Hong Kong J Radiol. 2020;23:198-207 | https://doi.org/10.12809/hkjr2017152

ORIGINAL ARTICLE **CME**

Prognostic Factors and Survival in Advanced Large Hepatocellular Carcinomas Treated with Combined Transarterial Chemoembolisation and Hypofractionated Image-guided Radiotherapy

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ABSTRACT

Objectives: *Large (≥10 cm) hepatocellular carcinomas (HCCs) carry a dismal prognosis and respond poorly to transarterial chemoembolisation (TACE). Combined TACE and hypofractionated image-guided radiotherapy (HIGRT) has emerged as a new treatment strategy. We evaluated its efficacy among these tumours and report the predictors of overall survival (OS).*

Methods: *Data from 55 consecutive cases treated with preplanned combined TACE and HIGRT from 2007 to 2017 were evaluated from a prospectively collected database. Patients with advanced HCCs ≥10 cm, ineligible for curative intervention and with Child-Pugh scores ≤B7, received one dose of preplanned TACE 4 weeks prior to HIGRT. HIGRT doses were individualised according to the dose constraints of uninvolved liver and neighbouring organs at risk. OS was the primary endpoint.*

Results: *In all, 55 patients with median tumour sizes of 15.3 cm were included. Tumour vascular thromboses and extrahepatic diseases were present in 25.5% and 32.7%, respectively. The median total equivalent dose in 2 Gy/fr (EQD_2, α/β ratio = 10) was 32.7 Gy. The 2-year OS reached 24.9%. Clinical benefit rate was 83.6% with a 1-year local control rate of 57.4%. Multivariate analyses revealed alpha-fetoprotein (AFP) level (hazard ratio = 2.2, p = 0.025) and subsequent local treatment (hazard ratio = 0.2, p = 0.001) to be independent OS predictors. Responders undergoing subsequent curative resection achieved significantly better median OS than those without.*

Conclusion: *Combined TACE and HIGRT achieved favourable survival outcomes among large HCCs. AFP level and subsequent local surgery were independent negative and positive OS predictors, respectively. Future studies are warranted.*

Key Words: *Carcinoma, hepatocellular; Chemoradiotherapy; Ethiodized oil; Prognostic factors*

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Submitted: 15 Sep 2019; Accepted: 17 Dec 2019

Contributors: NSMW, CLC and FASL designed the study. NSMW, CLC, CHMH, WWLY, CSYY, MKHC, VWYL and FASL acquired the data. NSMW and CLC analysed the data. NSMW and CLC drafted the manuscript. NSMW, FASL and FCSW critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: The authors have no conflict of interest to declare.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Approval: This study was conducted in accordance with the Declaration of Helsinki, with approval from the New Territories West Cluster Clinical & Research Ethics Committee (Ref NTWC/CREC/18064).

中文摘要

於晚期、大肝癌患者結合使用肝動脈化療栓塞法與影像導航之大分割放射治療之預後因素與存活分析

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目的：大型（不小於10公分）肝癌腫瘤預後尤為不良，對肝動脈化療栓塞法（TACE）的治療反應亦更為遜色。TACE與影像導航大分割放射治療（HIGRT）的結合療法已漸獲初步認可。我們藉此評估TACE及HIGRT於此類患者的結合運用之治療結果，並對總體存活期之預後因子作分析。

方法：本項研究以總體存活期為主要療效指標，於香港單一中心的前瞻性數據收集庫採納自2007至2017年接受TACE與HIGRT結合治療的連續病例。當中包括合共55名晚期、大型（不小於10公分）、不適合接受痊癒性手術切除、Child-Pugh不高於B7分級，以及於HIGRT的4週前曾接受一次性預先規劃的TACE之肝癌患者。HIGRT劑量均按照未受累肝臟部分及鄰近危急器官之劑量限制而作個別調整。

結果：共55名患者符合納入標準，其腫瘤大小中位數為15.3公分，而當中患有肝腫瘤血管栓塞和肝外轉移則分別佔所有病例的25.5%及32.7%。以分次劑量（fr）2 Gy作計算，HIGRT的總處方劑量中位數為32.7 Gy（EQD_2，α/β ratio = 10）。治療患者的2年整體存活率達24.9%，而臨床獲益率及1年局部控制率則分別達至83.6%和57.4%。多變項分析顯示高甲胎蛋白（AFP）水平（風險比值[HR] = 2.2，p = 0.025）和療後的局部肝內治療（HR = 0.2，p = 0.001）分別屬於獨立的正面及負面總體存活期之預後因素。其中療效理想因而成功接受根治性腫瘤切除之患者的總體存活期中位數更顯著超越未有接受手術切除之患者。

