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Scientific Article

Neutron radiation therapy for advanced thyroid cancers

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Abstract

Purpose: The aim of this study was to review institutional outcomes for advanced thyroid cancers treated with fast neutron radiation therapy (FNRT) and photon radiation therapy (RT).

Methods and materials: In all, 62 consecutive patients were analyzed. Fifty-nine had stage IV disease. Twenty-three were treated with FNRT and 39 with photon RT. Median follow-up was 14 months. The primary endpoint was overall survival (OS).

Results: There was no significant difference in median OS between FNRT and photon RT (26 vs 16 months; $P = .49$). Patients with well-differentiated histologies had superior median OS with photon RT (17 vs 69 months; $P = .04$). There was a nonsignificant trend toward improved OS with FNRT for medullary and anaplastic histologies.

Conclusions: Outcomes in this study are in line with historical results. There is an apparent detriment in OS with FNRT for well-differentiated histologies and a trend toward improved OS with medullary and anaplastic histologies that warrants further investigation.

Introduction

Thyroid malignancies are relatively rare. In the United States in 2015, it is estimated that there will be 62,450 new cases and 1950 deaths.[1] There has, however, been a recent increase in the incidence of thyroid cancer, mostly attributed to improvements in diagnostic techniques that can better identify early-stage disease.[2] Although accounting for only 0.3% of all cancer deaths, thyroid cancer is the most common endocrine malignancy and accounts for 64% of deaths from this type of disease.[3]

Thyroid cancers are generally divided into 4 broad categories based on histology: (1) well-differentiated malignancies (papillary thyroid cancer [PTC], follicular thyroid cancer [FTC], mixed papillary and follicular histology and Hürthle cell); (2) medullary thyroid cancer

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Conflicts of interest: None.

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[MTC]; (3) anaplastic thyroid cancer [ATC]; and (4) rare cancers that include lymphoma and sarcoma.[4] These various cancers generally arise from 2 predominant parenchymal cells within the thyroid, the follicular cells that concentrate iodine and develop into well-differentiated and ATC and parafollicular or C cells that produce calcitonin and give rise to MTC. The majority of thyroid cancers are well-differentiated, accounting for approximately 90% of all diagnoses. These include 75% PTC, 10% FTC, and 2% to 5% Hürthle cell. In addition, MTC accounts for 5% to 9% of diagnoses (6% sporadic and 3% familial) and ATC accounts for 1% to 2%. Finally, the remaining 2% of thyroid cancers are comprised of sarcomas, lymphomas and other rare entities.[5] Exposure to ionizing radiation is the only known extrinsic risk factor associated with thyroid carcinoma, most often resulting in PTC.[6]

Treatment strategies for the various thyroid malignancies are based upon histology, extent of tumor at diagnosis, and age. Separate stage groupings are recommended for well-differentiated, MTC, and ATC by the American Joint Committee on Cancer (AJCC).[7] Age is considered a prognostic factor in the case of PTC and FTC, with all patients younger than 45 years being either stage I or II based on the presence or absence of distant metastases. This staging scheme reflects the excellent outcomes associated with this population of patients, which is in stark contrast to those with ATC, who are all considered to have stage IV disease and generally have poor outcomes.[8,9]

The mainstay of therapy for thyroid carcinoma is surgical resection, typically with near-total or total thyroidectomy and neck dissection (including at least the central compartment).[10] In the case of well-differentiated thyroid cancers, which typically concentrate iodine, consideration is also made of subsequent radioiodine (RAI) remnant ablation. The use of adjuvant external beam radiation (EBRT) is controversial in this group (and for MTC); however, it is often indicated for patients older than 45 years of age with a high likelihood of microscopic residual disease or gross residual/unresectable disease.[10,11] The role for EBRT for ATC is well-established as a critical component of trimodality therapy for patients with limited disease and in the palliation of gross disease in unresectable cases.[12] In spite of this, outcomes are still poor, and ATC is considered relatively radioresistant.[13]

