



# Recurrent Papillary Thyroid Carcinoma to the Cervical Lymph Nodes: Outcomes of Compartment-Oriented Lymph Node Resection

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## Abstract

**Introduction** Recurrence of papillary thyroid carcinoma after initial treatment is challenging. Surgical reintervention is recommended, but cure after surgery is uncertain and surgical morbidity may be high. This study evaluates the effect of compartment-oriented lymph node dissection (LND) on clinical and biochemical cure rate as well as the related complications.

**Patients and methods** All patients who underwent LND for recurrent papillary thyroid carcinoma between 2000 and 2015 were included. Demography, the extent of the initial surgery, usage of <sup>131</sup>I, the pattern of recurrence, diagnosis, details of the surgical reintervention, histological findings, surgical morbidity, and clinical and biochemical outcomes were analyzed.

**Results** There were 11 (12.7%) males and 75 (87.2%) females with a mean age of 42.8 ± 14.6 years. Seventy-seven patients had undergone total thyroidectomy and in 67 (77.9%) some type of LN resection. In 76 (88.3%), <sup>131</sup>I was administered after the initial surgery. We localized suspicious lymph nodes by US in all patients, and metastases were documented before surgery by FNA in 63. Seven (8.13%) patients underwent central LND, 63 (73.2%) lateral LND and 16 (18.6%) both, central and lateral LND. Major complications occurred in 6 patients (6.9%). Sixty-two (72.0%) patients received <sup>131</sup>I after surgery. A second surgical re-exploration was performed in 30 (34.8%) patients, and 7 patients required 3 or more additional LND. In a mean follow-up of 59.4 ± 39 months, 51 (59.3%) patients are clinically, radiologically and biochemically free of disease.

**Conclusions** In this series, compartment-oriented lymph node resection of recurrent papillary thyroid carcinoma leads to a final clinical and biochemical disease-free status of 59.3% with 6.9% of major complications.

## Introduction

Papillary thyroid carcinoma (PTC) is a slowly progressing tumor, with a high cure rate and survival. Its incidence has increased, in part due to the development of better diagnostic tools and an increased use of thyroid imaging [1]. Primary treatment of PTC is surgery which includes resection of the thyroid and the affected lymph nodes (LN), followed in most patients by an ablative dose of <sup>131</sup>I.

Despite the fact that up to 80% of lymph nodes (LN) from the central compartment (CC) have microscopic involvement at the time of surgery, recurrence after

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surgical treatment and  $^{131}\text{I}$  administration ranges from 5 to 30% [2–5]. This can rise up to 60% when invasion to LN of the lateral compartment (LC) is present.

The main risk factors associated with recurrence of PTC are: age >45 years, male gender, tall cell variant, bigger tumor size, multifocality, capsule disruption, soft tissue extension, affected LN > 30%, metastatic LN in the LC, presence of thyroid stimulating immunoglobulin, p53 mutation and BRAF mutation [6–10]. The recurrence pattern, however, has been less frequently studied [2, 3, 11–13].

PTC-related mortality is less than 1%; treatment goals are to reduce recurrence, persistence and associated morbidity [10]. The main recurrence site of PTC is residual LN of the neck, being 19–65% in the CC and 5–50% in the ipsilateral LC of the main tumor [14–17]. Distant metastases present principally to the lungs and occur in close to 2% of the patients [18, 19].

Ideal treatment for recurrent PTC is also surgical, although other methods such as  $^{131}\text{I}$  or alcohol ablation can be used [10, 19–22]. Complete LND of the affected cervical compartments should be performed, unless previous complete compartment LND has been made. In that case, a selective approach is favored [10, 16, 21]. The main diagnostic methods for the detection of recurrence are a clinical examination, biochemical testing (thyroglobulin, Tg wash-out), imaging studies (US, CT, body scan), and fine-needle aspiration (FNA) [16, 23].

Morbidity associated with a cervical surgical reoperation is closely related to the recurrence site. Most frequent complications include hypoparathyroidism, vocal cord palsy, cervical nerve injury and chyle leak [21]. These complications negatively impact the quality of life [10, 24]. The cure is defined as serum Tg levels <2 ng/dL without clinical evidence of gross disease [10, 25, 26].

This study evaluates the effect of compartment-oriented LN dissection (LND) on clinical and biochemical cure rate as well as the related complications and recurrence pattern.

