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Original research

Clinicopathological pattern of lymph node recurrence of papillary thyroid cancer. Implications for surgery

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ABSTRACT

Introduction: Lymph nodal involvement in papillary thyroid cancers is very common, but the role of lymph node dissection is still controversial. Surgeons are consequently divided between opposed to and in favor of routine central neck dissection associated with total thyroidectomy.
Methods: Clinical records of 210 patients undergoing from January 2000 to December 2006 total thyroidectomy without routine lymph node dissection were retrospectively evaluated. One hundred and ninety eight patients (94.2%) underwent radioiodine ablation as well, followed by Thyroid Stimulating Hormone suppression therapy. In patients with loco regional lymph nodal recurrence, central (VI) and ipsilateral (III–IV) lymph node dissection was performed.
Results: Incidence of permanent hypoparathyroidism (iPTH < 10 pg/ml) and permanent vocal fold paralysis were respectively 1.4% and 1.9%. After an 8-year mean follow-up, the rate of loco regional recurrence was 4.2%–9/210 patients. In these cases selective lymph node dissection was carried out without complications.
Discussion: The role of neck dissection in papillary thyroid cancer management, is still subject of research and controversial regarding routine or therapeutic indications, surgical extension, its impact on local recurrence and survival.
Conclusion: A low loco regional recurrence rate may be observed after total thyroidectomy without prophylactic lymph node dissection. Lymph nodal recurrences were more frequent in young male patients, sometime affected by follicular variant, in each case less than 2 cm. There is a general agreement about the extension of therapeutic lymph node dissection, while routine central neck dissection is still controversial and may be indicated in high risk patients.

1. Introduction

In the management of papillary thyroid cancer (PTC), after considering the multifocal nature of this neoplasm [1], the effectiveness of radioactive iodine (RAI) treatment and thyroglobulin (Tg) serum levels during follow-up, there is a substantial agreement about total thyroidectomy (TT) and Thyroid Stimulating Hormone (TSH) suppression therapy. On the contrary, the role of lymph node dissection (LD), regarding its indication- routine or therapeutic-, extension – ipsi or contralateral- and outcomes, in terms of recurrence and survival, is still controversial. According to the recent American Thyroid Association (ATA) guide lines, routine central lymph node dissection (RCLD) is indicated in high risk patients with advanced primary tumors [2], while Udelsman et al. concluded that, to evaluate its benefits, prospective randomized trials are needed [3]. Prevention of a further recurrence, the high risk of positive lymph nodes and the lower morbidity rate of the first operation are evocated in favor of RCLD [4], often associated with a higher rate of complications, without demonstrable benefits in terms of long-term survival [5,6]. PTC "low aggressive behavior", demonstrated by low loco regional recurrence and mortality rates, makes analysis of the outcomes difficult. In an attempt to better clarify the impact of LD in treating PTC, we analyzed the clinicopathological pattern in nine patients with lymph nodal recurrence. Selective LD is indicated in case of metastatic lymph node, but, according to our experience, RCLD benefits, in absence of lymph

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nodal involvement, remain to be demonstrated. TT associated with RAI ablation allows favorable long-term results regarding recurrence and survival, as well as the role of routine LD needs to be more intensively investigated.

2. Methods

Clinical records of PTC patients, undergoing TT without LD, between January 2000 and December 2006, in absence of suspicious enlarged lymph nodes at preoperative ultrasonography and intraoperative inspection were analyzed. Patients undergone TT associated with LD during the same period were excluded from the study, as well as incidentally removed perithyroidal nodes in the specimens were considered criteria of exclusion. In every case, a preoperative diagnosis of PTC was obtained by US guided FNC. The preoperative work-up consisted of thyroid hormones, TSH, Tg and anti-Tg antibodies levels evaluation, and a high resolution ultrasonography of the neck. A pre-and postoperative fibrolaryngoscopy was performed in all patients. In thirty-six patients (17%), BRAF mutations were searched on tumor specimens. Tumor extent was evaluated according to the American Joint Committee on Cancer (AJCC) TNM.

