Received: 7 November 2015 | Accepted: 10 March 2016
DOI: 10.1002/jgf2.19

REVIEW ARTICLE

Journal of General and Family Medicine WILEY

Radiotherapy for liver cancer

Nobuyoshi Fukumitsu MD | Toshiyuki Okumura MD | Hideyuki Sakurai MD

Proton Medical Research Center, University of Tsukuba, Tsukuba, Japan

Correspondence
Nobuyoshi Fukumitsu, Proton Medical Research Center, University of Tsukuba, Tsukuba, Japan.
Email: fukumitsun@yahoo.co.jp

Abstract

In recent years, radiotherapy for liver cancer has accomplished much technical progress. The history of radiotherapy for liver cancer shows an endeavor to overcome the problem of how to raise the irradiation dose to lesions while suppressing the unnecessary irradiation dose to normal liver tissue. With the appearance of treatment using X-ray radiotherapy represented by three-dimensional conformal radiotherapy, stereotactic body radiotherapy and particle beam therapy using proton beams and carbon ion beams, radiotherapy has become a safe and effective treatment option for liver cancers.

KEYWORDS
liver cancer, particle beam therapy, radiotherapy, stereotactic body radiotherapy, three-dimensional conformal radiotherapy

1 | INTRODUCTION

Accurate localized diagnosis of liver cancers was difficult until the 1970s, and there was no curative radiotherapy technique to treat liver cancers while suppressing damage to the liver, which is relatively radiosensitive. However, as computed tomography became widespread for treatment planning in the 1980s, the localized diagnosis of lesions became easy; therefore, treatment could be performed while reducing liver damage. Radiotherapy is now recognized to be one of the primary effective tools for this local treatment. Here we outline contemporary liver cancer radiotherapy.

2 | THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY

Radiation used in three-dimensional conformal radiotherapy (3D-CRT) is usually X-rays. The device used in X-ray radiotherapy is called a linear accelerator. Radiation is beamed from a direction perpendicular to the body axis in most cases; however, it can be delivered from other directions in 3D-CRT. One advantage of 3D-CRT is that it means the shape of the irradiation field can be set three dimensionally enabling delivery of enough radiation to the target, condensing radiation to the target, while suppressing the irradiation dose to important tissue around the tumor. Technically, X-rays can be delivered from a fixed source in multiple directions or from a source that turns in a circle.

Often, 3D-CRT is used in cases when other treatments are not available due to portal vein tumor thrombosis (PVTT), unresectability, or some complications. A total irradiation dose around 45-50 Gy at a daily dose of 2 Gy is often reported. Figure 1 shows an axial and sagittal dose distribution image of a patient who receives radiation from four fixed ports.

There have been many prospective studies in which the response rate was 30%-80% and the 1 year survival rate was 25%-50% for PVTT or for inferior vena cava thrombosis (IVCT) patients.[1-4] Prospective and retrospective studies of unresectable cases have shown that the survival of patients who received transarterial chemoembolization (TACE) with radiotherapy was longer than patients who received only TACE, and a meta-analysis study also proved higher response and survival rates in the TACE-with-radiotherapy group.[5]

As for adverse effects, it has been reported that radiotherapy can be performed safely, with only elevation of the total bilirubin value in many cases.[5]

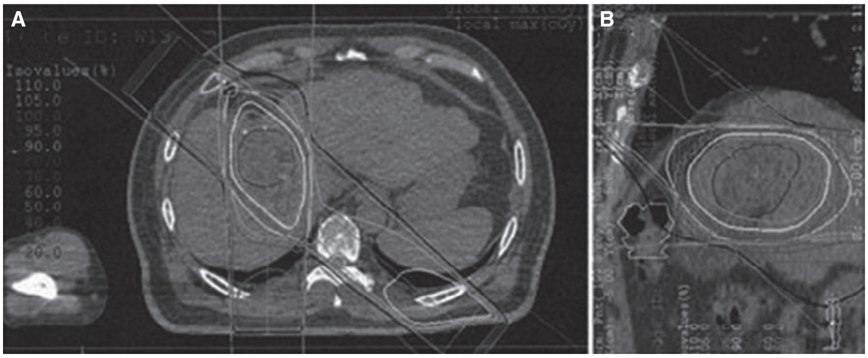

FIGURE 1 A dose distribution image of 3DCRT. (A) axial image, (B) coronal image. Isodose lines represent 95%-10% of the isocenter dose from inside to outside

