Surgical resection is the standard therapy for solitary primary or metastatic liver tumors. However, liver tumors are often unresectable at diagnosis and hepatectomy is invasive. Local therapies, such as radiofrequency ablation, are used instead, which can be challenging. Recent advances in modern radiotherapy, including stereotactic body radiation therapy (SBRT), have increased the use of radiotherapy as a curative modality. SBRT delivers ablative high doses of irradiation in small volumes. SBRT for liver tumors provided local control with potential survival benefits in patients with inoperable status. However, the following issues remain: primary vs. metastatic liver cancers; SBRT-related toxicity and prevention; pathological features of liver cancers; and potential SBRT strategies. We summarized a literature review to summarize the effectiveness of SBRT and patient tolerance and present the current status and future perspective of SBRT for liver tumors. SBRT is a potential game changer for multimodal therapy.

Surgical resection is the standard therapy for liver malignancies, including primary and metastatic liver tumors (1). Other local therapies, such as radiofrequency ablation (RFA), percutaneous ethanol injection therapy, and transarterial chemoembolization (TACE), are used as alternatives in medically-inoperable patients with hepatocellular carcinoma (HCC) and metastatic liver tumors (1-6). However, radical treatment for liver tumors can be challenging due to poor liver function, tumor location and progression, and anatomical barriers (2, 5). Furthermore, preservation of residual liver function is required, as liver tumors have high recurrence potential (5, 6).

High doses of radiation are required for HCC that would sometimes exceed the levels tolerated by the background liver. Radiotherapy has also been used for palliative care in liver tumors (7-9). Modern radiotherapies, including stereotactic body radiation therapy (SBRT), intensity-modulated radiotherapy (IMRT), and particle therapies, have recently attracted increasing attention as therapeutic modalities for various malignancies and have dramatically increased the use of radiation therapy as a curative modality (10-26).

Several studies using SBRT for liver tumors have reported high tumor response and local control rates (2, 3). However, certain issues regarding the current use of SBRT for liver tumors need to be addressed. These include the differences between primary and metastatic liver cancers, SBRT-related toxicity and prevention, the pathological features of liver cancers, and the clinical application of novel radiobiology-based SBRT strategies, such as a combination of SBRT with immunotherapy.

We conducted a review of the literature to summarize the effectiveness and patient tolerance of this new treatment modality, to summarize the differences between primary and metastatic liver tumors, to report the probable treatment-related toxicities and their prevention, and to describe recent significant updates on microinvasion, the biological behavior of SBRT, and combined therapy with immune therapy.
Stereotactic Body Radiation Therapy (SBRT)

The major feature that distinguishes SBRT from conventional radiation treatment is the delivery of large doses of radiation in a few fractions, which results in a high biologically effective dose (BED). The use of a high precision technique is critical to deliver a high dose of radiation to the target and keep rapid fall-off doses away from the target, thereby achieving maximum treatment efficacy with minimal toxicity to normal tissues (27).

The use of SBRT for extracranial tumors was developed at the Swedish Karolinska University by Blomgren and colleagues (28). SBRT is now widely accepted as a treatment option for lung and liver tumors characterized by their small size and limited numbers (29). The present status of SBRT for liver tumors is documented below.

SBRT for Primary Liver Cancers

The Barcelona Clinic Liver Cancer staging system is now widely accepted in clinical practice over the other staging systems (1). Orthotopic liver transplantation offers the best cure for liver cancer, even though the chances of transplantation are limited due to the lack of sufficient liver donors (30). Therefore, it is envisaged that radiotherapy would play the role of a radical therapy in the populations that require orthotopic liver transplantation as a cure rather than a bridging therapy (31, 32). Moreover, recent reports indicated that SBRT was as effective as TACE and RFA (33, 34). In a previous series, SBRT provided 1-, 2-, and 3-year local control rates of 56-100%, 53-95%, and 51-92%, and 1-, 2-, and 3-year survival rates of 32-100%, 55-100%, and 21-82% for HCC, respectively (11-19).