結論：研究結果顯示TACE與HIGRT的結合治療於大肝癌腫瘤患者取得良好的存活成果。高AFP水平及療後的局部肝內治療則分別為獨立的正面及負面總體存活期之預後因素。我們建議就此策略作進一步研究。

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health burden. According to the World Health Organization, HCC ranked fifth in incidence and third in cancer mortalities in 2018, in which incidence was highest among East Asia.[1] During 2016, HCC was the fifth commonest cancer and was the third commonest cause of cancer-related deaths in Hong Kong.[2] The majority of HCCs in Hong Kong are associated with hepatitis B infection, whose carriers commonly present with sizable tumours.[3] Large HCCs carry a dismal prognosis due to their frequent associations with multiple satellite lesion formation and vascular invasion.[4,5]

Resection, radiofrequency ablation, and liver transplantation provide the only chances of cure. Unfortunately, only 30% of patients are candidates for curative intervention at the time of presentation.[6] Among unresectable tumours, transarterial chemoembolisation (TACE) is the most widely adopted locoregional therapy.[7,8] Randomised trials have demonstrated its survival benefits over placebo.[9,10] Efficacy is, however, limited among those with large tumours or advanced disease. Shim et al[11] reported the 2-year survival of HCC patients receiving TACE was 42% versus 0% for tumour sizes of 5 cm to 7 cm and ≥8 cm, respectively. The median survival only reached 6 months among patients with locally advanced disease treated with TACE according to Yau et al.[12] This has illustrated the need for better treatment strategies in patients with sizable tumours.

In light of technological advancements, stereotactic body radiotherapy (SBRT) and/or hypofractionated image-guided radiotherapy (HIGRT) have emerged as promising local therapeutic options in patients with localised HCCs. Several prospective series have shown that SBRT was associated with encouraging local control (LC) rates of 64% to 100% at 2 years,

with limited toxicities.[13-16] Growing evidence has also demonstrated its effectiveness in patients with advanced tumours.[17] Intriguingly, emerging data support the potential synergistic effects of TACE and radiotherapy (RT). Multiple reports have demonstrated combining TACE and RT is associated with better outcome than with single-modality treatment strategies.[18-20]

The aim of our study was to evaluate the efficacy and safety of the combined TACE and HIGRT approach among large unresectable HCCs ≥10 cm, as well as to identify the predictive factors for overall survival (OS).

METHODS

Patients

This was a retrospective cohort of all patients treated with combined TACE and HIGRT for unresectable HCCs from 2007 to 2017 at Tuen Mun Hospital, Hong Kong. Management strategies were determined by the liver multidisciplinary team (MDT), in collaboration with surgeons and radiologists. A radiological diagnosis of HCC was made based on typical enhancement patterns according to the dynamic imaging criteria of the American Association for the Study of Liver Diseases.[8]

The criteria for treatment by combined TACE and HIGRT were: (i) patients deemed unsuitable for resection, liver transplantation, or local ablative therapies by the MDT; (ii) tumour size ≥10 cm; (iii) a minimum of 700 mL of uninvolved liver; (iv) an Eastern Cooperative Oncology Group (ECOG) performance score ≤2; (v) a baseline Child-Pugh (CP) liver score of A5 to B7; (vi) adequate organ function, defined as absolute neutrophil count ≥1.5 × 10^9/L, creatinine ≥1.5 × upper limits of normal, alanine aminotransferase or aspartate aminotransferase <2.5 × upper limits of normal, and international normalised ratio <1.7 without clinical evidence of ascites or encephalopathy. Extrahepatic disease was allowed, provided the greatest disease burden was intrahepatic. Patients with portal vein thrombosis were also included. Diffusely infiltrative HCCs were considered ineligible. The Barcelona Clinic Liver Cancer (BCLC) stages A to C were included according to its updated criteria in which SBRT was also recommended as one of the treatment options for stage A patients.[21]

Treatment

Transarterial Chemoembolisation

TACE was performed by superselective cannulation of the artery supplying the tumour. The emulsion was prepared by mixing ethiodised oil (lipiodol) with cisplatin in a 1:1 ratio by means of a pumping method.[22] The emulsion was then injected slowly under fluoroscopic guidance according to the size of the tumour and the arterial blood flow.[23] One dose of TACE was administered 4 weeks prior to HIGRT.

Hypofractionated Image-guided Radiotherapy

During the study period, various HIGRT techniques were used. Patients were immobilised with a customised device (Vac-Lok; MED-TEC, Orange City [IO], United States). Computed tomography (CT) [Philips CT Big Bore, Amsterdam, The Netherlands; 32 slices, helical scan] with multiphasic intravenous contrast was used to delineate the gross tumour volume (GTV). GTV was contoured according to the areas containing lipiodol and/or contrast enhancement as visualised on the planning CT image. Breath-hold CT or 4-dimensional CT (average phase or respiratory phase sorted) was used to determine the internal target volume and/or planning target volume (PTV). Motion management was done with maximum intensity projection, gating, active breathing control, or abdominal compression. RT was delivered by means of dynamic conformal arc therapy (Varian Clinac 2100CD; Varian Medical Systems, Palo Alto [CA], United States), intensity-modulated RT, or volumetric modulated arc therapy (Elekta beam modulator and Elekta Agility, Stockholm, Sweden).

