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Review

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Treatment of high-burden hepatocellular carcinoma: an oncologist perspective

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Abstract

Hepatocellular carcinoma (HCC) is recognized as a major global healthcare burden. Although there have been tremendous improvements in cancer screening and treatment, HCC mortality rate remains high. Many patients with HCC present late to medical attention and thus are not candidates for curative treatment. They typically have high tumor burden at presentation showing heterogeneity in anatomical factors and biochemical profile. Despite the relatively poor prognosis for these patients, significant improvements can still be made in survival if the optimal treatment modality is chosen. Currently, there is no international consensus on how to manage this group of heterogeneous, high-burden HCC. In this article, we will address this question by reviewing the latest available evidences. Our definition of "high-burden HCC" will be based on three factors: size, number of tumors and the presence of macrovascular invasion. The different treatment modalities, namely surgery, intra-arterial therapy, radiotherapy and systemic therapy, and their respective supportive evidences, will be discussed. In the end, we will summarize with our views on the future direction of research priorities for the management of high-burden HCC.

Keywords: Cancer, hepatocellular carcinoma, liver

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major healthcare burden in the world. It represents 6% and 9% of the global cancer incidence and mortality respectively[1]. It is the second most common cause of cancer-related death worldwide[1]. Although major advancements have been made in cancer screening, diagnosis

and treatment, prognosis of liver cancer remains poor. In 2012, World Health Organization estimated the incidence-to-mortality ratio of liver cancer to be as high as 95%[1].

One of the major challenges in treating HCC is its heterogeneity and complexity. In contrast to other cancers, the prognosis of HCC not only depends on the tumor load, but also on the underlying etiology as well as the remaining liver reserve. Multiple staging systems have been proposed in the management of HCC. Many of them classify the patients into three groups. The first group of patients are those with the best prognosis, with little tumor burden and good liver reserve. They are often offered treatment with curative intent. The second group represents those patients with advanced disease of which tumor load is high and liver reserve is poor. These patients have very few treatment options and are offered systemic therapy, enrollment into clinical trials or supportive treatment.

The third group is the intermediate group which includes patients who do not fulfill the criteria of the first and second group. They have high tumor burden yet with relatively good liver reserve, and are potential candidates for multiple or combination of therapies, some of which can be with curative intent. This is the group which is made up of the most heterogeneous patient population, and hence it remains a challenge to devise the best therapeutic strategy for them.

In this review, the latest therapeutic options for this heterogeneous, high-tumor burden group of HCC patients will be discussed. Firstly, we will define our target population of high-burden HCC based on the size, the number of tumors, and the presence of portal vein invasion. Secondly, we will outline the various therapeutic options available and evaluate their impact on survival. Thirdly, we will briefly discuss the etiological adjunctive treatment for high-burden HCC. Finally, we will summarize the future directions in the management of high-burden HCC.

DEFINITION

Multiple factors have been identified to affect the survival rates of patients with HCC. While many of them are surrogate markers of liver reserve, a few anatomical factors have also been found to persistently affect prognosis[2-4], including the size, the number of tumors and the presence of portal vein invasion. The application of these anatomical factors is important because it affects the choice of optimal treatment modalities.

Historically, large HCC is defined as tumors of size ≥ 5 cm, owing to the poor efficacy of radiofrequency ablation in managing HCC beyond that size. This is also the cutoff used in the Barcelona Clinic Liver Cancer (BCLC) staging system to classify tumors which are not amenable to curative treatment. Multiplicity of tumor is usually defined as number of tumors ≥ 3, and the higher number of tumors means curative treatment would unlikely be successful. Portal vein invasion is another important poor prognostic indicator, not only because it indicates an advanced disease, it would also limit the number of feasible treatment options. According to BCLC, portal vein invasion is a contraindication for transarterial chemoembolization (TACE). As a result, only systemic therapy and best supportive care are feasible options for this group of patients.

The focus of our discussion will be on treatment options available to high-burden HCC, which we define as HCC satisfying the following criteria: (1) presence of any tumor of size ≥ 5 cm; (2) number of tumors ≥ 3; (3) presence of portal vein invasion; and (4) without extrahepatic metastasis. This group of patients were traditionally considered to carry a grim outlook but recent treatment advancements have improved their prognosis.

TREATMENT OPTIONS FOR HIGH-BURDEN HCC

In the literature, a plethora of therapeutic options are available for high-burden HCC. These include surgery, TACE, transarterial radioembolization (TARE), radiotherapy (RT) and systemic therapy. The choice of

therapy depends on the extent of the disease, the liver function and the patient's performance status. Each treatment option will be discussed individually here.

Surgery

Previously thought only to have a role in early HCC, advancement in surgical techniques have enabled hepatic resection to become a therapeutic option for high-burden HCC. Although high quality evidence is still lacking, many retrospective studies have provided support for hepatic resection to be a safe and effective method in managing high-burden HCC. In fact, many Asian liver centers prefer hepatic resection, as long as it is feasible, to other local treatment options. We will now review the recent studies published between 2007 and 2017 to give the most updated picture of the efficacy of hepatic resection in the management of high-burden HCC[5-39] [Table 1]. Of note, few studies have examined the effect of tumor size and number of tumors independently on survival, so we would group them together in the following discussion, with large (≥ 5 cm) and multifocal tumor as one single population (large/multifocal HCC).

