Review

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Efficacy and safety of external-beam radiation therapy for hepatocellular carcinoma: An overview of current evidence according to the different target population

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Summary **Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. During the recent years, external-beam radiation therapy (EBRT) has been safely and effectively employed for the management of HCC. We overviewed the current evidence regarding the efficacy and safety of EBRT for HCC according to the different target population. PubMed database was searched for identifying English-language full-text articles regarding EBRT for the treatment of HCC. Search items were "hepatocellular carcinoma AND radiation therapy". Until now, preliminary evidence has suggested the following role of EBRT for HCC. 1) EBRT, especially stereotactic body radiation therapy, is an emerging choice of therapy for small HCC. 2) EBRT combined with non-surgical treatment can achieve an excellent intrahepatic tumor control and a potential survival benefit for huge HCC. 3) Adjunctive EBRT may improve the efficacy of transarterial chemoembolization for HCC with portal vein tumor thrombosis. 4) EBRT can relieve the pain and improve the quality of life for patients with extrahepatic metastases. 5) EBRT may be a bridge to liver transplantation by minimizing the tumor progression. 6) Adjunctive EBRT may reduce the tumor recurrence and improve the survival after resection. In summary, EBRT is a promising choice of treatment of HCC. However, more high-quality evidence is needed to further establish the status of EBRT for the management of HCC.**

Keywords: Liver cancer, radiation therapy, evidence, survival

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies (*1*). Treatment selection and prognostic assessment of HCC often depends on the tumor stage, performance status, and severity of liver dysfunction. Currently, there are lots of staging systems for HCC (*2-4*). Barcelona Clinic Liver Cancer (BCLC) staging system may be the most commonly used system for the management of HCC. According to the BCLC staging system, liver transplantation, surgical resection, and local ablative therapies, such as percutaneous ethanol injection or radiofrequency ablation (RFA), are recommended in the treatment of BCLC stage 0 or A HCC; transarterial chemoembolization (TACE) is recommended in the treatment of BCLC stage B HCC; and sorafenib is recommended in the treatment of BCLC stage C HCC (*5*). Except for the common therapeutic strategies, lots of novel therapeutic modalities have been widely explored (*6,7*).

Radiation therapy is a major traditional anticancer modality for solid tumors along with surgery and chemotherapy. In the past, the role of radiation therapy was very limited in the treatment of HCC due to the poor tolerance and low radiosensitivity of liver. Nowadays, internal radiation therapy, such as radioembolization, has been increasingly recognized for the management of HCC (*8,9*). By comparison, the role of external-beam radiation therapy (EBRT) needs further confirmation in HCC patients. Recently, the 2014 Korean Practice Guideline suggests that EBRT can be considered if patients have preserved liver function (*i.e.*, Child-Pugh class A or superb B), are not eligible for major treatments, have an incomplete response to TACE, or have portal vein invasion when the percentage of irradiated total liver volume receiving ≥ 30 Gy is ≤ 60% there is a demand for alleviating the symptoms caused by primary HCC or its metastases (*10*).

Modern EBRT has been employed for the management of HCC, which can deliver a higher radiation dose to the tumor more precisely and produce a lower risk of EBRT- induced liver disease (RILD) (*11*). More notably, EBRT can result in a high local tumor control rate of 70.0-100.0% in HCC patients (*12,13*). Considering a promising role of EBRT alone and in combination with other therapies for HCC, this paper aimed to overview the current evidence regarding the efficacy and safety of EBRT for HCC according to the different target population.

2. EBRT approaches

Modern EBRT approaches include 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic ablative body radiation therapy (SBRT), and image-guided radiation therapy. Three major EBRT approaches are reviewed in details as follows.

2.1. *3D-CRT*

In contrast to the conventional 2D-RT technique, 3D-CRT uses multiple coplanar or non-coplanar fields in order to reduce the high-dose exposure of normal tissues including the liver and bowels and to increase the tumor dose coverage. With the use of CT images for RT planning and a computerized treatment planning system, the tumor and surrounding normal liver can be accurately delineated, and the delivered dose and irradiated volume of the tumor and normal liver can be precisely evaluated. However, the risk of RILD remains high, especially in patients with Child-Pugh class B or C, prior TACE, portal vein invasion, and hepatitis B carrier status (*14,15*). Considering that these risk factors are unavoidable in patients undergoing CRT, 3D-CRT is useful to overcome these obstacles and improve the clinical outcomes in terms of tumor control and normal tissue toxicity.