There are only a limited number of reports of the use of SBRT for cholangiocellular carcinoma (CCC). In a previous series, SBRT provided a 1-year local control rate of 50-100% (20-21). Kopec et al. reported a median local control time and an overall survival time of 6.7 and 10.6 months, respectively, in 27 CCC patients who received SBRT (21). Over a median follow-up period of 5.4 years, the local control rate was 81.5%, after exclusion of intrahepatic recurrence (21).

SBRT can generally achieve excellent local control of primary liver tumors, even if the patient was not a good candidate for surgery or RFA.

SBRT for Metastatic Liver Tumors

Oligometastases have recently been recognized as a state in which the patient shows distant relapse in only a limited number of regions, and a possible benefit from local treatment for oligometastases has been reported for various malignancies (4, 35). Surgical resection is the standard treatment option for colorectal oligometastases and good outcomes have been reported (3, 6). Furthermore, reports indicate that other alternative local interventions provide excellent local control (4, 5). In these populations, the general condition of patients can deteriorate with disease progression and adverse events after treatment; therefore, minimally invasive treatments are preferred.

In recent years, high tumor control rates post-SBRT have dramatically changed the role of radiotherapy from palliative care to radical intent. SBRT can provide 1-, and 2-year local control rates of 62-100%, and 45-100% for liver metastases, respectively, and is therefore a potential therapeutic candidate for the treatment of oligometastases (17, 21-26).

Prescription Doses of SBRT for Liver Tumors

A dose-response relationship has been reported for conventional fractionated and stereotactic radiotherapy, although the best prescription dose of radiotherapy for HCC remains undecided (36, 37). Furthermore, the use of tumor control probability (TCP) models has been reported in terms of BED using the linear-quadratic (LQ) model with an assumed α/β ratio of 10 Gy for the tumor (BED10) (38). Lausch et al. estimated that a 90% probability of 6-month local control could be achievable by administration of 2 Gy per fraction with an equivalent dose of 84 Gy (BED10=100.8 Gy) (7). Jang et al. estimated that 51.1 Gy in 3 fractions (BED10=138.1 Gy) were necessary to achieve a 90% probability of 2-year local control (39). Sanuki et al. and Takeda et al. estimated a >90% probability of 3-year local control with 40 Gy in 5 fractions (BED10=72 Gy) that was intended to enclose the planning target volume (PTV) by the 80% isodose-line of the maximum dose (15, 16). Based on these data, we treated HCC with >80 Gy of BED10 designed to deliver 100% of the prescription dose to 95% of the PTV using intensity-modulated radiation therapy (IMRT) (40, 41). Notably, when there was no constraint on the PTV during planning, the maximum dose for PTV could be slightly escalated from the prescription doses (Figure 1).

For metastatic liver tumors, the prescription doses depend on the primary tumor; colorectal histology was a significant negative predictive factor (42, 43). In patients with colorectal cancer with a limited number of metastases, local control of metastatic lesions may be curative (3, 4, 6). Chang et al. reported that >117 Gy (e.g., 48 Gy in 3 fractions) would be required to achieve an estimated 1-year local control rate of 90% in a TCP model from a pooled analysis (24). Lausch et al. calculated 2 Gy per fraction with equivalent doses of 95 Gy (BED10=114 Gy) to achieve a 90% probability of 6-month local control (7). The need for dose escalation for liver or pulmonary metastases with colorectal histology has recently reported (25). Using a radiosensitivity index that reflected the expressible gene types, Ahmed et al. reported
that liver metastases from colorectal cancer were radio-resistant compared with other histological cancer types (43, 44). We hypothesized that metastatic liver tumors had different biological backgrounds and responses to irradiation, and that significant factors included tumor size, metastatic site, and primary histology.

For HCC and colorectal liver metastases <3 cm, we suggest prescription doses of greater than BED 10 of 80 and 100, respectively. Dose escalation and modification of the treatment schedule is required for metastatic tumors ≥3 cm (18, 23, 26).

