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Role of Radiotherapy in Liver Tumors: Recent Update

Research Article

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary tumor with an increased risk of mortality and morbidity. Treatment for HCC varies based on the progressivity of disease. Radiotherapy such as stereotactic body radiotherapy (SBRT) plays an important role in the treatment of HCC. The role of radiotherapy used to be very limited to liver tumors, but recently, radiotherapy with SBRT technique has shown very promising results, both in primary liver cancer and liver metastasis. This review shows the role of radiotherapy in HCC for every stage of HCC (monotherapy, combined or bridging therapy). In liver metastasis cases, radiotherapy shows an excellent, similar, and better local control when compared with radiofrequency ablation (depending on tumor status).

Keywords: *stereotactic body radiotherapy • liver • tumors • radiation*

1. Introduction

Primary liver tumors are the second most common cause of cancer death, with around 830,000 deaths reported in 2020. Liver cancer ranks the fourth most common cause of cancer death and is the sixth most commonly diagnosed cancer in the world. Hepatocellular carcinoma (HCC) is the most common primary liver tumor (around 80%–90%), followed by intrahepatic cholangiocarcinoma (iCCA), and others such as fibrolamellar carcinoma, hepatoblastoma, mesenchymal cancers. The main risk factors for HCC are hepatitis B and hepatitis C virus infection. Secondary liver tumors are usually metastases, accounting for 95% of hepatic malignancies, with the primary causes being breast cancer, lung cancer, colorectal cancer, and other cancers[1–4].

Liver diseases are largely attributable to complications of cirrhosis and HCC, with acute hepatitis accounting for a smaller proportion of deaths[5]. According to Globocan 2020, liver cancer accounted for around 5.4% of all cancers in Indonesia. According to data from National Referral Hospital Dr. Cipto Mangunkusumo Hospital, 67% of liver cancers were caused by chronic hepatitis B infection. The latest data released by the Ministry of Health Republic of Indonesia showed that the prevalence of hepatitis B in Indonesia was 7.5% and estimated that 17.5 million Indonesians suffer from hepatitis B. It is estimated that 20%–30% of people (3.5–5.2 million) will experience disease progression to cirrhosis and/or liver cancer[6,7].

There are different types of treatment for patients with liver cancer, such as surveillance, surgery, liver

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transplant, ablation therapy, embolization therapy, targeted therapy, immunotherapy, and radiation therapy (RT). These treatments vary based on whether it is localized liver cancer or locally advanced or metastatic liver cancer[8].

In recent years, radiotherapy has gradually become widely used as an important local therapy for HCC and has become an essential component of its comprehensive treatment. Radiotherapy is a treatment option for patients with unresectable tumor or for those who are medically inoperable due to comorbidity. However, early limitations in technology, such as limited accuracy and wide irradiation range of radiotherapy, and intrinsic radiosensitivity from the liver itself resulted in suboptimal treatment outcomes, radiation-induced liver disease (RILD), and inadequate dosages. With the emergence of precision radiotherapy techniques, these issues have gradually been overcome[1,9]. Radiotherapy offers high local control (LC) rates in unresectable HCC. In metastatic cases, radiotherapy can provide good palliation[10]. Technological advancement (e.g., stereotactic body radiotherapy [SBRT] and advanced proton beam therapy) enables precise delivery of radiation to increase tumor control, provide safe and effective treatment, and reduce side effects in the surrounding normal tissue[1,11].

In early-stage HCC, many promising prospective results of SBRT have been reported. However, SBRT is not usually indicated as a first treatment option in localized HCC according to several guidelines. SBRT is currently considered as a substitute therapy when conventional bridging therapies to transplantation, such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), are not applicable or fail in controlling tumors. SBRT may offer advantages in patients with borderline liver function who may not tolerate TACE or RFA, according to several reports. For oligometastases, the combination of SBRT with immune checkpoint inhibitors (ICIs) could potentially induce an abscopal effect in patients with HCC, which is expected to provide the rationale for SBRT in the treatment of oligometastatic disease in the near future[12].

This article discusses about the role of radiotherapy in liver tumors and gives a recent update.

