



Risk and survival of patients with medullary thyroid cancer: National perspective



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ABSTRACT

Background: Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor account for 1–2% of thyroid cancer. In this study, we aim to examine the characteristics and survival of patients with MTC.

Methods: A retrospective cohort study utilizing the National Cancer Data Base, 2004–2014. The study population included adults with either MTC (cases) or with differentiated thyroid cancer (DTC) (controls).

Results: A total of 2,776 MTC and 171,631 DTC patients were included. The median follow-up time for MTC was 55.5 months (interquartile range: 31.2–84.6 months). As compared to DTC, patients with MTC were more likely to be ≥ 45 -year old, male, and Black ($p < 0.001$). Neck dissection improved survival in patients with stage III [HR: 0.26, 95%CI: (0.10, 0.64), $p = 0.004$]. In patients with stages I and II, neck dissections did not add significant survival benefit to thyroidectomy [stage I, HR: 1.00, 95%CI: (0.54, 1.86), $p = 0.99$], [stage 2, HR: 0.72, 95%CI: (0.40, 1.29), $p = 0.27$]. However, neck dissections upgraded staging to N1A and N1B in 17.7% and 14.3% of patients with clinically N0 neck, respectively. In stage IV, thyroidectomy with neck dissection had the highest 5-year survival (84.9%), but this was not significantly different from thyroidectomy alone (84.1%); Patients who had thyroidectomy and EBRT with or without neck dissection had a lower survival than thyroidectomy alone ($p < 0.01$).

Conclusions: Neck dissection performed on patients with clinically N0 neck, is important for accurate staging and associate with improved survival in advanced stages. Thyroidectomy and neck dissection in stage IV not only have palliative role but also add survival advantage.

Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor that accounts for 1%–2% of thyroid cancers in the United States [1]. MTC derives from the neuroendocrine parafollicular calcitonin-producing (C) cells of the thyroid [2]. Sporadic MTC accounts for the majority of MTC, approximately 80%, while the remaining presents as part of inherited tumor syndromes, such as multiple endocrine neoplasia type 2A and 2B, or familial MTC [2].

Given the relative rarity of MTC, previous studies have been inconclusive in determining the most optimal management strategies [3]. The American Thyroid Association (ATA) 2015 revised guidelines recommend total thyroidectomy and prophylactic central neck dissection in patients with MTC and no evidence of nodal or distant metastasis [1]. The recommendation is based on multiple evidence from small studies

that found a high prevalence, 50–75%, of nodal metastasis regardless of tumor size [4,5]. Among other recommendation by the ATA 2015 guidelines is in the presence of extensive regional or metastatic disease less aggressive surgery in the central and lateral neck may be appropriate for palliative purposes and external beam radiotherapy (EBRT), systemic medical therapy, and other nonsurgical therapies should be considered to achieve local tumor control [1]. Most of these recommendations impact on long-term survival is still to be determined.

In this study, we aim to examine the characteristics of patients with MTC and to identify determinants of survival. To examine the impact of different management modalities on survival, we designed a factor that includes multiple classifications of all possible combinations of thyroidectomy, neck dissection, resection of regional/distant metastasis, and radiotherapy that have been utilized in the management of patients with MTC.

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Table 1
Descriptive statistics of the study population.

