

Original Research Article

Survival outcomes of locoregionally advanced papillary thyroid carcinoma

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ABSTRACT

Background: PTC carries an overall excellent prognosis. Most patients with PTC have small and asymptomatic disease. This raises the question whether overall rates overestimate the survival of those with advanced disease. We use our institutional data to report disease-free and overall survival of patients with locoregionally advanced PTC.

Methods: A retrospective study of 92 patients who underwent a total thyroidectomy from 2002 to 2019 at a single institution. Features of locoregionally advanced disease were defined as extra thyroid extension, primary tumor size ≥ 4 cm, or cervical nodal involvement. These and additional clinical and histological features were analyzed for association with recurrence and disease-free survival.

Results: Twenty-six patients had recurrence of disease. Patients with ETE, nonspecific cervical nodal involvement, or tumor size ≥ 4 cm had no significant increase in recurrence ($p=0.2554$, 0.1886 , 0.2278 , respectively). Patients with nodal metastasis to lateral neck compartment had a significant increase in recurrence ($p=0.0434$). 5-year overall survival was 95%.

Conclusion: PTC has an excellent prognosis even in the presence of advanced locoregional disease. However, lateral neck nodal involvement is associated with higher rates of recurrence and may be an indicator for more aggressive management.

Keywords: Thyroid, Malignancy, Recurrence, Survival, Papillary

INTRODUCTION

Papillary thyroid carcinoma is the most common thyroid malignancy and in general carries an excellent prognosis.^{1,2} This is especially true for papillary thyroid microcarcinomas.³ Around half of the diagnoses of thyroid malignancy pertain to small, asymptomatic, papillary thyroid cancers (PTC) that do not impact mortality.⁴

Despite the overall favorable survival rate, there are several factors that can impact the individual's prognosis.² The AGES scoring system published in 1987 incorporated Age, histologic Grade, Extrathyroidal

invasion and metastases, and tumor Size to predict the risk of dying from PTC.⁵ Presently, the American Thyroid Association classifies patients with macroscopic tumor invasion, incomplete resection, distant metastasis, or thyroglobulinemia as high-risk.⁶ PTC usually emerges with a painless and slow-growing neck mass.² Locally invasive thyroid cancer results from extrathyroidal tumor extension and may impact presentation based on the structures involved.^{7,8}

Involvement of structures such as the recurrent laryngeal nerve, esophagus, trachea, or metastasis to cervical lymph nodes requires a more extensive surgery and worsens the prognosis.⁹ The current system groups all patients with

age less than 55 into lower overall stages, despite differences in tumor size or nodal involvement.¹⁰ While this approach reflects the overall excellent prognosis of this disease, we understand that more specific prognostic indicators than what are reflected in the current staging system may change the risk profile and limit the applicability of the overall survival data to high-risk patients.¹¹⁻¹³ We define locoregionally advanced PTC as one with nodal involvement (central or lateral cervical nodes), extra thyroid extension or primary tumor size greater than 4 cm.

The goal of our study is to better understand the association between these features and disease recurrence in adult patients and the association between the same markers and recurrence in a subset of patients who are younger than 55 years of age. We hypothesize the presence of advanced disease features is linked with greater rates of recurrence.

METHODS

Data source

After an institutional review board approval, we conducted a retrospective review of 92 patient records who underwent total thyroidectomy from January 1, 2002 to December 31, 2019 at the Division of Otolaryngology, University of Wisconsin Hospital. The surgical billing database was queried using procedure codes to identify all patients who underwent total or subtotal thyroidectomy with neck dissection or substernal extension by one of the four head and neck surgical oncologists at our institution. This yielded a total of 146 patients, who underwent surgery between 2002 and 2021.

Patient selection

Each patient chart was reviewed and patients with a pathologic diagnosis of papillary thyroid carcinoma with advanced locoregional features were included.

Features of advanced locoregional disease were defined as central or lateral nodal involvement confirmed on pathology, any gross or histological extra thyroid tumor extension (ETE), and 3) size of primary tumor of 4 cm or greater. Patients with malignancies other than papillary thyroid carcinoma and those without advanced locoregional features were excluded.