2.2. *IMRT*

IMRT is an advanced form of conformal RT that facilitates the delivery of a higher radiation dose as compared to 3D-CRT. A computer-aided automated optimization process, known as inverse treatment planning, modulates the intensity of each beam to gain the desired target coverage while minimizing the dose to the normal organs. IMRT has the potential of dose escalation for HCC without an increased risk of RILD as compared to 3D-CRT, which signals the potential for improved survival and quality of life in HCC patients (*15,16*). However, there is no standard technique for IMRT delivery and the IMRT plan is not always better than the 3D-CRT plan.

2.3. *SBRT*

SBRT is generally defined as a treatment modality

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for delivering a high dose of radiation to the target in a few fractions (typically 1-5 fractions) with a high degree of precision. SBRT with a common linear accelerator usually utilizes multiple coplanar or non-coplanar static beams or multiple arc beams. To irradiate the tumor more accurately and to increase the sparing of the normal organs, SBRT is performed in combination with at least one kind of image-guided RT technique integrated into the treatment machine. During the last decade, the use of SBRT for HCC has increased substantially and the practice guidelines recommend SBRT as an alternative to the ablation/ embolization techniques, or when they have failed or are contraindicated (*10*). Generally, SBRT was used for the treatment of multiple small HCCs (< 5-6 cm) in patients with Child-Pugh class A or B.

3. Literature search

PubMed database was searched for identifying English-language full-text articles regarding EBRT for the treatment of HCC. Search items were "hepatocellular carcinoma AND radiation therapy".

4. Major findings

Table 1 summarized the survival of HCC patients treated with EBRT. Table 2A summarized the type and incidence of adverse events related to EBRT. Of note, severe EBRT- related adverse event was hardly reported. Additionally, EBRT-related toxicity could develop in all sites of body except cardiotoxicity (*17*). Only four studies provided the data regarding the grade of adverse events in patients treated with EBRT in Table 2B. Tables 3A and B summarized the study quality.

5. EBRT for small HCC

Surgical resection and LT are the first-line curative treatment options for small HCC (*5*). However, surgery is often contraindicated in HCC patients with poor liver function. EBRT, especially SBRT, becomes an emerging alternative for small HCC. Studies demonstrated that the tumor control rate of EBRT for small HCC was 89.9-100% and that the 1- and 3-year overall survival rates were 86.0-95.0% and 53.8-70.0%, respectively. Additionally, no RILD was reported, few adverse effects were observed, and the prevalence of grade III toxicity was 0-23.0% (*18-20*).

5.1. *EBRT for patients with poor liver function*

In a Canadian prospective study, Culleton *et al*. (*21*) performed SBRT in patients with Child-Pugh class B or C small HCC. None had any tumor progression at the irradiated site of HCC. Most of adverse effects after SBRT were grade I/II. The median survival time was 7.9 months and the 1-year overall survival rate was 32.3%.

5.2. *EBRT vs. resection*

In a Chinese comparative study, Su *et al*. (*22*) found that the local effect of SBRT was similar to that of surgical resection in small HCC patients with 1 or 2 nodules and Child-Pugh A cirrhosis. SBRT was less invasive and had fewer adverse effects than resection. Notably, a propensity score-matching analysis demonstrated that the 1-, 3-, and 5-year overall survival rates were statistically similar between HCC patients undergoing SBRT and those undergoing surgical resection (100%, 91.8%, and 74.3% *vs*. 96.7%, 89.3%, and 69.2%, respectively).

5.3. *EBRT vs. RFA*

Two studies compared the outcomes of SBRT *vs*. RFA for patients with small HCC. Wahl *et al*. (*23*) found that the time freedom from local progression was not significantly different between patients with HCC ≤ 2 cm undergoing SBRT and those undergoing RFA. The patients undergoing SBRT had lower pretreatment Child-Pugh scores and higher pretreatment alpha-fetoprote in levels and were submitted to more liver-directed treatments. No SBRT procedure-related death was reported. The rate of late toxicities was similar between the two groups. Seo *et al*. (*24*) also conducted a Markov model-based analysis and found a similar median survival time between patients with HCC ≤ 3 cm undergoing SBRT and those undergoing RFA (76.5 months *vs*. 77.4 months). The 5-year overall survival rate was 61.1% and 58.5% in SBRT and RFA groups, respectively.

5.4. *EBRT plus TACE vs. TACE alone*

In a Japanese study, Honda *et al*. (*25*) suggested that SBRT in combination with TACE should be effective for the treatment of hypervascular small HCC (≤ 3 cm). No acute toxicities were fatal. No RILD developed. In the combination therapy group, the 1- and 3-year overall survival rates were both 100.0%. By comparison, in the TACE alone group, the 1-, 2-, and 3-year overall survival rates were 88.9%, 73.6%, and 66.1%, respectively.

