ORIGINAL ARTICLE

Prognostic benefit of preoperative transarterial chemoembolization in upfront resectable large hepatocellular carcinoma: a multicentric propensity score based analysis of European high-volume centers

Fabio Giannone[1,2,3], Emanuele Felli[4], Federica Cipriani[5], Bruno Branciforte[6], Rami Rhaiem[7], Bader Al Taweel[8], Raffaele Brustia[9,10], Ephrem Salame[4], Fabrizio Panaro[8], Daniele Sommacale[9,10], Tullio Piardi[7], Guido Torzilli[6], Luca Aldrighetti[5], Catherine Schuster[2] & Patrick Pessaux[1,2,3]

[1]Department of Visceral and Digestive Surgery, University Hospital of Strasbourg, [2]Université de Strasbourg, Inserm, Institut de Recherche sur les Maladies Virales et Hépatiques, U1110, [3]Institut Hospitalo-Universitaire (IHU), Institute of Image-Guided Surgery, Strasbourg, [4]Liver Transplant and Surgery Department, Trousseau Hospital, Tours, France, [5]Hepatobiliary Surgery Division, IRCCS San Raffaele Scientific Institute, [6]Division of Hepatobiliary and General Surgery, Department of Surgery, Humanitas University, Humanitas Clinical and Research Center – IRCCS, Rozzano, Milan, Italy, [7]Department of Oncological Digestive Surgery, Hepatobiliary and Pancreatic Surgery Unit, University Reims Champagne-Ardenne, Reims, [8]Department of Surgery, Division of HBP Surgery and Transplantation, Saint-Eloi Hospital, University Hospital of Montpellier, Montpellier, [9]Department of Digestive and Hepato-pancreatic-biliary Surgery, AP-HP, Hôpital Henri-Mondor, Paris Est Créteil University, UPEC, and [10]Team "Pathophysiology and Therapy of Chronic Viral Hepatitis and Related Cancers", INSERM U955, Créteil, France

Abstract

Background: Hepatocellular carcinoma (HCC) have a dismal prognosis and any effective neoadjuvant treatment has been validated to date. We aimed to investigate the role of neoadjuvant transarterial chemoembolization (TACE) in upfront resectable HCC larger than 5 cm.

Methods: This is a multicentric retrospective study comparing outcomes of large HCC undergoing TACE followed by surgery or liver resection alone before and after propensity-score matching (PSM).

Results: A total of 384 patients were included of whom 60 (15.6%) received TACE. This group did not differ from upfront resected cases neither in terms of disease-free survival ($p = 0.246$) nor in overall survival ($p = 0.276$). After PSM, TACE still did not influence long-term outcomes ($p = 0.935$ and $p = 0.172$, for DFS and OS respectively). In subgroup analysis, TACE improved OS only in HCC $\geq$10 cm ($p = 0.045$), with a borderline significance after portal vein embolization/ligation ($p = 0.087$) and in single HCC ($p = 0.052$).

Conclusions: TACE should not be systematically performed in all resectable large HCC. Selected cases could however potentially benefit from this procedure, as patients with huge and single tumors or those necessitating of a PVE.

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Correspondence

Patrick Pessaux, Department of Visceral and Digestive Surgery, University Hospital of Strasbourg, 1, Place de l'Hôpital, Nouvel Hôpital Civil, 67100 Strasbourg, France. E-mail: patrick.pessaux@chru-strasbourg.fr

Introduction

Hepatocellular Carcinoma (HCC) accounts for about 80% of all liver cancer and it ranks as the third leading cause of cancer deaths worldwide.[1] As its cholangiocyte-derived counterpart, HCC shows a dismal prognosis with a relative 5-year survival rate of approximately 20%.[2] Even in case of resectable disease undergoing surgical treatment, outcomes do not differ significantly and recurrence rate remains high, reaching 70–80% in 5 years. Other curative-intent strategies are validated in the Barcelona Clinical Liver Cancer (BCLC) algorithm in alternative to surgery,[3] as local ablation or liver transplant, but not all of them are always available, with different factors – as size or numbers – limiting the indiscriminate use of this armamentarium. Large HCC, lesions with a maximum diameter equal or superior to 5 cm, represent for instance a real challenge in this context. Although belonging to the early stage of the BCLC

The paper is not based on a previous communication to a society or meeting.

