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RESEARCH ARTICLE

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Outcomes of surgery and postoperative radiation therapy in managing medullary thyroid carcinoma

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Abstract

Background and Objectives: We evaluated the outcomes of surgery with or without postoperative radiation therapy (PORT) in the management of medullary thyroid carcinoma (MTC).

Methods: From two tertiary cancer centers, 297 consecutive patients with MTC treated with PORT (n = 46) between 1990 and 2016 or surgery alone (n = 251) between 2000 and 2016 were reviewed.

Results: Ten-year cumulative incidences of locoregional and distant failure were 30.2% and 24.9% in the surgery cohort, and 16.9% and 55.2% in the PORT cohort. In the surgery alone cohort, T4 disease, extrathyroidal extension, N1 disease, extranodal extension (ENE), and residual disease after surgery were associated with local failure. The PORT cohort had significantly higher proportions of patients with T4 disease, N1 disease, ENE, and residual disease.

Conclusions: High-risk clinical features can help identify patients with MTC at high-risk for local failure after surgery alone. Patients with high-risk clinical features had effective locoregional control after PORT.

KEYWORDS
medullary thyroid carcinoma, thyroid malignancy, head and neck cancer, postoperative radiotherapy

1 | INTRODUCTION

Medullary thyroid cancer (MTC) is a rare tumor of parafollicular C-cells,[1] accounting 1%-5% of all thyroid tumors.[2,3] Eighty percent of MTC cases are sporadic, with the remainder associated with hereditary endocrine tumor syndromes caused by autosomal-dominant germline mutations in the *RET* proto-oncogene: multiple endocrine neoplasia 2A (MEN2A) and MEN2B.[4-6] Morbidity and mortality from MTC can be due to locoregional progression of disease, and locoregional control is important in its management,[7-10] particularly as approximately 50% of patients present with locally advanced disease.[2,11]

Andries Groen and Thomas Beckham should be considered joint first author.

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Surgery is the mainstay of local therapy for MTC, usually consisting of a total thyroidectomy with central and bilateral cervical lymph node dissection,[2] however several high-risk features increase the risk of local recurrence after surgery alone.[12] In the past MTC has been described as resistant to radiotherapy, although there are retrospective reports that demonstrate the value of radiotherapy.[13] There are no prospective data regarding the outcomes of radiotherapy in MTC. Given the paucity of literature on the outcomes of comprehensive local therapy of MTC, we sought to evaluate the outcomes of patients treated with surgery alone and surgery followed by postoperative radiotherapy (PORT) in a large cohort from two tertiary referral centers.

2 | MATERIALS AND METHODS

2.1 | Patients

The institutional review and privacy boards of both institutions approved this retrospective study with a waiver of informed consent. Patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act and data collection and analyses were performed according to national guidelines and the rules approved by the local ethics committee. Between January 2000 and November 2016, 251 consecutive surgically treated patients at Memorial Sloan Kettering Cancer Center and University Medical Center Groningen were included. Furthermore, between January 1990 and November 2016, 46 consecutive patients with MTC who received radiotherapy after surgical management, 80.4% adjuvant to surgery (within 120 days of last surgery) and 19.6% after this timeframe (range: 127-1073 days after surgery), were included. For simplicity, all radiation is referred to as PORT in this manuscript. Five patients who received radiotherapy alone without prior surgery were excluded from our analysis. Charlson Comorbidity Index[14] was calculated based on medical history and disease status documented at the time of initial consultation. The data that support the findings of this study are available upon request from the corresponding author and after Institutional Review Board approval of all institutions.

2.2 | Staging and pathologic findings

MTC was histologically confirmed by internal pathological review. T and N-stage were determined from the tumor extent at initial diagnosis. Evidence of distant metastasis (DM) was recorded at the time of surgery or start of PORT. Staging was performed according to the seventh edition of the AJCC cancer staging manual.[15]

2.3 | Radiotherapy technique

Target areas varied between practitioners, institutions and evolved over the time of treatment, but in general patients were prescribed as follows: (a) low-risk areas including the upper and lower paratracheal nodal levels and cervical lymph node levels II-V/upper mediastinum nodes level VIIA to 54 Gy, (b) high-risk areas including the operative or tumor bed, operative thyroid gland volume, tracheoesophageal grooves and central nodal compartment (level VI) to 60 Gy, (c) close or microscopically positive margins to 66 Gy, and (d) areas of gross disease to 70 Gy. The clinical target volume was defined as the gross tumor volume plus a margin for potential microscopic spread, including high-risk lymph node areas. The clinical target volume was expanded to a planning target volume to account for intrafraction patient motion and interfraction setup error.

