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CLINICAL INVESTIGATION **Thyroid**

POSTOPERATIVE EXTERNAL BEAM RADIOTHERAPY FOR DIFFERENTIATED THYROID CANCER: OUTCOMES AND MORBIDITY WITH CONFORMAL TREATMENT

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Purpose: To review institutional outcomes for patients treated for differentiated thyroid cancer with postoperative conformal external beam radiotherapy (EBRT).

Methods and Materials: This is a single-institution retrospective review of 131 consecutive patients with differentiated thyroid cancer who underwent EBRT between January 1996 and December 2005. Histologic diagnoses included 104 papillary, 21 follicular, and six mixed papillary-follicular types. American Joint Committee on Cancer stage distribution was Stage III in 2 patients, Stage IVa–IVc in 128, and not assessable in 1. Thirty-four patients (26%) had high-risk histologic types and 76 (58%) had recurrent disease. Extraglandular disease spread was seen in 126 patients (96%), microscopically positive surgical margins were seen in 62 patients (47%), and gross residual disease was seen in 15 patients (11%). Median EBRT dose was 60 Gy (range, 38–72 Gy). Fifty-seven patients (44%) were treated with intensity-modulated radiotherapy (IMRT) to a median dose of 60 Gy (range, 56–66 Gy). Median follow-up was 38 months (range, 0–134 months).

Results: Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and overall survival at 4 years were 79%, 76%, and 73%, respectively. On multivariate analysis, high-risk histologic features and gross residual disease predicted for inferior locoregional relapse-free survival, whereas high-risk histologic features, M1 disease, and gross residual disease predicted for inferior disease-specific and overall survival. The IMRT did not impact on survival outcomes, but was associated with less frequent severe late morbidity (12% vs. 2%).

Conclusions: Postoperative conformal EBRT provides durable locoregional disease control for patients with high-risk differentiated thyroid cancer if disease is reduced to microscopic burden. Patients with gross disease face significantly worse outcomes. The IMRT may significantly reduce chronic radiation morbidity, but requires additional study. © 2009 Elsevier Inc.

Thyroid cancer, Differentiated, Radiotherapy, Intensity-modulated radiotherapy (IMRT), Conformal, Postoperative, Adjuvant.

INTRODUCTION

Thyroid cancer constitutes 1% of newly diagnosed cancers in the United States, representing more than 20,000 cases each year. More than 90% of patients present with differentiated disease, which encompasses papillary, follicular, or mixed papillary-follicular histologic types. The cornerstone of management is surgery, complemented by ablative radioactive iodine (RAI) treatment as indicated by adverse histopathologic or clinical risk factors.

Postoperative external beam radiotherapy (EBRT) potentially improves locoregional disease control in the setting of incompletely resected high-risk disease (1–14). However, available data originate from retrospective institutional series with varying case selection criteria. Conflicting data from a small number of older reports (15–17) also suggest that adjuvant radiotherapy (RT) may not necessarily improve treatment outcomes. This has led to continuing controversy regarding the utility of adjuvant EBRT, especially for

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patients after their first surgical procedure and/or with microscopic residual disease. Our general institutional practice has been to offer postoperative EBRT to patients with recurrent disease and/or gross/microscopic residual disease, especially diffusely infiltrative disease that would preclude reoperation for subsequent recurrences.

The challenging location of the thyroid bed has a key role in determining the efficacy and therapeutic ratio of postoperative RT. The distribution of surgical dissection necessitated by locally advanced disease requires a large irregularly shaped treatment volume that includes or closely approximates normal structures in the central neck compartment and superior mediastinum. Parotid glands and skull base may also be at risk of radiation-related morbidity in cases of diffuse cervical nodal involvement. The geometry of the thyroid operative bed historically has led to undesirable dose reductions and/or treatment morbidity with older RT techniques. These challenges can now be better met with such modern radiation delivery methods as three-dimensionally guided RT (3D-RT) and, more recently, intensity-modulated radiation therapy (IMRT). In this report, we review our institutional treatment and morbidity outcomes for patients with differentiated thyroid cancer treated with these conformal techniques during a 10-year period after 1995.

METHODS AND MATERIALS

After approval from our Institutional Review Board, we retrospectively reviewed the medical records of 239 consecutive patients who presented to our department for definitive treatment after surgical management of thyroid malignancy between January 1996 and December 2005. We excluded 108 patients with nondifferentiated histologic types (including anaplastic, medullary, unclassified, or lymphoma) from analysis, yielding a study cohort of 131 patients. High-risk histologic type was defined as Hurthle cell, tall cell, clear cell, or poorly differentiated features.