2. Current Management of Liver Tumor

Effective treatment for early-stage HCC consists of resection, liver transplantation, and ablation. In patients with locally advanced disease, TACE, bland embolization, and radioembolization may be the options[13]. In patients with liver-confined disease and good liver function in whom neither TACE nor systemic therapy is possible, selective internal radiotherapy (SIRT) may be considered[14]. All tumors, irrespective of the location, may be amenable to RT (3D conformal RT, intensity-modulated RT [IMRT], or SBRT). Image-guided RT is strongly recommended to improve treatment accuracy and reduce treatment-related toxicity. SBRT is an advanced technique of hypofractionated RT with photons that deliver large ablative doses of radiation. SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated[9].

3. History of Radiotherapy in Liver tumor

Recent technological development has led to the concept of directed liver RT. The tumor volume and its proximity to organs at risk in the liver determine the irradiation technique, including repositioning methods, total dose delivered, and dose fractionation regimens[15].

Two-dimensional therapy is a method of estimating the locations of tumors from the front or lateral side of patients based on bony structures through kilovoltage (kV) X-ray–based plain radiographic images. In the middle of the 1990s, three-dimensional (3D) spatial information on patients' bodies and internal organs obtained through computed tomography (CT) became available as computerized data. This enabled the implementation of 3D RT using computers to plan simulated treatments. Four-dimensional (4D) RT was introduced in 2010 and has been ever spreading. 4D RT means taking the motion due to breathing into account in RT plans (Choi and Cho. 2016). Modern RT techniques employ modulated photon (IMRT, volumetric modulated arc therapy [VMAT]) or particle (intensity-modulated proton therapy [IMPT]) beams and the dosimetric gain over 3D conformal radiotherapy (3DCRT). Published surveys and reviews suggest a shift in usage from 3DCRT to VMAT specifically, combined with varying dose fractionation schemes (hypofractionation, SBRT, and simultaneous integrated boost [SIB]). The effect of image guidance (image-guided RT [IGRT]) and motion management systems on dose delivery, target positioning accuracy, and reproducibility warrant the assessment of collective clinical impact of these practices with modulated therapies[16].

The first report of radiation to the liver was published in 1924. This described the autopsy of a patient who received 200 kVp for 200 mA min showing marked pathological changes in the lymphoid tissue and

intrahepatic bile ducts and comparatively mild changes in the hepatocytes. In 1966, a report described the acute and chronic pathological findings in the livers of 12 patients who received whole liver irradiation to 30–59 Gy over 6 weeks for metastatic disease, and established the hallmark finding of veno-occlusion in association with classic RILD. The Radiation Therapy Oncology Group (RTOG) conducted studies in the 1970s and 1980s to examine the role of whole liver radiation for hepatic metastases. The RTOG 76-09 study reported on 109 patients with liver metastases and evaluated various fractionation schemes to the whole liver based on the presence of a single metastasis (30.4 Gy in 19 fractions with or without a 20-Gy boost, or 30 Gy in 15 fractions with or without a 20-Gy boost) or multiple metastases (30 Gy in 15 fractions, 25.6 Gy in 16 fractions, 20 Gy in 10 fractions, or 21 Gy in seven fractions). No classic RILD was seen in this study. A shift to partial radiation of the liver was made in the 1980s, and a seminal work demonstrated that partial liver volumes could be safely irradiated to high doses. As image guidance and conformal radiation techniques improved in the 1990s and early 2000s, it became clear that radiation could be delivered at higher doses to tumors in a shorter timeframe[17].

The use of external-beam RT (EBRT) in the treatment of liver tumors has had a limited role until recent years because of RILD (Navin *et* al., 2022). RILD has been defined as a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes (particularly serum alkaline phosphatase) occurring from 2 weeks to 4 months after radiotherapy. The underlying cause is a veno-occlusive disease in the central portion of each lobe. Fibrous occlusion of central veins is the result of the replacement by collagen of fibrin accumulated in endothelial cells of central veins after irradiation[18]. SBRT is a non-invasive treatment, EBRT method is used to very precisely deliver a high dose of radiation, either as a single dose or divided into three to five fractions (hypofractionated dose), which achieves local tumor control in challenging situations such as when the tumor size is >3 cm and the tumor location is close to central vessels and the biliary system[19,20].

