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## External Beam Radiotherapy with or Without Concurrent Chemotherapy in Advanced or Recurrent Non-Anaplastic Non-Medullary Thyroid Cancer

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### Abstract

**Background and Objectives:** To review clinical outcomes and toxicities in locally advanced differentiated thyroid cancer patients treated with external beam radiotherapy (EBRT) with or without concurrent chemotherapy (CCRT).

**Methods:** Between 1990 and 2012, 66 patients with gross residual/unresectable non-anaplastic non-medullary thyroid cancer were treated with EBRT.

**Results:** The median overall survival was 42.0 months. The overall locoregional progression-free survival (LPFS) at 3 years was 77.3%. CCRT resulted in a non-significant improvement in LPFS (90.0% vs. 73.0%,  $P = 0.347$ ). Poorly differentiated histology had significantly improved LPFS (89.4% vs. 66.1%,  $P = 0.020$ ), despite a significantly worse distant metastasis-free survival (43.9% vs. 82.5%,  $P = 0.023$ ).

Acute treatment-related toxicity included dermatitis, mucositis, and dysphagia with grade three rates of 12.1%, 19.7%, and 16.7%, respectively. The incidence of late toxicity was low. CCRT was only associated with a significant greater rate of acute grade 3 hoarseness (10.0% vs. 0.0%,  $P = 0.033$ ), but with no difference in the rate of grade 2 late toxicity.

**Conclusions:** EBRT is a safe and effective treatment modality with 90% LPFS at 3 years in patients with gross residual or unresectable nonanaplastic, non-medullary thyroid carcinoma treated with CCRT. Further incorporation of EBRT with concurrent chemotherapy may result in improved disease control.

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## Keywords

IMRT; thyroid cancer; chemoradiation; radiation therapy

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## INTRODUCTION

An estimated 60,220 new cases of thyroid cancer were diagnosed in the United States in 2013 (45,310 women and 14,910 men), the majority of which were differentiated (follicular or papillary) cancers [1]. The 10-year overall survival (OS) for papillary and follicular cancer is approximately 95% and 85%, respectively [2]. Despite excellent survival, up to one third of patients recur, two-thirds of whom recur locally [3].

As the primary treatment modality for differentiated thyroid cancer is surgical resection, the role of external beam radiotherapy (EBRT) is unknown. The only prospective randomized trial conducted failed to accrue patients because of the reluctance of multiple centers to adopt EBRT [4]. In the absence of prospective trials, the current indications for EBRT have largely been based on retrospective series [5]. Multiple single-institution experiences have shown EBRT to improve locoregional control in high-risk patients (i.e., microscopic/gross residual disease after surgical resection and unresectable disease) [6–18]. The American Thyroid Association Task Force and National Comprehensive Cancer Network recommend EBRT in papillary and follicular carcinomas only in patients with unresectable disease not amenable to RAI therapy, whereas they recommend the consideration of EBRT in patients over the age of 45 years with grossly visible extrathyroid extension and a high likelihood of microscopic residual disease, and in patients of any age with gross residual disease or unresectable bulky disease not amendable to RAI therapy [19,20].

Locoregional disease control is an important endpoint when examining outcomes after EBRT for thyroid cancer, as locally recurrent/locally advanced disease in the head and neck is associated with significant morbidity secondary to the proximity of many critical organs including the esophagus, larynx, brachial plexus, and spinal cord. The addition of EBRT can potentially limit the associated morbidity from uncontrolled locoregional disease such as obstruction of the esophagus and/or trachea, need for a laryngectomy, neurovascular compromise, pain, hemorrhage, and repeated surgical procedures. We sought to review the clinical outcomes and acute/late toxicities in locally advanced non-anaplastic thyroid cancer patients with gross residual or unresectable disease treated with EBRT with or without concurrent chemotherapy (CCRT).

## MATERIALS AND METHODS

The institutional review board approved this retrospective study with a waiver of informed consent. Between July 1990 and February 2012, 66 patients with pathologically confirmed gross residual or unresectable non-anaplastic thyroid cancer were treated with definitive-intent EBRT to the primary site at a large tertiary cancer center.

The T and N category was determined from the disease extent at the initial presentation (pathologically based in 90.0% of patients). At the time of radiation all patients had

locally advanced unresectable or gross residual disease (i.e., T4c or R2 disease). The M category was recorded at time of EBRT start. Staging workup included a complete history and physical examination, focused head and neck evaluation, complete blood counts, liver function tests, and chest X-ray [21].

### Pathological Findings

Non-anaplastic thyroid carcinoma was histologically confirmed by internal pathological review. Poorly differentiated thyroid carcinomas were defined on the basis of  $\geq 5$  mitosis/10 high-power microscopic fields (400 $\times$ ) and/or the presence of tumor necrosis. As previously reported this definition identifies patients with an intermediate prognosis between those with well-differentiated and anaplastic thyroid carcinoma [7,22,23].

