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ORIGINAL ARTICLE – COLORECTAL CANCER

Reirradiation Using Carbon Ions in Patients with Locally Recurrent Rectal Cancer at HIT: First Results

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ABSTRACT

Background. Locally recurrent rectal cancer remains a dreaded event because curative resection is unlikely to be performed in a large number of cases. Carbon ion radiotherapy offers physical and biologic advantages. A high precise local dose deposition and sparing of normal tissue is possible. This work summarizes our experience on feasibility and early toxicity of carbon ion radiotherapy in previously irradiated and operated patients.

Methods. Between 2010 and 2013, a total of 19 patients with a median age of 62 years (range 14–76 years) received carbon ion irradiation to treat locally recurrent rectal cancer at the Heidelberg Ion Beam Therapy Center (HIT). All patients had a history of surgery and pelvic radiotherapy of at least 50.4 Gy. Median dose was 36 Gy [relative biologic efficacy (RBE)] [range 36–51 Gy(RBE)], and median planning target volume was 456 ml (range 75–1,597 ml). Some patients were treated in the recruiting phase I/II of the PANDORA study (NCT01528683).

Results. Median follow-up was 7.8 months. Four patients were diagnosed with local relapse after carbon ion radiotherapy, and three patients developed distant metastases. Estimated mean local progression-free survival was 20.6 months by the Kaplan–Meier estimator. Two patients had preexisting rectovaginal fistula, and another patient had a preexisting presacral localized abscess formation in which the local relapse took place. No grade III or higher toxicities were observed.

Conclusions. Our first experiences in a pretreated patient group with a dismal prognosis are encouraging, and therapy-related side effects are mild. Longer follow-up is required to determine possible late effects and long-term disease control.

Rectal cancer is a widespread malignancy with one of the highest incidence rates in Western countries and is newly diagnosed in approximately 25,000 patients in Germany per year. Treatment of rectal cancer depends on initial staging. All curative treatment approaches include a complete tumor resection consisting of a transanal microscopic surgery for small T1 lesions and an anterior resection for most T2–4 tumors.[1] Randomized clinical trials have shown that preoperative chemoradiation significantly reduces the risk of local failure and recurrence after 10 years, from 10.1 to 7.1 % in clinical stage II and III disease.[2] A meta-analysis demonstrated that preoperative chemoradiotherapy (CRT) is more beneficial than single-modality radiotherapy (RT) in achieving a better pathologic response and a higher local control rate.[3] Usually preoperative CRT is provided over 5–6 weeks with simultaneous 5-fluorouracil or an even shorter regimen of 5×5 Gy directly before surgery.[4]

Even when the rate of local recurrences is low after multimodal treatment including CRT, surgery, and adjuvant chemotherapy, 81 % of all recurrences develop in field or at the margins.[5] A total of 78 % of the in-field relapses occur in the low pelvic and presacral region.[5] Whenever surgical resection can be reasonably performed, it remains the mainstay of therapy, but a high percentage of locally recurrent rectal carcinoma (LRRC) show osseous or vessel infiltration in the pelvis, making surgery difficult. However, in some cases, resection is not possible or cannot

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be performed safely for medical reasons such as comorbidities. For these patients, RT represents an alternative local intensified treatment option in contrast to palliative systemic therapies. Different groups have reported their experiences with RT in case of relapse in patients with and without a history of RT.[6,7] Using modern high-precision photon techniques such as image-guided or intensity-modulated RT, high doses can be delivered to the tumor area while sparing normal tissue, including organs at risk (e.g., large and small intestine, bladder, rectum). Fort treatment planning purposes, three-dimensional computed tomography (CT) and magnetic resonance imaging (MRI) may be used, and thus repeat irradiation can be provided for recurrent rectal cancer. Usually doses limited to 36–45 Gy are applied with small safety margins due to previous radiation exposure during initial therapy.