4. Role of RT in HCC

The diagnosis of HCC is usually based on non-invasive criteria, although there is a growing need for molecular characterization of the tumor using tissue biopsies in clinical practice. The management of HCC has markedly improved since the early 2010s. The first of the criteria is Milan Criteria (MC), but MC was too restrictive and excluded patients who might have benefited from liver transplantation. University of San Francisco California (UCSF) criteria were introduced in 2001[21]. In 2008, Toso *et al*. proposed the total tumor volume (TTV) concept. In 2009, Mazzaferro confirmed a socially acceptable prognosis (a 5-year survival rate of ≥70%) and analyzed the acceptable tumor burden of HCC lesions[22]. However, the majority of the patients are not eligible for surgery/transplant because of tumor extension or underlying liver dysfunction.

Many patients with HCC present with advanced disease, not amenable to curative therapies such as surgery, transplantation, or RFA[18]. Available treatment options for unresectable HCC include RFA, TACE, Transarterial Radioembolization (TARE), and EBRT/SBRT. The increasing role of radiotherapy in liver cancer is due to the advancement of imaging and radiation treatment planning.

In the field of radiation oncology, limited trials were found regarding RT in hepatic carcinoma. Several studies are summarized in Table 1. In summary, several studies showed SBRT as the best alternative modality of treatment for HCC as a bridging therapy for LC when RFA is difficult to perform for larger tumor[23–26]. A systematic review, randomized clinical trials, and several retrospective studies showed a combination of SBRT and TACE or TACE-RT showed better outcomes for HCC patients[27–31].

5. Role of RT in Liver Metastasis

The liver is one of the most frequent metastatic sites for various types of cancer. Liver resection is considered if resectable liver metastases from colorectal cancers and neuroendocrine tumors (NETs) are detected. The 5-year survival in patients with liver metastases who underwent hepatectomy varied from 17% to 72%, depending on the primary site[32]. Mostly, around 80%–90% of patients were unresectable at diagnosis. RFA can be applied to patients who are ineligible for surgical resection of liver metastasis. However, there are some limitations such as inferior LC compared to surgical resection and technical feasibility based on location, size, and visibility on ultrasonography of the liver metastasis. Stereotactic ablative radiotherapy (SABR) can result in better LC for liver metastases >2–3 cm, compared to RFA. The outcomes following SABR for liver metastasis from various primary sites showed a high 2-year LC rate of over 90%[33]. Table 2 summarizes several studies about the role of radiotherapy in liver metastasis. Several

Table 1: Radiation therapy in hepatic carcinoma.