3 | STEREOTACTIC BODY RADIOTHERAPY

Stereotactic body radiotherapy (SBRT) is the relatively new radiotherapy technique that has been developed since the 1990s. It aims to improve the local control of small tumors in the body trunk by centralizing radiation three dimensionally and reducing damage to the surrounding organs: It includes techniques to condense radiation and to hit the target accurately. Specifically, it meets three criteria: (i) higher dose to be delivered to a small target in a short term from multiple directions using a linear accelerator, (ii) geometrical accuracy finer than 5 mm in every treatment session, and (iii) immobilizing the patient in position and countermeasures for respiratory movement. Figure 2 shows a shell for human trunk fixation and the highly accurate position matching system. Figure 3 shows the highly precise positioning collation system. They are representative tools and systems of SBRT.

National medical insurance in Japan as of 2015 covers "primary liver cancer with a diameter <5 cm without metastasis lesions," and there are many reports of a total dose of radioactivity around 30-50 Gy at a daily dose of 6-15 Gy.

Even when the lesions treated are difficult to cure by other local treatment, relatively good outcomes are reported, such as a response rate of 50%-85%, 1 year local control rate of 65%-100%, 1 year overall survival rate 50%-90%, and 2 year local control rate of 90%-95%.[6-10]

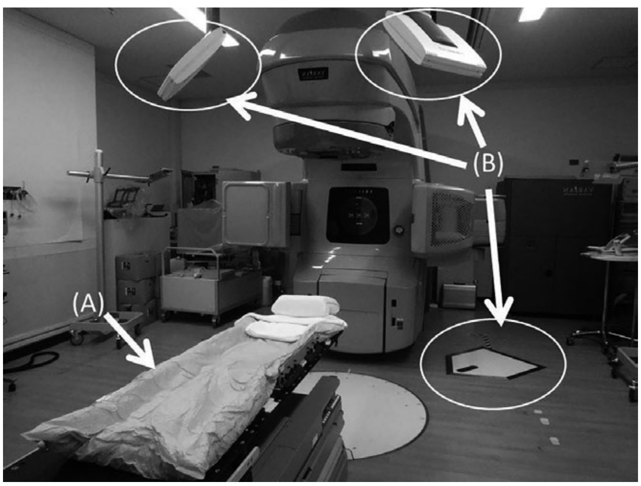

FIGURE 2 (A) A shell for human trunk fixation, (B) position matching system

Serious liver damage from the technique is very rare, and it is considered that SBRT can be performed safely on patients fitting Child-Pugh classification A or B.

4 | PARTICLE BEAM THERAPY

Particle beam therapy uses irradiation by high-energy protons, proton beam therapy, or by high-energy carbon ions, carbon ion beam therapy, produced by a synchrotron or cyclotron accelerator. Figure 4 shows a synchrotron accelerator. As X-rays go deeper into the body, the relative dose of radioactivity gradually decreases. In contrast, accelerated charged protons and carbon ions release their maximum energy just before they stop, creating a steep peak of energy called the Bragg peak. Furthermore, regulating the dose distribution in the depth direction can be accomplished by mixing different energy beams together, called the spread-out Bragg peak. Figure 5 shows the concepts of X-rays and particle beams. This principle enables irradiation to the lesions uniformly and simultaneously, while suppressing the irradiation dose to the surrounding normal tissue. The dose distribution is superior to X-ray therapy in both proton and carbon ion beam therapy; the main differences between them are that irradiation from any direction is possible in proton beam therapy and that carbon ion beam therapy has more biologic effect.