classification in case of single localization, these tumors show a poor prognosis if compared to smaller lesions.[4,5] When possible, surgical resection have largely demonstrated to improve long-term outcomes in these patients but risk of recurrence remains high.[6–10] Given the lack of validated neoadjuvant protocols, different authors reported the use of transarterial chemoembolization (TACE) before surgery in large HCC with the aim of inducing tumoral cell death, increasing R0 resection rates and thus improving outcomes.[11–13] However, results are far from being exhaustive with contradictory conclusions and a difficulty in finding those cases who could really benefit from this procedure. A large meta-analysis revealed that neoadjuvant TACE did not increase disease-free survival (DFS) and overall survival (OS) rates but favorable results were found when assessing exclusively cirrhotic patients.[14] Similarly, a multicentric cohort recently showed improved oncologic outcomes when performing this procedure before surgery in huge HCC ($\geq$10 cm).[11] Other unsolved issues derive from the statistical robustness of these studies, with possible selection bias, and not least, that almost all these series come from Asiatic centers, which present different underlying etiology as well as distinct genetic altered pathways.[15]

This study aimed to investigate the utility of preoperative TACE in upfront resectable HCC larger than 5 cm, analyzing cases from European centers gathered in a common database. By setting accurate inclusion criteria, a homogeneous cohort was therefore created in which long-term outcomes were evaluated by a propensity score matching (PSM) and in different subgroup of patients.

Methods

Study design

This is a retrospective study conducted on a multicentric international database following the items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[16] An informed consent was obtained before each procedure and the study was aligned to the ethical standards of the Helsinki declaration. Seven Italian and French centers provided data on patients affected by large HCC ($\geq$5 cm) undergoing TACE followed by surgical treatment (preoperative TACE, cases) or liver resection alone (upfront surgery, control) with a curative intent, from January 2012 and December 2020. Only cases considered as resectable at diagnosis were included, thus without prior systemic or local treatment – except for preoperative TACE followed by a planned surgery – or history of distant metastases. Upfront resectability was based on single institution decision. Due to the likely higher risk of recurrence in case of atypical resection[17,18] and the consequent possible selection bias, one of the inclusion criteria set before data collection was cases undergoing anatomical resection. Exclusion criteria were surgery for HCC recurrence, adjuvant systemic or local treatment (i.e. post-operative TACE or patients included in an experimental protocol with an adjuvant therapy), more than one preoperative TACE and surgical resection performed later than 10 weeks after the endovascular procedure. Patients with incomplete data, a follow-up inferior to 12 months or lost to follow-up were as well excluded from the analysis. Clinico-pathologic, peri-operative and histologic features were collected from all centers in a common database. Diagnosis of preoperative cirrhosis, its nature and Child–Pugh score were recorded. Portal hypertension was evaluated by platelet count and classified in a binomial variable according to its normal value (150.000×10^9/L). Intraoperative blood loss, transfusions and operative time were registered as an indirect marker of surgical complexity. Information on post-operative complications such as post-hepatectomy liver failure (PHLF) and hemorrhage (PHH) were collected and scored according to the ISGLS classification.[19,20] Overall post-operative complications were further graded according to the Clavien–Dindo classification.[21] Among histologic features, satellites nodules were defined as tumors inferior to 1 cm in diameter and located less than 1 cm to the main tumor. If this condition was not fulfilled, tumor was considered as multifocal. The final cohort was then divided according to the preoperative performance of a TACE in order to assess its prognostic meaning in terms of disease-free survival (DFS) and overall survival (OS).

Trans-arterial chemoembolization

There is no consensus on the use of preoperative TACE in large HCC, therefore the indication of performing this procedure before resection and its modalities were decided case by case according to surgeon and radiologist judgment in each institution. Given the multicentric nature of the study, type (doxorubicin or idarubicin) and dose of drug administrated varied among the centers, as well as the embolization material and the simultaneous combination of lipiodol. The procedure started by the insertion of a vascular catheter in the femoral artery. Superior mesenteric artery was first cannulated to exclude an accessory or replaced hepatic artery feeding the tumor. Then the coeliac artery was catheterized. The main first-order hepatic artery was chosen or, if possible, a more selective branch vascularizing all the tumor. The emulsion of the selected drug and the embolization agents was therefore injected. A final arteriography confirmed the success of the procedure. When PVE/PVL was further indicated in order to increase future liver remnant (FLR), a minimum delay of two/three weeks was respected between TACE and venous occlusion. Date of TACE, PVE/PVL and surgery as well as data regarding drug, agents and modalities of the two procedures were always recorded.

