Chapter 8:

Radiation Therapy

● Introduction

Radiotherapy was rarely performed for HCC until the 1970s when 2D planning with fluoroscopy was the main method of radiotherapy. The technology at the time was not accurate enough to identify intrahepatic tumors, so it was necessary to set a wide irradiation area to definitively capture the tumor. Together with the high-dose irradiation needed for curative therapy, there was high risk of ensuing liver failure.

In the 1980s, the introduction of CT-based 3D-CRT meant that the volume of the normal liver exposed to unnecessary irradiation could be reduced and it also allowed for quantitative measurement and prediction of radiation-induced liver toxicity on the dose-volume histogram. Because 3D-CRT also enabled intrahepatic tumors to be identified with precision, radiation therapy became the treatment modality of choice in difficult cases, such as patients with portal vein tumor thrombus with no clear indications for other treatment modalities. Even at that time though, it was difficult to achieve local cure by administering radiation therapy alone.

Technological advances in radiation oncology has enabled radiation doses to normal tissues to be reduced while focusing high-dose radiation at the tumor, through high-precision radiotherapy such as stereotactic body radiotherapy, particle therapy (proton therapy and heavy particle therapy), and intensity modulated radiation therapy (IMRT). These radiation therapies are used to treat various diseases and pathological conditions in Japan. Taking into account the balance between dose distribution and liver damage, HCC is treated mainly with stereotactic body radiotherapy and particle therapy, both of which aim to ahcieve local cure. In contrast, malignant tumors in other organs are now increasingly treated with IMRT. In principle, IMRT is a useful tool for reducing exposure of the digestive tract and normal liver tissue to unnecessary radiation. Its introduction in the clinical setting is expected, but currently its efficacy and safety in patients with HCC has not been fully elucidated.

For this fourth edition of the Guidelines, the literature search extracted a meta-analysis of conventional radiation therapy, stereotactic body radiotherapy, and particle therapy, which is cited for CQ50. However, the meta-analysis has several major problems; for example, (1) the analysis was performed on observational studies without any controls, (2) the conventional radiation therapy group contained patients receiving palliative care, and (3) some reported cases were duplicated. This suggests that the findings will be difficult to review and intepret accurately, and as such the meta-analysis should not be used to grade the recommendation for individual CQs.

It may be appropriate to classify the radiation therapy used today for HCC treatment into ablative radiotherapy for achieving local cure, such as stereotactic body radiotherapy and particle therapy, and adjuvant radiation therapy for supporting surgery and TACE, such as 3D-CRT. From this perspective, the current Guidelines (fourth edition) uses the same CQs from the third edition (2013 version) that are related to stereotactic body radiotherapy, particle therapy (proton therapy and heavy

particle [carbon ion] therapy), and 3D-CRT. However, other articles are also cited to establish the position of 3D-CRT as adjuvant radiation therapy for other treatment modalities (mainly TACE) and to present various radiation therapy options as a whole. Also, the CQ related to bone and brain metastasis from the second edition continues to be used.

The major problem associated with systematic reviews of technology in radiation therapy is that articles vary in their definition of individual radiological techniques in 3D-CRT and stereotactic body radiotherapy, which requires careful attention. Overall, only a few articles provide high-quality evidence that can be used to evaluate the indications for radiation therapy, and there are few RCTs compared to the number for other locoregional therapies. Consequently, there is insufficient evidence about the eligibility criteria and dose fractionation used in radiation therapy for HCC. Nevertheless, an increasing number of patients are requesting stereotactic body radiotherapy and particle therapy for reasons of advanced age, fewer complications, and the minimally invasive nature of radiation therapy, suggesting that the demand for radiation therapy will continue to increase in the clinical setting.

CQ48 Is stereotactic body radiotherapy recommended for HCC?

Recommendation

Weak recommendation: Stereotactic body radiotherapy may be performed in HCCs that are not indications for other types of locoregional therapies and for recurrent HCCs after various locoregional therapies, including HCC unresponsive to TACE.

■ Background

Hepatectomy, transplantation, and percutaneous ablation are regarded as curative therapies for early-stage HCC, but even a small solitary HCC may not be an indication for them depending on the location of the tumor and estimated residual liver function after treatment. TACE is recommended for such cases, but even selective embolization often does not provide adequate local control.