Although the indication for treatment is similar to X-ray radiotherapy, liver cancer that is hard to cure by other local treatments such as PVTT, IVCT, and huge tumors can be treated with particle beam therapy. When the irradiation dose is written in Gy equivalent (GyE), because the biologic effects of the particle beams are different from X-rays, there are many reports of a total dose of radioactivity 60-70 GyE at a daily dose of 2-6 GyE for proton beam therapy. Dose escalation studies of carbon ion beam therapy from 49.5 to 79.5 GyE reveal that a total dose of 72 GyE at a daily dose of 4.8 GyE is ideal,[11] and short-term treatment protocols, such as approximately 50 GyE in 1-2 weeks, are also carried out. Figure 6 shows a dose distribution image of the proton beam therapy of a patient with PVTT. The outermost line shows 10% of prescription doses and almost none of the normal liver is irradiated, as can be seen.

Many previous studies treated patients in Child-Pugh classification A or B whom it was difficult to give other local treatment.[12-15] A local control rate of more than 80% is reported in some

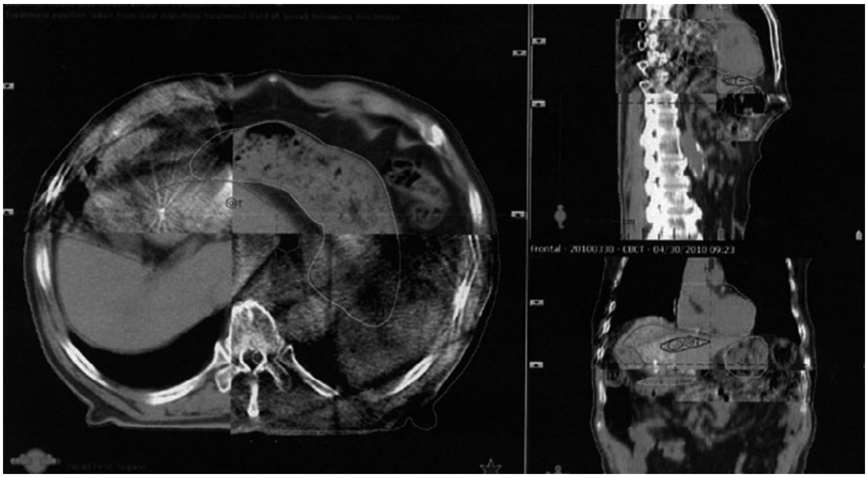

FIGURE 3 Positioning collation system. Planning computed tomography (CT) and onboard imaging CT can be compared

FIGURE 4 A synchrotron accelerator

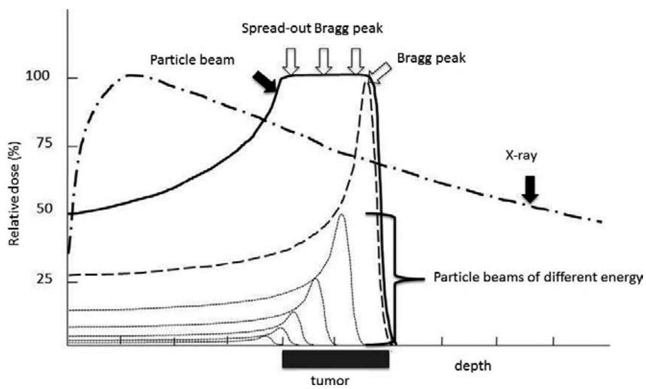

FIGURE 5 Relative dose and depth (comparison of X-rays and particle beams)

of the prospective studies of proton and carbon ion beam therapy. Adverse effects of radiotherapy are a concern in cases where lesions are close to the porta hepatis or gastrointestinal tract; however, proton beam therapy is effective for these lesions because dose distribution can be regulated. A example, though from our own research, is that we compared the prognosis of 266 patients treated in three protocols by the tumor location (i) 66 GyE with 10 fractions to the peripheral site; (ii) 72.6 GyE with 22 fractions close to the porta hepatis; and (iii) 77 GyE with 35 fractions close to the gastrointestinal tract, and concluded that local control rate is 98% (1 year), 87% (3 years), 81% (5 years) in total and these are not so different in each protocol.[16]

