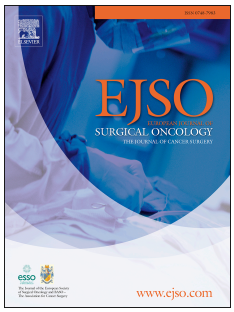
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Total thyroidectomy alone versus ipsilateral versus bilateral prophylactic central neck dissection in clinically node-negative differentiated thyroid cancer. A retrospective multicenter study

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Abstract

Background. Central neck dissection (CND) remains controversial in clinically node-negative differentiated thyroid cancer (DTC) patients. The aim of this multicenter retrospective study was to determine the rate of central neck metastases, the morbidity and the rate of recurrence in patients treated with total thyroidectomy (TT) alone or in combination with bilateral or ipsilateral CND.

Methods. The clinical records of 163 clinically node-negative consecutive DTC patients treated between January 2008 and December 2010 in three endocrine surgery referral units were retrospectively evaluated. The patients were divided into three groups: patients who had undergone TT alone (group A), TT with ipsilateral CND (group B), and TT with bilateral CND (group C).

Results. The respective incidences of transient hypoparathyroidism and unilateral recurrent nerve injury were 12.6% and 1% in group A, 23.3% and 3.3% in B, and 36.7% and 0% in C. Node metastases were observed in 8.7% in group A, 23.3% in B, and 63.3% in C. Locoregional recurrence was observed in 3.9% of patients in group A and in 0% in B and C.

Conclusions. We found no statistically significant differences in the rates of locoregional recurrence between the three groups. Therefore, TT appears to be an adequate treatment for these patients; CND is associated with higher rates of transient hypoparathyroidism and cannot be considered the treatment of choice even if it could help for more appropriate selection of patients for RAI. Ipsilateral CND could be an interesting option considering the lower rate of hypocalcemia to be validated by further studies.

Key words: central neck dissection, thyroid cancer, papillary thyroid carcinoma, lymph node metastasis

1. INTRODUCTION

Differentiated thyroid carcinoma (DTC) (particularly papillary) is the most common thyroid malignancy, accounting for more than 90% of all thyroid cancers [1-3]. Patients with DTC have an excellent prognosis, with 10-year survival rates exceeding 90% [1,2]. Total thyroidectomy (TT) is the most commonly performed primary procedure for DTC exceeding 10 mm in diameter [1,2].

Despite the excellent prognosis, cervical lymph node metastases are common, occurring in 20-50% of patients [4-11]. Micrometastases are even more common and may be observed in up to 90% of patients [1-3,6,7,9,12]. The central compartment (level VI) is the location where regional metastases initially occur and the most frequently involved [1,2,4,6,8,11].

Neck ultrasonography (US), the accuracy of which is increased by the use of fine-needle aspiration cytology (FNAC) and FNAC thyroglobulin (Tg) measurements, reliably evaluates the lateral compartment of the neck before thyroid surgery [1,13]. This procedure can detect non palpable lymph node metastases, thereby helping to plan therapeutic lateral dissections combined with TT [1]. In contrast, US is less reliable for preoperative detection of lymph node metastases in the central neck compartment [1,13]. The accuracy of neck US is limited by the fact that paratracheal lymph nodes are minute and located beneath the thyroid gland [1,13]. The air-filled trachea provides an additional element of disturbance [1,13].

Although central neck dissection (CND) is indicated in clinically node-positive disease, it remains controversial in patients with no clinical evidence of nodal metastasis [1,2]. Some authors recommend routine CND in order to prevent future recurrence, citing the high risk of positive lymph nodes, the accuracy of staging, better outcomes, reduced postoperative Tg levels, and a lower morbidity rate associated with initial thyroid surgery (compared with later operations), whereas others sustain that this procedure increases the risk of injury to the parathyroid glands and recurrent laryngeal nerves without any demonstrable benefits in terms of long-term outcome [1,2,14]. Furthermore, recurrence in this compartment is difficult to treat surgically, while CND during the initial thyroid surgery can be performed without extending the wound [1,15]. CND allows for

accurate pathologic staging of the lymph nodes and treatment of the micrometastases that may be responsible for recurrence or disease persistence [1,8,13].