The majority of thyroid cancers treated with EBRT are therefore locally advanced, node-positive, unresectable, and/or ATC. Local control and survival are suboptimal for patients with stage IV disease treated with conventional photon EBRT, with approximately 15% to 25% local recurrences in well-differentiated disease[8,14] and 30% in MTC.[15] Also, ATC typically has a median overall survival (OS) of only 4 to 5 months.[16,17] Beginning in the 1980s, there was a great deal of interest in examining the potential for improved outcomes with fast neutron RT (FNRT) versus photon radiation therapy (RT) in a wide variety of tumors.[18] This was driven by preclinical data showing improved cell killing for tumor cells that were hypoxic or in radioresistant phases of the cell cycle and preferential killing of repair-proficient tumor cells.[19] Several retrospective studies and a single prospective study demonstrated an advantage in local control with the use of high linear energy transfer neutron RT compared with photon RT in the treatment of a variety of salivary gland neoplasms, sarcomas of the bone and soft tissue, and metastatic renal cell carcinoma.[20–27]

Because of the encouraging data with other histologies and radiobiological rationale, we began treating patients with FNRT for advanced thyroid cancer in the mid-1980s, with the hypothesis that this modality could potentially improve survival in a patient cohort that typically did poorly with photon RT, particularly in the case of the "radioresistant" ATC, in which shorter treatment times might mitigate rapid tumor cell proliferation. In this study, we sought to compare the relative efficacy of FNRT and photon RT in the treatment of advanced thyroid malignancies over a 30-year period. Here we present our institutional experience, the first such retrospective study to explore the utility of FNRT in advanced thyroid cancer.

Methods and materials

After obtaining institutional review board approval, we retrospectively reviewed the medical records of 64 patients treated at our institution for primary thyroid malignancy from 1985 to 2015. Patients receiving palliation for distant metastases (DM) and those with second, synchronous primaries were excluded. One patient treated with FNRT had no follow-up or survival data and 1 in the photon RT group had a parathyroid primary. Both were excluded, leaving 62 patients for evaluation.

Twenty-three patients were treated with FNRT and 39 with photon RT. Patients were determined to be alive or deceased (date of death determined) from a review of medical charts, telephone interviews with patients, families, referring physicians, review of the social security death index, and/or review of local obituaries. Tumors arising in the thyroid gland were staged according to staging criteria as published by the AJCC (7th ed.) in 2010. This staging system is primarily based on age at presentation, the size and histology of the primary lesion, and the presence or absence of lymph node involvement and metastasis.[7]

Patient characteristics

All patients included in the study had evidence of 1 or more of the following: gross residual disease at the time of treatment, positive lymph nodes as determined by resection, lymph nodes with evidence of extracapsular

extension, bulky residual disease, the presence of multiple positive margins, radiographic evidence for residual disease, or a surgical report documenting the presence of residual disease. Many patients had multiple factors.

Patient characteristics in the 2 treatment groups were relatively well-balanced (Table 1). There were approximately equal numbers of men and women in the 2 groups. The median age at the time of treatment was 59 years in both groups, with a range from 22 to 88 years in the FNRT group and 19 to 88 years in the photon RT group. Documentation was available to stage the primary tumor in all patients. All 23 patients in the FNRT group had stage IV disease. Thirty-six of 39 patients in the photon RT group had stage IV disease, with 2 stage I and 1 stage II. All 3 non-stage IV patients had papillary histology and were <45 years old. Primary tumor histologies were generally well balanced between the 2 treatment groups, with fewer MTC (8% vs 30%) in the photon RT group.

We specifically assessed the presence or absence of DM disease at presentation in the ATC group because this has been shown to be prognostic for both disease-specific survival and OS.[28] In the FNRT group, 1 of 7 patients had DM compared with 6 of 17 in the photon RT group.

Treatment technique

Treatment characteristics are summarized in Table 2. Treatment modality was selected by the treating physician, and both FNRT and photon RT were used routinely during the study period. All patients in the FNRT group were treated using a Scanditronix cyclotron (Scanditronix, Uppsala, Sweden) with a 50.5-MeV proton-beryllium reaction used to produce the neutron beam. The depth-dose characteristics of the resulting beam are similar to an 8-MV photon beam. The unit has isocentric capabilities with a rotating gantry. Conformal field shaping was accomplished by the use of multileaf collimation. The median dose delivered to the gross tumor volume was 1920 neutron centigray (NcGy). The median fraction number was 16 and dose per fraction 120 NcGy. Treatments were delivered daily, 4 days per week. No patients were treated twice daily and only 2 received concurrent chemotherapy. FNRT doses were selected based on a relative biological effectiveness (RBE) of 3.3[29] for late effects in normal tissues, representing an equivalent of 6336 cGy of photon RT. Initially, patients were treated with doses of >2000 NcGy based on contemporary Radiation Therapy Oncology Group protocols. This dose was ultimately reduced to 1840 NcGy after the publication of studies revealing high rates of late complications at the higher doses.[30,31]

