JGH Open An open access journal of gastroenterology and hepatology
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JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.12793

ORIGINAL ARTICLE

High rates of treatment stage migration for early hepatocellular carcinoma and association with adverse outcomes: An Australian multicenter study

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Key words
early hepatocellular carcinoma, local tumor control, overall survival, percutaneous ablation, recurrence-free survival.

Accepted for publication 4 July 2022.

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Declaration of conflict of interest: Nothing to declare.
Author contribution: Kee Fong Loo contributed to the data collection and analysis, manuscript writing, and review. Richard J Woodman contributed to the data analysis and manuscript review. Damjana Bogatic contributed to the data collection and manuscript review. Kate Muller contributed to the manuscript review. Vidyaleha Chandran contributed to the data collection and manuscript review. Mohamed Asif Chinnaratha contributed to the manuscript review. John Bate contributed to the manuscript review. Kirsty Campbell contributed to the data collection and manuscript review. Matthew Maddison contributed to the data collection and manuscript review. Sumudu Narayana contributed to the ethics submission and manuscript review. Hien Le contributed to the manuscript review. David Pryor contributed to the manuscript review. Alan Wigg contributed to the study design, manuscript writing, and review.

Abstract

Background and Aim: The rate of contraindications to percutaneous ablation (PA) for inoperable early hepatocellular carcinoma (HCC) and subsequent outcomes is not well described. We investigated the prevalence and outcomes of inoperable early HCC patients with contraindications to PA, resulting in treatment stage migration (TSM).
Methods: Barcelona Clinic Liver Cancer (BCLC) 0/A patients diagnosed between September 2013 and September 2019 across five hospitals were identified. Primary endpoint was proportion of BCLC 0/A HCCs with contraindications to PA. Secondary endpoints included overall survival (OS), local tumor control (LTC), and recurrence-free survival (RFS). The causal effects of PA *versus* TSM were assessed using a potential outcome means (POM) framework in which the average treatment effects (ATEs) of PA were estimated after accounting for potential selection bias and confounding.
Results: Two hundred twenty patients with inoperable BCLC 0/A HCC were identified. One hundred twenty-two patients (55.5%) had contraindications to PA and received TSM therapy, 98 patients (44.5%) received PA. The main contraindication to PA was difficult tumor location (51%). Patients who received TSM therapy had lower median OS (2.4 *vs* 5.3 years), LTC (1.0 *vs* 4.8 years), and RFS (0.8 *vs* 2.9 years); $P < 0.001$, respectively, compared with PA. The ATE for PA *versus* TSM yielded an additional 1.11 years ($P = 0.019$), 2.45 years ($P < 0.001$), and 1.64 years ($P < 0.001$) for OS, LTC, and RFS, respectively. Three-year LTC after PA was suboptimal (65%).
Conclusion: Our study highlights high rates of contraindication to PA in early HCCs, resulting in TSM and poorer outcomes. The LTC rate for PA appears suboptimal despite being considered as curative therapy. Both findings support the exploration of improved treatment options for early HCCs.

Introduction

Liver cancer is the fourth leading cause of cancer-related death globally.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy, accounting for up to 80% of all cases worldwide, as well as in Australia.[2,3] Over the last four decades, the HCC incidence rate in Australia has increased by almost eight-fold, from 1.37 per 100 000 in 1982 to 8.60 per 100 000 in 2019,[3,4] which represents the fastest rising incidence of any cancer in Australia and therefore a significant challenge for the healthcare system. Due to increased uptake of ultrasound surveillance in at-risk individuals, HCC is being more frequently diagnosed at an earlier, curable stage in some jurisdictions.[5–7] Barcelona Clinic Liver Cancer (BCLC) classification is a widely accepted HCC staging system for prognosis assessment and treatment allocation.[6,7] In patients diagnosed with very early/early-stage HCC (BCLC stage 0/A), curative surgical therapies such as liver transplantation or resection are recommended.[6,7] Unfortunately, as little as 30% of patients are candidates for surgery at diagnosis.[8,9] Percutaneous ablation (PA) is the current standard curative therapy for early HCC patients ineligible for surgical therapy.[6,7] However, when PA therapy cannot be given to patients with early-stage HCC, patients commonly advance to non-curative treatments (treatment stage migration [TSM]). The rate of contraindication to PA and subsequent patient outcomes for receiving non-curative therapies based on TSM concept is not well described. Several retrospective studies have reported high rates of contraindication to PA (34–43%) in early HCC patients who were ineligible for surgery.[9–11] Emerging data support the effectiveness of alternative ablative options such as stereotactic body radiation therapy (SBRT); however, its incorporation into consensus guidelines is variable.[8,10,12,13] The current EASL HCC management guidelines cite a lack of robust evidence to support its use.[7]