2.4 | Follow-up

In patients with PORT, outcomes were estimated from the end of PORT, while for patients with surgery only, outcomes were estimated from the date of definitive surgery. Some surgical patients had staged operations, in which case the final operation in the series was the start of follow-up. Local progression free survival (LPFS) was defined as the time interval from end of treatment until progression of locoregional disease. Progression of locoregional disease was defined as an increase in the size of the primary tumor and/or regional lymph nodes detected by clinical/radiographic or pathological examination. Death was treated as a competing risk to LPFS and patients who were alive and disease free at last follow-up were censored at last date known alive. Distant metastasis free survival (DMFS) was defined as the time between end of treatment and. We considered distant metastasis to be any disease outside the cervical neck and the upper mediastinum. Death without DM was treated as a competing risk to DMFS and patients who were alive and without DM were censored at last date known alive. Patients without evidence of metastatic disease at the time of surgery or radiotherapy were followed to determine the DMFS, which was determined by either strong radiographic suspicion or pathological evidence of distant disease. Follow-up assessment included a physical examination, serum calcitonin, and carcinoembryonic antigen levels, neck ultrasound and/or computerized tomography (CT)/magnetic resonance imaging, and PET-CT as clinically indicated. Overall survival (OS) was assessed from the date of surgery or start date of PORT until death or last follow-up date; patients alive at last follow-up were censored

2.5 | Statistical analysis

We compared patient and clinicopathologic characteristics between those who had surgery only and those who also had PORT using Fisher's Exact test and the Wilcoxon rank-sum test, where appropriate. Given inherent clinical differences in these cohorts and demonstrated through our comparisons, all analyses were performed separately for those with and without PORT.

We estimated LPFS, OS, and DMFS with Kaplan-Meier methods and cumulative incidence where appropriate. The relationship

TABLE 1 Patient and clinical characteristics

	Complete cohort	Surgery only cohort	PORT cohort	*P* value
Sample size	297	251	46	
Sex				
Male	146 (49.2)	112 (44.6)	34 (73.9)	<.001
Female	151 (50.8)	139 (55.4)	12 (26.1)	
Follow-up, mo				
Median (range)	59.6 (0.3-319.0)	61.5 (0.3-215.1)	27.3 (2.3-319.0)	
Age at last surgery, y				
Median (range)	54 (2-88)	53 (2-88)	59 (29-77)	.014
≤45 y	87 (29.3)	79 (31.5)	8 (17.4)	.055
>45 y	210 (70.7)	172 (68.5)	38 (82.6)	
CCI score				
Median (range)	3 (2-7)	3 (2-7)	3 (2-7)	.33
Number of operations				
Median (range)	1 (1-6)	1 (1-3)	2 (1-6)	<.001
T-stage				
T1	122 (41.1)	118 (47)	4 (8.7)	<.001
T2	53 (17.8)	48 (19.1)	5 (10.9)	
T3	29 (9.8)	25 (10)	4 (8.7)	
T4	90 (30.3)	59 (23.5)	31 (67.4)	
Missing	3 (1)	1 (0.4)	2 (4.3)	
N-stage				
N0	132 (44.4)	129 (51.4)	3 (6.5)	<.001
N1	165 (55.6)	122 (48.6)	43 (93.5)	
Evidence of DM				
No	278 (93.6)	243 (96.8)	35 (76.1)	<.001
Yes	19 (6.4)	8 (3.2)	11 (23.9)	
ETE				
Yes	109 (36.7)	77 (30.7)	32 (69.6)	<.001
Unknown	2 (0.7)	0 (0)	2 (4.3)	
ENE				
Yes	120 (40.4)	85 (33.9)	35 (76.1)	<.001
Unknown	5 (1.7)	2 (0.8)	3 (6.5)	
Surgical margin status				
Negative	215 (72.4)	211 (84.1)	4 (8.7)	<.001
Microscopic	56 (18.9)	37 (14.7)	19 (41.3)	
Macroscopic	24 (8.1)	1 (0.4)	23 (50)	
Unknown	2 (0.7)	2 (0.8)	0 (0)	
RET mutation				
Yes	65 (21.9)	62 (24.7)	3 (6.5)	.07
Unknown	31 (10.4)	14 (5.6)	17 (37)	
Pretreatment calcitonin				
Median (range)	833.5 (0.3-260000.0)	787.0 (0.3-196500.0)	3118.0 (3.4-260 000.0)	.23
N missing	(103)	(86)	(17)	
Posttreatment calcitonin				
Median (range)	8.8 (0.2-1277 000.0)	5.8 (0.2-1277 000.0)	592.5 (0.5-541 000.0)	<.001

Note: Numbers represent frequency with percent of given cohort, unless otherwise specified.
Abbreviations: CCI, Charlson comorbidity index; DM, distant metastasis; ETE, extrathyroidal extension; ENE, extranodal extension; PORT, postoperative radiotherapy.

between clinicopathologic characteristics and outcomes were assessed with univariable and multivariable Cox proportional hazards and competing risks regression, where appropriate. We checked for multicollinearity in our multivariable models through tests of association between predictor variables. To prevent overfitting, for OS analyses, factors significant at $P < .05$ were included in backwards selection models with exit criterion of $P < .05$. For competing risks analyses, variables significant at $P < .05$ were included in multivariable models. If one or fewer factors were significant in univariable analyses at $P < .05$, no multivariable models were built.

