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ORIGINAL ARTICLE

Risk factors for local recurrence following lateral neck dissection for papillary thyroid carcinoma

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Abstract

Purpose We aimed to evaluate risk factors for local recurrence following lateral neck dissection (LND) for papillary thyroid carcinoma (PTC).

Methods Two hundred and nine patients who underwent therapeutic primary or reoperative LND for PTC were included.

Results One hundred eighty-one patients underwent primary LND at our Institution, the remaining 28 were referred for recurrence following LND outside the Institution. Comparing patients who required reoperation for recurrent lateral neck disease with those who did not recur, no significant difference was found concerning sex, tumor size, multifocal disease, extracapsular invasion, histological variant, pT stage ($P = \text{NS}$). At univariate analysis, age, mean number of removed lateral neck nodes at first operation, the extent of initial LND and surgery performed outside the Institution were risk factors for recurrence ($P < 0.001$).

Conclusions Limited LND and surgery performed at non referral Centers were non tumor-related risk factors for recurrence following therapeutic LND for PTC.

Keywords Papillary thyroid carcinoma · Lateral neck dissection · Recurrence of papillary thyroid carcinoma · Lymph node metastases · Reoperative lateral neck dissection

Introduction

Lateral neck lymph node involvement is quite common in patients with papillary thyroid carcinoma (PTC) either at the initial diagnosis either during follow-up [1, 2]. Lateral neck node metastases have been related with a higher rate of loco-regional recurrence and distant metastases [3–9].

Surgery is the cornerstone of the treatment for N1 PTC patients since lymph node metastases usually show low iodine avidity and cannot be amenable to radioiodine treatment [10]. Lateral neck dissection (LND) is considered a challenging surgical procedure and can be associated with several complications [11, 12].

Most of the guidelines recommend that LND should be performed only with therapeutic intent when lymph node involvement is proven (preoperatively or intraoperatively) and not for prophylactic purpose [13–16]. In spite of this consensus regarding the indications, the extension of therapeutic LND is still debated [13–18].

Several approach to lateral neck node dissection have been proposed raging from "cherry picking" to extensive radical neck dissection [16, 19–29]. Comprehensive compartment oriented LND (levels II–V) seems the best surgical option in PTC patients with lateral neck node metastases. Nonetheless in recent years limited dissection of the involved lateral neck levels has been proposed as an alternative to comprehensive LND (levels II–V) in order to reduce morbidity, but it theoretically carries an increased risk of local recurrence [18, 27–29].

In the present study, we aimed to evaluate risk factors for local recurrence following LND for PTC.

This paper is partially based on a work that has been selected as oral presentation at the 7th Biennial Scientific Meeting of European Society of Endocrine Surgeons, 19th–21st May 2016, Istanbul (Turkey).

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Materials and methods

Patients' population

All the patients who underwent therapeutic primary or reoperative LND for PTC between January 2008 and October 2014 were included in this study.

The following parameters were prospectively registered in a specifically designed database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA): age, sex, extent of surgical procedure, pathological diagnosis, extracapsular invasion, multifocal disease, number of removed, and metastatic lymph nodes, TNM staging [30].

For patients who were referred for recurrence following LND outside our Institution, data regarding initial operation and pathological report were obtained from patients medical charts. Follow-up evaluation was obtained by outpatient consultation or phone contact. In particular, all the patients were invited by phone contact to outpatient consultation. Thyroglobulin was measured by an ultra-sensible method in all the patients. If the patients were not available for outpatient consultation (i.e., death), the relatives were invited to provide all the medical charts to discriminate the cause of death (disease related/disease unrelated).

Study end point

To identify risk factors for local recurrence following LND for PTC.

Definitions

LND was performed in all the cases with therapeutic intent. Comprehensive LND was defined as compartment oriented functional LND, including levels II, III, IV, and V [16]. Limited LND was defined any dissection less than comprehensive LND. Pathological tumor staging was defined in accordance with the 2010 7th edition of the American Joint Committee on Cancer pTNM staging system [30].

