Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–5, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.01.016

CLINICAL INVESTIGATION

TREATMENT OF LOCALLY ADVANCED ADENOID CYSTIC CARCINOMA OF THE TRACHEA WITH NEUTRON RADIOTHERAPY

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Purpose: To examine the efficacy of fast neutron radiotherapy in the treatment of locally advanced adenoid cystic carcinoma (ACC) of the trachea and to compare outcomes with and without high-dose-rate (HDR) endobronchial brachytherapy boost.

Methods and Materials: Between 1989 and 2005, a total of 20 patients with ACC of the trachea were treated with fast neutron radiotherapy at the University of Washington. Of these 20 patients, 19 were treated with curative intent. Neutron doses ranged from 10.7 to 19.95 Gy (median, 19.2 Gy). Six of these patients received an endobronchial brachytherapy boost using an HDR ^{192}Ir source (3.5 Gy × 2 fractions). Median duration of follow-up was 46 months (range, 10–121 months).

Results: The 5-year actuarial overall survival rate and median overall survival for the entire cohort were 89.4%, and 97 months, respectively. Overall survival was not statistically different among those patients receiving an endobronchial boost compared with those receiving neutron radiotherapy alone (100% vs. 68%, $p = 0.36$). The 5-year actuarial locoregional control rate for the entire cohort was 54.1%. The locoregional control rate was not statistically different among patients who received an endobronchial boost compared with those who received neutron radiotherapy alone (40% vs. 58%, $p = 0.94$). There were no cases of Grade ≥3 acute toxicity. There were 2 cases of Grade 3/4 chronic toxicity.

Conclusions: Fast neutron radiotherapy is an effective treatment for locally advanced adenoid cystic carcinoma of the trachea, with acceptable treatment-related toxicity. © 2008 Elsevier Inc.

Adenoid cystic carcinoma, Neutron radiotherapy, Trachea.

INTRODUCTION

Tumors of tracheal origin are exceedingly rare, with a yearly incidence of 0.2 per 100,000 persons (1). Among primary tumors of the trachea, adenoid cystic carcinoma (ACC) is a common histology, second only to squamous carcinoma (1). Surgical resection has historically been the primary mode of treatment for ACC of the trachea (1, 2). Radiotherapy, on the other hand, has traditionally been reserved for patients with microscopically positive margins, invasion of a named nerve, or unresectable disease (3).

Given the indolent nature of ACC, a substantial proportion of patients present with locally advanced disease at diagnosis and consequently are not appropriate surgical candidates. Noninvasive treatment approaches have been used in this setting and include standard external beam radiotherapy, endobronchial brachytherapy, or a combination thereof (4, 5). Unfortunately data are sparse, with most published series including fewer than 5 patients. Consequently the optimal treatment of locally advanced tracheal ACC is not well characterized.

The role of high linear energy transfer (LET) radiation in the treatment of ACC was first explored by Batterman *et al*. (6). These data indicated an enhanced relative biologic effectiveness (RBE) for ACC with fractionated neutron radiotherapy over standard photon therapy. The superiority of neutron radiotherapy in the treatment of unresectable salivary gland neoplasms was later confirmed in a multi-institutional, randomized trial conducted by the Radiation Therapy Oncology Group (RTOG) and Medical Research Council (7). Single-institution, retrospective studies with long term follow-up continue to demonstrate excellent local control of ACC with neutron radiotherapy (8, 9).

With documented efficacy of neutron radiotherapy in other subsites of the head and neck, it is reasonable to hypothesize

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Presented in part at the American Radium Society Annual Meeting, Amsterdam, The Netherlands, May 5–7, 2007.

Conflict of interest: none.