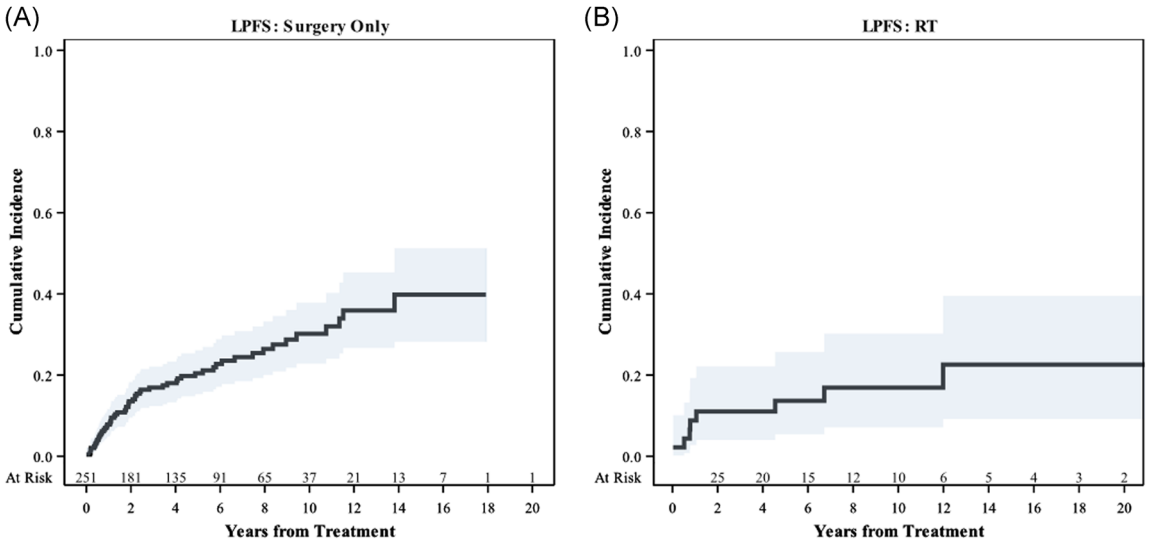

FIGURE 1 Locoregional recurrence for (A) surgery only patients and (B) PORT patients. The cumulative incidence of locoregional failure is depicted for the surgery only cohort (A) and the PORT cohort (B). Shading represents the 95% confidence interval of the estimate. The number of patients at risk is depicted above the x-axis. LPFS, local progression free survival; PORT, postoperative radiotherapy; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

Two sided *P*-values < .05 were considered statistically significant. All analyses were performed with SAS 9.4 (The SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient and tumor characteristics

The total sample included 297 patients, 251 without PORT and 46 with PORT. The median age was 54 years (range, 2-88 years). Patients who received PORT were older (median: 59 years; range, 29-77 years) compared to patients who only received surgery (median: 53 years; range, 2-88 years), $P = .014$ (Table 1). The median follow-up in survivors was 59 months (range, 0-319). Sixty-five patients (21.9%) had a known *RET* mutation and 31 (10.4%) had unknown *RET* mutations status. The rate of missing *RET* mutation was higher in patients with PORT (37%, 17/46) than in the surgery only cohort (5.6%, 14/251). The cohorts differed significantly on several characteristics with the patient receiving PORT having high-risk features such as more T4 disease, node positive disease, presence of DM, extrathyroidal extension (ETE), extranodal extension (ENE), and positive surgical margins (Table 1).

3.2 | Treatment characteristics

The median number of surgeries in the whole cohort was 1 (range, 1-6) with 84% (249/297) receiving one surgery, 13% (39/297) receiving two surgeries, 2% (5/297) received three surgeries and the remaining 1% (4/297) receiving 4 to 6 surgeries. Patients who received PORT had more surgeries (median: 2, range, 1-6) compared to surgery only patients (median: 1, range, 1-3), $P < .001$. The median PORT dose was 65.4 Gy (range, 23.4-70.0 Gy) in a median of 33 fractions (range, 13-38 fractions). PORT was initiated a median 67 days after last surgery (range, 30-1073 days). Three-dimensional conformal radiotherapy was used in 22 patients (47.8%) and intensity modulated radiotherapy was used in 24 patients (52.2%).