The total doses ranging from 4 Gy/fr to 6-10 frs, 5 fr/week, were individualised. The goal was to give the highest possible dose with respect to normal tissue constraints, in which the normal liver could receive an equivalent dose in 2 Gy (EQD_2, α/β ratio = 3) of 30 Gy <40% and mean dose <28 Gy. Dose constraints to other organs at risk (OARs) included the small bowel, stomach, large bowel, oesophagus, gallbladder, heart, ribs, skin, and kidney(s) [Table 1].

Table 1. Organ(s) at risk and corresponding dose constraint(s).

Organs at risk(s)	Dose constraint(s) (EQD_2, α/β ratio = 3)
Liver, gross tumour volume	≥700 mL
	Mean dose <28 Gy
	V30 <40%
Small bowel / stomach (D_{max})	44.8 Gy
Large bowel (D_{max})	50.4 Gy
Oesophagus / heart / gallbladder / rib / skin (D_{max})	56.0 Gy
Kidneys (bilateral)	V15 <50%
	Mean dose <18 Gy
Solitary kidney	V8 <10%

Abbreviations: D_{max} = maximum point dose to an organ or tumour target; EQD_2 = total equivalent dose in 2 Gy/fr.

Evaluation

Patients were assessed weekly during treatment, once every 2 weeks for the first 2 months, then once for the third month, followed by once every 3 months for the first 2 years and every 4 months thereafter by the MDT. Patients could also attend the oncology outpatient clinic should they require further assistance. Physical examination and liver function tests were performed on every follow-up. A triphasic liver CT scan was obtained at 3 months after HIGRT, every 3 months in the first year, and every 6 months thereafter. The tumour response was measured using Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1.[24]

The primary endpoint of the study was OS. The secondary endpoints were local in-field progression-free survival (PFS), LC, response rate, toxicities, and prognostic factors for OS. OS was calculated from the start of TACE until the date of final follow-up or death. Local in-field PFS was defined as the period from the date of starting TACE to the time of local, in-field disease progression or the time of patient death, whichever occurred first. LC was defined as the absence of progressive disease within the PTV. Patients with liver resection or transplantation or radiofrequency ablation during follow-up were censored for LC. A new lesion developing outside the PTV was regarded as an intrahepatic out-of-field failure.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[25] Acute adverse events (AEs) were defined as AEs that occurred within 3 months after HIGRT. All newly developed AEs or AEs that had progressed to 1 grade higher compared to baseline before treatment were considered as AEs from HIGRT. Classic radiation-induced liver disease (RILD) was defined as an anicteric elevation in alkaline phosphatase of at least twice the upper normal limit and non-malignant ascites within 4 months after the completion of HIGRT.

Statistics

The LC, local in-field PFS, and OS results were evaluated by means of Kaplan-Meier survival analysis. The log-rank test was used to compare outcomes among survival curves for identification of potential prognostic factors. Any factors that were significant in univariate analyses were subjected to multivariate analyses using the Cox proportional hazards regression model. A p value <0.05 was considered statistically significant. SPSS (Windows version 25.0; IBM Corp., Armonk [NY], United States) was used for statistical analysis.

RESULTS

Patient and Treatment Characteristics

A total of 55 patients were included in the study. Patient characteristics are listed in Table 2. The majority of patients were male (89.1%), had ECOG status of 1 (67.3%), were hepatitis B carriers (85.5%), BCLC stage C (50.9%), and with baseline median CP scores of A5. One-third of the patients (32.7%) had baseline extrahepatic metastases, 25.5% had vascular invasion and 41.8% had >1 baseline liver lesion. The median largest tumour dimension was 15.3 cm (range, 10.0-25.7 cm) with a median GTV of 1386.6 mL (range, 394.0-3990.7 mL). Median serum alpha-fetoprotein (AFP) level was 2429 ng/mL (range, 2.2-333,937.0 ng/mL).