### Radiotherapy Technique

The radiation technique, dose, and fractionation varied according to physician preference and clinical scenario. Fifty-one patients (77.3%) underwent intensity-modulated radiation therapy (IMRT). Our current radiation technique has been previously described [24]. Briefly, we treated (1) low-risk areas, including the upper and lower paratracheal nodal levels and cervical lymph node levels II–VI to 54Gy, (2) high-risk areas, including the operative or tumor bed, operative thyroid gland volume, tracheoesophageal grooves, and central nodal compartment, of microscopic disease, to 60Gy, (3) close or microscopically positive margins to 66Gy, and (4) areas of gross disease to 70Gy [24]. The gross tumor volume was defined as the gross extent of tumor visible by imaging studies and clinical examination. 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 intrafractional patient motion and interfractional setup error. All patients were immobilized in the treatment position using a three- or five-point Aquaplast mask (Orfit Industries, Wijnegem, Belgium) to control the movement of the head and neck.

Organs at risk (OAR) such as the parotid glands, larynx, lungs, esophagus, brachial plexus, and spinal cord were contoured. A dose-volume histogram was constructed to evaluate target coverage and the doses to the surrounding organs at risk. The dose to the OAR was limited to <26Gy mean parotid dose, <70Gy maximum point and <45Gy mean larynx dose, <21Gy mean lung dose, <34Gy mean esophagus dose, <65Gy maximum brachial plexus point dose, and <45Gy maximum spinal cord point dose. In addition, the volume of lung receiving 20Gy or more was limited to 37%.

### Toxicity and Response Assessment

Patients were assessed jointly by radiation oncology, medical oncology, endocrinology, and/or head and neck surgery weekly during the radiation course and at approximate intervals of 4, 8, and 12 weeks after completion of treatment, then every 3 months for 2 years, followed by every 6–12 months thereafter. In the early 2000s a standardized toxicity form was implemented to help improve the accuracy and reproducibility in recording treatment toxicities for dermatitis, nausea, vomiting, mucositis, xerostomia, dysphagia, hoarseness, fatigue, and need for a feeding tube. The incidence of the worst-grade toxicity

sustained by a patient up to 90 days after the start of radiation therapy was recorded as an acute toxicity event based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [25]. All late toxicity (>90 days post-treatment completion) was scored with the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring system [26].

### Statistical Analysis

Locoregional progression, distant metastasis, and death were recorded from the end of radiotherapy. Locoregional progression was defined as local (i.e., thyroid bed) or nodal (i.e., central compartment or cervical and superior mediastinal lymph nodes) disease progression (i.e., new or enlarging disease in the thyroid bed, central compartment, or lymph nodes on ultrasound, diagnostic RAI, positron-emission tomography (PET)/computed tomography (CT), CT, and/or magnetic resonance imaging (MRI)). Biopsy confirmation was not required. Stable disease with no evidence of progression was classified as “controlled.” If systemic therapy or adjuvant RAI was initiated after EBRT for clinical suspicion of progressive disease in the neck, these patients were classified as having locoregional progression. Patients without evidence of metastatic disease at time of EBRT were followed for the development of distant metastases; patients with M1 disease prior to EBRT were excluded from this subset-analysis.

The Kaplan–Meier method was used to calculate locoregional progression-free survival (LPFS), distant metastasis-free survival (DMFS), and OS [27]. The log-rank test was used to compare survival curves when indicated. Comparisons between cohorts were performed using either the Chi-square test or two-tailed log-rank test. A probability value of <0.05 was considered statistically significant for all analyses. All analyses were performed in SPSS statistics version 21 (IBM, Armonk, New York).

## RESULTS

### Patient and Tumor Characteristics

The median age was 65.8 years (interquartile range, 56.2–72.6) with an overall median follow-up of 35.0 months (interquartile range; 22.1–74.4) among surviving patients and 24.5 months (interquartile range; 13.6–54.1) for all patients.

Thirty-four patients (51.5%) had poorly differentiated histology. An additional 13 patients (19.7%) had high-risk pathology (12 tall cell variant papillary, 1 Hurthle cell). Of the 19 remaining patients, 9 had well-differentiated papillary carcinoma, 4 had moderately differentiated papillary carcinoma, and 7 had papillary thyroid carcinoma with no differentiation stated in the pathology report. There was no difference in age, sex, T category, N category, or the presence of distant metastasis between patients with well/moderately differentiated versus poorly differentiated histology (Table I).

### Treatment Characteristics

Pre-EBRT treatment characteristics are depicted in Figure 1. EBRT was administered to all 66 patients to a median dose of 66.3Gy (interquartile range, 60.0–70.0) in a median of

33 fractions (interquartile range, 33–35). CCRT was administered to 21 (31.8%) patients: doxorubicin (10mg/m<sup>2</sup>) was administered to 19 patients, and cisplatin (100mg/m<sup>2</sup>), cisplatin (60mg/m<sup>2</sup>) with etoposide (120mg/m<sup>2</sup>), and doxorubicin (10mg/m<sup>2</sup>) followed by paclitaxel (40mg/m<sup>2</sup>) were each administered to 1 patient. There was no difference in age, sex, T category, N category, presence of distant metastasis, radiation technique, or radiation dose between CCRT and EBRT patients (Table I). There was a significantly greater percentage of patients with poorly differentiated histology who underwent CCRT (71.4% vs. 42.2%,  $P=0.027$ ).