3.3 | Locoregional failure

3.3.1 | Surgery only cohort

The 5-and 10-year cumulative incidence of locoregional failure were 20.4% (95% confidence interval [CI]: 15.3%-26.1%) and 30.2% (95% CI: 22.8%-37.9%), respectively, for the surgery only cohort (Figure 1) A. Fifty-nine patients failed locoregionally, of whom 32 patients underwent additional surgery for local control.

In univariable analyses, patients with T4 disease (hazard ratio [HR]: 2.06; 95%CI: 1.22-3.46; $P = .007$), patients with *ETE* (HR: 2.61; 95%CI: 1.57-4.33; $P < .001$), patients with N1 disease (HR: 3.98; 95%CI: 2.22-7.13; $P < .001$), patients with ENE (HR: 3.42; 95%CI: 2.01-5.82; $P < .001$), and patients with residual disease (HR: 2.36; 95%CI: 1.35-4.14; $P = .003$) were at higher risk of local progression. No significant difference in LPFS was seen by age ($P = .21$), M-stage ($P = .51$), or *RET* mutation ($P = .16$; Table 2). In a multivariable model with T-stage ETE, N-stage, ENE, and residual disease, none of the factors were found to significantly predict LPFS ($P = .06$-77), although N-stage approached significance (HR: 2.34; 95%CI: 0.96-5.71; $P = .06$). Additionally, T-stage reversed direction, suggesting multicollinearity (Table 2). In the surgery only cohort, these five factors were significantly associated with one another (all $P < .001$), which further suggests multicollinearity may be present.

TABLE 2 Univariable and multivariable competing risks regression for LPFS

		LPFS: Univariable			LPFS: Multivariable		
		HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Surgery only cohort							
Age at last surgery, y	>45	0.72	(0.42-1.21)	.21	…		
	<=45	REF			…		
T-stage	T4	2.06	(1.22-3.46)	.007	0.61	(0.20-1.84)	.38
	T1-T3	REF			REF		
ETE	Yes	2.61	(1.57-4.33)	<.001	1.96	(0.66-5.85)	.23
	No	REF			REF		
N-stage	N1	3.98	(2.22-7.13)	<.001	2.34	(0.96-5.71)	.06
	N0	REF			REF		
ENE	Yes	3.42	(2.01-5.82)	<.001	1.49	(0.65-3.43)	.35
	No	REF			REF		
Evidence of DM	Yes	0.49	(0.06-4.04)	.51	…		
	No	REF			…		
Residual disease	Yes	2.36	(1.35-4.14)	.003	1.13	(0.49-2.58)	.77
	No	REF			REF		
RET mutation	Yes	0.63	(0.33-1.20)	.16	…		
	No	REF			…		
PORT cohort							
Age at last surgery, y	>45	1.13	(0.14-9.26)	.91	…		
	<=45	REF			…		
T-stage	T4	1.09	(0.22-5.29)	.91	…		
	T1-T3	REF			…		
ETE	Yes	2.96	(0.39-22.75)	.30	…		
	No	REF			…		
N-stage	N1	0.33	(0.05-2.26)	.26	…		
	N0	REF			…		
ENE	Yes	0.57	(0.12-2.81)	.49	…		
	No	REF			…		
Evidence of DM	Yes	0.48	(0.06-3.75)	.49	…		
	No	REF			…		
Residual disease	Yes	0.25	(0.08-0.79)	.018	…		
	No	REF			…		
RET mutation	Yes	3.06	(0.42-22.27)	.27	…		
	No	REF			…		

Note: Numbers represent frequency with percent of given cohort, unless otherwise specified.
Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; DM, distant metastases; ENE, extranodal extension; ETE, extrathyroidal extension; HR, hazard ratio; LPFS, local progression free survival; PORT, postoperative radiotherapy.

3.3.2 | PORT cohort

The 5-and 10-year cumulative incidence of locoregional failure were 13.7% (95%CI: 5.4%-25.7%) and 16.9% (95%CI: 7.1%-30.2%), respectively, (Figure 1B) for the PORT group. Eight patients failed locally. Among the eight local failures from the PORT cohort, two patients failed in the thyroid bed or tracheoesophageal groove, one of whom concomitantly failed in the cervical lymph nodes. The remaining six patients failed in the mediastinum, one of whom concomitantly failed in the cervical lymph nodes.

In the PORT cohort, patients with residual disease were at a lower risk of locoregional failure (HR: 0.25; 95%CI: 0.08-0.79; $P = .018$); however, no significant associations were found between any of the other predictors and LPFS ($P = .26$-$.91$; Table 2). Given that only one factor was significant and the number of events were limited, no multivariable model was built.