**Adverse Events of SBRT for Liver Tumors**

Manifestations of liver SBRT toxicity include fatigue, damage to the liver, gastrointestinal tract, and biliary duct, cytopenia, dermatitis, and rib fractures (12-26). Adverse events of radiotherapy depend on the treatment site, and the irradiated doses and volume and are categorized into either acute or late, based on their time of onset (45). In liver SBRT, it is often difficult to clearly separate acute and late phases of toxicities because liver damage with serum aminotransferase elevation occur weeks or months after SBRT (10). We focus on the major cases of toxicity involving the liver, gastrointestinal tract, and central bile duct.

**Hepatic toxicity.** The most important dose-limiting factor of liver radiotherapy is liver damage, such as radiation-induced liver disease (RILD). RILD is classified into 2 different clinical conditions, classic and non-classic RILD (8, 9).

In a retrospective analysis of SBRT involving 221 HCCs, Sanuki et al. reported a 1.1% occurrence rate of Grade 5 hepatic toxicity (15). There are differences in radiosensitivity between patients with normal and cirrhotic livers (9, 40). Moreover, Child-Pugh B, particularly scores ≥8, was considered a significant risk factor for severe hepatic toxicity and a poor prognosis (12, 18). Culleton et al. reported that survival among patients with a Child-Pugh score ≥8 was significantly shorter than among patients with Child-Pugh 7 in a study involving 29 HCC patients with Child-Pugh B or C who received SBRT (18). Furthermore, radiotherapy has the potential to reactivate hepatitis B virus and differentiating patients may be necessary (47).

As the liver is widely accepted as a parallel organ, a part of it can receive a high dose of irradiation as long as the functions as a whole organ are preserved (48-50). After SBRT, focal dysfunction was noted in the irradiated background liver. A liver volume >700 ml has been used as a dose constraint when the dose administered was less than 15 and 17 Gy in 3 fractions (13, 51, 52). Using magnetic resonance imaging (MRI), Sanuki et al. have shown that the threshold dose of focal liver dysfunction was 30 Gy and 25 Gy in 5 fractions in patients with Child-Pugh A and B, respectively (53). Doi et al. reported that focal liver dysfunction can occur at 40 Gy and 70 Gy of BED2 in the cirrhotic and normal liver, respectively, at the minimum dose.
suggested for SBRT for liver tumors (40, 41). Intrahepatic recurrence often occurs after radical treatment for both HCC and metastatic liver tumors, and such tumors have a chance to receive second radical treatment (5, 6). Therefore, prediction of the volume of liver dysfunction is essential in order to spare the residual liver volume (Figure 2).

The doses that the liver receives have a strong positive relationship with the irradiated target volume (41, 54). Particle therapy can reduce the liver volume that receives low to intermediate doses, resulting in the reduction of mean liver doses (55). A relevant clinical consideration is that particle therapy can benefit relatively large tumors, such as those >3 cm (particularly those >5 cm) and patients with poor liver function, which are limiting factors for SBRT (56).

Gastrointestinal injury. Gastrointestinal injuries, including bleeding, ulcers, and perforations have been described and the incidence of symptomatic gastrointestinal toxicities was less than 10% in majority of the previous reports.

Hoyer et al. reported 1 case of colonic perforation and 2 duodenal ulcers in patients in whose intestine received ≥30 Gy in 3 fractions from 64 patients receiving liver SBRT (57). Yamashita et al. reported that 6.9% of 130 patients receiving liver SBRT developed gastrointestinal toxicity of

