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Role of RAI in the management of incidental N1a disease in papillary thyroid cancer

Laura Y. Wang, MBBS*, Frank L. Palmer, BA*, Jocelyn C. Migliacci, MA*, Iain J. Nixon, MBChB*, Ashok R. Shaha, MD*, Jatin P. Shah, MD*, R. Michael Tuttle, MD†, Snehal G. Patel, MD*, and Ian Ganly, MD, PhD*

*Department of Surgery, Head and Neck Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

†Department of Medicine, Endocrine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

Abstract

Background—Following total thyroidectomy (TT) for papillary thyroid cancer (PTC), pathological assessment can occasionally reveal incidental perithyroidal lymph nodes (LNs) with occult metastases. These cN0pN1a patients often receive radioactive iodine (RAI) therapy for this indication alone. The aim of this study was to determine the central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

Methods—An institutional database of 3664 previously untreated patients with differentiated thyroid cancer operated between 1986 and 2010 was reviewed. 232 pT1-3 patients managed with TT and no neck dissection were subsequently found to have incidental level 6 LNs on pathology. Patients with other indications for RAI, such as extrathyroidal extension and close or positive margins, were excluded. One hundred and four patients remained for analysis. Kaplan-Meier method was used to determine central neck LN recurrence free survival (RFS).

Results—The median age of the cohort was 40 years (range 17–83). The median follow up was 53 months (range 1–211). The median number of positive LNs removed and maximum LN diameter was 1 (range 1–8) and 5mm (range 1–16mm), respectively. 67 (64%) patients had adjuvant RAI and 37 (36%) did not. Patients with vascular invasion ($p=0.01$), LNs >2mm ($p=0.07$) and >2 positive nodes ($p=0.06$) were more likely to be selected for adjuvant RAI therapy. Patients without RAI therapy had similar 5 year central neck LN RFS to those treated with RAI; 96.2% vs. 94.6% respectively ($p=0.92$).

Conclusion—There is no difference in the 5 year central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

Keywords

Papillary thyroid cancer; central compartment; incidental lymph nodes; N1a disease; nodal stage; survival outcome; recurrence outcome

Introduction

Following total thyroidectomy for papillary thyroid cancer (PTC), pathological assessment can occasionally reveal incidental perithyroidal lymph nodes (LN) with occult metastases. In the absence of prospective evidence, subsequent management of these patients is largely dependent on personal preferences, and institutional practices¹. Although management guidelines do not specifically address this clinical scenario, clinical N0 but pathological N1a patients often receive radioactive iodine (RAI) therapy, in the absence of other indications for RAI. This practice was, in part, justified by the 2009 American Thyroid Association (ATA) risk stratification of differentiated thyroid cancer². These clinical N0, pathological N1a patients were classified as intermediate-risk of recurrence as a result of microscopic nodal disease. In the anticipated 2015 ATA guidelines, the low-risk category will be expanded to incorporate patients with ≤ 5 pathological N1 micrometastases that measure <0.2 cm in dimension. The aim of this study was to determine the central compartment nodal recurrence free survival in patients treated without RAI compared to those who received RAI treatment.

Methods

Following approval by the Institutional Review Board, the records of 3664 consecutive patients treated surgically for differentiated thyroid cancer between 1986 and 2010 were identified from an institutional database. Patients with non-PTC, less than total thyroidectomy, neck dissection of the central or lateral neck, and those presenting with distant metastases were excluded. This left 248 PTC patients managed with total thyroidectomy and no planned neck dissection that had incidental level 6 LNs on pathology. Patients with other indications for adjuvant RAI therapy, such as presence of extrathyroidal extension (ETE) and close or positive margins, were then excluded. This left 104 patients for analysis. A flowchart showing the patients selected for analysis is shown in Figure 1.

At our institution, neck dissections are only carried out for clinically confirmed lymph node metastases, or if suspicious LNs are found on clinical examination, on preoperative imaging, or during surgery. Intraoperative LN biopsies for frozen-section are performed based on surgeon preference. If no LNs are suspected to contain metastases, then thyroidectomy alone is performed. We do not practice elective central compartment node dissection. Therefore, all included patients had either incidental occult LN metastases detected on pathological examination of perithyroidal tissue, which was included with the thyroidectomy specimen or positive LNs found on permanent sectioning after a negative frozen section biopsy.

