Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience

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Charged particle therapy is generally regarded as cutting-edge technology in oncology. Many proton therapy centres are active in the USA, Europe, and Asia, but only a few centres use heavy ions, even though these ions are much more effective than x-rays owing to the special radiobiological properties of densely ionising radiation. The National Institute of Radiological Sciences (NIRS) Chiba, Japan, has been treating cancer with high-energy carbon ions since 1994. So far, more than 8000 patients have had this treatment at NIRS, and the centre thus has by far the greatest experience in carbon ion treatment worldwide. A panel of radiation oncologists, radiobiologists, and medical physicists from the USA and Europe recently completed peer review of the carbon ion therapy at NIRS. The review panel had access to the latest developments in treatment planning and beam delivery and to all updated clinical data produced at NIRS. A detailed comparison with the most advanced results obtained with x-rays or protons in Europe and the USA was then possible. In addition to those tumours for which carbon ions are known to produce excellent results, such as bone and soft-tissue sarcoma of the skull base, head and neck, and pelvis, promising data were obtained for other tumours, such as locally recurrent rectal cancer and pancreatic cancer. The most serious impediment to the worldwide spread of heavy ion therapy centres is the high initial capital cost. The 20 years of clinical experience at NIRS can help guide strategic decisions on the design and construction of new heavy ion therapy centres.

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Introduction

Control of tumours non-invasively by use of charged particle therapy offers advantages over conventional radiotherapy, since a lower radiation dose is delivered to healthy tissues surrounding the tumour. Charged particles deposit energy far more selectively than x-rays do, allowing greater local control of the tumour, a lower probability of damage to healthy tissue in the treatment field, a low risk of complications, and the chance for rapid recovery after therapy.[1] Several new centres with large accelerators have been proposed, but debate about the cost–benefit ratio of this technique continues,[2] especially for heavy ions (generally $^{12}C^{6+}$). Although about 50 proton therapy centres are active worldwide, and more than 105 000 patients have been treated, only a few centres are using high-energy carbon ions at present (six in Asia and two in Europe); they had treated more than 13 000 patients as of December, 2013.[3]

Carbon ions have potential advantages over protons:[4] they provide a better physical dose distribution, because lateral scattering is lessened;[5] and they have higher relative biological effectiveness and a lower oxygen enhancement ratio; desirable features for eradication of radioresistant, hypoxic tumours.[6] The difference between densely ionising nuclei and sparsely ionising x-rays and protons offers further potential radiobiological advantages, such as reduced repair capacity, decreased cell-cycle dependence, and possibly stronger immunological responses.[7] Some have argued that protons represent a technical improvement for highly conformal therapy, and heavier ions might even allow treatment of cancers resistant to conventional x-ray therapy.[8] However, no clinical evidence to support this hypothesis is yet available.[9–12]

In the USA, where heavy ion therapy was developed and used in patients for the first time,[13] the National Cancer Institute (NCI) provided long-term support to translational research in charged particle therapy.[14] After a dedicated workshop in Bethesda, MD, USA, in 2013,[15] the NCI issued two calls for exploratory grant applications for planning for a national centre for particle-beam radiotherapy research in the USA. The high cost of a heavy ion therapy facility can only be justified by clinical evidence of their advantages over protons and x-rays.

Most of the patients who have been cured of cancer worldwide with carbon ions were treated at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan (figure 1). This independent administrative institute started clinical trials in June, 1994, to assess the clinical efficacy of carbon ions generated from the Heavy Ion Medical Accelerator (HIMAC; table 1). Since then, various trials have investigated the types of tumours that can be effectively treated with accelerated carbon ions, the optimum radiation dose-fractionation pattern for each type of tumour, and irradiation techniques for the precise delivery of carbon ions.

Until 2011, patients were treated by the passive modulation method to shape the spread-out Bragg peak. Now NIRS can treat patients with either passive scattering or three-dimensional raster scanning. The most promising technology for beam delivery in charged particle therapy is three-dimensional raster-scanning irradiation with a pencil beam; it allows the operator to paint particle radiation dose conformed over the irregularly shaped tumour.[5] However, a fast system is needed to change the energy of the beam pulse-to-pulse and thus to control depth-dose distribution. NIRS has implemented a unique method of multiple-energy operation with extended flat-tops[16] that enables a substantial reduction of the total irradiation time, while concurrently maintaining excellent depth-dose distributions (table 2).

