Chapter 7　Radiation Therapy

- **Introduction**

Three-dimensional (3D) conformal radiation therapy planned according to computed tomography (CT) was not widely used until the 1970s, and until this time, radiotherapy was rarely performed to treat hepatocellular carcinoma (HCC). In the past, accurate localization of intrahepatic tumors was difficult because of the configuration of radiation therapy rooms. Furthermore, because the liver is comparatively sensitive to radiation, improving antitumor effects resulted in a high risk of liver damage. Because 3D conformal radiation therapy has grown in popularity, the volume of normal liver tissue unnecessarily exposed to radiation has decreased. It is now possible to quantitatively evaluate and predict the risk of liver damage using dose–volume histograms (DVHs). In addition, the range of 3D conformal radiation therapy is not limited to particular areas of the liver; therefore, since the 1980s, radiotherapy has been performed primarily in patients with portal vein tumor thrombosis or those experiencing difficulty with other treatment options.

At present, stereotactic body radiation therapy and particle radiation therapy have emerged as techniques that are far superior to 3D conformal radiation therapy in terms of dose concentration, and their potential use in local, early-stage therapies is being investigated. Nevertheless, there are few reports with a high level of evidence that can help determine the criteria for radiotherapy, including particle radiation, and comparisons with other local therapies in randomized controlled trials (RCTs) will be difficult to perform. Furthermore, the history of radiotherapy for HCC is still quite recent at just over 20 years; therefore, a satisfactory consensus has not been reached for treatment criteria and methods, and certainly not for therapeutic effects and safety. On the other hand, the number of patients who are indicated for surgery but request to be examined for stereotactic body radiation therapy or particle radiation therapy is gradually increasing.

In this revised edition, in view of such status quo, a CQ pertaining to stereotactic body radiation therapy and particle radiation therapy [proton radiation therapy, heavy particle (carbon ion)

radiation therapy] has been newly added in addition to those pertaining to 3D conformal radiation therapy and distant metastases carried over from the previous edition (2009 edition). Furthermore, the various options for radiotherapy are discussed along with supporting evidence.

CQ48　Is three-dimentional (3D) conformal radiation therapy useful for HCC?

Recommendation

3D conformal radiation therapy can be considered for patients with portal vein tumor thrombus or unresectable tumors who are contraindicated for other standard treatment methods because of complications or other reasons **(Grade C1)**.

There is insufficient scientific evidence to support the extension of survival duration by radiotherapy alone. However, survival duration is expected to increase in unresectable cases if radiotherapy is combined with TACE **(Grade C1)**.

Furthermore, there are no evidence-based recommendations regarding total radiation dose, fractionation regimens used in radiation therapy, or liver function criteria for treatment.

- **Scientific Statement**

There were no reports that examined radiation therapy for HCC; therefore, we began by examining documents regarding HCC patient selection criteria for 3D conformal radiation therapy. The selection criteria used in these reports were classified into two groups. One group included reports studying patients with portal vein tumor thrombus or inferior vena cava tumor thrombus, and the other group consisted of reports studying patients with unresectable disease. The latter group also included patients with unresectable HCC because of tumor thrombus in blood vessels. Patient inclusion criteria such as the extent of HCC progression, hepatic function, and the presence or absence of concomitant therapies varied among reports. Furthermore, fractionation regimens for radiation therapy and total radiation also differed among reports. Eight reports of prospective

studies examining treatment outcomes in patients with portal vein thrombus or inferior vena cava thrombus demonstrated response rates ranging from 30% to 80.5% and 1-year survival rates ranging from 25% to 47.4% (LF10584[1] Level 4, LF10824[2] Level 4, LF11100[3] Level 4, LF11708[4] Level 4, L3F00409[5] Level 4, L3F00966[6] Level 2b, L3F01012[7] Level 4, L3F01013[8] Level 4). Some reports concluded that survival rates were significantly improved in patients who responded to treatment compared with those in nonresponders (LF10824[2] Level 4, L3F00409[5] Level 4, L3F01013[8] Level 4, LF11402[9] Level 4, LF11707[10] Level 4). However, according to a few reports, patients withdrew from studies because they were unable to continue scheduled treatments because of general deterioration of health (LF11707[10] Level 4, LF11100[3] Level 4). Although tumor size and deteriorating health were documented as reasons for withdrawal, the possible impact of adverse events due to radiotherapy cannot be ruled out. Nevertheless, all these reports and previously included reports have concluded that radiation therapy can be administered safely.