For patients with large/multifocal high-burden HCC treated with surgery, the median survival rate was 27.6 months, and the median 1-, 3-, and 5-year overall survival rates were 74.3%, 51.2%, and 39.2% respectively. Among patients treated with surgery, survival was particularly favorable among those with solitary large tumor (≥ 5 cm), with median 1-, 3-, and 5-year survival rates of 87.2%, 63.2%, and 56.1% respectively. Large tumor size has been repeatedly reported as a poor prognostic factor for HCC. This is consistent with the results we found in high-burden HCC treated with surgery [Table 2]: the median 1-, 3-, and 5-year overall survival rates for huge/multifocal tumor (≥ 10 cm) were 70.0%, 45.0%, and 36.0%, whereas those for moderately-large/multifocal tumors (≥ 5 and < 10 cm) were 73.0%, 55.1%, and 50.8% respectively. However, it is worth noting that larger tumors do not appear to be associated with higher post-operative mortality. The median postoperative mortality for huge/multifocal (≥ 10 cm) tumors was 2.6%, compared with 4.3% for large/multifocal tumors.

Portal vein invasion remains to be another poor prognostic factor for HCC patients despite advancements in treatment modalities, especially for tumors invading into the main or contralateral portal vein[40]. Surgery has been considered contraindicated by many institutions, including the BCLC system[41]. However, many studies, particularly those from the Asian centers, have reported hepatic resection to be safe and effective for patients with portal vein invasion[28,42-58] [Table 3]. The median 1-, 3- and 5-year overall survival rates for patients with all forms of portal vein invasion treated with surgery were 61.0%, 32.9% and 27.0% respectively. The prognosis worsens with the degree of portal vein involvement [Table 4]. For Vp1 and Vp2 involvement, the median 1-, 3- and 5-year overall survival rates after surgery were 69.1%, 42.2% and 38.7%, whereas for those with main portals or the 1st branch involvement (Vp3 and Vp4), the median 1-, 3- and 5-year overall survival rates after surgery were 52.8%, 23.4% and 14.6% respectively [Table 5].

Transarterial chemoembolization

Before the advent of intra-arterial therapy, surgery has been the mainstay of treatment for HCC. However, less than 30% of patients were eligible for liver resection due to advanced staging of the disease[59,60]. TACE revolutionized the treatment for high-burden HCC when it was first introduced in the early 90's[61-65]. It takes advantage of the differential portal and arterial contributions to the blood supply of the tumor and the normal liver parenchyma. Normal liver parenchyma receives majority of the blood supply from the portal vein while the tumor feeds itself mainly from the hepatic arteries. The effects of TACE are two-fold. First, it delivers cytotoxic drugs to kill tumor cells. At the same time, by embolization of the arterial supply to the tumor, it creates an ischemic environment while keeping the cytotoxic agents within the tumor. The overall effect is to induce tumor necrosis via both direct poisoning and starvation.

Nowadays, TACE is the treatment of choice for unresectable high-burden HCC. The positive efficacy of TACE has been reported in numerous case reports and retrospective studies since its introduction in

Table 1. Recent studies on the efficacy of surgical resection in the management of large/multifocal high-burden hepatocellular carcinoma