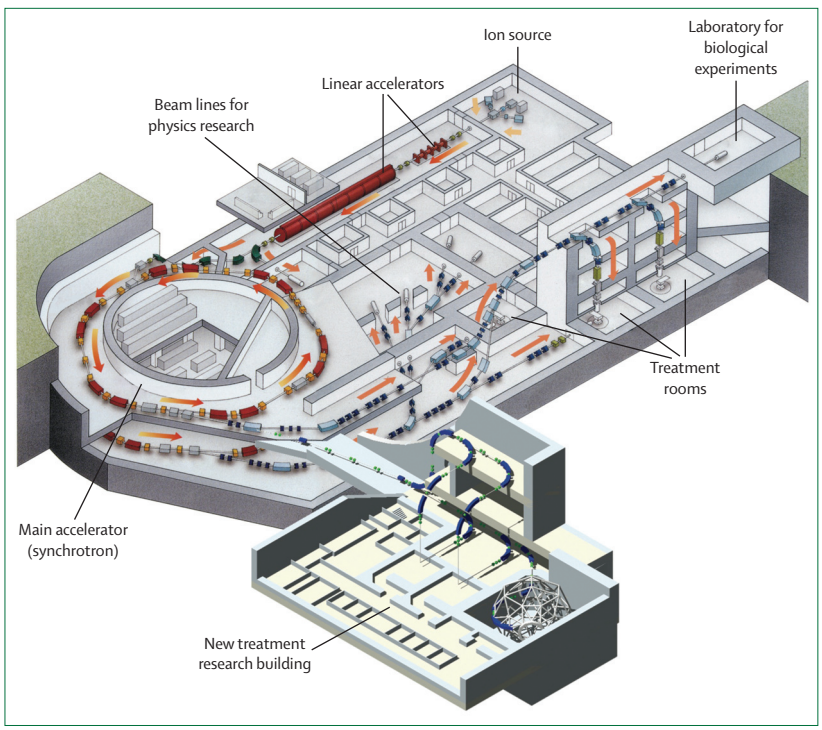

Figure 1: **The HIMAC (Heavy-Ion Medical Accelerator in Chiba) facility**

	Characteristics
Ion source	
Penning ionisation gauge; 10 GHz-ECR, and 18 GHz-ECR	8 keV/n; ion species H to Xe
Injector	
Radiofrequency quadrupole LINAC (0·6 m diameter × 7·3 m long)	800 keV/n
Alvarez LINAC (2·2 m diameter × 24 m long)	6 MeV/n
Main accelerator	
Synchrotron (42 m diameter)	100–800 MeV/n; repetition rate: 3·3 s
Irradiation rooms	
Three treatment rooms; four experimental rooms	..

ECR=Electron Cyclotron Resonance.

Table 1: **Characteristics of the Heavy Ion Medical Accelerator in Chiba**

NIRS decided to organise external peer review of the institute's research on carbon ion radiotherapy at a Joint Symposium with MedAustron in Wiener Neustadt, Austria, in December, 2013. The results of the clinical trials have been reported in many journals by the NIRS radiation oncologists (see, for example, reviews[17–20]), but this meeting gave an opportunity for external reassessment of the data and comparison with the most advanced techniques in Europe and the USA.

The evidence that carbon ion radiotherapy improves outcomes for patients with common cancers of poor prognosis has become stronger in the past 20 years. As of March, 2013, nearly 8000 patients had been treated at NIRS, with various solid tumours (figure 2, table 3). The results of phase 2 and phase 3 clinical trials under way at Heidelberg Ion Therapy Centre in Germany are awaited,[21] but in view of the continued debate on the cost–benefit ratio of this therapy, an external assessment of this large database is timely and necessary. Results of site-specific clinical trials with carbon ion radiotherapy are briefly reviewed in this report.

	Average	Maximum
Irradiation time (min)	1·2	3·8
Planning target volume (mL)	180	1300
Number of spots	35 200	167 000
Number of slices	49	145
Number of particles	$3·2 \times 10^9$	$1·7 \times 10^{10}$

NIRS=National Institute of Radiological Sciences.