Received Sept 14, 2007, and in revised form Dec 24, 2007. Accepted for publication Jan 3, 2008.

that there may also be a therapeutic advantage in the treatment tracheal ACC (7–9). For this reason, we have routinely treated high-risk and/or unresectable ACC of the trachea with fast neutron radiotherapy. An early analysis of our first 4 patients with tracheal ACC demonstrated inferior control rates in comparison with other anatomic subsites. We have speculated that this may be related to an underdosing of the tumor at the luminal surface, secondary to a lack of dose build-up at the air–tissue interface. More recently, in an attempt to improve local control rates, we have incorporated a high-dose-rate (HDR) endobronchial boost after completion of neutron therapy. Herein we report our institutional experience using neutron radiotherapy to treat locally advanced ACC of the trachea. In addition, we compare treatment outcomes with and without endobronchial boost.

METHODS AND MATERIALS

Between 1989 and 2005 a total of 20 patients with ACC of the trachea were treated with fast neutron radiotherapy at the University of Washington. Of the 20 evaluable patients, a total of 19 were treated with curative intent, whereas 1 patient had distant metastatic disease and was treated palliatively. The subsequent survival analysis includes only those patients treated with curative intent. Before the initiation of neutron radiotherapy, 9 patients underwent surgical debulking, and 11 underwent biopsy only. All patients were deemed unresectable and accordingly were not candidates for a gross total resection. Follow-up data were obtained by review of University of Washington medical records, contacting the patient's current physician, and/or contacting the patient directly. In cases in which the patient was lost to follow-up, survival data were obtained through the National Social Security Database.

Description of treatments

All patients were treated with a high-energy, hospital-based, Scanditronix (Uppsala, Sweden) MC 50 cyclotron, as previously described (10). The cyclotron utilizes a 50.5 MeV p $\rightarrow$ Be reaction and is equipped with an isocentric rotating gantry and multileaf collimation system, which permits the use of conformal field shaping. Fields were individualized according to the location and extent of the primary tumor. When possible, a margin of 2 to 3 cm was used between gross tumor volume and block edge. Fraction sizes ranged from 1 to 1.2 nGy. The median total dose was 19.2 nGy (range, 10.7–19.95 nGy). The most commonly used fractionation schema consisted of 1.2 Gy given 4 times per week to a total dose of 19.2 nGy. Radiobiologic studies suggest an RBE of 8 for ACC and 3–3.5 for normal late-reacting tissues (6). As such, a neutron dose of 19.2 Gy is estimated to be biologically equivalent to a photon dose of 154 Gy to ACC tumor and 67 Gy to normal late-reacting tissues.

Starting in November 2000, 6 of 7 patients received an HDR endobronchial brachytherapy boost after neutron radiotherapy. The single patient not receiving endobronchial boost was unable to return to Seattle because of out-of-town travel constraints. The endobronchial boost was delivered within 1 to 2 months of completing neutron radiotherapy. This interval was planned to allow for acute tissue recovery. The median interval between completion of neutron radiotherapy and the first endobronchial boost was 30 days (range, 15–46 days). Endobronchial catheters were placed under general anesthesia, and treatments were delivered with a MicroSelectron ^{192}Ir HDR unit (Nucletron, Veenendaal, The Netherlands). The longitudinal tumor extent was treated to a dose 3.5 Gy, prescribed to a median depth of 0.75 cm (range, 0.5–1 cm). A total of two treatments were delivered, for a cumulative dose of 7 Gy. The two treatments were separated by 1 week. All endobronchial catheter placements were performed collaboratively by two of the investigators (W.K. and M.M.).

Patient and tumor characteristics

The median follow-up period for all patients was 62 months (range, 10–121 months). The median age at the time of treatment was 46 years (range, 24–67 years). Sixty percent of patients (12) were male, and 40% (8) were female. Before any treatment intervention, including both surgery and radiotherapy, the median primary tumor diameter was 4.2 cm (range, 1.9–8.2). There were no statistically significant differences in age, gender distribution, presence/absence of involved lymph nodes, neutron dose, or presence/absence of pre-radiation debulking surgery among those who received endobronchial boost and those treated with neutron radiotherapy alone. However, the mean tumor diameter was significantly larger among those who received endobronchial boost (5.55 vs. 3.58 cm, $p = 0.022$). All pathologic slides were reviewed at our institution to confirm the diagnosis of ACC. Histologic subtyping and the presence/absence of perineural invasion were not routinely reported.

