Original Article

Predictive factors and pattern of locoregional recurrence after prophylactic central neck dissection in papillary thyroid carcinoma

Running head: Post-ablation Tg predicted local recurrence

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SYNOPSIS

Locoregional recurrence (LRR) rate after total thyroidectomy and prophylactic unilateral central neck dissection was 1% per year in the first 5 years and dropped to 0.2% per year in the next 5 years. Most (78.6%) LRRs involved the lateral compartment. Post-ablation stimulated thyroglobulin independently predicted LRR risk.

ABSTRACT

Background:

Prophylactic central neck dissection (pCND) at the time of the total thyroidectomy (TT) remains controversial in clinically nodal-negative (cN0) papillary thyroid carcinoma. Our study aimed to examine the predictive factors and pattern of locoregional recurrence (LRR) after pCND in the context of the postoperative sTg level.

Methods:

Three-hundred and forty-one patients who underwent TT and unilateral pCND were analyzed. Patients with an identifiable lesion on ultrasonography or whole-body scan within 6 months of surgery were excluded. A LRR was defined as an identifiable lesion on USG which was later confirmed by cytology/histology. Pre-ablation stimulated Tg (sTg) level was taken 2 months after surgery while post-ablation sTg level was taken 8 months after surgery. Cox regression was used in the univariate and multivariate analyses to identify significant independent factors for LRR.

Results:

After a follow-up of 66.6 ± 38.6 months, 14 (4.1%) suffered from LRR. The duration to first LRR was 36.4 ± 21.7 months. The estimated 5- and 10-year LRR rates were 5.1% and 6.1%, respectively. Of these 14 LRR, 3 (21.4%) involved the central compartment alone, 9 (64.3%) involved the lateral compartment alone and 2 (14.3%) involved both central and lateral compartments. After adjusting for other clinicopathological factors, post-ablation sTg level

≥1ug/L (HR=265.109,95%CI=1.132 – 62075.644,*p*=0.045) was the only independent predictor of LRR.

Conclusions:

Annualized risk of LRR after pCND was around 1% in the first 5 years and 0.2% in the subsequent 5 years. Most (78.6%) LRRs involved the lateral compartment. Post-ablation sTg ≥1ug/L significantly predicted risk of LRR.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma with an age-adjusted incidence doubled over the last 20 years [1,2]. Despite its relatively good prognosis, locoregional recurrence (LRR) is common [3]. With recognition of the concept of step-wise progression of nodal metastasis from the central (level VI) to the lateral compartment (levels II-V) and preoperative ultrasonography (USG) only identifies roughly half of the central nodal metastasis (CNM), routine prophylactic central neck dissection (pCND) at the time of the total thyroidectomy (TT) has been advocated [4-6]. However, this remains controversial in clinically nodal-negative (cN0) PTC [7]. Although pCND may reduce of LRR in the short-term, it is at the expense of higher morbidity and cost [8,9].

Despite the increasing number of studies assessing the value of pCND, few studies have focused on evaluating the predictive factors and pattern of short to medium term LRR after pCND. Given that pCND is increasingly being performed, a better understanding of these factors and pattern may not only help to assess risk of LRR but also tailor decisions regarding the need for adjuvant therapy (such as radioactive iodine (RAI) ablation, degree of thyrotrophin suppression) and frequency of surveillance after pCND. Although studies have identified clinicopathologic factors predictive of LRR and nodal recurrence after pCND [10-12], these factors were not evaluated in the context of the biochemical response after initial operation and RAI ablation. It has been recognized that the biochemical response to treatment (namely, post-surgical thyroglobulin (Tg) levels) is a significant predictor of recurrence in low-risk PTC [7,13-15]. In view of these findings, our study aimed to examine predictive factors and pattern of LRR in cN0 PTC after pCND in the context of the postoperative sTg level.

