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Adjuvant External Beam Radiation for Medullary Thyroid Carcinoma

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Abstract

Background—Adjuvant radiation is rarely used to treat medullary thyroid carcinoma (MTC). We hypothesized that external beam radiation therapy (EBRT) would improve overall survival (OS) in MTC patients.

Methods—The Surveillance, Epidemiology, and End Results (SEER) database identified patients who underwent total thyroidectomy and lymph nodes excision for MTC between 1988 and 2004. The Kaplan-Meier method was used for univariate comparisons of OS. Multivariate Cox proportional hazards models controlled for gender, age, lymph node status, tumor size, extent of disease, and EBRT.

Results—After 12 years, EBRT did not significantly improve OS (log rank, $p<0.14$). In node-positive patients, univariate analysis demonstrated an OS benefit with EBRT (log rank, $p<0.05$). In a multivariate model of node-positive patients, only increasing age ($p<0.001$) and tumor size ($p<0.001$) significantly influenced OS.

Conclusions—The OS benefit attributed to EBRT in node-positive patients by univariate analysis could not be duplicated when controlling for known prognostic factors.

Keywords

medullary thyroid carcinoma; radiation; survival

Introduction

Medullary thyroid carcinoma (MTC) is rarer than papillary and follicular thyroid carcinoma, representing approximately 3% to 10% of all thyroid malignancies.[1,2] Ten-year survival rates are generally below 80%.[3] Regional and distant metastases are not uncommon and, when present, significantly decrease survival. 10-year survival rates for patients with regional metastases approximate 70%[1–6], while those with distant metastases have survival rates of approximately 20%[7].

Total thyroidectomy is the primary treatment modality for MTC. [8,9] The management of regional lymph nodes is more controversial, but most experienced endocrine surgeons

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recommend performing at least a central neck lymphadenectomy of level VI nodes [8,10,11] and unilateral or bilateral modified radical neck dissections in select situations.[12–14]

C-cells, the cell of origin for MTC, do not concentrate iodine like follicular cells, making the use of radioactive iodine ineffective. While external beam radiation therapy (EBRT) has been described for the treatment of recurrent or metastatic MTC[15], it is not commonly used in the adjuvant setting.[14] Studies of the role of EBRT for treatment of MTC have been limited by small numbers of patients, institutional referral bias, and dated EBRT techniques.[15–18] We hypothesized that selective use of adjuvant EBRT in MTC patients would improve overall survival, and queried the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute for all MTC cases treated during the modern era from 1988 to 2004.

Methods

The SEER database was used to identify a population of patients with MTC. Approximately 26% of the United States population is currently represented by one of 17 population-based cancer registries that provide cancer incidence and survival data to SEER in addition to information on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up vital status. Current SEER registries include the states of Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah; the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, Seattle-Puget Sound, and San Jose-Monterey; the Alaska Native Tumor Registry, rural Georgia, Greater California, and Los Angeles County.

The SEER data was de-identified and therefore exempt from UC Davis Institutional Review Board approval. All cases of primary, histologically confirmed, MTC treated with total thyroidectomy and 1 lymph node removed between 1988 and 2004 were eligible for the study. Patients with distant metastases at the time of diagnosis were excluded. We also excluded patients with known secondary cancers, and those diagnosed only by death certificate or autopsy. SEER codes extent of disease for thyroid carcinoma into 11 categories based upon whether the primary tumor is confined to the thyroid, involves pericapsular or adjacent tissues, metastasizes distantly, or if disease extension is unknown. We categorized tumor extension within the thyroid capsule as “intrathyroidal disease” and extension beyond the thyroid capsule to adjacent tissues as “extrathyroidal disease”. Patients with distant metastases or unknown disease extension were eliminated from analysis. The final sample included 534 patients with MTC.