6. EBRT for huge HCC

In huge HCC (*i.e.*, tumor diameter ≥ 10 cm), microvascular invasion is more common and tumor grade is higher (*26*). Huge HCC often corresponds to the intermediate and advanced stages. Intermediate-stage HCC is treated with TACE, and advanced-stage HCC is treated with sorafenib (*27,28*). However, the 5-year overall survival rate of huge HCC treated with TACE is less than 10.0% (*29*). Additionally, the subgroup analysis

Table 1. Survival of HCC patients who underwent EBRT alone or in combination with other interventions: An overview

First author (year)	Country	Treatment	Total dose (Gy)	Fraction (*n*)	Case (*n*)	Survival time (months, Median)	1-year OS rate	2-year OS rate	3-year OS rate	5-year OS rate
EBRT for small HCC										
Sanuki (2014)	Japan	SBRT	35 or 40	5	185	NA	95.0%	83.0%	70.0%	NA
Yoon (2013)	Korea	SBRT	30 to 60	3	93	NA	86.0%	NA	53.8%	NA
Kimura (2015)	Japan	SBRT	48	4	65	41.0	92.3%	76.0%	NA	NA
Culleton (2014)	Canada	SBRT	30	6	29	7.9	32.3%	NA	NA	NA
Su (2017)	China	SBRT	NA	NA	117	NA	96.3%	NA	81.8%	70.0%
Wahl (2016)	US	SBRT	27 to 60	3 or 5	224	NA	74.0%	46.0%	NA	NA
Seo (2016)	Korea	SBRT	NA	NA	2,000	78.0	NA	NA	NA	61.1%
Honda (2013)	Japan	SBRT after TACE	48 or 60	4 or 8	365	NA	100%	NA	100%	NA
EBRT for huge HCC										
Que (2014)	Taiwan	SBRT	26 to 40	5	22	11.0	NA	NA	NA	50.0%
Han (2014)	Korea	EBRT plus non-surgical treatment	45 to 62.5	NA	116	14.8	59.5%	NA	19.7%	NA
Guo (2000)	China	EBRT after TACE	25 to 55	NA	107	18.0	59.4%	NA	28.4%	15.8%
Kim (2014)	Korea	EBRT after TACE	37.8 to 58	NA	283	15.3	NA	23.5%	NA	NA
EBRT for HCC with portal vein tumor thrombosis										
Zeng (2005)	China	EBRT	36 to 60	NA	158	8.0	34.8%	NA	NA	NA
Tang (2013)	China	3D-CRT	30 to 52	NA	371	12.3	51.6%	28.4%	19.9%	NA
Yoon (2012)	Korea	3D-CRT after TACE	21 to 60	5	412	10.6	42.5%	22.8%	NA	NA
Yu (2017)	Korea	3D-CRT after TACE	30 to 35	10	69	NA	NA	62.9%	NA	NA
Lu (2015)	China	3D-CRT plus TACE	40 to 52.5	2 to 6	63	13.0	62.4%	20.8%	NA	NA
EBRT for HCC with extrahepatic metastases										
Jiang (2012)	China	EBRT	47 to 60	NA	13	NA	NA	70.7%	NA	NA
Sun (2016)	China	IMRT plus sorafenib	NA	NA	45	21.9 (Mean)	91.1%	78.8%	NA	NA
Casamassima (2012)	Italy	SBRT	36	3	48	NA	39.7%	14.5%	NA	NA
Zhou (2014)	China	EBRT	2	NA	55	13.6	58.7%	32.3%	NA	NA
Park (2015)	Korea	WBRT	30	10	97	3.5	NA	NA	NA	NA
He (2009)	China	EBRT	32 to 66	NA	205	7.4	32.4%	13.2%	NA	NA
Kaizu (1998)	Japan	EBRT	20 to 65	NA	57	6.0	NA	NA	NA	NA
Seong (2005)	Korea	EBRT	12.5 to 50	NA	51	5.0	NA	4.0%	NA	NA
Yamashita (2007)	Japan	EBRT	46 to 60	NA	28	13.0	53.0%	33.0%	NA	NA
Zeng (2005)	China	EBRT	40 to 60	NA	125	9.4	42.1%	3.4%	NA	NA
EBRT as a bridge to LT for HCC										
Katz (2012)	US	SHORT	50	10	18	6.3	NA	NA	NA	NA
Guarneri (2016)	Italy	SBRT	36 to 48	3 to 5	8	3.2	NA	NA	NA	NA
O'Connor (2012)	US	SBRT	33 to 54	3	10	NA	NA	NA	NA	100%
Sapisochin (2017)	Canada	SBRT	8.5 to 54	1 to 6	379	NA	83.0%	NA	61.0%	61.0%
Moore (2017)	Israel	SBRT followed by LT	54	NA	23	NA	NA	NA	NA	NA
Andolino (2011)	US	SBRT followed by LT	44 or 40	3 or 5	60	NA	NA	69.0%	NA	NA
Postoperative adjuvant EBRT										
Yu (2014)	China	Postoperative 3D-CRT	60	NA	119	NA	96.2%	NA	72.6%	48.4%
Wang (2015)	China	Postoperative IMRT	NA	NA	33	NA	NA	NA	67.7%	NA
Bai (2016)	China	Postoperative 3D-CRT	32 to 48	NA	92	14.5	71.1%	NA	NA	NA

