Radiotherapy and Oncology 113 (2014) 364–370

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Particle therapy of adenoid cystic carcinoma

Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck ☆

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ARTICLE INFO

Article history:
Received 25 May 2014
Received in revised form 16 November 2014
Accepted 17 November 2014
Available online 29 November 2014

Keywords:
Adenoid cystic carcinoma
Particle therapy
Proton therapy
Carbon ion therapy

ABSTRACT

Background and purpose: The aim of this study was to retrospectively analyse the outcomes of cases of adenoid cystic carcinomas (ACCs) of the head and neck that were treated at a single institution with particle therapy consisting of either protons or carbon ions.

Methods and materials: Between February 2002 and March 2012, 80 patients were treated with proton therapy (PT) or carbon ion therapy (CIT) alone. PT and CIT were employed in 40 (50%) patients each, and more than half of the patients received 65.0 GyE in 26 fractions (n = 47, 59%).

Results: The median duration of follow-up was 38 months (range, 6–115 months). For all patients, the 5-year for overall survival (OS) rate, progression-free survival (PFS) rate, and local control (LC) rate were 63%, 39%, and 75%, respectively. No significant differences between PT and CIT were observed. The 5-year LC rates for T4 and inoperable cases were 66% and 68%, respectively. Twenty-one patients (26%) experienced grade 3 or greater late toxicities, including three patients who developed grade 5 bleeding from nasopharyngeal ulcers.

Conclusions: Particle radiotherapy for ACC achieves favourable LC, and its efficacy in inoperable or T4 cases is promising. There were no significant differences between PT and CIT in terms of OS, PFS and LC.
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Adenoid cystic carcinomas (ACCs), which arise from the secretory epithelial cells of the salivary glands, account for approximately 10% of all salivary gland tumours. These are rare malignancies and represent approximately 1% of all malignant tumours of the head and neck [1,2]. Although ACCs are characterised by a rather slow growth pattern, management of this disease is very difficult because of their insidious local growth pattern, propensity for perineural involvement, likelihood of distant metastasis and pronounced ability to recur over a prolonged period [3–6]. Surgery with or without postoperative X-ray radiotherapy (XRT) is widely accepted as the standard treatment for ACCs [7–15]. However, patients with inoperable tumours or gross residual disease show the worst outcomes, their local control rates are typically less than 50% [9,16–21]. The results of fast neutron beam therapy are not sufficient because of the low local control rate and the high rate of late complications [22–25]. In addition, there is no clear evidence with regard to the effects of chemotherapy [5,26].

Particle beams, such as those of protons and carbon ions, have a greater energy deposition than photon beams, which have a penetration depth up to a sharp maximum at the end of their range, which generates the so-called Bragg peak. Compared with conformal XRT, particle therapy thus creates an inherently three-dimensional conformal dose distribution without exposing the surrounding normal tissue to extra doses [27]. In April 2001, Hyogo Ion Beam Medical Center (HIBMC) became the first institution in the world to provide therapy consisting of either protons or carbon ions. The purpose of this study was to evaluate the treatment outcomes of patients with ACCs of the head and neck after treatment with proton therapy (PT) or carbon ion therapy (CIT).

☆ Presented at the 55th annual meetings of the American Society for Radiation Oncology (ASTRO), 22-25 September 2013, Atlanta, GA, USA.

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http://dx.doi.org/10.1016/j.radonc.2014.11.031
0167-8140/

Materials and methods

Study design and patients

The eligibility criteria for this retrospective study were as follows: (1) histologically confirmed ACC; (2) no lymph node or distant metastasis; (3) no previous treatment; (4) treatment with particle therapy alone; (5) treatment administered with radical intent; and (6) duration of follow-up greater than 6 months. Postoperative patients or those with recurrence were not included in this study. Each patient gave his or her written informed consent, approved by the Ethics Committee at our Institute.

The study patients presented between February 2002 and March 2012. The characteristics of patient and their treatments are shown in Table 1. The study included 80 patients and composed 27 men (34%) and 53 women (66%) with a median age of 59.5 years (range, 24–83 years). The most frequent primary site was the nasal cavity/paranasal sinuses ($n = 41$, 51%). Most patients presented with locally advanced disease (T3–T4; $n = 68$, 85%), and T4 cases comprised more than half ($n = 49$, 61%) of all cases. We considered the tumours that had infiltrated the clivus, the cavernous sinus, Meckel's space, the infratemporal fossa, the major nerves, the skull base or the brain to be inoperable prior to treatment. As a result, a total of 56 patients (70%) were deemed as inoperable at presentation. Twelve patients had T1–T2 diseases, and 7 of them were deemed inoperable because of their advanced age because of the comorbidities: 5 remaining patients rejected surgery.

Treatment planning system and protocols

After a custom-made thermoplastic cast was used to immobilise each patient in the supine position with an adequate head angle, 1-mm computed tomography (CT) slices and 1- to 3-mm magnetic resonance imaging (MRI) slices were obtained. Radiation treatments were planned on a CT-based three-dimensional treatment planning system (FOCUS-M [CMS [St. Louis, MO, USA and Mitsubishi Electric, Tokyo, Japan]] until April 2008 and Xio-M [CMS and Mitsubishi Electric] from May 2008). The target volumes and organs at risk were delineated on the CT–MRI fusion images. The clinical target volume (CTV) was generally defined as the gross tumour volume (GTV) plus a 5-mm basic margin. The base of the skull was included in the CTV routinely since 2009: as a result, the base of the skull was included in the CTV in 41 cases (51%). The planning target volume was defined as the CTV plus a setup margin of 3 mm.

