Table 14.3 Overview of clinical IBT studies for early-stage NSCLC

References	Year of publication	Ion/ Institution	Patient No All (IA/IB)	Total dose (GyE)	Fraction No	Total treatment time (w)	Local control (%) All (1A/1B)	Overall survival (%) All (1A/1B)	Lung toxicity ≥ Grade3 (%)	Median follow-up period (months)
Bush et al. [24]	1999	Proton/ LLMC	37[a]	51–73.8	10–41	2–5	2y: 87	2y: 39	No data	14 (3–45)
Bush et al. [25]	2004	Proton/ LLMC	68 (29/39)	51 or 60	10	2	3y: 74 (87/49)	3y: 44	0	30
Shioyama et al. [26]	2003	Proton/ PMRC	51 (9/19)	1A 60–81 1B 60–93	Median 3 Gy/Fr	Median 6	5y: (89/39)	5y: (70/16)	2.0	30 (18–153)
Hata et al. [27]	2007	Proton/ PMRC	21 (11/10)	50 or 60	10	2	2y: 95 (100/90)	2y: 74 (100/47)	0	25 (10–54)
Nakayama et al. [28]	2009	Proton/ PMRC	58[b] (30/28)	66 (peripheral) 72.6 (central)	10 (peripheral) 22 (central)	2 (peripheral) 5 (central)	2y: 97.0	2y: 97.8	3.6	17.7 (1.4–53.3)
Nihei et al. [29]	2006	Proton/ NCCHE	37 (17/20)	70–94	20	4–5	2y: 80 (94/62)[c]	2y: 84 (83/82)	8.1	24 (3–62)

Iwata et al. [30]	2010	Proton/ HIBMC	57 (27/30)	80 or 60	20 or 10	4 or 2	3y: 81	3y: 73	1.8	40
Iwata et al. [30]	2010	Carbon/ HIBMC	21 (14/7)	52.8	4	1	2y: 86	2y: 87	0	24
Miyamoto et al. [11]	2003	Carbon/ NIRS	81 (40/41)	68.4–79.2,59.4–95.4	9 or 18	3 or 6	5y: 74	5y: 42 (64.4/22)	3.7	52.6
Miyamoto et al. [12]	2007	Carbon/ NIRS	50 (29/21)	72	9	3	5y: 94.7	5y: 50 (55.2/42.9)	0	59 (6–83)
Miyamoto et al. [13]	2007	Carbon/ NIRS	79 (42/37)	52.8 or 60	4	1	5y: 90 (98/80)	5y: 45 (62/25)	0	38.6 (3–72)

[a]Stage I: 27, stage II: 2, stage IIIA: 8
[b]58 tumors of 55 patients
[c]Loco-regional free

Nihei et al. at the National Cancer Center Hospital East (NCCHE) in Kashiwa reported results of PT using 20 fractions and total doses of 70–94 GyE. The local control rate of this more classical fractionation scheme was almost the same as that of hypofractionated PT [29].

Iwata et al. compared PT and CIRT for stage I NSCLC. Both are available at HIBMC. The data are preliminary because CIRT began only in April 2005, whereas treatment with protons started already 2 years earlier. Local control and overall survival rates were above 85% after 2 years and compared excellently to X-ray SBRT [30]. The incidence of severe pneumonitis was low with both CIRT and PT. There was a direct correlation between the percentage of the total lung volume receiving a dose $\geq$ 20 Gy (V20) and the incidence of radiation pneumonitis [31]. V20 was lowest for four fractions of CIRT as compared to 10 or 20 fractions of PT due to the reduced penumbra of carbon ion beams (cf. Chap. 4 for details). However, beam directions were constrained in CIRT, because HIBMC has only three fixed beamlines for carbon. Part of the advantageous dose gradient of carbon could be compensated for by having more degrees of freedom for the beam directions using the proton gantry.

In some reports on PT, T1 disease had better local control and survival than T2 disease [26, 31]. A hypothesis for the inferior outcome of more advanced disease was that the total doses used with PT might be insufficient to control larger primary tumors [31], which contain higher numbers of tumor clonogens and areas of relatively radioresistant hypoxic tumor cells [26]. An estimation of the biologically effective dose (BED) administered to these different regimens support this idea. In contrast to a BED value of 123 for 52.8 GyE carbon ions in four fractions, it was only 96 for 10 fractions of 6 GyE protons [29]. In the case of hypofractionated irradiation, a comparison of BED between carbon and proton beams is difficult. A study for RBE of CIRT is currently underway at NIRS.

14.6 Conclusion

IBT is clearly beneficial for stage I NSCLC. Not only physical but also biological properties of carbon ions can bring an extra therapeutic gain for tumor control. It is theoretically possible in CIRT to safely perform hypofractionated irradiation with a significantly smaller number of fractions as compared to PT. However, there are still unclear issues between PT and CIRT, such as RBE for hypofractionated irradiation. To clarify the effectiveness of each modality for early stage NSCLC, well-planned randomized trials will be required.

References

1. H. Asamura, T. Goya, Y. Koshiishi, et al., A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J. Thorac. Oncol. **3**, 46–52 (2008)
2. W.R. Smythe, American College of Chest Physicians. Treatment of stage I non-small cell lung carcinoma. Chest **123**, 181S–187S (2003)

3. B. Jeremic, J. Classen, M. Bamberg, Radiotherapy alone in technically operable, medically inoperable, early-stage (I/II) non-small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. **54**, 119–130 (2002)
4. F.B. Zimmermann, M. Bamberg, M. Molls, et al., Radiation therapy alone in early stage non-small cell lung cancer. Semin. Surg. Oncol. **21**, 91–97 (2003)
5. Y. Nagata, M. Hiraoka, T. Mizowaki, et al., Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. Int. J. Radiat. Oncol. Biol. Phys. **75**, 343–347 (2009)
6. F.B. Zimmermann H. Geinitz, S. Schill, et al., Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. Lung Cancer **48**, 107–114 (2005)
7. H. Onishi, T. Araki, H. Shirato, et al., Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer **101**, 1623–1631 (2004)
8. S. Senan, F. Lagerwaard, Stereotactic radiotherapy for stage I lung cancer: current results and new developments. Cancer Radiother. **14**, 115–118 (2010)
9. H. Onishi, H. Shirato, Y. Nagata, et al., Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J. Thorac. Oncol. **2**(Suppl 3), S94–S100 (2007)
10. Y. Nagata, K. Takayama, Y. Matsuo, et al., Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int. J. Radiat. Oncol. Biol. Phys. **63**, 1427–1431 (2005)
11. T. Miyamoto, N. Yamamoto, H. Nishimura, et al., Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiother. Oncol. **66**, 127–140 (2003)
12. T. Miyamoto, M. Baba, N. Yamamoto, et al., Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypo-fractionated regimen. Int. J. Radiat. Oncol. Biol. Phys. **67**, 750–758 (2007)
13. T. Miyamoto, M. Baba, T. Sugane, et al., Carbon ion radiotherapy for stage I non-small cell lung cancer using a regimen of four fractions during 1 week. J. Thorac. Oncol. **2**, 916–926 (2007)
14. T. Sugane, M. Baba, R. Imai, et al., Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer. Lung Cancer **64**, 45–50 (2009)
15. T. Kanai, M. Endo, S. Minohara, et al., Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. **44**, 201–210 (1999)
16. T. Yasukawa, Y. Yamaguchi, H. Aoyagi et al., Diagnosis of hilar and mediastinal lymph node metastasis of lung cancer by positron emission tomography using ^{11}C-methionine. Jpn. J. Lung Cancer **36**, 919–926 (1996)
17. International Union Against Cancer (UICC), *TNM Classification of Malignant Tumors*, 6th edn., ed. by L.H. Sobin, Ch. Wittekint (Wiley-Liss, NewYork, 2002)
18. T. Sugane, M. Baba, N. Yamamoto, et al., Treatment planning in carbon ion radiotherapy for lung cancer. Paper presented at Proceedings of NIRS-MD Anderson Symposium on Clinical Issues for Particle Therapy, NIRS-M-210, Houston, TX, 20–21 Mar 2008, pp. 30–35
19. S. Minohara, T. Kanai, M. Endo, et al., Respiratory gated irradiation system for heavy-ion radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. **47**, 1097–1103 (2000)
20. T. Kanai, Y. Furusawa, K. Fukutsu, et al., Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat. Res. **147**, 78–85 (1997)
21. M. Endo, H. Koyama-Ito, S. Minohara, et al., HIPLAN-a heavy ion treatment planning system at HIMAC. J. Jpn. Soc. Ther. Radiol. Oncol. **8**, 231–238 (1996)
22. T. Miyamoto, M. Baba, K. Kagei, et al., Carbon ion radiotherapy in hypofraction regimen for stage I non-small cell lung cancer. Paper presented at Proceedings of NIRS-MedAustron Joint Symposium on Carbon ion Therapy in Cancer, NIRS-M-188, Chiba, 25–26 Feb 2006, pp. 25–28