To ensure an adequate follow-up period, patients who completed primary treatment after 2019 were excluded, since this data set was extracted in 2021. The remaining patient records were reviewed to extract demographic data including age at time of surgery, pathologic information, treatment type, recurrence/outcome information and factors contributing to recurrence. Patients with signs of residual disease after primary treatment and adjuvant treatment were removed from recurrence and survival analysis.

Statistical analysis

All data were analyzed by SPSS v.27 (SPSS Inc., Chicago, IL). Clinical and pathological variables are treated as independent variables and recurrence is the dependent variable. Continuous variables (means and medians) are treated as dependent variable based on recurrence. Means were compared using independent two sample t-test. Medians were compared using Mood's median test.

Categorical variables were compared using chi-squared test. Chi squared tests were also used to compare the relationship between number of features of advanced disease with various outcome features including location of recurrence and type of treatment after recurrence. Kaplan-Meier's curve was used to assess disease free survival based on presence of advanced disease features, with long rank test to determine significance.

Cox regression analysis was also used to assess how recurrence as a primary outcome relates to nodal involvement, positive lymph node ratio ≥ 0.5 , extra thyroid extension, tumor size ≥ 4 cm, male sex, age ≥ 55 . P value < 0.05 was considered significant. Subgroup analysis was done to assess recurrence in patient younger than 55 years. Means, medians and categorical variable were compared as described for larger population.

RESULTS

In this inquiry, we reviewed the charts of 92 patients who underwent total thyroidectomy with neck dissection or with substernal involvement between 2002 and 2019 and were found to have locoregionally advanced PTC. Three patients out of the 92 had signs of residual disease after both primary treatment and adjuvant radioactive iodine (RAI). One of the three had persistently elevated thyroglobulin levels without a clear source, and two patients had pulmonary metastases and persistently elevated thyroglobulin post RAI. These three patients were removed from recurrence and survival analysis. Pathology reports were frequently incomplete. Analysis was done based on valid (available) data.

A summary of patient demographics and disease characteristics and how those relate to recurrence are presented in Table 1. The 26 patients who had recurrence had a mean age of 47 years compared to the non-recurrence group with a mean age of 49 ($p=0.643$).

Of the 26 patients who had disease recurrence, four had a distant location of recurrence, outside of the thyroid bed area or cervical region. 9 patients had 1 feature of advanced PTC, none of these had distant location of recurrence; 12 patients had 2 features of advanced PTC, 3 of them had distant recurrence; 5 patients had all 3 features of advanced PTC and 1 had distant recurrence ($p=0.8217$). Of the same 26 patients who recurred, 16 were males and 4 of them recurred distally compared to 6

distant recurrences in the 10 females with recurrence ($p = 0.7430$). Fifteen of the 26 recurrences underwent revision neck dissection, four had RAI as secondary treatment, four elected for monitoring disease progression, one patient was referred to palliative care given advanced pulmonary metastases and two patients had external beam radiation as secondary treatment. Of the 9 patients with 1 feature of advanced disease, 5 underwent surgery to manage recurrence; of the 12 patients with 2 features of advanced disease 8 underwent surgery to manage recurrence; surgery was the main management of recurrence in 3 patients of the 5 who had all 3 features of advanced disease ($p=0.7987$). Univariate analysis of disease-free survival using Cox proportional hazard regression analysis showed that nodal involvement, LNR ≥ 0.5 , ETE, size ≥ 4 , male sex or age ≥ 55 were each not associated with a statistically significant decrease in disease free survival (Table 2). Advanced disease features were each not associated with significant decrease in DFS as shown in Figure 1.

Overall survival outcomes

By the end of the follow up period, with a median of 41-42 months, three of the 89 patients passed away. Two deaths were linked with thyroid cancer. One-year survival was 98.78%, three-year survival rate was 97.14% and five-year survival was 94.55%. Only 28 patients were followed for at least 10 years and contributed to a 10-year survival of 89.29%. Only 3 patients were followed for >220 months and contributed to a survival rate of 66.67%.