Abbreviations: HCC: hepatocellular carcinoma; OS: overall survival; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; EBRT: external-beam radiation therapy; 3D-CRT: three-dimensional conformal radiation therapy; IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy; WBRT: whole brain radiation therapy; SHORT: stereotactic hypofractionated radiation therapy; NA: not available.

Table 2A. EBRT-related adverse effects in HCC patients

Adverse effects	Incidence (%)	References with data
Systemic symptoms		
Fatigue	4.9-100	Culleton (2014); Su (2017); Que (2014); O'Connor (2012); Sapisochin (2017); Moore (2017); Yu (2014); Wang (2015)
Dizziness	6.7	Lu (2015)
Malaise	20.0	Lu (2015)
Anorexia	8.3-54.5	Yu (2017); Lu (2015); Sun (2016); Zhou (2014); Yamashita (2007); Zeng (2005)
Fever	7.7-20.0	Jiang (2012); Lu (2015); Bai (2016)
Weight loss	4.9	Su (2017)
Pain		
Liver pain	6.7	Lu (2015)
Rib pain	27.3	Que (2014)
Abdominal pain	10.0-100	Culleton (2014); Yu (2017); O'Connor (2012); Wang (2015)
Cutaneous		
Dermatitis	13.6-100	Que (2014); Yamashita (2007); Yu (2014); Wang (2015)
Skin induration	13.6	Que (2014)
Haematological		
Myeloid suppression	10.0-100	Tang (2013); Yu (2014); Bai (2016)
Leukocytopenia	8.3-100	Honda (2013); Lu (2015); Jiang (2012); Sun (2016); Zhou (2014); Yamashita (2007); Zeng (2005); Wang (2015)
Neutropenia	33.3	Yu (2017)
Thrombocytopenia	3.4-100	Culleton (2014); Honda (2013); Que (2014); Yu (2017); Jiang (2012); Sun (2016); Zhou (2014); Yamashita (2007); Zeng (2005)
Low hemoglobin	100	Honda (2013); Wang (2015)
Anemia	4.9-34.8	Su (2017); Yu (2017)
Biochemical		
Creatinine increased	100	Wang (2015)
Bilirubin increased	3.2-100	Culleton (2014); Su (2017); Honda (2013); Que (2014); Han (2014); Yu (2017); Yamashita (2007); Zeng (2005); Andolino (2011); Wang (2015)
ALT increased	3.7-100	Su (2017); Han (2014); Zeng (2005); Tang (2013); Yu (2017); Yamashita (2007); Zeng (2005); Andolino (2011); Wang (2015)
AST increased	20.7-100	Han (2014); Yu (2017); Wang (2015)
High serum transamialses	33.3-100	Honda (2013); Andolino (2011)
GLA increased	100	Wang (2015)
ALP increased	11.7-100	Que (2014); Yu (2017); Andolino (2011); Wang (2015)
Low albumin	28.3-100	Que (2014); Yu (2017); Andolino (2011); Wang (2015)
Gastrointestinal		
Gastrointestinal damage	8.7-27.3	Zhou (2014); Moore (2017)
Nausea	5.8-100	Culleton (2014); Su (2017); Que (2014); Yu (2017); O'Connor (2012); Yu (2014); Wang (2015)
Vomiting	2.9-100	Culleton (2014); Que (2014); Yu (2017); Lu (2015); Zhou (2014); O'Connor (2012); Sapisochin (2017); Yu (2014); Wang (2015); Bai (2016)
Diarrhea	2.9-100	Culleton (2014); Yu (2017); Zhou (2014); Yamashita (2007); Zeng (2005); Yu (2014)
Gastroduodenitis	3.2	Yoon (2012)
Gastroduodenal ulcer	0.9-100	Kim (2013); Yoon (2012); Yamashita (2007); Zeng (2005); Yu (2014)
Gastrointestinal bleeding	1.6-3.2	Wahl (2015); Zeng (2005); Tang (2013)
Abdominal distension	10.0	Culleton (2014)
Esophagitis	25.0	Sun (2016)
Hepatic		
RILD	1.6-100	Culleton (2014); Wahl (2015); Guarneri (2016); Moore (2017); Yu (2014)
Liver injury	20.0-38.9	Zhou (2014); Sapisochin (2017); Bai (2016)
Worsen Child-Pugh score	3.3-10.3	Sanuki (2014); Yoon (2013); Su (2017); Honda (2013); Katz (2011)
Worsen ascite	1.6-36.7	Wahl (2015); Lu (2015)
Infection	10.0	Bai (2016)
Pneumonia	50.0	Sun (2016)
Kidney injury	5.5	Zhou (2014)