Local recurrent disease was defined as clinically detectable disease in the thyroid bed. Nodal recurrent disease was defined as clinically detectable disease in the central and/or lateral compartment lymph nodes. Distant metastases (disease outside the thyroid bed and cervical lymph node) were identified in the presence of an elevated serum thyroglobulin (sTg) and/or sites of uptake on postoperative radioactive iodine scan, eventually confirmed by imaging studies.

Preoperative work up

Therapeutic LND was performed in all the patients with preoperatively or intraoperatively demonstrated lateral node metastases. All the patients scheduled for thyroidectomy with a cytological diagnosis of PTC or suspicious nodule underwent preoperative surgeon performed neck ultrasound examination to assess lateral neck nodes. Similarly, patients who previously underwent thyroidectomy with or without central node clearance with any forms of LND (from "cherry picking" to comprehensive compartment oriented LND) referred for recurrence following initial surgical treatment outside our Institution and in whom lateral neck recurrence was suspected or diagnosed (ultrasound, radioiodine uptake, fine needle aspiration biopsy (FNAB)) underwent preoperative surgeon ultrasound examination. In case of suspicion of lateral neck node metastases at preoperative ultrasound examination, confirmation of nodal involvement was obtained preoperatively by FNAB or intraoperatively by frozen section examination. Therapeutic LND was performed only in case of cytological or histological demonstration of lateral neck node metastases.

Surgical procedure

All the surgical procedures were performed by an experienced endocrine surgeon (RB, CPL, MR, CDC). All the patients underwent unilateral or bilateral comprehensive LND including levels II-III-IV and V, both as first time procedure with simultaneous total thyroidectomy and bilateral central neck (level VI) dissection or as a reoperative surgery after previous total thyroidectomy with or without central neck dissection and LND. In case level VI dissection had not been performed at initial surgery it was accomplished at the same time of LND even in the absence of overt preoperatively or intraoperatively demonstrated involvement.

LND was performed "en bloc" in a standard fashion through a horizontal (extended collar) skin incision.

Postoperative management and follow-up evaluation

The protocol for the postoperative management and follow-up evaluation of patients with PTC has been previously described in detail [10, 30–32]. Briefly, postoperative suppressive levothyroxine (LT4) treatment was administered to all cases. All the patients underwent sTg and anti-Tg antibody measurements under suppressive LT4 treatment and an ultrasound neck scan 3 to 6 months after surgery. ^{131}I ablation (RAI) was performed on the basis of stage and risk factors, according to the American Thyroid Association Guidelines.

Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS 15.0 for Windows® -

SPSS Inc., Chicago, IL, USA). The χ^2 test was used for categorical variables, and the *t* test was used for continuous variables.

Results

Overall 209 patients were included in the present study: 71 males and 138 females with a mean age of 43.6 ± 16.3 years (range 13–84). Patients' characteristics are reported in Table 1.

All the patients underwent therapeutic LND for PTC: 181 patients underwent primary LND (levels II–V) at our Institution, the remaining 28 were referred for recurrence following LND outside the Institution.

Among the 181 patients who underwent primary comprehensive LND at our Institution a bilateral LND was performed in 23 cases.

At a mean follow-up of 51.1 ± 22.7 months (range 12–92), two patients who underwent total thyroidectomy plus level VI dissection plus unilateral comprehensive LND as initial operation experienced nodal recurrence, requiring reoperation: one patient 3 years after initial surgical treatment and one 4 years after initial operation. In both patients the final histology of the first operation showed a pT3pN1b PTC (4/18 and 17/22 central neck nodes positive for metastases, respectively; 5/25 and 12/46 lateral neck nodes positive for metastases, respectively). In both patients, contralateral lateral lymph node metastases were diagnosed at III and IV level, respectively, during the follow-up and a comprehensive contralateral LND was accomplished. Final histology confirmed lateral neck node metastases in both cases (7/21 and 11/32 lateral neck nodes positive for metastases, respectively). To date both patients showed no other local and/or nodal recurrences.