All patients in the photon RT group were treated using linear accelerators capable of producing 6 MV photons or greater. Conformal field shaping was accomplished by using either multileaf collimation or custom Cerrobend blocks. More recently, patients have been treated with intensity modulated RT with a dose painted technique. The median dose delivered to the gross tumor volume was 6380 cGy (range, 500-7200) in a median of 33 fractions. The median dose per fraction was 212 cGy. Eight of 39 patients were treated with twice-daily regimens, and 14 of 39 received concurrent chemotherapy.

Table 1 Patient characteristics

	Neutron		Photon	
	No.	(%)	No.	(%)
Sex				
Male	11	48	22	56
Female	12	52	17	44
Age, y				
Median	59		59	
Range	22-88		19-88	
American Joint Committee on Cancer stage				
I	0	0	2	5
II	0	0	1	3
IV	23	100	36	92
Histology				
Papillary	6	26	17	44
Follicular	1	4	0	0
Medullary	7	30	3	8
Anaplastic	7	30	17	44
Other	2	9	2	5
Anaplastic with distant metastases				
Yes	1	14	6	35
No	6	86	11	65

Table 2 Treatment characteristics

	Neutron		Photon	
	No.	(%)	No.	(%)
Dose (NcGy/cGy)				
Median	1920		6380	
Range	1380-2040		500-7200	
Fractions				
Median	16		33	
Range	12-17		2-60	
Dose/fraction				
Median	120		212	
Range	115-123		120-300	
Twice-daily treatment				
Yes	0	0	8	21
No	23	100	28	72
Unknown	0	0	3	8
Concurrent Chemotherapy				
Yes	2	9	14	36
No	21	91	25	64

NcGy, neutron centigray.

Statistical analysis

The primary endpoint of this study was OS. This was defined from the date of the last fraction of RT. Survival rates were calculated using the Kaplan-Meier method. Survival rates were calculated for all patients based on primary tumor histology and treatment type (FNRT vs photon RT). For the purposes of our analysis, PTC and FTC were grouped together as "well-differentiated" histologies. Subset analyses were performed, comparing FNRT versus photon RT by histology. Log-rank tests were applied to compare OS between groups and subgroups. Uni- and multivariate Cox proportional hazard models were constructed to test for statistical association with OS. All statistical calculations were performed using OriginPro, version 9.1 (OriginLab Corporation, Northampton, MA).

Results

All patients

Median follow-up was 14 months for the entire patient cohort and 29 months for surviving patients. Median follow-up in the FNRT group was 17 months versus 11 months in the photon RT group. At the time of analysis, 19 of 23 FNRT and 28 of 39 photon RT patients had died (83% and 72%, respectively). Three FNRT and 8 photon RT patients were alive (within 6 months of data collection), with only 1 FNRT (12 months) and 3 photon RT patients (2, 5, and 34 months) lost to follow-up. There was a statistically significant difference in OS when comparing histology (Fig 1, log-rank $P < .0001$), with median OS of 54, 36, and 4 months for MTC, well differentiated, and ATC, respectively. The Kaplan-Meier estimated OS at 1 year was 90%, 78%, and 23% respectively. There was no difference in OS between FNRT and photon RT-based treatment when examining the entire patient cohort, with median OS of 26 and 16 months, respectively (Fig 2, $P = .49$). The following covariates were examined for the entire cohort: age, gender, histology, radiation type, and presence/absence of concurrent chemotherapy. By univariate analysis, increasing age, anaplastic histology, and concurrent chemotherapy predicted worse OS, with hazard ratios (HR) of 1.04 (95% CI [confidence interval], 1.02-1.07), 2.19 (95% CI, 1.59-3.12), and 3.25 (95% CI, 1.68-6.27), respectively. On multivariate analysis, both anaplastic histology and concurrent chemotherapy remained significant, with HR of 2.08 (95% CI, 1.41-3.05) and 2.32 (95% CI, 1.19-4.50), respectively.