**Figure 2.** A 65-year-old man with HCC. HCC was found with hypervascularity just dorsal to the low-density area in which RFA was performed (A, contrast-enhanced CT, arrow). Purple and orange lines indicate the ITV and PTV, respectively. SBRT of 44 Gy in 4 fractions was applied (B). Blue line indicates the potential hepatocyte dysfunction area (BED_{2}=50 Gy). A low intensity area was found in the follow-up Gd-EOB-DTPA enhanced-MRI 3 months after SBRT (C). MRI was fused with planning CT, with use of a fiducial marker (Gold Anchor™; Naslund Medical AB, Huddinge, Sweden), as a landmark. The patient was included in our prospective study (approval no. 28-16). HCC: Hepatocellular carcinoma; RFA: radiofrequency ablation; CT: computed tomography; ITV: internal target volume; PTV: planning target volume; SBRT: stereotactic body radiation therapy; BED: biologically effective dose; D95: prescribed dose to cover 95% of the PTV; Gd-EOB-DTPA: gadolinium ethoxybenzyl-diethylene-triaminepentaacetic acid; MRI: magnetic resonance imaging.
Grade 2 or above (22). Kang et al. reported that 6.4% and 4.3% of patients experienced Grade 3 gastrointestinal toxicity and Grade 4 gastric ulcer perforation, respectively, in 47 HCC patients (15). In addition, Barney et al. reported that the combination of SBRT and a vascular endothelial growth factor inhibitor increased the risk of Grade 3 or greater gastrointestinal toxicities (58).

Kopek et al. recommended V21Gy ≤1 cc for the duodenum in abdominal SBRT, based on dose–volume data (29). Bae et al. concluded that the Dmax was the best dosimetric predictor for severe gastroduodenal toxicity and the Dmax of 35 Gy and 38 Gy in 3 fractions was associated with a probability of 5% and 10% severe gastroduodenal toxicity, respectively (59).

Kavanagh et al. recommended that the volume of stomach receiving >22.5 Gy should be minimized and ideally limited to less than 5 ml, with a maximum point dose of ≤30 Gy for three-fraction SBRT (60). Sanuki et al. suggested that severe toxicities could be avoided when the distance between the target and the bowel is >2 cm (61).

Central hepatobiliary tract toxicity. Eriguchi et al. documented asymptomatic bile duct stenosis in 2/50 patients receiving >20 Gy in 5 fractions to the central liver, and concluded that SBRT for liver tumors in the hepatic hilum was feasible with minimal biliary toxicity (62).

Osmundson et al. reported the following: 23 patients (24.0%), including 14 of 20 patients with CCC, developed hepatobiliary toxicity ≥Grade 2 in 96 patients with liver tumors who received SBRT (63). Furthermore, CCC, biliary stent, V BED10 ≥21 cc, V BED10 66 ≥24 cc, and DmeanBED 10 ≥14 Gy to the central hepatobiliary tract were associated with hepatobiliary toxicity (63). Therefore, there can be potential dose constraints due to central hepatobiliary tract toxicity.

The same groups analyzed resected surgical specimens and reported radiation-induced pathological changes in the bile duct 25 months after SBRT (64). They showed fibrotic changes in different tissues in the hepatic hilum, involving the bile duct, porta hepatitis, portal vein, and adjacent peritoneum. The bile duct was thickened not only in the area adjacent to the tumor but also on the contralateral side that was uninvolved by the tumor.

The same group, in a study of 130 patients who received liver SBRT, has recently suggested V BED10 40 <37 ml and V BED10 30 <45 ml as dose-volume constraints in SBRT for primary liver tumors (65). The anatomical structures in the hepatic hilum make radical treatment for liver tumors more challenging; therefore, SBRT can be a feasible treatment option.

Current Issues and Future Perspective of Liver SBRT

Current unsolved questions remain regarding the pathological features of liver cancers and potential SBRT strategies, including radiobiology-based SBRT and SBRT combined with immunotherapy. We discussed these issues above.

Current status of biology-based SBRT. Brown et al. reported that endothelial cell damage and vascular damage can cause secondary cancer cell apoptosis and fractionated radiotherapy has an increased antitumor effect, based on the impact of reoxygenation (66). Shibamoto et al. concluded that a 72-hour break period from SBRT could promote reoxygenation that enhances the indirect effects of ionizing radiation, resulting in improved tumor control (67). There is no prospective clinical trial directly comparing the 2 SBRT schedules, with or without a break.