Year	Place	Authors	Type (S/M/A)	Size: ≥5 cm	Size: 5-10 cm	Size: ≥10 cm	Number of patients (*n*)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median survival (months)	Post-operative mortality (%)	Recruitment year
2007	South Korea	Cho *et al*.[5]	S	-	61	-	61	85.0	59.0	52.9	-	1.6	1998-2001
2007	South Korea	Lee *et al*.[6]	A	-	-	100	100	66.0	44.0	31.0	-	2.0	1997-2003
2007	Singapore	Pandey *et al*.[7]	A	-	-	166	166	-	-	28.6	20.0	3.0	1995-2006
2007	Canada	Shah *et al*.[8]	A	-	-	24	24	-	-	54.0	-	8.3	1993-2004
2007	UK	Young *et al*.[9]	A	-	42	-	42	70.0	45.0	45.0	-	7.0	1994-2006
2008	Japan	Shimada *et al*.[10]	A	-	-	85	85	-	-	31.5	27.6	1.2	1988-2004
2008	France	Chirica *et al*.[11]	A	20	-	-	20	73.0	56.0	45.0	-	-	1998-2004
2008	Japan	Taniai *et al*.[12]	A	-	-	29	29	-	33.6	33.6	-	6.9	1987-2006
2008	Taiwan	Wang *et al*.[13]	A	58	-	-	58	58.0	32.0	22.0	-	-	1990-2006
2008	Taiwan	Wang *et al*.[14]	A	243	-	-	243	81.5	64.4	50.5	60.4	-	1986-2002
2009	Australia	Ng *et al*.[15]	A	-	-	44	44	66.4	38.1	27.8	21.5	-	1990-2008
2009	China	Yang *et al*.[16]	A	260	-	0	260	87.0	55.5	38.2	45.5	2.3	1992-2002
2009	Korea	Choi *et al*.[17]	A	-	-	50	50	70.0	50.2	40.2	-	-	1996-2006
2009	Taiwan	Ho *et al*.[18]	A	294	-	-	294	77.4	51.9	36.6	37.9	-	1981-2000
2010	Greece	Delis *et al*.[19]	A	66	-	-	66	69.0	37.0	32.0	-	-	2002-2008
2010	Taiwan	Lin *et al*.[20]	A	93	-	-	93	83.0	49.0	-	27.6	5.4	2001-2007
2010	Italy	Ramacciato *et al*.[21]	M	20	-	-	20	-	-	33.6	-	-	2000-2006
2010	Italy	Ramacciato *et al*.[21]	S	31	-	-	31	-	-	56.1	-	-	2000-2006
2010	USA	Schiffman *et al*.[22]	A	78	-	-	78	-	-	20.0	-	-	1999-2005
2010	China	Wang *et al*.[23]	A	-	189	-	189	70.0	51.2	36.5	-	7.5	1991-2004
2011	Japan	Yamashita *et al*.[24]	A	0	-	53	53	74.0	43.0	35.0	-	3.8	1995-2007
2011	China	Luo *et al*.[26]	A	85	-	0	85	70.6	35.3	23.9	-	2.4	2004-2006
2011	China	Zhou *et al*.[27]	S	85	-	-	85	93.8	56.2	47.0	-	-	1995-2002
2012	Italy	Ruzzenente *et al*.[25]	S	0	13	-	13	76.9	68.4	68.4	-	0.0	1995-2009
2012	Taiwan	Chang *et al*.[28]	A	478	-		-	74.6	51.8	40.7	-	2.7	1991-2006
2012	Serbia	Galun *et al*.[29]	A	32	-	-	32	-	-	-	26.0	0.0	2001-2008
2012	Taiwan	Huang *et al*.[30]	A	-	-	74	74	61.9	39.4	28.9	20.4	-	2001-2005
2012	USA	Shrager *et al*.[31]	A	-	-	130	130	56.9	30.3	18.8	17.0	6.9 before 2002 2.3 after 2002	1992-2010
2013	Switzerland	Allemann *et al*.[32]	A	-	-	22	22	-	-	45.0	27.0	0.0	1997-2009
2013	Japan	Ariizumi *et al*.[33]	A	-	-	177	177	61.0	46.0	42.0	38.5	-	1990-2008
2014	China	Yin *et al*.[34]	A	88	-	-	88	76.1	51.5		41.0	1.1	2008-2010
2015	Taiwan	Chan *et al*.[35]	A	-	-	54	54	78.5	61.4	54.2	-	-	2005-2010
2016	Taiwan	Chang *et al*.[36]	A	-	2306	-	2306	82.1	-	50.8	-	-	2002-2010
2016	Taiwan	Chang *et al*.[36]	A	-	-	912	912	68.5	-	35.0	-	-	2002-2010
2016	Taiwan	Liu *et al*.[37]	A	224	-	-	224	88.0	76.0	63.0	-	-	-
2016	China	Zhao *et al*.[38]	A	82	-	-	82	77.0	56.0	43.0	-	-	2005-2011
2017	South Korea	Jin *et al*.[39]	S	206	-	-	206	89.3	67.4	58.0	-	-	2008-2010

A: studies consider large tumors (≥ 5 cm) with or without multifocal tumors as one single population group; S: studies only consider solitary large tumors; M: studies only consider multifocal tumors, of which size can be ≤ 5 cm

the 90's. But high-quality evidences only came in 2002, when two randomized controlled trials (RCTs) demonstrated the improvement in outcomes for patients with unresectable HCC when treated with TACE compared to conservative management[66,67]. Subsequent meta-analysis involving 7 RCTs also demonstrated an improvement in 2-year survival rate [odds ratio 0.53; 95% confidence interval (CI): 0.32-0.89; $P = 0.017$)[68]. Although this meta-analysis was later criticized for being small scale, using heterogeneous study population, and employing non-standardized TACE techniques and materials, many subsequent studies consistently reproduced the positive effects that TACE brought about in treating unresectable high-burden HCC[20,26,34,37,39,56,69-71] [Table 6].

For high-burden HCC treated with TACE, the median 1-, 3- and 5-year overall survival rates were 68.4%, 42.1% and 31.1% [Table 7]. In the case of solitary large (≥ 5 cm) HCC, the median 1-, 3-, and 5-year overall

Table 2. Summary of median overall survival of large/multifocal high-burden hepatocellular carcinoma treated with surgery

	Solitary large tumor	Moderately-large/multifocal (≥ 5 cm and < 10 cm)	Huge/multifocal (≥ 10 cm)	Overall
1-year survival (%)	87.2	73.0	70.0	74.3
3-year survival (%)	63.2	55.1	45.0	51.2
5-year survival (%)	56.1	50.8	36.0	39.2

Table 3. Recent studies on the efficacy of surgical resection in the management of high-burden hepatocellular carcinoma with portal vein invasion