### Locoregional Progression-Free Survival

The 3-year actuarial LPFS was 77.3% (Fig. 2A). Twelve patients (18.2%) developed locoregional progression at a median of 11.4 months (interquartile range, 4.6–18.4). Four patients failed in the thyroid bed/central compartment alone, 5 in the lateral cervical neck alone, and 3 simultaneously in the thyroid bed/central compartment and lateral neck.

Patients with metastatic disease at time of EBRT had a significantly worse LPFS compared with those with localized disease (3-year actuarial LPFS, 61.4% vs. 88.4%;  $P=0.043$ ) (Fig. 2B). Poorly differentiated histology had significantly improved LPFS compared with well/moderately-differentiated histology (89.4% vs. 66.1%,  $P=0.020$ ) (Fig. 2C). CCRT resulted in a non-significant improvement in the actuarial 3-year LPFS (90.0% vs. 73.0%,  $P=0.347$ ) (Fig. 2D). There was no difference in the LPFS between patients with gross residual and unresectable disease (70.8% vs. 81.1%,  $P=0.393$ ).

### Distant Metastases

Of the 34 patients without evidence of metastatic disease prior to EBRT, 16 (47.1%) developed distant metastases at a median of 15.6 months (interquartile range, 10.3–36.0) resulting in a 3-year actuarial DMFS of 59.4% (Fig. 3A).

Patients with poorly differentiated histology had significantly worse DMFS (43.9% vs. 82.5%,  $P=0.023$ ) (Fig. 3B). There was no difference in the DMFS between patients treated with CCRT compared with EBRT alone (53.8% vs. 63.5%,  $P=0.622$ ) (Fig. 3C).

### Overall Survival

The median OS was 42.0 months and the actuarial 3-year OS was 54.4% (Fig. 4A). Thirty-nine patients (59.1%) died at a median of 19.4 months post-EBRT completion (interquartile range, 11.3–42.6). The median survival for patients with metastatic disease at the time of EBRT was significantly shorter than those without evidence of metastatic disease (25.9 vs. 77.7 months,  $P=0.003$ , respectively) (Fig. 4B).

Patients with poorly differentiated histology had a non-significantly shorter median OS compared with patients with well-differentiated or moderately differentiated histology (40.0 vs. 70.9 months,  $P=0.114$ ) (Fig. 4C). There was no difference in the median OS between patients treated with CCRT versus EBRT alone (43.1 vs. 37.1 months,  $P=0.941$ ) (Fig. 4D).

## Toxicity

Acute treatment-related toxicity included dermatitis, mucositis, and dysphagia with grade 3 rates of 12.1%, 19.7%, and 16.7%, respectively. Seven EBRT-alone (15.6%) and 5 CCRT (23.8%) patients required treatment breaks for a median of 3 and 1 days, respectively ( $P = 0.395$ ). Concurrent chemotherapy was only associated with a significant greater rate of acute grade 3 hoarseness (10.0% vs. 0.0%,  $P = 0.033$ ) (Table II), but with no difference in the rate of grade 2 or greater late toxicity, including hoarseness (5.0% versus 0.0%,  $P = 0.159$ ) (Table III). Seven (10.6%) patients required a tracheostomy: 5 (7.6%) patients had a tracheostomy tube placed prior to RT, 1 (1.6%) patient required a tracheostomy during EBRT, and 1 (1.6%) patient required a tracheostomy post-EBRT.

Twenty-two patients (33.3%) required a gastrostomy tube (G-tube): 15 (22.7%) patients had a G-tube in place prior to initiation of EBRT, 6 (11.8%) patients required a reactive G-tube (defined as G-tube placement during EBRT or within 90 days of completing EBRT), and 1 (2.2%) patient required a late G-tube (placed 3 months after completion of EBRT). There was no significant difference in the rate of reactive G-tube between the EBRT-alone and CCRT cohorts (8.3% vs. 20.0% patients,  $P = 0.239$ ). Grade 3 or greater late dysphagia was 10.3% ( $n = 4$ ) in EBRT alone and 5.0% ( $n = 1$ ) in CCRT patients ( $P = 0.097$ ) secondary to G-tube dependence in four patients, of which two underwent G-tube placement prior to starting EBRT, and cricopharyngeus stenosis requiring dilatation in 1 EBRT-alone patient. No tracheoesophageal fistulas were noted.

## DISCUSSION

Differentiated thyroid cancers respond well to surgical resection and appropriately selected adjuvant therapy, which may include RAI with or without TSH suppression. Nonetheless a subset of these patients will have a locoregional recurrence. Salvage therapies include additional surgery, RAI, and/or EBRT. The use of EBRT in the salvage setting remains controversial given a lack of prospective studies and concern for unnecessary treatment-related toxicity. Similar concerns exist when considering EBRT for the definitive treatment of unresectable disease.