In contrast, particle beam therapy using protons (^{1}H) or carbon ions (^{12}C) offers advantageous physical and biologic properties, even compared to high-precision photon RT. Physical characteristics include a low dose deposition within the entry channel of every single beam, followed by a steep dose deposition in the spread-out Bragg peak, followed by a sharp dose falloff. Furthermore, ^{12}C offers significant biologic advantages through an increased induction of clustered DNA double-strand breaks within the irradiated cells, which are difficult to repair. This results in an enhanced relative biologic efficacy (RBE) compared to reference irradiation with photons.

This new treatment modality seemed worth being tested in rectal cancer patients with isolated recurrences in the pelvic region in a controlled clinical trial. Whereas ^{12}C showed good results in a wide variety of malignancies and in reirradiation settings, clinical data on ^{12}C-reirradiation in rectal cancer patients are scarce.[8–10] Additionally, there is a complete lack of ^{12}C RT for this indication using the active raster-scanning technique, which permits higher-precision particle beams. Active beam delivery using the raster scanning method is highly focused by using a pencil beam that is moved by two magnetic dipoles, leading to a point-by-point scan of the target structure. At our institution, the beam is generated by a synchrotron, which allows the energy to be switched from one pulse to another to shape the particle range in the irradiated tissue. The target volume can be scanned in all three dimensions, and even irregular shapes can be scanned without requiring further hardware such as collimators or compensators. The main advantage of this method compared to passive beam shaping, as practiced in most particle therapy facilities, is the better precision of the delivered particle beams, especially at the proximal, distal, and lateral target borders. Moreover, fewer nuclear fragments are produced as a result of the avoidance of the hardware material in the beam line to shape the passive beam, which leads to a higher dose to the entrance channel and thus to adverse normal tissue contamination.[11]

Smaller patient groups are reported from Japanese institutions that examined the therapeutic efficacy of passive scattered ^{12}C beams in primarily diagnosed rectal cancer patients.[12–14] Overall local control rates were encouraging, and toxicity was comparable and mild. However, reirradiation protocols always carry the risk of increased toxicity rates. Therefore, we here present the first data, including feasibility, outcomes, and toxicity, in patients after ^{12}C re-irradiation in case of LRRC in the pelvic region.

PATIENTS AND METHODS

Patient Selection

Patients were mainly selected according to the PANDORA clinical trial protocol (NCT01528683); inclusion criteria were LRRC represented by an inoperable lesion (macroscopic tumor up to 1,000 ml in volume), prior photon RT of 20 to 60 Gy, and absence of any distant metastasis.[15] However, we also included in our analysis patients who did not fulfill the PANDORA study protocol inclusion criteria. All patients were seen and evaluated in an interdisciplinary setting including specialists from gastroenterology, medical oncology, visceral surgery, radiology, and radiation oncology.

Patient Characteristics

From 2010 to 2013, the disease of a total of 19 patients with LRRC was reirradiated with ^{12}C at the Heidelberg Ion Therapy Center (HIT) (Table 1). Median age was 62 years (range 14–76 years), and there were nine female and ten male patients. All patients had been previously irradiated with at least 50.4 Gy (median 50.4 Gy, range 50.4–60.4 Gy) and had undergone at least one resection due to rectal carcinoma. One patient had a history of two RT series (50.4 Gy in the primary setting using conventional pelvic RT and CyberKnife-based radiosurgery with 19 Gy to treat an in-field relapse) (Table 2). A further patient previously underwent intraoperative radiotherapy with 15 Gy additionally delivered to the conventional pelvic RT. The applied ^{12}C doses at our institution varied from 36 to 51 Gy(RBE) in single fractions of 3 Gy(RBE). Median duration between initial RT and ^{12}C re-RT was 47.4 months (range 17–110 months). The median planning target volume (PTV) was 456 ml (range 75–1,597 ml).