Year	Place	Authors	Type (S/A)	Size: ≥ 5 cm	Size: 5-10 cm	Number of patients (*n*)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median survival (months)	Recruitment year
2010	Taiwan	Lin *et al*.[20]	A	78	-	78	39	2	-	15.8	2001-2007
2011	China	Luo *et al*.[26]	A	-	83	83	67.2	26	18.9	19.5	2004-2006
2014	China	Yin *et al*.[34]	A	-	85	85	51.8	18.1	-	14	2008-2010
2014	China	Jianyong *et al*.[69]	S	190	-	190	87.9	76.3	57.9	-	2002-2008
2014	China	Jianyong *et al*.[69]	A	139	-	490	68.4	46	40.8	-	2002-2008
2015	South Korea	Lee *et al*.[70]	S	68	-	68	89.8	72.8	49.6	-	-
2016	Japan	Kudo *et al*.[56]	A	-	-	1576	82.2	40.2	21.1	-	1997-2006
2016	Taiwan	Liu *et al*.[37]	S	229	-	229	74	44	35	-	-
2017	South Korea	Jin *et al*.[39]	A	489	-	489	67.7	38.2	27.2	-	2003-2010
2017	Japan	Nouso *et al*.[71]	A	76	-	76	-	47.3	21.4	72	2001-2015

A: studies consider large tumors (≥ 5 cm) with or without multifocal tumors as one single population group; S: studies only consider solitary large tumors

Table 4. Classification of portal vein invasion

Degree of invasion
Vp0: no evidence of tumor thrombus invasion
Vp1: tumor thrombus distal to but not in the second-order branches
Vp2: tumor thrombus in the second-order branches
Vp3: tumor thrombus in the first-order branches
Vp4: tumor thrombus in the main trunk or contralateral or both

Table 5. Summary of median overall survival of high-burden hepatocellular carcinoma with portal vein invasion treated with surgery

	Vp1 and Vp2	Vp3 and Vp4	Overall
1-year survival (%)	69.1	52.8	61.0
3-year survival (%)	42.2	23.4	32.9
5-year survival (%)	38.7	14.6	27.0

survival rates were higher: 87.9%, 72.8%, and 49.6%. In this group of high-burden HCC, TACE appeared to be inferior to surgical resection in prolonging survival. However, if we focus on solitary large HCC (≥ 5 cm) only, TACE appeared to outperform surgical resection [Table 7]. Therefore, it appears that surgery should be the choice of treatment when the tumor is "resectable", while TACE could be considered in the case of solitary large tumor.

TACE is commonly considered contraindicated in HCC with portal vein invasion due to the potential risk of acute liver failure resulting from post-TACE ischemia, as the normal liver parenchymal blood supply from the portal vein is already compromised. However, this contraindication has not been validated in large trials. On the contrary, a number of small retrospective studies have shown that TACE could be performed safely in patients with portal vein tumor thrombus (PVTT), provided that there was adequate liver reserve and the establishment of collateral blood circulation around the obstructed PVTT was sufficient[72,73].

Table 6. Recent studies on the efficacy of transarterial chemoembolization in the management of high-burden hepatocellular carcinoma

Year	Place	Authors	Vascular invasion	Number of patients (*n*)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median survival (months)	Recruitment year
2009	Japan	Ban *et al*.[42]	Vp3 and Vp4	45	69.6	37.4	22.4	20	1992-2008
2010	China	Shi *et al*.[53]	Vp1 and Vp2	139	52.1	25.1	-	-	2001-2003
2010	China	Shi *et al*.[53]	Vp3	169	38.2	17.7	-	-	2001-2003
2010	China	Shi *et al*.[53]	Vp4	78	24.7	3.6	-	-	2001-2003
2012	Taiwan	Chang *et al*.[28]	-	160	57.6	33.8	29.1	-	1991-2006
2012	China	Peng *et al*.[43]	All types	201	42	14.1	11.1	20	2002-2007
2012	China	Chen *et al*.[50]	All types	88	31.1	15.2	-	9	2006-2008
2012	Japan	Matono *et al*.[52]	Vp3 and Vp4	29	62.1	24.1	17.2	16.6	1985-2005
2013	USA	Roayaie *et al*.[46]	All types	165	-	-	14	13.1	1992-2010
2013	China	Tang *et al*.[54]	All types	186	40.1	13.6	-	10	2006-2008
2013	France, Italy, Japan, Argentina, USA	Torzilli *et al*.[55]	All types	297	76	49	38	-	1990-2009
2014	Taiwan	Liu *et al*.[48]	Vp1 to Vp3	247	85	68	61	64	2002-2012
2014	Hong Kong	Chok *et al*.[57]	Vp3	71	45.8	22.7	11.2	10.9	1989-2010
2015	Japan	Kojima *et al*.[44]	Vp3 and Vp4	25	68	32	12	21.5	2001-2010
2016	Japan	Kokudo *et al*.[45]	All types	1877	74.8	49.1	39.1	34	2000-2007
2016	Korea	Lee *et al*.[47]	Vp1 to Vp3	40	-	-	-	19.9	2000-2011
2016	China	Zheng *et al*.[49]	All types	96	86.5	60.4	33.3	-	2000-2008
2016	China	Li *et al*.[51]	Vp4	50	35.6	0	0	-	2010-2013
2016	China	Zhang *et al*.[58]	Vp1 to Vp3	113	68.9	34.3	30.8	18.2	2005-2012
2016	Japan	Kudo *et al*.[56]	Vp3 and Vp4	852	59.8	34.3	25	-	1996-2007
2016	Japan	Kudo *et al*.[56]	Vp2	714	69.1	42.2	29.2	-	1996-2007
2016	Japan	Kudo *et al*.[56]	Vp1	1908	84.9	62.4	48.2	-	1996-2007