EBRT with or without concurrent chemotherapy is an effective treatment for patients with gross residual or unresectable non-anaplastic thyroid cancer with greater than an 85% locoregional control rate in patients with non-metastatic disease at time of EBRT. EBRT was well tolerated, as the majority of patients had grade 2 or less acute toxicity and minimal late toxicity. While this is not the first study reporting on the efficacy of EBRT for patients with gross residual/unresectable nonanaplastic thyroid cancer, we uniquely report on a cohort of patients who were predominantly treated with a modern RT technique, as 77.3% of patients were treated with IMRT.

Chow et al. [6] reported on the role of EBRT in papillary thyroid carcinoma in 124 patients with gross residual disease of which 69 underwent EBRT at Queen Elizabeth Hospital in Hong Kong from 1960 to 1997. At 10 years those who underwent EBRT had significantly improved 10-year rates of locoregional control (56.2% vs. 24%,  $P = 0.0019$ , respectively). In a subsequent update Chow et al. reported on the outcomes of 217 patients with gross



residual disease after primary surgery. In this updated report they found that EBRT with or without RAI improved locoregional control (63.4% vs. 24%,  $P < 0.0001$ ) and cancer-specific survival (74.1% vs. 49.7%,  $P = 0.001$ ) [28]. None of the patients were treated with modern radiotherapy techniques, such as IMRT.

The Princess Margaret Cancer Center experience reported the outcomes of 46 patients with postoperative macroscopic residual disease, of which 13 received postoperative RT alone and 20 received postoperative EBRT and RAI [12]. No patient was treated with IMRT. The 5-year local relapse free rate was 62%, which is considerably lower than our 3-year rate of 90.0% in patients treated with CCRT. For unclear reasons the RT dose had a considerable range, from 5 to 65Gy.

In a more modern report, M.D. Anderson reported on their experience with postoperative EBRT for differentiated thyroid cancer with conformal treatment [8]. Schwartz et al. reported on 131 patients, of which only 15 had gross residual or unresectable disease, treated with IMRT (43.5%) or conventional EBRT. Patients were treated to a median RT dose of 60 Gy in 30 fractions; 82% of patients received RAI prior to EBRT, and all patients received TSH suppression. Of the 15 patients (11%) with gross residual or unresectable disease at time of EBRT, 4 had a complete response, 3 had a partial response, 6 had stable disease, and 2 progressed through treatment. All four patients with a complete response remained disease free at a median of 21.5 months. Four of the six patients with stable disease ultimately progressed within 3–21 months.

A Phase I study demonstrating the safety of IMRT in locally advanced thyroid cancer reported a 31% grade 3 dysphagia rate and a 38.5% grade 3 dermatitis rate [29]. Four of the 13 patients (30%) developed L'Hermitte's syndrome of which all cases resolved spontaneously. Comparably, our 16.7% grade 3 dysphagia rate and 12.1% grade 3 dermatitis rate were considerably lower despite 30% of our patients being treated with CCRT.

Treatment efficacy is highly dependent on tumor localization. Significant scarring and anatomical variation from previous and often multiple head and neck surgeries (median, 2; range, 0–8 in this series) make neck ultrasonography and CT scans with or without contrast difficult to interpret. Multiple studies have reported on the utility of fluorodeoxyglucose (FDG)-PET in the detection of local recurrence, cervical lymph node metastases, and distant metastases in patients with well-differentiated thyroid cancer, particularly in those with RAI-refractory disease as FDG uptake is inversely correlated with RAI uptake [30–33]. As such, we now routinely use FDG-PET-CT to aid in tumor delineation. Accurate tumor delineation will help improve treatment outcomes and reduce treatment-related toxicity. Further incorporation of MRI may also result in improved tumor delineation and should be considered if the anatomy is particularly difficult to interpret.

Chemoradiation appeared to correlate with improved LPFS, but statistical significance was not met. Nevertheless, these data are concordant with what is known for other head and neck sites; concurrent chemoradiation results in superior locoregional disease control [34,35]. Interestingly, tumors with poorly differentiated histology had significantly improved locoregional progression-free survival despite a significantly greater rate of



distant metastases compared with patients with well-/moderately differentiated histology. As patients with poorly differentiated histology were more likely to receive concurrent chemoradiation, this is a plausible explanation that merits further study. Our data did not suggest any benefit in the prevention of distant metastatic disease from the use of low-dose concurrent radiosensitizing chemotherapy.

New and effective systemic agents such as multikinase inhibitors, selective kinase inhibitors, and histone deacetylase inhibitors have dramatically changed our clinical armamentarium for patients with metastatic disease [5,36,37]. Of particular interest is the report of enhanced RAI uptake in patients treated with selumetinib, a mitogen-activated protein kinase (MAPK) inhibitor, which given the short course of drug therapy would allow a kinase inhibitor free interval during which EBRT could be considered [38]. While promising, studies are needed to determine the timing and sequencing of systemic therapies, low-dose radiation sensitizing chemotherapy, and EBRT.