No	Author (year)	Study design	Endpoint (s)	Patients/ subjects	Intervention	Outcome
1	Bae *et al*. [25]	Systematic review/meta-analysis	Outcomes and hepatic toxicity after SBRT for liver-confined HCC	Seventeen observational studies between 2003 and 2019	1889 patients with HCC treated with ≤9 SBRT fractions	The 3- and 5-year OS rates after SBRT were 57% (95% CI: 47%–66%) and 40% (95% CI: 29%–51%), respectively. The 3- and 5-year LC rates after SBRT were 84% (95% CI: 77%–90%) and 82% (95% CI: 74%–88%), respectively. Five-year LC and OS rates of 79% (95% CI: 0.74–0.84) and 25% (95% CI: 0.20–0.30), respectively, were observed in the individual patient data analyses. SBRT is an effective treatment modality for patients with HCC with mature follow-up
2.	Kim *et al*. [23]	Retrospective study	Efficacy of SBRT and RFA for HCC, FFLP	Patients treated for HCC between 2012 and 2016	668 patients who underwent RFA of 736 tumors and 105 patients who underwent SBRT of 114 tumors	SBRT-treated tumors were more advanced, larger (median: 2.4 vs. 1.6 cm), and more frequently located in the subphrenic region than RFA-treated tumors ($P < 0.001$). SBRT is an effective alternative treatment for HCC when RFA is not feasible due to tumor location or size
3	Wahl *et al*. [24]	Retrospective study	Outcomes between SBRT and RFA for HCC	HCC patients from 2004 to 2012	224 patients with inoperable, nonmetastatic HCC underwent RFA (n = 161) to 249 tumors or image-guided SBRT (n = 63) to 83 tumors	One- and 2-year FFLP for tumors treated with RFA were 83.6% and 80.2%, respectively, and for tumors treated with SBRT were 97.4% and 83.8%, respectively. Increasing tumor size predicted for FFLP in patients treated with RFA (HR: 1.54 per cm; $P = 0.006$), but not with SBRT (HR: 1.21 per cm; $P = 0.617$). Overall survival 1 and 2 years after treatment was 70% and 53% after RFA and 74% and 46% after SBRT, respectively
4	Rim *et al*. [31]	Hybrid meta-analysis	Comparison between RFA and ablative RT for HCC	Twenty-one studies	4,638 patients	Pooled 1- and 2-year survival rates for HCC studies were 91.8% and 77.7% after RFA and 89.0% and 76.0% after ablative RT, respectively; ablative RT can yield oncologic outcomes similar to RFA, and suggests that it can be more effective for the treatment of tumors in locations where RFA is difficult to perform or for large-sized tumors
5	Dumago *et al.* [27]	Systematic review/meta-analysis	Utility of SBRT, with or without TACE, for early-stage HCC patients not amenable to standard curative treatment options	Literature, comparative studies	Five studies (one Phase II randomized controlled trial, one prospective cohort, and three retrospective studies) compared SBRT versus TACE	Clinical outcomes improved significantly in all groups having SBRT as a component of treatment versus TACE alone or further TACE
6	Wong *et al*. [28]	Retrospective study	Outcomes of nonresectable HCC patients who had TACE versus SBRT after TACE (TACE + SBRT)		49 patients were in the TACE + SBRT group and 98 patients were in the TACE group	TACE + SBRT is safe and results in better survival in nonresectable HCC patients
7	Shen *et al*. [29]	Retrospective study	Comparison of efficacy between SBRT and Sorafenib, when given after TACE Efficacy in comparison to SBRT + sorafenib, when combined with TACE	77 HCC patients with macroscopic vascular invasion receiving TACE–SBRT or TACE–sorafenib combination therapies	26 patients (33.8%) received TACE–SBRT treatment and 51 (66.2%) received TACE–sorafenib treatment	HR of OS to PFS for the TACE–SBRT approach and the TACE–sorafenib approach was 0.36 (95% CI: 0.17–0.75; $P = 0.007$) and 0.35 (95% CI: 0.20–0.62; $P < 0.001$), respectively. For HCC patients with macrovascular invasion, TACE plus SBRT could provide improved OS and PFS compared to TACE–sorafenib therapy
8.	Yoon *et al*. [30]	Randomized clinical trial	Efficacy and safety of TACE plus RT compared with sorafenib for patients with HCC and macroscopic vascular invasion	Randomized, open-label clinical trial, 90 treatment-naive patients with liver-confined HCC showing macroscopic vascular invasion	Sorafenib (400 mg twice daily; 45 participants [the sorafenib group]) or TACE (every 6 weeks) plus RT (within 3 weeks after the first TACE, maximum 45 Gy with a fraction size of 2.5–3 Gy; 45 participants [the TACE-RT group])	At week 12, the PFS rate was significantly higher in the TACE-RT group than in the sorafenib group (86.7% vs 34.3%; $P < 0.001$). The TACE-RT group showed a significantly higher radiologic response rate than the sorafenib group at 24 weeks (15 [33.3%] vs. 1 [2.2%]; $P < 0.001$), a significantly longer median time to progression (31.0 vs. 11.7 weeks; $P < 0.001$), and significantly longer overall survival (55.0 vs. 43.0 weeks; $P = 0.04$). Curative surgical resection was conducted for five patients (11.1%) in the TACE-RT group owing to downstaging
9	Sapisochin *et al*. [26]	Observational study	Safety and efficacy of SBRT on an intention-to-treat basis compared with TACE and RFA as a bridge to liver transplantation in a large cohort of patients with HCC	379 patients	SBRT (n = 36, SBRT group), TACE (n = 99, TACE group), or RFA (n = 244, RFA group)	SBRT can be safely utilized as a bridge to LT in patients with HCC, as an alternative to conventional bridging therapies

OS: overall survival; CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; RFA: radiofrequency ablation; RT: radiotherapy; SBRT: stereotactic body radiotherapy; LC: local control; LT: Liver Transplantation; FFLP: freedom from local progression; TACE: transarterial chemoembolization, PFS: progression-free survival.

Table 2: Studies about SBRT in liver metastasis.