23. J.D. Cox, J. Stetz, T.F. Pajak, Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int. J. Radiat. Oncol. Biol. Phys. **31**, 1341–1346 (1995)
24. D.A. Bush, J.D. Slater, R. Bonnet, et al., Proton-beam radiotherapy for early-stage lung cancer. Chest **116**, 1313–1319 (1999)
25. D.A. Bush, J.D. Slater, B.B. Shin, et al., Hypofractionated proton beam radiotherapy for stage I lung cancer. Chest **126**, 1198–1203 (2004)
26. Y. Shioyama, K. Tokuuye, T. Okumura, et al., Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. **56**, 7–13 (2003)
27. M. Hata, K. Tokuuye, K. Kagei, et al., Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. Int. J. Radiat. Oncol. Biol. Phys. **68**, 786–93 (2007)
28. H. Nakayama, S. Sugahara, M. Tokita, et al., Proton beam therapy for patients with medically inoperable Stage I non-small-cell lung cancer at the University of Tsukuba. Int. J. Radiat. Oncol. Biol. Phys. **78**, 467–471 (2010)
29. K. Nihei, T. Ogino, S. Ishikura et al., High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. **65**, 107–111 (2006)
30. H. Iwata, M. Murakami, Y. Demizu, et al., High-dose proton therapy and carbon-ion therapy for stage I non-small cell lung cancer. Cancer **116**, 2476–2485 (2010)
31. K. Tsujino, S. Hirota, M. Endo, et al., Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int. J. Radiat. Oncol. Biol. Phys. **55**, 110–115 (2003)

Chapter 36
HIMAC: A New Start for Heavy Ions

Tadashi Kamada and Hirohiko Tsujii

Abstract In 1994, carbon ion radiotherapy (CIRT) was initiated at the National Institute of Radiological Sciences (NIRS) in Japan using the Heavy Ion Medical Accelerator in Chiba (HIMAC), which was the world's first heavy ion accelerator complex dedicated to medical use. Among several types of ion species, carbon ions were chosen for cancer therapy because they were presumed to possess optimal properties in terms of biologically effective dose localization.

This chapter will cover the evolution of CIRT over the last 15 years and highlight the clinical results achieved at NIRS.

36.1 Introduction

In Japan, the decision for a medical accelerator using ions heavier than protons was made in 1984 at NIRS. HIMAC was the world's first heavy ion accelerator complex intended primarily for clinical use (Fig. 36.1). The accelerator complex took almost a decade to build and was completed by the end of 1993. One year later, in 1994, clinical trials using carbon ion beams generated from the HIMAC were initiated [1]. Carbon was chosen because of the favorable properties (cf. Chap. 4 for details). The HIMAC has operated since its opening as a multipurpose facility available for joint cancer treatment and research in biology and physics by both Japanese and foreign investigators.

T. Kamada (✉)
National Institute of Radiological Sciences, Research Center of Charged Particle Therapy, Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan
e-mail: t_kamada@nirs.go.jp

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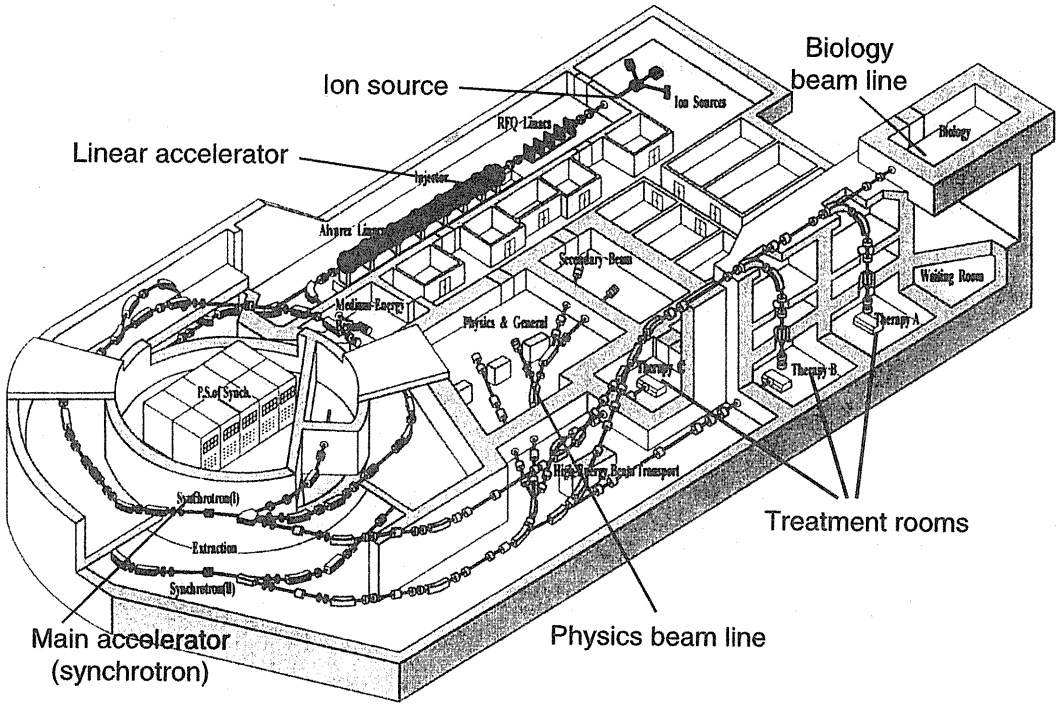

Fig. 36.1 Heavy ion medical accelerator in Chiba (HIMAC)

36.2 CIRT at NIRS

Since June 1994 until spring 2011, almost 50 protocols have been conducted in an attempt to determine the optimal dose fractionation and irradiation method for the treatment of specific diseases. The number of patients has increased year by year, and the facility has meanwhile reached a capacity permitting nearly 700 patients to be treated each year (Fig. 36.2). In February 2011, nearly 5900 patients had been registered. The categories of disease that can be treated in routine clinical practice include lung cancer, prostate cancer, head and neck cancer, skull base tumors, ocular melanoma, bone and soft-tissue sarcoma, liver cancer, and pelvic recurrences of rectal cancer (Fig. 36.3).