PATIENTS AND METHODS

Patients

From July 2003 – June 2013, 351 consecutive patients with cN0 PTC underwent surgery at our institution. To exclude the possibility of residual disease due to inadequate preoperative assessment and/or surgical resection, those with identifiable locoregional disease on USG or post-RAI whole-body scan (WBS) within 6 months of surgery were excluded. Therefore 341 (97.2%) patients were eligible for analysis. All post-surgical patients were followed up within 4 weeks in a multi-disciplinary oncology clinic. A follow-up visit was conducted at 3-month intervals in the first 2 years, 6-month in the subsequent 3 years and annually thereafter. Clinical examination, neck USG and non-stimulated Tg level were done during the follow-up visit. Locoregional recurrence (LRR) was made by a combination of basal Tg trend, USG, CT/ MRI or FDG-PET scan and confirmed by fine needle aspiration cytology (FNAC). LRR was defined as an identifiable lesion on USG which was later confirmed on FNAC and/or histology. The side and location of LRR was recorded. To ensure complete follow-up data of all 341 patients, a careful manual search of all patients' status in the territory-wide Clinical Management System (CMS) was performed. The CMS is a computerized database linking up all public hospitals within our region.

Methods

All relevant clinical, laboratory, radiologic, and perioperative data were collected prospectively and follow-up data were regularly updated in a computerized database. Details of surgical treatment, criteria for radioactive iodine (RAI) ablation and follow-up protocol had been described previously.[16,17] Total thyroidectomy was the preferred procedure for PTC ≥1cm. A routine ipsilateral pCND was performed for all regardless of tumor extent. The pCND consisted

of the removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally from the medial border of common carotid artery to the midline of the trachea. The ipsilateral recurrent laryngeal nerve was mobilized along its entire cervical course. An intraoperative nerve stimulator was used to confirm its functional integrity [18]. Parathyroid autotransplantation was readily performed.

Serum calcium and phosphate levels were measured postoperatively. Calcium +/- vitamin D supplements were prescribed if symptomatic or calcium <1.70mmol/L. Those who discontinued supplements in the presence of normocalcemia within 6 months were considered temporary and those who needed for >6 months were considered permanent hypoparathyroidism. Perioperative direct laryngoscopy was performed to assess vocal cord function. Vocal cord palsy (VCP) lasting > 6 months was regarded permanent.

All postoperative Tg levels were measured at the same laboratory using the same immunometric assay. The assay used was the Immulite 2000 (Diagnostic Products Corp. Roche, Los Angeles, CA). This was calibrated against the CRM- 457 standard. Normal reference range was <0.5 – 55 ug/L and sensitivity was <0.2 ug/L).Stimulated Tg (sTg) was defined as a Tg level measured in the presence of TSH >30 ug/L either by thyroxine withdrawal or recombinant TSH injections. The pre-ablation sTg level was taken approximately 2 months after surgery while the post-ablation level was taken approximately 8 months after surgery (6-7 months after RAI ablation). Tg autoantibodies were measured at the same time and those with elevated Tg autoantibodies were excluded from Tg analysis. The decision for RAI ablation was based on presence of ≥1 risk factors such as tumor size >1.5cm, CNM, extrathyroidal extension and microscopic positive margin. Three giga-Becquerels (GBq) or 80millicuries (mCi) I131 was given as a standard fixed ablative dose.

Statistical analysis

Statistical analysis was performed by chi-square or Fisher's Exact test to compare categorical variables, and Mann-Whitney U was used to compare continuous variables between groups. For correlation between two continuous variables, the Pearson correlation test was performed. Continuous variables were expressed as mean±SD. LRR rate was estimated using the Kaplan-Meier method. Variables which were significant in the univariate analysis were entered into multivariate analysis. Cox regression analysis with a variable entrance criterion of 0.05 or less was conducted to identify independent factors. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Our cohort was mostly females (81.5%) and ethnic Chinese (88.0%). The mean age at operation was 49.0 ± 14.6 years old. The mean (±SD) tumor size was 1.73 ± 1.12cm. The mean (±SD) total number of CLNs and positives CLNs retrieved after unilateral pCND were 7.2 ± 4.1 and 1.8 ± 2.3, respectively. The incidence of CNM was 22.3%. In terms of surgical morbidity, 19 (5.6%) suffered from temporary VCP while 2 (0.6%) developed permanent VCP. Four (1.2%) patients developed permanent hypoparathyroidism while 44 (12.9%) patients suffered from temporary hypoparathyroidism. After a mean follow-up of 66.6 ± 38.6 months, all patients were still alive. There were 14 patients with LRR. Of these 14 LRR, 3 involved the central compartment alone while 9 involved the lateral compartment alone and 2 involved both central and lateral compartments. There were no recurrences in the thyroid bed or tracheal wall. The mean duration to first LRR was 36.4 ± 21.7 months. The estimated 5- and 10-year LRR rates were 5.1% and 6.1%, respectively.