Table 1 Demographic, clinical, operative, pathologic, and follow-up characteristics of all the included patients who underwent lateral neck dissection

	Lateral neck dissection
Patients	209
Age (±SD) (range), years	42.8 ± 16.3 (13–84)
Male/female	71/138
Multifocality, y/n	148/61
Extracapsular invasion, y/n	101/108
pT stage T1/T2/T3/T4	79/21/105/4
Histology subtypes PTC—Classic/Follicular/Other	150/27/32
Bilateral lateral neck dissection, y/n	25/184
No. of removed lateral neck nodes (±SD) (range)	36.4 ± 19.5 (10–128)
No. of metastatic lateral neck nodes (±SD) (range)	5.8 ± 7.4 (1–58)
Lateral neck lymph node ratio (±SD) (range)	0.2 ± 0.2 (0–1)
Follow-up (±SD) (range), months	51.3 ± 22.7 (12–92)
Last TG on (±SD) (range)	2.1 ± 5.0 (0–28.4)
Disease-related deaths	0
Disease-unrelated deaths	6

SD standard deviation

All the patients who were referred for recurrence had undergone limited LND outside our Institution. All of them underwent RAI treatment after initial surgical treatment. In all the cases lateral neck lymph node involvement was documented at US examination and confirmed with FNAB. All the 28 patients who were referred for recurrence following limited LND outside the Institution, underwent comprehensive completion LND (levels II–V) at our Institution. A bilateral LND was accomplished in two cases. At a mean follow-up of 52.7 ± 23.2 months (range 12–88), no patient showed any other local and/or nodal recurrences.

No patient died for cancer-related causes. Overall, six patients died for unrelated causes.

Comparing patients who required reoperation for recurrent lateral neck disease (28 operated outside and two at our Institution) with those who did not recur, no significant difference was found concerning sex, tumor size, multifocal disease, extracapsular invasion, histological variant, pT stage at first operation (P = NS) (Table 2). At univariate analysis, age (48.2 ± 21.1 vs 41.8 ± 15.2 years), the mean number of removed lateral neck nodes at first operation (8.3 ± 8.5 vs 38.5 ± 19.6) and lateral neck lymph node ratio (metastatic nodes/removed nodes) (0.4 ± 0.2 vs 0.2 ± 0.1), the extent of initial LND (limited vs comprehensive LND) and surgery performed outside the Institution were risk factors for lateral neck recurrence ($P < 0.001$) (Table 2).

LND-related complications were observed more frequently following reoperative LND (two internal jugular vein thrombosis, one hematoma, one transient ischemic attack, one self-limiting lymphatic leak) than following primary LND (one internal jugular vein thrombosis, two hematomas, one transient ischemic attack, three self-limiting lymphatic leaks, one transient Claude Bernard Horner syndrome) ($P < 0.05$).

Discussion

Regional lymph node involvement occur in approximately 30–80% of patients with PTC [1, 2]. Lateral neck node metastases of PTC (N1b TNM stage) are known to be predictive of poorer disease-free survival and cancer-specific survival, especially in older patients (>45 years) [3–5].

Table 2 Demographic, clinical, operative, pathological, and follow-up characteristics at first operation of patients with or without evidence of lateral neck node recurrences at follow-up

	No recurrence	Recurrence	*P* value
Patients	179	30	
Age (±SD) (range), years	41.8 ± 15.2 (18–84)	48.2 ± 21.1 (13–81)	**<0.05**
Male/female	62/117	10/20	**NS**
Multifocality, y/n	126/53	22/8	**NS**
Extracapsular invasion, y/n	83/96	18/12	**NS**
pT stage T1/T2/T3/T4	73/18/86/2	6/3/19/2	**NS**
Histology subtypes PTC—Classic/Follicular/Other	132/23/24	18/4/8	**NS**
Bilateral lateral neck dissection, y/n	22/157	3/27	**NS**
No. of Removed lateral neck nodes (±SD) (range)	38.5 ± 19.6 (10–128)	8.3 ± 8.5 (1–31)	**<0.001**
No. of metastatic lateral neck nodes (±SD) (range)	6.3 ± 7.3 (1–58)	2.8 ± 1.9 (1–8)	**<0.05**
Lateral neck lymph node ratio (±SD) (range)	0.2 ± 0.1 (0–0.7)	0.4 ± 0.2 (0.1–1)	**<0.001**
Follow-up (±SD) (range), months	51.1 ± 22.7 (12–92)	52.7 ± 23.2 (12–88)	**NS**
Comprehensive LND (levels II–V)/Limited LND	179/0	2/28	**<0.001**
First surgery outside our Institution, y/n	0/179	28/2	**<0.001**

SD standard deviation

NS not significant, $p > 0.05$

Significance <0.05 are reported

Moreover, pN1b patients may be at increased risk for recurrence in the lateral neck compartment [2, 9]. Lateral neck recurrence is usually associated with poor prognosis [4, 9].