Recent advances in computer sciences and technology have led to the development of stereotactic body radiotherapy. This modality delivers high-dose radiation per fraction to the tumor with pinpoint precision, and it safely provides high local control in a few fractions over a short period. Here, we investigated the outcome and role of stereotactic body radiotherapy in patients with HCC.

■ Scientific Statement

This CQ is a continuation of CQ49 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016

extracted 164 articles. This was narrowed down to 38 in the first screening based on article titles and abstracts. After the content was examined, prospective studies of stereotactic body radiotherapy as well as retrospective studies with large sample sizes were selected; studies involving different stages of HCC were excluded. As a result, the second screening extracted 13 articles, which did not, however, contain any studies or RCTs with high-quality evidence. Therefore, the clinical significance of stereotactic body radiotherapy in patients with HCC was reviewed from phase I or II prospective studies and retrospective studies. The content of articles cited in the third edition was also reviewed, but none provided new insights or additional data with high-quality evidence comparable to that provided by the 13 articles extracted here. Therefore, the current edition does not include the articles cited in the third edition.

Almost all of the studies involved stereotactic body radiotherapy for HCCs for which treatment with either surgery or percutaneous ablation was difficult. Cases unresponsive to TACE[1] and various cases of recurrence after locoregional therapy[2,3] were also the target of stereotactic body radiotherapy. Treatment method, clinical outcome, and the incidence of adverse events mostly depended on the size, number, and stage of tumor as well as liver function. Patients had Child-Pugh A/B liver function in many phase I/II clinical studies and retrospective studies[1-9].

Studies in patients with BCLC stage 0-B HCC[1-5,7-9] have shown that many institutions limit the radiation dose to the normal liver[1,2,5] and therefore the incidence of severe liver toxicity. However, one of the studies[5] also reported that low-dose volumes could potentially cause liver toxicity in patients with BCLC stage B HCC. In the study comparing RFA and stereotactic body radiotherapy in 2 groups of patients matched by propensity score[7], stereotactic body radiotherapy was associated with significantly better local control rates in patients with HCC > 2 cm, even though there was no significant intergroup difference in local control or overall survival rate. Comparison of treatment methods reveals inconsistency in terms of total radiation dose (27-60 Gy), number of fractions (3-10 times), prescription methods, and dose inhomogeneity in the target tumor, suggesting that a radiation therapy method that can be recommended has yet to be established. The 1-, 2-, and 3-year local control rates were 91-100%, 84-95%, and 92-96%, respectively, and the 1-, 2-, and 3-year survival rates were 74-100%, 46-87%, and 54-74%, respectively[1-5,7-10]. In the study by Kang et al., the 2-year local control rate in patients with HCC unresponsive to TACE was also as high as 95%[1]. Although overall survival rate depends on the patient characteristics in each study, in the study by Takeda et al., the 3-year survival rate was 73% in patients with primary solitary HCC[10]. Because neither of these studies used a control group, it is not possible to determine the beneficial effect of stereotactic body radiotherapy on survival based on the scientific evidence available; however, given the good outcomes such as the 3-year local control rate of > 90% and the 3-year survival rate of > 70%, stereotactic body radiotherapy may be a viable option for patients who are not suitable candidates for other locoregional therapies.

In studies involving mainly BCLC stage B/C HCC, patients underwent various treatments primarily because of differences in the size, number, and stage of their HCC and differences in their liver function[6,11-13]. In addition, inconsistency in total radiation dose (24-55 Gy) and the number of fractions (6-15 times) suggests the lack of a well-established radiation therapy method that can be recommended. One-year local control rate was 80-87%, 1-year overall survival rate was 49-50%, and median survival time was 8-17 months.