Statistical analysis

Locoregional control rates, disease-free survival rates, and overall survival rates were calculated with an actuarial life-table method (11). Corresponding plots were constructed with the Kaplan-Meier method. The log–rank test (two-tailed) was used to evaluate for statistically significant differences in outcomes among the two treatment arms (11). Univariate analysis using Cox regression was used to determine which patient characteristics and treatment parameters were predictive of locoregional failure (12). Differences in patient characteristics between the two treatment arms were calculated with a *t*-test for continuous variables and with a χ^2 test for dichotomous variables (12). Values of $p \leq 0.05$ were considered statistically significant. Statistical analysis was performed with SPSS 13.0 (SPSS, Chicago, IL).

RESULTS

Overall survival, disease-free survival, and locoregional control

The overall survival and disease-free survival curves for all patients are illustrated in Figs. 1 and 2. The 5-year actuarial overall survival rate and median overall survival for the entire cohort were 89.4%, and 97 months, respectively. The 5-year actuarial disease-free survival rate and median disease-free survival for the entire cohort were 28.4% and 49 months, respectively. Overall survival was not statistically different among those patients receiving an endobronchial boost compared with those receiving neutron radiotherapy alone (100% vs. 68%, $p = 0.36$). Similarly, disease-free survival was not statistically different among those patients receiving an endobronchial boost compared with those receiving neutron radiotherapy alone (30% vs. 28%, $p = 0.60$).

The locoregional control curve for all patients is depicted in Fig. 3. The 5-year actuarial locoregional control rate for the entire cohort was 54.1%. Median locoregional control has not yet been reached. The locoregional control rate was not statistically different among patients who received an

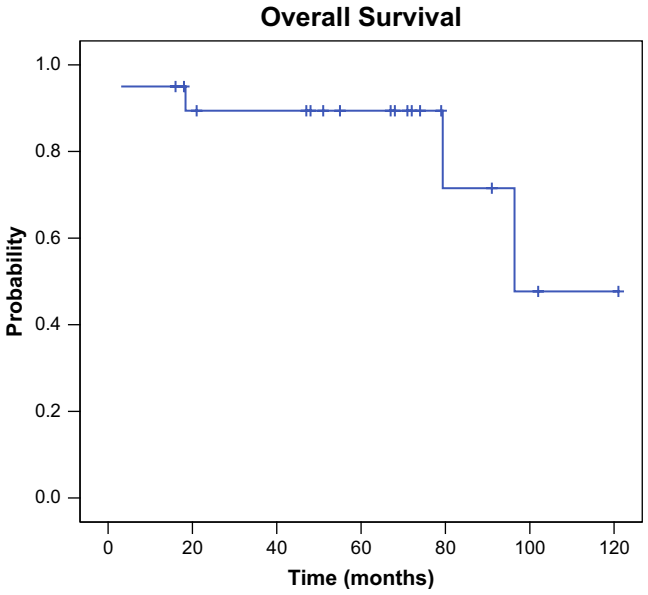

Fig. 1. Overall survival for all patients.

endobronchial boost compared with those who received neutron radiotherapy alone (40% vs. 58%, $p = 0.94$). Locoregional control as a function of the presence/absence of endobronchial boost is illustrated in Fig. 4.

Univariate analysis was performed to assess the parameters predictive of locoregional recurrence in this patient population. The parameters examined included tumor size, gender, lymph node status, presence/absence of endobronchial brachytherapy boost, and neutron dose. None of the examined parameters were predictive of locoregional recurrence on univariate analysis (Table 1).