The median total equivalent dose (EQD_2, α/β ratio = 10) was 32.7 Gy (28 Gy in 7 fr). Subsequent local or

Table 2. Baseline patient characteristics and demographics.*

Characteristic	TACE+HIGRT Total (n = 55)
Age (years)	57 (37-82)
Sex	
Male	49 (89.1%)
Female	6 (10.9%)
Aetiology	
Hepatitis B carrier	47 (85.5%)
Hepatitis C carrier	4 (7.3%)
ECOG status	
0	16 (29.1%)
1	37 (67.3%)
2	2 (3.6%)
CP class	
A	48 (87.3%)
B	7 (12.7%)
Tumour size (cm)	15.3 (10.0-25.7)
No. of tumours	
1	32 (58.2%)
2	6 (10.9%)
≥3	17 (30.9%)
Vascular invasion	14 (25.5%)
Extrahepatic metastases	18 (32.7%)
Lymph node(s)	14 (25.5%)
Bone	0
Visceral	7 (12.7%)
BCLC staging	
A	16 (29.1%)
B	11 (20%)
C	28 (50.9%)
AFP (ng/mL)	2429.0 (2.2-333,937.0)

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group; HIGRT = hypofractionated image-guided radiotherapy; TACE = transarterial chemoembolisation.
* Data are shown as median (range) or No. (%).

systemic treatment was allowed, in which 18.2% (n = 10) of patients underwent subsequent hepatic resection with curative intent. A total of 47.3% (n = 26), 7.3% (n = 4), and 5.5% (n = 3) subsequently received targeted therapy, chemotherapy, or immunotherapy, respectively (Table 3).

Survival and Prognostic Factors

The median follow-up time for all patients was 8.5 months (range, 1.5-110.4 months). The median OS was 9.5 months (95% confidence interval [CI] = 5.2-13.7 months; range, 2.6-111.8 months) across the studied population, with the 1-year and 2-year OS reaching 43.6% (95% CI = 30.5%-56.7%) and 24.9% (95% CI = 13.4%-36.4%), respectively (Figure 1). The median local in-field PFS reached 15.1 months (95% CI = 2.1-28.1 months) [Figure 2].

Table 3. Treatment characteristics.*

Treatment characteristics	TACE+HIGRT (n = 55)
HIGRT	
Dose (Gy [EQD_2, α/β ratio = 10])	32.7 (28.0-46.7)
Subsequent treatment	
Hepatic resection	10 (18.2%)
Targeted therapy	26 (47.3%)
Chemotherapy	4 (7.3%)
Immunotherapy	3 (5.5%)
Nil	12 (21.8%)

Abbreviations: HIGRT = hypofractionated image-guided radiotherapy; TACE = transarterial chemoembolisation.
* Data are shown as median (range) or No. (%) of patients.

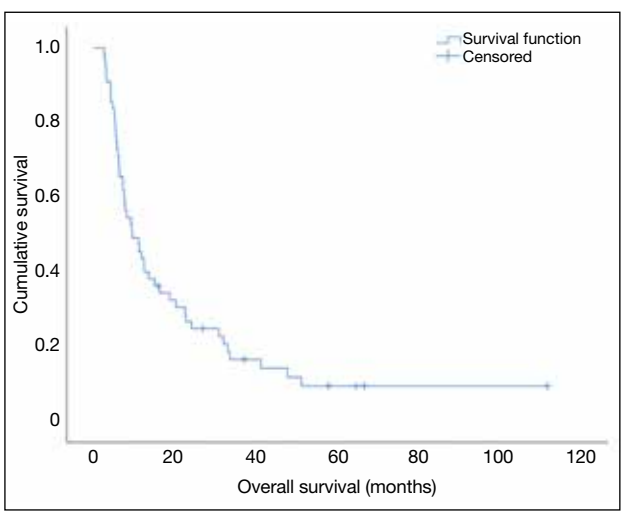

Figure 1. Overall survival.

By means of Kaplan-Meier analysis, the best RECIST treatment response was significantly associated with OS (partial response [PR] vs. stable disease [SD] vs. progressive disease, respectively: 15.0 vs. 11.2 vs. 4.2 months, p = 0.002) [Figure 3]. It was also observed that the presence of systemic treatment was associated with better OS (15.0 vs. 7.5 months, p = 0.037) [Figure 4].

Univariate analysis revealed serum AFP (≥400 ng/mL), treatment response according to RECIST criteria, and subsequent local and systemic anti-cancer treatment were significant prognostic factors for OS. On

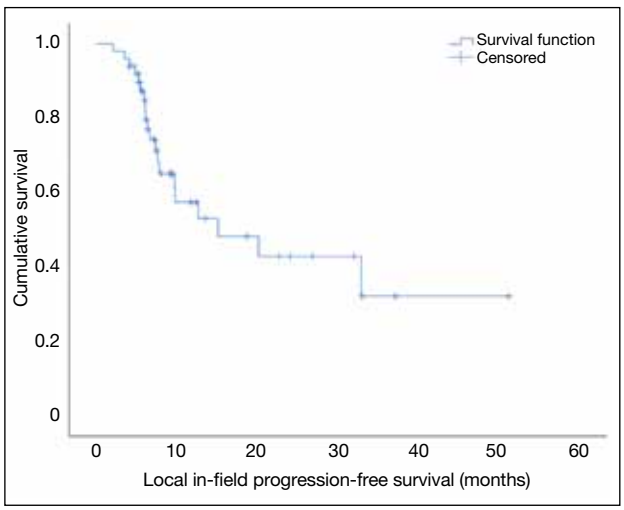

Figure 2. Local in-field progression-free survival.