In subgroup analysis focusing on patients below the age of 55 years, out of 55 patients, 16 had disease recurrence. Mean thyroid weight in the recurrence group was 40.44 g compared to 21.05 g ($p=0.0098$). LVI was the only binary characteristic associated with increased recurrence. 8 of 15 patients with document LVI recurred compared to 6 out of 30 patients without LVI ($p=0.0075$).

The 16 patients who recurred had a mean of 11.33 positive central lymph nodes compared to 4.65 in the other 39 patients ($p=0.0002$). Those same 16 patients with recurrence had a mean of 9.00 positive lateral lymph nodes compared to 3.06 in the no recurrence group ($p=0.0001$). Remaining characteristics of this subgroup are displayed in Table 3. Advanced disease features in patients <55 years of age were each not associated with significant decrease in DFS as shown in Figure 2.

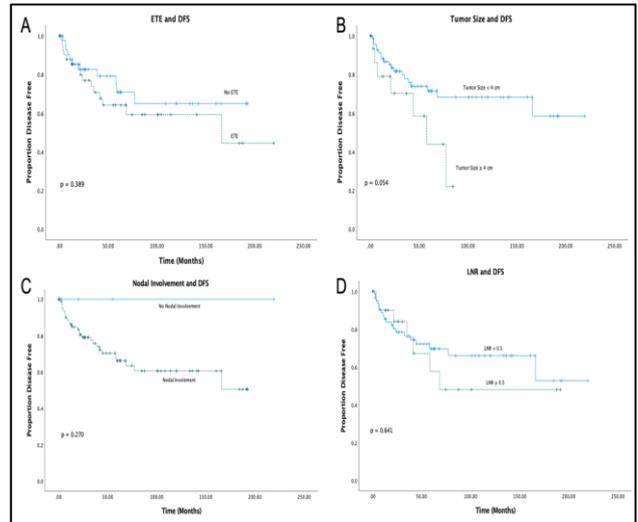


Figure 1: Kaplan Meier curve for disease free survival for patients (A) with vs without extra thyroid extension, (B) with vs without tumor size of 4 cm or greater, (C) with vs without nodal involvement and (D) with vs without positive lymph node ratio of 0.5 or greater.

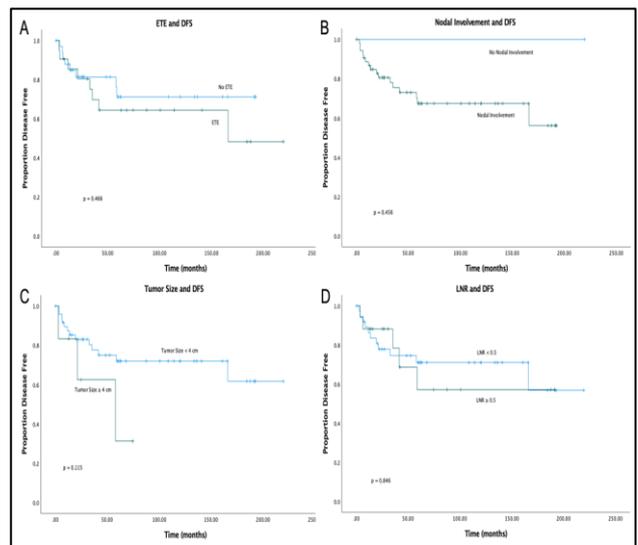


Figure 2: Kaplan Meier curve for disease free survival for patients < 55 years old (A) with vs without extra thyroid extension, (B) with vs without tumor size of 4 cm or greater, (C) with vs without nodal involvement and (D) with vs without positive lymph node ratio of 0.5 or greater.

Table 1: Number of recurrences in adults with locoregionally advanced PTC based on various clinical and histopathological features.

Characteristic	Overall	Recurrence	No recurrence	P value
N	89	26	63	
f/u time month (median IQR)	41.42 (13.61-77.36)	20.24 (6.86-40.81)	55.27 (22.21-106.45)	0.0042*
Sex	Female	10	31	0.3551

Continued.