The clinical trials began with a small dose per fraction. At first, the average number of fractions was almost 18. All these early trials were carried out as dose-escalation studies. It was found that a very high dose per fraction could be administered and the average number of fractions could be reduced from 18 to 12–13 over the last several years leading to improvements in patient throughput (Fig. 36.4).

HIMAC has three treatment rooms with fixed vertical and/or horizontal beam lines. In order to conform the dose to a target volume, the beam lines in the treatment room are equipped with a pair of wobbler magnets to modulate the beam width, plus beam scatterers, ridge filters, multileaf collimators, and the ability to administer a compensation bolus (see also next chapter). An appropriately sized ridge filter,

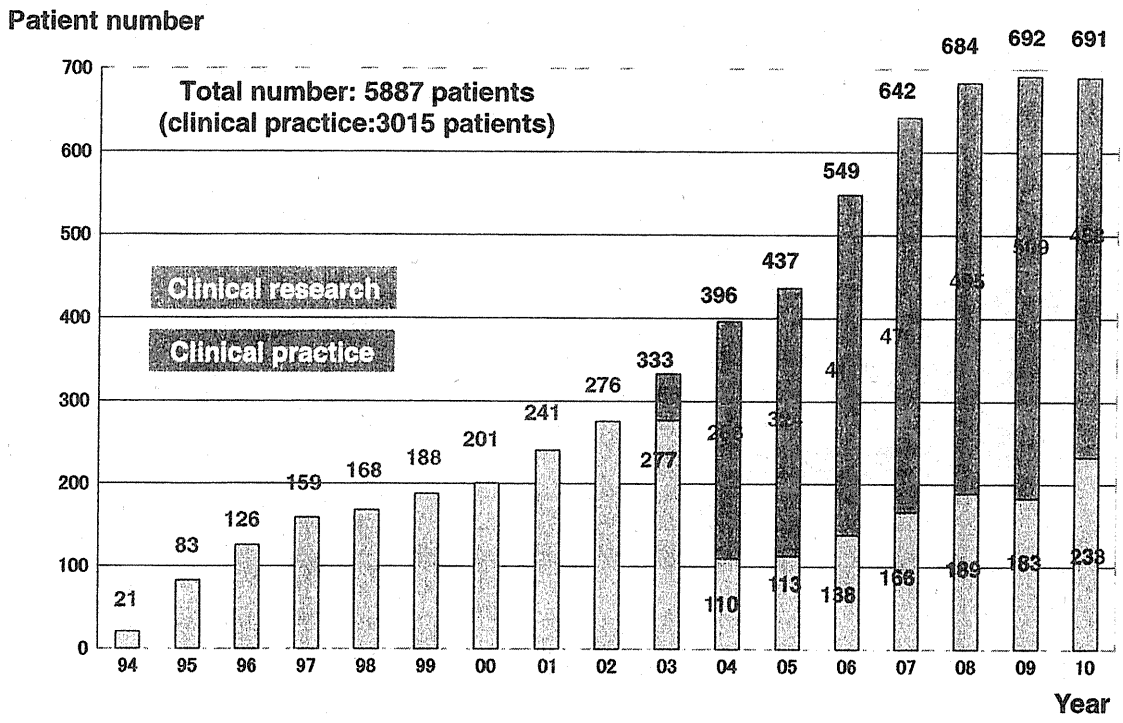

Fig. 36.2 Annual patient accrual in carbon ion radiotherapy (CIRT) at NIRS

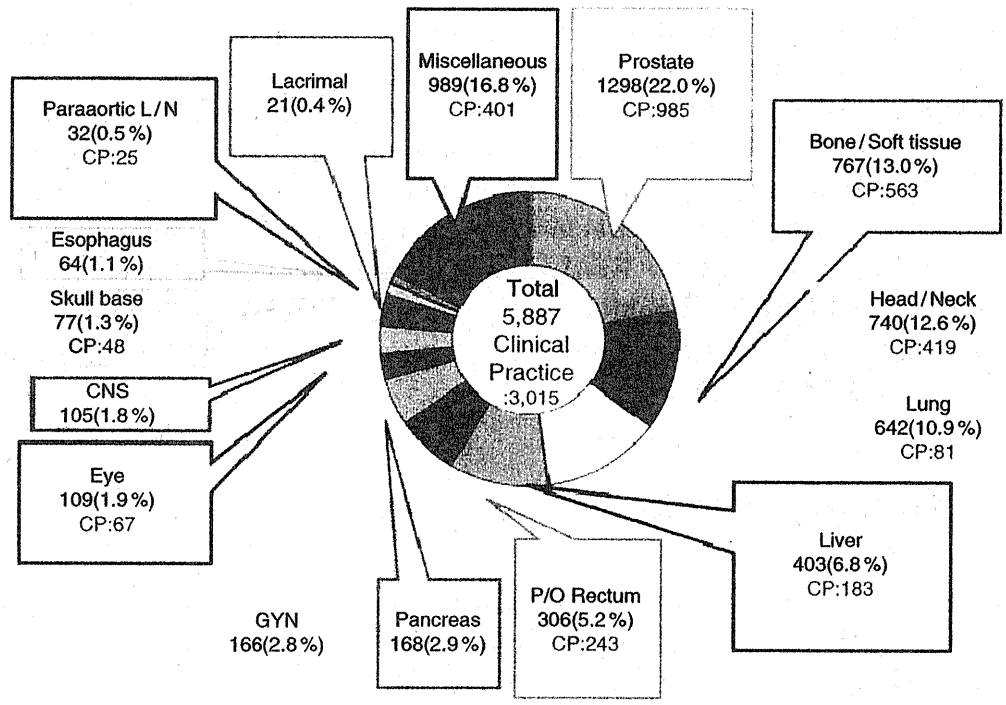

Fig. 36.3 Patient distribution enrolled in CIRT at NIRS (Treatment Period: June 1994 to February 2011)

which corresponds to, and determines the size of the spread-out Bragg peak (SOBP), is selected to avoid unnecessary dose to normal tissues along the beam path in each port.