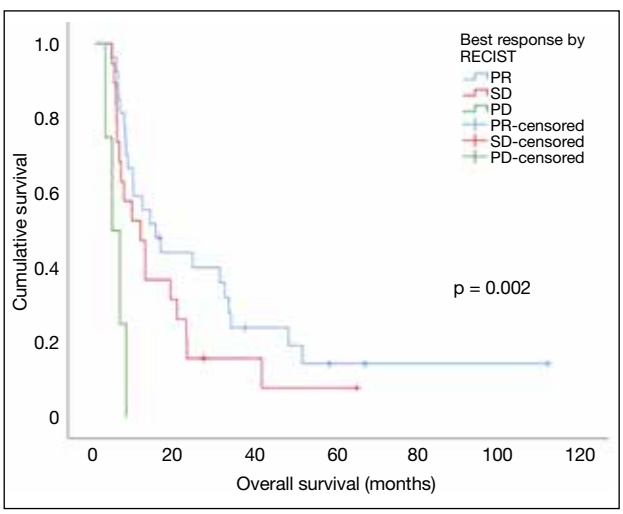

Figure 3. Comparison of overall survival between different tumour responses according to RECIST.
Abbreviations: PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SD = stable disease.

subsequent multivariate analysis, high AFP levels (≥400 ng/mL) and the presence of subsequent local anti-cancer treatment remained negative and positive independent OS predictors, respectively (Table 4).

Local Control and Pattern of Failure

The 1-year local, in-field control rate reached 57.4% (95% CI = 40.8%-74.0%) and the 2-year LC rate remained at 42.8% (95% CI = 23.9%-61.7%). The clinical benefit rate (complete response [CR], PR, and SD) according to RECIST 1.1 criteria was up to 83.6% (n = 46), of which 49% (n = 27) of the patients achieved PR and 34.5% (n = 19) attained SD. Of all evaluable patients, 80% (n = 40, missing data = 5) remained free from local progression at the time of evaluation; 64% (n = 32, missing data = 5) developed out-of-field intrahepatic progression; 2% (n = 1, missing data = 4) developed vascular invasion, while 50% (n = 26, missing data = 3) developed extrahepatic metastases.

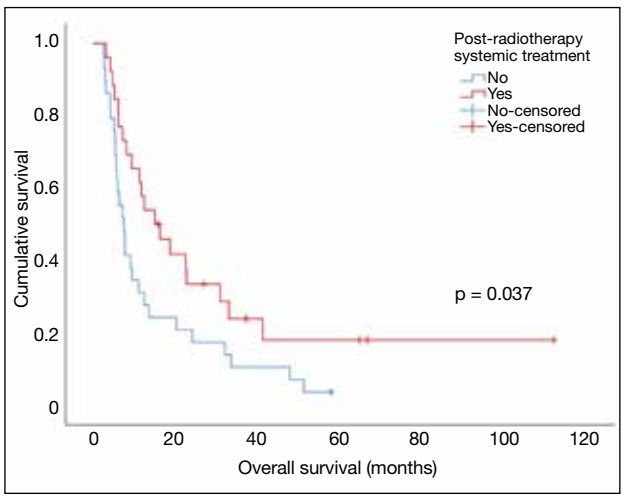

Figure 4. Comparison of overall survival between patients with or without subsequent systemic therapy.

Curative Treatment among Treatment Responders

A total of 10 patients (18.2%) were able to undergo subsequent curative resection following HIGRT. Of those without baseline extrahepatic metastases, 27% (10 out of 37) were successfully downstaged to undergo curative resection. Eight (80%) had a baseline CP score of A5 while two (20%) had a CP score B7, one (10%) had vascular invasion and all were ECOG status 0-1 at baseline. The EQD_2, α/β ratio = 10 remained 32.7 Gy (28 Gy in 7 frs) for the majority. Of the 10 final pathological specimens, two (20%) had pathological CR. Apart from one patient (10%) with an R1 resection, all of the remaining (n = 9, 90%) achieved R0 resections. Early postoperative mortality within 30 days was not observed. The median OS among these patients reached 41.2 months (95% CI = 19.1-63.2 months), which was significantly higher than those who did not undergo surgery (9.5 months, 95% CI = 4.2-14.7 months, p = 0.003, Figure 5). Figure 6 demonstrates tumour response to combination TACE and HIGRT with marked interval shrinkage.

Table 4. Prognostic factors associated with overall survival.

