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Original article

Re-irradiation of adenoid cystic carcinoma: Analysis and evaluation of outcome in 52 consecutive patients treated with raster-scanned carbon ion therapy

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ABSTRACT

Background: Treatment of local relapse in adenoid cystic carcinoma (ACC) following prior radiation remains a challenge: without the possibility of surgical salvage patients face the choice between palliative chemotherapy and re-irradiation. Chemotherapy yields response rates around 30% and application of tumouricidal doses is difficult due to proximity of critical structures. Carbon ion therapy (C12) is a promising method to minimize side-effects and maximize re-treatment dose in this indication. We describe our initial results for re-irradiation in heavily pre-treated ACC patients.

Methods: Patients treated with carbon ion therapy between 04/2010 and 05/2013 ($N = 52$ pts, median age: 54 a) were retrospectively evaluated regarding toxicity (NCI CTC v.4), tumour response (RECIST) and control rates. 48 pts (92.3%) received carbon ions only, 4 pts received IMRT plus C12.

Results: 4 pts were treated following R1-resection, 43 pts for inoperable local relapse. Most common tumour sites were paranasal sinus (36.5%), parotid (19.2%), and base of skull (17.3%). Pts received a median dose of 51 GyE C12/63 Gy BED and cumulative dose of 128 Gy BED [67–182 Gy] after a median RT-interval of 61 months. Median target volume was 93 ml [9–618 ml]. No higher-grade (>°II) acute reactions were observed, 7 pts showed blood–brain-barrier changes (°I/II: 8 pts; °III: 2 pts), 1 pt corneal ulceration, xerophthalmia 7 pts, °IV bleeding 1 pt, tissue necrosis 2 pts, otherwise no significant late reactions. Objective response rate (CR/PR) was 56.6%. With a median follow-up of 14 months [1–39 months] local control and distant control at 1a are 70.3% and 72.6% respectively. Of the 18 pts with local relapse, 13 pts have recurred in-field, 1 pt at the field edge, 3 pts out of field, and one in the dose gradient.

Conclusion: Despite high applied doses, C12 re-irradiation shows moderate side-effects, response rates even in these heavily pre-treated patients are encouraging and present a good alternative to palliative chemotherapy. Though most local recurrences occur within the high-dose area, further dose escalation should be viewed with caution.

Local relapse in head and neck cancer is a very difficult therapeutic situation. Chemotherapy rarely produces durable tumour control; therefore surgery as a potentially curative treatment option is the mainstay of salvage local therapy. For adenoid cystic carcinoma, the situation becomes even more complex: skull base invasion and perineural spread often prevent complete resections in the primary situation. Anatomical sites and relative radioresistance of the disease mandate initial high radiation doses for tumour control. In case of local relapse, treatment options are limited. First treatment of choice is salvage surgery. If this is not possible, patients' options are limited: even highly aggressive chemotherapy regimens for adenoid cystic carcinoma achieve only objective response rates up to 30% [1], new agents such as EGFR- or tyrosine-kinase inhibitors mostly stabilize disease for some time [2–5]. Only one tyrosine kinase inhibitor has been shown to produce objective responses [6].

Re-irradiation has rarely been used in the past for fear of considerable early and late toxicity; in addition, recurrent tumours

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could be shown to be more radiation-resistant than their initial clone [7]. Neutron and charged particle therapy produced encouraging local control rates albeit at considerable side-effects [8,9]. There is emerging evidence that re-irradiation can lead to long-term local control in a selected subset of patients, [10–13] but local control remains strongly dependent on re-irradiation dose [11,13,14]. With the advent of modern radiotherapy techniques such as stereotactic radiotherapy and IMRT, proportion of severe treatment-related side-effects can be reduced [13,15–17] and modern techniques for re-irradiation are increasingly offered to patients with locally recurrent head and neck cancer. While substantial data including prospective phase I and II trials have been reported for squamous cell head and neck cancer (SCCHN), there are little data on retreatment of malignant salivary gland tumours. Application of tumouricidal doses remains a challenge though due to the proximity of critical structures in the head and neck. Charged particle therapy in active beam application produces very sharp dose gradients [18] and hence may improve outcome in this desperate situation. We present our experience on re-irradiation of adenoid cystic carcinoma of the head and neck with scanned carbon ion beams.