The prognostic importance of lymphatic involvement in locoregional recurrence and long-term survival remains a matter of debate. It has traditionally been accepted that regional lymph node metastases in DTC may increase regional recurrence rates but do not ultimately affect survival rates, although some recent studies have suggested a possible role of lymph node metastasis from papillary thyroid cancer in reducing patient survival [1,3,5,9,16,17]. Recent studies confirm that in high-risk patients (i.e. male patients, aged > 50 years, T stage > 3 cm in diameter with locoregional infiltration, multifocality, and BRAF postitivity) lymph node metastases affect the outcome, primarily by predicting a greater rate of regional recurrence [1,2,12].

Because of the risk of complications following prophylactic CND, more limited (ipsilateral) CND has recently been proposed as an alternative safer treatment for patients with unilateral DTC [2,18,19].

The aim of this multicenter retrospective study was to determine the rate of metastases in the central neck of patients considered free of regional disease following preoperative investigation (cN0) and examine the morbidity and the rate of recurrence in patients with DTC treated with TT with concomitant bilateral or ipsilateral CND compared with those undergoing TT alone.

2. Materials and methods.

2.1. Study design. A retrospective study was conducted using data obtained from three high-volume endocrine surgery units on patients who had undergone TT between January 2008 and December 2010. Inclusion criteria were preoperative cytological diagnosis of DTC and the absence of suspicious enlarged lymph nodes following US or intraoperative inspection. This retrospective study identified 163 consecutive clinically node-negative patients with DTC. Patients were divided into three groups according to the procedures performed: patients who had undergone TT only and no CND formed group A; those who had undergone TT with concomitant ipsilateral CND formed

group B (iCND); and patients who had undergone TT combined with bilateral CND formed group C.

The selection was made based on the preferences of the unit (in one unit all patients underwent TT) and the order of presentation of patients. In case of ipsilateral CND, frozen section analysis was performed to determine whether to go on with bilateral CND.

Patient demographics, preoperative data, pathological findings, postoperative complications (including recurrent nerve injury, hypoparathyroidism, neck hematoma and wound infection) and locoregional or distant recurrence were assessed.

The work has been approved by the local institutional ethical committees of University of Cagliari, Second University of Naples, and Università Cattolica del Sacro Cuore of Rome; all patients gave informed consent to the work.

This study was carried out on behalf of the SICO (Italian Society of Surgical Oncology) Endocrine Oncoteam.

2.2. Preoperative assessment. All the patients included in the study had undergone a preoperative physical examination, high-resolution neck US, FNAC of suspicious nodules, and measurement of serum thyroid hormones, TSH, Tg, and anti-Tg antibodies; preoperative fibrolaryngoscopy was also routinely performed.

2.3. Thyroidectomy. In each participating centre, surgical procedures were performed by two or three experienced endocrine surgeons (who perform at least 100 thyroidectomies per year). In each patient, extracapsular TT was performed; recurrent laryngeal nerves were routinely exposed until their insertion into the larynx, and preservation of the parathyroid glands was always sought. Bilateral CND included the removal of pre-laryngeal, pretracheal, and both the right and the left paratracheal nodal basins. Homolateral CND included removal of the pre-laryngeal, pretracheal and the paratracheal nodal basins on the side of the tumor [20]. Drainage was routinely used. Serum calcium levels were assayed on the first and second postoperative day, and then on the basis of the evolution of clinical and biochemical parameters. In the case of hypocalcemia, PTH levels were

determined. Hypoparathyroidism was defined as PTH < 10 pg/ml (normal range = 10-65 pg/ml). In the case of suspected recurrent nerve injury, a fibrolaryngoscopy was performed to assess vocal cord mobility. Post-operative laringoscopy was performed in a total of 18 patients.

Thyroid cancer was classified according to the TNM classification system adopted by the AJCC (7^{th} edition, 2010). Locally invasive carcinoma was defined as T3 or T4 based on TNM staging. Lymph node yield was defined as the number of lymph nodes harvested from each patient.

2.4. Follow up.

Indications for radioiodine ablation were: tumor size > 10 mm; extracapsular thyroid invasion or locoregional extension; lymph node involvement; aggressive histological subtypes; and multifocal disease. Suppressive L-Thyroxine therapy was routinely administrated. Serum Tg and Tg-antibody levels were assayed every 6 months together with neck US. The diagnosis of recurrent disease was confirmed with US-guided FNAC of lymph nodes and Tg washing of FNAC aspirates. Patients considered disease-free underwent Tg detection after rhTSH stimulation and neck US (ATA Guidelines 2009).