Abbreviations: HCC: hepatocellular carcinoma; EBRT: external-beam radiation therapy; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GLA: glutamy aminotransferase; ALP: alkaline phosphatase; RILD: radiation-induced liver disease. *Note*: Data regarding EBRT-related adverse effects from the studies of Seo (2016) , Park (2015), Seong (2005) and He (2009) cannot be obtained.

Table 2B. Grade of EBRT-related adverse effects in HCC patients

Grade of adverse effects	EBRT for small HCC Kimura (2015)	EBRT for huge HCC Guo (2000)	EBRT for HCC with extrahepatic metastases Casamassima (2012)	EBRT for HCC with extrahepatic metastases Kaizu (1998)
	SBRT	EBRT	SBRT	SHORT
I	-	-	-	-
II	-	-	2.1%	22.8%
III	-	9.2%	-	7.0%
IV	1.7%	-	-	-
V	-	-	-	1.8%

Abbreviations: HCC: hepatocellular carcinoma; EBRT: external-beam radiation therapy; SBRT: stereotactic body radiation therapy; SHORT: stereotactic hypofractionated radiation therapy. *Note*: EBRT-related adverse effects were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0.

Table 3A. Quality assessment of retrospective studies using Newcastle Ottawa Scale

Author (year)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohort on the basis of design or analysis	Assessment of outcomes	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total scale
Sanuki (2014)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Yoon (2013)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Kimura (2015)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Su (2017)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Wahl (2016)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Seo (2016)	1 point	0 point	1 point	0 point	1 point	1 point	1 point	1 point	6 points
Honda (2013)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Que (2014)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Han (2014)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Guo (2000)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Kim (2014)	1 point	0 point	1 point	0 point	1 point	1 point	1 point	1 point	6 points
Zeng (2005)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Tang (2013)	1 point	0 point	1 point	0 point	1 point	1 point	1 point	1 point	6 points
Yoon (2012)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Lu (2017)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Jiang (2012)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Sun (2016)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Casamassima (2012)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Zhou (2014)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Park (2015)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
He (2009)	1 point	1 point	1 point	0 point	0 point	1 point	0 point	0 point	4 points
Kaizu (1998)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Seong (2005)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Yamashita (2007)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Zeng (2005)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	0 point	6 points
Katz (2012)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Guarneri (2016)	1 point	0 point	1 point	0 point	0 point	1 point	1 point	1 point	5 points
O'Connor (2012)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Sapisochin (2017)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Moore (2017)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Andolino (2011)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Wang (2015)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Bai (2015)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points

Note: Study quality was assessed as follows: low quality = 0-4; high quality = 5-8.

Table 3B. Quality assessment of prospective studies using Newcastle Ottawa Scale

Author (year)	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohort on the basis of design or analysis	Assessment of outcomes	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total scale
Culleton (2014)	1 point	1 point	1 point	0 point	0 point	1 point	1 point	1 point	6 points
Yu (2017)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points
Yu (2014)	1 point	1 point	1 point	0 point	1 point	1 point	1 point	1 point	7 points

Note: Study quality was assessed as follows: low quality = 0-4; high quality = 5-8.

of a randomized controlled trial showed little effect of sorafenib in patients with macrovascular invasion and/or extrahepatic spread (*30*). Recent studies showed that EBRT alone or combined with non-surgical treatment might achieve an excellent intrahepatic tumor control and a potential survival benefit of huge HCC.

6.1. *EBRT alone*

Between 2009 and 2011, Que *et al*. (*31*) performed SBRT for 22 patients with huge HCC. The local control rate was 55.5%. The investigators found that 22.7% and 63.6% of patients obtained a complete and partial response, respectively. Acute toxicities related to radiation therapy were tolerable and mild. The median survival time was 11.0 months. The 1-year overall survival rate was 50.0%.

6.2. *EBRT plus non-surgical treatment*

Between 2001 and 2010, Han *et al*. (*32*) performed EBRT in combination with TACE, hepatic arterial infusion chemotherapy, or systemic chemotherapy in 116 patients with huge HCC. The local control rate was 81.0%. The median survival time was 14.8 months. The 1- and 3-year overall survival rates were 59.5% and 19.7%, respectively.