Subgroup analysis

Given the inherent differences in prognosis and tumor biology depending on histology, we also performed subgroup analyses by histology for FNRT versus photon RT. For well-differentiated histologies (PTC/FTC), there was a statistically significant difference in OS favoring photon RT (Fig 3), with median OS of 17 months for FNRT and 69 months for photon RT ($P = .04$). By Cox proportional hazard modeling, the HR was 0.34 (95% CI, 0.12-0.97), favoring photon RT. For patients with MTC, there was a trend toward an improvement in OS, with a median OS of 211 months for FNRT and 54 months for photon RT (Fig 4); however, this was not statistically significant ($P = .19$).

Anaplastic histology

There was no significant difference in OS between FNRT and photon RT for patients with ATC (Fig 5), with median OS of 7 and 3 months, respectively ($P = .20$). The Kaplan-Meier estimated OS at 1 year was 29% and 21%, respectively. In addition, we examined the effect of

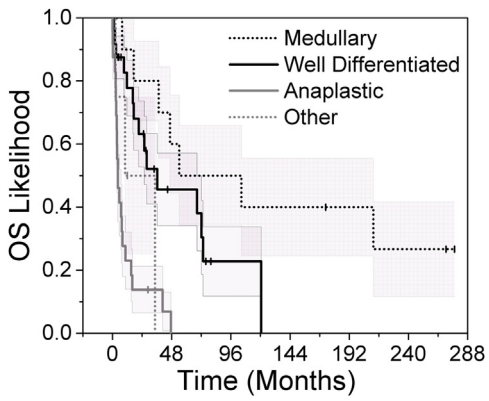

Figure 1 Survival outcomes based on primary histology. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival.

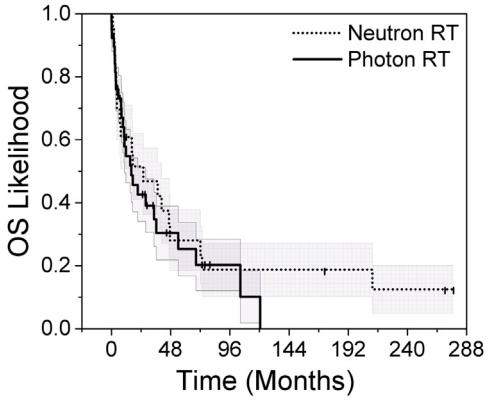

Figure 2 Survival outcomes based on treatment modality. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

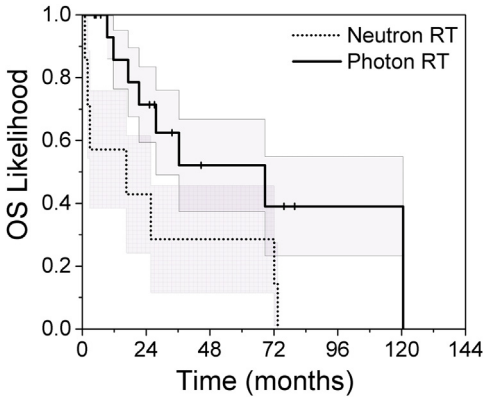

Figure 3 Survival outcomes for well-differentiated histologies based on treatment modality. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

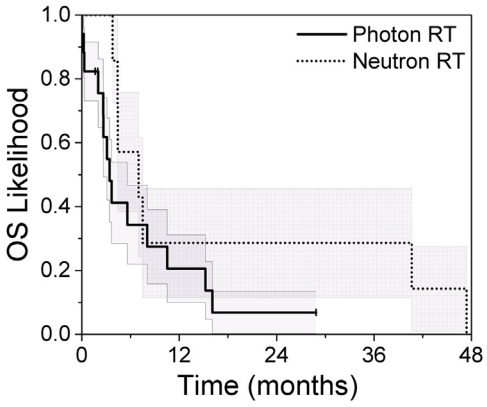

Figure 5 Survival outcomes for anaplastic thyroid cancer based on treatment modality. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

DM on survival in the ATC subset. In our study, there was no significant difference in OS overall, with median OS of 3 months with DM and 6 months without ($P = .45$, data not shown). To attempt to examine any benefit for FNRT on local control, we examined the OS of the ATC patients without DM with respect to treatment type (Fig 6). Here, there was a trend toward improved OS with FNRT (median OS 7 vs 4 months); however, this did not reach significance ($P = .15$). Of note, the 2 patients to survive for more than 2 years were in the FNRT group (41 and 47 months).