While this study supports EBRT as a safe and effective treatment for patients with gross residual/unresectable non-medullary, non-anaplastic thyroid carcinoma, certain study limitations merit discussion. We included patients treated over a quarter century and as such, unaccountable variation may exist in pathological classification, radiation techniques, and sensitivity in detecting disease recurrence. Given a lack of robust tumor mutation analysis (i.e., BRAF, PIK3CA, AKT, PTEN, TP53), we were unable to account for biological differences between tumors, which have been associated with RAI resistance and a higher rate of tumor recurrence and cancer death [5]. We acknowledge that there was variability in the choice to use concurrent chemotherapy, which could not be accounted for by patient or tumor characteristics, though tumors with poorly differentiated histology were more likely to be treated with CCRT. As with any retrospective review the accurate classification of acute and late toxicities is dependent on accurate and meticulous documentation. Fortunately, since the year 2000 our institution adopted a systematic system to document treatment-related toxicities.

## CONCLUSION

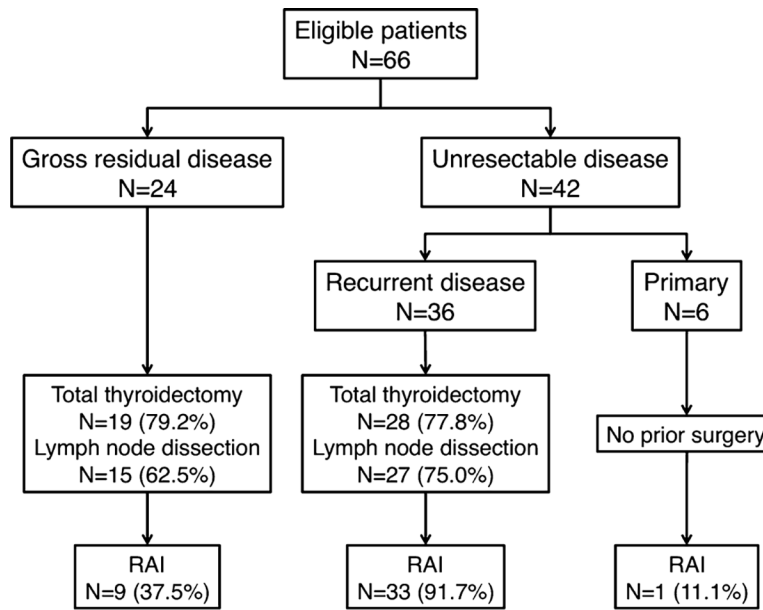
Surgery and RAI with or without TSH suppression is the standard of care for patients with differentiated thyroid carcinoma. In patients with gross residual or unresectable disease, EBRT is a safe and effective treatment modality with greater than 85% locoregional control in patients with non-metastatic disease and 90% locoregional control in patients treated with CCRT. The addition of EBRT can potentially limit the associated morbidity with uncontrolled locoregional disease, even in patients with widely metastatic disease. Further incorporation of EBRT with low-dose radiation-sensitizing concurrent chemotherapy including modern targeted therapies may result in improved treatment outcomes. Prospective studies are needed to validate the safety and efficacy of radiation and chemoradiation.