## Patients and methods

A retrospective cohort study was performed. All patients undergoing LND for the first recurrence of PTC between 2000 and 2015 were included. Demography, characteristics of the initial operation, morbidity, usage of  $^{131}\text{I}$ , site of recurrence, Tg levels before and after surgical reintervention, additional LND and final outcome were registered. Exclusion criteria included the presence of antithyroid antibodies or distant metastases at the time of LN recurrence as well as the existence of a second malignancy.

All patients were followed by cervical US, and in selected cases, additional imaging studies were performed

(TBS, CT, SPECT, PET). In most cases, recurrence was confirmed by FNA cytology and Tg measurement in the biopsied specimen.

Surgical exploration was planned in accordance with the preoperative imaging and the extent of the initial operation. Operative findings and complications were recorded. Cure was considered when no structural disease (clinical or radiological) was found and serum Tg was <2 ng/dL.

## Results

From 2000 to 2015, 155 patients were diagnosed with recurrent PTC. LND was performed on 141. From these 141 patients, 55 patients were excluded due to concomitant metastatic disease (38), the presence of a second malignancy (14) or insufficient follow-up. Distant metastases were ruled by CT or total body scan after  $^{131}\text{I}$  in 8. Therefore, the study group included 86 patients: 11 were men (12.7%) and 75 women (87.2%). Mean age at recurrence was  $42.8 \pm 14.6$  years. The initial surgery had been performed in our institution in 80.2% of the patients. Total thyroidectomy was performed in 77 patients and some form of LND in 67 (77.9%).

The diagnosis of PTC was confirmed in all patients. The most common histological type was the classical pattern (84.8%). Fifty-six patients (65.11%) had at least one positive metastatic lymph node at the time of the initial surgery, and 53.4% had more than 30% of positive nodes in the specimen. Staging of the initial resection is shown in Table 1. The presence of some indicators of aggressive disease behavior according to the modified 2015 ATA guidelines [10] is shown in Table 2. After initial surgery, 90.6% of patients received at least one dose of  $^{131}\text{I}$ , (100–250 mCu per dose, max 3). Serum Tg was measured after the primary procedure in 82/86 patients, and it was >2 ng/dL, in 21 (24.4%). This group of patients had no clinical evidence of disease after the initial surgery but may represent biochemical persistent disease. Mean time between the initial surgery and the diagnosis of recurrence was 30.9 months in the group of patients who had Tg > 2 ng/dL and 52.5 months in those whose Tg after the initial operation was <2 ng/dL.

Seventy-eight patients (90.6%) received RAI after the primary procedure, and total body scan was performed after ablation. Residual uptake in the thyroid bed was detected in all of them. In addition, abnormal uptake in the lateral neck was found in 9 patients and in the mediastinum in 4. Tg was >2 ng/dL in 6 of these 13 patients and normalized over time in 1. The remaining 7 patients had normal Tg. Some of these patients may be classified as patients with persistent disease. Mean time between the initial surgery and the diagnosis of recurrence was

**Table 1** TNM staging at diagnosis

Patient age <45 years old at diagnosis				Patients
I	Any T	Any N	M0	
II	Any T	Any N	M1	0
Patient age >45 years old at diagnosis				Patients
I	T1a	N0	M0	
	T1b	N0	M0	1
	T1a	Nx	M0	3
	T1b	Nx	M0	1
II	T2	N0	M0	0
III	T1a	N1a	M0	1
	T1b	N1a	M0	0
	T2	N1a	M0	0
	T3	N0	M0	2
	T3	N1a	M0	7
	T3	Nx	M0	4
IVa	T1A	N1b	M0	0
	T1B	N1b	M0	0
	T2	N1b	M0	1
	T3	N1b	M0	9
	T4a	N0	M0	1
	T4a	N1a	M0	1
	T4a	N1b	M0	0
	T4a	Nx	M0	1
IVb	T4b	Any N	M0	0
IVc	Any T	Any N	M1	0
Total				86

**Table 2** Presence of indicators of aggressive disease according to the modified 2015 ATA guidelines

Indicators of aggressive behavior	N (%)
LN metastases	56 (65.1)
Tumor invasion to adjacent structures	53 (61.6)
Vascular invasion	29 (33.7)
Aggressive histology	8 (9.3)
Multifocal papillary carcinoma	39 (45.3)
Incomplete resection	4 (4.6%)
RAI-avid metastatic foci in the neck in the first post-treatment whole-body RAI scan	9 (10.4%)

27.0 ± 29.4 months in the group of patients who had abnormal uptake and 56.3 ± 70.9 months in those who had only residual uptake to the thyroid bed after the initial operation.