Treatment Planning

Patients were immobilized in the supine position with an indexed positioning of the lower extremities using a

TABLE 1 Patient and treatment details

Characteristic	Value
Number	19
Gender, *n* (%)	
Male	10 (53 %)
Female	9 (47 %)
Age, year, median, range	62 (14–76)
Karnofsky performance score, %, median (range)	90 (70–100)
Maximum tumor diameter as measured by treatment planning CT scan, cm, median (range)	5.8 (1.2–11.2)
Planning target volume, ml, median (range)	456 (75–1,597)
Bone infiltration, *n*	
Yes	15
No	4
No. patients with 1–3 distant metastasis	3
RT dose, *n* (%)	
36 Gy(RBE)	13 (68 %)
39 Gy(RBE)	1 (5 %)
42 Gy(RBE)	2 (11 %)
45 Gy(RBE)	2 (11 %)
51 Gy(RBE)	1 (5 %)
No. of ^{12}C beams, *n*	
1 beam	8
2 beams	11

CT computed tomography, *RBE* relative biologic efficacy

TABLE 2 Patients' pretreatment details

Characteristic	Value
Initial grade	
G2	12
G3	3
Unknown	4
Initial tumor stadium	
T category	
T1[a]	1
T2	4
T3	9
T4	3
Unknown	3
N category	
N0	8
N+	9
Unknown	2
Previous radiotherapy	
EBRT dose, Gy, median (range)	50.4 (50.4–60.4)
IORT dose, Gy, median[b]	15
Repeat RT dose with radiosurgery, Gy, median[c]	19
Time period between previous RT and current ^{12}C RT, months, median (range)	47.4 (12.9–110)

EBRT external-beam radiotherapy, *IORT* intraoperative radiotherapy, *RT* radiotherapy, *TNM* tumor, node, metastasis classification system

[a] The T1-classified patient had a T1N0 tumor at initial diagnosis but developed local relapse after resection. After repeated resection, this patient underwent adjuvant RT; the recurrent tumor was not classified according to TNM category

[b] One patient was treated with an additional IORT with electrons during primary resection after neoadjuvant chemoradiation

[c] One patient was treated with CyberKnife-based radiosurgery in case of local recurrent rectal cancer after previous EBRT

ProSTEP (Elekta, Sweden) immobilization device to account for a precise repositioning of the pelvic area. For treatment planning, a contrast-enhanced CT was performed, and on an individual, case-by-case basis, further imaging was recommended, including MRI and ^{18}F-fludeoxyglucose-positron emission tomography imaging, for optimal target definition.

Typical organs at risk were contoured including the small intestine, bladder, spinal cord, rectum, and vagina. Dose constraints of normal tissue were respected according to Emami et al.[16] Target definition included the gross tumor volume (GTV) based on the area of contrast enhancement on T1-weighted MRI. A clinical target volume was defined as the GTV enlarged by an anatomically adopted safety margin of 5–10 mm depending on tumor location. Finally, the PTV was generated on individual factors, such as patient positioning and beam angles chosen, and was between 3 and 10 mm. Carbon ion RT planning was performed using the treatment planning software PT-Planning (Siemens Healthcare, Erlangen, Germany), including biologic plan optimization based on the local effect model developed by GSI (Gesellschaft für Schwerionenforschung, Darmstadt, Germany); it is designed for RBE calculation in different tissue types and for selected endpoints.[17] Briefly, the dependency of RBE on the physical and biologic properties are stronger than in conventional RT. The local effect model therefore incorporates photon- and carbon ion-based cell-survival data as well as the knowledge on the different topographical or local pattern of dose deposition between photons and charged particles along the beam (e.g., DNA double strand breaks). Energy deposition patterns on a molecular level (DNA level) are considered and integrated in the local effect model. The resulting RBE values depend on dose and cell type.

In the current clinical setting, the Syngo RT treatment planning system was used, which works with an $\alpha\beta$-value of 2 Gy, which fits well to serious late adverse events (stricture; rectal or intestinal bleeding or ulceration).