Table 7. Comparison of median overall survival of high-burden HCC treated with surgery and TACE

	Solitary large HCC (surgery)	Solitary large HCC (TACE)	Overall (surgery)	Overall (TACE)
1-year survival (%)	87.2	87.9	74.3	68.4
3-year survival (%)	63.2	72.8	51.2	42.1
5-year survival (%)	56.1	49.6	39.2	31.1

HCC: hepatocellular carcinoma; TACE: transarterial chemoembolization

A small number of studies have explored the possibility of TACE as a palliative treatment in high-burden HCC with portal vein invasion[43,48,49,74-78] [Table 8]. The median 1-year overall survival rate was 50.5%. Even fewer studies have reported the median 3-year overall survival rate, likely due to the poor prognosis associated with portal vein invasion. No study thus far has compared difference in survival rate between segmental branches involvements (Vp1 and Vp2) and 1st branch or main trunk involvement (Vp3 and Vp4).

It is worth noting that many studies included in this review used conventional TACE (cTACE). However, drug-eluting bead TACE (DEB-TACE), since its introduction in 2006, was believed to be superior to cTACE. It has been demonstrated to have a lower toxicity profile compared to cTACE[79]. However, studies so far failed to prove its ability to consistently prolong survival[79-84]. Moreover, as a relatively new agent, only a paucity of studies has looked at its effect on high-burden HCC, particularly those with portal vein invasion. More studies are needed for this particular population of patients.

Transarterial radioembolization

Although TACE has been shown to be an effective therapy for high-burden unresectable HCC, it is associated with substantial systemic toxicities. In a Cochrane review in 2011, post-embolization syndrome, with clinical manifestations of transient fever, abdominal pain and elevated transaminases, was reported to occur in up to 80% of the patients receiving TACE[85]. Other serious adverse events, albeit uncommon, include acute renal failure, ascites, encephalopathy and transient liver failure[79].

Table 8. Recent studies on the efficacy of transarterial chemoembolization in the management of high-burden hepatocellular carcinoma with portal vein invasion

Year	Place	Authors	Vascular invasion	Number of patients (*n*)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median survival (months)	Recruitment year
2012	China	Niu *et al*.[78]	All types	115	27.8	-	-	8.67	2007-2010
2012	China	Peng *et al*.[43]	All types	402	37.8	7.3	0.5	13.1	2002-2007
2014	India	Ajit *et al*.[74]	All types	17	47.0	-	-	10	2011-2013
2014	Taiwan	Chern *et al*.[75]	Vp3 and Vp4	50.0	54.0	10.0	-	6.2	2006-2012
2014	Taiwan	Liu *et al*.[48]	Vp1 to Vp3	181	60	42	33	32	2002-2012
2016	China	Zheng *et al*.[49]	All types	134	77.6	47.6	20.9	-	2000-2008
2017	Korea	Choi *et al*.[76]	Vp1 and Vp2	50	-	-	-	9.4	2003-2012
2017	USA	Gorodetski *et al*.[77]	All types	133	-	-	-	4.53	2006-2013

In view of this, much effort has been made to devise new intra-arterial therapies with less systemic toxicities. In recent years, TARE has become an alternative to TACE in treating high-burden HCC. TARE is an intra-arterial therapy that involves the delivery of microspheres containing yttrium-90 into the hepatic arteries. TARE asserts the main effect through the internal radiotherapy delivered by Y-90, a radioactive substance, which causes necrosis of the tumor.

As data is lacking for TARE, much of the evidences came from retrospective studies of experimental intent[86-94]. These studies either looked into the efficacy of TARE by itself, or made a comparison with TACE, the gold standard for unresectable high-burden HCC. The median survival rate for high-burden HCC treated with TARE was 15.0 (range: 11.5-20.0) months, with a response rate of 41.5% by the mRECIST criteria [Table 9]. In those studies comparing TARE and TACE retrospectively, they were not able to show any difference between survival[88,93,94]. However, TARE was found to be associated with longer time-to-progression, less toxicity and shorter hospital stay comparing with TACE, suggesting that it may be a more favorable treatment modality for unresectable high-burden HCC. As for large solitary tumor or multifocal tumors, where TACE is known to be ineffective due to the severe adverse effects[95], TARE could also be a preferred alternative.

Despite its better safety profile, TARE is not yet considered standard treatment by a number of clinicians. Apart from the lack of high quality evidence to support its efficacy on high-burden HCC, TARE is an expensive procedure and it requires specialized training for implementation[96]. Given the promising results from retrospective studies, more clinical trials are needed in the coming years to formally evaluate its effectiveness and safety profile, and its potential to replace TACE's role in the treatment of unresectable high-burden HCC.

Radiotherapy

External radiation historically had limited role in the management of HCC. This is mainly due to the radiotoxicity on the non-tumorous surrounding tissue. Radiation induced liver disease (RILD) is a common side effect of radiotherapy for liver cancer. In the RTOG 84-05 dose escalation study, among the patients receiving whole liver RT of 33 Gy in 1.5 Gy, around 10% of patients experienced RILD[97].