3.4 | Overall survival

3.4.1 | Surgery only cohort

Five-and 10-year OS were 89.3% (95%CI: 84.1%-92.8%) and 75.7% (95%CI: 66.3%-82.8%), respectively, with 37 deaths by the end of follow-up (Figure 2A). In univariable analyses, all factors tested were significantly associated with OS (Table 3). Patients who were older than 45 (HR: 3.14; 95%CI: 1.30-7.58; $P = .011$), patients with T4

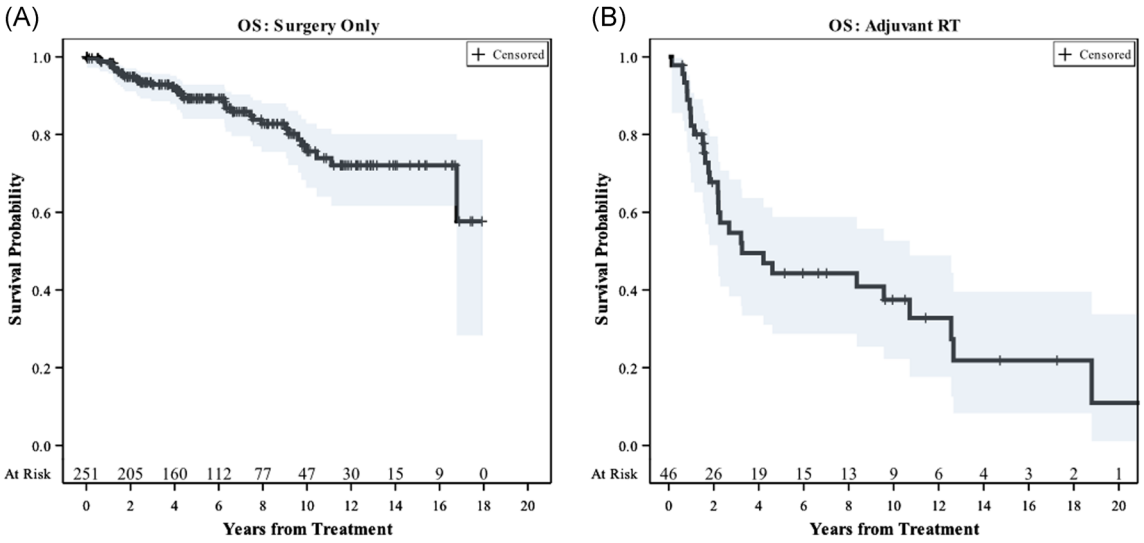

FIGURE 2 Overall survival for (A) surgery only patients and (B) PORT patients. Kaplan-Meier estimates of overall survival for the (A) surgery alone and (B) PORT cohorts. Shading indicates the 95% confidence interval of the estimate. The number of patients at risk are depicted above the x-axis. OS, overall survival; PORT, postoperative radiation therapy; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

disease (HR: 3.80; 95%CI: 1.99-7.28; $P < .001$, patients with ETE (HR: 2.87; 95%CI: 1.50-5.50; $P = .002$), patients with N1 disease (HR: 2.29; 95%CI: 1.15-4.55; $P = .019$), patients with metastases at the time of surgery (HR: 5.18; 95%CI: 1.83-14.71; $P = .002$), and patients with residual disease (HR: 3.69; 95%CI: 1.88-7.22; $P < .001$), were all at a higher risk of death on univariable analyses compared to their respective reference groups. Patients with *RET* mutation were at a lower risk of death (HR: 0.29; 95%CI: 0.10-0.84; $P = .023$).

Given the number of deaths, we entered these significant factors into a backwards selection model. After backwards selection, age at last surgery (HR: 2.75; 95%CI: 1.14-6.65; $P = .025$), T-stage (HR: 2.98; 95%CI: 1.51-5.92; $P = .002$), and M-Stage at the time of surgery (HR: 3.26; 95%CI: 1.10-9.68; $P = .033$) remained in the model as significant predictors of OS (Table 3).

3.4.2 | PORT cohort

The 5-and 10-year OS were 44.3% (95%CI: 28.7%-58.8%) and 37.5% (95%CI: 22.3%-52.7%; Figure 2B) for the PORT cohort. By the end of follow-up, 29 patients died with a median estimate of 3.3 years (95%CI: 2.2-10.7 years) after PORT. Patients with ENE were at a lower risk of death (HR: 0.32; 95%CI: 0.13-0.83; $P = .018$). No other factors were found to be significantly associated with OS ($P = 0.14$-0.59; Table 3).