The role of radiotherapy has not been directly demonstrated in any reported RCT, although multiple prospective and retrospective studies have suggested that prognosis is improved when radiotherapy is used with transcatheter arterial chemoembolization (TACE). A meta-analysis performed by Meng et al. evaluated the efficacy and safety of TACE + radiotherapy for unresectable HCC (L3F00985[11] Level 2a). A total of 1,476 patients were studied in five RCTs and 12 comparative clinical trials, and the results showed that response rates and 1-, 2-, 3-, and 5-year survival rates were significantly higher with TACE + radiotherapy patients than with TACE monotherapy patients. In terms of adverse events, elevated total bilirubin levels were observed with a significantly high frequency in patients treated with TACE + radiotherapy compared with those in patients treated with TACE alone; however, the incidence of nausea and vomiting, leukopenia, and increased alanine aminotransferase (ALT) levels was not significantly different. These results must be interpreted carefully, however, because the meta-analysis included a large number of nonrandomized trials.

Moreover, the total radiation dose was determined to be a prognostic factor for survival according to reports examining radiotherapy combined with arterial infusion chemotherapy (LF10649[12] Level 4, LF11384[13] Level 4), radiotherapy combined with TACE therapy (LF11178[14] Level 4, L3F00132[15] Level 5, LF11032[16] Level 5), and radiation therapy alone (LF11101[17] Level 4, L3F01010[18] Level 5, L3F01014[19] Level 5, L3F01023[20] Level 5). Reports of treatment using radiotherapy alone in patients with portal vein thrombus or inoperable disease have also shown that prognosis is dependent on radiation dose (LF11707[10] Level 4, LF11354[21] Level 4, LF10822[22] Level 4). However, the two studies examining radiotherapy combined with arterial infusion chemotherapy (LF10649[12] Level 4, LF11384[13] Level 4) included cases of intrahepatic cholangiocarcinoma and liver metastases from colon cancer. Therefore, the data must be interpreted with care because it has not been determined whether the results can be applied to HCC. On the basis of the findings described above, it appears that TACE combined with radiotherapy may improve the prognosis to a greater extent than TACE alone.

- **Explanation**

There were only a few reports with a high level of evidence, and the majority included noncontrolled, phase I/II level prospective studies or retrospective studies. In recent years, technological advances in intensive radiation therapy have facilitated liver irradiation, which had not been performed conventionally, and it is now believed that radiotherapy can be performed relatively safely if patients are properly selected for treatment. It is commonly acknowledged that liver irradiation may be risky in patients with severely impaired liver function. However, additional data on long-term outcomes is required because data on selection criteria and treatment safety as well as the torelable of radiation dose of the liver is currently insufficient.

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CQ49 Is stereotactic body radiation therapy useful for HCC?

Recommendation

Stereotactic body radiation therapy can be considered for cases of HCC that are not indicated for other local therapies (no metastatic lesions, diameter ≤ 5 cm). However, there is insufficient scientific evidence to conclude that stereotactic body radiation therapy extends survival duration

(Grade C1).

Moreover, there are no scientific evidence-based recommendations regarding total radiation dose, fractionation regimens used in radiation therapy, or liver function criteria for treatment.

- **Scientific Statement**

There are no relevant RCTs or other reports providing high-level evidence, and there are no reported criteria for administering stereotactic body radiation therapy. For these reasons, we examined the significance of phase I/II level prospective studies and retrospective studies that reported the results of stereotactic body radiation therapy for HCC.