All patients received 3D-RT or IMRT after computed tomography (CT)-based simulation. The CT imaging included the entire thorax to permit incorporation of both lung volumes into treatment planning. Every case in this series was formally presented to members of the full head-and-neck clinical service for physical examination, discussion, and quality assurance.

Seventy-four patients received conventional EBRT by means of extended opposed anterior/posterior fields supplemented by off-cord photon boost fields or en face electron fields after delivery of 40–45 Gy. Fifty-seven patients received IMRT after July 2000. With either technique, the superior mediastinum was treated to a prophylactic dose of 45–50 Gy. Definitive postoperative doses and extended inferior coverage of the middle or inferior mediastinum was pursued if these regions were involved with disease and/or the patient underwent mediastinal nodal dissection.

The IMRT was delivered by means of a step-and-shoot multileaf collimation through a static treatment gantry using a monoisocentric technique. From July 2000 through August 2003, IMRT treatment planning was performed with a CORVUS treatment planning system (CORVUS, Version 4.0; Nomos Corp., Pittsburgh, PA). A Pinnacle3 system (Version 6.2b or later; Philips Medical Systems, Andover, MA) was used after August 2003. Regions of grossly positive margins or gross residual disease typically were prescribed 63–66 Gy in 30 daily fractions to a high-dose clinical target volume (CTV)1. An intermediate-dose CTV2 encompassing regions of the operative bed directly involved with disease, as well as immediately adjacent soft tissues and draining nodal basins, were treated to a dose of 60 Gy in 30 daily fractions. An adjuvant dose of 56 Gy in 30 daily fractions was prescribed to a CTV3 encompassing the entirety of the surgical resection bed with a 1–2-cm (minimum, 0.5-cm) margin. Finally, prophylactic coverage of at-risk cervical and mediastinal nodal stations was provided by a CTV4 treated to 54 Gy in 30 daily fractions. A representative treatment plan is shown in Fig. 1. Constraints for normal tissue structures were set at 45 Gy for spinal cord, a mean dose of 26 Gy for parotid glands, and 20 Gy to whole lungs, whereas larynx and esophagus were contoured as avoidance structures with low priority weighting to prevent compromising intended CTV1 or CTV2 coverage. The mean dose range delivered to CTV1 was 62.1–74.9 Gy (median, 68.6 Gy), whereas the mean dose range delivered to CTV2 was 59.8–72.6 Gy (median, 62.4 Gy). The mean percentage of the prescribed dose range delivered to CTV1 was 101.0–107.9% (mean, 103.4%). The volume range of CTV1 receiving less than the prescribed dose was 0.0–7.7% (mean, 0.9%).

The end points of this study were local relapse-free survival (LRFS), disease-specific survival (DSS), and overall survival (OS). These were defined from the date of completion of RT and estimated by using the Kaplan-Meier method. Any evidence of residual disease after irradiation of gross disease was scored as an immediate local failure. Univariate correlates were determined by using log-rank test and Cox proportional hazards testing. Multivariate analysis was performed using Cox proportional hazards models. We included covariates in our multivariate models if they were significant on univariate analysis with a p value corrected for multiple comparisons by means of the Bonferroni method ($p \leq 0.004$, derived from $p = 0.05/12$ univariate tests). To minimize bias and inaccuracy with retrospective grading of posttreatment morbidity, late radiation-related toxicity occurring 3 months or later after completion of treatment was defined according to a three-point scale as absent, minor to moderate, or severe. The latter designation was assigned if the patient was hospitalized for medical management, required surgical intervention, or died as a direct result of a late RT-related morbid event (consistent with toxicity Grade ≥ 4). Analyses were performed using StatView, Version 5 (SAS Institute, Inc., Cary, NC), and significance was determined at $p < 0.05$, with the exception of Bonferroni-corrected $p < 0.004$, which was used for populating our proportional hazards models, as described.

RESULTS

Patients

Patient characteristics are listed in Table 1. Median age was 57 years (range, 18–83 years, with 106 patients [81%] $\geq$ 45 years old). There were 75 men (57%) and 56 women (43%). Disease histologic types consisted of 104 papillary (79%), 21 follicular (16%), and six mixed papillary-follicular cancers (5%). Thirty-four patients (26%) had high-risk histologic types (12 Hurthle cell, 11 poorly differentiated, nine tall cell, and two clear cell). Seventeen of 21 patients with follicular disease (81%) had high-risk histologic features. Seventy-six patients (58%) had recurrent disease at presentation to our institution; these patients underwent a median of two (range, one to six) definitive surgical resections before RT. Forty-four patients (34%) presented for definitive surgery at initial diagnosis, and 9 (7%) presented for additional treatment after incomplete