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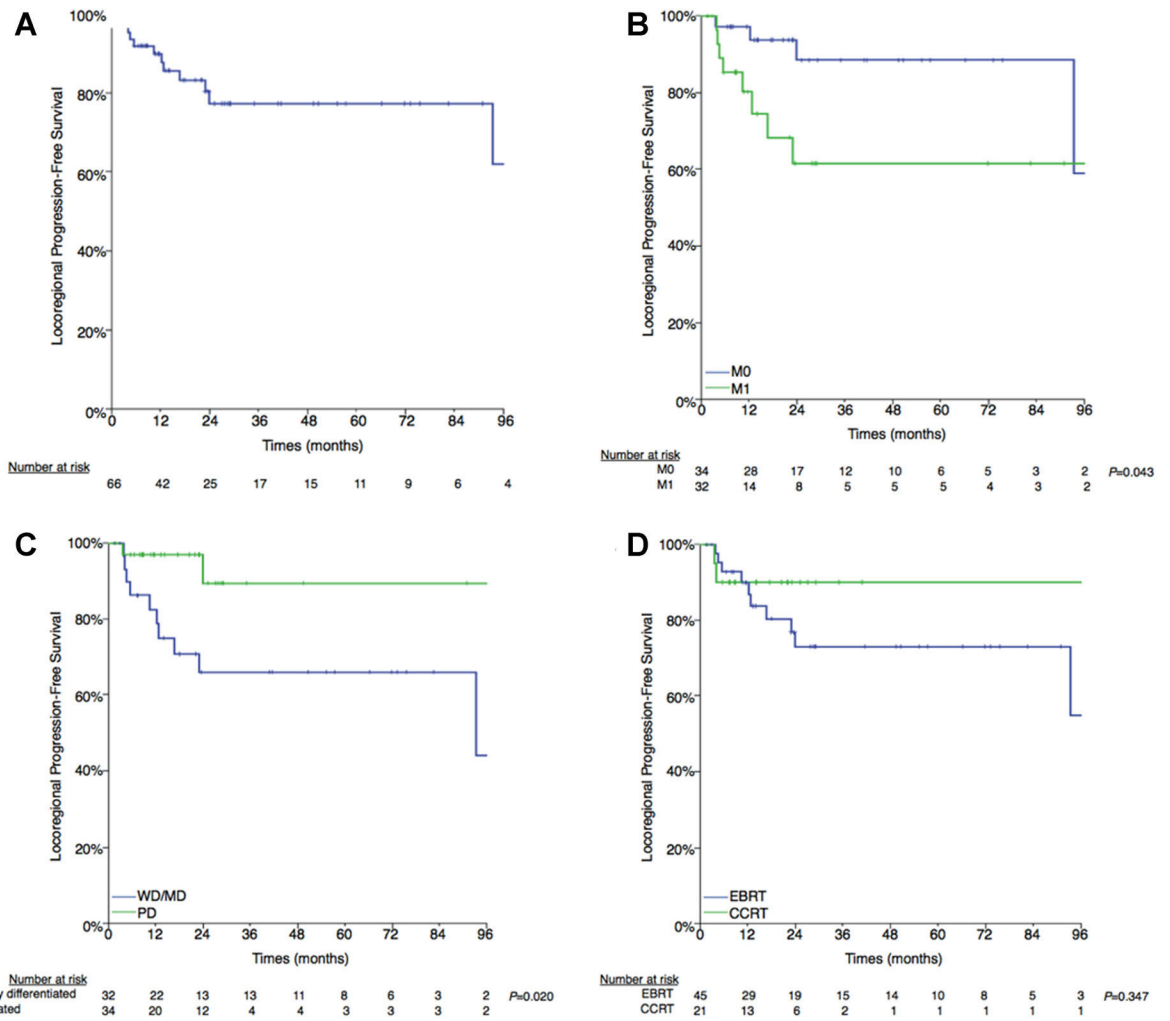
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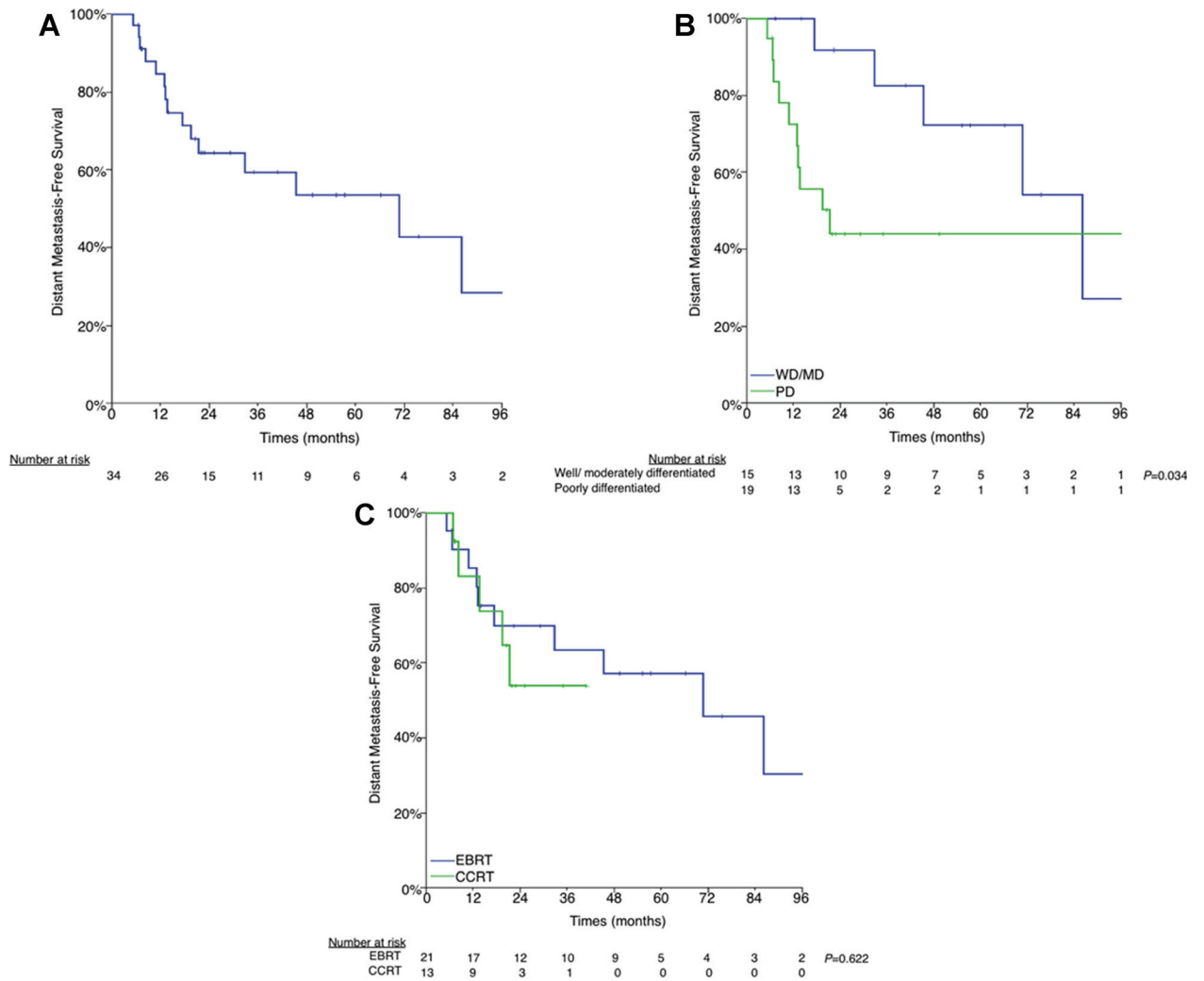