Therefore, the aim of this work was to perform a retrospective multicenter study to evaluate (i) the proportion of inoperable early-stage HCC referred for PA but ineligible due to contraindications; (ii) the clinical impacts on survival in patients who had contraindications to PA and experienced TSM; and (iii) the local tumor control (LTC) following PA in a large, real-world cohort. To estimate the causal treatment effects using this observational dataset, we used a potential outcome mean (POM) approach, with inverse probability of treatment weights (IPTW) used to correct for missing data on the potential outcomes and selection bias.

Methods

Study population. All patients diagnosed with HCC between September 2013 and September 2019 and managed at five tertiary hospitals across South Australia and Northern Territory were identified retrospectively from relevant hospital-based electronic and paper medical records. HCC was diagnosed based on typical radiological findings using multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), and/or pathological confirmation according to the EASL criteria.[7]

Inclusion criteria were: BCLC stage 0 or A HCC, ineligible for surgical therapy (transplantation/resection) as decided by the HCC multidisciplinary meeting, received either PA or TSM therapy including transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), SBRT, systemic therapy as the initial treatment following HCC multidisciplinary meeting recommendation, and minimal follow up ≥3 months.

Exclusion criteria were: incomplete/missing critical data such as BCLC stage of HCC and treatment date, received combination therapies such as TACE + ablation as the initial treatment, received ablation using alcohol, received first treatment TACE or ablation as bridging therapy for liver transplant performed within 6 months or best supportive therapy.

Treatment allocation was via two HCC multidisciplinary teams associated with two major tertiary hospitals in South Australia. Each team contained hepatologists, hepatobiliary and transplant surgeons, liver specialized interventional radiologists, medical and radiation oncologists, and liver cancer nurses. These teams received all referrals across South Australia and Northern Territory, a population of approximately two million people.

PA techniques included radiofrequency ablation or microwave ablation. The rate and contraindications to PA were assessed in early HCC patients who were deemed ineligible for surgical therapy. The technique of TACE procedure performed was conventional TACE (cTACE), using epirubicin, followed by embolization with gelfoam or polyvinyl alcohol particles.

Study endpoints. The primary endpoint of our study was the proportion of BCLC 0/A HCC with contraindications to PA. Secondary endpoints included overall survival (OS), LTC, and recurrence-free survival (RFS) between the PA and TSM groups. OS was defined as the time from the date of first treatment to the date of death or last follow up if alive. LTC was defined as the absence of tumor progression of the treated target lesion/s on CT/MRI after the first treatment. RFS was calculated from the date of first treatment to the date of tumor recurrence or last follow up/death date if no recurrence was detected, in patients who had achieved complete tumor response after first treatment. Patients who received the best supportive care or SBRT as TSM therapy were excluded from the analyses of OS, LTC, and RFS. Patients who received SBRT were excluded from these analyses due to low numbers in the study and emerging evidence suggesting this is potentially a curative therapy.[8,10,13] Each tumor nodule treated was assessed on follow-up imaging to determine the LTC rate.

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)[14] criteria were used to assess tumor response after treatment based on the radiological assessment with multiphasic contrast-enhanced CT or MRI. Complete tumor response was defined as the disappearance of all target lesion/s in the axial imaging plane and/or absence of arterial phase hyperenhancement at the first radiological assessment after treatment.

Statistical methods. Continuous variables were summarized using median ± interquartile ranges (IQR) or mean ± SD and compared by Student's *t*-test or Mann–Whitney *U* test. Categorical variables were summarized as frequencies (percentages) and compared using Chi-squared or Fisher's exact test as appropriate. The unadjusted estimated probability of survival (OS, RFS) and LTC was described using the Kaplan–Meier (KM) method and compared between treatment groups using the log-rank test. We assessed the