The selection of the beam type was based partly on availability—from February 2002 to June 2002, only CIT was available; from April 2003 to March 2005, only PT was available; and from April 2005, treatment plans for both PT and CIT were available. Accordingly, after April 2005, treatment was simultaneously planned for each patient with either PT or CIT. The relative biological effectiveness (RBE) values for protons and carbon ions at HIBMC were determined on the basis of radiobiological experiments. The RBE value for PT was 1.1, while the RBE value for CIT was 3.0 [28]. After a comparison of the dose distribution and the dose–volume histogram, the radiation oncologists selected the most appropriate treatment beam to use for. Thus, PT and CIT were employed in 40 (50%) patients each, and a representative case is shown in Fig. 1.

Nine patients (11%) received 57.6 GyE in 16 fractions, 47 patients (59%) received 65.0 GyE in 26 fractions and 20 patients (25%) received 70.2 GyE in 26 fractions. The biological effective dose (BED) was calculated with the linear quadratic (LQ) model to compare the effects of the treatment and late complications with different fraction sizes and total doses [29]. The BED was calculated as follows: $\mathrm{BED\ (GyE)} = nd\ [1 + d/(\alpha/\beta)]$, where n is the number of fractions, and d is the dose/fraction. The α/β ratio was 10 GyE for tumours and 3 GyE for normal tissues. $\mathrm{EQD}_{(\alpha/\beta)/2}$ signifies the equivalent dose as 2-Gy fractions for some value of α/β. $\mathrm{EQD}_{(\alpha/\beta)/2}$ was calculated as follows: $\mathrm{EQD}_{(\alpha/\beta)/2} = \mathrm{BED}/[1 + 2/(\alpha/\beta)]$ [30].

Follow-up evaluation

The duration of the follow-up period was calculated from the initial date of particle therapy. Patients were observed at 3-month intervals for the 1 to 3 years after the start of therapy and at 6-month intervals thereafter. Regular follow-up studies included a physical examination, endoscopy, diagnostic imaging (i.e., CT and/or MRI), and blood tests. Acute reactions and late complications were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 [31].

Statistical analysis

Continuous and categorical variables are presented as medians with ranges and as frequencies with percentages. The baseline characteristics of the patients in the two treatment groups were compared with the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. The overall survival (OS), progression-free survival (PFS) and local control (LC) curves were estimated with the Kaplan–Meier method and were compared with the log-rank test. A multivariate analysis was performed with the Cox proportional-hazards model. Possible associations between the following factors and prognosis (in terms of OS, PFS, and LC) were explored: age ($\leqslant$60 vs. >61 years), sex, T classification (T1–T3 vs. T4), the primary tumour site (nasal cavity and paranasal sinuses vs. others), indications for surgery at presentation (operable vs. inoperable), particle type (PT vs. CIT), GTV volume (<37.0 vs. $\geqslant$37.0 ml), CTV coverage with 95% of prescription dose (CTV V_{95}) (<95% vs. $\geqslant$95%), CTV margin (<3 vs. $\geqslant$3 mm), radiation field including the skull base (yes vs. no) and $\mathrm{EQD}_{10/2}$ (<68 vs. $\geqslant$68 GyE). The factors that were found to have values of $P < 0.1$ in log-rank tests were then subjected to multivariate analysis with the Cox proportional-hazards model. The results are presented as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). All P values are two-sided and P values of less than 0.05 were considered to be statistically significant. We used Fisher's exact test to compare the late complications in the patients who were followed up for 24 months or more. The statistical analyses were performed with SPSS Statistics 17 (IBM, Armonk, NY, USA).

Results

The median duration of the follow-up period for all cases in the study was 38 months (range, 6–115 months). The follow-up was longer for patients in the PT group (median, 53 months) compared with patients in the CIT group (median, 26 months), although this difference was not statistically significant ($P = 0.065$).

The median prescribed dose was 67.7 $\mathrm{GyE}_{10/2}$ (65.3–74.7 $\mathrm{GyE}_{10/2}$) in $\mathrm{EQD}_{10/2}$ and 71.5 $\mathrm{Gy}_{3/2}$ (70.0–89.6 $\mathrm{GyE}_{3/2}$) in $\mathrm{EQD}_{3/2}$. No significant differences were found with regard to the $\mathrm{EQD}_{10/2}$ and $\mathrm{EQD}_{3/2}$ between the PT and CIT groups ($P = 0.223$, 0.427, respectively). The median volumes of GTV, CTV and PTV were 36.7 ml (1.2–257.0 ml), 73.3 ml (6.3–313.74 ml) and 122.3 ml (18.7–431.2 ml), respectively.

For all patients, the 3/5 year OS, PFS, and LC rates were 82%/63%, 54%/39%, and 84%/75%, respectively (Fig. 2A).

The log-rank test showed no significant differences between the PT ($n = 40$, 50%) and CIT ($n = 40$, 50%) groups with respect to OS (Fig. 2B), PFS (Fig 2C), and LC (Fig. 2D). However a significant difference was observed during the follow-up period between the patients in the PT group and the patients in the CIT group. Therefore,