Survival time was calculated as the number of months between the date of diagnosis and whichever occurred first: date of death, date last known to be alive, or December 31, 2004. SEER regularly updates the date of last known vital status. The survival endpoint used was death due to any cause. Patients lost to follow-up or those surviving beyond December 31, 2004 were coded as censored observations. A maximum follow-up period of 12 years was used.

Univariate Kaplan-Meier survival analysis was performed stratifying patients according to nodal status with survival curves compared using the log rank test for patients receiving no EBRT versus EBRT. After confirming the proportional hazards assumption, a multivariate Cox proportional hazards model controlling for patient age, gender, tumor size, nodal status, and extent of disease was utilized. Analyses were conducted using STATA version 10 (StataCorp, College Station, Texas). All statistical tests were two-tailed, with significance indicated by $p \leq 0.05$.

Results

Patient Characteristics

Of 534 patients with MTC who underwent thyroidectomy with ≥ 1 lymph node analyzed by histopathology, EBRT was given to 66/534 (12.4%) while no radiation was given to 468/534 (87.6%). Demographic and prognostic factor information of the study population is presented in Table 1. Briefly, significant differences were noted between patients receiving and not receiving EBRT with respect to gender, nodal status, and extent of disease. Males were more likely than females to receive EBRT. Patients receiving EBRT were more likely to have node-positive disease. Interestingly, patients with extrathyroidal spread of disease were significantly less likely to receive EBRT than patients with medullary thyroid cancer limited to the thyroid capsule. Race/ethnicity, tumor size, and age were not significantly different between the two groups.

Univariate Analysis

In a univariate analysis, at a maximum 144 months of follow-up, EBRT was not associated with a significant improvement in overall survival (log rank, $p<0.14$). In node-positive patients, however, EBRT demonstrated a significant survival benefit (log rank, $p<0.05$).

Multivariate Analysis—All Patients

Recognizing that several factors may contribute to mortality in MTC, we constructed a Cox proportional hazards model controlling for gender, age, tumor size, nodal status, extent of disease, and use of EBRT. A summary of the multivariate analysis can be found in Table 2. Lack of EBRT did not significantly influence overall survival (Hazard Ratio (HR) 1.39, Confidence interval (CI) 0.57 to 3.37; $p=0.47$). Significant factors negatively influencing overall survival included increasing primary tumor size, per mm (HR 1.02, CI 1.01 to 1.03; $p<0.001$), increasing age (HR 1.04, CI 1.03 to 1.06; $p<0.001$) and nodal positivity (HR 2.35, CI 1.31 to 4.20; $p=0.004$).

Multivariate Analysis—Node Positive Patients

In a multivariate analysis restricted to node positive patients, EBRT failed to influence overall survival (HR 1.31, CI 0.52 to 3.25; $p=0.57$). Both increasing tumor size (HR 1.05, CI 1.03 to 1.06; $p<0.001$) and patient age (HR1.04, CI 1.02 to 1.07; $p<0.001$) remained significant factors in this high-risk population (Table 3).

Given that trends in EBRT may change over time, we assessed the number of patients receiving EBRT by year of diagnosis and found minimal changes over time. When year of diagnosis was included in the multivariate analysis, it was associated with a HR of 0.99 (CI 0.93 to 1.05, $p=0.78$) while not significantly altering the results reported in Tables 2 and 3.

Discussion

Few patients are offered EBRT for the adjuvant treatment of MTC. While this approach may be valid, it is not based upon prospective, randomized data. Retrospective studies have been somewhat conflicting. Samaan and colleagues published a retrospective analysis from the MD Anderson Cancer Center that primarily sought to differentiate survival rates between sporadic and familial forms of medullary thyroid cancer.[19] As a secondary goal of the study, the researchers examined the effect of EBRT on survival. They concluded that patients receiving EBRT demonstrated significantly poorer survival, even after controlling for age, extent of disease, and surgery. The patients in this study were treated over a time period (1943 to 1987) that may not be reflective of modern radiotherapy techniques

however, and subsequent studies have suggested a greater role for EBRT in improving local/regional control.