Table 2: **Scanning beam characteristics in the new treatment building facility at NIRS**

Clinical trials

Head and neck

Results of proton therapy for cancers of the head and neck are difficult to interpret, because protons were frequently used as a boost or combined with surgery in large variety of pathological types. Studies at NIRS[19] and the GSI Helmholtz Centre for Heavy Ion Research in Germany[22] showed that carbon ion radiotherapy provided favourable outcomes for patients with radioresistant head and neck tumours such as mucosal malignant melanoma and adenoid cystic carcinoma. A comparison of local control achieved with a total carbon dose of either 57·6 GyE or 64·0 GyE for adenoid cystic carcinoma showed that late local recurrences were more likely in the lower-dose group. A comparative analysis with the data from the Heidelberg Ion Therapy Centre based on histological stratification and examining other prognostic factors would help to clarify the reasons. The high rate of metastatic disease after carbon ion radiotherapy alone in mucosal melanoma has been successfully reduced by combination of this radiotherapy with DAV chemotherapy (daunomycin, cytarabine, and vincristine).

For the future, the panel recommended that beam scanning should be implemented to reduce adverse effects on normal tissue, and that treatment schedules shorter than 16 fractions should be investigated.

Lung cancer

Hypofractionated radiotherapy is regarded as an alternative to surgery for localised non-small-cell lung cancer, with x-ray stereotactic body radiotherapy[23] or protons. At NIRS, for peripheral stage I non-small-cell lung cancer, the number of fractions was reduced in different trials from 18 to nine, then four, and finally to a

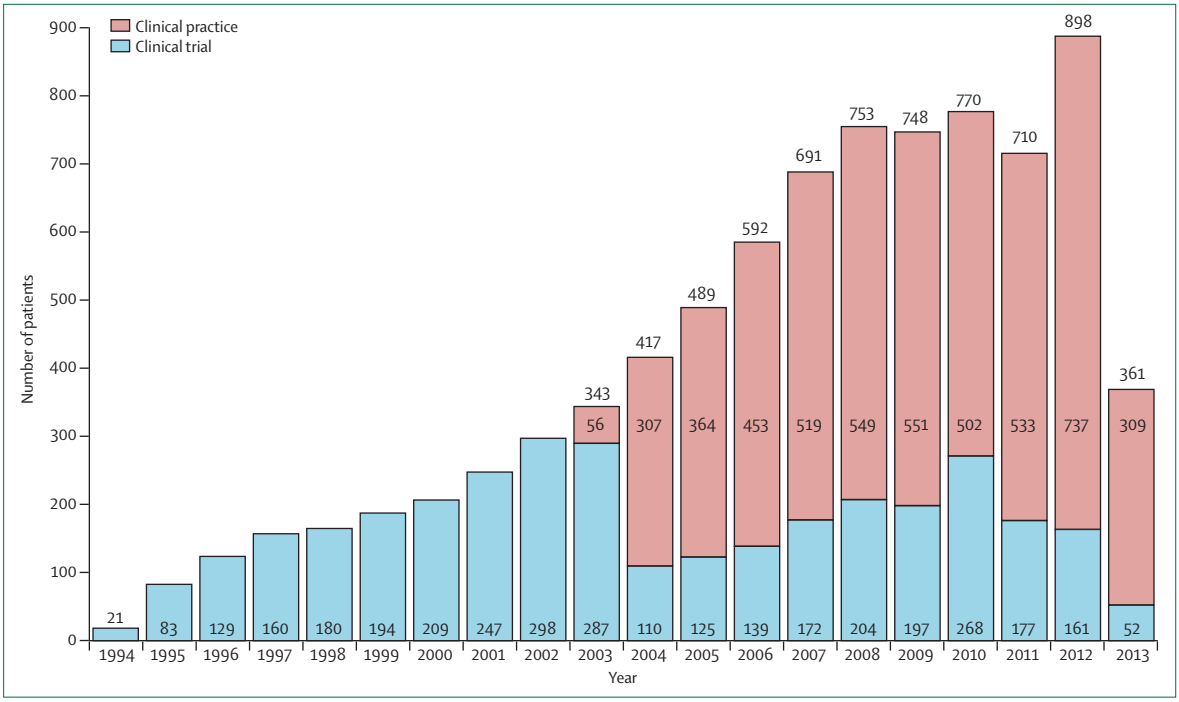

Figure 2: **Number of patients treated at National Institute of Radiological Sciences with carbon ion radiotherapy each year from June, 1994, to August, 2013**

