American Journal of Otolaryngology–Head and Neck Medicine and Surgery xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

Long-term outcomes of central neck dissection for cN0 papillary thyroid carcinoma☆

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ARTICLE INFO

Article history:
Received 5 April 2017
Available online xxxx

Keywords:
Central neck dissection
Papillary thyroid carcinoma
Elective
Locoregional recurrence
Hypoparathyroidism
Survival

ABSTRACT

Objective.
The risk-benefit ratio of central neck dissection (CND) in patients affected by papillary thyroid carcinoma (PTC) without clinical or ultrasonographic (US) evidence of neck lymph node metastasis (cN0) is currently debated. The aim of this study was to evaluate long-term outcome of CND on locoregional recurrence, distant metastasis, survival, and postoperative complications in a large series of patients with cN0-PTC.
Study Design.
Observational retrospective controlled study.
Methods: Clinical records of patients ($n = 610$) surgically treated for cN0-PTC at the Otolaryngology Unit of the Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, from January 1984 to December 2008, were retrospectively reviewed. Study population was divided into three groups according to surgical treatment: Group A, total thyroidectomy ($n = 205$); Group B, total thyroidectomy and elective ipsilateral CND ($n = 281$); Group C, total thyroidectomy and bilateral CND ($n = 124$).
Results: Of a total of 610 patients, 305 (50%) were classified as low-risk, 278 (45.57%) as intermediate-risk, and 27 (4.43%) as high-risk. Response to initial therapy was excellent in 567 patients (92.95%), acceptable in 21 (3.44%), and incomplete in 22 (3.61%), with no significant differences among groups. Locoregional recurrence was detected in 32 (5.2%) out of 610 patients. Distant metastasis was found in 15 patients (2.5%). Statistical analysis showed no significant differences in the rates of locoregional recurrence ($p = 0.890$) or distant metastasis ($p = 0.538$) among groups. Disease-specific mortality and overall survival did not significantly differ among groups ($p = 0.248$ and 0.223, respectively). Rate of permanent hypoparathyroidism was significantly higher in Group C patients compared to those in Groups A and B.
Conclusion: CND does not confer any clear advantage in the treatment of low-risk patients, regardless of surgical procedure. Instead, bilateral CND may be effective in limiting disease relapse and/or progression in patients at higher prognostic risk. Our data indicate that elective CND does not confer any clear advantage in terms of locoregional recurrence and long-term survival, as demonstrated by outcomes of the study Groups, regardless of their different prognostic risk. Elective CND allows a more accurate pathologic staging of central neck lymph nodes, despite its increasing the risk of permanent hypoparathyroidism. Intraoperative pathologic staging is a valuable tool to assess the risk of controlateral lymph node metastasis in the central neck compartment and to limit more aggressive surgery only to cases, otherwise understaged, with lymph node metastasis.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for >90% of all thyroid cancers [1]. While regional lymph node metastasis is present in a large number of patients at time of diagnosis, preoperative ultrasound (US) reveals metastatic involvement of the central neck in only 50% of cases with pathologic lymph nodes found on definitive pathology, seemingly due to the presence of

☆ This study was presented at the "2nd World Congress on Thyroid Cancer", July 10-14,2013, Toronto, Canada.

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http://dx.doi.org/10.1016/j.amjoto.2017.06.004
0196-0709/

the overlying thyroid gland [2]. Elective central neck dissection (CND) has been proposed in the treatment of PTC without clinical and US evidence of lymph node metastasis in the neck (cN0). The rationale of this procedure is to remove clinically non-detectable pathologic lymph nodes to reduce the rate of recurrent disease [3–6] and to allow a more accurate pathologic staging of lymph nodes of the central compartment. Notably, according to the American Joint Committee on Cancer (AJCC) prognostic classification, the shift of patients older than 45 years from N0 to N1 would result in their conversion from stage I to stage III [7].

Nevertheless, there is no consensus regarding possible beneficial effects of elective CND on recurrence and survival. Proponents of elective CND affirm that this procedure allows treatment of the micrometastasis that may be responsible for recurrent disease [8]. Further, lymph node metastasis has been related to a higher risk of recurrence and to a significant negative impact on survival [9–11]. Instead, some studies indicate that lymph node metastasis does not influence long-term prognosis [12–17]. Moreover, CND is not a procedure without potential risks even in experienced hands, with an increased rate of recurrent laryngeal nerve (RLN) injury and hypoparathyroidism [18–21]. Hence, routine use of CND should be adequately weighed because the morbidity associated with this procedure could be unjustified on the basis of postoperative pathologic findings.

The present study aimed to investigate the risk-benefit ratio of CND in patients surgically treated for cN0-PTC. The primary endpoints of the study were to measure the response to initial therapy, the rates of locoregional and distant metastasis, and postoperative complications. The secondary endpoint was to evaluate the survival rates of the study population.