Schwartz and colleagues reported on a group of 34 MTC patients with advanced disease treated with EBRT between 1995 and 2004 and demonstrated excellent 5-year relapse-free survival, disease-free survival and overall survival rates of 87%, 62%, and 56%, respectively.[15] Brierly and colleagues retrospectively examined 73 patients with MTC treated between 1954 and 1992 with an end-point of disease-specific survival.[4] Forty-six of these patients received EBRT. Although use of EBRT did not influence disease-specific survival in the population as a whole, a subgroup at higher risk for local/regional recurrence due to microscopic residual disease, nodal positivity, or extrathyroidal invasion did receive a significant improvement in the rate of local/regional recurrence at 10 years (86% versus 52%, $p<0.05$). Similar results have been reported elsewhere.[17]

In addition to the unknown benefit of EBRT, many treating physicians are reluctant to irradiate the thyroid and its draining lymphatics due to concern for toxicity. Using conventional radiotherapy techniques, it would be difficult to administer appropriate radiation doses to this area without causing significant toxicity to surrounding vital structures, such as the spinal cord, trachea, larynx, esophagus, pharynx, and parotid glands. However, with the advent of intensity–modulated radiation therapy (IMRT), higher doses of radiation can be administered while sparing normal tissues. Rosenbluth and colleagues [20], reviewed outcomes and toxicity in a series of 20 thyroid cancer patients treated with IMRT. Although most patients developed acute toxicities, these effects were manageable with routine proactive clinical care, with no evidence of Grade IV toxicities.[20] In a phase I trial of 13 patients, Urbano et al [21] showed that IMRT could be administered with an acceptable level of acute toxicity, although long term results were lacking.

In an attempt to circumvent some of the biases associated with past retrospective institutional studies on the role of EBRT in the treatment of MTC, we utilized the SEER database of the National Cancer Institute. We feel that these data better capture national trends in treatment and outcomes and can provide a rational basis for the development of future randomized clinical trials. These data may still reflect a selection bias, whereby patients with more advanced disease, and therefore worse prognoses, may be offered EBRT more readily than patients with earlier, more localized disease, but we tried to ameliorate this by controlling for those factors identified as significant differences between patients who received EBRT and those who did not.

Although no improvement in overall survival was detected in patients receiving EBRT on multivariate analysis, the wide CI (0.57–3.37) reflects the sparse use of EBRT in our patient population as a whole (n=66, 12.4%). Further study utilizing a larger sample of patients receiving EBRT may be necessary to document a benefit similar to that noted in our univariate analysis of node-positive patients. After stratification for node-positivity, univariate analysis suggested a significant improvement in overall survival in patients receiving EBRT. Those receiving EBRT demonstrated an estimated 10-year survival of 87% compared to 70% in the group not receiving radiation. We were unable to perform a multivariate analysis among node-negative patients, as only 3 of these patients received EBRT.

The survival rates we documented were better than noted in other series and may reflect our method of patient selection, which eliminated patients with distant metastases, those undergoing less than total thyroidectomy, and those without any lymph nodes analyzed. Despite our promising results, our multivariate analysis found only two independent

predictors of overall survival: increasing age and tumor size. Although statistically significant, the survival effect is small and may have limited clinical significance.