Discussion

Thyroid cancer is a rare diagnosis, with each primary histology mandating tailored treatment approaches resulting in varying outcomes. For well differentiated and MTC, EBRT is recommended in advanced cases in which local recurrence is likely. For ATC, it is used as part of trimodality therapy. At our institution, patients with advanced thyroid cancer have been treated with both FNRT and photon RT. Here we report our institutional experience, comparing these modalities for the first time.

Our current series presents outcomes from a very high-risk patient cohort treated over the past 30 years. Nearly all patients (97%) had stage IV disease according to the 2010 AJCC staging criteria, and all had evidence of either gross residual disease, nodal metastases with or without extracapsular extension, positive margins, or recurrence. Twenty-four patients (39%) had ATC. Despite these adverse features, estimated OS at 1 year for the cohort was 90%, 78%, and 23% for well differentiated, MTC, and ATC, respectively. These compare favorably with similar data for OS at 1 year for all stage IV patients of 77.5 and 65.4 for PTC and FTC, respectively; 55% for

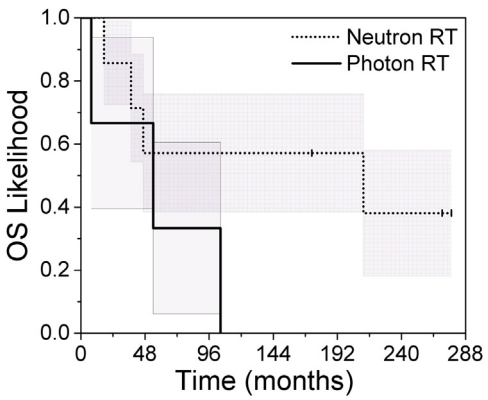

Figure 4 Survival outcomes for medullary thyroid cancer based on treatment modality. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

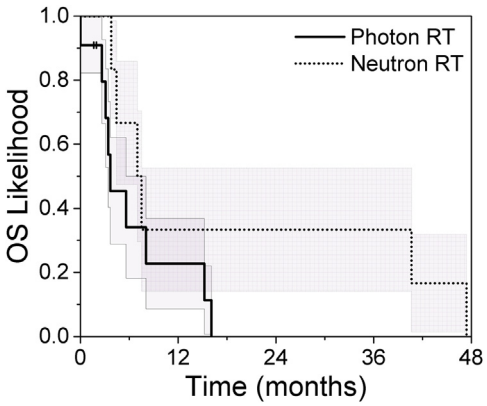

Figure 6 Survival outcomes for patients with anaplastic thyroid cancer and no evidence of distant metastasis. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

MTC; and 17.8% for ATC.[7] On multivariate analysis, patients with advancing age, ATC, and concurrent chemotherapy had worse OS. The first 2 factors would be expected to lead to worse survival because age is an independent prognostic factor in AJCC staging and ATC has a dismal overall prognosis. In this case, the presence of chemotherapy is most likely indicative of more advanced disease warranting aggressive therapy in the ATC subset. For the overall cohort, there was an increase in median OS from 16 to 26 months when comparing photon RT and FNRT, respectively. This finding was not statistically significant $P = .49$; however, it is worth noting that there is a separation of the survival curves after the first year, potentially indicating an improvement in durable local control with FNRT.