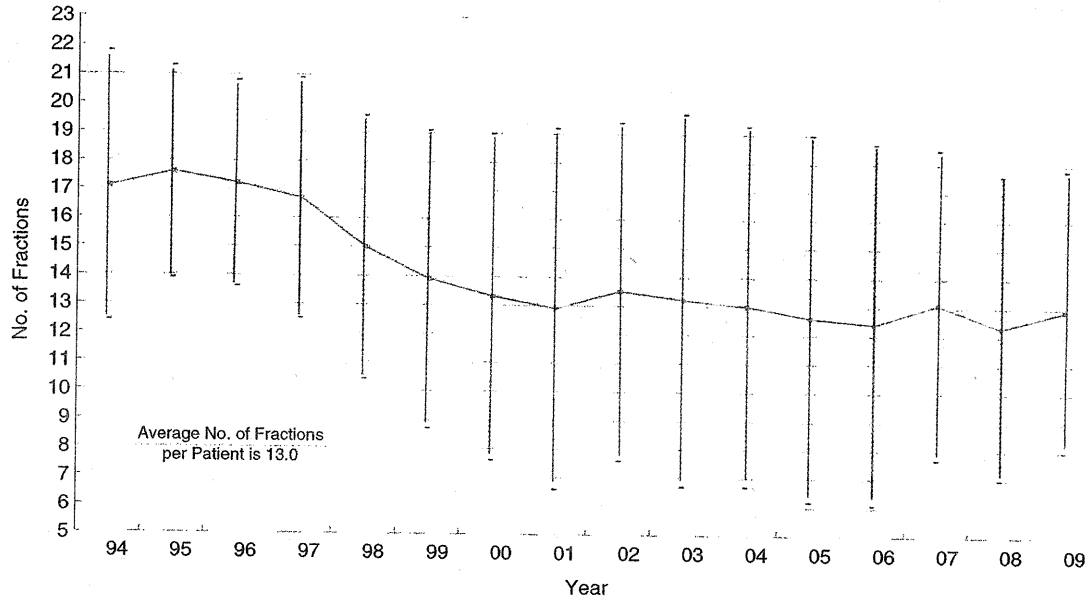

Fig. 36.4 Average number of fractions used in CIRT at NIRS

The patients are positioned in customized cradles and immobilized with a low-temperature thermoplastic. A set of 5-mm thick CT images is taken for treatment planning with the immobilization devices in place. Respiratory gating of both the CT acquisition and the therapy is performed when indicated [2].

Three-dimensional treatment planning is performed using HIPLAN software, which was developed for CIRT [3]. A margin of 5 mm is usually added to the clinical target volume to create the planning target volume. Dose is calculated for the target volume and any nearby critical structures and expressed in Gray-Equivalent (GyE = carbon physical dose in Gray × Relative Biological Effectiveness {RBE}) [4, 5].

CIRT is given once daily, on 4 days per week (Tuesday to Friday). At every treatment session, the patient's position is verified with a computer-aided online positioning system (Fig. 36.5).

36.3 Treatment Results by Tumor Type

Head and neck cancer, lung, liver, and prostate cancer, postoperative rectal cancer recurrences, and bone and soft-tissue sarcomas are the six most commonly treated tumors in NIRS studies.

36.3.1 Head and Neck Cancer

CIRT was first applied to the treatment of patients with head and neck tumors and five clinical trials were conducted at NIRS (Fig. 36.6). Two dose optimization studies with different fractionation (protocols of 18 fractions over 6 weeks and

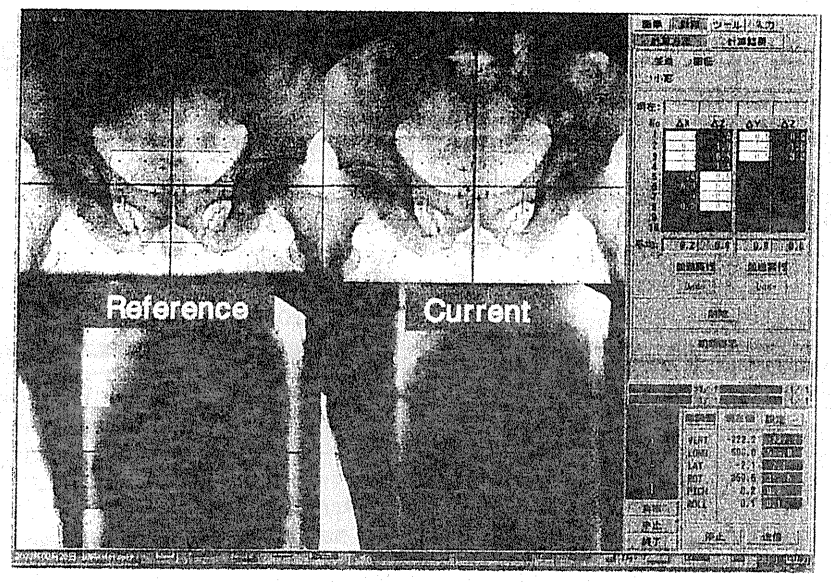

Fig. 36.5 Online positioning using an orthogonal X-ray TV system

16 fractions over 4 weeks) were followed by a phase II fixed dose study [6]. During the phase II study, a high distant metastasis rate in melanoma and a poor local control rate in sarcoma with standard doses (total doses of 57.6 GyE or 64 GyE over 4 weeks) were found by subgroup analysis. New protocols modified for melanoma and sarcoma were created; a concurrent chemocarbon therapy protocol for melanoma and a high-dose protocol (70.4 GyE in 16 fractions over 4 weeks) for sarcoma.

More than 700 locally advanced tumors were treated with carbon ions in these five studies. The treatment results obtained so far can be summed up by stating that a very favorable local control rate of 70–80% has been achieved for locally advanced adenocarcinoma, adenoid cystic carcinoma, malignant melanoma in the nasal cavity and paranasal sinus, squamous cell carcinoma, and sarcomas.

36.3.2 Lung Cancer

Patients with inoperable stage I non-small cell lung cancer (NSCLC) were treated in several protocols. The results have been quite promising and more than 600 patients were enrolled in the lung studies. Clinical trials in lung cancer were started with 18 fractions over a 6-week dose-escalation study. Two subsequent protocols shortened the overall treatment time to 3 weeks. The 3-year local control rates were 65–95%, and the 5-year survival rates were 40–50%. The results of these studies are better than those of conventional radiotherapy, and almost the same as those of surgery [7]. We have conducted a fixed 4-fractions-in-1-week protocol since 2000. That way, a very high dose can be given with acceptable side effects. A single-fraction dose escalation study was started in 2003 (cf. Chap. 14 for details).