Patterns of failure and salvage therapy

Among the 19 patients treated with curative intent, there were 12 documented failures. The site of first failure was distant in 6 patients and local in 6 patients. In the patients

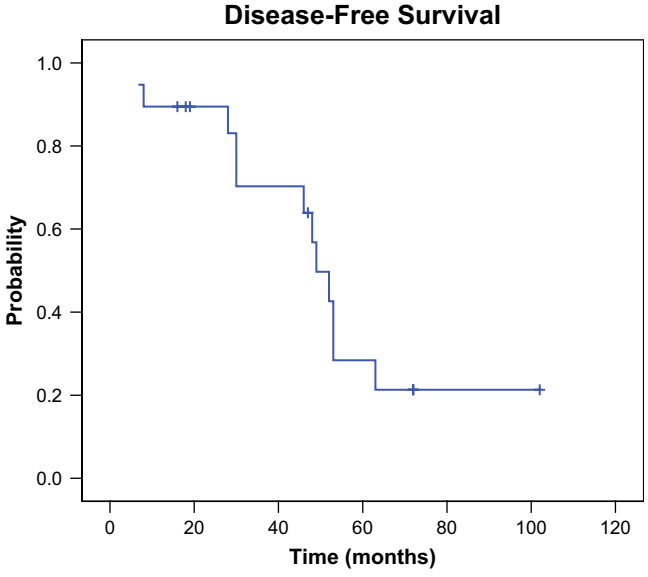

Fig. 2. Disease-free survival for all patients.

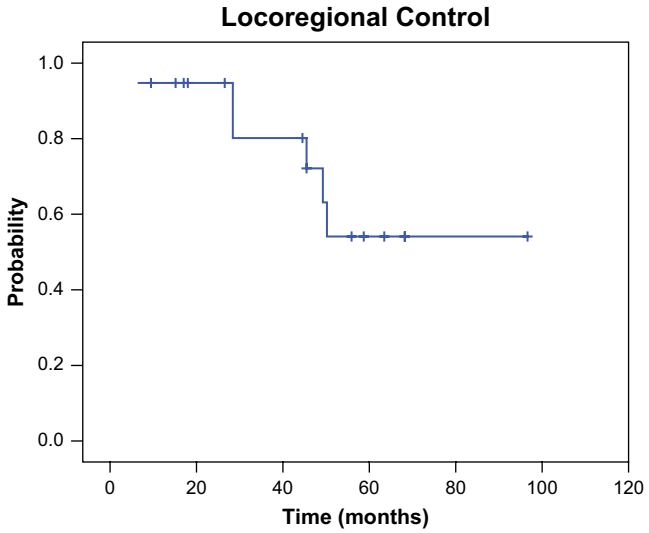

Fig. 3. Locoregional control for all patients.

who failed distantly, metastases were identified in the lungs (4 patients), brain (1 patient), and bony spine (1 patient). Among patients who failed locally, all 6 occurred within the neutron treatment portal. In reviewing the dosimetry, there were 4 patients who failed in the high-dose region. This included the high-dose region of the neutron treatment portal and where applicable, the high-dose region of the endobronchial dose cloud (2 patients). The other 2 patients were treated before the era of three-dimensional treatment planning, and consequently it was not possible to assess whether the local recurrence fell within the high-dose region of the treatment portal. This data are summarized in Table 2.

After local failure, the following salvage therapies were used: tracheal stent placement (4 patients), bronchoscopy with tumor core out, resection with a tracheotomy, and chemotherapy consisting of imatinib mesylate. The 5-year actuarial survival rate after salvage was 67%, and median survival after salvage has not yet been reached.

Treatment-related morbidity

Complications were scored according to RTOG morbidity scoring criteria. Among the entire patient cohort, there were

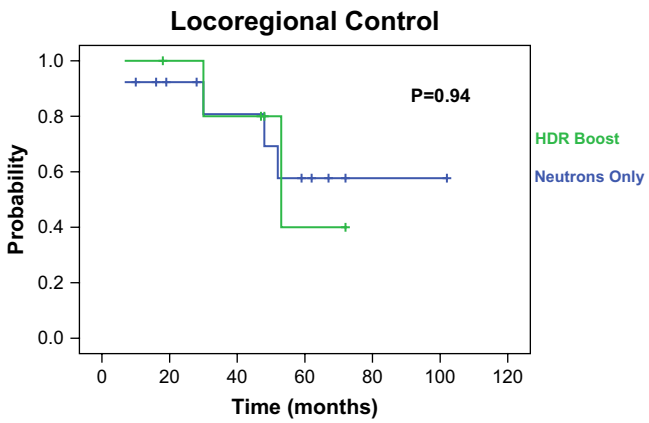

Fig. 4. Locoregional control as a function of the presence/absence of high-dose-rate endobronchial brachytherapy boost.