causal average treatment effect (ATE) for PA *versus* TSM therapy using a POM survival analysis. POM is a two-stage approach to estimating causal treatment effects with estimation of the probability of receiving a particular treatment using a logit regression model used in the first step, followed by estimation of the mean time to outcome using a Weibull censoring model. The probabilities of treatment are used as IPTW in the survival model to create a pseudo-population in which there is balance in treatment probability between the two treatment groups. As such, the observed associations can be treated as causal treatment effects. This approach to analysis allows estimation of both the average time to the outcome if a single treatment were used for the whole study population, as well as the ATE, being the difference in mean time to outcome if all subjects were treated with PA *versus* TSM therapy. Model covariates for both the treatment and censoring models included age, gender, cirrhosis, Child–Pugh score, alpha fetoprotein (AFP), model for end-stage liver disease score, number of tumors, tumor size, and alcohol etiology. Results are reported as mean (95% confidence interval [CI]) time to outcome (POM) and mean (95% CI) ATE. POM and ATE estimates were obtained using version 16 of Stata's "stteffects" command (StataCorp, College Station, TX, USA). A two-tailed Type 1 error rate of alpha = 0.05 was used for significance testing.

In addition to ATE and POM analyses, we also performed a multivariate analysis using Cox regression using the same covariates to identify significant predictors for OS, LTC, and RFS, with results reported as hazard ratios (HR) and 95% CI.

Ethical approvals. Ethical approval was granted by the Human Research Ethics Committees of the Adelaide Local Health Networks, CALHN Research Governance (Reference Number 12167) and the Northern Territory Menzies School of Health Research, prior to commencement of the study.

Results

Study population. Between September 2013 and September 2019, 377 HCC patients with BCLC stage 0/A were identified. Of those, 38 patients were excluded due to incomplete/missing critical data, lost to follow up, follow time <3 months, patients who received TACE or ablation as bridging therapy for liver