Publications on RBE values of rectal cancer are scarce, so we referred to our in-house in vitro data on HCT 116 rectal cancer cell lines. Experimental data revealed an RBE value of approximately 2.5 (unpublished data).[18] In future versions of the treatment planning system, biologic planning will be more adaptive, thus integrating a higher amount of different tumor and normal tissue specific parameters. Daily patient positioning was controlled by comparison of digitally reconstructed radiographs with on-board kilovoltage imaging as described previously.[10,19]

Radiotherapy

Single fractions of 3 Gy(RBE) were applied in all patients. Patients treated in the phase I PANDORA study received doses according to the dose escalation protocol with fraction numbers from 12 to 18, leading to theoretical overall doses of 36–54 Gy(RBE).[15] Doses were prescribed to the maximum of the calculated dose distribution for the PTV. Treatment planning aims in the coverage of the PTV by the 90 % isodose line. Dose specification is based on biologic equivalent dose because of the high relative biologic effectiveness (RBE) of carbon ions, which differs throughout the target volume due to its dependence on various factors. RBE will be calculated at each voxel throughout the target volumes and biologic optimization will be performed. Single doses of 3 Gy(RBE) carbon ions are established in our institution because the first patients were treated by this modality at the GSI in Darmstadt (Germany). The proposed regimen for the treatment of LRRC was set to 12 × 3 Gy(RBE) for the first step in the dose escalation PANDORA trial. Referring to a large experience in treating sacral chordoma with similar and also higher doses in nearly the same anatomical region, we consider this dose schedule to be safe and putatively effective.[8,10,20]

A total of 8 patients received RT via a single lateral ^{12}C-beam and 11 patients with two lateral opposing beams on a horizontal beam treatment room (Fig. 1).

Follow-up

Patients are currently undergoing follow-up visits with physical examination, laboratory tests, and CT and MRI. Progression-free survival was determined as time period between the first day of RT and appearance of any local recurrence or progression. Observed toxicity was categorized according to the Common Toxicity Criteria of Adverse Events, version 4.03.