single fraction. Respiratory gating and image-guided treatments were used to mitigate the effect of target motion. The results with carbon ion radiotherapy in stage IA non-small-cell lung cancer are similar to the best stereotactic body radiotherapy results reported worldwide. For stage IB disease, carbon ion radiotherapy results seem superior to those reported for photon stereotactic body radiotherapy in terms of local control and lung toxicity. Despite high local control, disease-specific survival is much lower in stage IB than in stage IA because distant metastatic recurrences are common. Combination of carbon ion radiotherapy with systemic therapy is therefore essential to improve survival. A dose-escalation study for single-fraction treatment is under way at NIRS, in which higher local control and survival have been observed with minor toxicity. At present, the single-fraction dose is escalated to 50 GyE with high local control and acceptable adverse effects.

Bone and soft-tissue tumours

Medically inoperable sacral chordomas are deemed to be incurable. Therefore, the 5-year local control rate of 88% and survival of 86% achieved at NIRS are excellent outcomes; however, they carry a cost of late side-effects. 15 of 95 patients with sacral chordoma developed severe sciatic nerve side-effects, but eight remained able to walk with or without a supportive device.[24] In view of the poor prognosis for these patients without carbon ion radiotherapy, these side-effects could be acceptable, but efforts to reduce adverse effects on the sciatic nerve are needed. Analysis of the relations between dose, length, volume, and toxicity could indicate whether scanning with dose-painting would be a realistic approach to lessen sciatic-nerve toxic effects.

In skull-base tumours, good local control was reported with the highest dose schedules. Electrophysiological monitoring of patients[25] might predict possible late toxic effects.

	Total number of patients (%)	Clinical practice
Prostate	1731 (22%)	1399
Bone and soft tissue	1033 (13%)	780
Head and neck	854 (11%)	529
Lung	795 (10%)	207
Liver	485 (6%)	250
Post-operative rectum	408 (5%)	338
Pancreas	353 (4%)	113
Gynaecological	207 (3%)	10
Eye	128 (2%)	86
CNS	106 (1%)	0
Para aortic lymph node	94 (1%)	87
Skull base	85 (1%)	56
Oesophagus	71 (1%)	0
Lacrimal gland	24 (<1%)	1
Scanning	11 (<1%)	0
Miscellaneous	1547 (20%)	715

Table 3: **Distribution of patients treated with carbon ion radiotherapy at the National Institute of Radiological Sciences by tumour type**

Prostate cancer

Use of protons for treatment of prostate cancer is controversial.[26] Retrospective analysis of the US Medicare database showed no difference in toxic effects between treatment with protons and intensity-modulated radiotherapy with x-rays.[27,28] At NIRS, about 1000 patients have been treated with carbon ion radiotherapy hypofractionation (16 fractions over 4 weeks) for prostate cancer with minor toxic effects. Mid-term follow-up data for high-risk prostate cancer are promising. Long-term data and comparative assessment of toxicity and efficacy with other treatment modalities will be reported in future publications. Incorporation of MRI and spectroscopy in the planning process can improve the quality of treatment.

The panel recommended that future reporting should include the definition of biochemical failure, metastatic recurrence rates, comprehensive morbidity assessment, and quality-of-life assessment, as is done for proton therapy.[29] Lately, patients have been treated with the scanning beam in the new NIRS facility with 12 fractions in 3 weeks. Even shorter hypofractionated schedules might be possible. Sparing of the urethra by use of scanning is now possible in the new facility (figure 1).

Hepatocellular carcinoma

The outcome of hepatocellular carcinoma is generally poor because only 10–20% of cases are surgically operable; overall 5-year survival is about 15%. Gated irradiation (with delivery of the carbon ion radiotherapy synchronised with the breathing cycle to reduce organ motion variables in delivering dose to the tumour) could be an important approach for hepatocellular carcinoma. In 69 patients treated with four fractions at NIRS, the treatment-related hepatic impairment was negligible; the 5-year local control rate was 81% and survival was 33%, results similar to those for proton therapy with 20 fractions.[30] The NIRS results for large tumours near the porta hepatis reflect major progress in treatment of hepatocellular carcinoma because no efficient alternatives are available. Since 2003, an accelerated schedule of two fractions in 2 days has been used in more than 110 patients, with minor toxic effects. Local control and survival are better with a higher total dose. The relations between dose, volume, and toxicity will be assessed and reported.