Characteristic		Overall	Recurrence	No recurrence	P value
	Male	48	16	32	
Age (mean (SD))		49 (18.38)	47 (20.33)	49 (17.63)	0.643
Operative method	TT /c CND	14	2	12	0.537
	TT /c CND /c LND	65	22	43	
	TT /c LND	8	2	6	
	TT	2	0	2	
Adjuvant RAI	Yes	81	24	57	0.7835
	No	8	2	6	
Laterality	Right	29	10	19	0.5427
	Left	25	5	20	
	Bilateral	32	11	21	
	-	3	0	3	
Tumor size	≥ 4 cm	17	7	10	0.2278
	< 4 cm	72	19	53	
Nodal involvement	Yes	85	26	59	0.1886
	No	4	0	4	
Largest nodal metastasis in cm (mean (SD))		2.51 (1.87)	2.32 (1.21)	2.60 (2.11)	0.5488
Thyroid weight in g (mean (SD))		31.43 (30.73)	39.94 (40.93)	27.79 (24.71)	0.1054
ETE	Yes	43	15	28	0.2554
	No	46	11	35	
Resection margin	Clear	63	15	48	0.0602
	Involved	17	8	9	
	-	9	3	6	
PNI	Yes	2	1	1	0.3587
	No	63	14	49	
	-	24	11	13	
LVI	Yes	22	11	11	0.0097*
	No	58	12	46	
	-	9	3	6	
Length of admission in days (median IQR)		2 (2-3)	2 (2-4)	2 (1-3)	0.0634
RLN invasion	Yes	11	7	4	0.0073*
	No	78	19	59	
Trachea invasion	Yes	4	2	2	0.3495
	No	85	24	61	
Esophagus invasion	Yes	1	1	0	0.1175
	No	88	25	63	
Central node METS	Yes	70	22	48	0.3778
	No	19	4	15	
N of central METS (mean (SD))		6.09 (5.56)	9.05 (7.02)	4.73 (4.17)	0.002*
Lateral node METS	Yes	70	24	46	0.0434*
	No	19	2	17	
N of lateral node METS (mean (SD))		5 (3.81)	7.5 (4.14)	3.70 (2.90)	0.0001*
LNR ≥ 0.5	Yes	21	7	14	0.6348
	No	68	19	49	

*: p values <0.05, Dashes (-): missing data. TT: total thyroidectomy. CND: central neck dissection. LND: lateral neck dissection. RAI: radioactive iodine. ETE: extra thyroid extension. PNI: perineural invasion. LVI: lymphovascular invasion. LNR: lymph node ratio.

Table 2: Univariate cox proportional hazard regression analysis of disease-free survival for patients with locoregionally advanced papillary thyroid carcinoma.

Characteristic	N	HR	(95% CI)	P value
Nodal involvement	85	21.86	(0.01-90K)	0.468
LNR ≥0.5	21	1.23	(0.52-2.93)	0.642
ETE	43	1.41	(0.65-3.06)	0.392
Size ≥4	17	2.31	(0.96-5.54)	0.062
Male sex	48	1.20	(0.54-2.67)	0.654
Age ≥55	34	1.43	(0.64-3.19)	0.384

Table 3: Number of recurrences in adults < 55 years old with locoregionally advanced PTC based on various clinical and histopathological features.

Characteristic	Overall	Recurrence	No recurrence	P value
N	55	16	39	
f/u time month (median IQR)	52.37 (19.30-119.97)	16.45 (6.46-39.87)	62.89 (26.70-136.27)	0.9312
Sex				0.4479
Female	25	6	19	
Male	30	10	20	
Age (mean (SD))	37 (11.67)	33 (10.08)	39 (11.93)	0.0697
Operative method				0.3307
TT /c CND	10	2	8	
TT /c CND /c LND	40	14	26	
TT /c LND	5	0	5	
TT	0	0	0	
Adjuvant RAI				0.8679
Yes	52	15	37	
No	3	1	2	
Laterality				0.2822
Right	16	5	11	
Left	19	3	16	
Bilateral	18	8	10	
-	2	0	2	
Tumor size				0.2322
≥ 4 cm	6	3	3	
< 4 cm	49	13	36	
Nodal involvement				0.518
Yes	54	16	38	
No	1	0	1	
Largest nodal metastasis in cm (mean (SD))	3 (1.92)	2.79 (1.22)	2.81 (2.18)	0.9727
Thyroid weight in g (mean (SD))	27.13 (26.58)	40.44 (43.93)	21.05 (8.13)	0.0098*
ETE				0.2479
Yes	21	8	13	
No	34	8	26	
Resection margin				0.3447
Clear	40	10	30	
Involved	10	4	6	
-	5	2	3	
PNI				0.0621
Yes	1	1	0	
No	43	9	34	
-	11	6	5	
LVI				0.0075*
Yes	15	8	7	
No	36	6	30	
-	4	2	2	
Length of admission in days (median IQR)	2 [1-3]	2 [2-4]	2 [1-2.75]	0.2841
RLN invasion				0.5072
Yes	2	1	1	
No	53	15	38	
Trachea invasion				0.5072
Yes	2	1	1	
No	53	15	38	
Esophagus invasion				n/a
Yes	0	0	0	
No	55	16	39	
Central node METS				0.1941
Yes	46	15	31	

