and 2014 2504 patients were submitted to TT with or without prophylactic lymphadenectomy in our Department of Surgical Sciences at the University of Cagliari; final diagnosis was DTC in 1154 (46.08%). 241 were male and 913 female; mean age was 51.93±14.57. The clinical records of these patients were retrospectively reviewed to analyze the histopathological features and the results. The data were collected from retrospective chart review. In all cases, surgery was performed by three experienced endocrine surgeons. The preoperative work-up consisted of free thyroid hormone (FT3, FT4), thyrotropin (TSH), Tg and anti-Tg antibody (TgAb) measurements, and high resolution ultrasound (US) of the neck by a skilled sonographer. A pre- and postoperative fibrolaryngoscopy was routinely performed in all patients. In suspected cases, a preoperative US-guided fine-needle aspiration cytology (FNAC) was performed. Patient demographics and postoperative complications were recorded, including neck hematomas requiring reoperation, transient or permanent hypoparathyroidism, transient or permanent vocal cord palsy, and distant and locoregional recurrence detected by postoperative surveillance. Hypoparathyroidism (defined as a parathyroid hormone (PTH) level < 10 pg/ml; normal values range between 10 to 65 pg/ml) was considered permanent when it lasted for more than six months. Permanent recurrent laryngeal nerve injury was defined as vocal fold paralysis, confirmed with laryngoscopic examination, persisting for more than six months. Qualitative data were expressed as percentages, while quantitative data were expressed as the mean value ± standard error of the mean (SEM). The study was approved by the Institutional Ethical committee of the University of Cagliari.

Results

In 1044 cases we observed a papillary cancer (90.5%), in 110 a follicular carcinoma (9.5%); microcarcinomas were 399 (34.5%) (Table 1).

Tumor size varied from 0.3 to 70 mm, with an average value of 14.12±12.415. Thyroid weight varied from 5 to 348 g, with a mean value of 35.23±34.72. Multifocality was present in 323 cases (28%), in 142 unilateral (12.3%) and in 181 bilateral (15.7%) (Table 1).

Thyroiditis coexisted in 472 patients (40.9%), Graves' disease in 48 (4.1%), multinodular toxic goiter in 38 (3.3%), toxic adenoma in 5 (0.4%), and multinodular goiter in 404 (35%) (Table 2).

Complications were: postoperative bleeding in 20 patients (1.7%), in 8 cases conservatively treated (0.7%)

TABLE 1 - DTC. HISTOPATHOLOGICAL CHARACTERISTICS.

Type	Number	%
Papillary	1044	90.5
Follicular	110	9.5
Microcarcinoma	399	34.5
Multifocality	323	28
Unilateral multifocality	142	12.3
Bilateral multifocality	181	15.7

TABLE 2 - DTC. COEXISTENCE WITH OTHER THYROID DISEASES.

Disease	Number of patients	%
Thyroiditis	472	40.9
Graves' disease	48	4.1
Multinodular toxic goiter	38	3.3
Plummer's adenoma	5	0.4
Multinodular goiter	404	35

TABLE 3 - DTC. COMPLICATIONS OF SURGERY.

Complication	Number	%
Postoperative bleeding	20	1.7
Transient unilateral vocal cord paralysis	20	1.7
Definitive unilateral vocal cord paralysis	10	0.86
Transient bilateral vocal cord paralysis	1	0.08
Definitive bilateral vocal cord paralysis	0	0
Transient hypoparathyroidism	351	30.4
Definitive hypoparathyroidism	24	2.07
Chylous fistula	1	0.08
Wound infection	2	0.17
Seroma	2	0.17

TABLE 4 - DTC RECURRENCE. HISTOLOGY AND FIRST OPERATION.