Locally recurrent rectal cancer

This cancer usually has a dismal prognosis. With photon radiotherapy plus chemotherapy, for inoperable tumours, 5-year local control is typically less than 50% and survival less than 20%, although control rates up to 75% and survival of 40% have been reported in small, highly selected case series.[31] At NIRS, the 5-year local control rate was 93% and survival 45% in a large group of patients (n=136). In a later study in 23 patients with locally recurrent rectal cancer, who had received pelvic photon irradiation as part of their primary treatment, 3-year overall was 65% and disease-specific survival 51%. If local control cannot be achieved in locally recurrent rectal cancer, the risk of severe neuropathic pain from tumour progression or infection approaches 100%. Therefore, grade 3 peripheral neuropathy or infection in six (26%) of the 23 patients after carbon ion radiotherapy seems acceptable. Follow-up studies of patients receiving carbon ion radiotherapy alone in this study showed a high rate of distant metastases, and combination of this radiotherapy with systemic therapy should be investigated. The surgical-spacer technique developed at NIRS to create space between the intestines and the tumour target with a teflon panel surgically installed before carbon ion radiotherapy, could be a safe approach for concurrent systemic therapy and more severe hypofractionation.

Pancreatic cancer

Pancreatic cancer is a major cause of cancer mortality, and its incidence is increasing. The prognosis of pancreatic cancer is poor; it is the only cancer for which deaths are predicted to increase in Europe in 2014 and beyond.[32] Although comparison of carbon ion radiotherapy with standard treatment in potentially resectable pancreatic cancer is difficult, the NIRS results are better than those reported worldwide after surgery alone or with combined modalities. In locally advanced unresectable pancreatic cancer, a two-step approach was used at NIRS to optimise carbon ion radiotherapy and gemcitabine doses. In the first phase, the radiotherapy dose was fixed at 43·2 GyE in 12 fractions delivered over 3 weeks concurrently with gemcitabine. The initial weekly gemcitabine dose was 400 mg/m²; it was increased first to 700 mg/m² and then to 1000 mg/m². In the second phase, the gemcitabine dose was fixed at 1000 mg/m² weekly, and the carbon ion radiotherapy dose was raised in 5% increments. This study design, typical for NIRS, resulted in a concurrent schedule with a 2-year local control rate of 58% and 2-year overall survival of 54% for the 45·6–55·2 GyE cohorts (n=47). Median survival (longer than 2 years) was two times longer in the NIRS studies than for the best standard option, intensity-modulated radiotherapy plus gemcitabine (median survival about 1 year).[33]

The plans to use scanning carbon ion radiotherapy with respiratory gating, a gantry, and a more comfortable position for the patient are logical. In potentially resectable pancreatic cancer, systemic therapy should be integrated into the preoperative schedule at NIRS. The results in locally advanced unresectable pancreatic cancer suggest a therapeutic breakthrough. NIRS should coordinate a confirmatory, preferably multi-institutional trial, of the best schedule. Further reduction in the number of fractions will increase cost-utility and throughput of patients, thereby facilitating the use of carbon ion radiotherapy plus gemcitabine for more patients and in more centres. The topography of local recurrence should be compared with pretreatment PET to assess the potential for further improvements by use of dose-painting.

Cervical cancer

In uterine squamous-cell cancer, treatment results at NIRS are better than the best previously reported for conventional x-ray radiotherapy, but are not as good as those for image-guided adaptive brachytherapy,[34] except for carbon ion radiotherapy of more than 72 GyE. Chemoradiation and adjuvant chemotherapy were lacking, and they are regarded as essential (level 1 evidence) to improve local, regional, and systemic control.[35] In uterine adenocarcinoma, carbon ion radiotherapy has been targeted primarily at potentially non-resectable tumours. Local control and survival achieved in 57 patients seemed better than those for conventional photon therapy with or without chemotherapy.

The review panel recommended that to provide convincing clinical evidence, NIRS should increase numbers of patients and the duration of follow-up in a prospective protocol with a prestated hypothesis, with sufficient power to prove these results. Systemic therapy has been integrated into a comprehensive protocol, but we cannot yet assess whether combined chemotherapy and carbon ion radiotherapy will improve survival. For the adaptive approach, repeated MRI is necessary. Further analysis of the relations between dose, volume, and toxicity is needed. Integration of image-guided adaptive brachytherapy as a boost to upfront carbon ion radiotherapy might be an option.