Variable	Overall survival					
	Univariate		p Value	Multivariate		p Value
	HR	95% CI		HR	95% CI	
Age ≥55 years	0.631	0.346-1.148	0.131			
Sex (male)	1.202	0.471-3.070	0.701			
ECOG status (1 or 2)	1.921	0.977-3.777	0.058			
CP class B	1.109	0.465-2.645	0.816			
Hepatitis B infection	1.232	0.552-2.752	0.611			
Hepatitis C infection	1.567	0.502-4.890	0.439			
AFP ≥400 ng/mL	2.193	1.155-4.166	0.016	2.222	1.104-4.470	0.025
Tumour size ≥15 cm	1.533	0.865-2.715	0.143			
>1 tumour	1.511	0.831-2.748	0.176			
Vascular invasion	0.682	0.334-1.393	0.294			
Extrahepatic metastasis	1.237	0.676-2.261	0.491			
Best RECIST response (SD vs. PR)	1.568	0.825-2.981	0.17	1.141	0.561-2.321	0.716
Best RECIST response (PD vs. PR)	6.531	2.071-20.597	0.001	1.807	0.370-8.828	0.465
Subsequent local treatment	0.186	0.074-0.465	<0.001	0.193	0.073-0.512	0.001
Subsequent systemic treatment	0.547	0.307-0.974	0.04	0.651	0.330-1.285	0.216

Abbreviations: 95% CI = 95% confidence interval; AFP = alpha-fetoprotein; CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SD = stable disease.

Adverse Events

Treatment completion rate was excellent at 94.5%, of which the treatment delay/suspension rate was low at 12.7%. The rate of severe AEs, defined as Common Terminology Criteria for Adverse Events grade ≥3, were rare. One patient (1.8%) had grade 5 gastrointestinal bleeding from the development of a gastric ulcer within 8 weeks post-RT. The remaining severe AEs were all attributed to haematological toxicities (anaemia: n = 4, 7.3%; thrombocytopoenia: n = 2, 3.6% and neutropoenia: n = 1, 1.8%). There were otherwise no other severe AEs (Table 5).

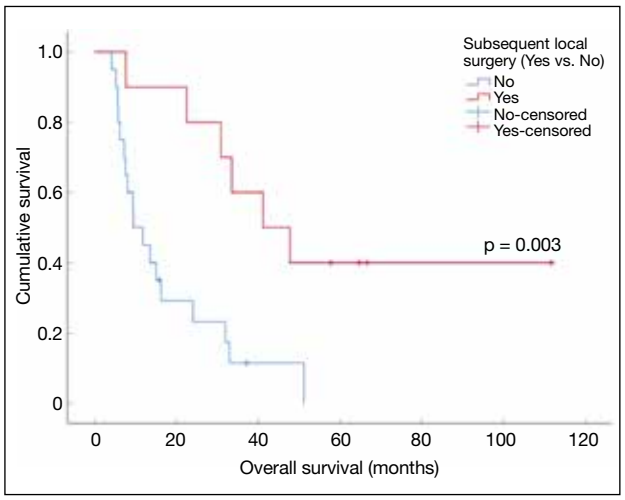

Figure 5. Comparison of overall survival between patients with or without subsequent local curative surgery.

DISCUSSION

This is the first study to report the role of combination TACE and HIGRT among patients with HCCs ≥10 cm. The baseline characteristics exhibited by our patients reflected those with advanced disease status with a substantial rate of high median baseline AFP exceeding 2000 ng/mL, vascular invasion (25.5%), extrahepatic metastases (32.7%), and tumour multiplicity (41.8%), which was consistent with reports describing the aggressive disease nature, delayed presentation, and poor prognoses of large tumours.[26,27] Although BCLC class A patients (according to the updated staging criteria) were also included in the study, they were all deemed unresectable by the MDT due to technical difficulties such as unfavourable tumour position, inadequate liver function, and medical risk.

There has always been an unmet need to improve the poor survival outcomes of large or locally advanced HCCs.[28] Our study population achieved a superior 2-year OS of 24.9%, contrasting with Shim et al's reporting of a 0% 2-year OS for tumours ≥8 cm treated with TACE alone,[11] suggesting a highly efficacious treatment combination. It was also intriguing to observe patients without baseline extrahepatic metastases, nearly 30% of whom were able to undergo subsequent curative surgery with a high R0 resection rate (two achieved pathological CR) without early postoperative mortality, and in which a translation to significant OS benefit was observed. A high proportion (80%) of our patients remained free from local progression at time of analysis further supports our