Patient demographic information, surgical details, and histopathological details including number of positive LNs, size of largest positive LN, and presence of LN extracapsular spread (ECS) were recorded. LN diameter was defined as the diameter of the largest LN

containing a focus of metastatic thyroid cancer. The presence of ECS was defined as tumour extension beyond the LN capsule. As this study includes patients with pathology reports from 1986 through 2010, all LN features were not reported in patients from the earlier years. Analysis of LN characteristics was limited to patients with available pathology details. Size cutoff of micrometastatic positive LNs was based on other studies in the literature³⁴. Details of postoperative adjuvant RAI therapy were recorded and patients then stratified into 2 groups: those who received RAI and those who did not. Postoperative serum thyroglobulin (Tg) levels were taken as the lowest Tg level prior to adjuvant RAI therapy or within 1 year of surgery if no RAI was administered. Tg measurements for patients with raised Tg antibodies within the same time period were excluded from analysis. Since 1999, Tg values have been measured using the Dynotest-TgS immunoradiometric assay (Brahms, Inc., Berlin, Germany; functional sensitivity 0.6 µg/l normalized to Certified Reference Material 457)⁵.

The primary outcome of interest was central compartment nodal recurrence free survival (RFS). LN recurrences were determined by clinical examination supplemented with imaging and fine needle aspiration. Patients with biochemical recurrences alone, defined by elevated thyroglobulin (Tg) levels were not considered to be sufficient measures for nodal recurrence outcome. Outcomes data were calculated at 5 years. Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY). Pearson's chi-squared test was used to compare variables between the RAI and no RAI groups. Survival outcomes were analyzed using the Kaplan-Meier method. Univariate analysis was carried out by the log rank test. A *p* value less than 0.05 was considered significant.

Results

The median age of the cohort was 40 years (range 17–83). The median follow up was 53.4 months (range 1–211). The median number of positive LNs identified was 1 (range 1–8). The median LN diameter was 5mm (range 1–16mm). Sixty-seven (74%) patients received adjuvant RAI and 37 (34%) patients had no RAI. Table 1 shows patient, tumour and treatment characteristics for the RAI and no RAI groups. Those with vascular invasion ($p=0.01$), LNs >2mm ($p=0.07$) and > 2 positive nodes ($p=0.06$) were more likely to be selected for adjuvant RAI therapy. There were no statistically significant differences in terms of age, primary tumour size ($p=0.23$), multicentricity ($p=0.67$), LN extracapsular spread ($p=0.37$) or postoperative Tg measurements ($p=0.22$). Central neck recurrence occurred in 5 patients; 4 patients in the RAI group and 1 patient in the no RAI group. Figure 2 demonstrates the Kaplan Meier plot for central neck nodal recurrence for patients who received adjuvant RAI therapy and those who did not. Patients with and without RAI therapy had similar 5 year central neck LN RFS of 94.6% and 96.2%, respectively ($p=0.92$).

Discussion

After total thyroidectomy for PTC, histopathological examination occasionally detects unexpected microscopic LN metastases in the perithyroidal tissue. Physicians are faced with a clinical dilemma of whether or not to treat these patients with adjuvant RAI therapy. Patients with pathologically confirmed central compartment LN metastases were previously

considered to be ATA intermediate-risk of recurrence and as such, many clinicians administer adjuvant RAI therapy to destroy suspected nodal metastases with the intention of reducing risk of recurrence in these patients². The new 2015 ATA management guidelines are anticipated to recognise that this upstaging of patients with micrometastatic nodal disease is likely unwarranted. The new expanded criteria for ATA low-risk category will include patients with micrometastases in the central compartment. The management and outcomes of patients with occult, perithyroidal LN metastases however has not been studied. In this study we analyzed the outcomes of patients with T1-3 PTC tumours with incidentally discovered level 6 lymph nodes. We report that selected patients, without any adverse features in the primary tumour and with incidental nodal disease <2mm can be safely managed without adjuvant RAI.

Numerous publications have described LN characteristics such as size and number of lymph nodes to be predictive of recurrence^{6,7}. The American Thyroid Association recently published a detailed systematic review quantifying thyroid cancer nodal volume and its relationship to prognosis. It was observed that recurrence rates in PTC have varied greatly, between 0%-42%, depending on size of primary tumour as well as the volume of nodal disease⁴. The literature has reported on a wide range of metastatic LN sizes between 0.2cm and 3cm, to be associated with greater recurrence rates⁶⁻⁸. Publications from our institution suggest that LN extracapsular spread may also be prognostic⁹. As the prognostic impact of central LN characteristics is elucidated, N1a disease should no longer be considered a homogeneous entity requiring RAI therapy in all circumstances.