Table 1 shows a comparison of clinicopathological features between those with LRR (group I) and those without LRR (group II). Extrathyroidal extension, multifocality and lymphovascular invasion (LVI) and CNM were significantly more common in group I ($p<0.05$). However, among those with tumor multifocality, those with ≥3 tumor foci were not associated with a higher LRR rate than 2 foci (6/53 vs. 8/62, $p=1.000$). Central lymph node ratio (CLNR) was significantly higher in group I than II (72.9% vs. 24.2%, $p=0.010$). Both pre-ablation sTg and post-ablation sTg levels were significantly higher in group I than II (11.2 vs. 7.5ug/L,$p<0.001$ and 6.2 vs. 3.8 ug/L,$p<0.001$).

Table 2 shows the univariate analysis of LRR using Cox-regression. Similar to the direct comparison between group I and II, tumor multifocality, LVI, CLNR, CNM, pre-ablation sTg and post-ablation sTg were significantly associated with rate of LRR.

Table 3a shows the multivariate analysis of clinicopathological factors for LRR. Both tumor multifocality (HR=6.783, 95%CI=1.440 – 31.957,*p*=0.015) and CNM (HR=6.713, 95%CI=1.613 – 27.936,*p*=0.009) were independent prognostic predictors for higher LRR.

Table 3b shows the multivariate analysis of all factors for LRR. Since pre-ablation sTg and post-ablation were inter-related, both were entered in a separate Cox-regression for LRR and post-ablation sTg was the only significant factor of the two (*data not shown*). Therefore, only five significant factors (not including pre-ablation sTg) were entered into the multivariate analysis. After adjusting for the other four clinicopathological factors, post-ablation sTg level (HR=1.017; 95%CI=1.001 – 1.054,*p*=0.041) was the only independent predictor. When post-ablation sTg was entered as a categorical variable (<1, ≥1ug/L), HR (95%CI) became 265.109 (1.132 – 62075.644), *p*=0.045. After excluding those with Tg autoantibodies, if patients were categorized into 3 groups based on post-ablation sTg level (<1ug/L (n=216), ≥1ug/L but <10.0ug/L (n=67) and ≥10.0ug/L (n=31)), the 10-year LRR rates were 0.0%, 23.3% and 33.7%, respectively (*p*<0.001). Figure 1 shows the cumulative LRR curves between these three groups.

Table 4 shows a summary of the 14 patients who developed LRR after pCND. None of these patients had detectable Tg autoantibodies. The lowest post-ablation sTg to develop LRR was 1.1ug/L and that patient developed LRR 31.7 months after pCND. Nine of the 14 patients with LRR had post-ablation sTg ≥1ug/L but <10.0ug/L and the other 5 patients had post-ablation sTg ≥ 10.0ug/L. There was no significant correlation between CLNR and time to LRR (ρ=0.250, *p*=0.388) or between post-ablation sTg and time to LRR (ρ=0.041, *p*=0.888).

DISCUSSION

This was one of the first studies aimed at evaluating the predictive factors and pattern of cN0 PTC after pCND in the context of postoperative sTg levels. Unlike previous studies, our analysis only analyzed patients with no identifiable lesion on USG and WBS within 6 months of initial operation. Our data showed that the chance of LRR was very low. The 5- and 10-year LRR rates were 5.1% and 6.1%, respectively. These data implied that the estimated LRR rate for the first 5 years was approximately 1% per year and dropped to an even lower level (approximately 0.2% per year) for the subsequent 5 years. Barczynski *et al.* reported similar results in a large cohort and found the 5- and 10-year LRR rates after bilateral pCND to be 4.3% and 5.5%, respectively [18]. Kruijff *et al.* also recently reported similar rates with 5- and 10-year rates of 5% and 8%, respectively, although their cohort did not comprise entirely cN0 PTC patients [19]. Hartl *et al.* reported an even lower LRR rate when their 317 patients who underwent both bilateral pCND and prophylactic ipsilateral lateral neck dissection were analyzed. They reported that only 2 (0.6%) patients developed LRR after a median follow-up of 4 years [20]. However, given the likelihood of higher morbidity in a disease with an already excellent prognosis, the cost benefit ratio of routine lateral neck dissection would be questionable [21].