Table 1. Treatment parameters and patient characteristics predictive of locoregional recurrence

Variable	Hazard ratio	*p*
Tumor size (≤4 cm vs. >4 cm)	1.6	0.57
Gender (male vs. female)	2.2	0.38
Lymph node status (negative vs. positive)	1.2	0.84
HDR boost (no vs. yes)	0.94	0.94
NRT dose (<18 nGy vs. ≥18 nGy)	0.80	0.84

Abbreviations: HDR = high-dose-rate brachytherapy; NRT = neutron radiotherapy.

17 patients (85%) who experienced acute Grade 1/2 toxicity. This included 11 cases of dermatitis and 11 cases of esophagitis. There were no cases of Grade ≥3 acute toxicity. There were 2 cases of Grade 3/4 chronic toxicity. This included 1 case of tracheal stenosis and 1 case of brachial plexopathy. The patient with tracheal stenosis was managed with endoluminal stent placement and reported symptomatic improvement. The patient experiencing brachial plexopathy was treated with a photon equivalent dose of 65 Gy to the brachial plexus in an attempt achieve adequate tumor coverage. A thorough discussion of the potential for this complication was discussed with the patient before initiation of radiation treatment. This complication was managed with pentoxifylline and physical therapy, with nearly complete resolution of neurologic symptoms.

DISCUSSION

In this study we report our institutional experience with neutron radiotherapy as primary treatment for locally advanced ACC of the trachea. Given the rarity of tracheal ACC, there are no prospective trials to help define the optimal treatment regimen for this disease process. Available data are largely limited to case reports and small retrospective series (1, 2, 4, 13, 14). In fact, our series of 20 patients represents one the largest studies dedicated specifically to the management of tracheal ACC.

Although there are a paucity of data to support any single treatment modality, surgical resection remains the mainstay of therapy in those patients who are thought to be appropriate candidates. Some retrospective studies suggest that surgery alone or in combination with radiotherapy may improve survival and locoregional control (1, 2, 13, 15). One large series from Massachusetts General Hospital demonstrated improved long-term survival among patients with resectable tracheal ACC compared with those with unresectable disease (15). Retrospective studies such as these are unfortunately fraught with inherent bias. The majority of unresectable patients are classified as such owing to extensive regional disease or airway involvement. This relates to the fact that the maximal resectable tumor length in the trachea is constrained by the tension at the anastomosis (16). In the absence of a prospective comparison, the optimal local therapy for tracheal ACC remains undefined.

Regardless, there are a significant proportion of patients who present with locally advanced disease and consequently

Table 2. Patterns of failure

Parameter	*n* (%)
Site of 1st failure	
Local	6 (50)
Distant	6 (50)
Site of local failure	
Outside of NRT field	0
Within NRT field	6 (100)
In high-dose region (NRT and/or HDR)	4 (66)
Site of distant failure	
Lungs	4 (66)
Brain	1 (17)
Spine	1 (17)

Abbreviation as in Table 1.

are ineligible for a potentially curative resection. In such cases, photon radiotherapy has typically been used as primary management. Historical data suggest that high LET radiation may offer a biologic advantage over standard photon therapy in the treatment of adenoid cystic carcinoma. Batterman *et al*. (6) were the first to demonstrate an enhanced RBE with neutrons in the treatment of ACC metastatic to the lung. They reported an RBE of 8 for ACC, compared with an RBE of 3–3.5 for most late-reacting, normal tissues. This translates into a therapeutic gain of 2.5 over conventional photon radiotherapy and is thought to be the basis for the favorable results observed with neutrons in subsequent clinical trials (7, 8).