■ Explanation

Although there is insufficient scientific evidence to show that stereotactic body radiotherapy improves survival in HCC patients, it has a high local control rate comparable to that of surgery and RFA and higher than that of TACE. Although many of the patients who underwent stereotactic body radiotherapy in the cited studies were elderly and had recurrent HCC, the 3-year survival rate was favorable for small HCCs, at 54-74%. Because this treatment modality is relatively new, candidates are selected from patients who are not eligible for surgery and percutaneous ablation. It is also performed as salvage therapy for patients with recurrent tumor or residual tumor after RFA or TACE. Stereotactic body radiotherapy is a painless and bloodless treatment modality that safely treats tumors located at the porta hepatis or dome of the liver. It also safely treats tumors next to or infiltrating blood vessels or the bile duct and tumors that are not indications for percutaneous ablation. The outcome of stereotactic body radiotherapy is not affected by intratumoral blood flow. These unique features make the modality a valid treatment option for HCC.

The size and stage of HCC indicated for stereotactic body radiotherapy varies by geographic region, probably because the role of stereotactic body radiotherapy that supplements existing treatment modalities varies by geographic region. In countries like Japan, where the well-established screening system often detects HCCs in the early stage, many early-stage HCCs are treated with high-dose stereotactic body radiotherapy and the emphasis is on tumor control rather than on tolerance of the liver. In contrast, in the United States, Europe, and China, stereotactic body radiotherapy is performed for relatively advanced HCCs. Dose reduction is sometimes inevitable in the case of large tumors because of liver toxicity. Therefore, total dose and fraction number should be modified based on tumor size, liver volume, and hepatic functional reserve. Largely due to differences in the size, number, and stage of HCC and liver function, no studies to date have provided scientific evidence about specific dose fractionation methods, total dose, and liver function that may be recommended for stereotactic body radiotherapy. It should be noted that, as of 2017, only stereotactic body radiotherapy for primary HCC ≤ 5 cm without metastasis is covered by Japan's National Health Insurance system. When administering radiation therapy for HCC to which the above definition does not apply, particle therapy (CQ49) and 3D-CRT (CQ50) may be considered. During the meeting for finalizing recommendations, the General Affairs Committee unanimously

decided to grade the recommendation weak for stereotactic body radiotherapy.

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CQ49 Does particle therapy (proton therapy and heavy particle [carbon ion] therapy) effectively treat HCC?

Recommendation

Weak recommendation: Particle therapy (proton therapy and heavy particle [carbon ion] therapy) may be performed for HCCs that are not indicated for other types of locoregional therapies.

■ Background

Charged particle beams have finite ranges, and because dose concentration is one of the physicochemical properties, compared with X-rays, charged particles deliver higher doses of radiation while also preserving liver function. Because increasing numbers of institutions can now perform particle therapy, it is important to evaluate the utility of particle therapy as a novel locoregional therapy option for HCC.

■ Scientific Statement

This CQ is a continuation of CQ50 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 29 articles. This was narrowed down to 9 articles in the first and second screening based on the following inclusion criteria: RCTs or non-RCTs with experimental, placebo, and no-treatment (control) groups and recurrence-free survival or overall survival as the primary endpoint. Following comprehensive review of the 9 articles extracted here, the 13 articles from the third edition, and 1 review article[1] (the reason for inclusion is described later) so as to exclude duplicates, a total of 18 articles are cited for CQ49.

One of these articles describes a phase III RCT of proton therapy (70.2 Gy [relative biological effectiveness; RBE] in 15 fractions over 3 weeks) and the current standard therapy TACE in 69 patients who had a clinical or pathologic diagnosis of HCC and met either the Milan criteria or University of California San Francisco transplant criteria[2]. Interim analysis results showed a significantly higher 2-year local control rate in the proton therapy (88%) than in the TACE group (45%), even though there was no intergroup difference in the 2-year survival rate. Total days of hospitalization due to adverse events within 30 days of proton therapy or TACE was 24 and 166 days, respectively, indicating significantly fewer hospital days with proton therapy.