Larger tumors are usually a SBRT exclusion criterion, although the response to SBRT in cases of relatively small tumors remains unclear (16, 22, 24, 34, 41).

Biological assessment could identify potential factors that improve treatment outcomes, such as escalated doses, treatment schedule with a break, combined therapy with ideal chemotherapy, patient selection, and use of particle therapies (26, 54, 55).

Microscopic extension of liver tumors in terms of clinical tumor volume margin. Clinical tumor volume (CTV) is frequently equal to the gross tumor volume (GTV) in SBRT (68). It is still poorly understood whether CTV margins are necessary to include both gross and microscopic disease. We document below the possible CTV margins reported regarding liver tumors.

Approximately 95% of patients with HCC who could be candidates for SBRT had microscopic extension of ≤2 to 3.5 mm (69, 70).

Bi et al. devised a scoring system based on the combination of these factors, including the tumor boundary, tumor markers, and liver transaminases, and suggested that an increase in the GTV by approximately 5 to 8 mm was necessary to cover microscopic invasion with ≥95% probability (71).

Qian et al. suggested that 3-8.5 mm CTV margins were necessary in order to cover microscopic invasions in 139 resected specimens of colorectal liver metastases (72). We previously reported that a larger margin for the GTV tended to improve local control and survival outcomes and, to the best of our knowledge, this is the first report establishing the requirement of CTV margins in clinical data (26). Further clinical trials are required to assess the need for CTV margins.

Perspective of immuno-SBRT. This response can lead to systemic induction of antitumor immunity, causing tumor shrinkage in distant sites from the irradiated areas, known as the abscopal effect. The abscopal effect is induced by irradiation via an indirect effect on T lymphocytes (73). The abscopal effect is well established, although SBRT combined with anti-cytotoxic T-lymphocyte-associated protein-4
(CTLA-4) therapy, ipilimumab, resulted in unexpected clinical complete responses in distant sites from the irradiated areas; this occurred in a range of malignancies, such as metastatic melanoma and metastatic lung cancer (74-76).

Immune checkpoint inhibitors represent a significant breakthrough and a promising strategy in recent cancer treatments. Synergistic effects of immuno-radiotherapy have recently been reported in clinical and pre-clinical studies, including the increased possibility of the abscopal effect, which may lead to a significant change in treatment strategies for metastatic cancers (74-78).

The optimal treatment schedule for a combination of radiotherapy and immunotherapy is still not understood even today. Wild et al. found that hypofractionation could minimize the toxic effects on circulating lymphocytes in SBRT for pancreatic cancer (79). Young et al. reported enhanced efficacy of immune-radiotherapy administered concurrently with radiotherapy compared with sequential administration (80). Bang et al. found that larger doses of radiotherapy and short breaks between immunotherapy and radiotherapy increased the rate of toxicity (81).

In recent reports on immune-radiotherapy, radiotherapy was largely delivered using SBRT or a short course of palliative radiation, although the optimal method of radiotherapy delivery remains unknown. By expanding its application range from small tumors to metastases, SBRT appears to have good potential to achieve newer objectives in systematic disease.

Limitations

Our review has a number of limitations. First, there are only a small number of randomized trials examining the use of SBRT in HCC with no report on metastatic liver tumors. Second, as the chances of patients receiving surgical resection after SBRT are limited, the biological characteristics of each tumor that received SBRT are not well defined. Liver tumors include a range of tumors, such as HCC, CCC, and metastatic tumors from different primary sites. These diversities make the role of liver SBRT more complicated and challenging. Additional prospective studies involving large sample sizes are required to consolidate the evidence on SBRT, assess the benefit of escalated doses of SBRT for each tumor type in terms of local control and survival, define superiority or inferiority compared with that of local treatment modalities, and thus develop a standardized treatment protocol.

Conclusion

For liver tumors, SBRT is safe and effective, with excellent local control achieved. Therefore, novel strategies should be developed based on new knowledge of biological responses to radiation therapy. State-of-the-art liver SBRT remains a pioneering strategy and a possible game changer in multimodal therapy.

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