Non-stimulated serum Tg > 2 ng/dL at the time of the diagnosis of LN metastasis was seen in 32 patients (37.2%). Mean values were 10.3 ± 27.5 ng/dL. We identified suspicious LN by US in all patients. FNA was performed in 82.5% of patients. The cytological diagnosis of LN

**Table 3** Recurrence site to different compartments

Compartment	No. of patients
Homolateral Lateral Alone	46.5% (40)
Contralateral Lateral Alone	16.2% (14)
Bilateral Lateral	10.4% (9)
Homolateral Central and Homolateral Lateral	9.3% (8)
Homolateral Central Alone	8.1% (7)
Contralateral Central and Contralateral Lateral	3.4% (3)
Bilateral Central	1.1% (1)
Homolateral Central and Contralateral Lateral	1.1% (1)
Homolateral Central and Bilateral Lateral	1.1% (1)
Contralateral Central and Bilateral Lateral	1.1% (1)
Bilateral Central and Bilateral Lateral	1.1% (1)
Contralateral Central and Homolateral Lateral	0
Contralateral Central Alone	0
Bilateral Central and Homolateral Lateral	0
Bilateral Central and Contralateral Lateral	0

**Table 4** Type of the performed lymph node dissection

Compartment	Compartmental approach	Selective approach
Right Central	9	9
Left Central	6	9
Right Lateral	34	15
Left Lateral	36	12

metastasis was established in 63 patients (87.5%). Tg measurements in the FNA wash-out were performed in 51 patients. It was >10 ng/dL in 82% of the group who had serum Tg values <2 ng/dL and in 86.9% of those who had serum Tg > 2 ng/dL, respectively. In terms of the site of recurrence, the most common site of recurrence was the lateral compartment on the same side of the primary thyroid tumor at 46.5% (Table 3).

Lymph node dissection of the CC alone was performed in 8.1%. This includes patients who had and did not have central LND during initial operation. The LC was dissected in 73.2%, and both the CC and the LC were dissected in 18.6% (Table 4). LN were confirmed in the specimen in 98.8% of patients, with a mean number of metastatic and resected LN of 2.43/4.5 from the CC (range 0–20 dissected LN, 0–20 metastatic LN) and 2.41/14.4 from the LC (range 0–46 dissected LN, 0–12 metastatic LN). Parathyroid tissue was identified in the resected specimen in 6.9% (6) patients, one of them with transient hypocalcemia.

Major complications occurred in 6.9% (6) patients. There were 2 cervical hematomas that required surgical drainage, 1 permanent hypoparathyroidism, 1 phrenic nerve palsy, 1 surgical site infection and 1 chyle leak that required surgical closure.

**Table 5** Cure rate after subsequent LND

Number of LND	Number of patients	Achieved cure status	%
1	86	40	46.5
2	30	10	33.3
3	6	1	16.6
>3	2	0	0
Total	86	51	59.3

Seventy-two percent of patients received a mean dose of  $^{131}\text{I}$  of 175mCu after LND. Serum Tg was measured 6 months after surgery for the local recurrence, and 67 patients (77.9%) had a non-stimulated Tg < 2 ng/dL. During follow-up, 30 patients (34.8%) required surgical reintervention for recurrent disease. Mean time for the second recurrence was 2.3 years. Cure after the first LND was achieved in 40 patients (46.5%), in 10 patients (33.3%) after the second LND and in one additional patient after the third LND. No further LND achieved a cure status in the remaining patients (Table 5).

After a mean follow-up of  $59.4 \pm 39$  months, 51 (59.3%) patients are both clinically and biochemically free of disease, 36 (41.8%) have a persistent disease, and four (4.6%) have died. One patient died from locoregional disease, an additional patient from locoregional + metastatic disease, one from a pulmonary embolism and one from an unknown cause. Both of them had metastatic disease at last follow-up (Fig. 1).