3.5 | Distant failure

3.5.1 | Surgery only cohort

Of the 243 patients without distant metastases after surgery, 47 subsequently developed metastases. The 5-and 10-year cumulative incidence of metastatic disease were 17.0% (95%CI: 12.1%-22.5%) and 24.9% (95%CI: 18.0%-32.4%; Figure 3A). Patients with T4 disease were at a higher risk of distant failure than T1-T3 (HR: 2.19; 95%CI: 1.21-3.95; $P = .009$). Additionally, patients with ETE (HR: 2.52; 95%CI: 1.42-4.49; $P = .002$), N1 disease (HR: 2.94; 95%CI: 1.61-5.39; $P < .001$), ENE (HR: 3.68; 95%CI: 2.06-6.57; $P < .001$), and residual disease (HR: 2.46; 95%CI: 1.29-4.69; $P = .006$) were all at a significantly higher risk of distant metastases on univariable analyses. No significant difference in DMFS was found based on *RET* mutation ($P = .15$) or age ($P > .95$; Table 4). We entered T-stage, ETE, N-Stage, and ENE into a multivariable model. Similar to LPFS analyses, none of the factors were significantly associated with DMFS on multivariable analyses ($P = .07$-$.89$), although ENE approached significance (HR: 2.84; 95% CI: 0.93-8.65; $P = .07$; Table 4).

3.5.2 | PORT cohort

Of the 35 patients without metastases at the start of radiation treatment, 19 subsequently developed distant metastases. The 5-and 10-year cumulative incidence of metastatic disease were 50.8% (95% CI: 32.3%-66.6%) and 55.2% (95%CI: 35.5%-71.2%) (Figure 3B). No significant differences were seen in DMFS for any of the predictor variables in the PORT cohort ($P = .22$-$.84$; Table 4).

4 | DISCUSSION

The standard of care for patients with sporadic or hereditary MTC is surgical resection, usually consisting of total thyroidectomy and dissection with central and bilateral cervical lymph node compartments.[2] However, even with recommended standard surgery, locoregional progression is not uncommon. The 10-year cumulative incidence of locoregional failure of our surgery only cohort of 30.2% is consistent with reports from other smaller series.[16-18] Given the

TABLE 3 Univariable and multivariable Cox regression for overall survival

		LPFS: Univariable			LPFS: Multivariable		
		HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Surgery only cohort							
Age at last surgery, y	>45 <=45	3.14 REF	(1.30-7.58)	.011	2.75 …	(1.14-6.65)	.025
T-stage	T4 T1-T3	3.80 REF	(1.99 -7.28)	<.001	2.98 …	(1.51-5.92)	.002
ETE	Yes No	2.87 REF	(1.50-5.50)	.002	… …		
N-stage	N1 N0	2.29 REF	(1.15-4.55)	.019	… …		
ENE	Yes No	2.09 REF	(1.09-3.98)	.026	… …		
M-stage	M1 M0	5.18 REF	(1.83-14.71)	.002	3.26 …	(1.10-9.68)	.033
Residual disease	Yes No	3.69 REF	(1.88-7.22)	<.001	… …		
RET mutation	Yes No	0.29 REF	(0.10-0.84)	.023	… …		
PORT cohort							
Age at last surgery, y	>45 <=45	1.39 REF	(0.42-4.66)	.59	… …		
T-stage	T4 T1-T3	1.39 REF	(0.56-3.46)	.48	… …		
ETE	Yes No	1.63 REF	(0.69-3.85)	.27	… …		
N-stage	N1 N0	0.33 REF	(0.07-1.46)	.14	… …		
ENE	Yes No	0.32 REF	(0.13-0.83)	.018	… …		
Evidence of DM	Yes No	1.86 REF	(0.76-4.57)	.17	… …		
Residual disease	Yes No	1.69 REF	(0.40-7.21)	.48	… …		
RET mutation	Yes No	0.37 REF	(0.05-2.83)	.34	… …		

Abbreviations: CI, confidence interval; ENE, extranodal extension, ETE, extrathyroidal extension; HR, hazard ratio; PORT, postoperative radiotherapy.

risk of locoregional progression after surgery alone, it is important to evaluate which features may predict locoregional progression. Previous reports have found that patients with ETE, lymph node involvement, and ENE are considered to be at high-risk for locoregional progression.[2,17] In our surgery only cohort, T4 disease, ETE, N-stage, ENE, and residual disease (microscopic and macroscopic) were associated with a decreased locoregional progression free survival on univariable analysis. Due to this high degree of multicollinearity, these factors effectively canceled each other out in the model as they share the same underlying information in predicting locoregional progression. The parameter estimates in the multivariable analyses are therefore not reliable estimates of each individual feature's association with locoregional progression.