No.	Author (year)	Study design	Endpoint(s)	Patients/ subjects	Intervention	Outcome
1	Jackson *et al*. [34]	Retrospective study	FFLP with SBRT and RFA for the treatment of intrahepatic metastases	161 patients with 282 pathologically diagnosed unresectable liver metastasis	RFA (n = 112) or SBRT (n = 170)	Treatment with SBRT (HR: 0.21, 95% CI: 0.07–0.62; $P = 0.005$) and smaller tumor size (HR: 0.65, 95% CI: 0.47–0.91; $P = 0.01$) were associated with improved FFLP Treatment with SBRT or RFA is well tolerated and provides excellent and similar LC for intrahepatic metastases <2 cm in size. For tumors ≥2 cm in size, treatment with SBRT is associated with improved FFLP and may be the preferable treatment
2.	Rim *et al*. [31]	Hybrid meta-analysis	Oncologic outcomes and clinical consideration of RFA and ablative RT for intrahepatic malignancies	Studies comparing RFA and ablative RT for HCC	Twenty-one studies involving 4,638 patients	Pooled 1- and 2-year survival rates for metastasis studies were 88.2% and 66.4% after RFA and 82.7% and 60.6% after RT, respectively
3	Palma *et al*. [38]	Phase II randomized trial	OS, PFS, toxicity, and QOL	Controlled primary malignancy and one to five metastatic lesions, with all metastases being amenable to SABR	99 patients	Common primary tumor types were breast, lung, colorectal, and prostate. Five-year OS of SABR + SOC was 42.3%, compared to 17.7% in the SOC arm. No significant difference in adverse events and QOL between arms
4	Mendez *et al*. [36]	Retrospective study	Outcomes of SBRT for liver metastasis	A shared web-based registry of patients with liver metastases treated with SBRT was developed by 13 centers (12 in the Netherlands and one in Belgium)	515 patients	The most used fractionation scheme was 3 × 18–20 Gy (36.0%), followed by 8 × 7.5 Gy (31.8%), 5 × 11–12 Gy (25.5%), and 12 × 5 Gy (6.7%). Actuarial 1-year LC was 87%; 1-year OS was 84%. Toxicity of grade 3 or greater was found in 3.9% of the patients SBRT should be considered a valuable part of the multidisciplinary approach for treating liver metastases
5	Yu *et al*. [35]	Retrospective study	Treatment outcomes of RFA and SBRT for CRLM	222 colorectal cancer patients with 330 CRLM	• RFA (268 tumors in 178 patients) • SBRT (62 tumors in 44 patients)	SBRT and RFA showed similar LC in the treatment of patients with CRLM. Tumor size was an independent prognostic factor for LC, and SBRT may be preferred for a larger tumor
6	de la Peña *et al*. [37]	Literature review	SBRT in the management of liver metastasis regarding LC, OS, and toxicity	24 patients with 32 liver metastases		Colorectal carcinoma was the most common primary cancer. Overall 1- and 2-year LC rates were 82% (95% CI: 70%–98%) and 76.2% (95% CI: 45%–90%), respectively. SBRT achieved excellent LC and OS rates with low toxicity in patients with liver metastases
7	Lee *et al*. [39]	Retrospective study	Comparison between RFA and SBRT	11 studies involving 2238 patients	Three studies for liver metastasis	The pooled 2-year LC rate was higher in the SBRT arm (83.6% vs. 60.0%, $P < 0.001$). LC was equivalent to RFA and SBRT for HCC and better for SBRT in the treatment of liver metastases

HCC: hepatocellular carcinoma; CRLM: colorectal cancer liver metastases; FFLP: freedom from local progression; LC: local control; PFS: progression-free survival; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy, SOC: standard of care; CI: confidence interval; HR: hazard ratio, RT: radiation therapy; OS: overall survival; QOL: quality of life; SABR: stereotactic ablative radiotherapy

studies reported SBRT showed similar outcomes with RFA for LC, low toxicity in smaller tumor size, and intrahepatic liver metastasis[34–37]. SBRT is the treatment of choice for the treatment of larger tumor with intrahepatic metastasis.

6. Conclusion

HCC and metastatic liver cancer are the most common liver tumors. With the development of RT technology, RT to the liver is a feasible therapeutic option. There is room for RT in HCC for every stage of HCC (monotherapy, combined, or bridging therapy). In liver metastasis cases, RT shows an excellent, similar, and better LC in comparison to RFA (depending on tumor status). Further studies are needed (clinical trials) for a better understanding of SBRT in comparison with other liver-directed therapies (RFA, TACE).

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