

Surgical treatment of papillary thyroid carcinoma without lymph nodal involvement

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SUMMARY: Surgical treatment of papillary thyroid carcinoma without lymph nodal involvement.

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Background. In the treatment of differentiated thyroid cancer (DTC), in absence of enlarged lymph nodes, the role of routine central lymph node dissection (RCLD) remains controversial. The aim of this study is to analyze data resulting from total thyroidectomy (TT) not combined with RCLD in the treatment of DTC.

Methods. We retrospectively evaluated the clinical records of 80 patients treated between January 1996 and December 2003 with TT without RCLD, in absence of suspected enlarged lymph nodes at preoperative ultrasonography and intraoperatively during neck exploration. In this series, 75 patients (93.7%) underwent radioiodine (RAI) abla-

tion, followed by Thyroid Stimulating Hormone (TSH) suppression therapy. In case of locoregional lymph nodal recurrence, a central (VI) and ipsilateral (III-IV) selective lymph node dissection was performed.

Results. Incidence of permanent hypoparathyroidism (iPTH < 10 pg/ml) and unilateral temporary vocal fold paralysis were respectively 2.55% and 2.55%. Locoregional recurrence, with positive cervical lymph nodes, after a 10.3 ± 4.7 years mean follow-up was observed in 3 patients (3.75%). They were submitted to a central (VI) and ipsilateral (III-IV) selective neck dissection without significant complications.

Conclusions. In our series, TT not combined with RCLD was associated to a low locoregional recurrence rate, even if the lack of a control group treated with RCLD does not allow any generalized assumption. RCLD may be indicated in high risk patients, in whom lymph nodal recurrence is more frequent. More prospective randomized studies are needed to better define the role of RCLD and postoperative radioiodine ablation.

KEY WORDS: Total thyroidectomy - Papillary thyroid cancer - Routine central lymph node dissection - Radioactive iodine ablation.

Introduction

Thyroid carcinoma is the most common endocrine malignancy accounting for about 1% of all human cancers and representing in the USA the fifth most common cancer in women (1-3). The differentiated papillary thyroid cancer (PTC) is the most common histotype comprising about 90% of all thyroid cancers (1-3). The prognosis of PTC patients is usually favorable with 10 years survival rate of about 90% (4-8). However, about 20% of patients face the morbidity of disease recurrences, mainly loco-regional, and PTC-related deaths (9, 10). In this context, it is worth to note that cervical lymph

node micrometastases are observed up to 90% of papillary thyroid cancer cases, demonstrating that lymph nodal involvement is very common (11).

Total thyroidectomy (TT), selective radioactive iodine (RAI) ablation and Thyroid Stimulating Hormone (TSH) suppression therapy guarantee optimal long-term results. On the contrary, in absence of enlarged lymph nodes, the role of routine central lymph node dissection (RCLD) (level VI) remains subject of research and controversies.

Central neck dissection may reduce loco-regional recurrence rate and postoperative serum Tg levels, but is often associated to a higher risk of injury to parathyroid gland and recurrent laryngeal nerves, without any demonstrable benefits in terms of long-term survival (12). We retrospectively analyzed the role of TT not combined with RCLD in differentiated thyroid cancer (DTC) patients, without involvement of lymph nodes at preoperative ultrasonography and intraoperative exploration.