The American Thyroid Association states that local PORT should be considered in patients with a high-risk for local recurrence and those at risk of obstruction of the airway.[2] However, the indications and efficacy of PORT for MTC have not been established prospectively, and retrospective reports are limited. Brierly et al[17] showed in one of the largest prior reports of patients with MTC, there was no difference in local or regional relapse-free rates between patients who received PORT (n = 46) and those that were observed after surgery (n = 27). However, in high-risk patients, defined as those with microscopic residual disease, ETE or lymph node involvement, the 10-year LPFS was 86% with PORT and 52% for those with no PORT (n = 25; *P* = .049). While this may suggest that risk factors for local failure can be mitigated successfully with PORT, the authors assessed LPFS and OS from the time of diagnosis. They did not properly account for the time between diagnosis and PORT where they may be incorrectly attributing the effects of PORT on outcomes before PORT has taken place. This has been referred to in the literature as the time

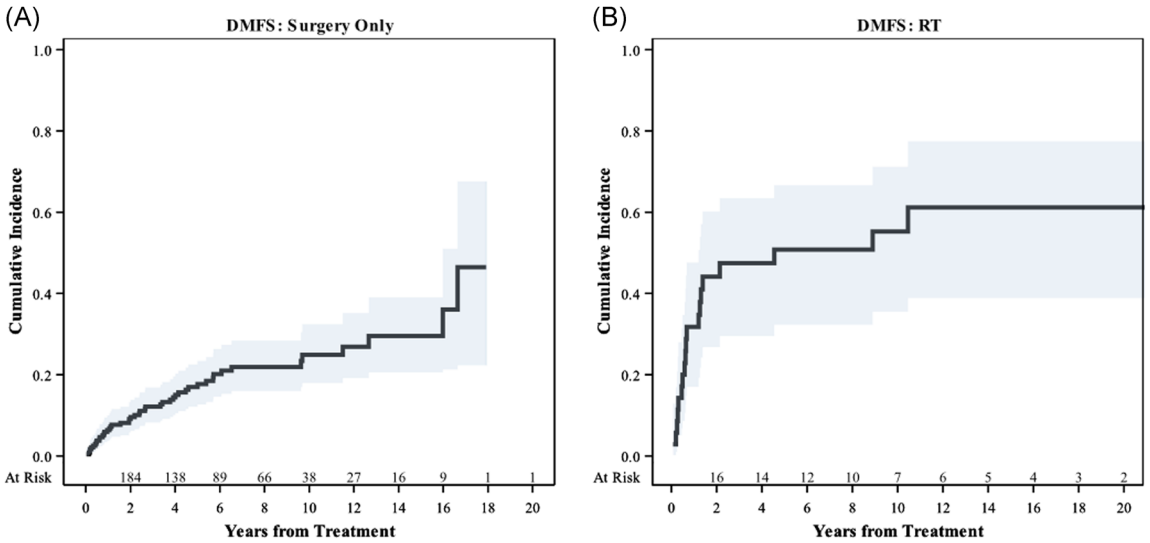

FIGURE 3 Distant metastases for (A) surgery only patients and (B) PORT patients. The cumulative incidence of distant metastatic failure is depicted for the surgery only cohort (A) and the PORT cohort (B). Shading represents the 95% confidence interval of the estimate. The number of patients at risk is depicted above the x-axis. DMFS, distant metastasis free survival; PORT, postoperative radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

immortal or time dependent bias.[19] Martinez et al[20] showed no OS benefit of PORT in patients with MTC and positive lymph nodes in an analysis of the SEER data from 1998 to 2004. However, the effect on LPFS was not reported and other critical determinants of risk of local failure such as ENE and margin status were not included. Schwartz et al[13] showed a 5-year LPFS of 87% and 5-year OS of 56% in 34 patients who received PORT for high-risk features after surgery including stage IV disease, recurrent disease, and positive surgical margins. The patients were treated with a median dose of 60 Gy with conformal techniques. In another study, 51 patients with PORT with doses from 60 to 65 Gy were analyzed and on multivariable analysis postoperative residual disease status ($P < .001$) was the only significant variable for local progression free survival.[21] Surprisingly, in our patients with PORT, residual disease was associated with a reduced risk of local progression, although residual disease was so common (91%) in patients with PORT and so few locoregional failures occurred (n = 8) that this finding may not be reliable.