Overall assessment and recommendation

Clinical

NIRS is a pioneer in carbon ion radiotherapy and has contributed major paradigm shifts for radiotherapy and more generally for oncology. Besides improvements over the already favourable results achieved for some rare cancers, such as bone and soft-tissue tumours, the results reported lately support the hypothesis that carbon ion radiotherapy improves outcomes for several common cancers with poor prognosis. Therefore, more patients worldwide should have access to treatments based on carbon ion radiotherapy.

Optimisation of the therapeutic protocol has progressed over many years and is dependent on the tumour site. For a given disease entity, the therapeutic schedule (eg, radiotherapy alone, radiotherapy with chemotherapy, preoperative irradiation) is initially based on scientific evidence. The features of carbon ion radiotherapy and systemic therapy are identified by educated guess. With these factors, the first level of the clinical study starts. In combined treatments, systemic therapy is optimised first (eg, locally advanced unresectable pancreatic cancer), keeping carbon ion radiotherapy constant. Carbon ion radiotherapy is optimised by dose escalation or hypofractionation. Preoperative carbon ion radiotherapy, a small planning target volume, a radiosensitive tumour, and crucial organs of parallel architecture are factors that favour hypofractionation. Concurrent chemotherapy, low α/β ratio of crucial organs, and crucial organs of serial architecture are factors that favour dose escalation with conventional dose and fraction. In hypofractionation, the decreases in the numbers of fractions are typically around 16, 12, eight, four, two, then one (eg, non-small-cell lung cancer).

The most serious obstacle to worldwide availability of carbon ion radiotherapy is the high cost.[36] To reduce cost, the panel recommended that the following should be prioritised: clinical and biological research in ultra-short fractionation schedules, including their use in combined modalities; reduction in size and cost of the technology and equipment needed for carbon ion radiotherapy and their integration in clinics; and research on improving throughput of patients including use of a gantry, immobilisation and positioning devices, and their application in clinical practice.

The long-term follow-up of thousands of patients treated at NIRS without evidence of increased risk of secondary cancers argues against concerns about possible higher risks of secondary cancer induction for carbon ion radiotherapy than for proton or photon radiotherapy,[37,38] but no detailed statistical analysis has yet been done. Similar concerns for protons are not supported by epidemiological data published in 2013.[39] A very important step will be to publish the analysed incidence of secondary malignancies induced by carbon ion radiotherapy in patients treated at NIRS.

Methods of follow-up, outcome assessment, data archiving, and analysis have changed over time. Thus, reporting of long-term carbon ion radiotherapy-optimisation studies is difficult. The panel recommended that NIRS provide detailed reporting of methodological changes during studies, especially for changes in the systems scoring clinical outcome. To enable comparison of the NIRS carbon ion radiotherapy results with those obtained with x-rays or protons, NIRS is encouraged to make more general use of quality-of-life assessment, and to announce clinical trials worldwide and undertake international registration of the trials.

The latest clinical data on carbon ion radiotherapy were published in 2014 book,[20] but they should be published as soon as possible in peer-reviewed journals. The panel found that these results expand the cancers that are likely candidates for carbon ion radiotherapy to include locally advanced unresectable pancreatic cancer, hepatocellular carcinoma near the porta hepatis, and locally recurrent rectal cancer.

The panel made specific recommendations for future clinical studies. Investigation is needed into how to shorten the total treatment time in head-and-neck, prostate, and locally recurrent rectal cancers. Concurrent and adjuvant systemic therapy in stage IB lung, locally recurrent rectal, and cervical cancers should be investigated. Analysis of the relations between dose, volume, and effect and topography of local recurrence is needed to validate target concepts and to estimate the potential of dose-painting. Scanned beams and (adaptive)

dose-painting should be used to increase the safety window for fewer fractions at higher dose hypofractionation and concurrent systemic therapy. Treatment should be started with a scanned beam for moving targets. MRI should be used for adaptive therapy of cervical cancer.

Randomised phase 3 clinical trials are still missing. NIRS is still attempting to develop the best established carbon ion radiotherapy, which could then be proposed for randomised trials in the future. Because the number of patients treated at NIRS is still small for each tumour site, an organisation named Japan Carbon ion Radiation Oncology Study Group (J-CROS) has been set up consisting of four carbon ion radiotherapy institutes in Japan (NIRS, Gunma, Hyogo, and Saga).