However, with the recent advancements in irradiation technique, treatment modalities such as 3D-conformal RT (3D-CRT) and stereotactic body radiation (SBRT) have emerged as feasible options to treat high-burden HCC. With these technologies, high dose radiation can be effectively delivered to a precise area, sparing the surrounding normal liver tissue. This is particularly important for those patients with high-burden HCC who are not eligible for surgery or local therapies due to suboptimal liver reserve, anatomical locations of the tumors or poor performance status. Therefore, radiotherapy has become an attractive alternative in those cases.

Table 9. Recent studies on the efficacy of transarterial chemoembolization in the management of high-burden hepatocellular carcinoma

Year	Place	Authors	Number of patients (*n*)	Evaluation criteria	Time to progression (months)	Median survival (months)	Response rate (%)	Recruitment year
2010	European	Hilgard *et al.*[86]	108	EASL	10	16.4	40	-
2010	USA	Salem *et al.*[89]	291	WHO	7.9	BCLC-B: 13.3 BCLC-C: 6.0	42	-
2010	USA	Carr *et al.*[90]	99	WHO	7.9	11.5	41	-
2011	European	Sangro *et al.*[87]	325	-	-	12.8	-	-
2011	USA	Salem *et al.*[88]	123	WHO	13.3	20.5	49	1999-2008
2013	Italy	Mazzaferro *et al.*[92]	52	RECIST/WHO/EASL	11	15	40.4	2007-2009
2013	USA	Moreno-Luna *et al.*[93]	61	mRECIST	-	15	51	2005-2008
2015	Korea	Kim *et al.*[91]	40	mRECIST	18	-	63.8	2008-2010
2015	Germany	El Fouly *et al.*[94]	44	mRECIST	13.3	16.4	37%	2009-2011

Multiple retrospective studies, albeit small scale, have demonstrated the efficacy and safety of 3D-CRT and SBRT in treating high-burden HCC[54,98-109] [Table 10]. The response rates of these two techniques ranged from 22% to 76.2%, and the 1-year survival rates ranged from 16.7% to 55%. Given that this group of patients are expected to be in much poorer conditions than those amenable to surgery or intra-arterial embolization, the results achieved are encouraging. However, there has been no direct comparison between 3D-CRT and SBRT, and variability of results was wide. Therefore, larger scale studies are needed to establish the role of RT in managing high-burden HCC.

Systemic therapy

Our definition of high-burden HCC excludes patients with extrahepatic metastasis, for whom systemic therapy would be the preferred option. However, even for patients without extrahepatic metastasis, when all the other treatment modalities fail, systemic therapy would be the last resort. In this section, we will discuss the systemic therapies which are applicable to high-burden HCC [Table 11].

Targeted therapy

Traditional systemic therapy has never been favored for a long time in treating advanced HCC due to its poor efficacy and the general cytotoxicity which preclude its application in this group of frail patients. It was only since 2008, we celebrated the introduction of sorafenib, a multikinase inhibitor, which has been demonstrated to prolong survival in two large randomized controlled trials[110,111]. In the SHARP trial, the median survival of patients with advanced disease treated with sorafenib was 10.7 months, *vs.* 7.9 months in those who received placebo (harzard ratio 0.69, 95%CI: 0.55-0.87; $P < 0.001$). The Asia-Pacific trial was able to replicate similar findings, suggesting sorafenib to be an effective drug across patients with advanced HCC regardless of etiology and ethnicity.

Since then, much effort has been spent on exploring newer targeted therapies. Unfortunately, none of the trials in the past decade was able to identify a better targeted agent in treating advanced HCC[112-116]. Only recently in 2017, Bruix *et al.*[117] in the RESORCE trial has found regorafenib, an oral multikinase inhibitor that blocks angiogenesis, oncogenesis, metastasis and tumor immunity, to be an effective second line treatment for patients who have failed sorafenib. The median survival rate for patients on regorafenib after sorafenib use was 10.6 months compared to 7.8 months in the placebo group. The side effects associated with regorafenib use are typical of multi-kinase inhibitors, including hypertension, hand-foot skin reaction and gastrointestinal disturbances. Rate of drug-related adverse events leading to discontinuation of regorafenib is similar to that of sorafenib (10% *vs.* 11%)[110,117]. Regorafenib thus has become the only clinically proven second line systemic drug available in sorafenib-resistant cases thus far.