Continued.

Characteristic		Overall	Recurrence	No recurrence	P value
	No	9	1	8	
N of central METS (mean (SD))		6.69 (6.48)	11.33 (7.41)	4.65 (4.87)	0.0002*
Lateral node METS	Yes	44	14	30	0.3731
	No	11	2	9	
N of lateral node METS (mean (SD))		4.72 (4.20)	9 (4.51)	3.06 (2.64)	0.0001*
LNR ≥ 0.5	Yes	17	5	12	0.972
	No	38	11	27	

*: p-values < 0.05 Dashes (-): missing data. TT: total thyroidectomy. CND: central neck dissection. LND: lateral neck dissection. RAI: radioactive iodine. ETE: extra thyroid extension. PNI: perineural invasion. LVI: lymphovascular invasion. LNR: lymph node ratio.

DISCUSSION

PTC is the most common differentiated thyroid malignancy and carries an overall favorable prognosis. However, several factors have been categorized as high risk with the potential to negatively impact the prognosis. These include factors reflecting advanced locoregional disease^{6,14}. The AJCC 8th Edition Cancer Staging Manual indicates a worse prognosis in patients ≥ 55 with a primary tumor ≥ 4 cm, involvement of cervical lymph nodes, gross extra thyroid extension or distal metastasis. Results show that patients ≥ 18 years of age with locoregionally advanced tumors did not have an increased risk of recurrence when categorized based on presence of a primary tumor ≥ 4 cm, ETE, and nodal involvement ($p = 0.2278, 0.1886, 0.2554$, respectively). Those younger than 55 also did not have a significant increase in recurrence with primary tumor ≥ 4 cm, ETE, and nodal involvement ($p=0.232, 0.248$ and 0.518 , respectively). This speaks of the indolent nature of the disease that predominates even in the presence of locoregionally advanced disease. However, in our main group, those with positive lateral compartment lymph nodes had significantly higher rates of recurrence ($p = 0.0434$). In our age-based subgroup, lateral nodal metastasis was not associated with increased recurrence ($p=0.373$).

Therefore, the presence of lateral compartment nodal metastases may be an indication for more aggressive adjuvant management and closer follow up period, for patient older than 55. This does not align with the results reported by Lee et al, which demonstrated that PTC metastasized to central or lateral nodes was not correlated with increased rates of recurrence¹. Patients who had recurrence had a mean number of involved nodes in the central and lateral compartments greater than what we observed in the recurrence free group ($p=0.002$ and 0.0001 , respectively). Mean values of number of central and lateral nodal metastases remained significantly greater in those who recurred ($p=0.0002$ and 0.0001 , respectively). While patients with recurrence had a statistically greater mean value of involved cervical nodes, the ratio of positive lymph nodes to total nodes evaluated did not show a statistically significant correlation with recurrence ($p=0.6348$ in main group,

0.972 in subgroup). This is difficult to interpret but could be due to more extensive neck dissections in those with more advanced disease that was identified preoperatively, increasing the number of uninvolved nodes sent to pathology. Notably, nearly all the patients returned by our inclusion/exclusion criteria had nodal involvement leading to a small comparison group ($n=4$).