6.3. *EBRT plus TACE*

Between 1989 and 1998, Guo and Yu (*33*) treated 107 unresectable huge HCC patients with TACE followed by EBRT. Most of side effects occurred after TACE and were transient, and the overall 3-month response rate was 48.6%. The median survival time was 18.0 months. The 1-, 3-, and 5-year overall survival rates were 59.4%, 28.4%, and 15.8%, respectively.

6.4. *EBRT plus TACE vs. TACE alone*

Kim *et al*. (*34*) compared the outcomes of patients with EBRT after TACE *vs.* TACE alone. This combination therapy had significantly superior progression-free survival, intrahepatic control, and overall survival than TACE alone.

7. EBRT for HCC with portal vein tumor thrombosis (PVTT)

Although sorafenib is the first-line treatment option for advanced HCC, its efficacy in HCC patients with PVTT is frequently questioned (*35*). Additionally, PVTT can lead to the reduction of hepatic blood supply and development of severe portal hypertension related complications, such as gastroesophageal variceal bleeding and ascites (*36*), which limits the selection of treatment options. Very localized HCC accompanied by PVTT in patients with preserved hepatic function can be surgically resected (*37,38*). However, surgical removal of tumor thrombus is rarely performed probably owing to the limited hepatic reserve (*39*). TACE may be performed safely in HCC patients with PVTT (*40*), but its efficacy is unsatisfactory (*41*). Recently, EBRT has been used as an alternative treatment for HCC with PVTT achieving a high response rate.

7.1. *EBRT vs. TACE or resection*

In 2005, Zeng *et al*. (*42*) compared the outcomes of EBRT *vs*. TACE or resection for the treatment of HCC with PVTT. The most common adverse effects of radiation therapy were loss of appetite and nausea. The median survival time was 8.0 and 4.0 months in the EBRT and TACE/resection groups, respectively. The 1-year overall survival rate was 34.8% and 11.4% in EBRT and TACE/resection groups, respectively. In 2013, Tang *et al*. (*43*) also compared the outcomes of 3D-CRT *vs.* surgical resection for resectable HCC with PVTT. The median survival time was 12.3 and 10.0 months in 3D-CRT and resection groups, respectively. The 1-, 2-, and 3-year overall survival rates were 51.6%, 28.4%, and 19.9% *vs.* 40.1%, 17.0%, and 17.0% in 3D-CRT and resection groups, respectively ($P = 0.029$). Both studies suggested a superiority of 3D-CRT over TACE/resection for HCC with PVTT.

7.2. *EBRT plus TACE*

In 2012, Yoon *et al*. (*44*) analyzed 412 patients treated with 3D-CRT after TACE for HCC and PVTT. Acute toxicities were mostly mild, such as fatigue, anorexia, and nausea. The objective response rate was 27.9% (complete response rate: 3.6% and partial response rate: 24.3%). The median survival time was 10.6 months. The 1- and 2-year overall survival rates were 42.5% and 22.8%, respectively. Additionally, in 2017, Yu *et al*. (*45*) reported the safety and efficacy of TACE followed by 3D-CRT in such patients. The median follow-up time was 11.4 months. Liver function status was not significantly worsened after treatment. The 3-month objective response rate at the radiation therapy targeted area was 69.6%. The 2-year overall survival, recurrence-free survival, and progression-free survival rates were 62.9%, 47.6%, and 14.3%, respectively.

7.3. *EBRT plus TACE vs. TACE alone*

In 2015, Lu *et al*. (*46*) compared the outcomes of 3D-CRT plus TACE *vs.* TACE alone. No serious adverse reactions requiring treatment were reported. In the combination treatment group, the median survival time was 13.0 months; and the 1- and 2-year overall survival rates were 62.4% and 20.8%, respectively. By comparison, in the TACE alone group, the

median survival time was 9.0 months; and the 1- and 2-year overall survival rates were 56.5% and 18.8%, respectively. The overall survival was statistically significant between the two groups ($P = 0.047$). Thus, compared with TACE alone, the combination treatment might improve the survival of HCC patients with PVTT.

8. EBRT for HCC with extrahepatic metastases

Currently, extrahepatic metastases can be frequently observed due to the prolonged survival of advanced HCC patients. The most common metastatic organ from HCC was the lung followed by adrenal gland, brain, bone, and lymph node, *etc*. (*47-50*). Unfortunately, there is no standard treatment for HCC with extrahepatic metastases. Although the resection of isolated metastatic lesions from some malignancies may provide a survival benefit, its role for extrahepatic metastases from HCC is not well-established (*51*). Recently, EBRT has been used as a palliative treatment to relieve the pain and improve the quality of life in HCC patients with extrahepatic diseases, thereby leading to a satisfactory treatment response.

8.1. *Lung metastases*

8.1.1. *EBRT alone*

Jiang *et al*. *(52*) indicated a pronounced efficacy of EBRT for lung metastases. A total of 13 patients with lung metastases from HCC underwent EBRT. Adverse effects were mild. The median progression-free survival time was 13.4 months. The 2-year survival rate was 70.7%.