		Study population, N = 174,407, (%) ^a	Thyroid cancer (%) ^a		p ^b
			Well differentiated, n = 171,631	Medullary, n = 2776	
Age (yr.)	18 - < 45	70,543(40.5)	69,782(40.7)	761(27.4)	< 0.001
	45 - < 65	76,764(44.0)	75,535(44.0)	1,229(44.3)	
	≥65	27,100(15.5)	26,314(15.3)	786(28.3)	
Gender	Male	39,111(22.4)	37,973(22.1)	1,138(41.0)	< 0.001
	Female	135,296(77.6)	133,658(77.9)	1,638(59.0)	
Race	White	149,047(85.5)	146,651(85.5)	2,396(86.31)	< 0.001
	Black	12,882(7.4)	12,637(7.4)	245(8.8)	
	Hispanic	1,689(1.0)	1,670(1.0)	19(0.7)	
	Other	10,789(6.2)	10,673(6.2)	116(4.2)	
Stage	I	130,386(74.76)	129,363(75.4)	1,023(36.9)	< 0.001
	II	14,263(8.18)	13,669(8.0)	594(21.4)	
	III	19,822(11.37)	19,535(11.4)	287(10.3)	
	IV	9,936(5.7)	9,064(5.3)	872(31.4)	
Charlson/Deyo score	0	147,303(84.5)	145,006(84.5)	2,297(82.7)	0.06
	1	22,715(13.0)	22,322(13.0)	393(14.2)	
	2	3,544(2.0)	3,474(2.0)	70(2.5)	
	≥3	845(0.5)	829(0.5)	16(0.6)	
Hospital volume (thyroid cancer/yr.)	Low: 1–8	17,852(10.2)	17,126(10.0)	258(9.3)	< 0.001
	Medium - low: 9–34	71,327(40.8)	70,286(41.0)	995(35.8)	
	Medium: 35–130	68,319(39.1)	67,106(39.1)	1,212(43.7)	
	High: ≥ 131	17,424(10.0)	17,113(10.0)	311(11.2)	
Insurance	None	4912(2.8)	4820(2.8)	92(3.3)	< 0.001
	Private	127,686(73.2)	125,930(73.4)	1756(63.3)	
	Medicaid	10,661(6.1)	10,505(6.1)	156(5.6)	
	Medicare	288,58(16.6)	28,108(16.4)	750(27.0)	
	Other governmental	2290(1.3)	2268(1.3)	22(0.8)	

^a Percentage values may not add up to 100% due to rounding.

^b Chi-square test.

Table 2
Characteristics of patients with medullary thyroid cancer as compared to patients with well-differentiated thyroid cancer. (N = 174,407).

Factor	Medullary thyroid cancer (%)	aOR ^a	95%CI	p ^b
Age (yrs.)	< 45	1.1	1 [Reference]	
	45 - < 65	1.6	1.40 1.28, 1.54	< 0.001
	≥65	2.9	2.42 2.09, 2.80	< 0.001
Gender	Male	2.9	2.30 2.12, 2.48	< 0.001
	Female	1.2	1 [Reference]	
Race	White	1.6	1 [Reference]	
	Black	1.9	1.27 1.11, 1.45	< 0.001
	Hispanic	1.1	0.75 0.48, 1.18	0.21
	Other	1.1	0.70 0.58, 0.84	< 0.001
Hospital volume (thyroid cancer/yrs.)	Low: 1–8	1.5	0.77 0.65, 0.92	0.003
	Medium - low: 9–34	1.4	0.75 0.66, 0.85	< 0.001
	Medium: 35–130	1.8	0.97 0.86, 1.10	0.66
	High: ≥ 131	1.8	1 [Reference]	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

^a The model includes: age, gender, race, comorbidities index score, hospital volume, and insurance.

^b Multivariate logistic regression model.

Materials and methods

The study is a retrospective cohort analysis utilizing the National Cancer Data Base (NCDB), 2004–2014. The NCDB is a joint program of the Commission on Cancer of the American College of Surgeons (ACS) and the American Cancer Society. The ACS has executed a business associate agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually. The NCDB is de-identified data that are except from approval of the Institutional Review Board [6].

The primary study objective is to assess demographic and clinical factors associated with MTC as compared to well-differentiated thyroid cancer (DTC). The secondary study objective is to assess various treatment options associated with overall survival in patient with MTC.

The study population included adult patients (age ≥ 18 years) who had either DTC (controls) or MTC (cases). A diagnosis of DTC is based on International Classification of Diseases for Oncology third edition (ICD-O-3: 8050, 8260, 8340, 8341, 8342, 8343, 8344, 8330, 8331, 8332, 8335, 8450) and a diagnosis of MTC is based on the following codes (ICD-O-3: 8510, 8345, 8346, 8347).

Independent factors that were considered for their confounding effect included: Age (18 - < 45, 45 - < 65, ≥65), Gender, Race (White, Black, Hispanic, Other), cancer stage based on American Joint Committee on Cancer 7th edition (stages: I, II, III, IV) [7], Charlson/Deyo comorbidity score as coded in the database (0, 1, 2, ≥3), hospital volume classification followed quartile classification based on the total

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