In terms of the pattern of LRR, our data showed that the majority of LRR (11/14 or 78.6%) were mostly located in the lateral compartment. Of the 14 LRRs, 9 (64.3%) were solely confined to the lateral compartment while 3 (21.4%) occurred solely in the central compartment. Kruijff *et al.* reported that the rate of structural LRR in the lateral compartment almost doubled that of the central compartment after a more liberal use of unilateral pCND at the time of TT (67% vs. 32%, $p<0.01$) [19]. Barczynski *et al.* reported a higher difference in LRR rate between lateral and central compartments after bilateral pCND (93.8% vs. 6.3%) [19]. In terms of which was the

most frequent involved side (relative to that of the primary tumor), the ipsilateral side was significantly more likely as the first site of LRR than contralateral side (72.7% vs. 9.1%). This finding agrees with previous studies [10-12,18-20] and could be explained by the step-wise progression of nodal metastasis originating from the ipsilateral central to ipsilateral lateral compartment [4]. In fact, since all 14 patients with LRR had at least one CLN containing metastasis (pN1a) at initial operation, we postulate that perhaps some of these patients with LRR might have had small volume of disease in the lateral compartment(s) which was present at initial operation but remained undetectable by USG and WBS in 6 months after surgery. This postulation is supported by the fact that both the pre-ablation sTg and post-ablation sTg levels were significantly higher in those with than without LRR and therefore, this implied that there was a small volume of residual disease which was detectable biochemically but not radiologically.

In terms of which factors might help in predicting LRR, our data found post-ablation sTg level to be the most significant predictor for LRR. Although, previous studies have identified several clinicopathologic factors such as tumor size, CNM and CLNR to be associated with higher LRR, they did not analyze them in the context of post-surgical sTg levels. Several studies including the 2009 revised American Thyroid Association guidelines have emphasized the importance of the biochemical response to treatment and found that incorporating it into the traditional risk stratification (or the so-called “dynamic risk assessment”) could provide a more accurate assessment on recurrence risk [7,23,24]. Based on the classification of response to initial therapy 6-24 months after RAI as described by Tuttle *et al*., 9 of our 14 LRRs would have been classified as “acceptable response” while the other 5 as “incomplete response”. According to the same study, half of the latter group would have harbored structurally identifiable disease [23].

The implications are firstly, the biochemical response after treatment remained the most important predictor of LRR after TT and unilateral pCND. Our multivariate analysis (Table 3b) confirmed that post-ablation sTg was most significant among other clinicopathologic factors described in this and other studies [19,20]. Nevertheless, since post-ablation sTg is not available before RAI, multifocality and CNM remained important in the decision for RAI (Table 3a). Secondly, those with post-ablation sTg<1 ug/L had little to no LRR risk whereas those with post-ablation sTg ≥1 ug/L had significantly higher LRR risk. Perhaps, this higher risk group should undergo longer TSH suppression and more intense surveillance studies, although the real benefits of these measures on recurrence or mortality remain unclear. On the other hand, those with lower risk might require less suppression and surveillance. Thirdly, since 11 (78.6%) LRR had some lateral compartment involvement, perhaps those patients at-risk of LRR should have more careful follow-up studies on their lateral compartments especially in the first 5 years of surgery.

Despite these findings, our data should be interpreted cautiously as this was a moderate-sized retrospective study with relatively short follow-up and few LRR. Furthermore, since all pCND were unilateral, contralateral CNM could not be completely ruled out. Nevertheless, our data only showed a low incidence of LRR (3/14) occurring in the contralateral side. Given the higher morbidity in bilateral pCND, we still believe unilateral pCND might be more preferable. Another shortcoming was that the few patients with post-ablation sTg ≥ 1ug/L might have overly exaggerated the percentages of LRR.