The mainstay of treatment of well-differentiated thyroid cancer is surgical resection with continued debate surrounding the need for total (or near-total) thyroidectomy versus unilateral lobectomy.[32,33] In a study of more than 50,000 patients with PTC, total thyroidectomy was shown on multivariate analysis to predict improved local recurrence and survival rates for tumors >1 cm, and therefore current American Thyroid Association recommendations include total thyroidectomy in most cases.[10,34] RAI ablation routinely follows surgery for patients with extrathyroidal extension or tumors >4 cm. It is also often indicated for tumors >1 cm with known lymph node metastases or other high-risk factors.[10] RAI administration has been shown to improve locoregional relapse-free rate in these patients, but not in those with lower risk factors.[35] EBRT has typically been reserved for patients presenting with extensive local disease, particularly those with positive margins, gross residual disease, or nodal metastases. In 1 retrospective study from Essen (Germany), the addition of EBRT to surgery, RAI, and thyroid-stimulating hormone suppression improved time to locoregional recurrence ($P = .004$) and time to distant failure ($P = .0003$).[36] The patients in that study were all >40 years old with pT4 disease, and the effect was most significant in those with nodal disease. In addition, a study from Hong Kong demonstrated a survival benefit for patients with gross residual disease after surgery, with OS at 5 years 67% versus 38% without RT ($P = .001$).[37] Although there are some conflicting reports in the literature, the majority of studies show an improvement in locoregional control and/or survival with the addition of EBRT.[8,38] In spite of this improvement, approximately 15% to 25% of patients will experience local recurrence.[8] A recent retrospective study from Manchester (UK) investigated patterns of recurrence after EBRT. The authors showed that 12 of 49 (24%) treated patients had local recurrence, with 4 in the thyroid bed and 8 in the regional lymph nodes.[14] Given the inadequate local control, even after EBRT, we investigated whether the use of FNRT in the well-differentiated patient subgroup could be beneficial. However, for the patients treated in our cohort, FNRT appears to confer a significant survival detriment when compared with photon RT, with OS at 1 year 57% versus 86% ($P = .04$), respectively. For any retrospective study, there are inherent biases in patient selection that could account for the difference seen; however, the patients appear to be relatively well distributed. The explanation for this is unclear. FNRT doses were selected based on isoeffective normal tissue tolerances rather than a known RBE for thyroid malignancies; however, the RBE for neutrons has been shown to be up to 8 for certain slow-growing malignancies such as adenoid cystic carcinomas.[29] Because well-differentiated thyroid cancers are also relatively slow growing, tumor underdosing versus photon RT is unlikely, though possible. It is also possible that an increase in toxicity with FNRT could be responsible for this difference, particularly because patients at the beginning of our study were treated with a higher dose (>2000 NcGy) versus 1840 NcGy in the modern era. Doses of >2000 NcGy have been shown to cause a 40% incidence of grade 3 to 5 late toxicities in head and neck cancer patients.[31]

In contrast to thyroid cancers arising from follicular cells, there is little role for RAI in MTC because parafollicular cells do not concentrate iodine. The standard of care therefore is total thyroidectomy (because of the high rate of bilateral disease).[11] Again, as with well-differentiated disease, EBRT is reserved for patients with locally advanced disease with a high risk of local recurrence. Historical data suggest a limited role for EBRT in the treatment of MTC, with 1 retrospective French study demonstrating a 30% in-field recurrence rate in the treatment of 59 patients in the adjuvant setting.[15] This was reinforced by a recent Surveillance Epidemiology and End Results (SEER) study that showed no survival benefit in patients with involved nodes.[39] As with well-differentiated disease, however, the intent in treating with EBRT is to improve local control, and several small retrospective studies have shown it to be effective in this regard.[40,41] For example, a recent study from M D Anderson examined 34 patients with a high risk of local recurrence. There was no control arm in the study; however, an 87% local relapse-free rate at 5 years compares favorably with historical data.[42] The data in our study highlight the uncertain benefit of EBRT in MTC, with only 10 patients treated over the course of 30 years. Although there is a large difference in median OS, with 211 months for FNRT and 54 months for photon RT, this finding is not significant ($P = .19$), as might be expected with such small patient numbers. That all long-term survivors are in the FNRT is interesting however and lends itself to further study. As with all thyroid cancers however, enrolling patients in prospective studies is complicated by the low number of patients eligible for EBRT, particularly in the case of MTC.

Unlike well-differentiated and MTC, ATC has a uniformly grim prognosis, with median OS of 5 months and