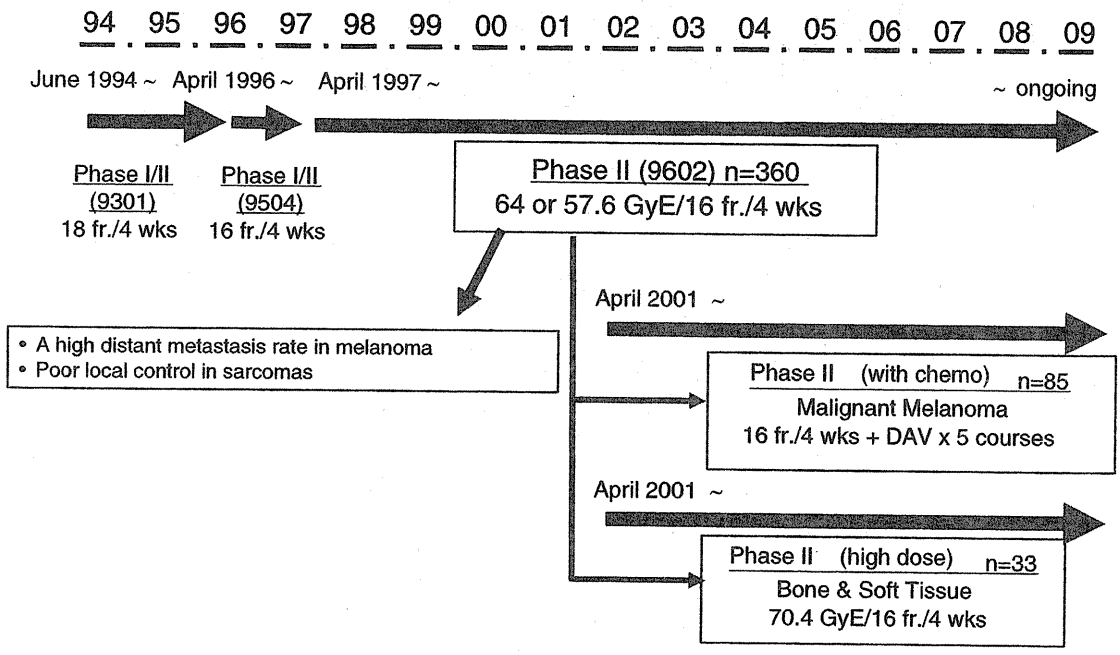

Fig. 36.6 Protocols for head and neck tumors

36.3.3 Liver Cancer

For liver cancer, 15 fractions over 5 weeks were employed as initial dose optimization study [8]. The overall treatment time of 5 weeks was then shortened to 3, 2, and 1 week in subsequent studies [9]. More recently, a fourth clinical trial using an even shorter irradiation schedule of 2 fractions over 2 days has just been completed with encouraging results in terms of a favorable local control rate and the absence of any particular serious adverse reactions. No unwanted skin reactions of grade 2 or higher were observed. For liver function, no toxicities greater than grade 3 occurred. Almost 400 patients with liver cancer have been treated with CIRT using these protocols.

36.3.4 Prostate Cancer

A total of three clinical trials have been carried out for patients with prostate cancer. The first CIRT trial protocol (20 fractions over 5 weeks) with concomitant endocrine therapy was conducted for B2-C stage patients [10]. The eligibility criteria for the second trial were less stringent. CIRT-only was applied to stage A2–B1 prostate cancer and CIRT plus endocrine therapy for stage B2–C disease. In the first clinical trial, the most serious toxicities were recorded in the rectum among patients exposed to the highest dose level of 72 GyE. Dose volume histogram (DVH) analysis was performed to identify the tolerance dose of the rectum, using a rectal DVH curve that permits prediction of the risk of rectal reactions. This curve has made it possible

to prevent severe rectal reactions in new patients at the time of treatment planning. As a result, the safe dose distribution for the digestive tract was established and no serious toxic reactions were encountered in the subsequent clinical trials. A total dose of 63 GyE was found to be an optimal dose for 20 fractions over a 5-week protocol. The overall treatment time was then shortened to 4 weeks and showed better outcomes [11]. The total number of prostate cancers treated with carbon ions is now nearly 1,300. We are now proceeding to a clinical trial with an even shorter regimen of 12 fractions in 3 weeks.

36.3.5 Bone and Soft-Tissue Sarcomas

Bone- and soft-tissue sarcomas are generally considered to be radioresistant. Advanced tumors originating in the trunk, in particular, are in many cases not resectable and have a poor prognosis. The use of carbon ion beams does offer a favorable prospect of improved local control in view of their superior biological dose distribution (Fig. 36.7). The patients enrolled in our initial dose escalation trial were primarily subjects not responding to surgery or they were totally inoperable. This trial produced favorable local control of approx. 85% at 5 years. It has been realized that chordoma and osteosarcoma are the prime candidates for CIRT [12–15]. In some 10% of those patients, the lesions were close to the body surface so that it was not possible to avoid exposure of the skin to high-radiation doses. They developed severe reactions such as skin ulceration. In the meantime, more experience has been gained and significant improvements in irradiation techniques have been achieved that such severe toxicity has no longer been observed (Fig. 36.8).

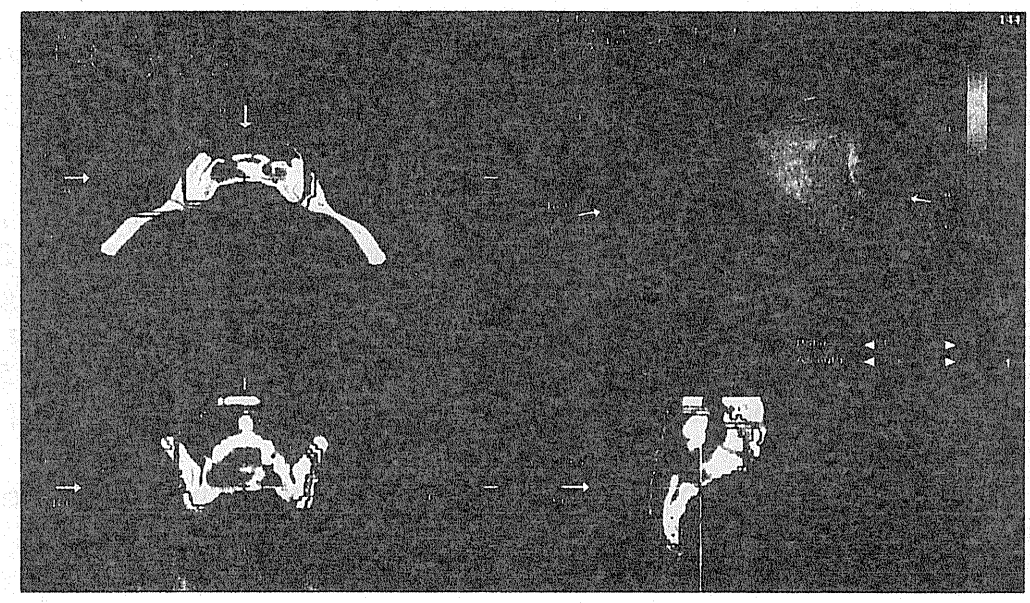

Fig. 36.7 Example of the dose distribution of CIRT in an osteosarcoma

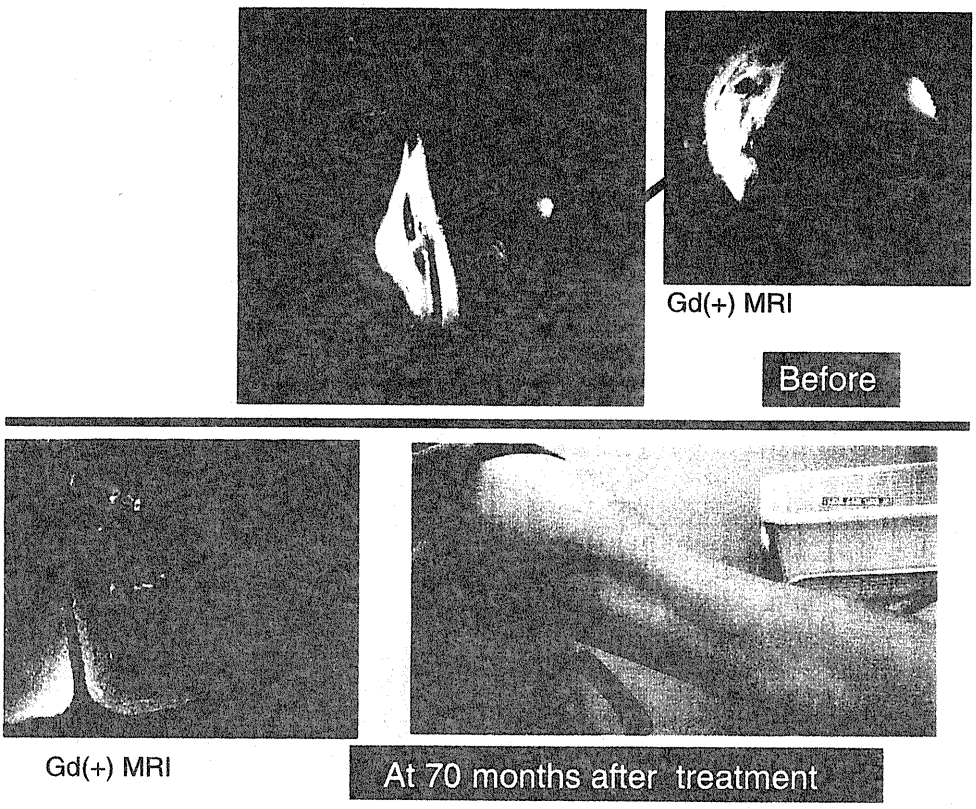

Fig. 36.8 Malignant fibrous histiocytoma of the left arm. The tumor received 70.4 GyE of carbon ions in 16 fractions over 4 weeks. Complete tumor regression and almost no skin reaction were observed at 70 months after treatment

Bone and soft-tissue tumors in the trunk are the most typical lesions qualifying for CIRT and more than 750 patients have been treated.