Conclusion

The incidence of LRR after seemingly curative TT with pCND was around 1% in the first 5 years and 0.2% in the subsequent 5 years. Of these LRRs, the majority (78.6%) involved the

lateral compartment while the other 21.4% involved the central compartment only. The post-ablation sTg was the most significant predictor of LRR with a tendency for higher rate of LRR with post-ablation sTg levels ≥1.0ug/L.

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Table 1. A comparison of clinicopathological characteristics between those with locoregional recurrence (Group I) and those without (Group II)

Variables	**Group I (n=14)**	**Group II (n=327)**	***p*-value**
Age (years)	48.9 ± 15.7	49.1 ± 14.5	0.797
Sex (male : female)	2 : 12	61 : 266	0.889
Presented as a palpable swelling	11 (78.6)	235 (71.9)	0.358
Preoperative serum TSH (mIU/L)	1.0 ± 0.3	1.4 ± 1.2	0.408
Tumor size (cm) - >1.5cm	1.9 ± 0.9 7 (50.0)	1.7 ± 1.1 128 (39.1)	0.517 0.418
Extrathyroidal extension	6 (42.9)	83 (25.4)	**0.041**
Multifocality	9 (64.3)	96 (29.4)	**0.008**
Lymphovascular invasion	5 (35.7)	39 (11.9)	**0.009**
Coexisting thyroiditis	2 (14.3)	52 (15.9)	0.651
Tumor bilaterality	2 (14.3)	64 (19.6)	0.557
Number of CLNs retrieved	5.2 ± 1.5	7.3 ± 4.2	0.683
Number of positive CLNs retrieved	3.6 ± 1.6	1.7 ± 2.3	0.096

CLNR	72.9 ± 27.6	24.2 ± 27.8	**0.010**
CNM (pN1a)	14 (100.0)	62 (19.0)	**<0.001**
Stage by *TNM* - Stage I / II - Stage III / IV	 10 (71.4) 4 (28.6)	 214 (65.4) 113 (34.6)	0.105
MACIS score	5.2 ± 5.0	4.9 ± 4.6	0.531
RAI ablation	14 (100.0)	239 (73.1)	0.110
Pre-ablation sTg (ug/L)#	11.2 ± 11.4	7.5 ± 13.6	**<0.001**
Post-ablation sTg (ug/L)#	6.2 ± 10.9	3.8 ± 5.8	**<0.001**

Abbreviations: TSH = Thyroid stimulating hormone; CLNR = central lymph node ratio; CNM = central nodal metastasis; *TNM* = 7th edition Tumor, Node and Metastasis staging system; MACIS = Metastases, Age, Completeness of surgery, Invasion and Size; RAI = radioiodine; sTg = stimulated thyroglobulin

#excluding those with Tg autoantibodies

Table 2. Univariate analysis of factors associated with locoregional recurrence after unilateral prophylactic central neck dissection

	Univariate analysis		
Variables	**Hazard ratio**	**95% CI**	***p*-value**
Age	1.003	0.968 – 1.039	0.883
Female sex	0.791	0.176 – 3.546	0.760
Preoperative TSH level	1.821	0.517 – 6.452	0.351
Primary tumor size	1.021	0.623 – 1.675	0.934
Extrathyroidal extension	2.869	0.875 – 9.410	0.082
Tumor multifocality	10.422	2.332 – 46.572	**0.002**
Lymphovascular invasion	1.587	1.000 – 2.521	**0.049**
Coexisting thyroiditis	1.242	0.258 – 5.984	0.787
Tumor bilaterality	1.266	0.649 – 2.468	0.489
No. of CLNs retrieved	0.887	0.724 – 1.087	0.248
No. of positive CLNs retrieved	1.141	0.885 – 1.471	0.309
CLNR	1.029	1.003 – 1.056	**0.029**
CNM (pN1a)	8.738	2.303 – 33.158	**0.001**
MACIS score	1.129	0.766 – 1.665	0.540
Radioiodine ablation	2.977	0.194 – 45.786	0.434
Pre-ablation sTg#	1.006	1.004 – 1.008	<**0.001**
Post-ablation sTg#	1.016	1.010 – 1.022	<**0.001**