In most of the reports, therapy was indicated for patients in whom other procedures or local therapies were difficult to perform. In terms of liver function, several phase I studies were limited to patients with Child–Pugh class A disease (L3F01010[1)] Level 4, L3F01027[2)] Level 2b, L3F00946[3)] Level 2b), whereas other phase I/II studies and retrospective studies did treat patients with Child–Pugh class A or class B disease (L3F01083[4)] Level 2b, L3F01097[5)] Level 4, LF11470[6)] Level 4, L3F00970[7)] Level 4, L3F00112[8)] Level 4, L3F00015[9)] Level 4, L3F00118[10)] Level 4). In the early studies, the incidence of adverse events was high in several reports; however, recent studies using normal liver dose constraints found that the incidence of serious radiation-induced liver damage is relatively low. Because there is some variation among reports in terms of radiation dose and dose constraint criteria for the normal liver, scientific evidence supporting the recommendation of fractionation regimens for radiotherapy, radiation doses, or liver function criteria is insufficient.

Treatment outcomes were reported as follows: a response rate of 49%–86%, a 1-year local control rate of 65%–100%, and a 1-year survival rate of 51%–92.2% (L3F01010[1)] Level 4, L3F01027[2)] Level 2b, L3F00946[3)] Level 2b, L3F01083[4)] Level 2b, L3F01097[5)] Level 4, LF11470[6)] Level 4, L3F00970[7)] Level 4, L3F00112[8)] Level 4, L3F00015[9)] Level 4, L3F00118[10)] Level 4). Because none of the studies used control groups, it was difficult to demonstrate with scientific evidence

whether stereotactic body radiation therapy extended survival time. However, their results showed that some of the outcomes were favorable, with a 2-year local control rate of 90%–95% (L3F01083[4] Level 2b, L3F01097[5] Level 4) and a 3-year survival rate of 42.1%–58.6% (L3F00970[7] Level 4, L3F00112[8] Level 4). Stereotactic body radiation therapy is therefore worth considering for patients who cannot be treated with other local therapies.

- **Explanation**

Stereotactic body radiation therapy was introduced in the 1990s and is a relatively new radiotherapy technique that administers high radiation doses to the tumor that can result in local control. However, the long-term treatment outcomes have not been clearly determined. At present, the techniques and equipment used in stereotactic body radiation therapy differ among institutions, and patient selection criteria also vary among institutions. It is therefore challenging to establish guidelines with scientific evidence for radiotherapy fractionation regimens, total radiation doses, and liver function treatment criteria. According to the abovementioned reports, however, there is a general growing acceptance that stereotactic body radiation therapy can be performed rather safely in patients with Child–Pugh class A or B disease if the proper dose constraints are maintained. Moreover, as of 2013, the National Health Insurance will cover stereotactic body radiation therapy for the treatment of HCC as "primary liver cancer with a primary lesion diameter of 5 cm or less, with no metastasis" in Japan. For HCC patients who do not meet the criteria, 3D conformal radiation therapy or particle radiation therapy can be considered as discussed in CQ48.

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CQ50　Is particle radiation therapy [proton therapy, heavy particle (carbon ion) radiation therapy] useful against HCC?

Recommendation

Particle radiation therapy [proton radiation therapy, heavy particle (carbon ion) radiation therapy] can be considered for HCC that is difficult to treat with other local therapies. Particular consideration may be given to therapeutically intractable tumors such as those with portal vein or inferior vena cava tumor thrombus and large lesions **(Grade C1)**.

- **Scientific Statement**

No RCTs have compared the current standard treatment for HCC against particle radiation therapy. Therefore, the significance of particle radiation therapy was investigated on the basis of the results of phase I/II level prospective studies and retrospective studies on particle radiation therapy for HCC.