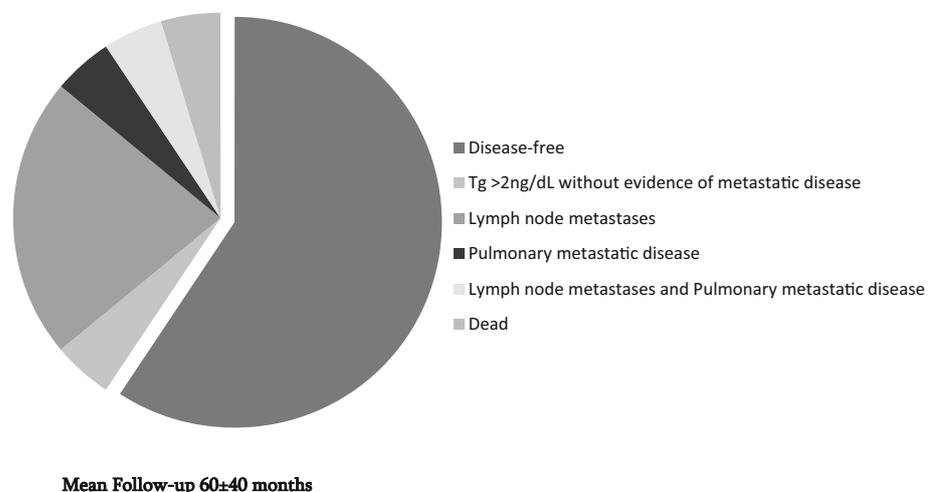
## Discussion

Once LN regional recurrence of PTC is identified, LND is the suggested treatment for most patients [10]. Most PTC recurs within 5 years after diagnosis, and mean time among

different series [2, 4, 25, 27–38] is 29 months (range 21–36) (Table 6). Our time of recurrence of 51.9 months was significantly more prolonged than the time reported in other series, which may be influenced by the lack of patients' adherence to follow-up in some cases.

Serum non-stimulated Tg is useful in detecting recurrence, which can be biochemically confirmed by stimulated Tg and localized by imaging techniques. It has been recognized that some patients may have low values of Tg in the presence of recurrence. Hughes [4] found that 3/61 patients (4.9%) had stimulated Tg levels <2 ng/dL, Al-Saif [30] found that 15/70 patients (21.4%) had non-stimulated Tg < 2 ng/dL, and Lang [39] found that 27/81 patients (33.3%) had stimulated TG < 2 ng/dL. Non-stimulated Tg < 2 ng/dL was found in 53 (61.6%) of our patients.

Among the imaging studies, US has been the most commonly used to document and localize LN recurrence due to lack of radiation and great sensitivity/specificity [23]. In our study, all patients underwent US evaluation and the morphologic findings suggestive of the disease were found in all patients. Other imaging techniques such as CT or whole-body gamma scan were rarely used and therefore were not analyzed in the study. Despite the demonstration of suspicious LN by US, the diagnosis of metastatic PTC was confirmed by cytology or Tg measurement in the wash-out of the FNA in more than 80% of the patients. In a study by Lesnik et al. [23] where the accuracy of US alone, CT alone and the combination of both was compared in patients undergoing primary and reoperative surgery, the authors found that in the reoperative situation, the combination of US and CT had higher sensitivity for the identification of LN in both the CC (88%) and the LC (93%) than the US or the CT alone, leading to change in the surgical strategy in 27% of patients.

**Fig. 1** Patient outcomes at the last follow-up

**Table 6** Comparative of mean metastatic lymph nodes, recurrence site and cure rate

Authors	Patients	Follow-up	Time to recurrence	<sup>131</sup> I administration	Metastatic LN (mean)	Recurrence site CC/LC/both	Serium Tg	Cutoff value	No evidence of disease	No structural disease
Rubello et al. [27]	31	2–24	27.3	100%	5.9	29%/58%/13%	NR	NR	NR	80.6%
McCoy et al. [28]	24	18	NR	NR	NR	NR	Both	<2	50%	NR
Lee 2008 [29]	15	30	NR	NR	NR	33%/20%/47%	Both	<2	64%	100%
Al-Saif et al. [30]	90	60	36	100%	2	54%/30%/16%	Both	<0.9	27%	NR
Clayman et al. [31]	210	87	21	77%	7	24%/0%/76%	Stimulated	NR	66%	74%
Schuff [25]	75	6	NR	NR	7	18%7%/75%	Both	<2	41%	72%
Roh et al. [2]	22	32	NR	73%	6.9	0%/64%/36%	NR	NR	NR	91%
Tufano et al. [32]	120	41.5	36	NR	2	41%/0%/59%	Both	NR	NR	100%
Shaha [33]	27	28	NR	NR	NR	42%/0%/58%	Both	<1	56%	80%
Hughes et al. [4]	61	15.5	24.7	89%	NR	22%/45%/33%	Non-Stimulated	<2	21%	72%
Harari et al. [34]	44	2–24	NR	NR	NR	28%/51%/21%	NR	<2	42%	51%
Lang et al. [35]	81	89.5	33.6	100%	4	10%/70%/20%	Stimulated	<2	32.1%	NR
Lee et al. [36]	151	57.5	25.7	93%	3	31.8%/67.5%	Stimulated	<1	51.5%	84%
Salari et al. [37]	181	40	NR	87%	2	NR	Stimulated	<0.2	58%	NR
Chéreau et al. [38]	102	100	19	100%	NR	4.9%/61.7%/143.7%	NR	NR	84%	NR
Current series 2017	86	59	51	90%	3.3	8%/73%/18%	Non-stimulated	<2	59.3%	63.9%