Hypoparathyroidism and nerve palsy were defined as permanent if they persisted for more than 12 months after surgery.

2.5. Statistical analysis.

Pearson chi-squared tests were used for categorical data analysis; ANOVA was used for continuous variables. Data are reported as the mean value ± standard error of the mean. Calculations were performed using MedCalc® 12.7.0.0. Results were considered statistically significant if p values were ≤ 0.05.

3. Results.

Between January 2008 and December 2010, 163 patients (127 women and 36 men) with a preoperative diagnosis of DTC underwent surgery; patient mean age was 44.4 ± 11.8 years. Autoimmune thyroiditis was present in 45 (29.4%) patients, and a family history of thyroid cancer

was reported in 9 (5.5%) patients. The patients were divided into three groups according to the criteria stated in section 2.1; group A comprised 103 patients (63.2%); group B comprised 30 patients (18.4%); and the remaining 30 patients (18.4%) comprised group C (Table 1).

3.1. Surgical treatment and outcomes (Table 2).

Group A (TT): The mean operative time was 64.2 ± 18.7 minutes and the mean postoperative stay was 2.4 ± 0.8 days. Transient hypoparathyroidism was observed in 13 (12.6%) patients, permanent hypoparathyroidism in 1 (1.9%), transient recurrent nerve injury was seen in 1 (1%) patient and wound infection in 1 patient (1%).

Group B (iCND): The mean operative time was 69.8 ± 28.2 minutes and the mean postoperative stay was 3.2 ± 0.8 days. Transient hypoparathyroidism was reported in 7 (23.3%) patients, permanent hypoparathyroidism in 1 (3.3%) and transient recurrent nerve injury in seen in 1 (3.3%) patient.

Group C (CND): The mean operative time was 90.5 ± 31.8 minutes and the mean postoperative stay was 3.9 ± 1.5 days. Transient hypoparathyroidism was observed in 11 (36.7%) patients and permanent hypoparathyroidism in 1 (3.3%); no nerve injuries were reported.

3.2. Pathologic data (Table 3).

Group A (TT): Mean tumour size was 14.2 ± 9 mm; microcarcinomas were reported in 45 (43.7%) patients. Classic papillary thyroid carcinoma was observed in 64 (62.1%) patients, follicular variant of papillary carcinoma in 24 (23.3%), tall cell carcinoma in 10 (9.7%), follicular carcinoma in 4 (3.9%) and Hürthle cell carcinoma in 1 (1%) patient. Pathologic examination revealed an angioinvasive carcinoma in 6 (5.8%) cases, a locally invasive carcinoma in 19 (18.4%) and a multifocal neoplasm in 36 (35%). In 21 (20.4%) patients, perithyroid lymph nodes were found in the specimen. Overall, node metastases were observed in 9 (8.7%) patients.

Group B (iCND): Mean tumour size was 13.5 ± 7.5 mm; microcarcinomas were observed in 15 (50%) cases. Papillary thyroid carcinoma was reported in 19 (63.3%) patients, follicular variant of

papillary carcinoma in 9 (30%) and tall cell carcinoma in 2 (6.7%) patients. Angioinvasive carcinoma was reported in 7 (23.3%) patients, locally invasive carcinoma in 10 (33.3%) and multifocal tumours in 17 (56.7%). The mean lymph node yield was 5.8 ± 2.2 and node metastases were observed in 7 (23.3%) patients.

Group C (CND): Mean tumour size was 12.4 ± 4.9 mm; microcarcinomas were reported in 13 (43.3%) patients. Papillary thyroid carcinoma was observed in 24 (80%) patients, follicular variant of papillary carcinoma in 5 (16.7%) and tall cell carcinoma in 1 (3.3%) patient. Histopathological examination revealed an angioinvasive carcinoma in 9 (30%) patients, a locally invasive tumour in 6 (20%) and a multifocal neoplasm in 18 (60%). The mean lymph node yield was 12.4 ± 4.9 and node metastases were observed in 19 (63.3%) patients.