In addition, approximately 70 GyE irradiation can be carried out for PVTT, IVCT, or a huge tumor relatively easily using the physical advantage of the dose concentricity of particle beam therapy.[17,18] Good treatment effect is shown with these tumors; thus, particle beam therapy is one of the effective treatment options for less controllable lesions.

Adverse effects are extremely rare. Patients of Child-Pugh classification A or B are treated in many facilities, and reduction in liver function is within an almost negligible range in most of the cases.

As of 2015, particle beam therapy can be performed at 13 facilities in Japan. The treatment is offered as advanced medical treatment (not covered by national health insurance) in all those facilities, and the treatment cost is approximately 2 500 000–3 000 000 yen.

5 | TREATMENT TO DISTAL METASTASIS

There are few reports on the treatment of distant metastasis of only liver cancer; thus, we present an outline of the treatment of distant metastasis without identifying the original tumor.

Pain reduction rate in radiotherapy for bone metastasis is as high as 50%-90%, and the treatment in the short term is standard for the pain relaxation. Moreover, ^{89}Sr was approved for national medical insurance in Japan in 2007 as a pain reduction radiopharmaceutical for bone metastasis.

As for brain metastasis, local control is conducted by boosting stereotactic radiation in whole brain irradiation. There is an extension of the survival period in patients whose relatively long-term prognosis is good.

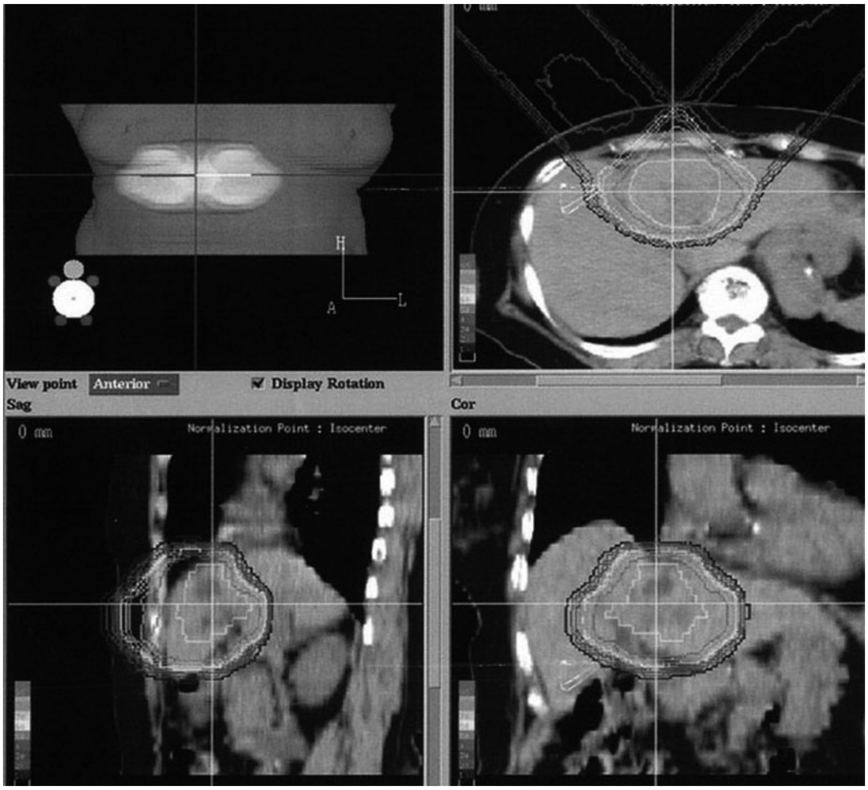

FIGURE 6 A dose distribution image of the proton beam therapy. Isodose lines represent 95%-10% of the isocenter dose from inside to outside

