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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