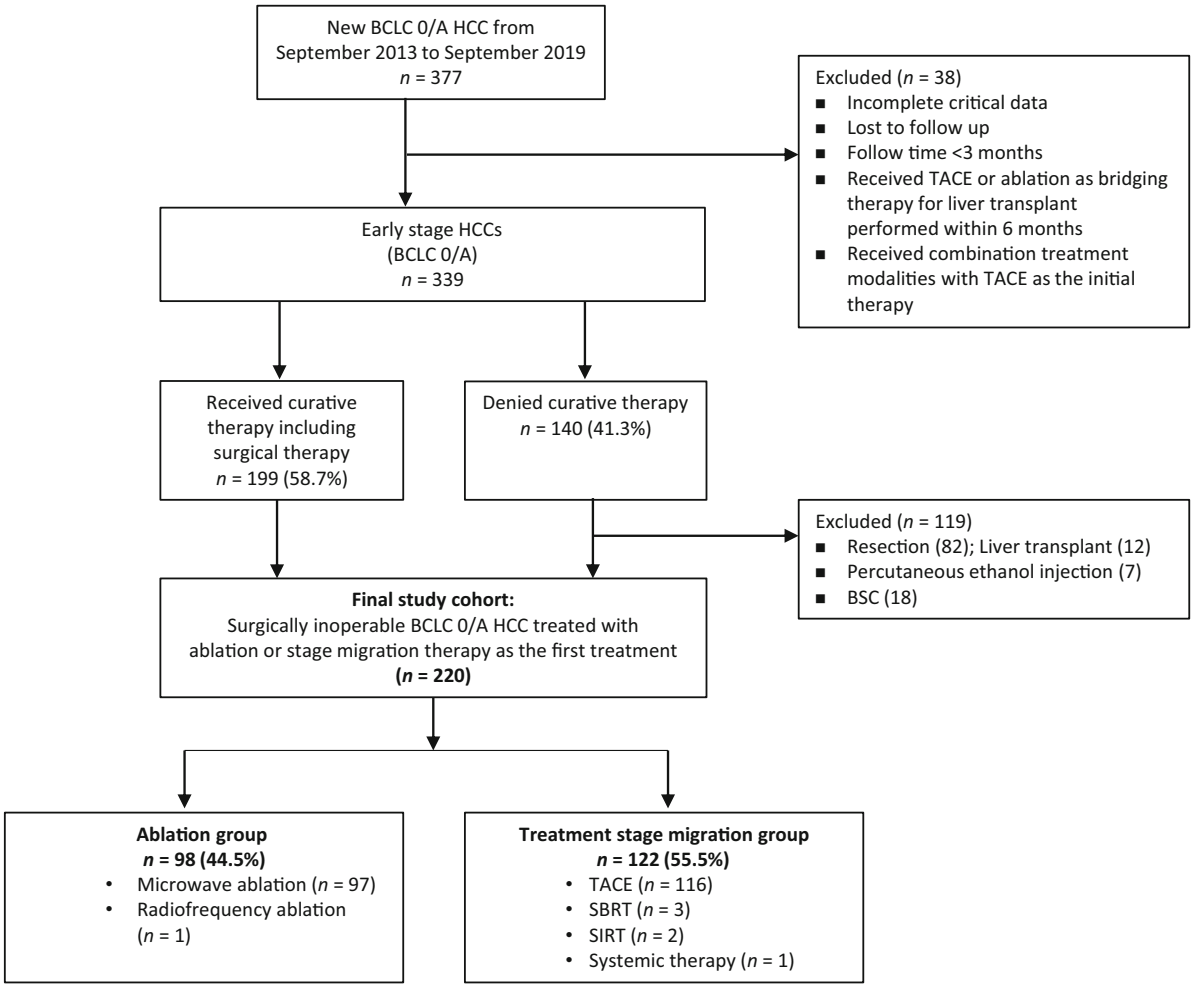

Figure 1 Consort diagram of study flow and patient selection for inclusion. BCLC, Barcelona Clinic Liver Cancer; BSC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

Table 1 Baseline clinical characteristics of treatment groups

	Treatment group						
	Overall Cohort[†] ($n = 220$)		Ablation ($n = 98$)		Stage migration ($n = 122$)		
	n	% or (IQR)	*n*	% or (IQR)	*n*	% or (IQR)	*P*-value[‡]
Patient characteristics							
Males	173	79%	73	74%	100	82%	0.178
Females	47	21%	25	26%	22	18%	
Age—median, (IQR)	62.5	(56–72)	65	(58–76)	62	(55.25–70)	0.295
ECOG							
0	165	75%	73	74%	92	71%	0.227
1	40	18%	15	15%	25	24%	
2	10	5%	8	8%	2	3%	
3	3	1%	1	1%	2	2%	
Etiology of Liver Disease							
HCV	44	20%	20	20%	23	19%	0.813
Alcohol	45	20%	19	19%	26	21%	0.775
NASH	45	20%	22	22%	23	19%	0.594
HCV + ETOH	48	22%	20	20%	27	22%	0.803
HBV	29	13%	11	11%	18	15%	0.499
Others	5	2%	3	3%	2	2%	0.054
Cirrhosis	206	94%	93	95%	113	93%	0.492
Child–Pugh A	160	73%	75	77%	85	70%	0.289
Child–Pugh B	52	24%	20	20%	32	26%	
Tumor characteristics							
Number of lesions							
1	167	76%	83	85%	84	69%	0.016
2	41	19%	13	13%	28	23%	
3	12	5%	2	2%	10	8%	
Largest diameter (mm)—median, (IQR)	20	(16–31)	24	(20–28)	33.5	(23–46)	<0.0001
BCLC stage 0	56	25%	45	46%	11	9%	<0.0001
BCLC stage A	164	75%	53	54%	111	91%	
AFP (μg/L)—median, (IQR)	6	(3–30)	6	(3–11.25)	8	(4–37)	0.084
MELD score—median, (IQR)	9	(8–12)	9	(8–12)	10	(8–12.25)	0.809

[†]Refer to BCLC 0/A HCC patients ineligible for surgery.

[‡]Comparison between treatment groups.

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ETOH, alcohol; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NASH, non-alcoholic steatohepatitis.

transplant performed within 6 months, or received combination treatment modalities with TACE as the initial therapy (2 patients with TACE + ablation, 2 patients with TACE + SBRT). All patients were discussed in the HCC multidisciplinary meeting for a consensus treatment plan. One hundred nineteen patients were excluded as they received surgical therapy (82 liver resections; 12 liver transplants), percutaneous ethanol injection, or best supportive care. Thus, 220 (65%) inoperable patients with BCLC 0/A HCC received either PA or TSM therapy as the initial treatment were included in the study (Fig. 1). No patients in our study cohort received liver transplantation as their initial treatment.

Baseline clinical and tumor characteristics. The median follow-up time was 23 months (IQR 11–37 months) for the whole cohort, 26 months for the PA group, and 19 months for the TSM group. The clinical characteristics of the study patients are summarized in Table 1. Several significant differences were present between the PA and TSM groups. The PA group had significantly more frequent single tumor nodule (85 *vs* 69%), smaller median tumor diameter (24 *vs* 33.5 mm), higher proportion of BCLC stage 0 (46 *vs* 9%), and lower median AFP (6 *vs* 8 μg/L).

