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Management and outcome of clinically evident neck recurrence in patients with papillary thyroid cancer

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Abstract

Background—The aim of this study was to report our incidence of clinically evident neck recurrence, salvage neck management and subsequent outcomes in patients with papillary thyroid cancer. This is important to know so that patients with thyroid cancer can be properly counselled about the implications of recurrent disease and subsequent outcome.

Methods—An institutional database of 3664 patients with thyroid cancer operated between 1986 and 2010 was reviewed. Patients with non-papillary histology, gross residual disease and those with distant metastases at presentation or distant metastases prior to nodal recurrence were excluded from the study. Of these, 99 (3.0%) patients developed clinically evident nodal recurrence. Details of recurrence and subsequent therapy were recorded for each patient. Subsequent disease specific survival (sDSS), distant recurrence free survival (sDRFS) and nodal recurrence free survival (sNRFS) were determined from the date of first nodal recurrence using the Kaplan Meier method.

Results—Of the 99 patients, 59% were female and 41% male. The median age was 41 years (range 5–91). The majority of patients had pT3/4 primary tumors (63%) and were pN+ (78%) at initial presentation. The median time to clinically evident nodal recurrence was 28 months (range 3–264). Nodal recurrence occurred in the central neck in 15 (15%) patients, lateral neck in 74 (75%) patients and both in 10 (10%) patients. After salvage treatment, the 5 year sDSS was 97.4% from time of nodal recurrence. The 5 year sDRFS and sNRFS were 89.2% and 93.7% respectively.

Conclusion—In our series, isolated clinically evident nodal recurrence occurred in 3.0% of patients. Such patients are successfully salvaged with surgery and adjuvant therapy with sDSS of 97.4% at 5 years.

Keywords

Papillary thyroid cancer; lymph nodes; neck recurrence; outcomes; survival

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Introduction

There is great controversy about the true incidence of recurrence in papillary thyroid cancer (PTC). Long term overall PTC recurrence rates are commonly referenced at 30%^{1,2}. However, recurrence rates vary widely depending on the extent of primary disease and on the method of recurrence measurement^{3,4}. Recurrence rates are greater if one includes subcentimeter nodes identified on high resolution ultrasound with elevated thyroglobulin measurements. Recurrence due to clinically evident nodal recurrence which require further surgery is less common. The majority of regional recurrences manifest within the first few years after initial therapy⁵. Of those who develop regional nodal recurrence, few patients ultimately succumb to their disease. Although prognostic factors of PTC have been extensively investigated, patient outcomes after clinically evident nodal recurrence remain unclear. The objectives of our study were twofold. Firstly, to report the incidence of clinically evident nodal recurrence in a large cohort of previously untreated patients managed at a single tertiary care institution. Secondly, to describe the subsequent treatment of these patients and report the long-term outcomes after salvage treatment.

Methods

Following institutional review board approval, the records of 3664 consecutive patients treated with primary thyroid surgery for differentiated thyroid cancer at Memorial Sloan Kettering Cancer Center (MSKCC) between 1986 and 2010 were reviewed. Patients with non-papillary histology, gross residual disease and those with distant metastases at presentation or distant metastases prior to nodal recurrence were excluded from the study, leaving 3344 cases. Of these, 99 (3.0%) PTC patients developed clinically evident nodal recurrence which required further treatment. All patients had biopsy proven neck recurrence prior to further treatment. Patients with subclinical recurrence, defined as subcentimeter nodules in the central or lateral neck with or without an elevated thyroglobulin level, were not included in this study.

Patient demographics, primary surgical and histopathological details were recorded. Details of all adjuvant radioactive iodine (RAI) treatments or radiotherapy (RT) were also recorded. Clinically evident nodal recurrence was identified by clinical examination and imaging studies with ultrasound (US) or CT scan and were confirmed with cytology or histopathology.

Disease outcomes included subsequent disease specific survival (sDSS), subsequent distant recurrence free survival (sDRFS) and subsequent nodal recurrence free survival (sNRFS). These outcomes were calculated from the date of first nodal recurrence. sDSS was calculated using the date of last follow up with an MSKCC physician from the thyroid cancer multidisciplinary team. Details of death were determined from the social security death index and hospital records. Biochemical disease in the absence of imaging disease was not considered sufficient evidence of tumor recurrence. Imaging studies to detect recurrence included US, diagnostic RAI, computer tomography, and positron emission tomography scans. Patients with evidence of structural disease at the time of last follow-up and died during follow up were considered to have had disease specific death.

Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY). Variables were compared within groups using Pearson's chi-squared test. Survival outcomes were analyzed using the Kaplan-Meier method. Outcomes data were calculated at 5 years.

Results

Initial patient, disease and management characteristics

Of 3364 patients, 99 (3.0%) patients developed clinically evident nodal recurrence. Table 1 shows the patient, primary disease and initial treatment characteristics of the patients that developed nodal recurrence. Of the 99 patients, 59% were female. The median age of the cohort was 41 years (range 5–91) at time of initial PTC diagnosis. The majority of patients had locally advanced disease (63% T3 or T4 disease) and presented with nodal disease in 78% (42% N1a and 35% N1b disease). At the time of primary surgery, 85 (86%) patients underwent total thyroidectomy and 14 (14%) less than total thyroidectomy. Central neck dissection was performed in 25 (25%), lateral neck dissection in 9 (9%), both in 24 (24%) and not performed in 41 (41%) patients. Adjuvant RAI was administered to 74 (75%) patients.

Nodal recurrence location and treatment

Nodal recurrence details are summarized in Table 2. The median time to clinically evident nodal recurrence was 28 months (range 3–264). The median follow up from the time of nodal recurrence was 50 months (range 1–330). Nodal recurrence occurred in the central neck compartment alone in 15 (15%) patients, lateral neck compartment only in 74 (75%) patients and both neck compartments in 10 (10%) patients.

The majority of patient were treated either with surgery alone (65/99 66%) or surgery with adjuvant therapy (22/99 22%). Ten patients (10%) were treated without surgery (RAI and/or external beam radiation therapy (EBRT) and 2 (2.0%) patients were observed without treatment.

Outcomes after Nodal recurrence

Subsequent Disease Specific Survival—The 5 year sDSS was 97.4% from time of nodal recurrence (Figure 1A). A total of 4 patients died of disease during follow up. All 4 patients died after developing lung metastases, 1 patient also developed brain metastases (Table 3).

Subsequent Distant Recurrence—Eight patients (8.0%) went on to develop distant disease at a median of 85 months (range 5–130) from time of nodal recurrence. Five patients developed isolated lung metastases, 1 patient had lung and brain metastases, 1 lung and bone and 1 patient developed isolated bone metastases. The 5 year sDRFS was 89.2% (Figure 1B).

Subsequent Nodal Recurrence—Twelve of the 99 patients went on to develop a further episode of nodal recurrence at a median of 118 months (range 76–300) from the time of initial nodal recurrence. At 5 years, the sNRFS was 93.7% (Figure 1C).

Discussion

In our experience, the incidence of clinically evident nodal recurrence after initial surgery for patients with well-differentiated PTC was 3%. The majority of patients can be salvaged such that the 5 year subsequent DSS is 97.4%.

Our low rate of clinically evident nodal recurrence merits a detailed discussion. The literature generally reports on combined local and regional recurrence free survival, with limited breakdown of recurrence sites by thyroid bed and regional lymph node (LN) recurrence. Traditionally, the recurrence figure of 30% by Mazzaferri et al is commonly quoted^{1,2}. In this study, two thirds of the recurrences were locoregional. However, subsequent publications have reported much lower figures. Durante et al reported 1.4% locoregional recurrence rate in 1020 PTC patients⁶, Ito et al reported 7% reoperation rate in the central neck compartment in a series of 5969 PTC patients⁷ while Coburn et al reported 9.4% regional LN recurrence in 382 patients with differentiated thyroid cancer⁸. Yim et al reported 10.0% locoregional recurrence rate in a series of 1357 PTC patients and Shen et al published central neck recurrence rate of 11.6% and lateral neck recurrence rate of 21.7%. In a recent review by Randolph et al, locoregional recurrence rates in PTC ranged widely between 0–42% based on the size of primary tumor and volume of initial LN metastases³. This review suggested the range of recurrence figures was determined by the variety of inclusion criteria and outcomes reported in these studies. Locoregional recurrence rate of 24% was reported with 40 years of follow-up by the Mazzaferri series². This is in contrast to the low recurrence rate of 3.0% that we report in our study. One explanation for the high rate reported by Mazzaferri could be the longer follow-up period that the Mazzaferri cohort underwent. However, given that approximately 84% of neck reoperations occur within the first 2 years of primary surgery, additional follow-up beyond the first 5 years is unlikely to dramatically impact nodal recurrence rates. Of note, data collection from the Mazzaferri series started in the 1960's, on military personnel and their families under the care of military general surgeons. These surgeons were not specialty trained and the technique of carrying out subtotal thyroidectomy was readily accepted at that time. These 2 factors are associated with higher recurrence and mortality rates⁹.