3.3. Follow-up.

Group A (TT): Mean follow-up was 46.1 ± 27.8 months. Postoperative radioactive iodine (RAI) was administered in 59 (57.3%) patients. Nodal recurrences were observed in 4 (3.9%) patients and no distant metastases were reported. Among the 4 patients with regional recurrence, pathologic examination revealed a classic papillary carcinoma in 3 cases and a follicular variant of papillary carcinoma in one case. In all patients, neoplasm size was >10 mm extrathyroid invasion of the tumour was present in 2 cases and multifocal carcinoma occurred in 2 cases. Nodal recurrences occurred in the central neck compartment in 2 cases, in the lateral compartment in 2. The patients were submitted to CND in 2 cases and lateral neck dissection in 2. No complications were observed and the patients are now disease free.

Group B (iCND): Mean follow-up was 71.1 ± 9.8 months. Postoperative RAI was administered in 19 (63.3%) patients. No nodal recurrences or distant relapses were reported.

Group C (CND): Mean follow-up was 72.5 ± 8.4 months. Postsurgical RAI was administered in 26 (86.7%) cases; no nodal recurrences or distant metastases were observed.

3.4. Comparison of the three groups.

The demographic data for the three groups were similar. Mean operative time and postoperative stay were shorter in Group A ($p < 0.001$). The incidence of postoperative transient hypoparathyroidism was lower in Group A ($p = 0.01$), whereas no differences in the incidence of permanent hypoparathyroidism and nerve palsy were present. Subhistotypes of DTC were similar among the three groups. Angioinvasive and multifocal carcinomas were less frequent in group A ($p < 0.01$ and $p < 0.05$), but there were no significant differences in the frequency of locally invasive cancer. The lymph node yield was higher in groups B and C versus group A ($p < 0.001$) and the detection of lymph node metastases was more common in patients of group B and C ($p < 0.001$). Postoperative RAI administration was higher in group B and C ($p < 0.05$) compared with group A. There were no statistically significant differences in terms of regional recurrence among the three groups.

4. Discussion

Prophylactic CND in clinically node-negative DTC patients still remains controversial [5,12]. Lymph node metastases in level VI nodes are common, but their impact on the prognosis and the best treatment strategy remain unclear [2,7].

Proponents claim prophylactic CND is accompanied by a decrease in post-operative Tg serum levels and a lower risk of recurrence, without affecting the operative risk of the initial surgery and saving future morbidity caused by a second operation [3,9,12,21]. The meta-analysis by Lang et al. [22] reports that patients who undergo TT associated with prophylactic CND have a 35% lower risk of locoregional recurrence compared with those who undergo TT alone. Randolph et al [23] recently showed that prognosis is negatively impacted if 5 or more metastatic lymph nodes are identified during neck dissection. Opponents of prophylactic CND argue that lymph node dissection does not improve survival, and lymph nodes that are not clinically evident are probably not clinically significant with respect to their impact on disease prognosis and risk of recurrence

[14,24]. Furthermore, routine CND increases the risk of recurrent laryngeal nerve injury and hypoparathyroidism [14].

According to the ATA and the Unità di Endocrino-Chirurgia (Endocrine Surgery Unit) guidelines, prophylactic dissection should be performed in high-risk patients with advanced primary tumours (T3 or T4) by surgeons with high-volume case loads in order to decrease definitive complications [7,12]. A recent consensus report by the European Society of Endocrine Surgeons (ESES) stated that larger tumours (T3, T4), patients aged 45 years and older or 15 years and younger, male patients, patients with bilateral or multifocal tumours and patients with known involved lateral lymph nodes should all be candidates for routine unilateral level 6 dissection [25].

Identification of nodal metastases in the central neck is challenging in the absence of histologic analysis [26]. Although high resolution US is the most frequently recommended imaging modality for evaluating cervical lymph node metastasis, its sensitivity for the detection of lymph node metastases in the central compartment is relatively low (23-55%), while its specificity is 69-92% [15,16,27,28]. The sensitivity of computed tomography (CT) in the central compartment is slightly higher than that of US, but it is not sufficiently sensitive to detect small central lymph node metastases (sensitivity 41-62%; specificity 44-93%) [15,16,27,28]. The combination of US and CT gives similar results (sensitivity 46%; specificity 88%) [15,16].

Some surgeons have attempted sentinel lymph node biopsy using radioisotopes or blue dye to identify occult metastatic lymph nodes and guide therapeutic CND. Although some authors have reported the sensitivity of sentinel node biopsy to be as high as 100%, most report relatively low sensitivities, ranging from 65% to 87%, and relatively high false-negative rates [16]. The efficacy of routine sentinel lymph node biopsy is controversial and it is not widely used in the management of occult metastases in DTC [16].