Methods

Patients

Treatment decision in all patients was based on interdisciplinary consensus. Treatment-related toxicity was prospectively collected, patient data were retrospectively analysed.

Radiotherapy

Patients were immobilized using individual fixation devices (scotch cast or thermoplastic head masks). As a standard, treatment planning was carried out on 3 mm CT and contrast-enhanced MRI scans for 3D image correlation.

Carbon ion therapy was carried out at the Heidelberg Ion Beam Therapy Centre (HIT) in active beam application (raster-scanning method [18]) in 3 GyE per fraction (exception: 1 patient received 3.5 Gy/fraction) and 5–6 fractions per week under daily image guidance with orthogonal X-rays and position correction in six degrees of freedom [19].

Re-irradiation target volume included only the visible local relapse with a small safety margin (ca. 2 mm), no elective nodal irradiation was carried out. There were 4 exceptions in this cohort receiving combination treatment with IMRT and carbon ion boost. These patient's prior radiotherapy interval was either very long or the prior radiotherapy dose was negligible in the area of relapse. In these cases, C12 volume included the visible tumour plus small safety margin, the IMRT volume included visible tumour, area at risk of microscopic spread and locoregional nodal levels.

In all cases, cumulative dose to the brain stem and spinal cord was kept below 60 Gy and 50 Gy respectively assuming around 50% recovery of the CNS [20]. In the cases where optic nerves were involved in the tumour process, high probability of loss of vision was discussed with the patients prior to treatment start. Dose prescription was highly individual in each patient's case taking into account time to prior radiotherapy as well as prior radiotherapy dose.

Follow-up

Patients received regular follow-ups including MRI scans and clinical exams 6–8 weeks post completion of radiotherapy, 3, 6, and 12 months thereafter. Regular follow-ups with their attending ENT or maxillofacial specialist were encouraged.

Analysis

Response following re-irradiation was analysed using RECIST criteria [21], acute and late toxicity was evaluated according to NCI CTCAE v.4.03. Control and survival rates were estimated using Kaplan–Meier analysis [22] of the Addinsoft XLSTAT Life® package. Locoregional control was calculated from the first day of treatment to occurrence of locoregional failure, progression-free survival was measured from the first day of treatment to occurrence of locoregional failure, distant failure, or death.

Results

Fifty-two patients with adenoid cystic carcinoma received re-irradiation using carbon ion therapy for local relapse between 04/2010 and 05/2013.

Median age of these patients was 55 years [35–78 years], median follow-up to date is 14 months [1–39 months], 13 patients have deceased thus far. Seven out of 52 patients underwent surgery for local relapse, 45 patients (86.5%) had macroscopically visible tumour prior to re-irradiation. Tumour stages were mostly advanced (T4: 76.9%) while nodal and distant metastases (N+:

Table 1
Patient characteristics and radiotherapy.

Patient characteristics		
	Pts	%
Re-treatment site		
Paranasal sinus	19	36.5
Base of skull/intracranial	11	21.2
Parotid	10	19.2
Submandibular gland	3	5.8
Nasopharynx	2	3.8
Pterygopalatine fossa	2	3.8
Orbit	2	3.8
Lacrimal gland	1	1.9
Auditory canal	1	1.9
Jaw angle	1	1.9
Re-treatment stage		
T2	2	3.8
T3	10	19.2
T4	40	76.9
T4a	6	11.5
T4b	34	65.4
N1	1	1.9
N2a	1	1.9
N2b	3	5.8
N2c	1	1.9
M1	15	28.8
Prior surgery	7	13.5
Macroscopic tumour at re-RT	45	86.5
Radiotherapy		
IMRT + C12-boost	4	7.7
C12 only	48	92.3
	Median (Gy/GyE)	Range (Gy/GyE)
Prior radiotherapy		
Nominal dose	66	20–115
BED	66	20–133
Re-irradiation		
Nominal dose	51	36–74
BED	63	45–82
Cumulative life-time dose		
BED	128	67–182
Interval between RT courses	61 mo	9–620 mo
Treatment volume		
CTV (C12)	93 ml	6–618 ml
CTV (IMRT); 4 pts only!	334 ml	211–344 ml

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