Recent studies have investigated risk factors for recurrence in N1b patients, demonstrating that several patients and lymph node-related factors (including age, lymph node size, extranodal extension, lymph node ratio) are of importance for the risk of recurrence and poor prognosis [3–5, 33].

However, at least from a theoretical point of view, lymph node ratio is related not only to the tumor burden but also to the extension of the lymph node dissection.

Interestingly, despite there is a consensus regarding the indication for therapeutic LND in the endocrine surgical community, the extension of the dissection is still matter of debate. Comprehensive compartment oriented LND (levels II–V) seems the best surgical option in PTC patients with lateral neck node metastases [16]. Nonetheless, limited dissection of the involved lateral neck levels has been proposed as an alternative to comprehensive selective LND (levels II–V) in order to reduce morbidity, but it theoretically carries an increased risk of local recurrence [12].

A literature review of five retrospective studies found inconsistent evidence for the appropriate extent of LND in the treatment of metastatic differentiated thyroid cancer, with some evidence for using either modified radical neck dissection or less extensive dissections [17]. It has been reported that levels III and IV are the most common sites of lateral neck node metastases [18]. As a consequence selective dissection of levels III and IV could seem adequate in the treatment of regionally metastatic PTC [18], especially when there is no suspicion of lymph node metastases in those levels, or when multilevel aggressive neck metastasis is not found [34].

In a review of neck dissection for PTC during four decades, Palazzo et al. [35] reported that there has been a move away from both formal modified radical neck dissection and "cherry picking" of individual nodes toward selective LND. On the other hand, other studies have shown that in patients undergoing LND, the rate of involvement of lymph nodes in levels II and V approaches that of levels III and IV [12, 26–35]. Indeed, it has been recently suggested that omitting the dissection of the levels II and V during therapeutic LND carries the potential risk to miss metastatic lymph node respectively in two-thirds and one-fifth of the pN1b patients, respectively [12].

The results of the present study demonstrate that, besides patients and tumor-related factors, also the extension of the LND and, probably, surgeon's experience, are risk factors for recurrence following LND for PTC.

This finding is of utmost importance since lateral neck node recurrence following LND represents a challenging event for both patients and surgeons due to the difficulties of reoperation, including an increasing risk of postoperative morbidities [11, 12]. Indeed, also in our series the complications rate following reoperative LND was significantly higher than in primary surgery.

As a consequence, our results strongly support the concept that patients with lateral neck node metastases from

PTC should undergo comprehensive LND, including lateral neck levels from II to V, and should be treated at referral Centers by experienced surgeons.

We have to underline that the present study has some important limitations. First of all it is a retrospective study. Secondary, most of the patients who were referred for recurrence underwent previous limited LND as documented by clinical charts but the first nodal dissection was not the same for all patients (level II–III dissection/level III–IV dissection/cherry picking with/without level VI dissection). Nonetheless, the vast majority of the patients who had recurrence following LND, were referred to our Institution after being operated at nonreferral Centers and some pathological data (including extranodal extent and size of lymph node metastases) were not available for analysis.

Nonetheless, one of the strong points of the present study is the fact that it represents one of the largest series of pN1b PTC patients observed and homogenously treated and followed up at a single Institution during a relatively short time period.

In conclusion, despite the results of the present study may be influenced by selection bias, limited LND and surgery performed at non referral centers seem to represent non tumor-related risk factors for recurrence following therapeutic LND for PTC. In the presence of lateral neck node metastases of PTC, a comprehensive LND should be performed in third care referral Centers.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical standards All procedures performed in this study were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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