With the introduction of high resolution ultrasound and the use of serum thyroglobulin, it is now possible to detect subclinical recurrent disease in the neck due to small subcentimeter nodes. We did not include these patients in our study and therefore it is likely that we have underestimated the true recurrence rate in our patient cohort. However, it is now recognized that the majority of these patients do not require any treatment as the majority of subclinical disease remains indolent^{10,11}. The decision to operate in patients with subclinical disease has to be weighed against the possible complications which may result from such surgery^{10,11}. It is also possible that some of the patients in our cohort may represent persistent disease rather than recurrence since there were several patients who developed disease within 3 months of initial therapy. In these patients it is likely that subclinical disease

was present initially and this became clinically and radiologically evident on the posttreatment ultrasound scan. This would tend to overestimate the recurrence rate.

In our series, the majority of nodal recurrences were managed surgically with or without additional RAI therapy. Occasionally, in earlier years, the management of nodal recurrence was with non-surgical modalities alone. The majority of patients were successfully salvaged with a subsequent survival at 5 years of 97.4%. This compares favorably with reports from the literature. In a series of 329 PTC patients with initial central nodal recurrence, Ito et al reported DSS of 95% at 5 years⁷. Other institutional publications have reported death due to disease ranging between 0% to 16% of patients after locoregional recurrence^{2,12–14}. In a study of DSS after salvage neck reoperation in PTC, conducted through the Californian Cancer Registry, DSS was found to be approximately 90% at 5 years⁵. Our 5 year disease specific death rate of 3.6% is within the lower end of the reported range presented in the literature. Therefore, we can conclude that despite nodal recurrence, the 5 year subsequent survival in these patients remains very high at 97.4%.

Few publications in the literature report subsequent nodal or distant recurrence outcomes after initial nodal recurrence. Those that do, tend to report subsequent locoregional and distant failure rates in term of a percentage figure, making comparisons difficult as each series is associated with a different length of follow-up. For example, subsequent locoregional failure was reported in 9.6% patients by Yim et al and in 18.2% of patients by Onkendi et al^{12,13}. In this current series, only 12 (12.1%) patients went on to develop a second episode of clinically evident nodal failure after treatment of their initial nodal recurrence, corresponding to a 5 years sNRFS of 93.7%.

Distant recurrence free survival after the development of nodal disease is also infrequently reported in the literature. Yim et al reported 5/83 (6.0%) patients subsequently developed distant disease after treatment for nodal recurrence¹³. This is comparable to the subsequent distant failure rate of 8 (8.1%) patients and 5 year sDRFS of 89.2% observed in this present study.

Our study has some limitations that require discussion. Firstly, this is a retrospective cohort with patients managed at a single institution over a 25-year period. As such, we cannot account for changes in follow-up management practices over this time. In particular, postoperative neck ultrasound and thyroglobulin measurements were not routine prior to 2000–2005. Prior to this time, recurrence was determined on clinical examination and then confirmed by fine needle aspirate. It is therefore probable that we may have misclassified patients as being free of disease in patients not assessed by US or thyroglobulin (Tg) and this would have resulted in an underestimation of nodal disease recurrence. Although serum Tg is a more sensitive marker of differentiated PTC disease^{4,13–18}, its use in determining indication and success of nodal recurrence treatment can be problematic. The use of biochemical determinants of persistent or recurrent disease can lead to additional surveillance and intervention along with its associated morbidity. This is particularly of concern for the many patients that are already at very low risk from their disease. In this regard, one can argue that the use of structural disease is a more clinically meaningful measure of outcome.