8.1.2. *EBRT alone vs. EBRT plus sorafenib*

Sun *et al*. (*53*) compared the outcomes of IMRT alone *vs.* IMRT combined with sorafenib for the treatment of 45 HCC patients with lung metastases. In the IMRT alone group, only one case developed anorexia. In the combination treatment group, most of the toxicities were mild and related to sorafenib. The 1- and 2-year overall survival rates were 66.8% and 30.4% *vs.* 91.1% and 78.8% in IMRT alone and IMRT plus sorafenib groups, respectively. Thus, EBRT plus sorafenib may be a more promising approach in such patients.

8.2. *Adrenal metastases*

Casamassima *et al*. (*54*) treated 48 HCC patients with adrenal metastases by SBRT. The 2-year local control rate was 90.0%. Toxicities were well-tolerated. The median follow-up time was 16.2 months. The 1- and 2-year overall survival rates were 39.7% and 14.5%, respectively. Zhou *et al*. (*55*) also treated 55 patients with adrenal metastases from HCC by EBRT. Adverse effects were mild to moderate. All patients experienced the pain relief after the completion of EBRT. The median survival time was 13.6 months. Thus, EBRT may be a good palliative therapy for adrenal metastases from HCC.

8.3. *Brain metastases*

The prognosis of HCC patients who developed brain metastases is extremely poor, with a reported median survival time of 1.0-3.0 months (*56,57*). Park *et al*. (*58*) treated 97 patients with brain metastases from HCC by EBRT alone or after surgery and/or radiosurgery. The median survival time was 3.5 months, which was superior to the previous data (*56,57*). The whole brain radiation therapy may be a choice of treatment for brain metastases.

8.4. *Bone metastases*

Bone metastases are a common cause of pain in metastatic HCC. EBRT has been reported to be effective in palliating painful bone metastases with a partial pain relief rate of 80.0-90.0% and a complete pain relief rate of 50.0% (*59*). The 1- and 2-year overall survival rates were 32.4% and 13.2%, respectively (*60*). The median survival time of patients treated with EBRT for bone metastases from HCC was 5.0-7.4 months (*60-62*). A large cohort of HCC patients with bone metastases treated with EBRT suggested that acute EBRT-associated toxicities were mild or absent (*60*). Therefore, palliative EBRT might be considered for bone metastases from HCC.

8.5. *Lymph node metastases*

Since HCC invasions are mostly hematogenous, lymph node metastases are uncommon. The incidence of lymph node involvement in HCC patients treated with surgery was reportedly 5.1-7.5% (*63*), but the incidence from an autopsy series was 25.5-42.0% (*64*). Yamashita *et al*. (*65*) performed EBRT on 28 HCC patients with lymph node metastases. Five (18.0%) patients achieved a complete response and 18 (64.0%) patients achieved a partial response. The median survival time was 13.0 months, and the 1- and 2-year overall survival rates were 53.0% and 33.0%, respectively. Zeng *et al*. (*66*) also suggested that the use of EBRT could improve the survival of patients with lymph node metastases from HCC. The median survival time of patients treated with EBRT was significantly longer than that of patients who did not undergo EBRT (9.4 months *vs.* 3.3 months, $P < 0.001$). The 1- and 2-year overall survival rates were 42.1% and 19.9% *vs.* 3.4% and 0% in patients who underwent EBRT and did not undergo EBRT, respectively ($P < 0.001$). Thus, EBRT may be an effective palliative treatment option for lymph node metastases from HCC with a good performance status.

9. EBRT as a bridge to LT for HCC

LT represents the best treatment option for selected HCC (*67*). However, the use of LT is limited by the shortage of donor organs. Many patients need a long waiting time on the transplant list and may drop out because of tumor progression (*68*). According to the American Association for the Study of Liver Diseases guidelines regarding the management of HCC, bridging therapies should be applied if the waiting time is longer than 6 months (*69*). Local treatment as a bridge to LT has been utilized to minimize the tumor progression and reduce the post-transplant recurrence. TACE and RFA are the most common bridging therapies, but generally recommended for only patients with well-compensated cirrhosis (*5*). Recent studies suggested the potential role of EBRT in such patients. EBRT might be an effective bridging therapy for HCC patients awaiting LT, which may provide an excellent local control with minimal side effects, downsize or stabilize tumors prior to LT, and achieve a good pathological response.