36.3.6 Rectal Cancer

Although postoperative rectal cancer recurrence in the pelvis has decreased as a result of improvements in surgical procedures, the incidence is still almost 20% [16–18]. Many of the patients with local recurrence are not eligible for surgical resection and are frequently referred to conventional radiation therapy; yet the results are still far from being acceptable. Many of the literature reports give a 50% survival period of 12 months and a 3-year survival rate of approxrimately 10%, and the role of radiotherapy is often described as palliative [19].

Over 300 patients have so far been treated with CIRT and no particularly serious toxic reactions have been discovered. The results in terms of local control and survival rate are extremely favorable in comparison with conventional radiotherapy and are comparable to those achieved with surgery.

Table 36.1 Activity numbers of CIRT facilities in the world

Name	Start	No. of Pts.	Until	Country
NIRS	1994	5,887	2011.2	Japan
GSI	1997	440	2008.7	Germany (closed)
HIBMC	2002	915	2010.9	Japan
IMP	2006	126	2010.11	China
HIT	2009	200	2010.10	Germany
GHMC	2010	90	2010.12	Japan
		7,658		

NIRS National Institute of Radiological Sciences *GSI* GSI Helmholtzzentrum für Schwerionenforschung *HIBMC* Hyogo Ion Beam Medical Center *IMP* Institute of Modern Physics *HIT* Heidelberg Ion-Beam Therapy Center *GHMC* Gunma University Heavy Ion Medical Center

36.4 Future Prospects for CIRT

CIRT is an effective treatment modality for many cancers. Compared with other treatment modalities, however, it has to be admitted that it is rather costly. HIMAC with its 42-m-diameter synchrotron ring was built at costs of roughly 33 billion yen (US $360 million). For the benefits of carbon ions to be available to the public at large, it is of paramount importance to develop a lower cost and more compact system. In view of this, NIRS embarked on the development of a compact system that has the same performance as the HIMAC at about one third of its cost and size (cf. Chap. 37). In March 2010, the new compact facility at Gunma University in Maebashi, Japan, was completed. They have just started their carbon beam treatment as the third CIRT facility in Japan – after NIRS and Hyogo Ion Beam Medical Center.

More than 7500 patients have been treated with carbon ion beams worldwide since 1994, and nearly 80% were treated at NIRS (Table 36.1). Now five carbon ion beam facilities are operating, including the facility at Gunma University. Three more facilities are under construction in Europe and planning is in progress at ten or more institutions worldwide (cf. Chap. 41). There has been a growing interest in using CIRT for cancer treatment in the last decade. NIRS has been pivotal in providing the preclinical and clinical data for this field, and other facilities have successfully reproduced them [20].

The future development and expansion of CIRT requires further progress. The new NIRS system with respiration-gated scanning and a compact rotating gantry should be instrumental in that respect.

36.5 Summary

CIRT at NIRS has made significant progress with a total of 5,887 patients registered by the end of February 2011.

By location, it is effective in the head and neck (including the eye), the base of the skull, lung, liver, prostate, bone and soft tissue, and pelvic recurrence of rectal cancer. By pathological type, CIRT is effective against adenocarcinoma for which photon beams are relatively ineffective, as well as against sarcomas of the bone and soft tissue.

CIRT offers significant advantages over conventional radiotherapy due to its extremely favorable physical and biological dose distribution. These unique features lend themselves to convenient hypofractionated regimens. For lung and liver cancer, in particular, an ultrashort irradiation schedule with only 1 or 2 sessions is available. For prostate, head and neck, base of the skull, pelvic recurrence of rectal cancer, and bone and soft-tissue sarcomas, treatments with 12 fractions over 3 weeks are possible.

Toxicities initially associated with dose escalation are no longer encountered. But clinical trials need to be continued not the least to investigate if the therapeutic outcome of up to now intractable tumors such as malignant glioma or cancer of the pancreas, can also be improved.

References

1. H. Tsujii, S. Morita, T. Miyamoto, et al., Preliminary results of phase I/II carbon-ion therapy at the NIRS. J. Brachyther. Int. **13**, 1–8 (1997)
2. S. Minohara, T. Kanai, M. Endo, et al., Respiratory gated irradiation system for heavy-ion radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. **47**, 1097–1103 (2000)
3. M. Endo, H. Koyama-Ito, S. Minohara, et al., HIPLAN - a heavy ion treatment planning system at HIMAC. J. Jpn. Soc. Ther. Radiol. Oncol. **8**, 231–238 (1996)
4. T. Kanai, Y. Furusawa, K. Fukutsu, et al., Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat. Res. **147**, 78–85 (1997)
5. T. Kanai, M. Endo, S. Minohara, et al., Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. **44**, 201–210 (1999)
6. J. Mizoe, H. Tsujii, T. Kamada, et al., Dose escalation study of carbon ion radiotherapy for locally advanced head and neck cancer. Int. J. Radiat. Oncol. Biol. Phys. **60**, 358–364 (2004)
7. T. Miyamoto, N. Yamamoto, H. Nishimura, et al., The working group for lung cancer: carbon ion radiotherapy for stage I non-small cell lung cancer. Radiother. Oncol. **66**, 27–140 (2003)
8. H. Kato, H. Tsujii, T. Miyamoto, et al., Liver Cancer Working Group. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. Int. J. Radiat. Oncol. Biol. Phys. **59**, 1468–1476 (2004)
9. H. Kato, S. Yamada, S. Yasuda, et al., Four-fraction carbon ion radiotherapy for hepatocellular carcinoma. Proc of 40th Ann Meeting Am Soc Clin Oncol, New Orleans, USA, June 5-8, 2004 J. Clin. Oncol. **22**, 4090 (2004)
10. K. Akakura, H. Tsujii, S. Morita, et al., The Working Group for Genitourinary Tumors: Phase I/II clinical trials of carbon ion therapy for prostate cancer. Prostate **55**, 252–258 (2004)
11. H. Tsuji, T. Yanagi, H. Ishikawa, et al., Working Group for Genitourinary Tumors. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. **32**, 1153–1160 (2005)
12. T. Kamada, H. Tsujii, T. Yanagi, et al., Working Group for Bone and Soft Tissue Sarcomas: Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. J. Clin. Oncol. **20**, 4466–4471 (2002)