TT without lymphectomy	15
TT with lymphectomy	10
Papillary classic	22
Papillary, tall cell variant	2
Follicular	1
Nodal metastasis	7
Multicentricity	9
Extrathyroidal invasion	8

and in 12 cases surgically treated (1%); a transient unilateral vocal cord paralysis occurred in 20 cases (1.7%) and a definitive one in 10 (0.86%); a transient bilateral paralysis in 1 patient (0.08%) submitted to emergency tracheotomy for acute respiratory failure; a transient hypoparathyroidism was recorded in 351 patients (30.4%), a definitive one in 24 (2.07%); a chylous fistula surgically treated was recorded in one patient (0.08%), a wound infection in 2 (0.17%), and a seroma in 2 (0.17%) (Table 3). We had no definitive bilateral vocal cord paralysis and no mortality.

A nodal recurrence occurred in 25 patients (2.16%) while no patient developed distant recurrence during follow-up. An ipsilateral III-IV level node recurrence was found in 24 cases, a VI level node recurrence in 1 case. 20 patients were female and 5 male; 10 patients had been submitted to TT with central neck dissection, 15 patients to TT without it. Histology was papillary cancer in 24 cases (in 2 cases tall cell variant) and follicular in 1. In 9 cases a thyroiditis was present at first intervention; in 7 cases there were nodal metastases, in 9 the tumor was multicentric, and in 8 there was extrathyroidal invasion (Table 4). Mean size of recurrence was 21.18 mm. No patient died during follow-up. No data reached statistical significance.

Discussion

Treatment guidelines published in Western countries basically recommend TT as the initial surgery for DTC, and although they allow LI for limited "low-risk cases", the definitions of "low-risk" are not consistent (9). The controversy regarding the extent of thyroidectomy required persists, mainly because little is known about the long-term outcomes of DTC patients who have been treated by LI (9).

Bilimoria et al. (16) reported that TT had improved the survival rate of patients with tumors larger than 1 cm supporting TT as the initial surgery for DTC patients. For DTC < 1 cm there is no difference in outcomes between TT and LI (16). They reported increased recurrence rates in LI patients for all size of tumors compared to TT patients. Based on this evidence the ATA guidelines now recommend TT for all lesions over 1 cm and LI only for lesions under 1 cm in low risk patients (recommendation 26) (11), which is also the recommendation of the consensus statement from the European Thyroid Cancer Taskforce (27). Loh et al. (28) found that LI resulted in increased rates of both recurrence and deaths compared with TT.

Nixon et al. (14) report that for intraglandular cancers, the rates of death due to disease are below 1% over a period of 10 years in patients treated with either LI or TT. Although for overall survival, advanced age and

male gender were predictors of poor outcome in this group of patients, neither T stage, nor surgical procedure was significant on multivariate analysis (14) showing that the extent of surgical resection did not have any impact on overall or disease specific survival. In addition, there was no difference in either local or regional recurrence in patients with intraglandular cancer under 4 cm in size.

Indeed several groups have demonstrated that TT does not improve survival, even among high-risk patients (9, 12, 15). Matsuzu et al. (9), in their study of 1088 cases and a follow-up of 17.6 year demonstrated that age 45 years or older, tumor larger than 40 mm, extrathyroidal invasion, and clinical lymph node metastasis were significant risk factors for a poor outcome, concluding that LI (without RAI therapy) represents a valid alternative to TT for selected patients (younger than 45 years, tumor diameter of 40 mm or less, and without clinical lymph node metastasis or extrathyroidal invasion).

Our experience is based only on TTs and one of the reasons that led us to opt for this choice is the extreme difficulty in identifying low-risk patients preoperatively. For example, the presence of an aggressive variant (e.g tall cell) and of multifocality are not identifiable preoperatively. Our incidence of recurrence was very low: a nodal recurrence occurred in 2.16% of patients while no patient developed distant recurrence during follow-up. Even if the incidence of recurrence was very low, it is also true that our data confirm the difficulty of predicting preoperatively the cases at high risk. However, some elements appear important as the multicentricity, the extrathyroid invasion and the presence of lymph node metastases at the time of thyroidectomy.

Another reason for performing TT as the initial treatment for DTC is the possibility of intrathyroidal metastasis in the contralateral lobe, because bilateral cancers have been reported in 30-85% of DTC patients (9, 15, 29). However the recurrence rate in the remnant thyroid gland at 25 years in the study of Matsuzu (9) was just 6.5%, and it was almost the same as the rates in previous reports (17, 22, 30, 31). Thus, the possibility of intrathyroidal metastasis in the contralateral lobe should not be the only one sufficient reason to justify routine TT in all DTC cases (9).