Table 5. Overall incidence of adverse events.*

Adverse event	CTCAE grade (n = 55)			
	Grade 0	Grade 1	Grade 2	Grade ≥3
Haematological				
Anaemia	38 (69.1%)	7 (12.7%)	6 (10.9%)	4 (7.3%)
Leucopoenia	38 (69.1%)	11 (20.0%)	5 (9.1%)	1 (1.8%)
Thrombocytopaenia	29 (52.7%)	20 (36.4%)	4 (7.3%)	2 (3.6%)
Gastrointestinal				
Nausea/vomiting	37 (67.3%)	16 (29.1%)	2 (3.6%)	0
Gastroduodenal mucositis/ulcer	0	0	0	1 (1.8%)
Hepatic				
AST/ALT elevation	37 (67.3%)	16 (29.1%)	2 (3.6%)	0
Hyperbilirubinaemia	44 (80%)	7 (12.7%)	4 (7.3%)	0
RILD	0	0	0	0
Fatigue	28 (50.9%)	19 (34.5%)	8 (14.5%)	0
Fever	54 (98.2%)	1 (1.8%)	0	0
Pain	52 (94.5%)	3 (5.5%)	0	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; RILD = radiation-induced liver disease.
* Data are shown as No. (%).

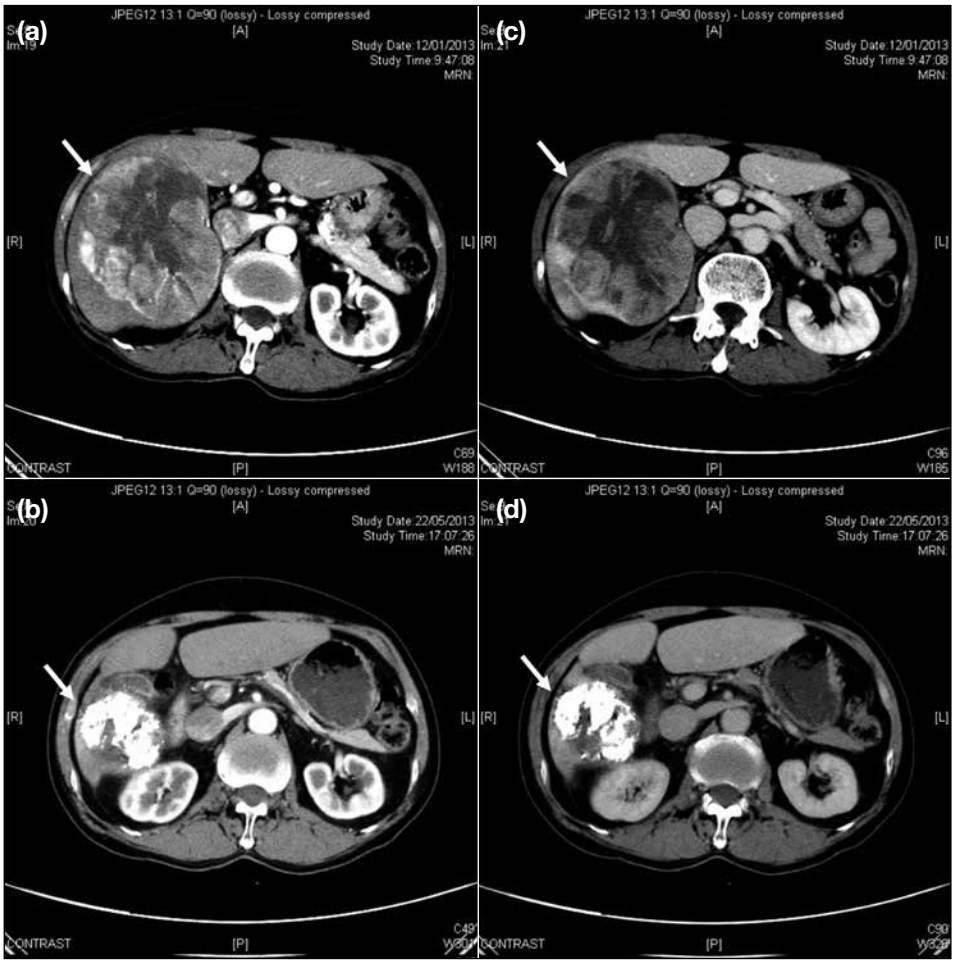

Figure 6. Contrast axial computed tomography scans demonstrating tumour response before (a, c) and after (b, d) combination transarterial chemoembolisation and hypofractionated image-guided radiotherapy. (a, b) Arterial phase. (c, d) Portal venous phase. Arrows indicate the irradiated primary tumour with satisfactory lipiodol uptake and significant interval shrinkage.

hypothesis of an improved LC with such a combination strategy.