The majority of reports enrolled patients who could not undergo other local therapies and had with Child–Pugh class A or B liver disease. The efficacy of proton therapy and heavy particle (carbon ion) radiation therapy was reported in two retrospective studies for each therapy, and the local control rates were favorable at 80% or higher (LF10646[1)] Level 2b, L3F00926[2)] Level 2b, LF11353[3)] Level 2b, L3F00955[4)] Level 2b). The incidence of adverse events was extremely low in these studies, and particle radiation therapy was deemed safe to perform. Although the radiation dose used in particle radiation therapy was generally high compared to x-ray radiation therapy, doses varied among reports; therefore, there is no recommendable fixed total radiation dose or fractionation regimen for radiotherapy with scientific evidence.

HCC lesions can be located adjacent to the hepatic portal area or the gastrointestinal tract, making radiation-induced adverse events a concern. It has been reported, however, that proton therapy can be effective against lesions in these regions by controlling the radiation dose and irradiation range

(L3F01072[5] Level 4, L3F00992[6] Level 4, L3F00991[7] Level 4, L3F00943[8] Level 4, L3F00987[9] Level 2b). Furthermore, favorable treatment outcomes have been demonstrated for giant HCC and tumors with portal vein or inferior vena cava thrombus (L3F01062[10] Level 4, L3F01018[11] Level 4, L3F01052[12] Level 4, L3F01019[13] Level 4). Although these studies were all based on retrospective analyses, particle radiation therapy is expected to play a definite role in HCC treatment and can be considered for patients who are not good candidates for other therapies.

- **Explanation**

Particle radiation therapy for HCC was introduced in the 1980s. In particle radiation therapy, there is a steep energy peak known as the Bragg peak that can increase the radiation dose to the lesion without increasing the dose to the normal liver, unlike X-ray radiotherapy. As particle radiation has gained in popularity in recent years, prospective studies have also reported favorable results. This is a promising treatment for HCC patients who are elderly or have portal vein tumor thrombus or giant tumors; however, certain limitations do exist, such as the limited number of facilities that can provide particle radiation therapy and the current status of this therapy as advanced medical care.

Although high-level evidence studies examining the outcomes of particle radiation therapy are still required, particle radiation therapy for HCC is generally effective and can be performed safely. It is also a possible treatment option for patients who cannot be treated with other treatment methods.

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CQ51 Is radiation therapy indicated for distant metastases from HCC?

Recommendation

Radiotherapy is generally effective in alleviating pain due to bone metastases and is a recommended therapy for HCC **(Grade B)**.

In order to extend the survival duration in patients with brain metastases, an appropriate combination of whole-brain irradiation and stereotactic radiation therapy or treatment with either method is recommended. **(Grade B)**

- **Scientific Statement**

There are no clinical studies with high-level evidence that examined distant metastases from only HCC. Therefore, we used currently available data collected from search results as high-level evidence, without the primary organ of origin specified.

The rate of pain relief achieved with radiotherapy in patients with painful bone metastases is high at 50%–90% (LF11732[1)] Level 1a, LF11721[2)] Level 1a), and although no RCTs have directly compared radiotherapy with no treatment, therapy is currently administered as a standard

treatment to alleviate pain. The Radiation Therapy Oncology Group compared dose fractionation regimens and conducted a multicenter cooperative study in which four types of fractionation schemes were tested. Solitary metastatic tumors were treated with 40.5 Gy/3 weeks and 20 Gy/1 week, and multiple metastases were treated with 15 Gy/1 week–30 Gy/2 weeks. The partial pain relief rates were 85% and 82% for solitary metastasis and 78%–87% for multiple metastases; therefore, different fractionation regimens did not result in a significant difference in pain relief rate. Furthermore, no significant difference was observed between groups in time to pain relief and the duration of pain relief (LF11730[3] Level 1b). On the basis of these results, low-dose short-term therapies seem to be effective as long-term therapy. A meta-analysis also supported this conclusion (LF11732[1] Level 1a); therefore, when the objective is pain relief, a single fraction of radiotherapy seems sufficient. However, the single fraction group was associated with a high rate of repeated treatments; therefore, fractionated radiotherapy should also be investigated. However, the guidelines established by the American Society for Radiation Oncology state that fractionation makes no difference in the efficacy of pain relief; therefore, single fraction radiotherapy should be proactively considered (L3F01205[4]).