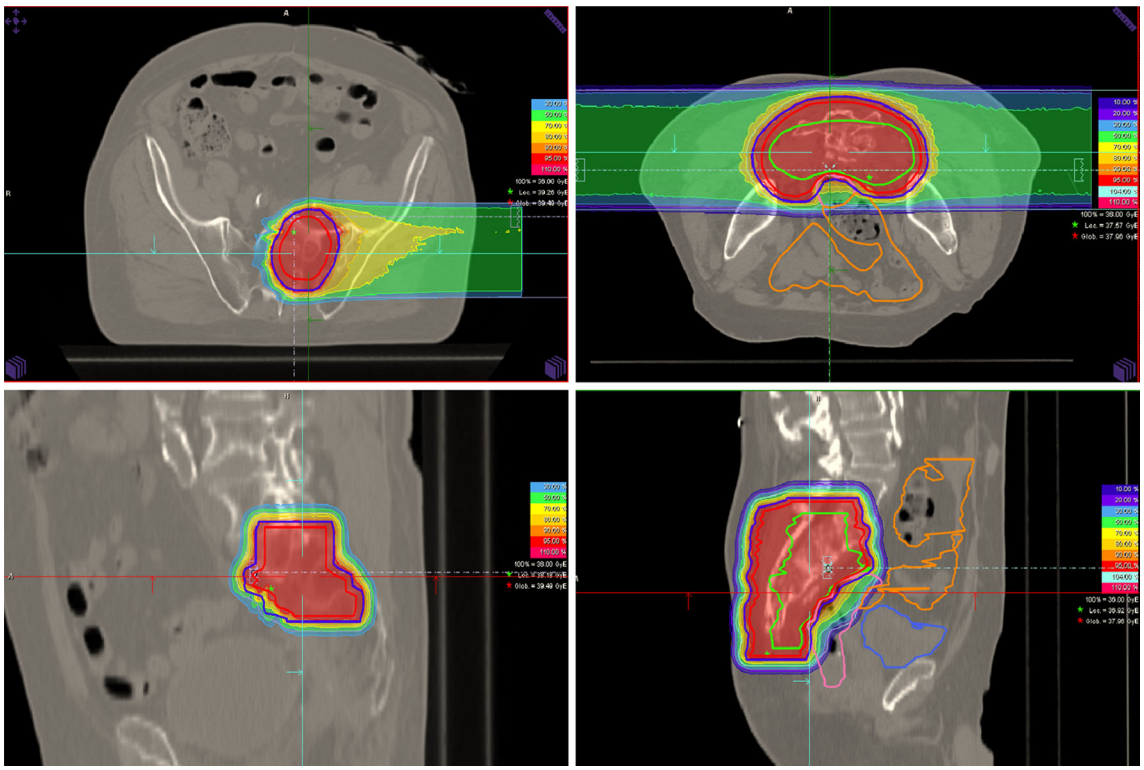

FIG. 1 Example of single-beam ^{12}C treatment plan (*left*) demonstrating dose distribution in axial (*top left*) and sagittal (*bottom left*) CT slices. Example of a 2-opposed beam plan demonstrating dose distribution in axial (*top right*) and sagittal (*bottom right*) direction

RESULTS

Survival and Local Control

Median follow-up of all patients was 8 months. Three patients (16 %) died during the observation period. Four patients (21 %) experienced local progression after RT, and three patients (16 %) were diagnosed with distant metastases. During follow-up, three patients died after 3.3, 3.4, and 32.3 months. Calculated median overall survival for patients that were still alive was 9.1 months. Because of the short follow-up period, most patients were still alive and under observation at the time of this writing, so the median survival cannot yet be computed.

Local progression was seen in four patients after 2.1, 4.6, 16.5, and 20.6 months; systemic progression with distant metastasis was observed in three patients in whom no local progression was observed (Fig. 2). Estimated local progression according to the Kaplan–Meier estimator was 20.6 months, but most of the patients have not yet experienced disease progression. One patient developed a distant lymphatic relapse of rectal cancer. PTV (less than 600 ml or greater than 600 ml, 24.8 vs. 15.2 months, respectively) and applied dose (36 Gy(RBE) vs. $\geq$36 Gy(RBE), 20.2 vs. 15.2 months, respectively) were not predictive of local failure.

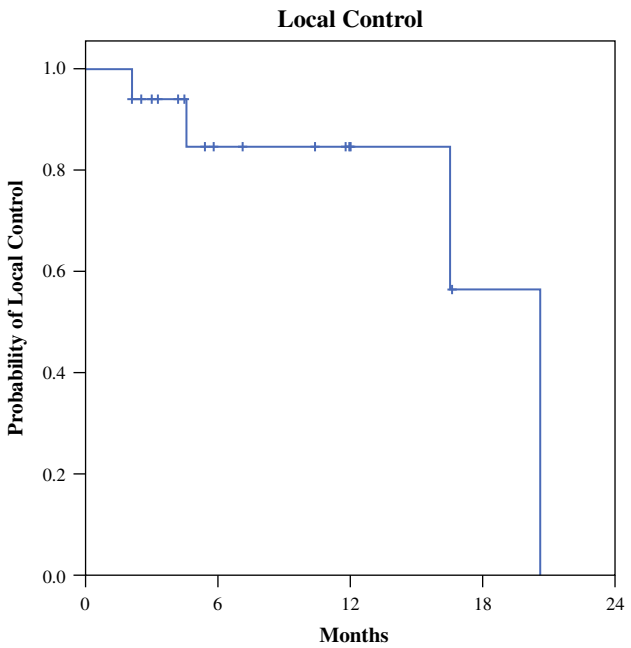

FIG. 2 Kaplan–Meier curve for progression-free survival, starting with the first day of ^{12}C treatment

Toxicity

Two patients had preexisting rectovaginal fistulas without signs of acute inflammation at the initiation of RT. One did not develop any complication during and after RT. The other showed an increase of the fistula and slight signs of mild inflammation, but neither surgery nor further drainage were necessary.