The literature search extracted 6 studies reporting the utility of proton therapy and and 2 prospective studies reporting the utility of heavy particle therapy. In these studies, proton therapy had a 2-year local control rate of 88-96%[2-4] and a 5-year local control rate of 87.8-90.2%[5,6]. For heavy particle therapy, the 3- and 5-year local control rates were 81% and 93%, respectively[6,7]. A phase I study of proton therapy demonstrated the dose-dependency of local effect: the complete

tumor disappearance rate significantly increased as the radiation dose increased from 60 Gy (RBE) in 20 fractions to 66 Gy (RBE) in 22 fractions and then 72Gy (RBE) in 24 fractions (p = 0.039)[8]. The overall survival rate after proton therapy was 59-66% at 2 years[2, 4], 33% at 3 years[9], and 38.7-42.3% at 5 years[5,8], while the 5-year survival rate after heavy particle therapy was 25-36.3%[6,7]. A single-center comparative study of proton therapy and heavy particle therapy reported no significant difference in local control rate or overall survival rate[6].

Particle therapy may cause adverse events when HCC is located near the porta hepatis or the digestive tract. A previous study, although observational in nature, that used different dose fractionation protocols in proton therapy showed no significant difference between different protocols in the local control rate or survival rate in patients with such lesions: proton therapy achieved a 3- and 5-year local control rate of 87% and 81%, respectively, and a 3- and 5-year overall survival rate of 61% and 48%, respectively[10]. Three studies of treatment outcomes in patients with various pathological conditions after proton therapy had a median survival rate in the range of 13.2 to 22 months in patients with HCC accompanied by portal vein tumor thrombus[11,12], and the 1-year recurrence-free survival rate was 64% in patients with giant HCC > 10 cm[13]. Although obtained retrospectively, these findings do suggest, with some degree of certainty, that proton therapy is beneficial in the treatment of HCC. Therefore, proton therapy may be used in patients who are not suitable candidates for other treatment modalities.

Particle therapy has an extremely low rate of adverse events and is performed safely in patients with HCC[3,4,7-9,14-16]. In addition, ICGR15 is an effective predictor of prognosis specifically in Child-Pugh A patients[17].

Table 3 shows the results of representative prospective and retrospective studies of particle therapy. Although Reference 1 is a review article, it is cited here under CQ48 as an exception because it contains data from prospective studies that were not published in original articles.

■ Explanation

Particle therapy has been used to treat HCC since the 1980s. In the early years, mainly retrospective observational studies reported effective local control with proton therapy, but prospective studies have also reported similar findings more recently. A recent RCT of proton therapy and TACE showed the efficacy and safety of proton therapy for HCC that was not a good candidate for locoregional therapies. However, proton therapy has not been compared with surgical resection, the standard locoregional therapy, or with other percutaneous ablation procedures, suggesting that more high-level studies are needed to establish the role of proton therapy as a locoregional therapy. Nonetheless, as suggested by the retrospective observational studies, proton therapy is probably a viable treatment option for giant HCC and HCC accompanied by portal vein tumor thrombus or inferior vena cava tumor thrombus. HCC is thought to respond similarly to proton therapy and heavy

particle therapy.

At present, particle therapy (proton therapy and heavy particle therapy) appears to be effective and safe for use in HCC and therefore may be a viable treatment option for HCCs that are difficult to treat with conventional locoregional therapies. The radiation dose administered is higher in proton therapy than that in X-ray radiotherapy, but because different doses were used in previous studies, there is no well-established dose fractionation method or total radiation dose backed by scientific evidence that can be recommended. As of 2017, particle therapy is an approved advanced medical treatment for localized HCC in Japan. During the meeting for finalizing recommendations, the General Affairs Committee unanimously decided on a weak recommendation for proton therapy.

Table 3. Primary outcomes of prospective and retrospective observational studies using particle therapy for HCC

	Study design	Patients (n)	Dose per fraction (f)	Local control rate	Survival	Late adverse events
Proton therapy						
Bush et al. (2016)[2]	RCT	33	70.2 Gy (RBE) / 15 f	88% (2 years)	MST 30 months, PFS 48% (2 years), OS 59% (2 years)	Severe adverse events were rare; 2 patients were admitted for liver failure
Bush et al. (2011)[15]	Phase II clinical study	76	63 Gy (RBE) / 15 f	60/76 (n)	Median PFS, 36 months	5 (of 76) patients had Grade 2 hematologic adverse events; none had significantly decreased liver function
Hong et al. (2016)[3]	Phase II clinical study	49	58.05-67.5 Gy (RBE) / 15 f	94.8% (2 years)	MST 49.9 months	4 patients had Grade 3 adverse events
Fukumitsu et al. (2009)[5]	Phase II clinical study	51	66 Gy (RBE) / 10 f	87.8% (5 years)	38.7% (5 years)	3 patients had rib fracture and 1 patient had Grade 3 radiation pneumonitis; 3 patients had improved CP class and 8 patients had worsened CP class
Kawashima	Phase II clinical	30	76 Gy (RBE) / 20	96% (2 years)	66% (2 years)	8 patients had liver failure;