Classification of Thyroid Cancer (7th edition, 2010). Postoperative diagnosis of lymph node recurrence was detected by US guided FNC and Tg washing of FNC aspirates, performed in case of enlarged lymph node $\geq$1 cm. Patient demographics, postoperative complications, including neck hematoma requiring reoperation, 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 iPTH level <10 pg/ml (normal value = 10–65), hypoparathyroidism was determined, and it was considered permanent if persisting for more than 6 months and requiring medical therapy. Vocal fold palsy, confirmed by fibrolaryngoscopy, was considered permanent when lasting for more than 6 months. Tg and TSH was determined by Immunite 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). Each surgeon participating to the study used a similar technique in performing TT, as well as central and lateral lymph node dissection. An ultrasonic scalpel, Harmonic Ace® (Ethicon Endosurgery) was utilized in 35 cases, and in selected cases hemostasis was optimized by means of Floseal® Hemostatic Matrix (Baxter Zurich – Switzerland). Routinely, recurrent laryngeal nerves were identified and exposed, as well as parathyroid glands were identified and preserved. In case of suspected devascularized or incidentally removed parathyroid glands, a muscular autoimplantation followed. Serum calcium and intact parathormone levels were assayed on the first postoperative day, and subsequently on a clinical basis evaluation. In case of postoperative loco regional recurrence, a selective central and ipsilateral (VI, III, IV) lymph node dissection was performed according to the American Academy of Otolaryngology – Head and Neck Surgery [7]. After surgery, 198 patients (94.2%) underwent adjuvant RAI ablation (1850-3700 MBq-^{131}I). Apart from lymph node involvement, indications for postoperative 131I treatment are a tumor >1.0 cm, extra-capsular thyroid invasion or loco regional extension, an unfavorable histological subtype (follicular, diffuse sclerosing, or tall cells papillary cancer), multifocal disease, BRAF-positive tumor specimens. To obtain adequate levels of endogenous TSH (>30 mU/ml), that are associated with an increased radioiodine uptake, 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). Post-therapy whole-body scan was performed 4–7 days after RAI treatment. Neck ultrasonography and monitoring of serum Tg and Tg-antibodies levels were carried out every 6 months during suppressive L-tiroxine treatment. A serum Tg level $\leq$1 ng/ml was considered as undetectable. Surveillance for possible recurrence in patients considered disease-free was achieved by Tg detection after rhTSH stimulation (American Thyroid Association Guidelines 2009) and neck ultrasound. Diagnosis of disease recurrence in the cervical lymph nodes was based on US-guided FNC, Tg washing of FNC aspirates and serum Tg levels monitoring. The most recent guide lines were considered and LD benefits, complications and impact on loco regional recurrence rate, and mortality were evaluated. Qualitative data were expressed in percentage, while quantitative data as means.

3. Results

Two hundred and ten PTC patients, 180 women and 30 men (F/M ratio = 6/1), with a 42-year mean age (14–79), were submitted to TT (Table 1). In 19 patients (9%), parathyroid tissue was implanted in the strap muscles, and in 23/210 cases (10.9%) parathyroid tissue was identified in the final pathology analysis. Incidence of surgical complications is reported in Table 2. In one patient (0.4%) a neck hematoma, requiring surgical re-exploration, was observed. The mean tumor size was 1.4 cm (0.7–2.4), and a microcarcinoma ($\leq$1 cm) was diagnosed in 61 patients (29%). Histotype was classic in 172 patients (81.9%), follicular variant in 28 (13.3%), Hürthle cells in 8 (3.8%), tall cells in 2 (0.9%). Thirty-two patients (15.2%) had multifocal tumors – 24 classic variant, 8 follicular variant. Twenty-four patients (11.4%) had a loco regional infiltration (T3) by classic variant tumor in 19 cases and by follicular variant tumor in 5 cases. A BRAF mutation was discovered in 21 out of 36 tested patients (58.3%). pTNM stage of the patients and pathological data are shown in Table 1. No patient developed distant recurrence during an 8-year mean follow-up (6–13).

After TT and RAI ablation, 9 cases (4.2%) of nodal recurrence – 6 central recurrences (VI) and 3 ipsilateral recurrences (III–IV) – were observed. Demographic characteristics were the following: five males – median age 42 years (18–79) – and 4 females – median age 34 years (22–68) with a M/F ratio = 1/0.8. The median elapsed time between TT and lymph node recurrence was 28 months (12–82). Seven patients had classic variant, two had follicular variant PTC (BRAF mutation was not evaluated); median Tg value was 6.4 ng/ml (0.2–16 ng/ml) (Tg > 2 ng/ml in 7 patients and <2 ng/ml in 2 patients) and Tg-antibodies value was >40 UI/ml in 6 patients and <40 UI/ml in 3 (range 5.6–1852 UI/ml). In each

Table 1
Demographic and pathological data of the 210 PTC patients.

Patients	Male	14.2%
	Female	85.7%
	Mean age	42 years
Histology	Classic	81%
	Follicular-variant	13.3%
	Hürthle cell – variant	3.8%
	Tall cell – variant	0.9%
Tumor	Mean size	1.4 cm
	Unique	84.8%
	Multifocal	15.2%
	Microcarcinoma	29%
	Loco regional infiltration	11.4%
pTNM stage	I	61.4%
	II	32.3%
	III	6.1%