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Patients and methods

The authors analyzed clinical records of 80 DTC patients without lymph nodal involvement, submitted to TT, not combined with RCLND, between January 1996 and December 2003. Incidentally removed perithyroidal nodes in the specimens were considered a criterion of exclusion. 38 DTC patients, with positive or suspected lymph nodes, submitted during the same years to TT combined with different types of cervical lymph node dissection were also excluded from the analysis. In every case a preoperative diagnosis of DTC was obtained by ultrasound (US) guided fine-needle cytology (FNC) (13-15), and preoperative work-up consisted of thyroid hormones, TSH, Tg and anti-Tg antibodies levels evaluation, and high resolution US of the neck by a skilled ultrasonographer. A pre- and postoperative fibrolaryngoscopy was routinely performed. In ten patients (12.5%) BRAF mutations were searched on tumour specimen (16). Tumour extent was evaluated according to the American Joint Committee on Cancer (AJCC) TNM Classification of Thyroid Cancer. During follow-up, in case of enlarged lymph nodes ≥ 1 cm, postoperative diagnosis of lymph nodal recurrence was performed by US guided FNC, and Tg washing of FNC aspirates. Patient demographics, postoperative complications, including transient or permanent hypoparathyroidism, transient or permanent vocal cord palsy, distant and loco regional recurrence, detected by postoperative surveillance, were recorded. In case of a PTH level < 10 pg/ml (normal value=10-65), hypoparathyroidism was considered permanent if persisting for more than 6 months. Vocal fold palsy, confirmed by fibrolaryngoscopy, was considered permanent when lasting for more than 6 months. Tg and TSH were determined by Immunita immunoassay (Siemens Healthcare Diagnostics) with sensitivities of 0.2 ng/mL and 0.03 mIU/L, respectively. Anti-Tg antibodies were detected by Quanta Lite enzyme-linked immunosorbent assay (Inova Diagnostics) and we considered 40 UI/ml as cut-off value of Anti-Tg Abs (normal value = 0-60 UI/ml).

During surgical operation, in absence of enlarged lymph nodes from the larynx to the thoracic inlet, lymph node dissection was not performed. In each case, recurrent laryngeal nerves were identified and exposed until their insertion in the larynx, and parathyroid glands were identified. In case of suspected devascularized or incidentally removed parathyroid glands, a muscular autoimplantation followed. In selected cases haemostasis was optimized by means of Flo-seal® Hemostatic Matrix (Baxter Zurich - Switzerland). On the first postoperative day, and subsequently on a clinical basis evaluation, serum calcium and intact parathyroid hormone levels were assayed. In patients affected by postoperative loco regional recurrence, a selective central and ipsilateral (VI, III, IV) lymph node dissection was performed. After surgery, 75 patients (93.7%) underwent adjuvant RAI ablation (1850-3700 MBq-¹³¹I). Apart from lymph node involvement, indications for postoperative ¹³¹I treatment were a tumour > 1.0 cm, extra-capsular thyroid invasion or loco regional extension, unfavourable histological subtype (follicular, diffuse sclerosing, or tall cells papillary cancer), multifocal disease, BRAF positive tumour specimens. To obtain adequate levels of endogenous TSH (>30 mU/ml), patients stopped L-T4 replacement 3-4 weeks before radioiodine treatment; when L-T4 withdrawal was not indicated, TSH stimulation was achieved with Recombinant Human Thyrotropin (rhTSH) (Thyrogen® - Genzyme corporation). Whole-body scan was performed 4-7 days after RAI treatment. Routinely, suppressive l-tiroxine treatment was indicated. Neck ultrasound and monitoring of serum Tg and Tg-antibodies levels were performed every 6 months. A serum Tg level ≤ 1 ng/ml was considered as undetectable. Recurrence in the cervical lymph nodes was detected by US-guided FNC, Tg washing of FNC aspiration and serum Tg levels monitoring. Qualitative data were expressed in percentage, while quantitative data as the mean value \pm standard deviation.

Results

80 DTC patients, 66 women and 14 men (F/M ratio=4.7/1), with a mean age of 41.21 ± 10.47 years, were submitted to TT from January 1996 to December 2003 (Table 1). A parathyroid tissue muscle autoimplantation was performed in 6 patients (7.5%). Temporary and definitive hypoparathyroidism were respectively 8.75% and 2.55%, while 2.55% was the incidence of temporary unilateral vocal cord palsy (vcp). Permanent or bilateral vcp were never observed. Mean tumour size was 1.47 ± 0.53 cm and a microcarcinoma (<1 cm) was diagnosed in 15 patients (18.75%). The histotype was classic in 68 patients (85%), follicular variant in 10 (12.5%), Hürthle cells in 2 (2.5%). Twelve patients (15%) had multifocal tumours - 11 classic variant, 4 follicular variant. Nine patients (11.25%) had a loco regional infiltration (T3) by classic variant tumour in 7 cases and by follicular variant tumour in 2 cases. A BRAF mutation was discovered in 6 out of 10 tested patients. Patients pTNM stage and pathological data are shown in Table 1. Distant recurrence was not observed during a 10.3 ± 4.7 DS years follow-up. In 3 cases (3.75%) a nodal recurrence - 2 central (VI) and 1 ipsilateral (III-IV) - was observed after TT and RAI ablation (2 male and 1 female, median age of 38 years). Two patients had classic variant, one had follicular variant DTC (Tg >2 ng/ml in 2 patients and <2 ng/ml in 1 patient). In every case a bilateral central and ipsilateral selective lymph node dissection (VI,III,IV) was performed, followed by another session of metabolic radiotherapy. Significant perioperative complications were not observed.