6 | CONCLUSION

Radiotherapy for liver cancer used to have many technical problems that were hard to overcome, and it was only considered for palliative treatment due to the low tolerable dose for normal liver tissue. However, now we can provide treatment for local control with little invasion due to technical progress such as the improvement of imaging, three-dimensional treatment planning, reproducible irradiation technique, and precise management of the irradiation treatment system. In fact, there is an increasing tendency for patients who come to hospital to ask for SBRT and particle beam therapy even though surgery or other local treatment is available.

On the other hand, despite a history well over 20 years of radiotherapy for liver cancer, there is still no consensus about indications for treatment nor about methods, not to mention effects and safety. Although there are many reports about effectiveness and safety, they do not refer to evidence-rich data for deciding the criteria for radiotherapy. More evidence-rich data are required in order to popularize radiotherapy for liver cancer to help these patients in future.

One of the problems has been the limited number of facilities offering particle beam therapy; however, the number of treatment facilities is gradually tending to increase in recent years in Japan, and more facilities are under construction or planned as of 2015. As an advanced country in the field of particle beam therapy, second in the world for number of treatment facilities, Japan has acquired the distinction along with the USA, which has the most facilities, of leading the world in this field. Particle beam therapy is currently performed in Japan as advanced medical treatment not covered by Japanese national medical insurance, but that insurance is expected to cover it in the near future.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. Shirai S, Sato M, Suwa K, et al. Feasibility and efficacy of single photon emission computed tomography-based three-dimensional conformal radiotherapy for hepatocellular carcinoma 8 cm or more with portal vein tumor thrombus in combination with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys. 2010;76:1037–44.
2. Lin CS, Jen YM, Chiu SY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. Jpn J Clin Oncol. 2006;36:212–7.
3. Ishikura S, Ogino T, Furuse J, et al. Radiotherapy after transcatheter arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Clin Oncol. 2002;25:189–93.
4. Huang CJ, Lian SL, Chen SC, et al. External beam radiation therapy for inoperable hepatocellular carcinoma with portal vein thrombosis. Kaohsiung J Med Sci. 2001;17:610–4.
5. Meng MB, Cui YL, Lu Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2009;92:184–94.
6. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26:657–64.

7. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys. 2010;78:486–93.
8. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011;81:e447–53.
9. Louis C, Dewas S, Mirabel X, et al. Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results. Technol Cancer Res Treat. 2010;9:479–87.
10. Choi BO, Jang HS, Kang KM, et al. Fractionated stereotactic radiotherapy in patients with primary hepatocellular carcinoma. Jpn J Clin Oncol. 2006;36:154–8.
11. Kato H, Tsujii H, Miyamoto T, et al. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. Int J Radiat Oncol Biol Phys. 2004;59:1468–76.
12. Kawashima M, Furuse J, Nishio T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol. 2005;23:1839–46.
13. Bush DA, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer. 2011;117:3053–9.
14. Imada H, Kato H, Yasuda S, et al. Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis. Radiother Oncol. 2010;96:231–5.
15. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2009;74:831–6.
16. Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. Int J Radiat Oncol Biol Phys. 2011;81:1039–45.
17. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. Cancer. 2011;117:4890–904.
18. Sugahara S, Oshiro Y, Nakayama H, et al. Proton beam therapy for large hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2010;76:460–6.

How to cite this article: Fukumitsu N, Okumura T, Sakurai H. Radiotherapy for liver cancer. *J Gen Fam Med*. 2017;18: 126–130. https://doi.org/10.1002/jgf2.19