Statistical analysis

Categorical data were reported as absolute number with relative proportions (%) and compared by the $\chi 2$ test with Yates correction if necessary, or Fischer's exact test if indicated. Continuous data were expressed as median and range and compared using Student's t test or Mann–Whitney U test in case

of normal distribution. Kaplan–Meier analysis were performed and survival outcomes compared using log-rank test for categorical variables and through Cox test in case of continuous data. Hazard Ratios and the relative 95% CI were always reported. Significant variables at the univariate analysis were included in the Cox multivariate analysis. A PSM was then performed to create two homogeneous cohorts and thus reduce the bias of treatment selection. Covariates used to create the model included gender, age, ASA, platelets level, preoperative cirrhosis, history of viral infection, AFP at diagnosis, type of approach, type of hepatectomy, PVE/PVL performed, tumor size at diagnosis, number of nodules, microvascular infiltration (MVI), capsular invasion, satellites nodules and margin status. Despite several attempts, undergoing preoperative PVE/PVL was the only feature which could not be balanced between the two groups. A nearest neighbor matching without replacement with a ratio 2:1 was therefore chosen to create the largest sample size as possible preserving, at the same time, the homogeneity of all the remaining variables. Survival analysis were repeated between the two new groups. Subgroups analysis were further performed to assess a possible benefit of preoperative TACE in a selected group of patients. All tests were 2-tailed and level of significance was set at $p < 0.05$. All statistical computations were performed using SPSS (SPSS Statistics, version 26.0, IBM Corp) or R (R Project for statistical computing, version 4.2.2, R Core Team).

Results

General features and peri-operative outcomes

After data collection, a total of 384 patients resected for a HCC $\geq$5 cm and respecting all inclusion and exclusion criteria were included in the final cohort. Of these, 324 (84.4%) underwent upfront surgery whereas 60 (15.6%) were previously treated by TACE. Table 1 shows main features of the whole population. The two groups were extremely heterogeneous in terms of baseline, operative and histologic characteristics. Patients with a neoadjuvant TACE had a significantly higher ASA score ($p = 0.014$) and AFP level ($p = 0.001$). As regards operative data, these patients underwent more often an open ($p < 0.001$), major hepatectomy ($p < 0.001$) requiring preoperative PVE ($p < 0.001$) compared to controls undergoing upfront resection. Histologic data comparison revealed that tumors treated by TACE had a lower differentiation grade ($p < 0.001$), presented less frequently a MVI ($p = 0.023$) and a capsular invasion ($p = 0.017$) and were more often multiple ($p = 0.027$). When assessing perioperative outcomes, preoperative TACE was associated with longer operative times ($p = 0.023$), major blood loss and intraoperative transfusions ($p = 0.029$ and $p = 0.037$) and a higher risk of severe postoperative complications ($p < 0.001$).

All significant variables were used for the PSM statistical model. The new cohort consisted of 180 patients of whom 120 (66.7%) underwent upfront surgery. Except for the FLR hypertrophy, the two groups were balanced in all baseline, operative and histological features (Table 1). No differences in peri- and postoperative outcomes were found in this new cohort between TACE and upfront surgery group.

Survival analysis in the whole cohort and after PSM

Median follow-up for the whole cohort was 24 months (range: 0–127 months). Death occurred in 112/324 patients (34.6%) undergoing upfront resection and in 15/60 (25%) with preoperative TACE, whereas recurrence was observed in 173/324 (53.4%) and 35/60 (58.3) patients without and with neoadjuvant TACE, respectively. There was no difference in DFS ($p = 0.246$, Fig. 1a) and OS ($p = 0.276$, Fig. 1b) between the two groups. Univariate and multivariate analysis of all possible prognostic factors for DFS and OS are shown in Table 2 and 3. Independent predictors of impaired DFS were AFP $\geq$400 ng/mL (HR: 1.645, $p = 0.046$), minimally-invasive vs open approach (HR: 0.725, $p = 0.045$), extension of hepatectomy (HR: 1.434, $p = 0.014$), tumor number (HR: 1.507, $p = 0.018$), MVI (HR: 1.683, $p < 0.001$) and satellite nodules (HR: 1.584, $p = 0.003$). In OS multivariate Cox regression only severe post-operative complications (HR: 2.151, $p = 0.004$) and MVI (HR: 2.074, $p < 0.001$) turned out to be significantly associated with decreased patient survival. The same analysis was performed in the PSM cohort. Of the 120 patients undergoing upfront liver resection, 68 (56.7%) experienced disease recurrence and 45 (37.5%) died at follow-up. Despite covariates balancing, preoperative TACE was not associated with improved oncological outcomes, neither in terms of DFS ($p = 0.935$, Fig. 1c) nor OS ($p = 0.172$, Fig. 1d). After matching, type of approach and extension of hepatectomy lost their independent prognostic role for disease recurrence at multivariate regression analysis (Table 2), whereas presence of multiple HCC became an independent predictor of survival (HR: 1.859, $p = 0.028$. Table 3).