In the J-CROS cooperative group, NIRS will undertake prospective multi-institutional studies (phase 1/2 and phase 2) on such tumours as those of the head and neck, non-small-cell lung cancer (mainly T2 tumours), hepatocellular carcinoma, pancreatic cancer, locally recurrent rectal cancer, and bone and soft-tissue sarcoma. The tumours were chosen on the basis that the therapeutic techniques have not been fully established, or should be further improved for local control and survival, or assessed for reproducibility of NIRS clinical results by other institutes.

The new J-CROS studies might also include glioblastoma multiforme. This disorder has been treated in many ways, including fast neutrons, mesons, and boron neutron capture therapy, but the results remain disappointing. At NIRS, a preliminary phase 1/2 trial showed the potential efficacy of carbon ion radiotherapy for glioblastoma multiforme in terms of better survival in patients who received higher dose than in those assigned a lower dose arm.[40] Subsequently, a small group of patients with glioblastoma multiforme were treated with carbon ion radiotherapy alone and then combined with temozolomide. This study did not find significantly different results compared with those from the previous trial. An exploratory retrospective study suggested a potential benefit of carbon ions in patients with high-grade gliomas.[41] Although the best regimen for glioblastoma multiforme might not yet have been developed, this hypothesis is now being investigated prospectively in the randomised CLEOPATRA clinical trial at Heidelberg Ion Therapy Centre.[42] Combined therapies including boosts of protons or carbon ions might provide a breakthrough in the future, and efforts in this direction should not be abandoned.

Radiobiology

The NIRS radiobiology programme should intensify its efforts to strengthen international collaborations, especially with carbon ion radiotherapy facilities in Europe, to achieve the goal of an international standard for the use of the biologically effective dose in treatment planning with ion beams.[43] This goal is particularly important for hypofractionation, where different values of relative biological effectiveness are likely to be needed from those for conventional fractionation regimens. To make use of the full potential of carbon beam scanning, detailed biological modelling is needed. The introduction of a modified microdosimetric kinetic model[44] will allow NIRS to adapt optimisation procedures to various biological features such as fractionation schemes and cell sensitivity. In hypofractionation schedules, the use of a dose-dependent relative biological effectiveness is necessary to take into account the lower value at high dose or fraction.[45] Additional research directed at harmonisation of treatment reports with procedures at other centres is strongly encouraged.[46,47] The use of the unit gray-equivalent (GyE or CGE) does not accord with the recommendations of the SI. Absorbed dose (in Gy) should always be reported at specified points or in specified volumes,[43] and the International Commission on Radiological Units, in collaboration with the International Atomic Energy Agency, is working on the definition of the correct unit for the isoeffective dose.

The panel judged the experimental combination of heavy-ion therapy and immunotherapy studies in mice to be the highlight of the work presented. The combination of radiotherapy and immunotherapy has the potential to improve survival of patients, exploiting the dependence of immunotherapy drugs on immunogenic factors released after tumour-cell death.[48] Very high doses of radiation (eg, those used in stereotactic body radiotherapy) and densely ionising radiation (eg, in carbon ion radiotherapy) are potentially more effective in eliciting immunogenic responses than are lower x-ray doses.[7] The combination of carbon ion radiotherapy and dendritic cells, successfully tested for suppression of lung metastases in mice, seems to be almost ready for translation into clinics. Some of the clinical results reported above (ie, the combination of CIRT with DAV in MMM and Gemcitabine in LAUPC) represent more than an additive effect and might indicate an immunogenic response to carbon ion radiotherapy.

Medical physics

Technology introduced at NIRS, which is based on a fast three-dimensional scanning-irradiation system for moving targets, a treatment-planning system for fast scanning, and a patient-handling system with robotic arms and two/three-dimensional autoregistration software, has proven time efficient and reliable. The panel encouraged NIRS to continue the commissioning of the moving-target irradiation and preparing the phase-controlled rescanning system and the tumour-tracking gating system for clinical use.

The realisation of multiple-energy operation with extended flat-tops allows variation of the beam energy within a single synchrotron cycle. Application of this mode of operation to fast raster-scanning irradiation would substantially reduce the total irradiation time,

improve the beam quality, and concurrently maintain clinically required depth-dose distributions.