Sometimes metastatic central lymph nodes can be detected during thyroidectomy by palpation or inspection, and this can guide therapeutic CND [16,24]. In the study by Ji and colleagues [16], sensitivity and specificity of the intraoperative surgeon’s judgement was assessed as relatively low

(35.7% and 72.5%) and the false-positive and false-negative rates were high, while the positive predictive value of an enlarged lymph node was only 15.2%. Most enlarged lymph nodes were found to display reactive hyperplasia, and this may be correlated with Hashimoto's thyroiditis [16].

In the presence of suspicious lymph nodes, some authors suggest that the use of intraoperative frozen sections should be considered [12,18,19]. Frozen section examination on the ipsilateral central neck nodes can be employed to assess the risk of contralateral central neck metastases and potentially modify the extension of the CND [18,19]. However, given the low impact on the outcome of occult nodal metastases, the use of the frozen section examination currently appears questionable.

A number of authors have suggested routine unilateral (ipsilateral) CND, which may be useful in a subset population of DTC patients with reduced complications [8,19,29]. A prospective study by Moo and colleagues [29] reports that no patients with a tumour size of 10 mm or less had positive lymph nodes bilaterally, compared with 31% of patients with tumours larger than 10 mm. Thus, ipsilateral CND may be sufficient for the treatment of patients with tumours sized 10 mm or less [5,29].

In the present series of 163 clinical node-negative DTC patients who underwent TT alone or TT combined with ipsilateral or bilateral CND, similar locoregional nodal recurrence rates were observed after long-term follow-up in the three groups. Follow-up was slightly shorter in group A because of the organization of patient monitoring in the unit in which only TT was performed.

According to the literature, CND results in a high rate of unexpected lymph node metastases (23.3% in ipsilateral and 63.3% in bilateral CND) that affect the protocol treatment, suggesting the need for RAI ablation, which is not otherwise indicated, particularly in cases of tumours $\leq$ 10 mm. In fact, in the present retrospective study, RAI ablation was performed in 57.3% of patients in group A, in 63.3% of group B, and 86.7% of group C. However, in these cases, the benefits of RAI and the related complications remain a topic of controversy.

The lymph node recurrence rate observed in the current series after long-term follow-up was low and not statistically different between the three groups of patients, even if regional recurrences exclusively occurred in group A. Although all three groups were similar in terms of demographics, clinical and pathological findings, the retrospective nature of this analysis, the small number of patients, the high incidence of microcarcinomas and the extensive use of RAI ablation constitute limitations of this study and preclude the drawing up of definitive conclusions. In particular, the small number of patients in the neck dissection groups greatly limits the ability to draw any definitive conclusions. Another limitation of this study is that follow-up is slightly shorter in patients of TT group: it cannot be excluded that some patients of this group tend to recur late. Furthermore, all surgeons in this study perform at least 100 thyroidectomies per year; so, these findings may only be applicable to high volume surgeons; low volume surgeons are likely to have significantly higher complication rates. Moreover, post-operative laringoscopy was not routinely performed and this could lead to an underestimation of the incidence of RLN injury. Recurrences occurred in 2 patients with extrathyroidal invasion and in 2 patients with multifocal tumours; all tumours were > 10 mm and in one case > 50 mm. All patients were reoperated without major complications and are now disease free.

In the opinion of many endocrine surgeons, prophylactic CND is associated with higher morbidity, in particular, injury to the parathyroid gland (especially the lower glands), with rates of transient hypoparathyroidism at 14-60%, permanent hypoparathyroism at 0-14%, transient vocal cord paralysis at 0-10% and permanent recurrent laryngeal nerve injury at 0-5% [1-3,13,30-32]. Our experience confirms the high rates of transient hypoparathyroidism after CND: the rates were 12.6% in group A, 23.3% in group B and 36.7% in group C; the differences were statistically significant. No statistically significant difference was observed for recurrent nerve injury, while operative times were statistically longer in group C.

Our results are in line with other reports in the literature and lead us to sustain that prophylactic CND should not be carried out on a routine basis for the treatment of DTC.