Our data suggest that neutron radiotherapy is an effective treatment for locally advanced tracheal ACC and may offer a therapeutic benefit over other commonly used treatment modalities. With a 5-year overall survival rate of 89.4% and a 5-year locoregional control rate of 54.1%, our results compare favorably with historical controls. One of the larger series, published by the M. D. Anderson Cancer Center, reports on 74 patients treated for primary tracheal neoplasms (17). Among these 74 patients there were 19 with histologically confirmed ACC. The reported 5-year overall survival and disease-specific survival rates for patients with tracheal ACC were 42% and 48%, respectively. It is noteworthy that many of these patients were surgical candidates and as such may have represented a more favorable group than those examined in our series.

Beginning in November 2000, eligible patients were offered an HDR endobronchial brachytherapy boost after neutron radiotherapy. This was prompted by an early analysis of our data, which suggested suboptimal local control rates among the first 4 tracheal ACC patients treated with neutron radiotherapy alone (8). Initially consideration was given to neutron dose escalation; however, there were concerns about the risk for late tissue toxicity. More importantly, it was proposed that poor local control rates may be related to an underdosing of the tumor at the luminal surface, secondary to a lack of dose build-up at the air–tissue interface. Endobronchial brachytherapy boost was thought to be the safest and most logical means of addressing this issue. External beam radiotherapy in combination with endoluminal brachytherapy has also been reported by other groups. Harms *et al*.

(18) previously published their series of 25 patients with tracheal carcinoma, 10 of whom were treated with a combination of external beam radiation and endoluminal brachytherapy. Results among patients with ACC were encouraging, with a 5-year overall survival rate of 85.7% and locally controlled disease in 6 of 8 patients at last follow-up.

Our analysis did not detect a local control advantage when endobronchial brachytherapy was combined with neutron radiotherapy; however, these results should be interpreted with caution given the small number of patients and relatively short follow-up time in this series. Moreover, the mean tumor diameter among patients receiving endobronchial boost was significantly larger than that of the patients receiving neutron radiotherapy alone, suggesting an imbalance in the study arms. Collectively, these factors may explain the lack of observed benefit with endobronchial brachytherapy boost.

In our series the location of first failure was evenly distributed between local and distant sites, underscoring the need for better local and systemic therapies. Although many systemic agents have been attempted in the setting of ACC, results have thus far have been disappointing (19). The role of systemic therapy nevertheless remains an area of active investigation. Although durable local control continues to be a challenge, the data with neutrons are certainly encouraging, especially when one considers that this is a patient population with locally advanced disease.

Without a randomized trial to guide therapy, it is difficult to make definitive recommendations about the optimal local treatment for tracheal ACC. That being said, the largest published experience exists with surgical resection, and consequently this remains the standard against which other treatment modalities should be tested (15–17). Patients with good performance status and disease that is deemed resectable by a thoracic surgeon should be offered surgery. Postoperative radiotherapy should be reserved for those patients with positive margins and/or invasion of a named nerve (3). Unfortunately, approximately 25% of all patients with tracheal ACC will present with unresectable disease (16). Our data suggest that neutron radiotherapy offers a 54% 5-year local control rate and a 90% 5-year overall survival rate in this challenging patient population. On the basis of these results, we recommend that patients with unresectable, locally advanced tracheal ACC should be considered for referral to a neutron center. Longer follow-up and larger patient numbers are needed to determine whether the incorporation of an endobronchial boost will ultimately improve locoregional control rates. Given that all local failures occurred within the treatment field and the majority within the high-dose region, consideration should be given to further dose escalation with endoluminal brachytherapy.

CONCLUSIONS

Fast neutron radiotherapy is an effective treatment for locally advanced adenoid cystic carcinoma of the trachea, with acceptable treatment-related toxicity.

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