The theoretical and experimental study of interplay effects of the scanning beam with the moving target served as a basis for modifications in the beam-delivery system. The work not only shows the need for such motion-mitigation techniques in scanning-beam delivery but also proves that the implementation of gating and rescanning techniques at NIRS achieves much improved dose distributions within phantoms. This study is essential before these techniques are implemented clinically.

Gantries are attractive for use during carbon ion radiotherapy, because CT for treatment planning is done with the patient fixed in the treatment position, and many treatment protocols require the beam to be rotated around the patient fixed in the treatment-planning position for quality and intercomparison purposes. The carbon gantry designed at NIRS[49] consists of ten combined-function superconducting magnets, allowing very compact geometry. In the current NIRS progress report, a superconducting rotating-gantry for carbon ion radiotherapy is presented that is much smaller in size and weight (<300 tons) than the gantry used at Heidelberg Ion Therapy Centre (600 tons). This development will greatly extend the treatment capabilities in cancer radiotherapy.

Conclusion

Before NIRS started carbon ion radiotherapy in 1994, the US NCI supported clinical trials[14] for two decades to investigate the clinical efficacy of heavy-charged particles at the Lawrence Berkeley National Laboratory, Berkeley, CA, until the closure of the Bevalac accelerator facility (1975–93). In the first decade after the inception of the carbon ion radiotherapy clinical trials at NIRS, it was the only facility in the world conducting carbon ion radiotherapy. The second decade (2004–13) was marked by acceptance of the clinical worth of carbon ion radiotherapy by medical communities worldwide, and clinical facilities were constructed and clinical trials started at the Heidelberg Ion Therapy Centre[50] (Heidelberg, Germany; start of treatment in 2009), CNAO[51] (Pavia, Italy; 2012), and three other carbon ion radiotherapy facilities in Japan and two in China. Several other facilities are under construction and will soon become available for clinical trials.[3]

The coming third decade of carbon ion radiotherapy is expected to be the period when clinical trials will be undertaken at several facilities worldwide. A few phase 3 clinical trials on protons versus carbon ions are already under way at the Heidelberg Ion Therapy Centre.[12] Similar trials are planned at CNAO, where a trial in collaboration with France Hadron (Lyon) is also planned, comparing carbon ion radiotherapy with intensity-modulated radiotherapy for head and neck tumours with 16 fractions. The J-CROS project will involve the Japanese facilities in multicentre trials for several new tumour sites, which are emerging as most attractive for carbon ion radiotherapy and for which breakthroughs are possible, including head and neck cancer, locally advanced unresectable pancreatic cancer, hepatocellular carcinoma, and locally recurrent rectal cancer. Finally, a project is under way to design two randomised trials in cooperation with the NCI and the Radiation Therapy Oncology Group, respectively, on pancreatic cancer and soft-tissue sarcomas. We should strive to coordinate the trials, register the protocols in an international registry, and carry out more coordinated randomised trials. To facilitate a meaningful comparison of these carbon ion radiotherapy results, worldwide announcement and international registration of these coordinated clinical trials will be provided.

Through international cooperation, the carbon ion radiotherapy community should coordinate therapy planning and delivery in such a way that clinical results can be compared readily, with reliable and verifiable dosimetry reporting. In this respect, the report on dose and volume specifications for prescribing and reporting ion beam therapy is eagerly awaited.

We hope more carbon ion radiotherapy facilities in planning stages will be constructed, and more clinical trials will take place worldwide. We hope that carbon ion radiotherapy clinical trials will be completed in the USA, where the pioneering work was done.

Search strategy and selection criteria

The primary source of this report is the NIRS reports and oral presentations in the meeting at MedAustron, Austria, in December, 2013. The NIRS reports included references. The authors added additional references for comparison with clinical experience in Europe and the USA. References were searched on the Internet using the keywords "protons", "carbon ions", "heavy ions", and "clinical trials".

Contributors

TK and HT prepared the material for the peer review and presented it to the external review panel. JD, WDN, RM, RO, and RP reviewed the clinical results. WDN wrote the report on clinical results. EAB and MD reviewed the radiobiology results. OJ and SV reviewed the medical physics results. WTC chaired the commission and wrote the final report to NIRS. All authors contributed in writing the paper.

Declaration of interests

We declare that we have no competing interests. TK and HT work at NIRS. JD,RO, and RM are scientific directors of carbon ion radiotherapy facilities in Europe.

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