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Carbon ion therapy

Prognostic factors of adenoid cystic carcinoma of the head and neck in carbon-ion radiotherapy: The impact of histological subtypes

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ABSTRACT

Purpose: The aim of this study was to evaluate the effect of histological subtypes of head and neck adenoid cystic carcinoma (ACC) on the results of carbon-ion radiotherapy (CIRT).

Material and methods: Of the 113 patients with ACC who were treated with CIRT between December 2006 and July 2013, 100 patients with identified histological subtypes were enrolled in this study. CIRT at a total dose of 57.6 or 64.0 Gy (RBE) was administered in 16 fractions. Histological grading was defined as the presence or absence of a solid growth pattern.

Results: Median follow-up was 60 months. 5-Year local control (LC), overall survival (OS) and distant metastasis free survival (DMFS) of all patients were 68.6%, 74.8% and 65.7%, respectively. On multivariate analysis, the prescribed dose ($p = 0.001$) and gross tumor volume ($p = 0.002$) were significant independent risk factors for LC. No significant difference for local control of solid/non-solid growth patterns was found ($p = 0.093$). Solid growth pattern was an independent risk factor for both OS ($p = 0.033$) and DMFS ($p = 0.024$).

Conclusions: CIRT appears able to locally control solid growth pattern ACC in the head and neck. Improved intervention is needed to extend DMFS and OS.

Adenoid cystic carcinoma (ACC) of the head and neck (HNACC) is one of the most prevalent salivary gland malignancies [1]. Histologically, ACC can be categorized into three growth patterns: cribriform, tubular and solid. Tumors composed of solid patterns show a more aggressive behavior than cribriform and tubular patterns, and are the strongest risk factor for loco-regional recurrence and distant metastasis after surgery, the current standard treatment [2–10].

Photon therapy is indicated in cases of inoperable ACC, but local control (LC) remains insufficient, with rates reported between 26.5 and 56% [11,12]. Fast neutron therapy, perhaps owing to a higher liner energy transfer (LET), improved local control of ACC compared with photon radiotherapy [13]. Douglas and colleagues reported a series of 151 patients with HNACC treated with fast neutron therapy, finding 5-year locoregional control and overall survival (OS) of 57% and 72%, respectively. However, fast neutrons have an inferior dose distribution when compared with particle irradiation, potentially leading to over irradiation of healthy tissue or insufficient dose delivered. Carbon-ions have a similar LET to fast neutrons, resulting in a larger relative biological effectiveness (RBE) compared to photons or protons [14]. Moreover, the physical characteristics of carbon ions, owing to the ability to generate a spread-out Bragg peak (SOBP), allow for an improved dose distribution compared to fast neutron. As such, carbon-ion radiotherapy (CIRT) may be capable of definitive treatment for locally advanced HNACC. Jensen et al. [15] reported a series of 309 HNACC patients treated with intensity modulated radiotherapy and CIRT-boost, yielding a 5-year LC and OS of 58.5% and 74.6%, respectively. Mizoe and colleagues [16] reported on 69 patients with locally advanced HNACC treated with CIRT alone. In their study, 5-year LC and OS were 73% and 68%, respectively.

However, the impact of the histological subtype of ACC in definitive radiotherapy, including CIRT, is unclear. The aim of this

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study is to evaluate the effect of histological subtypes, specifically solid vs non-solid growth pattern, on CIRT for HNACC.

Materials and methods

Patient and tumor characteristics

Eligibility criteria of patients receiving definitive CIRT for head and neck cancer have been described previously [16]. From December 2006 to July 2013, 113 patients with HNACC received CIRT in our institute. Of these, 100 patients with identified histological subtypes according to the World Health Organization classification were enrolled in this study. The characteristics of the patients and tumors are summarized in Table 1.

This study was approved by the local Institutional Review Board (15-001) and was carried out in accordance with the Declaration of Helsinki. This trial is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), identification number 000024598.

Histological subtypes

Tumor histology was separated into solid and non-solid histological subtypes [10]. In this study, 17 patients were diagnosed with solid histology, and 83 patients without.