Abbreviations: TSH = thyroid stimulating hormone; CLN = central lymph node; CNM = central

nodal metastases; CLNR = central lymph node ratio; CI = confidence interval

#excluding those with Tg autoantibodies

Table 3a. Multivariate analysis of clinicopathological factors only (i.e. factors available before radioiodine ablation) for locoregional recurrence after unilateral prophylactic central neck dissection

Covariates	**Hazard ratio**	**95% confidence interval**	***p*-value**
Tumor multifocality	6.783	1.440 – 31.957	**0.015**
Lymphovascular invasion	2.288	0.635 – 8.264	0.206
CLNR	1.022	0.991 – 1.053	0.168
CNM (pN1a)	6713	1.613 – 27.936	**0.009**

Table 3b. Multivariate analysis of all factors associated with locoregional recurrence after unilateral prophylactic central neck dissection

Covariates	**Hazard ratio**	**95% confidence interval**	***p*-value**
Tumor multifocality	3.062	0.192 – 48.938	0.429
Lymphovascular invasion	2.341	0.332 – 16.495	0.393
CLNR	1.011	0.972 – 1.052	0.584
CNM (pN1a)	1.973	0.875 – 2.15	0.966
Post-ablation sTg*	1.027	1.001 – 1.054	**0.041**

Abbreviations: CLNR = central lymph node ratio; CNM = central nodal metastases; sTg = stimulated thyroglobulin

*if entered as a categorical variable with a cut-off of ≥1ug/L, the HR (95%CI) became 265.109 (1.132 – 62075.644), *p*=0.045.

Table 4. A summary of the 14 patients with locoregional recurrence (LRR) after unilateral central neck dissection

	Age / Sex	ETE	Multifocality / no. of foci	LVI	CLNR	CNM	Post-ablation sTg (ug/L)#	Time to LRR (months)	Site of LRR (neck compartment)
Patient 1	62/F	+	+ / 2	+	7/9	+	12.0	97.2	Contralateral central
Patient 2	30/F	-	-	+	1/8	+	17.0	28.9	Ipsilateral lateral
Patient 3	20/M	+	+ / 2	-	3/3	+	8.7	50.0	Ipsilateral lateral
Patient 4	46/F	+	+ / 2	+	3/5	+	45.1	40.6	Bilateral lateral
Patient 5	44/F	-	+ / 2	-	4/5	+	3.9	24.4	Contralateral lateral
Patient 6	18/F	-	+ / 4	-	5/5	+	2.5	55.3	Ipsilateral lateral
Patient 7	54/F	-	+ / 6	-	1/5	+	9.7	18.7	Bilateral central
Patient 8	40/M	+	+ / 11	-	5/5	+	1.1	31.7	Ipsilateral central & lateral
Patient 9	51/F	-	-	-	4/5	+	22.5	29.1	Ipsilateral lateral

Patient 10	66/F	+	+ / 2	+	3/4	+	6.7	40.1	Contralateral central & lateral
Patient 11	54/F	-	-	-	3/5	+	13.4	14.9	Ipsilateral central
Patient 12	77/F	-	-	-	5/5	+	3.4	13.6	Ipsilateral lateral
Patient 13	56/F	-	-	-	4/5	+	3.7	44.7	Ipsilateral lateral
Patient 14	57/F	+	+ / 2	+	3/4	+	7.4	21.1	Ipsilateral lateral

Abbreviations: + = present ; - = absent ; ETE = extrathyroidal extension ; LVI = lymphovascular invasion ; CLNR = central lymph node ratio; CNM = central nodal metastasis

#none had Tg autoantobodies

LEGENDS

Figure 1. The cumulative locoregional recurrence curve of the three groups with post-ablation stimulated thyroglobulin level (<1ug/L (n=216), ≥1ug/L but <10.0ug/L (n=67) and ≥10.0ug/L (n=31)) after excluding those with Tg autoantibodies.