TABLE 1 - DEMOGRAPHIC AND PATHOLOGICAL DATA OF 80 DTC PATIENTS (%).

Patients	Male	17.5
	Female	82.5
	Mean age [†]	41.21 ± 10.47 years
Histology	Classic	85
	Follicular-variant	12.5
	Hürthle cell - variant	2.5
Tumour	Mean size [†]	1.49 ± 0.53 cm
	Unique	85
	Multifocal	15
	Microcarcinoma	18.75
	Locoregional infiltration	11.25
pTNM stage	I	67.5
	II	26.25
	III	6.25

[†] Mean value \pm standard deviation.

Discussion and conclusions

After TT not combined with RCLD, followed by RAI ablation in 93.7% of cases, a 3.75% loco regional nodal recurrence rate was observed after 10.3 ± 4.7 DS years follow-up. Our analysis demonstrates that patients undergoing TT not combined with RCLD, in absence of suspected enlarged lymph nodes at preoperative US and intraoperative exploration, have a low risk of loco-regional recurrence. In the treatment of low-risk DTC patients, as in the most thyroid diseases, TT is the operation of choice (17-22), while the role of prophylactic central neck dissection remains controversial. In most cases routine lymph node dissection does not affect patient's prognosis, although some authors affirm that it can improve survival (23). The high incidence of lymph node metastases, the insufficient diagnostic accuracy of ultrasonography in 1/3 of DTC patients, and the failure of ^{131}I ablation in about 30% of cases, are considered in the indication to RCLD. Even if the recent American Thyroid Association Guidelines recommend RCLD in DTC, especially in high-risk patients (24), the role of routine lymph nodal dissection, considering its morbidity, remains controversial (25). RCLD permits a better cancer staging, reduces postoperative serum Tg levels, but Udelsman concludes that to evaluate the benefits of RCLD, prospective randomized trials are needed (26). TT followed by RAI treatment and TSH suppression therapy guarantees optimal long-term results with a low incidence of loco-regional lymph node recurrence. Regarding outcomes,

reoperation (lymph node dissection) is usually not associated with higher morbidity, as confirmed by Shen (12). After TT combined with RCLD, the author do not report significant advantages as regards long-term results (12). RCLD seems to have a role in DTC staging and is useful to modify the treatment protocol, as demonstrated by Travagli that reported a 30% increase in the number of patients with T1 DTC (preoperatively considered to be N0), for whom ^{131}I ablation was indicated following routine central and lateral nodal dissection, demonstrating unexpected nodal metastases (27). In absence of enlarged lymph node, and when RAI treatment is advisable (a tumour > 2cm in a patient > 50 years old) routine lymph node dissection is not indicated. The absence of a control group of patients, submitted to TT combined with prophylactic central lymph node dissection, was the main limitation of this retrospective study.

In low-risk patients with tumours ≤ 1 cm, lymph node dissection may discover metastases requiring RAI ablation, while in that cases already scheduled to undergo iodine treatment, the role of RCLD should be better defined. Nevertheless, in high-risk patients, RCLD may reduce loco-regional recurrence rate and postoperative serum Tg levels. In the treatment of DTC without suspicious enlarged lymph node we believe that prophylactic neck dissection is not indicated. Given the trend in the literature towards prophylactic lymphadenectomy, and the avoidance of RAI treatment, more prospective randomized studies are needed to better define the role of RCLD and postoperative radioiodine ablation.

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