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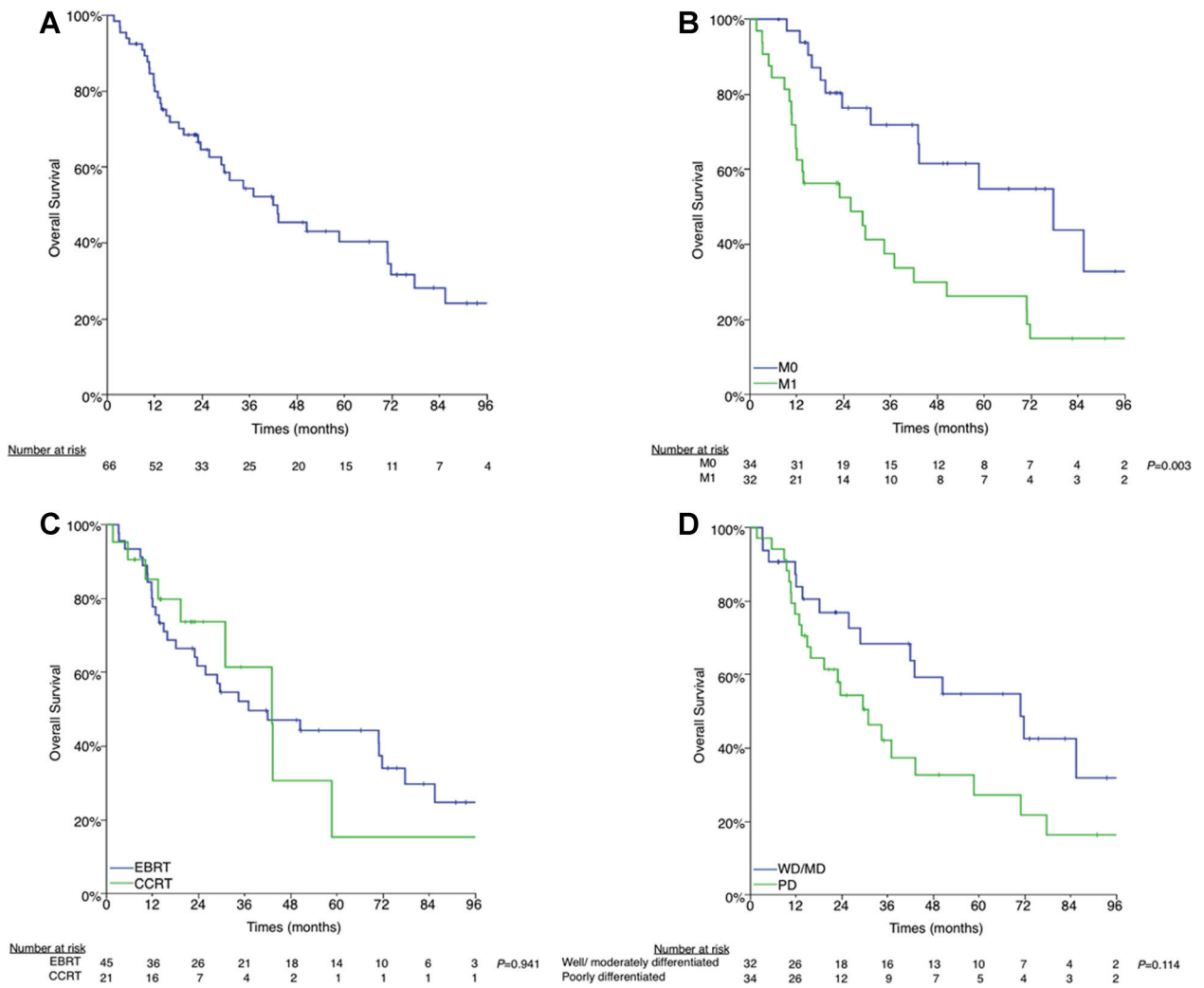
**Fig. 1.** Pre-external beam radiation therapy treatment characteristics. RAI, radioiodine.