et al. (2005)[4]	study		f			no incidence of liver failure in 9 patients with ICGR15 < 20%
Kim et al. (2015)[8]	Phase I clinical study	27	60 Gy (RBE) / 20 f-72 Gy (RBE) / 24 f	71.4-83.3% (3 years)	42.3% (5 years)	None had ≥ Grade 2 late adverse events; 4 patients had a decrease in CP score by 1 point and 1 patient had an increase in CP score by 1 point
Hong et al.(2014)[18]	Phase I clinical study	15	45-75 Gy (RBE) / 15 f	1 of 15 patients had recurrence at the margin	33% (3 years)	1 patient had Grade 1 gastrointestinal bleeding; 1 patient had Grade 5 gastrointestinal perforation
Lee et al. (2014)[11]	Retrospective study	27	50-66 Gy (RBE) / 20-22 f	9 of 27 patients had local recurrence	OS 33.3% (2 years) MST 13.2 months	None had ≥ Grade 3 late adverse events
Heavy particle therapy						
Kato et al. (2004)[7]	Phase I/II clinical study	24	49.5-79.5Gy (RBE) / 15f	81% (3 years)	25% (5 years)	None had severe liver damage; none had a decrease in CP score by ≥ 2 points
Tsujii et al. (2007)[1]	Phase I/II clinical study, phase II clinical study	82 44	48-70 Gy (RBE) / 4-12 f 52.8 Gy (RBE) / 4 f	87% (3 years) 95% (3 years)	26% (5 years) 35% (5 years)	(not listed) (not listed)
Proton and heavy particle therapy						
Komatsu et al. (2011)[6]	Retrospective study	242 101	Proton therapy: 52.8-84.0 Gy (RBE) / 4-38 f Heavy particle	Proton therapy: 90.2% (5 years) Heavy particle therapy: 93% (5 years)	Proton therapy: 38% (5 years) Heavy particle therapy: 36.3% (5 years)	Proton therapy: 8 patients had ≥ Grade 3 late adverse events Heavy particle therapy: 4 patients had ≥ G3 late

			therapy: 52.8-76.0 Gy (RBE) / 4-20 f			adverse events

MST, median survival time; PFS, progression free survival (rate/duration); OS, overall survival; CP, Child-Pugh

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CQ50 When is 3D-conformal radiotherapy recommended for HCC?

Recommendation

Weak recommendation: Three-dimensional CRT may be performed when stereotactic body radiotherapy and particle therapy are difficult to perform in patients who are not candidates for other standard treatments due to portal vein tumor thrombus, unresectable HCC, or internal complications.

■ Background

When administering radiation therapy for HCC, if all conditions are met, stereotactic body radiotherapy or particle therapy should be performed with radiation at doses high enough to achieve adequate local control. However, few medical institutions in Japan are equipped for stereotactic body radiotherapy or particle therapy, and therefore 3D-CRT, which is performed relatively widely, is indicated instead. The radiation dose administered in 3D-CRT is often not enough to yield curative outcomes. Here, we investigated the role of radiation therapy with a non-curative dose of radiation.

■ Scientific Statement

This CQ is a continuation of CQ48 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 334 articles. This was narrowed down to 55 in the first screening based on article titles and abstracts. A careful examination of the content of each article in the second screening extracted 15 articles about prospective studies, systematic reviews, and meta-analyses of clinical response after

3D-CRT and retrospective comparative studies of 3D-CRT and other treatment modalities. A total of 16 articles, including 1 article from the third edition, are cited for CQ50.