Table 1
Description of the study cohort ($n = 610$ patients).[a]*

Age (years)		
Mean ± SD	49 ± 14	610
Median	49	
Range	16–90	
Age at diagnosis (years)		
< 45	39.7%	242
≥ 45	60.3%	368
Gender		
Female	77.9%	475
Male	22.1%	135
Surgical treatment		
Group A (TT)	33.6%	205
Group B (TT and ipsilateral CND)	46.1%	281
Group C (TT and bilateral CND)	20.3%	124
pN1a		
TT	4.4% *	9 *
TT and ipsilateral CND	24.2%	68
TT and bilateral CND	68.55%	85
pN0		
TT	–	–
TT and ipsilateral CND	75.8%	213
TT and bilateral CND	31.45%	39
pNx		
TT	95.6%	196
TT and ipsilateral CND	–	–
TT and bilateral CND	–	–
Follow up (months)		
Mean ± SD	113 ± 53	610
Range	4–340	

SD: standard deviation; TT: total thyroidectomy; CND: central neck dissection; AJCC: American Joint Committee on Cancer; Tg: thyroglobulin; TgAb: anti-thyroglobulin antibodies. LNR: lateral neck recurrence. CNR: central neck recurrence.
[a] Perithyroid metastatic lymph nodes.

2. Methods

2.1. Patients

This retrospective controlled observational study was approved by the institutional review committee of the Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy.

The clinical records of 1810 patients with histopathological diagnosis of PTC surgically treated at the Otolaryngology Unit of the Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy, from January 1984 to December 2008 were retrospectively reviewed. Patients were included if they had a histopathological diagnosis of any variant of cN0-PTC. Patients were excluded from the study in case of previous neck surgery and/or previous external beam radiation treatment. The following data were retrieved from the patient files: age at diagnosis and gender, surgical treatment, pathological findings, radioactive iodine (RAI) dose, postoperative complications, follow-up results. This study cohort was also investigated in a previous paper focusing on identifying predictive factors for lateral neck recurrence [22]. Six hundred and seventy-nine patients met inclusion criteria, 69 of whom (10.2%) were lost during follow-up and were therefore excluded from the study. The remaining 610 patients formed the study cohort, detailed in Table 1.

2.2. Preoperative evaluation, surgical strategy, and postoperative care

Before surgery, routine blood count, serum chemistry, albumin-adjusted total serum calcium, physical examination, and indirect laryngoscopy or flexible fiberoptic laryngoscopy were obtained in all patients; preoperative neck US has been routinely used since 1990. At our institution, patients with preoperative cytological diagnosis of PTC between 1984 and 1996 were treated with total thyroidectomy. Since 1997, routine management of patients with a preoperatively diagnosed cN0-PTC has consisted in total thyroidectomy and elective ipsilateral CND. Elective CND implies that no lymph node metastases were found preoperatively, either clinically or by imaging studies. CND specimens are intraoperatively evaluated by frozen-section pathology; in cases of histological evidence of lymph node metastasis, contralateral CND is performed. On the basis of treatment received, patients were therefore grouped as follows:

Group A included 205 patients (33.61%) treated with total thyroidectomy. This group included patients surgically treated for benign thyroid disease with an incidental diagnosis of PTC on final pathology, and patients with preoperative cytological diagnosis of cN0-PTC surgically treated before 1997.

Group B consisted of 281 patients (46.06%) who received total thyroidectomy and elective ipsilateral CND. Of these, 186 (66.19%) had a negative intraoperatively performed frozen-section pathology, which was not performed in the remaining 95 (33.81%) due to anatomosurgical conditions exposing RLN at a great risk of injury.

Group C consisted of 124 patients (20.33%) who underwent total thyroidectomy and bilateral CND. Contralateral paratracheal CND was performed in 68 of these patients (54.83%), who had an initial indication to total thyroidectomy and ipsilateral prophylactic CND, due to evidence of lymph node metastasis on intraoperative frozen-section pathology. The remaining 56 patients (45.17%) underwent initial prophylactic bilateral CND because of an isthmic or a bilateral cN0-PTC.

After surgery, all patients included in the study underwent albumin-adjusted total serum calcium level measurement on postoperative days 1 to 3, and flexible fiberoptic laryngoscopy before discharge. After discharge, all patients received TSH suppression therapy, basic serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb) levels, and neck US. All patients of the study received RAI therapy 2 to 4 months after surgery. Dose ranged from 2960 to 5550 MBq. A whole-body scan (WBS) was performed before RAI therapy and then again six months later.

2.3. Follow up and risk stratification

For prognostic purposes, patients were retrospectively classified according to the American Joint Committee on Cancer (AJCC) staging system [23] and to the American Thyroid Association (ATA) initial risk

Please cite this article as: Giordano D, et al, Long-term outcomes of central neck dissection for cN0 papillary thyroid carcinoma, American Journal of Otolaryngology–Head and Neck Medicine and Surgery (2017), http://dx.doi.org/10.1016/j.amjoto.2017.06.004