Carbon-ion radiotherapy

Patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic shell. A set of 2.5-mm-thick computed tomography (CT) images was taken for treatment planning. Magnetic resonance imaging (MRI) was routinely performed for the identification of the tumor, after planning CT image fusion. Determination of the gross tumor volume (GTV) was based on contrast-enhanced MRI. The clinical target volume (CTV) had minimum margins of 5.0 mm added around the GTV. CTV included neural tracts to the skull base and peripheral site so as to account for potential perineural spread. A margin of 2–3 mm was added around the CTV to create the planning target volume (PTV). The CTV margins of areas proximal to critical organs (e.g. eye wall, optic nerve, optic chiasm and brain stem) were reduced as necessary. Three-dimensional treatment planning was performed using HIPLAN software (National Institute of Radiological Sciences, Chiba, Japan) [17].

CIRT dose was expressed in photon-equivalent doses, defined as the physical dose multiplied by the RBE of the carbon ions. The biological flatness of the SOBP was normalized by the survival fraction of the human salivary gland tumor cells at the distal region of the SOBP, where the RBE of carbon ions is estimated to be 3.0 [14].

CIRT was administered on a fractionated schedule comprising 57.6 or 64.0 Gy (RBE) in 16 fractions in 4 weeks. In this study, 33 patients were treated with 57.6 Gy (RBE) and 67 with 64.0 Gy (RBE).

Table 1
Patients and tumor characteristics.

Age (y)	
Median	57
(Range)	(19–79)
Gender	
Male	35
Female	65
History of operation	
Yes	15
No	85
T classification	
T1-3	27
T4	61
No specific T classification	12
N classification	
N0	94
N1	5
N2	1
N3	0
M classification	
M0	100
M1	0
Solid components in ACC	
Presence	17
Absence	83
Tumor site	
Nasal cavity and paranasal sinus	50
Oral cavity, pharynx and salivary grand	42
Others	8
GTV, (ml)	
Median (Range)	38.6 (0.6–235.3)

Abbreviations: ACC, Adenoid cystic carcinoma; GTV, Gross tumor volume.

Evaluation

Followup consisted of CT or MRI every 3 months for the first 2 years post-treatment years, and thereafter every 3–6 months depending on patient condition. Local control was defined as no evidence of tumor regrowth in the PTV.

Acute reactions in normal tissues were classified according to the Radiation Therapy and Oncology Group (RTOG) scoring system. Late reactions were classified according to the National Cancer Institute Common Terminology of Criteria for Adverse Effect (CTCAE) version 4.0.

Statistical analyses

The cumulative incidences of LC, OS and distant metastasis free survival (DMFS) were evaluated using the Kaplan–Meier method. Age, gender, surgical history, prescribed dose, T classification, N classification, histological subtypes, tumor site, and GTV were evaluated as potential risk factors for LC, OS, and DMFS. Subgroups were compared using the univariate log-rank test. All statistically-significant ($p < 0.05$) factors on univariate analysis were included in a multivariate analysis using the Cox proportional hazards model. P-values less than 0.05 were considered statistically significant, and all statistical tests were 2-sided. These statistical tests were performed with the assistance of SPSS ver. 19 (IBM SPSS, IBM Corporation, Somers, NY).

Results

Median follow-up was 60 months (range, 6–116 months). No patient was lost to follow-up. Of the 32 patients with local recurrence, 29 developed recurrence within the PTV and 3 on the margin of the PTV. One patient developed cervical lymph node metastasis. Of the 33 patients with loco-regional recurrence, 20 patients received salvage treatments: 10 received surgery, 6 repeat CIRT, 3 Cyber Knife, and 1 boron neutron capture therapy. 30 patients developed distant metastasis. The most common site for distant metastasis was lung (70%), followed by bone (17%), and liver (6%). 20 patients died of their disease, and 9 of unrelated causes. The cumulative 5-year LC, OS, and DMFS of all patients were 68.6% (95% confidence intervals [CI], 71.6–90.1), 74.8% (95% CI, 82.4–97.8) and 65.7% (95% CI, 70.3–91.3), respectively (Fig. 1).