The literature search did not extract any RCTs that showed the clinical role of radiation therapy alone. However, several prospective and retrospective studies and meta-analyses of these studies reported that the addition of radiation therapy to TACE improved prognosis in patients with unresectable HCC[1–5]. Overall survival was significantly better after TACE + radiation therapy than after TACE alone, but this result should be interpreted with care because the meta-analyses included many non-randomized comparative clinical trials (CCTs). Huo et al. included CCTs in their meta-analysis[2], but they also performed a subgroup analysis of RCTs only. In the pooled analysis of 22 studies including the CCTs, the OR for 1-, 2-, 3-, and 5-year survival was 1.36 (95% CI, 1.19-1.54; $p < 0.001$), 1.55 (95% CI, 1.31-1.85; $p < 0.001$), 1.91 (95% CI, 1.55-2.35; $p < 0.001$), and 3.98 (95% CI, 1.89-8.51; $p < 0.001$), respectively, whereas in the subgroup analysis of RCTs only, the OR was 1.36 (95% CI, 1.12-1.66; $p < 0.001$), 1.79 (95% CI, 1.33-2.40; $p < 0.001$), 2.32 (95% CI, 1.64-3.28; $p < 0.001$), and 6.32 (95% CI, 1.58-25.30; $p = 0.01$), respectively. Together, these results show that combination therapy with radiation therapy significantly improves survival rates, and regardless of the inclusion of CCTs, OR increases with longer follow-up observation. Compared with TACE alone, the TACE + radiation therapy group had a significantly high incidence of gastroduodenal ulcer (OR, 12.8; 95% CI, 1.57-104.34; $p = 0.02$), elevated ALT (OR, 2.46; 95% CI, 1.30-4.65; $p = 0.01$), and elevated total bilirubin (OR, 2.16; 95% CI, 1.05-4.45; $p = 0.04$), with no significant differences in esophagitis/duodenitis, leukopenia, thrombocytopenia, fever, or nausea/vomiting. Similar findings were reported in recent retrospective studies[6,7].

A meta-analysis demonstrated the clinical significance of combining TACE with RFA, PEI, HIFU, or radiation therapy[8]. Although two types of radiation therapy were used (3D-CRT and radiation therapy without the method specified), analysis of the RCTs only showed that the TACE + radiation therapy group had significantly better treatment outcomes than TACE alone, with an OR for 1-year survival of 1.37-1.48 and an OR for 3-year survival of 2.32-2.88. Another analysis that included only one RCT revealed no significant survival benefit of RFA (1-year survival rate; OR 1.25; 95% CI, 0.68-2.30), HIFU (no significant difference in 3-year survival rate), or PEI (no significant difference in 1-year survival rate). This suggests that radiation therapy is superior to the other modalities as an adjuvant therapy for TACE.

Two studies reported on the clinical role of radiation therapy as adjuvant therapy for surgery[9, 10]. In an RCT conducted by Yu et al., patients who had multicentric HCC with ≤ 1 cm surgical margins were divided into two groups: postoperative adjuvant radiation therapy and no adjuvant therapy[10]. Despite no significant differences in the recurrence-free survival rate or overall survival rate, the 5-year recurrence-free survival rate in patients with HCCs ≤ 5 cm was significantly longer in the radiation therapy group (42.9%) than in the no-adjuvant therapy group (21.5%). In a comparative

study of the effect of preoperative adjuvant radiation therapy in patients with HCC and tumor thrombus in the main portal vein, patients who underwent radiation therapy prior to surgery had a significantly better 2-year survival rate in (20.4%) than those who underwent surgery alone (0%)[9].

The beneficial effect of radiation therapy alone on survival was suggested by 2 retrospective studies[11,12]. In the first study, patients with advanced HCC underwent radiation therapy (n = 29) or palliative care only (n = 18)[11]. Mean overall survival was significantly better in the radiation therapy group (45.9 months; 95% CI, 32.0-59.8 months) than in the palliative care group (4.8 months; 95% CI, 2.0-7.6 months; $p < 0.001$), although the radiation therapy group were also treated with other modalities such as TACE, hepatectomy, and chemotherapy. In the second study involving patients with resectable portal vein tumor thrombus, the 3D-CRT + TACE group had a significantly better 3-year survival rate (19.9%, n = 185) than the surgery group (13.6%, n = 186; $p = 0.029$)[12].