The incidence of recurrence depends on numerous factors, most of which can be identified only after surgery. In the study by Kim [28], the risk factors correlating with ipsilateral lymph node metastasis were a tumour size greater than 10 mm and extrathyroidal extension, while the risk factors associated with contralateral lymph node metastasis were extrathyroidal extension and ipsilateral lymph node metastasis. In the present study, all 4 cases of recurrent DTC occurred in patients with tumours > 10 mm (in one case > 50 mm) and in 2 cases extrathyroidal extension was present. However, the small number of recurrences does not allow to draw any definitive conclusions.

In conclusion, DTC has a high rate of central lymph node metastasis even in clinically node-negative patients; nevertheless, in the present study there was no statistically significant difference in the rates of locoregional recurrence between the three modalities of treatment. For this reason, we can but propose that TT appears to be an adequate treatment for clinically node-negative DTC. CND is associated with a higher rate of transient hypoparathyroidism, while the rate of permanent complications is very low and not significantly different from patients who underwent TT alone. Anyway, CND is not supported in our study as a treatment of choice even if it could help for the more appropriate selection of patients for RAI treatment and it requires further study groups to assess its usefulness in high-risk patients, particularly to prevent locoregional recurrence. However, the benefits of RAI and the related complications remain a topic of controversy and our study does not bring definitive results about it. Ipsilateral CND could be an interesting treatment option considering the lower rate of hypocalcemia compared to bilateral CND, but the incidence of temporary hypoparathyroidism is still higher than TT so its role must be validated by further studies. Multi-institutional studies with larger series of patients and longer follow-up periods are necessary to draw definitive conclusions about the potential benefits of prophylactic CND for patients with clinically node-negative DTC.

Conflict of interest statement

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No conflict of interest

Ethics

The work has been approved by the local institutional ethical committees of University of Cagliari, Second University of Naples, and Universita` Cattolica del Sacro Cuore of Rome; all patients gave informed consent to the work.

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Tables

Table 1. Demographic data.

	Group A (n=103)	Group B (n=30)	Group C (n=30)	p value
Sex (M:F)	26:77	4:26	6:24	0.36
Age (years)	45.4±12.2	45.8±10.5	39.7±10.5	0.05
Autoimmune thyroiditis	29 (28.2%)	6 (20%)	10 (33.3%)	0.50
Familial thyroid cancer	4 (3.9%)	2 (6.7%)	3 (10%)	0.41

Table 2. Surgical treatment, outcomes and follow up.

	Group A (n=103)	Group B (n=30)	Group C (n=30)	p value
Operative time (minutes)	64.2±18.7	69.8±28.2	90.5±31.8	<0,001
Postoperative stay (days)	2.4±0.8	3.2±0.8	3.9±1.5	<0,001
Follow-up (months)	46.1±27.8	71.1±9.8	72.5±8.4	<0,001
Transient hypoparathyroidism	13 (12.6%)	7 (23.3%)	11 (36.7%)	0.01
Persistent hypoparathyroidism	2 (1.9%)	1 (3.3%)	1 (3.3%)	0.86
Recurrent nerve injury	1 (1.0%)	1 (3.3%)	0	0.46
Postoperative RAI	59 (57.3%)	19 (63.3%)	26 (86.7%)	0.012
Regional recurrence	4 (3.9%)	0	0	0.30

RAI: Radioactive iodine

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Table 3. Pathologic data

	Group A (n=103)	Group B (n=30)	Group C (n=30)	p value
Tumour size (mm)	14.2±9	13.5±7.5	12.4±4.9	0.49
Microcarcinoma	45 (43.7%)	15 (50%)	13 (43.3%)	0.81
Histological subtype:				
- Classic papillary carcinoma	64 (62.1%)	19 (63.3%)	24 (80%)	0.18
- Follicular variant	24 (23.3%)	9 (30%)	5 (16.7%)	0.47
- Tall cell variant	10 (9.7%)	2 (6.7%)	1 (3.3%)	0.5
- Follicular carcinoma	4 (3.9%)	0	0	0.3
- Hurtle cell carcioma	1 (1%)	0	0	0.74
Multifocal	36 (35%)	17 (56.7%)	18 (60%)	<0.05
Lymph node yield	2.6±2.2	5.8±2.2	12.4±4.9	<0.001
Node metastases	9 (8.7%)	7 (23.3%)	19 (63.3%)	<0.001
Angioinvasive	6 (5.8%)	7 (23.3%)	19 (63.3%)	<0.001
Locally invasive	19 (18.4%)	10 (33.3%)	6 (20%)	0.21

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