13. R. Imai, T. Kamada, H. Tsuji, et al., Working Group for Bone and Soft Tissue Sarcomas. Carbon ion radiotherapy for unresectable sacral chordomas. Clin. Cancer Res. **10**, 5741–5746 (2004)
14. R. Imai, T. Kamada, H. Tsuji, et al., Working Group for Bone and Soft Tissue Sarcomas. Effect of carbon ion radiotherapy for sacral chordoma. Results of phase I-II and phase II clinical trials. Int. J. Radiat. Oncol. Biol. Phys. **77**, 1470–1476 (2009)
15. Y. Nishida, T. Kamada, R. Imai, et al., Clinical outcome of sacral chordoma with carbon ion radiotherapy compared with surgery. Int. J. Radiat. Oncol. Biol. Phys. **79**, 110–116 (2010)
16. S. Galandiuk, H.S. Wieand, C.G. Moertel, et al., Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg. Gynecol. Obstet. **174**, 27–32 (1992)
17. F. Bozzetti, L. Mariani, R. Micel, et al., Cancer of the low and middle rectum: local and distant recurrence and survival in 350 radically resected patients. J. Surg. Oncol. **62**, 207–213 (1992)
18. J.L. McCall, M.R. Cox, D.A. Wattchow, Analysis of local recurrence rates after surgery alone for rectal cancer. Int. J. Colorectal. Dis. **10**, 126–132 (1995)
19. H.J. Wanebo, R.J. Koness, M.P. Vezeridis, et al., Pelvic resection of recurrent rectal cancer. Ann. Surg. **220**, 586–595 (1994)
20. D. Schulz-Ertner, C.P. Karger, A. Feuerhake, et al., Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. Int. J. Radiat. Oncol. Biol. Phys. **68**, 449–457 (2007)

V. 研究成果の刊行物・別刷
(研究分担者)

Treatment Strategy for Hepatocellular Carcinoma with Major Portal Vein or Inferior Vena Cava Invasion: A Single Institution Experience

Hiroyuki Yoshidome, MD, PhD, Dan Takeuchi, MD, PhD, Fumio Kimura, MD, PhD, Hiroaki Shimizu, MD, PhD, Masayuki Ohtsuka, MD, PhD, Atsushi Kato, MD, PhD, Katsunori Furukawa, MD, PhD, Hideyuki Yoshitomi, MD, PhD, Masaru Miyazaki, MD, PhD

BACKGROUND: The prognosis of patients with hepatocellular carcinoma (HCC) invading the main trunk of the portal vein and the inferior vena cava is dismal. The best strategy for treatment is not well known.

STUDY DESIGN: We retrospectively reviewed the medical records of 641 patients treated for HCC between 1990 and June 2009. Eighty-four (13%) of these patients had HCC, with a tumor thrombus invading the main trunk or the first-order branch of the portal vein, or the inferior vena cava. Thirty-four patients underwent hepatectomy and 50 patients underwent transcatheter arterial chemoembolization (TACE). We specifically focused on these 34 patients to describe our results of surgical treatment for advanced HCC.

RESULTS: Among the 34 patients who underwent hepatectomy, preoperative TACE was performed in 15 patients. Six patients were identified as having a tumor size reduction or necrosis of 50% or higher (TE3) by TACE. The median operative duration was 355 minutes. Postoperative morbidity and mortality rates were 44% and 2.9%, respectively. The 5-year survival rate after hepatectomy was 20%, which was better than that of patients after TACE alone. The response after preoperative TACE (hazard ratio 4.65; 95% CI, 1.39 to 15.5) and tumor diameter (hazard ratio 2.78; 95% CI, 1.16 to 6.64) were identified as significant favorable preoperative prognostic factors for survival using the multivariable Cox model. Patients with tumors smaller than 10 cm and TE3 effect had a more favorable survival than patients with tumors 10 cm or larger and who did not have a good TACE outcome.

CONCLUSIONS: A combination of aggressive surgical treatment and effective preoperative TACE treatment for HCC with major vascular invasion may be beneficial for selected patients. (J Am Coll Surg 2011;212:796–803. © 2011 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is among the most common malignant diseases worldwide, and is one of the leading causes of cancer-related deaths.[1,2] Liver resection and transplantation, radiofrequency ablation, and transcatheter arterial chemoembolization (TACE) are possible modalities for achieving a cure. The presence of vascular invasion, such as tumor thrombus of the portal vein or hepatic vein, is one of the most important prognostic factors for HCC.[3] There is controversy with respect to the best treatment for advanced HCC invading the main trunk/the first-order branch of the portal vein (Vp4/3) or the inferior vena cava (Vv3) because of the increased risk of intrahepatic recurrence, leading to a decreased survival. The natural history of untreated HCC with Vp4/3 is dismal; the median survival of these patients was reported to be 2.7 months.[4] Although the Asian consensus summit stated that hepatic resection for HCC should be considered if there is no evidence of gross vascular invasion and portal thrombosis,[5] the only hope for cure for such advanced HCC is an aggressive surgical resection to improve the prospects for long-term survival of patients who would otherwise have a dismal prognosis.[6] Recent advances in vascular and hepatobiliary surgical techniques have increased the indications for a surgical resection of such advanced tumors, although there is a relatively high surgical risk.

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From the Department of General Surgery, Chiba University Graduate School of Medicine, Chiba, Japan.

Correspondence address: Masaru Miyazaki, MD, Department of General Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-Ku, Chiba, 260-8670, Japan. email: masaru@faculty.chiba-u.jp

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Abbreviations and Acronyms
HCC = hepatocellular carcinoma
IVC = inferior vena cava
TACE = transcatheter arterial chemoembolization
TE = therapeutic effect
THVE = total hepatic vascular exclusion

A rapid remnant liver recurrence after hepatic resection is frequently experienced in HCC with Vp4/3 or Vv3, so patients with rapid remnant liver recurrence may gain no survival benefit from hepatectomy.[6,7] Surgical procedures to remove a tumor thrombus in the inferior vena cava (IVC) are somewhat complicated due to the extension of the thrombus, so it is often necessary to use the total hepatic vascular exclusion (THVE) technique or to occasionally use cardiopulmonary bypass depending on the site of the spread of the tumor thrombus.[8-10] Previous reports have included only a limited number of patients who had undergone surgical treatment for HCC with Vv3.[11,12]

Some patients with these conditions have experienced prolonged survival after TACE therapy, but few patients are likely to survive more than 1 year.[13] In contrast, preoperative TACE is a useful modality to prolong survival in selected patients with HCC and portal vein invasion.[14] We previously reported that preoperative TACE may also be effective for prolonging the survival of selected patients with HCC and Vv3.[15] Furthermore, adjuvant chemotherapy may be required for these patients with advanced HCC to prolong survival.[16,17] Taken together, the most appropriate strategy for treatment of HCC with a tumor thrombus invading the major vasculature remains to be determined. We describe here our experiences with surgical treatment for these highly advanced HCC patients, and discuss the benefits and limits of surgical treatment to provide preliminary criteria that can be used to determine whether or not a hepatectomy is justified for such HCC with a tumor thrombus invading the major vasculature.