Another limitation of our cohort is the relatively short follow up period. There may be patients with nodal recurrence who are lost to follow up. This would artificially improve our NRFS. However, as the majority of nodal recurrence in PTC occur within the first 2–3 years of diagnosis⁵, we do not expect the true nodal recurrence rate to be significantly higher than 3.0% with longer follow-up. Outcomes after nodal recurrence are reported here with a median follow up 50 months. It may be likely that with additional follow-up, DSS and sDfRS may decrease. However, as nodal recurrence events tend to occur early, we expect that sNRFS would remain the same with additional follow-up.

In conclusion, in this series of PTC patients, clinically evident nodal recurrence occurred in 3.0% of patients. Salvage management is mainly surgical with or without additional RAI therapy. Patients continue to experience excellent outcomes after nodal disease recurrence, with a subsequent 5 year DSS of 97.4%.

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Synopses

The aim of this study was to report our institution's incidence of clinically evident neck recurrence, subsequent management and outcomes. Clinically evident nodal recurrence occurred in 3.0% of our patients. Such patients are successfully salvaged with surgery and adjuvant therapy with subsequent disease specific survival of 97.4% at 5 years.

Figure 1A.
Five year subsequent disease specific survival following salvage neck management

Figure 1B.
Five year subsequent distant recurrence free survival following salvage neck management

Figure 1C.
Five year subsequent neck recurrence free survival following salvage neck management

Table 1

Initial patient, treatment and tumor characteristics

	n= 99	%
Gender		
Female	58	38.6%
Male	41	41.4%
Age		
<45 years	58	38.6%
45 years	41	41.4%
Thyroid Surgery		
Less than total	14	14.1%
Total thyroidectomy	85	85.9%
Neck Dissection		
None	41	41.4%
Central compartment	25	25.3%
Lateral compartment	9	9.1%
Central & lateral	24	24.2%
pT Stage		
T1	26	26.3%
T2	10	10.1%
T3	47	47.5%
T4	16	16.2%
pN Stage		
N0/X	22	22.2%
N1a	42	42.4%
N1b	35	35.4%
AJCC Stage		
Stage 1	59	59.6%
Stage 2	1	1.0%
Stage 3	14	14.1%
Stage 4	25	25.3%
ATA Risk Group		
Low	6	6.1%
Intermediate	69	69.7%
High	24	24.2%
Adjuvant RAI		
No	25	25.3%
Yes	74	74.7%

RAI –radioactive iodine. Range of RAI dose was 60.5 to 268 mCi

Table 2

Nodal recurrence characteristics

	n= 99	%
Time to nodal recurrence (months)		
Median	27.8	–
Range	3–264	–
Site of nodal recurrence		
Central compartment	15	15.2%
Lateral compartment	74	74.7%
Central and lateral	10	10.1%
Recurrence management		
Surgery only	65	65.7%
Surgery and RAI	22	22.2%
RAI only	6	6.1%
RT	4	4.0%
Observation only	2	2.0%

m – months

RAI – radioactive iodine

RT – radiotherapy

FU – follow up

Table 3

Details of patients who died following neck recurrence 6 patient deaths; 4 disease specific deaths and 2 deaths due to other causes

Age/Gender	Stage	ATA Risk Category	Primary RAI	Site of NR	NR Treatment	Overall Survival (months)	Cause of death
64.4F	T3N1b	High	Yes	Central, lateral	RT	30.2	Lung metastases
70.9F	T1bN1b	Intermed	Yes	Lateral	Surgery & RAI	135.5	Lung metastases
55.9M	T4aN1a	High	No	Lateral	Surgery	144.6	Lung metastases
72.4F	T4aN1a	High	Yes	Lateral	Surgery	142.6	Lung metastases
91.3M	T4aN1a	High	No	Lateral	Surgery	49.7	Other
85.3F	T4aNX	High	No	Lateral	Surg & RAI	102.3	Other

RAI – radioactive iodine treatment

NR – nodal recurrence