9.1. *EBRT as a bridge to LT*

At the University of Rochester Medical Center, Katz *et al*. (*70*) evaluated the bridging role of stereotactic hypofractionated radiation therapy for 18 HCC patients. The most common side effect was fatigue. Neither toxicity grade III nor RILD occurred. All patients were alive without any recurrence. Guarneri *et al*. (*71*) also investigated the role of SBRT prior to LT in 8 patients with HCC. The complete response rate was 61.5% and the minimal pathological response rate was 15.3%. Two patients developed toxicity grade II, and 1 patient developed a non-classic RILD. During a median follow-up of 9.6 months, 7 patients were alive and free of disease. Besides, at the Baylor Radiosurgery Center, O'Connor *et al*. (*72*) studied 10 patients treated with LT after SBRT. Four of them experienced acute toxicities, most of which were grade I. During a median follow-up of 62.0 months, all patients were alive without any tumor recurrence. Notably, the 5-year overall survival and disease-free survival rates were both 100%. In a retrospective study, Moore *et al*. included 23 early stage HCC patients who were not eligible for resection or local therapy but underwent SBRT (*73*). The median overall survival time was 34.2 months without any lethal SBRT-related adverse event. After SBRT, 16 patients became eligible for LT. Among them, 11 patients underwent LT with an excellent 1-year survival rate. Similarly, Andolino *et al*. (*12*) studied 60 patients with liver-confined HCC treated with SBRT. After SBRT, 23 patients underwent LT, and the progression free survival and overall survival rates at 2 years were 69.0% and 96.0%, respectively. By comparison, 27 patients did not subsequently undergo LT, and the progression free survival and overall survival rates at 2 years were only 33.0% and 47.0%, respectively.

9.2. *EBRT vs. TACE or RFA*

Sapisochin *et al*. (*74*) found that SBRT might be as effective as TACE or RFA for maintaining HCC patients on the LT waiting list. The rates of drop-out and postoperative complications were similar between them. The 1-, 3-, and 5-year survival rates from the time of waiting list were similar among them (83.0%, 61.0%, and 61.0% in the SBRT group; 86.0%, 61.0%, and 56.0% in the TACE group; 86.0%, 72.0%, and 61.0% in the RFA group, $P = 0.400$).

10. Postoperative EBRT

Surgical resection is technically difficult for centrally located HCC (*75*) and HCC located close to the major vessels (*76*). In such patients, postoperative EBRT might be potentially useful.

10.1. *Postoperative EBRT for centrally located HCC*

A study by Yu *et al*. (*77*) evaluated the role of 3D-CRT after narrow-margin resection for centrally located HCC. Fifty-eight of 119 patients were treated with postoperative 3D-CRT. No RILD occurred. Notably, in the subgroup analysis, postoperative 3D-CRT significantly improved the recurrence-free survival of patients with small HCC (≤ 5 cm), but not the overall survival.

10.2. *Postoperative EBRT for HCC located close to the major vessels*

In an exploratory study, Wang *et al*. (*78*) treated 116 HCC patients located close to the major vessels by narrow-margin (< 1.0 cm) resection. Among them, 33 patients received postoperative IMRT and 83 did not receive IMRT. During a median follow-up time of 33.0 months, the observed toxicities were mild and no patient developed any RILD. Patients receiving narrow-margin resection plus IMRT had a significantly lower incidence of early recurrence than those receiving narrow-margin resection alone. The 3-year overall survival and disease-free survival rates of narrow-margin resection plus postoperative IMRT were significantly superior to those of narrow-margin resection alone. Additionally, the overall survival and disease-free survival rates of narrow-margin resection plus postoperative IMRT were similar to those of wide-margin resection.

10.3. *Postoperative EBRT vs. postoperative TACE*

Bai *et al*. (*79*) evaluated the outcomes of adjuvant 3D-CRT *vs*. TACE after resection for 92 HCC patients with PVTT. No serious adverse event was observed. The

6- and 12-month overall survival rates were 88.9% and 71.1% in postoperative 3D-CRT group and 80.0% and 53.3% in postoperative TACE group. The median overall survival and disease-free survival were not significantly different between postoperative 3D-CRT and TACE groups.

11. Conclusions

Based on the current evidence, EBRT should be considered in the following conditions. First, EBRT should be a potential alternative choice of therapy for small HCC, especially if the tumor was unresectable. Second, EBRT should be considered for relieving the pain for patients with extrahepatic metastases, especially the bone pain. Third, adjunctive EBRT may be considered in patients with huge HCC, HCC patients with PVTT, HCC patients awaiting LT, and HCC patients treated with resection. However, the role of EBRT remains limited due to the relatively low level of evidence. A majority of studies were retrospective (n = 33), and a minority of studies were prospective (n = 3). No randomized controlled trial regarding EBRT was performed. Additionally, most of evidence was from Eastern countries. Thus, high-quality clinical trials should be needed to further establish the status of EBRT for the treatment of HCC.

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