Several limitations of the SEER data utilized for our study make demonstrating a beneficial survival effect of radiation difficult. First, we are unable to determine, to some degree, the adequacy of surgery performed. We have attempted to diminish this concern by including only those patients who received “standard” surgical treatment for their MTC. At minimum, we considered this to be a total thyroidectomy and lymphadenectomy. Patients were considered to have had a lymphadenectomy if they had ≥ 1 lymph node resected at the time of surgery. Due to database constraints, we have no reliable way of knowing whether the lymphadenectomy was part of the planned procedure or occurred incidentally. Furthermore, we are unable to distinguish those patients with palpable nodal disease who underwent more extensive lymphadenectomy. These patients would be expected to have more lymph nodes removed at the time of surgery, but would also be expected to have an overall worse prognosis due to the more extensive burden of disease and increased likelihood of occult distant metastases that would be unaffected by local/regional radiation therapy. Several researchers have utilized serum levels of calcitonin and, more recently, CEA as important determinants of local/regional control and surrogates of disease outcomes such as recurrence and overall survival.[22,23] We did not have access to serum calcitonin or CEA levels for this analysis, but these are prone to similar limitations. Persistently elevated levels of calcitonin or CEA following surgery could indicate residual local/regional disease that could potentially benefit from EBRT or could represent clinically occult distant metastases that would not be expected to respond to EBRT.

The chosen endpoint of our analysis was overall survival. We concede that, for a local/regional treatment such as EBRT, disease-free survival may be a more appropriate endpoint. Our ability to reliably determine disease recurrence using SEER data is limited, however, as has been reported by other researchers.[24] We believe it is reasonable, in the case of MTC, to hypothesize that improved local/regional control of disease may influence overall survival given the often indolent nature of the disease. Indeed, this is the rationale for performing a total thyroidectomy rather than a lobectomy and a thyroidectomy with nodal dissection rather than a thyroidectomy alone.

Conclusion

Our multivariate analysis could not define a specific survival benefit attributable to EBRT in node-positive MTC patients. However, the promising univariate results and relatively small numbers of patients receiving EBRT in our analysis indicate that further study is necessary to define its role in the treatment of MTC. Prospective, randomized data from patients treated with optimum surgical technique are needed to prove or disprove the value of EBRT for MTC.

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Table 1

Demographic and tumor-specific factors of 534 patients with MTC diagnosed and treated between 1998 and 2004.

		External Beam Radiation (%) (N=66)	No radiation (%) (N=468)	p Value
Gender				
	Male	36 (54.5)	191 (40.8)	p=0.04*
	Female	30 (44.5)	277 (59.2)	
Age				
	< 50 years	41 (62.1)	248 (53)	p=0.16
	≥ 50 years	25 (37.9)	220 (47)	
Race				
	White	57 (86.4)	401 (85.7)	p=0.33
	Black	6 (9.1)	24 (5.1)	
	Asian	3 (4.5)	35 (7.5)	
	Other	0 (0)	8 (1.7)	
Tumor Size				
	< 2cm	20 (30.3)	136 (29.1)	p=0.85
	≥ 2cm	32 (48.5)	231 (49.4)	
	Missing	14(21.2)	101 (21.6)	
Nodal Status				
	Node Negative	3 (4.5)	217 (46.4)	p<0.001*
	Node Positive	63 (95.5)	251 (53.6)	
Extent of Disease				
	Intrathyroid	41 (62.1)	78(16.7)	p<0.001*
	Extrathyroid	17 (25.8)	333 (71.1)	
	Missing	8 (12.1)	57 (12.2)	

*Statistically significant

Table 2

Multivariate model of overall survival for 534 patients with MTC.

	Hazard Ratio	Confidence Interval	P
Gender	0.99	0.59 to 1.66	0.98
No Radiation	1.39	0.57 to 3.37	0.47
Node Status	2.35	1.31 to 4.20	0.004*
Age (per year)	1.04	1.03 to 1.06	<0.001*
Tumor Size (per mm)	1.02	1.01 to 1.03	<0.001*
Extrathyroidal extent	1.44	0.75 to 2.79	0.28

*Statistically significant

Table 3

Multivariate model of overall survival for 205 patients with node-positive MTC.

	Hazard Ratio	Confidence Interval	P
Gender	0.72	0.38 to 1.37	0.31
No Radiation	1.31	0.52 to 3.25	0.57
Age	1.04	1.02 to 1.07	<0.001*
Tumor Size	1.05	1.03 to 1.06	<0.001*
Extent of Disease	1.46	0.75 to 2.81	0.262

*Statistically significant