Contraindications to PA. Of the 220 treatment naïve patients with early-stage HCC ineligible for surgery, 98 patients (44.5%) received PA, whereas 122 patients (55.5%) received TSM therapy as the initial treatment due to contraindications to PA, following HCC multidisciplinary team recommendations. The medical records for all patients denied curative therapy with PA were reviewed, and a maximum of two major contraindications were recorded (Table S1, Supporting information). The two main contraindications to PA were difficult tumor location and large tumor size (>3 cm), accounting for 51 and 48% of patients, respectively.

Of the 98 PA treatments, the most common modality used was microwave ablation (97 treatments); one patient received radiofrequency ablation. TACE was the most common TSM therapy (116 patients; 95%). Other TSM therapies included SIRT (two patients), SBRT (three patients), and systemic therapy (one patient). SIR-Spheres Y-90 resin microspheres was the standard

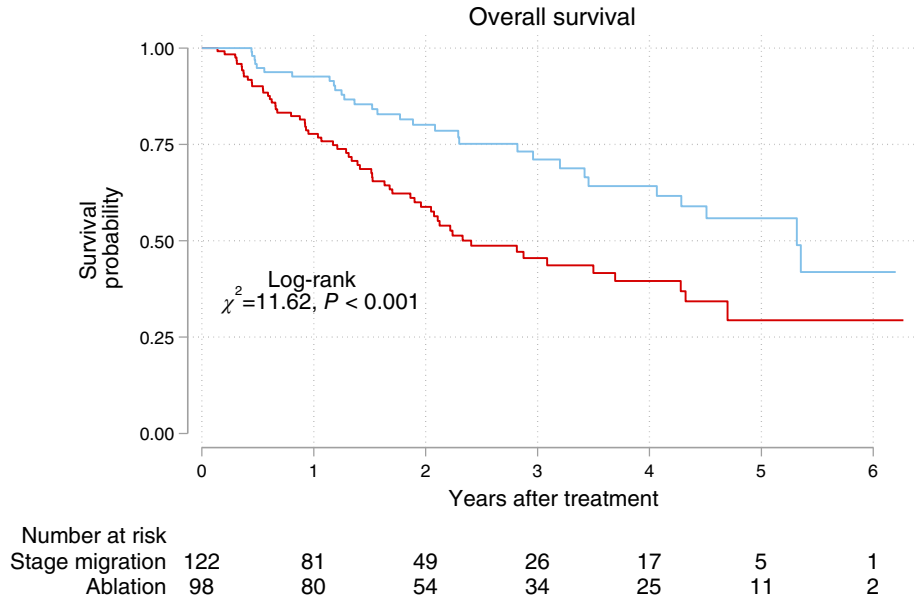

Figure 2 Kaplan–Meier analysis comparing overall survival in Barcelona Clinic Liver Cancer 0/A hepatocellular carcinoma patients treated with percutaneous ablation or stage migration therapy. (——) Stage migration; (——), ablation.

radioembolization technique performed at our centers. Sorafenib was the systemic therapy given in all cases.

Overall survival. Of the 220 study patients, 90 died within the follow-up period, with the median OS of 4.1 years for the whole study cohort (95% CI 2.87–5.31). Patients who received TSM therapy as the initial treatment had significantly shorter median OS when compared with the ablation group (2.4 *vs* 5.3 years; log-rank $\chi^2 = 11.62$, $P < 0.001$) (Fig. 2). The survival rates at 1, 3, and 5 years were also shorter in the TSM group (Table 2).

Multivariate analysis for variables associated with poorer survival is shown in Table S2. Older age, Child–Pugh score, and AFP level were all identified as variables independently associated with poor OS. Ablation treatment (*vs* TSM treatment) yielded better OS (HR 0.69, 95% CI 0.38–1.21, $P = 0.22$), although it was not statistically significant.

Local tumor control. Ninety-eight tumor nodules were treated with PA and 115 with TSM therapy. TSM therapy as the initial treatment was associated with lower median LTC in comparison to tumors treated with ablation (1.0 *vs* 4.8 years; log-rank $\chi^2 = 37.06$, $P < 0.001$) (Fig. 3). The LTC rates at 1, 3, and 5 years were also significantly lower in tumors treated with TSM therapy (Table 2). The 3-year LTC rates for PA *versus* TSM therapy were 65.2% *versus* 18.8%, respectively ($P < 0.001$).