In our experience multifocality was present in 28% of patients, in 12.3% unilateral and in 15.7% bilateral. These rates are lower than those reported in the literature; the significance of this finding is not clear. Perhaps the high incidence of microcarcinomas associated to other thyroid diseases such as Hahimoto's thyroiditis or nontoxic goitre could explain these low rates of bilateral cancer.

Another reason for performing TT as the initial sur-

gical treatment for DTC is as a preparation for RAI ablation (9, 19); some studies have reported an improved outcome after RAI ablation (9, 32), but others were unable to identify any benefit (9, 33); a recent report by Iyer (34) demonstrated the absence of any benefit of RAI ablation and showed a higher risk of secondary carcinogenesis in DTC patients younger than age 45 years, suggesting that RAI ablation, especially in patients younger than age 45 years, must be carefully considered. A meta-analysis conducted by Sawka et al. (35) failed to provide convincing evidence that RAI improves either survival or the overall tumor recurrence rate. An indisputable advantage of TT is that when performed in combination with RAI ablation, the patient's serum Tg level can be used as a sensitive marker for recurrence (9, 36). We believe that this element is crucial to ensure a good follow-up to the patient and it is extremely difficult psychologically to give it up for both the physician and the patient. However, TT is followed by a higher rate of surgical complications than LI, even though the postoperative rates of permanent bilateral laryngeal nerve injury and hypoparathyroidism are very low when TT is performed by experienced surgeons (9, 37). LI has been shown to resulting in lower complication rates in large retrospective studies (14, 38-40). Our complication rate was very low compared to the literature data reporting 1.7% of postoperative bleeding, 1.7% of transient unilateral vocal cord paralysis and 0.86% of definitive, and 0.08% of transient bilateral paralysis, 30.4% of transient and 2.07% of definitive hypoparathyroidism. Although these data are very encouraging, we must also add that LI undoubtedly eliminates definitely the risk of hypoparathyroidism and bilateral injuries of the recurrent nerves.

The need for lifelong thyroid hormone replacement in patients who have undergone TT may also be an important factor to be considered (9, 41). However, this element appears less important, especially given that many patients undergoing LI must subsequently make use of levothyroxine (42).

Nixon (14) currently recommend TT for patients with nodules in the contralateral lobe (over 0.5 cm detected clinically or on ultrasonography), clinically significant lymph node metastases, gross extra thyroidal extension and evidence of distant metastases. Increased availability of high definition preoperative ultrasonography has resulted in increased detection of contralateral nodules and this has resulted in a higher rate of TT carried out in recent years compared to the past (rising from 30% to around 75%). We believe this is the greatest problem in performing a LI in an endemic area. In fact, especially in a region such as Sardinia with endemic goiter and with a high incidence of autoimmune disorders such as thyroiditis (43) it is extremely difficult to find a safe contralateral lobe. We report that

a thyroiditis coexisted in 40.9% of patients, a multi-nodular nontoxic goiter in 35%, a Graves' disease in 4.1% and a multinodular toxic goiter in 3.3%. In our experience this fact was the element mostly limiting LI choice.

For these reasons, in agreement with Bilimoria (16) and Sosa (44), we recommend TT for all patients with DTC ≥ 1 cm; for DTC <1 cm it is necessary to exclude concomitant thyroid diseases, a careful evaluation of the contralateral lobe, and to share with the patient the therapeutic strategy with a careful and accurate informed consent.

Conclusions

TT remains the safest treatment in DTC, especially if performed in high volume centers in which complications can be minimized. LI can be a viable and safe alternative in small (< 1 cm) unifocal tumors in patients at low risk. LI in tumors larger than 1 cm should be validated by further studies and cannot be currently considered a standard of care. The use of LI is limited in endemic areas by the association with other thyroid diseases. A correct and detailed information of the patient is essential before planning surgery.

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