**Fig. 2.** A: Locoregional progression-free survival. B:M0 versus M1. C: Well-/moderately differentiated versus poorly differentiated histology. D:External beam radiation therapy (EBRT) versus concurrent chemoradiation therapy (CCRT).



**Fig. 3.**  
 A: Distant metastasis-free survival. B: Well-/moderately differentiated versus poorly differentiated histology. C: External beam radiation therapy (EBRT) versus concurrent chemoradiation therapy (CCRT).



**Fig. 4.**  
**A:** Overall survival. **B:** M0 versus M1. **C:** External beam radiation therapy (EBRT) versus concurrent chemoradiation therapy (CCRT). **D:** Well-/moderately differentiated versus poorly differentiated histology Presented in part as an oral presentation at the 2nd World Congress on Thyroid Cancer on July 10–14th, 2013 in Toronto, Canada and as a poster at the Multidisciplinary Head and Neck Cancer Symposium on February 20–22, 2014 in Scottsdale, Arizona.



TABLE I.

## Patient, Tumor, and Treatment Characteristics

Characteristics	N (%)			P-Value	N (%)		P-Value
	Overall (N = 66)	EBRT (N = 45)	CCRT (N = 21)		WD/MD Histology (N = 32)	PD histology (N = 34)	
Median follow-up (months)	24.5	30.0	21.9	0.067	35.3	23.0	0.335
Age							
<45 years	5 (7.6%)	4 (8.9%)	1 (4.8%)		3 (9.4%)	2 (5.9%)	
45 years	61 (92.4%)	41 (91.1%)	20 (95.2%)	0.555	29 (90.6%)	32 (94.1%)	0.592
Gender							
Male	34 (51.5%)	24 (53.3%)	10 (47.6%)		18 (56.3%)	16 (47.1%)	
Female	32 (48.5%)	21 (46.7%)	11 (52.4%)	0.665	14 (43.8%)	18 (52.9%)	0.455
Tumor stage							
T1	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
T2	5 (7.6%)	3 (6.7%)	2 (9.5%)		3 (9.4%)	2 (5.9%)	
T3	4 (6.1%)	4 (8.9%)	0 (0%)		1 (3.1%)	3 (8.8%)	
T4	57 (86.4%)	38 (84.4%)	19 (90.5%)	0.353	28 (87.5%)	29 (85.3%)	0.560
Regional node stage							
N0	11 (16.7%)	8 (17.8%)	3 (14.3%)		5 (15.6%)	6 (17.6%)	
N1	55 (83.0%)	37 (82.2%)	18 (85.7%)	0.723	27 (84.4%)	28 (82.4%)	0.826
Distant metastasis							
No	34 (51.5%)	21 (46.7%)	13 (61.9%)		15 (46.9%)	19 (55.9%)	
Yes	32 (48.5%)	24 (53.3%)	8 (38.1%)	0.249	17 (53.1%)	15 (44.1%)	0.464
Histology							
WD/MD	32 (48.5%)	26 (57.8%)	6 (28.6%)		—	—	
PD	34 (51.5%)	19 (42.2%)	15 (71.4%)	0.027	—	—	
Concurrent chemotherapy							
EBRT	45 (68.2%)	—	—		26 (81.3%)	19 (55.9%)	
CCRT	21 (32.3%)	—	—		6 (18.8%)	15 (44.1%)	0.027
Radiation technique							
EBRT	15 (22.7%)	12 (26.7%)	3 (14.3%)	0.264	7 (21.9%)	8 (23.5%)	0.873
IMRT	51 (77.3%)		33 (73.3%)		25 (78.1%)	26 (76.5%)	

EBRT, external beam radiation therapy; CCRT, concurrent chemoradiation therapy; WD/MD histology, well-differentiated/moderately differentiated histology; PD histology, poorly differentiated histology; IMRT, intensity-modulated radiation therapy.

**TABLE II.**

## Acute Grade 3 or Greater Toxicity

<b>Toxicity</b>	<b>EBRT</b>	<b>CCRT</b>	<b>P-Value</b>
Dermatitis	4 (9.1%)	4 (20.0%)	0.221
Nausea	1 (2.3%)	0 (0%)	0.497
Vomiting	1 (2.3%)	0 (0%)	0.497
Mucositis	10 (22.7%)	3 (15.0%)	0.476
Xerostomia	1 (2.3%)	0 (0%)	0.497
Dysphagia	5 (11.4%)	6 (30.0%)	0.067
Hoarseness	0 (0%)	2 (10.0%)	0.033
Fatigue	2 (4.5%)	1 (5.0%)	0.936

Analysis limited to 44 and 20 patients, respectively. CCRT, concurrent chemoradiation therapy; EBRT, external beam radiation therapy.

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**TABLE III.**

## Late Grade 2 or Greater Toxicity

<b>Toxicity</b>	<b>EBRT</b>	<b>CCRT</b>	<b>P-Value</b>
Dermatitis	1 (2.6%)	0 (0%)	0.470
Xerostomia	8 (20.5%)	4 (20.0%)	0.963
Dysphagia	7 (17.9%)	4 (20.0%)	0.848
Hoarseness	0 (0%)	1 (5.0%)	0.159
Fatigue	2 (5.1%)	2 (10.0%)	0.481

Analysis limited to 39 and 20 patients, respectively. CCRT, concurrent chemoradiation therapy; EBRT, external beam radiation therapy.

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