Patients who received PA ($n = 98$) achieved complete tumor response rate more frequently in comparison to patients who received liver-directed TSM therapy (TACE = 113; SIRT = 2), 86% *versus* 56% ($P < 0.001$).

Multivariate analysis was performed to test for variables associated with LTC (Table S2). Older age, alcohol etiology, and lack of complete tumor response to initial therapy were independently associated with decreased LTC. Ablation treatment group *versus* TSM treatment was also independently associated with improved LTC (HR 0.25, 95% CI 0.13–0.48, $P = 0.001$).

Recurrence-free survival. Patients who received TSM therapy as the initial treatment had significantly lower RFS when compared with the ablation group (0.8 *vs* 2.7 years; log-rank $\chi^2 = 34.84$, $P < 0.001$) (Fig. 4). The RFS rates at 1, 3, and 5 years were also significantly lower in the TSM group (Table 2).

Multivariate analysis was performed to test for variables associated with RFS (Table S2). Alcohol etiology and lack of

Table 2 Overall survival, local tumor control, and recurrence-free survival in Barcelona Clinic Liver Cancer 0/A HCC patients according to the first treatment received

	Overall survival (%)			Local tumor control (%)			Recurrence-free survival (%)		
	Ablation	TSM	*P*-value	Ablation	TSM	*P*-value	Ablation	TSM	*P*-value
1 year	92.6	77.7	0.004	88.4	48.2	<0.001	78.1	40.7	<0.001
3 years	71.1	45.5	<0.001	65.2	18.8	<0.001	45.3	9.7	<0.001
5 years	55.8	29.4	<0.001	46.0	18.8	<0.001	27.1	7.7	<0.001

TSM, treatment stage migration.

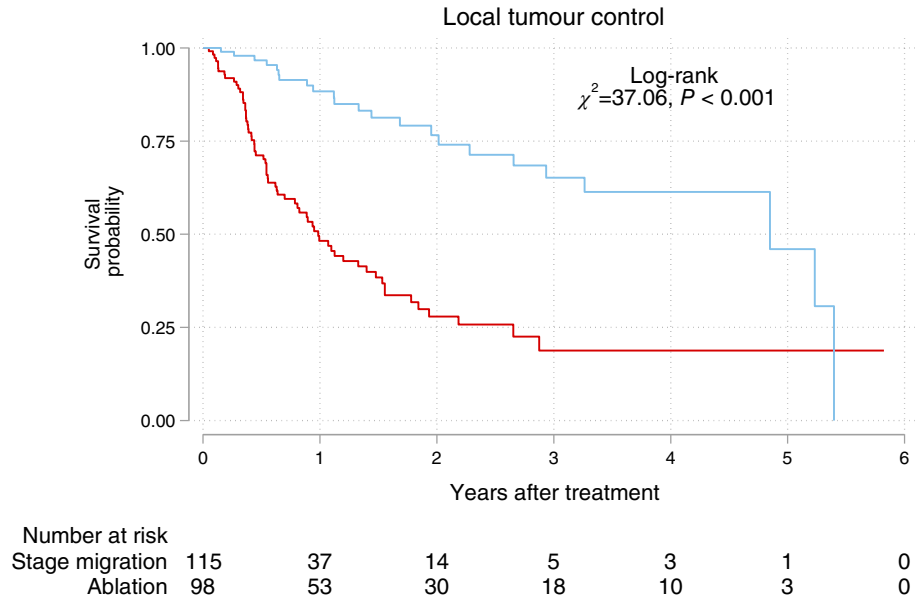

Figure 3 Kaplan–Meier analysis of local tumor control in Barcelona Clinic Liver Cancer O/A hepatocellular carcinoma patients treated with percutaneous ablation or stage migration therapy. (——) Stage migration; (——), ablation.

complete tumor response were independently associated with HCC recurrence. Ablation treatment *versus* TSM treatment group (HR 0.35, 95% CI 0.21–0.59, $P = 0.001$) was also the only other covariate with a significant association with RFS.

POM and ATE. The results for the POM survival time and ATEs for each outcome are shown in Table 3. The potential mean outcome time for the whole study population, treated using TSM therapy for OS, LTC, and RFS, were 1.86, 0.96, and 0.93 years, respectively. There was a significant ATE for PA *versus* TSM therapy for each outcome, with an additional 1.11 years ($P = 0.019$), 2.45 years ($P < 0.001$), and 1.64 years ($P < 0.001$) for OS, LTC, and RFS respectively, if the whole population were treated with PA *versus* TSM therapy (Table 3).