An individualised dosage for HIGRT was pivotal. Mean liver dose was reported to be independently associated with CP score progression after RT, and that a mean liver dose of >28 Gy EQD_2, α/β ratio = 3 was associated with a 5% risk of RILD.[29,30] It has also been suggested that the risk of liver function impairment following TACE and RT was more common when V30 >40% EQD_2, α/β ratio = 3 among large HCCs.[31] In addition, a study has suggested that fractionated RT could offer dosimetric advantages over the 5-fr regimen among large HCCs which were close to OARs.[32] It was therefore justifiable that our institutional protocol adopted such dose constraints and fractionated doses in tailoring RT prescriptions. Large HCCs often limit dose escalation due to their close proximities to surrounding OARs with limited residual normal liver reserve. In our study, treatment was well tolerated with a high completion rate approaching 95%. Severe (grade ≥3) AEs were rare, and most were related to transient, reversible haematological disturbances. Despite concerns for liver decompensation following TACE and/or SBRT among HCC patients with pre-existing compromised liver function, there were no identifiable occurrences of classic RILD or of severe liver function derangement. We have hereby demonstrated the safety and feasibility of our RT regimen in combination with pre-RT TACE for large HCCs.

Despite the modest prescribed RT doses (median EQD_2, α/β ratio = 10, 32.7 Gy, range, 28.0-46.7 Gy) in our study, high 1-year LC and clinical benefit rates were observed. Multiple studies have demonstrated that combined TACE and RT are associated with better outcome than either treatment alone.[19,20] A previous meta-analysis also demonstrated that a TACE-RT interval <4 weeks was associated with better tumour response compared to longer intervals.[18] We suggest that prior chemoembolisation reduces viable tumour burden,

thereby enhancing the therapeutic effect of a lower RT dose for better LC. Future studies exploring the underlying mechanisms of possible augmented effects of TACE and HIGRT would yield invaluable information.

Multivariate analysis has identified baseline AFP ≥400 ng/mL and subsequent local treatment as independent prognostic factors for OS. AFP has been recognised as a poor prognostic factor for HCC, in which a cut-off of 400 ng/mL has been included in the Cancer of Liver Italian Program scoring system.[33] The system was reported to be a good predictor of recurrence based on a respective Chinese cohort of predominantly patients with hepatitis B following curative surgery for HCC.[34]

In spite of achieving durable LC and high clinical benefit rates among primary tumours treated with the combined TACE and HIGRT approach, out-of-field intrahepatic or extrahepatic progression remained mostly inevitable, resulting in a precipitous OS decline beyond 2 years. Our data presented significant OS benefit among patients who underwent curative surgery after combined TACE and HIGRT, and there was also a trend towards improved OS among patients with radiological response post-TACE and HIGRT according to the RECIST scores. Taken together, future studies investigating the role of combined TACE and HIGRT as a neoadjuvant strategy among selected patients for upfront unresectable HCCs are much anticipated.[35] Furthermore, a statistically significant, lengthened OS with addition of systemic therapy following TACE and HIGRT by Kaplan-Meier and univariate analysis was identified. This has shed light on future trials investigating the optimal combination strategies with merging systemic therapies that were not available at the time of investigation.

This study carries several limitations. This was a single-centre study in which potential bias might have been introduced. Our study spanned across a long period of 10 years with use of three different RT techniques, which might have influenced the treatment outcome. A substantial proportion of our patients underwent subsequent treatment; the impact of initial TACE and HIGRT treatment might have been diminished. Our sample size was modest, in which a larger scale, multi-centre, prospective, randomised trial would have facilitated a more comprehensive analysis of the prognostic factors for OS. However, our study has the unique advantage of having long-term, experienced and consistent partnerships with MDTs, treatment personnel, RT planning, and treatment facilities. As a result, heterogeneity in patient selection and overall management strategies were minimised throughout the treatment period. Lastly, some might suggest that radioembolisation with ^{90}yttrium (^{90}Y)-tagged glass (TheraSphere; MDS Nordion, Ottawa, Canada) or resin (SIR-Spheres; Sirtex Medical, Lane Cove, Australia) is a viable alternative among the studied population.[36,37] For instance, Salem et al[35] reported comparable outcomes to TACE in terms of response rate (42%) and time-to-progression (7.9 months) for a sample of 291 patients with median tumour sizes of 7 cm.[37] Although ^{90}Y radioembolisation in smaller tumours (range, 2.3-3.7 cm) has been investigated in a more recent Phase II trial by Salem et al,[38] suggesting a significantly better time to progression with ^{90}Y (>26 months vs. 6.8 months), it remains unclear whether radioembolisation could result in comparable outcomes in terms of survival and safety profile as demonstrated in our study with TACE and HIGRT.

CONCLUSION

Combined TACE and HIGRT achieved favourable survival outcomes and good local tumour control with low toxicities among large HCCs. High AFP levels and subsequent local surgery were independent negative and positive OS predictors, respectively, by means of multivariate analysis. Future prospective trials are warranted to determine its optimal integration into local and systemic therapies to ultimately combat these large, aggressive HCCs carrying a distinctly dismal prognosis.

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