In addition, in a retrospective study of patients with unresectable HCC accompanied by portal vein tumor thrombus who received sorafenib (n = 36) or radiation therapy (n = 28), median survival was 4.4 months (95% CI, 0.7-17.5 months) and 5.9 months (95% CI, 0.6-103 months), respectively, with no significant intergroup difference ($p = 0.115$)[13]. However, after propensity score matching based on systemic conditions, overall survival was significantly improved in the radiation therapy group (10.9 months; 95% CI, 2.8-103 months) compared with the sorafenib group (4.8 months; 95% CI, 0.7-17.3 months; $p = 0.002$). Also, in retrospective studies, overall survival was significantly better after combination therapy with TACE + radiation therapy than after sorafenib therapy in patients with unresectable HCC accompanied by portal vein tumor thrombus[14,15].

However, a meta-analysis of 3D-CRT, stereotactic body radiotherapy, and particle therapy showed that stereotactic body radiotherapy and particle therapy are superior treatment modalities to 3D-CRT in improving survival[16]. This meta-analysis compared particle therapy and conventional radiation therapy (radiation therapy corresponding to X-ray therapy other than stereotactic body radiotherapy, which basically means 3D-CRT here) in a cohort of 73 patients from 70 non-comparative observational studies. Overall survival was significantly higher at 1 and 3 years for those receiving particle therapy than for those receiving 3D-CRT, with a relative risk of 1.68 (95% CI, 1.22-2.31; $p < 0.001$) and 2.46 (95% CI, 1.72-3.51; $p < 0.001$), respectively. In contrast, the relative risk of stereotactic body radiotherapy to particle therapy was 0.98 (95% CI, 0.83-1.18; $p = 0.44$) for 1-year survival and 1.02 (95% CI, 0.73-1.42; $p = 0.46$) for 3-year survival, with no significant intergroup difference[16].

■ Explanation

No previous studies have provided high-quality evidence for the efficacy of radiation therapy alone, but several meta-analyses have consistently shown improvements in overall survival with combination TACE and radiation therapy. However, all the meta-analyses contained CCTs as well as

RCTs and most were conducted in China; none were conducted in Japan, the United States, or Europe. Because radiation therapy is seldom administered in combination with TACE in Japan, further studies are needed to establish TACE + 3D-CRT as a treatment option in daily clinical practice. Even though the meta-analyses are believed to provide high-quality evidence, the Revision Committee has decided not to recommend combination therapy with TACE + 3D-CRT because it is difficult to match the content of the individual meta-analyses to actual clinical management of HCC in Japan. Also, although some studies have evaluated the clinical role of radiation therapy as an adjuvant therapy for surgery, they are still relatively few and had inconsistent results. Therefore, further results from similar studies are awaited.

For patients who do not have other locoregional therapy options to choose from, 3D-CRT alone has been shown, albeit retrospectively, to improve overall survival. Thanks to recent technological advances in radiation therapy, stereotactic body radiotherapy and particle therapy quickly became available in clinical practice and allowed for higher doses to be administered than with 3D-CRT. Therefore, it may be practicable to prioritize stereotactic body radiotherapy and particle therapy, which likely provide high anticancer effects and improve overall survival. In a meta-analysis by Qi et al., stereotactic body radiotherapy and particle therapy significantly improved survival rates compared with conventional radiation therapy[16]. However, the meta-analysis was conducted with observational studies lacking controls, some patients in the conventional-radiation therapy group were receiving palliative care, and there was some duplication of reported patients. Accordingly, the results of this meta-analysis should be interpreted with care. Also, stereotactic body radiotherapy or particle therapy may not be available for some patients not only because of medical reasons such as tumor and patient condition, but also because of geographic reasons as only a limited number of institutions are equipped to perform them. Such patients may benefit from 3D-CRT, which has been shown, although not with a high level of evidence, to improve overall survival compared with palliative care and sorafenib therapy. Based on these findings, 3D-CRT is expected to improve overall survival and is therefore recommended for patients for whom other treatment modalities are contraindicated. In the meeting for finalizing recommendations, the General Affairs Committee unanimously decided to grade the recommendation weak.

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