Immunotherapy

Although targeted therapy seems to have hit a roadblock, other routes of development have been ongoing. Immunotherapy is the most notable one. Ever since the introduction of immune checkpoint inhibitors

Table 10. Recent studies on the efficacy of radiotherapy in the management of high-burden hepatocellular carcinoma

Year	Place	Authors	Method	Number of patients (*n*)	Dose/ fraction	Evaluation criteria	1-year survival (%)	3-year survival (%)	Median survival (mos)	Response rate (%)	Recruitment year
2007	Japan	Toya *et al*.[103]	3DCRT	38	17.5-50.4 Gy; 1.8-4 Gy/Fr	mRECIST	39.4	-	9.6	44.7	1999-2005
2009	China	Huang *et al*.[83]	3DCRT	326	60 Gy; 2-3 Gy/Fr	-	16.7	-	3.8	25.2	1997-2005
2010	Korea	Oh *et al*.[104]	TACE + 3DCRT	40	30-54 Gy; 2.5-5 Gy/ Fr	-	72	-	19	62.8	2006-2007
2012	Korea	Yoon *et al*.[108]	TACE + 3DCRT	412	21-60 Gy; 2-5 Gy/Fr	mRECIST	42.5	-	10.6	28.1	2002-2008
2013	Canada	Bujold *et al*.[101]	SBRT	102	30-54 Gy; 6 Gy/Fr	mRECIST	55	-	17	44	2004-2010
2013	Korea	Bae *et al*.[99]	SBRT	35	30-60 Gy; 3-5 Gy/Fr	mRECIST	52	21	14	41	2003-2011
2013	China	Tang *et al*.[54]	TACE + 3DCRT	185	30-52 Gy; 3-4 Gy/Fr	-	42.2	17.3	12.3	-	2006-2008
2014	Canada	Culleton *et al*.[100]	SBRT	29	19.7-46.8 Gy; 6 Gy/ Fr	mRECIST	32.3	-	7.9	-	2004-2012
2014	Korea	Cho *et al*.[105]	TACE + 3DCRT	67	30-45 Gy; 2-4.5 Gy/ Fr	-	-	-	14.1	-	2007-2011
2016	Japan	Matsuo *et al*.[98]	SBRT	43	45-55 Gy; 10-15 Gy/ Fr	-	49.3	-	11	67	2008-2013
2016	Japan	Matsuo *et al*.[98]	3DCRT	54	45-50 Gy; 15-25 Gy/ Fr	-	29.3	-	6	46	2008-2013
2016	Japan	Okazaki *et al*.[109]	3DCRT	56	22-50 Gy; 2 Gy/Fr	mRECIST	-	-	6.4	22	2007-2013
2017	Taiwan	Lo *et al*.[102]	SBRT	89	25-60 Gy; 4-6 Gy/Fr	-	45.9	24.3	10.9	76.2	2007-2015

TACE: transarterial chemoembolization

to cancer treatment, results of clinical studies have far exceeded expectation. In 2013, the journal *Science* has selected cancer immunotherapy as the Breakthrough of the Year[118]. Cancer immunotherapy has been shown to be effective in treating cancers in multiple tissue organs, most notably lung cancer, melanoma and renal-cell carcinoma[119-121].

Latest studies have demonstrated promising results in the application of immunotherapy in treating advanced HCC[122,123]. Nivolumab, a PD-1 inhibitor, has been shown to prolong survival in patients with advanced HCC unsuitable for surgery or other local therapies[123]. In an international phase 1/2 trial (CheckMate040), nivolumab was demonstrated to have an objective response rate of 15%-20% in patients with advanced HCC, irrespective of line of therapy[123]. This was a significant improvement to the first-line sorafenib therapy, with a response rate of 2%-3%[110], and the second-line regorafenib therapy, with a response rate of 7%[117]. The overall 9-month survival rate was 74%, which showed a marked improvement compared to the median survival of 6 months for untreated advanced HCC.

Despite the relatively promising results shown in immunotherapy on HCC, studies so far conducted were relatively small scale. Larger scales are needed to evaluate the efficacy of immunotherapy on HCC.

ETIOLOGICAL ADJUNCTIVE TREATMENT FOR HIGH-BURDEN HCC

While we have discussed above the different treatment modalities available for high-burden HCC, it is also of paramount importance to control the underlying risk factors during treatment. By far, HBV and

Table 11. Clinical trials on systemic therapy in the management of advanced HCC

Drug name	Class	Trial name	Year	Authors	Phase	Case	Control	Result
Sorafenib	Oral multikinase inhibitor	SHARP	2008	Llovet *et al*.[110]	Phase 3	299	303	Median survival: 10.7 (sorafenib) *vs*. 7.9 months (placebo); $P < 0.001$
Sorafenib	Oral multikinase inhibitor	Asia-Pacific	2009	Cheng *et al*.[111]	Phase 3	150	76	Median survival: 6.5 (sorafenib) *vs*. 4.2 months (placebo); $P = 0.014$
Cabozantinib	Oral multikinase inhibitor	CELESTIAL	2012	Verslype *et al*.[134]	Phase 2	41	-	Granted orphan drug status by FDA
Ramucirumab	Anti-VEGF2 monoclonal	REACH	2015	Zhu *et al*.[112]	Phase 3	283	282	Median survival: 9.2 (ramucirumab) *vs*. 7.6 months (placebo); $P = 0.14$
Regorafenib	Oral multikinase inhibitor	RESORCE	2017	Bruix *et al*.[117]	Phase 3	379	193	Median survival: 10.6 (regorafenib) *vs*. 7.8 months (placebo); $P < 0.0001$
Tivantinib	Oral multikinase inhibitor	JET-HCC	2017	Kobayashi *et al*.[135]	Phase 3	134	61	Press release announced that the METIV-HCC phase 3 study did not meet its primary end point of improving survival
Lenvatinib	Oral multikinase inhibitor	REFLECT	2017	Cheng *et al*.[116]	Non-inferior study	478	476 (sorafenib)	Median survival: 13.6 (lenvatinib) *vs*. 12.3 months (sorafenib)
Ramucirumab	Anti-VEGF2 monoclonal	REACH (subgroup analysis)	2017	Zhu *et al*.[112]	Phase 3	CP-A and baseline AFP > 400 ng/mL: 68	CP-A and baseline AFP > 400 ng/mL: 83	Median survival: CP-A: 8.6 (ramucirumab) *vs*. 4.8 months (placebo); $P = 0.01$
						CP-B and baseline AFP > 400 ng/mL: 52	CP-B and baseline AFP > 400 ng/mL: 48	Median survival: CP-B: 5.7 (ramucirumab) *vs*. 3.6 months (placebo); $P = 0.04$
Nivolumab	Immunotherapy	CheckMate 040	2017	El-Khoueiry *et al*.[123]	Phase 1/2	Dose escalation phase: 48 Dose-expansion phase: 214		Response rate of 83% in 6 months; 74% in 9 month in dose expansion phase

AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma

HCV infections are the most important risk factors for HCC. Together, they account for 80% of the HCC worldwide[124]. The use of antivirals not only reduces the incidence of HCC in viral carriers, it is also effective in reducing HCC recurrence and prolonging survival. This is because viral reactivation is a major complication of HCC treatment. Patients with high-burden HCC are particularly at risk of viral reactivation due to chronic immunosuppression, higher tumor load and poorer liver reserve. Uncontrolled viral reactivation may provoke acute hepatitis, fulminant liver failure and even death.

Evidence supporting the use of antivirals as adjunctive treatment of HCC has been reviewed elsewhere[125,126]. In general, antivirals should be administered prior to treatment of HCC once the patient is known to be a virus carrier. For HBV-related HCC, the benefit of antivirals is seen in patients treated by surgery[127], TACE[128] or radiotherapy[129]. For HCV-related HCC, evidence is available for older generation interferon-based antivirals that they reduce tumor recurrence[130,131]. On the contrary, the newer generation of antivirals, e.g. direct-acting antivirals (DAA), have been shown to increase the chance of HCC recurrence[132,133]. However, these studies had been criticized for being small scale, short duration of observation period and lacking a proper control group. Further studies thus are needed to elucidate the effectiveness of DAAs as adjunct in the treatment of HCV-related HCC.

DISCUSSION AND CLOSING REMARKS

Our definition of high-burden HCC focuses on the "grey zone" where tumors are neither metastasized nor localized enough to have an obvious choice of treatment modality. Though they carry a worse prognosis

than the classically defined intermediate-stage HCC, if the optimal treatment can be chosen for this group of patients, the impact on their survival rates can be significant. Results from various retrospective and cohort studies in the past decade have been encouraging, providing strong support for multimodality treatment in the management of high-burden HCC.

In this review, we showed that surgical approach to high-burden HCC, if feasible, provides the highest median survival across all treatment modalities. Nonetheless, there has not been a large-scale RCT that quantified its positive effect in managing high-burden HCC in direct comparison with other treatment modalities.

In cases where surgical resection is not feasible, intra-arterial embolization is commonly adopted as an alternative treatment modality. Thus far, studies have not been able to demonstrate a significant difference in survival between the two available intra-arterial embolization options, TACE and TARE. Overall, TARE appears to be superior in terms of providing a better safety profile and associating with fewer adverse outcomes. Nonetheless, it is a novel method for HCC and expertise might only be available in selective tertiary centers.

Advancements in irradiation technique have enabled radiotherapy to emerge as another unconventional treatment option for high-burden HCC. Early results in 3D-CRT and SBRT have been promising but further evidences are needed to delineate their role in managing high-burden HCC.

Targeted therapy has been in a bottleneck for treating high-burden HCC since the introduction of sorafenib. Regorfanib, now being the second-line agent to sorafenib, is the only newer targeted agent thus far that has been proved effective in managing high-burden HCC. On the other side, breakthroughs have been made in immunotherapy in the past decade with promising results with nivorumab and other immunostimulating agents. Many RCTs are underway to further establish the role of immunotherapy in managing HCC and we expect more results to emerge in the next few years.

As majority of the HCCs are attributed from HBV or HCV infection, the use of antivirals as adjunctive treatment is also of paramount importance. It can effectively reduce HCC recurrence and prolong survival. Despite early studies regarding use of DAAs in the treatment of HCV-related HCC suggest higher tumor recurrence rate, those studies have been heavily criticized of poor design. Further studies are needed to elucidate the role of DAAs as an adjunctive treatment for HCV-related HCC.

In summary, high-burden HCC remains a difficult cancer entity to manage. Yet, multiple treatment options are available of which optimal selection can effectively prolong survival for this group of patients. Treatment modalities are evolving in the management of high-burden HCC and promising results from retrospective and cohort studies are plentiful. But high-quality studies are lacking. Larger scale controlled studies with more specific patient selection criteria are needed for various treatment modalities, to further assess and compare the benefits of these different options.

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Authors' contributions

Conceptualization: Chan LL, Chan SL
Literature search: Chan LL
First draft: Chan LL
Revision and final proofread: Chan LL, Chan SL

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