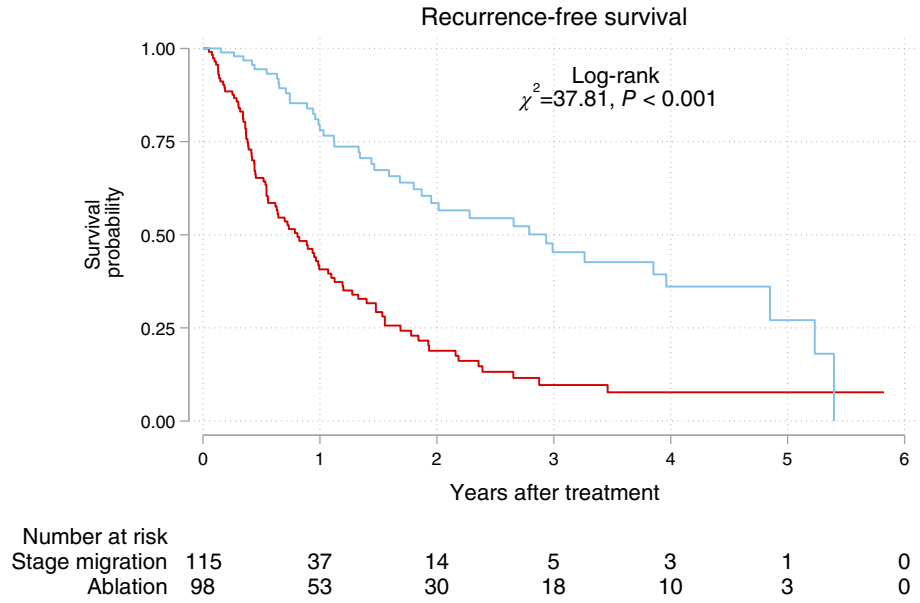

Figure 4 Kaplan–Meier analysis of recurrence-free survival in Barcelona Clinic Liver Cancer 0/A hepatocellular carcinoma patients treated with percutaneous ablation or stage migration therapy. (——) Stage migration; (——), ablation.

Table 3 Potential outcome mean and average treatment effect for study outcomes

	POM[†] (95% CI)	ATE[‡] (95% CI)	*P*-value[§]
Overall survival (years)	1.86 (1.32, 2.40)	1.11 (0.18, 2.03)	0.019
Local tumor control (years)	0.96 (0.69, 1.23)	2.45 (1.54, 3.36)	<0.001
Recurrence-free survival (years)	0.93 (0.74, 1.11)	1.64 (1.03, 2.26)	<0.001

[†]POM: Average time to the outcome if treatment stage migration were used for the whole study population.
[‡]ATE: The difference in mean time to outcome if all subjects were treated with percutaneous ablation *versus* treatment stage migration therapy.
[§]*P*-value for ATE *versus* zero: Estimates were obtained using a survival treatment effects estimation with inverse probability weights, a Logit treatment model, and a Weibull censoring model. Model covariates included age, gender, cirrhosis, Child Pugh score, alpha fetoprotein, model for end-stage liver disease score, number of tumors, tumor size, and alcohol etiology.
ATE, average treatment effect; CI, confidence interval; POM, potential outcome mean.

Discussion

Although a TSM strategy for treating HCC in early-stage, potentially curable HCC patients is common in real-world practice, its frequency and impact on outcomes are not well described. Our study reported a high rate of contraindications to PA (55.5%) in early-stage HCC patients who were ineligible for surgery. This finding is supported by other studies reporting a similarly high rate of contraindications to PA (34–43%),[9,11,15] and is likely to reflect real-world practice. The two main contraindications to PA were difficult tumor location (51%) and large tumor size >3 cm (48%) in our study cohort.

We note one single-center study in 2012 that reported low rate of contraindication to PA (12.9%).[16] This difference may relate to highly skilled operators in specialized centers using sophisticated techniques such as the induction of artificial pleural effusions and artificial ascites to improve lesion accessibility.[16] However, this technique was not used in our study cohort and is not commonly used in the Australian setting. We believe that the high rate of contraindications to PA demonstrates the frequent technical limitations of PA therapy for early-stage HCC in real-world practice, which is underappreciated in our view.