Our surgery only and PORT cohorts differed significantly on several important high-risk characteristics, including tumor stage, nodal stage, metastasis, ETE, ENE, and surgical margin status. Indeed, it is clearly apparent that presence of one or more of these features was directly related to the decision to proceed with PORT. We attempted to construct a propensity matched analysis of these groups to better compare outcomes between high-risk patients receiving surgery alone and those receiving PORT, but found the groups too fundamentally different to create the model. Despite this imbalance in features associated with a high-risk of local recurrence, patients with PORT may appear to have a lower rate of local recurrence than the surgery alone cohort when looking at the point estimates. While this may suggest that PORT should be considered in patients with MTC who would clinically benefit from enhanced locoregional control, as we state above, these groups cannot be directly compared. Further, the confidence intervals of these groups overlap, suggesting that the true population estimate may not differ between these groups. It must also be noted that patients with PORT had shorter median follow-up and OS with a higher incidence of distant metastases than the surgery alone group. Given these differences, patients with PORT generally had a shorter evaluation period during which to develop locoregional failure. Moreover, patients may be evaluated differently after the development of distant metastases compared to patients without known disease activity. In a patient without evidence of metastatic disease, a small locoregional recurrence may be detected by careful physical exam or on imaging in contrast to a patient with disseminated disease whose locoregional disease control may not be scrutinized unless it is symptomatic. Finally, while a statistically rigorous evaluation of systemic therapy utilization is not within the scope of this study, more patients in the PORT group received some form of systemic therapy before their LPFS censorship (37%) compared to the surgery alone group (5.0%). Thus, it should be noted that systemic therapy could have contributed to locoregional control in these patients.

It is important to mention several limitations of the present study. This is a retrospective cohort study, and interpretation should be with the limitations inherent to retrospective studies kept in mind. Numerous factors go into deciding appropriate therapy for a patient, many of which cannot be easily determined from the medical record. Underlying prognostic and clinical differences existed between patients who received PORT and those that did not, limiting our attempts to compare these groups directly. The start of follow-up was different between the two cohorts, with patients with PORT initiating follow-up after completing radiation, which obscures their clinical course before radiation which was in some cases after multiple local relapses after management with

TABLE 4 Univariable and multivariable competing risks regression for DMFS

		DMFS: Univariable			DMFS: Multivariable		
		HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Surgery only cohort							
Age at last surgery, y	>45 <=45	1.01 REF	(0.54-1.90)	>.95	… …		
T-stage	T4 T1-T3	2.19 REF	(1.21-3.95)	.009	0.82 REF	(0.29-2.32)	.71
ETE	Yes No	2.52 REF	(1.42-4.49)	.002	1.37 REF	(0.44-4.25)	.58
N-stage	N1 N0	2.94 REF	(1.61-5.39)	<.001	1.09 REF	(0.35-3.40)	.89
ENE	Yes No	3.68 REF	(2.06-6.57)	<.001	2.84 REF	(0.93-8.65)	.07
Residual disease	Yes No	2.46 REF	(1.29-4.69)	.006	1.30 REF	(0.46-3.71)	.62
RET mutation	Yes No	0.59 REF	(0.28-1.22)	.15	… …		
Age at last surgery, y	>45 <=45	1.14 REF	(0.32-4.04)	.84	… …		
PORT cohort							
T-stage	T4 T1-T3	1.92 REF	(0.67-5.47)	.22	… …		
ETE	Yes No	1.83 REF	(0.63-5.30)	.26	… …		
N-stage	N1 N0	0.48 REF	(0.10-2.25)	.35	… …		
ENE	Yes No	0.79 REF	(0.20-3.19)	.74	… …		
Residual disease	Yes No	1.30 REF	(0.50-3.42)	.59	… …		
RET mutation	Yes No	0.42 REF	(0.08-2.21)	.31	… …		

Abbreviations: CCI: Charlson comorbidity index; CI, confidence interval; DMFS, distant metastasis free survival; ENE, extranodal extension; ETE, extrathyroidal extension; HR, hazard ratio; PORT, postoperative radiotherapy.

surgery alone. This may further bias the PORT cohort with respect to features such as DMFS and OS, as patients with recurrent disease are expected to have worse outcomes than those with successful initial definitive management. We did not report the surgical complications and radiation induced toxicity profiles, although we do not expect these to be different in patients with MTC from previous reports on surgical and radiotherapy outcomes in patients with thyroid cancer.[22]

5 | CONCLUSIONS

Optimal local therapy is an important factor in managing MTC and represents curative therapy in nonmetastatic disease. Surgery alone can effectively manage many patients with MTC, but several features were associated with risk for local failure. In patients receiving PORT for high-risk clinical features, effective local control was observed.

6 | SUMMARY

We reviewed outcomes of local therapy for patients with medullary thyroid carcinoma from two tertiary cancer centers and report the outcomes of 297 patients who underwent surgery with or without radiation therapy. Surgery alone is a successful modality in most cases, but there are several high-risk features which predict for local recurrence. In patients who received radiotherapy, good local control was achieved despite high-risk features.

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