This may have contributed to the lack of significance when comparing recurrence based on presence or absence of nodal involvement. No significant difference was observed in our Kaplan Meier curve assessing disease free survival in those with nodal involvement compared to patients without nodal involvement ($p=0.270$ in main group, 0.456 in subgroup). To work around the limitation of a small comparison group, we repeated our survival analysis using ratio of involved lymph nodes. While those with $LNR \geq 0.5$ had a decreased DFS, it was not statistically significant ($p=0.641$ in main group, 0.0846 in subgroup). It is noteworthy that all 4 patients without nodal involvement remained disease free for the entirety of the follow-up period.

ETE did not show a statistically significant increase in recurrence in the main group or subgroup ($p=0.1886$ and 0.248 , respectively). ETE was not associated with reduction in DFS on Kaplan Meier curve for main group or subgroup either ($p=0.389$ and 0.466 , respectively). However, when viewing individual markers of gross ETE, RLN involvement was significantly associated with increased recurrence in main group but not in our subgroup ($p=0.0073$ and 0.507 , respectively). The impact of ETE in PTC has been debated. Kim et al reported that extra thyroid involvement of a single, such as the RLN, or multiple structures did not impact recurrence or overall survival significantly.¹⁵ On the other hand, Ito et al. concluded that significant ETE of PTC was a strong predictor of recurrence and decreased survival.¹⁶

Large size of primary tumor is another feature of locoregionally advanced disease. While our chi square analysis failed to show a significant difference in recurrence among all adults based on size, Kaplan Meier curve showed the greatest decrease is DFS in those primary tumors ≥ 4 cm ($p=0.054$) and closest to statistical significance in our univariate cox analysis. On the other hand, the decrease in DFS in adults younger than 55 was

not statistically significant, when based on presence of tumor size ≥ 4 cm ($p=0.115$). Lee et al did not find a significant difference in recurrence in PTC with primary tumors > 20 mm compared to those with smaller tumors and Ito et al found no significant difference in recurrence when primary tumor size was > 4 cm.^{1,16}

Recent studies have reported the ten-year survival rate of PTC to be more than 95%. In our study, three of 28 patients died over ten years. While the limited number of patients who were followed-up with for ten years may contribute to the relatively lower 10-year survival rate in our study, a nearly 90% survival rate is consistent with the overall indolent pathology. Of note, 3 patients were followed for more than 18 years and one of them passed away making the survival proportion 66.67%. This is likely a significant underestimation of survival, largely due to the very small number of cases followed that far out.

Our results show that a distant location of recurrence and likelihood of undergoing surgical management after recurrence were not significantly increased when patients had more features of locoregionally advanced disease. However, our sample only included 4 patients with distant location of recurrence, and this limits our ability to make meaningful conclusions on the association between locoregional advancement and location of recurrence or type of secondary treatment. Interestingly, Ito et al. found ETE to be associated with a distant location of recurrence.¹⁶ The small number of distant recurrences limited our ability to perform subgroup analysis.

There are some limitations to this study. First being is that this study is a retrospective study, which means all of the survival data and tumor pathology were extracted from available data in our electronic medical record. Pathology reports were frequently missing information. We also used documented deaths to assess overall survival. Transferring to a different healthcare system before passing or missing death documentation from our medical record may have occurred. Second, our study was limited to patients from a single institution and the population was relatively small with smaller subgroups. Future research would be to consider large scale, multi-center, prospective studies to eliminate these limitations.

CONCLUSION

The study of locoregionally advanced papillary thyroid carcinoma (PTC) found that traditional features like tumor size, extrathyroidal extension (ETE), and nodal involvement were not individually associated with increased recurrence in adults, including those under 55.

However, positive lateral compartment lymph nodes were significantly linked to higher recurrence in the overall adult group, suggesting their importance as a specific prognostic indicator for patients aged 55 and older. While

the number of involved lymph nodes was higher in recurrent cases, the lymph node ratio was not, possibly due to more extensive dissections. Recurrent laryngeal nerve involvement, a specific ETE marker, also showed a significant association with recurrence in the main cohort. Despite these findings, the overall prognosis remains good. Our study's retrospective nature, single-institution data, and limited sample size necessitate further large-scale, prospective research to validate these observations and refine prognostic tools for personalized PTC management.

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