The question of whether or not incidentally found central neck LNs require further adjuvant RAI has not been studied. In our series, 64% of patients with incidental N1a disease were determined to be at risk for recurrence and therefore received adjuvant RAI therapy following surgery. Patients with vascular invasion were significantly more likely to receive postoperative RAI therapy compared to those without vascular invasion ($p=0.01$). Although the presence of vascular invasion has been associated with increased risk of disease recurrence¹⁰, there are inadequate data to determine whether RAI ablation has benefits after adjusting for tumour size and patient age². Nevertheless, at our institution the presence of vascular invasion was associated with greater rates of RAI therapy administration.

RAI therapy is not without adverse-effects; consideration must be given to the balance of minimizing iatrogenic harm versus preventing cancer morbidity. Uptake outside the thyroid gland results in salivary and lacrimal dysfunction which results in a significant, deleterious impact on patients' quality of life¹¹ as well as a small but significant increase in the rate of secondary malignancy at high doses^{12,13}. Clinical indications for adjuvant RAI therapy are frequently based on limited data and guidelines often leave decisions to clinician discretion². Although management recommendations should ideally be based on prospective randomized studies, in the absence of such studies, the analysis presented here is a very useful adjunct to physician judgment in the management of PTC patients with incidentally discovered, low volume central compartment nodal disease.

It is important to point out the limitations of our study. This is a retrospectively conducted study with inherent patient and physician related selection bias relating to the administration

of RAI therapy. However, at Memorial Sloan Kettering Cancer Center, we have a large experience in managing patients with thyroid cancer with a multidisciplinary team approach. Therefore selection bias will be limited due to this extensive experience. Another limitation is the small sample size, which can limit a rigorous statistical analysis. However, our database of 3664 patients is one of the largest single institution cohorts reported. It is highly probable that the pathological details reported in our analysis are not recorded in many other institutional datasets. We would encourage other institutions with detailed synoptic reporting on pathology, to analyze their data and verify the results presented here. Lastly, one may argue that follow-up was limited, thereby underestimating the true risk of recurrence. However, previous literature now reports that recurrence is most likely in the first 2–3 years following treatment¹⁴. Therefore, with a follow-up of 53 months, the majority of recurrences would have occurred in our patient cohort.

Our data therefore provide further evidence for the anticipated 2015 ATA risk stratification system which will categorise patients with low volume central neck disease as low risk. We report that in selected PTC patients with incidental central compartment nodal disease there is no difference in the 5 year central compartment nodal recurrence-free survival in patients treated without RAI compared to those that received RAI treatment.

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Figure 1.
Flowchart of inclusion patients

Figure 2.
Central neck recurrence free survival in pN1a M0 patients without neck dissection, without extrathyroidal extension and and negative margins

Table 1

Comparison of patient demographics with and without RAI ablation

	No Adjuvant RAI		Adjuvant RAI		<i>p Value</i>
	n=37	%	n=67	%	
Gender					
Female	31	83.8%	44	65.7%	0.05
Male	6	16.2%	23	34.3%	
Age					
< 45 yrs	26	70.3%	41	61.2%	0.36
45 yrs	11	29.7%	26	38.8%	
Size					
2 cm	30	81.1%	50	74.6%	0.23
4 cm	7	18.9%	12	17.9%	
> 4 cm	0	0.0%	5	7.5%	
T Stage					
T1a	13	35.1%	21	31.3%	0.41
T1b	17	45.9%	29	43.3%	
T2	7	18.9%	12	17.9%	
T3	0	0.0%	5	7.5%	
Multifocality					
No	16	43.2%	26	38.8%	0.66
Yes	21	56.8%	41	61.2%	
Vascular Invasion					
Absent	35	94.6%	48	73.8%	0.01
Present	2	5.4%	17	26.2%	
ECS					
Absent	27	90.0%	41	95.3%	0.37
Present	3	10.0%	2	4.7%	
LN size					
0.2cm	8	33.3%	7	14.9%	0.07
>0.2cm	16	66.7%	40	85.1%	

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		No Adjuvant RAI		Adjuvant RAI		p Value
		n=37	%	n=67	%	
No. of Positive LNs						
1		25	67.6%	33	49.3%	0.07
>1		12	32.4%	34	50.7%	
2		32	86.5%	47	70.1%	0.06
>2		5	13.5%	20	29.9%	
Post surgery Tg level						
1 µg/l		23	95.8%	45	86.5%	0.22
>1 µg/l		1	4.2%	7	13.5%	

RAI – radioactive iodine, ECS – extracapsular spread, LN – lymph node, Tg - thyroglobulin