In an ECOG RCT conducted by Horton et al. in 1971, it was demonstrated that whole-brain irradiation extended survival time and improved the general condition of patients with brain metastasis (LF11745[5] Level 1b). RCTs that compare frequently used fractionation schemes for whole brain irradiation, such as 20 Gy/1 week, 30 Gy/2 weeks, and 40 Gy/4 weeks, are being reported. None of the reports has identified the most effective dose fractionation scheme by the indicators of the survival duration, symptom improvement rate, or duration of general condition. There have also been advancements in stereotactic radiosurgery techniques, resulting in the widespread implementation of the procedure. Kondziolka et al. demonstrated that the control rate for intracranial lesions was significantly increased, but the survival duration was not significantly improved when patients with 2–4 brain metastatic lesions and a maximum diameter of 2.5 cm or less were treated with stereotactic radiosurgery in addition to whole-brain irradiation, which was a

standard therapy, in an RCT performed at a single institution (LF11746[6] Level 1b). In addition, Andrews et al. performed a multicenter cooperative RCT to determine the significance of adding stereotactic radiosurgery to whole-brain irradiation in patients with 1–3 brain metastatic lesions with a maximum diameter of 4 cm or less, demonstrating that patients with single lesions survived longer if treated with stereotactic radiosurgery (LF11734[7] Level 1b). Furthermore, a meta-analysis of these two RCTs has shown that adding stereotactic radiosurgery to whole-brain irradiation preserves the general condition of the patient, improves local control, and extends the overall survival duration in patients with single brain metastasis who are recursive partitioning analysis (RPA) class I patients [patients who satisfy all of the following: Karnofsky performance status (KPS) of 70 or higher, primary lesion control, age less than 65 years old, and no extracranial metastasis] (L3F01231[8] Level 1a). On the other hand, the JROSG99-1 RCT was examining whether the omission of whole-brain irradiation and the administration of stereotactic body radiation therapy alone could be an appropriate treatment option for patients with a small number of metastatic lesions in the brain (LF11735[9] Level 1b). Omission of whole-brain irradiation did not decrease the survival duration in patients with 1–4 brain metastatic lesions; however, a combination treatment with whole-brain irradiation was found to significantly decrease the intracranial recurrence rate. The above reports support the use of stereotactic radiosurgery alone as a treatment option for patients with 4 or fewer lesions, although whole-brain irradiation is still considered an important standard therapy at this time.

Although HCC patients were rarely involved in these reports, Gaspar et al. set guidelines based on a systematic review. Data were extremely limited, yet they found that treatment outcomes of whole-brain irradiation may differ according to the type of tumor histopathology and concluded that the use of different dose-fractionation schedules based on histopathology could not be supported (L3F01165[10]). There is no solid basis to determine whether the treatment outcome for HCC would be different from that for primary cancer of other organs or other pathological type. Therefore, treatment plans should be designed on the basis of the evidence obtained in the above reports.

- **Explanation**

The critical points regarding treatment of distant metastases are alleviation and prevention of tumor symptoms. In particular, because tumor control in patients with brain metastases is directly connected to survival, it is extremely important to select an appropriate treatment plan. A large number of RCTs have studied radiotherapy for bone and brain metastases without the primary organ of origin specified, and their results have generally been consistent. In that respect, it can be said that ample evidence has been established in terms of treatment plans. However, as stated earlier, only a few studies have examined HCC patients with distant metastases, and there is limited evidence supporting the applicability of these findings to distant metastases from HCC. Caution is therefore required while applying the contents of this CQ to treatment.

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