One patient had a preexisting (pre-)sacral abscess formation with tumor manifestations that were treated with antibiotics. After RT, the abscess formation showed a premature enlargement and a further progression of the tumor content. A further patient had a lymphatic fistula as a consequence of surgery with no signs of inflammation during RT and after follow-up.

In general, gastrointestinal toxicities occurred in two patients with grade II side effects and five patients with grade I side effects (Table 3). Skin erythema was seen in one patient (grade II). Hematologic side effects were also observed and were classified as grade I in two patients (erythrocyte count). There were no cases of nausea or pain aggravation during RT and at first follow-up.

DISCUSSION

Reirradiation with ^{12}C for LRRC seems to provide moderate local control with acceptable toxicity, considering the difficult clinical situation with previous radiotherapy and surgeries. Further dose escalation and longer follow-up may improve the preliminary data; however, the need for careful patient selection limits application of the protocol in a larger patient population. The introduction of preoperative chemoradiation and radiation protocols led to a significant reduction of local recurrence rates in rectal cancer patients.[2,4] Nevertheless, local relapse is still a serious event in preirradiated patients, depending on localization and infiltration of anatomic structures. In many patients, surgical repeat resection cannot be performed safely; therefore, multimodal treatment approaches, including modern RT techniques and systemic agents, are necessary. The presented patient group was treated with carbon ion beams, with therapy performed as reirradiation in case of LRRC. Progression-free survival was encouraging, and toxicity rates were low.

TABLE 3 Toxicity

Site	Grade	*n* (%)
Gastrointestinal	I	5 (26 %)
	II	2 (11 %)
Hematological	I	2 (11 %)
Skin	I	1 (5 %)

Reports on reirradiation in LRRC patients are rare and heterogeneous considering RT dose and concurrent systemic treatment. In the recent study of Das et al., a hyperfractionated accelerated RT protocol was examined in previously irradiated patients with LRRC.[21] The median dose of pretreatment RT was 47 Gy (range 25–70 Gy). Patients irradiated more than 1 year before received a dose of 39 Gy in two 1.5 Gy fractions per day, and those patients who had pelvic RT less than 1 year before were treated with 30 Gy using the same fractionation schedule. Freedom from local progression was achieved in 33 % after 3 years, with a borderline significant difference between the patient group that underwent additional surgical resection after repeated RT and those that did not (47 and 21 %, respectively). Furthermore, a secondary surgical resection led to a significant survival advantage, leading to a 3-year overall survival of 66 % in the resection group compared to 27 % in RT-only patients. Overall acute toxicity was relatively mild, with only two patients (4 %) experiencing grade III events, with nausea and vomiting. Late toxicity rates were higher, with 13 patients (26 %) developing grade III and IV toxicity events, mainly due to small bowel and bladder side effects.

There also exist re-RT protocols including concurrent chemotherapy application. Valentini et al. performed an Italian multicenter phase II study examining a preoperative hyperfractionated chemoradiation for LRRC patients.[22] Fifty-nine patients were treated with twice-daily 1.2 Gy up to a total dose of 30 Gy to a target volume encompassing the GTV with a 4 cm margin. Subsequently a boost was applied to the GTV plus a 2 cm margin with further 10.8 Gy in the same fractionation scheme. Chemotherapy with 5-fluorouracil was applied simultaneously with 225 mg/m^2 per day, 7 days a week. Tolerance of study treatment was good, and no patient developed grade IV toxicity. Acute grade III gastrointestinal side effects were observed in only 5.1 % of all patients. Late toxicity was seen in one patient with small bowel obstruction requiring surgery. Actuarial survival rates were 87.5, 58.9, and 39.3 % after 1, 3, and 5 years. Median local control was 20 months, and median disease-free survival was 15.5 months. Forty-four percent of all patients experienced at least a partial response of their tumor to chemoradiation. A total of 66.1 % of all patients underwent surgery, and a majority had a complete tumor resection without evidence of residual disease.