a 20% 1 year survival rate.[17] This is reinforced by a recent SEER analysis that showed a median OS of 4 months and a 19.3% 1 year OS.[16] Patients typically present with a rapidly growing neck mass that can be rapidly fatal without intervention because airway compromise; therefore, current American Thyroid Association recommendations include a clear discussion of goals of care and rapid multidisciplinary evaluation before proceeding.[12] Surgical excision is routinely the standard of care, either in an attempt to obtain negative margins or to debulk gross disease in the palliative setting. Given the rapid repopulation of ATC, many groups have investigated aggressive adjuvant therapy, with EBRT with or without chemotherapy.[8] The SEER study mentioned previously is 1 of the largest population-based studies, in which 120 of 197 patients received EBRT, with improved OS in the subset with invasion into surrounding structures ($P = .05$). There was no benefit if the cancer was capsule confined. In addition, a retrospective study from Princess Margaret Hospital showed an OS benefit for radical surgery and definitive RT compared with palliative RT (11.1 vs 3.2 months, $P < .0001$)[43]; however, this and many other studies are potentially compromised by selection bias in the treatment groups, with healthier patients with better prognostic factors receiving more aggressive care. One recent prospective study performed at the Institut Gustave-Roussy (France) examined an aggressive multimodality approach in 30 patients, with surgery followed immediately by chemotherapy with cisplatin and doxorubicin for 2 cycles. Patients then received hyperfractionated EBRT with 1.25 Gy twice a day to a dose of 40 Gy (patients treated later received boosts to 50-55 Gy). This study produced quite remarkable results, with 1- and 3-year OS of 43% and 27%, respectively.[44] Median OS was 10 months in this cohort, indicating a potential for improved outcomes with this technique; however, it was associated with significant esophagitis and neutropenia. In contrast, a recent retrospective study from M D Anderson examined the outcomes for ATC in the modern era, again using surgery with concurrent chemotherapy and RT. In their study of 53 patients (with 31 treated with definitive intent), 81% received chemotherapy. Estimated OS at 1 year was 29% for patients treated definitively, more in line with historical data. Of note, patients without DM receiving >50 Gy had better OS.[28] As can be seen, in spite of recent advances in chemotherapy and treatment techniques, OS in ATC remains poor. Because ATC is considered radioresistant to traditional photon RT, we hypothesized that FNRT might overcome this radioresistance and that the shorter treatment time might reduce the effect of rapid repopulation and improve OS. Overall, ATC patients in our study had a median OS of 4 months, in line with those published in the literature. The use of FNRT improved this to 7 months, with a 1-year estimated OS of 29%; however, this increase was not statistically significant ($P = .20$). When removing patients with DM, median OS remained 7 months versus 4 months for photon RT ($P = .15$). Therefore, in this cohort of 24 ATC patients, there does not appear to be a clear benefit for FNRT over photon RT. It is possible that inherent biases in the treatment groups may preclude a difference from being seen. Also, the comparison may be underpowered and any effect on local control may be rendered irrelevant as patients typically die of DM (even with no evidence of DM at presentation). Interestingly, the 2 patients with longest survival in the ATC group (44 and 47 months) received FNRT. A number of patients in the photon RT group (71%) received concurrent chemotherapy (most often low-dose doxorubicin). This was a negative prognostic factor for survival in both the uni- and multivariate analysis, indicating that concurrent chemotherapy should be used with caution; however, this could again represent bias in patient selection.

We acknowledge potential limitations of our study. Upon review of the charts, there were insufficient data to report locoregional control or toxicity in our patient cohort. These data are important and should be prospectively collected in future studies. One of the strengths of our study is the high number of true events collected for data analysis, with very few censored events or patients lost to follow-up. In addition, selection biases, physician preference, and nonrandomization to treatment arms are always problematic and difficult to reconcile in retrospective reviews. The rarity of thyroid cancer and the excellent outcomes for well-differentiated and low-grade disease are reflected in the small number of patients treated at our institution over a 30-year period and explain the heterogeneity in histology, extent of disease, and treatment technique. These issues have led to failed attempts to perform prospective, randomized studies in thyroid cancer, with a recent European multicenter study of differentiated thyroid carcinoma unable to accrue sufficient patients secondary to clinician's beliefs and referral patterns.[45] Given the difficulties with accruing patients to randomized studies, we are limited to carefully performed retrospective studies such as ours, reporting for the first time a comparison of FNRT and photon RT in patients with thyroid cancer. Here we show overall treatment results that compare favorably with those published in the literature. Accepting the implications of a nonrandomized study, we show that FNRT may be detrimental in the treatment of well-differentiated histologies. In addition, we show that there may be a small (but not significant) benefit for FNRT in the treatment of MTC and ATC and recommend further research in this area. In the case of ATC, there has been much interest recently in the use of tyrosine kinase inhibitors, such as sorafenib,[46] imatinib,[47] and axitinib,[48] and BRAF inhibitors,[49] which have all demonstrated activity in ATC. It may be beneficial to combine these "targeted therapies" with aggressive RT to improve both local and distant control, and a trial with FNRT may make sense in this setting.

Conclusions

In this retrospective review of a single-institution experience treating locally advanced thyroid cancer, FNRT does not confer a survival benefit in comparison with traditional photon techniques. Indeed, there is an apparent detriment in OS with FNRT for well-differentiated histologies. The trend toward improved OS with medullary and anaplastic histologies warrants further investigation.

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