A subsequent problem related to this high rate of contraindications to PA is TSM to non-curative therapy. In this cohort, 55.5% of inoperable patients with early-stage HCC had TSM therapies. To the best of our knowledge, our study is the first to compare important oncological outcomes in this specific subgroup of surgically inoperable early-stage HCC patients who received curative therapy (PA) *versus* patients who received non-curative TSM therapies as the initial treatment. The outcomes in those who received TSM were significantly poorer with lower OS, LTC, and RFS on the Kaplan–Meier, POM, and ATE analyses. Poorer outcomes for patients receiving TSM treatments were also seen using multivariate Cox regression for LTC and RFS, but not for OS. Both POM and ATE and Cox regression analyses adjusted for several adverse clinical and tumor characteristics in the TSM group, yet the TSM treatment group remained independently associated with these poor outcomes.

Another concerning finding from our study was the relatively high local recurrence rate for small HCC tumors treated with PA. Although PA is considered a curative therapy, we found that patients treated with PA had high rates of local recurrence at 1, 3, and 5 years (12, 35 and 54%, respectively). These high local recurrence rates could not be explained by poor selection as all tumors treated were ≤3 cm in maximal diameter, the standard accepted indication for PA treatment. Moreover, all interventional radiologists involved in the PA treatments for our study cohort were liver specialized and experienced with this technique. Although early randomized studies and some single-center studies have reported better outcomes for local recurrence,[16–19] we believe the local recurrence rates for PA reported in our study are more reflective of the real-world practice and are supported by a number of recent studies reporting a similarly high local recurrence rates (23–54%) within 3 years.[20–23] The explanation for the high local recurrence after PA is unclear, but likely relates to technical factors such as suboptimal tumor visibility under USS guidance during PA, challenging subphrenic tumor locations,[21] leading to incomplete tumor ablation.

Taken together, these study findings demonstrate vulnerabilities associated with current HCC treatment algorithms using PA for surgically inoperable early-stage HCC, when implemented in real-world settings. Patients who are not eligible for surgical therapies are effectively placed in "double jeopardy" when referred for PA. The first risk they face is not being eligible for PA with subsequent migration of stage and treatment to non-curative therapies associated with poorer LTC and survival. The second risk they face is from the frequent failure after PA to provide effective LTC. The purpose of this paper is to highlight the limitations of PA within current algorithms in clinical practice, which in our view do not appear to be sufficiently recognized. These limitations suggest the need for improved quality assurance measures surrounding the delivery of PA and randomized controlled trials of alternative, potentially curative treatments for inoperable patients with early-stage HCC. SBRT is a leading contender for such a trial as it has demonstrated excellent LTC rates (>90% up to 3 years) in non-randomized studies.[8,10,13,24,25]

There are several limitations of our study. Firstly, its retrospective and non-randomized design limits our ability to exclude selection bias, with differences in baseline clinical characteristics potentially explaining the poorer outcomes in the TSM group. To overcome this potential bias, we used a POM approach that allowed for estimation of marginal treatment effects rather than the typical estimation of conditional treatment effects using a standard Cox regression approach. However, the potential for selection bias remains a possibility, to the extent that unobserved cofounders were not included in the model for treatment assignment. Despite this limitation, the range of the ATEs was all within the range of biological plausibility. A further limitation was likely heterogeneity in the technical aspects of PA and TACE delivery and radiology reporting by multiple care providers across different centers. Nevertheless, this heterogeneity is reflective of real-world practice in many healthcare centers. Major study strengths include a large patient cohort and

multicenter design. A further strength is that treatment allocation was by HCC multidisciplinary teams and according to current BCLC treatment algorithms.

In conclusion, this real-world, multicenter study confirmed that there was a high rate of contraindications to PA, resulting in TSM and poorer outcomes for inoperable early-stage HCC patients. PA was associated with improved oncological outcomes compared with TSM therapy; however, the local recurrence rate remained suboptimal for this therapy, which is regarded as a curative therapy in guidelines.

Patient consent. Patient consent was waived by our Ethics Committee in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Data availability statement. All data generated or analyzed during this study are included in this published article; the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Contraindications to percutaneous ablation in surgically inoperable BCLC 0/A patients ($n = 122$).
Table S2. Multivariate analyses for overall survival (OS), local tumor control (LTC), recurrence-free survival (RFS) using Cox regression.
Table S3. Multivariate analyses for overall survival (OS), local tumor control (LTC), recurrence-free survival (RFS) using Logistic Regression Model.