Modified from Urken [22]

LN lymph node, CC central compartment, LC lateral compartment, Tg thyroglobulin, NR not reported

In this study, the most common site of recurrence was the lateral compartment, ipsilateral to the largest thyroid tumor. This finding has been persistently reported in some series [3, 4, 12, 15], whereas other authors have found that the most common site for recurrence is the central compartment [2, 13]. A potential explanation for differences in the pattern of LN recurrence is the extent of the disease at initial surgery and the type of surgery. For example, Conzo et al. [13] analyzed 210 patients with localized PTC who underwent TT without LND. In a mean follow-up of 28 months, recurrence was found in nine patients (4.2%), in 6 to the central and 3 to the lateral compartment. De Meer et al. [11], on the other hand, analyzed the recurrence pattern of 97 patients with LN involvement at the initial surgery. From the 33 patients (34%) with LN metastases in the central compartment (N1a), 10 (30%) presented LN recurrence in a mean follow-up of 44 months. By contrast, 36 of the 61 patients (59%) who had lateral LN metastases

at initial surgery (N1b) developed recurrence in a mean follow-up of 7 months.

Patients developing LN recurrence may represent a particular subset of patients with more aggressive tumors. In our series, 65% of the patients who recurred presented with LN metastases at the time of the initial surgery. There has been widespread interest in identifying potential indicators of LN metastases. In a study from O'Neill et al. [3], a close association between elevated serum Tg at 12 months postoperatively and the percentage of recurrence to the LN was found, suggesting closer follow-up in these patients. In a study from the Netherlands [11], a higher rate of recurrence was found in the group of patients who presented with LN metastases to the LC at the time of the initial operation. Yim et al. [26] found an association between serum Tg > 5 ng/dL after the first LND and the development of a subsequent recurrence. It was interesting to see that despite the fact that 77.9% of patients achieved

**Table 7** Comparison of major complications after lymph node dissection

Authors	Patients	Cervical hematoma	Nerve palsy	Hypoparathyroidism	Chyle leak	Other	Total (%)
Al-Saif et al. [30]	90	NR	0	0	1	NR	1.4
Roh et al. [2]	22	0	4	2	1	0	17.1
Tufano et al. [32]	120	0	0	3	0	0	2.7
Hughes et al. [4]	61	NR	0	0	1	2	5
Lang et al. [35]	81	NR	1	0	NR	2	9.2
Onkendi et al. [40]	410	7	2	13	7	10	9.5
Lee et al. [36]	151	1	1	4	3	0	6.3
Salari et al. [37]	181	3	0	6	3	4	8.8
Cheréau et al. [38]	102	1	1	0	1	1	3.9
Current series 2017	86	2	0	1	1	2	6.9
Mean values	130.4	2	0.9	2.9	2	2.33	7.08

levels of non-stimulated Tg < 2 ng/dL after the first surgical reoperation, 32.8% of these and 42.1% of those with Tg > 2 ng/dL required a second reoperation to resect metastatic LN.

The mean number of resected and metastatic LN during the first reoperation was  $4.5 \pm 5.0$  and  $2.4 \pm 4.4$  from the CC,  $14.4 \pm 14.3$  and  $2.41 \pm 2.7$  from the LC. Some authors have reported a similar number of metastatic LN when dissection is performed in the CC and 6.8 when both the CC and the LC are dissected [2, 25, 27, 30–32, 35–37] (Table 6).

Major complications occurred in six patients (6.9%). Our complication rate is contrasted to other series [2, 4, 30, 32, 35–38, 40] in Table 7. We can observe they range from 1.4 to 17.1%, being hypoparathyroidism the most common of them followed by chyle leak and cervical hematoma. None of our patients developed recurrent laryngeal nerve palsy.

## Conclusions

From the analysis of our series, we can see that 59.3% achieved a disease-free status after LN dissection. Patients with recurrent PTC required an average of 1.36 surgical reoperations, with a complication rate of 6.9%. We recognize as limitations of our study the retrospective nature and the small sample size.

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