Sun et al. recently published a comparable treatment regime including re-RT using hyperfractionation of 2 × 1.2 Gy per day for 3 weeks up to a dose of 36 Gy with concurrent capecitabine in 72 patients.[23] Afterward resectability was evaluated, and a total of 18 patients underwent surgery. Patients with disease not suitable for resection continued combined-modality RT up to 51.6–56.4 Gy. A total of 59.7 % showed at least a partial response to the treatment. Acute toxicities included grade III to IV diarrhea and hematologic side effects in 9.7 and 8.3 %, respectively. Higher late toxicity consisted of small bowel obstruction with an incidence rate of 1.4 %.

The accordance of our data on ^{12}C re-RT toxicity levels of conventional pelvic re-RT plus concurrent chemotherapy is almost comparable to that of the above-mentioned studies. However, in contrast to our results on acute toxicities, a small percentage of patients experienced grade III toxicities due to re-RT and systemic agents. Obvious advantages of our strategy on toxicity prevention is the superiority in precision of particle beams compared to photons (especially to non-intensity modulated radiotherapy techniques as applied in the mentioned studies) and the omission of any systemic agent during and shortly after RT. Therefore, no extra toxicity will occur due to an additional use of systemic treatments.

Nevertheless, a total of four patients experienced a further local relapse after ^{12}C-RT, two of them premature, during the first 6 months after RT start. Carbon-ion RT still remains an experimental radiation modality, and therefore it is highly important to continue patient treatment in controlled clinical studies. Implemented biologic optimization algorithms at HIT have to be evaluated continuously and constantly correlated with clinical findings to ensure patient safety and therapeutical benefit.[24–26] Particle therapy, including ^{12}C and ^{1}H, seems to be promising in multimodal oncologic concepts. There are two main advantages of ^{12}C beams over proton beams. At first, ^{12}C undoubtedly exerts a higher RBE, leading to a higher amount of clonogenic cell death, even in almost radioresistant tumors (e.g., adenoid cell carcinoma, chordoma, chondrosarcoma, hepatocellular carcinoma).[19,27–29] RBE values vary from at least 2 to more than 5, implicating a high tumoricidal potential. On the other hand, ^{1}H beams account for only a mean RBE of approximately 1.1.[11] In addition, as a result of the physical properties of ^{12}C, the dose distribution is more conformal than that of ^{1}H. The ratio of dose in the spread-out Bragg peak compared to the entrance channel is larger for carbon ions. Furthermore, ^{12}C atoms have a larger mass and are therefore less prone to nuclear interactions, which allows a higher dose conformality and a higher sharpness in the lateral dose gradient (penumbra).[11] Finally, these arguments represent theoretical biologic and dosimetric benefits of ^{12}C over ^{1}H. Nevertheless, these advantages require more costly facilities, and biologic dose computation still remains a matter of debate. At our institution, we set up several clinical trials (including the PANDORA trial) to evaluate which is the better of the two particle modalities in terms of benefit to our patients.

Results of this treatment concept seem promising, and overall toxicity was low. However, longer follow-up is needed before we can draw definitive conclusions on therapeutic effect. Furthermore, longer follow-up is required to determine possible late effects and long-term control of disease of patients treated in the phase I/II clinical trial protocol PANDORA.

Disclosure Daniel Habermehl, Martin Wagner, Malte Ellerbrock, Markus W. Büchler, Oliver Jäkel, Jürgen Debus and Stephanie E. Combs declare no conflict of interest.

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