METHODS

Patients and preoperative evaluation

We treated 641 patients with HCC between January 1990 and June 2009. Three hundred fifty-four of these patients underwent liver resection for HCC, including living donor liver transplantation in 3 patients, and 287 patients underwent TACE or chemotherapy. The medical records of these patients were retrospectively reviewed. According to the classification of primary liver cancer by the Liver Cancer Study Group of Japan,[18] the patients were defined as having a tumor thrombus in the main trunk (Vp4) and the first-order branch (Vp3) of the portal vein, and the IVC through the hepatic vein (Vv3). In our series, 84 patients had HCC with Vp4/3 or Vv3. Among the patients who had HCC with Vp4/3 or Vv3, 34 patients underwent hepatic resection and 50 patients underwent TACE (Table 1). All of these patients were preoperatively evaluated by abdominal ultrasonography, thoracoabdominal dynamic CT, and MRI, and some patients underwent abdominal angiography. The extent of the tumor thrombus to the portal vein or IVC was accurately assessed by these imaging techniques. Multidetector-row CT was used for evaluation from 2002 on. Identical thoracoabdominal dynamic CT was performed for reevaluation before the hepatectomy in patients undergoing preoperative TACE therapy. The remnant liver functional reserve was predicted from the indocyanine green retention rate at 15 minutes. Hepatectomy was performed regardless of the number of tumors whenever remnant liver functional reserve was predicted to be preserved. The future remnant liver volume was predicted by CT volumetry in every patient beginning in 1998. Since 1998, patients with a predicted remnant liver volume ≥35% of the total liver volume underwent liver resection without preoperative portal vein embolization. The indication for TACE was based on a lack of sufficient liver functional reserve and the remnant liver volume for hepatectomy. Data collected for each patient included clinical features, laboratory data, pathologic margin status, and surgical details. Assessment of the direct treatment effect on target nodules by preoperative TACE was defined by the classification of primary liver cancer by the Liver Cancer Study Group of Japan.[18] For assessing the direct effect of TACE, the tumor-necrotizing effect and tumor size reduction rate were calculated based on the reduction in size or disappearance of hypervascularity as defined by either dynamic CT or the histopathologic findings.

Table 1. Selected Characteristics of Patients with Hepatocellular Carcinoma Who Underwent Hepatectomy (n = 354) or Who Underwent Interventional Therapy (n = 287) Between January 1990 and June 2009

Characteristic	n	%
Surgical resection	354	
HCC with tumor thrombus (Vp3/4, Vv3)	34	9.6
First-order branch of the PV (Vp3)	14	41.2
Main trunk of the PV (Vp4)	9	26.5
IVC invasion (Vv3)	8	23.5
Vp3 + Vv3	1	2.9
Vp4 + Vv3	2	5.9
Transcatheter arterial chemoembolization	287	
HCC with major vascular invasion (Vp3/4, Vv3)	50	17.4
Total	641	

HCC, hepatocellular carcinoma; IVC, inferior vena cava; PV, portal vein.

Surgical procedures

An abdominal or thoracoabdominal incision was used for surgery. The liver was mobilized for suitable resection. The extent of liver resection was classified according to Couinaud's anatomic classification. To remove the tumor thrombus in the portal vein, an open tumor thrombectomy was performed in 23 patients, and use of a Fogarty catheter was necessary for 3 patients. In patients with Vv3, after intraperitoneal exploration, the IVC and major tributaries were controlled by placing vessel loops above and below the portion in which the tumor thrombus was located. Vascular control of the IVC was achieved through total hepatic vascular exclusion (THVE) in 9 patients, including concomitant hypothermic isolated hepatic perfusion in 1 patient. The location of the suprahepatic IVC clamping was determined by the site of the extent of tumor thrombus of the IVC. As recommended, prophylactic antibiotics were administered to all patients.

Follow-up

After performing a hepatic resection, all patients were followed up. The levels of serum tumor markers such as alpha-fetoprotein (AFP) or protein induced by vitamin K absence-II (PIVKA-II) were determined every 3 months. Ultrasonography or thoracoabdominal CT were performed to examine patients for recurrence. Patients were followed until death or until August 31, 2010.

Statistical analysis

Summary statistics were constructed for the baseline values, using frequencies and proportions for categorical data, and means and standard deviations (SD) for continuous variables. We compared the patient characteristics using Fisher's exact test for categorical outcomes. A p value of <0.05 was considered significant. For time-to-event outcomes, the distributions of time to the first event were compared using the log-rank test; the Kaplan-Meier method was used to estimate the absolute risk of each event for each group, and hazard ratios and 95% confidence intervals were estimated by the Cox proportional hazards model. To indentify the baseline and clinical variables associated with the overall survival time, a multivariable analysis was performed using the Cox proportional hazard model with a stepwise selection procedure. The stepwise procedure was set at a threshold of 0.10 for inclusion and 0.05 for exclusion. In order to clarify the issues in multiple comparisons, the Bonferroni correction was applied to correct for the number of subgroup (3 groups) analyses; the significance level was adjusted to 0.016 (0.05/3). All statistical analyses were performed using the SPSS version 11.5 software program and the SAS software program (version 9.2 SAS Institute Inc).

Table 2. Comparison of Patient and Tumor Characteristics Between Those Receiving Surgical Treatment (n = 34) and Those Having Transarterial Chemoembolization (TACE, n = 50) in Patients with Hepatocellular Carcinoma with Vp3/4 or Vv3

Characteristic	Resection (n = 34)	TACE (n = 50)	p Value
Age, y, median (range)	60 (41–75)	60 (39–77)	0.69
Male sex	29 (85)	45 (90)	0.52
HBV/HCV/NBNC/HBHC, n	8/15/11/0	6/31/12/1	0.26
AFP > 10,000 ng/mL	12 (35)	16 (32)	0.82
ICGR15 >15%	14 (41)	35 (70)	0.013
Child-Pugh A	29 (85)	43 (86)	>0.9
Solitary tumor	16 (47)	6 (12)	0.001
Tumor size ≥ 10 cm	13 (38)	20 (40)	>0.9

Data are n (%) unless otherwise indicated.
AFP, alpha-fetoprotein; HBHC, both HBV and HCV positive; HBV, hepatitis B virus antigen positive; HCV, hepatitis C virus antibody positive; ICGR15, indocyanine green retention rate at 15 minutes; NBNC, non-B nor non-C; TACE, transarterial chemoembolization.

RESULTS

Patient characteristics and preoperative therapy

Characteristics of the patients are shown in Table 2. A total of 34 patients who had HCC with a tumor thrombus (Vp4/3, Vv3) and underwent hepatic resection were identified; 29 (85%) were men and 5 were women. The median age was 60 years old (range 41to 75 years old). Alpha-fetoprotein levels greater than 10,000 ng/mL were seen in 12 (35%) patients. A tumor diameter greater than 10 cm was seen in 13 (38%) patients. Sixteen (47%) patients had a solitary tumor. Twenty-nine (85%) patients were classified as having Child-Pugh A status.

Preoperative TACE was performed in 15 patients. The therapeutic effect (TE) of TACE was classified by the percentile ratio of tumor reduction or necrosis by an enhanced abdominal CT or pathologic examination, as detailed in Table 3. Six patients were identified as having tumor reduction or necrosis of 50% or more after TACE (TE3). The other 9 patients were identified as being TE2. The Vv3 tumor thrombus had decreased in size at the confluence of the inferior vena cava and hepatic vein after treatment with preoperative TACE in 2 patients.

Surgical outcomes and complications

An anatomic liver resection was performed in all 34 patients. Major liver resection (≥3 Couinaud's segments) was performed in 25 (74%) patients. Minor liver resection was performed in 9 patients, including sectionectomy in 5 patients and segmentectomy in 4 patients (Table 3). The median operative time was 355 minutes (range 225 to 561