Subgroup analysis

Comparison of prognostic outcomes was then performed in specific subgroups of patients in order to assess a potential benefit of preoperative TACE in certain situations as insufficient FLR or cirrhosis (Fig. 2). The first analysis was focused on patients undergoing PVE. This cohort included 87 cases of whom 47 (54%) were preceded by TACE. Kaplan–Meier curves showed no differences in this subgroup in terms of recurrence ($p = 0.376$) whereas a tendency towards an improved survival was observed, although not reaching a statistical significance ($p = 0.087$). Another class of patients explored was those with an underlying cirrhosis. Of the whole population, 185 (48.2%) showed a cirrhotic liver at pathological report and 27 of these (14.6%) received neoadjuvant TACE. Even in this subgroup, this procedure did not show any benefit when analyzing DFS ($p = 0.751$) and OS ($p = 0.495$) curves. Finally, we separately assessed long-term outcomes in HCC between 5 and 10 cm and huge ($\geq$10 cm) HCC. Patients with HCC between 5 and 10 cm ($n = 305$, 79.4%) underwent TACE in 41 cases (13.4%) without

Table 1 Patients characteristics in the whole cohort and after PSM (ratio 2:1)

Variable	Before matching (n = 384)			After PSM (n = 180)		
	Upfront Resection n = 324	Preoperative TACE n = 60	p	Upfront Resection n = 120	Preoperative TACE n = 60	p
	n (%)			n (%)		
Age (years), SD	69.89 (9.6)	69 (7)	0.604	69 (9)	69 (7)	0.874
Sex						
Male	252 (77.8)	54 (90)	**0.031**	104 (86.7)	54 (90)	0.520
Female	72 (22.2)	6 (10)		16 (13.3)	6 (10)	
BMI (kg/m^2), SD	25 (4.4)	26.7 (4.1)	**0.024**	25.8 (4.3)	26.7 (4.1)	0.429
ASA						
I	30 (9.3)	–	**0.014**	4 (3.3)	–	0.551
II	175 (54)	27 (45)		50 (41.7)	27 (45)	
III	116 (5.8)	32 (53.3)		64 (53.3)	32 (53.3)	
IV	3 (0.9)	1 (1.7)		2 (1.7)	1 (1.7)	
Preoperative cirrhosis						
No	164 (50.6)	33 (55)	0.702	64 (53.3)	33 (55)	0.768
A	158 (48.8)	27 (45)		55 (45.8)	27 (45)	
B	2 (0.6)	–		1 (0.8)	–	
Normal platelets count, ($\geq$150 × 10^9/L)						
No	81 (25)	12 (20)	0.406	24 (20)	12 (20)	1
Yes	243 (75)	48 (80)		96 (80)	48 (80)	
History of viral infection (HBV/HCV)						
No	191 (59)	44 (73.3)	**0.036**	76 (63.3)	44 (73.3)	0.180
Yes	133 (41)	16 (26.7)		44 (36.7)	16 (26.7)	
AFP at diagnosis, ng/mL						
$\leq$400	307 (94.8)	50 (83.3)	**0.001**	106 (88.3)	50 (83.3)	0.352
>400	17 (5.2)	10 (16.7)		14 (11.7)	10 (16.7)	
HCC median size at diagnosis (mm), SD	70 (41.6)	75 (29)	0.117	72 (43.7)	75 (29)	0.958
PVE/PVL performed						
No	284 (87.7)	13 (21.7)	**<0.001**	94 (78.3)	13 (21.7)	**<0.001**
Yes	40 (12.3)	47 (78.3)		26 (21.7)	47 (78.3)	
Approach						
Open	186 (57.4)	52 (86.7)	**<0.001**	96 (80)	52 (86.7)	0.270
Minimally-invasive	138 (42.6)	8 (13.3)		24 (20)	8 (13.3)	
Extension of hepatectomy						
Minor	186 (57.4)	6 (10)	**<0.001**	22 (18.3)	6 (10)	0.146
Major	138 (42.6)	54 (90)		98 (81.7)	54 (90)	
Intraoperative blood loss (ml), SD	350 (466)	500 (571)	**0.029**	400 (600)	500 (571)	0.076
Operative time (min), SD	289 (92)	330 (85)	**0.023**	300 (106)	330 (85)	0.265
Intraoperative blood transfusion						
No	281 (86.7)	45 (75)	**0.037**	99 (82.5)	45 (75)	0.236
Yes	43 (13.3)	15 (25)		21 (17.5)	15 (25)	
Post-operative complications						
PHLF	36 (11.1)	9 (15)	0.390	19 (15.8)	9 (15)	0.884
PHH	5 (1.5)	–	1	2 (1.7)	–	0.553
Death	3 (0.9)	2 (3.3)	0.131	2 (1.7)	2 (3.3)	0.602

(*continued on next page*)

Table 1 (*continued*)

Variable	Before matching (n = 384)			After PSM (n = 180)		
	Upfront Resection n = 324	Preoperative TACE n = 60	p	Upfront Resection n = 120	Preoperative TACE n = 60	p
	n (%)			n (%)		
Severe post-operative complications (CD ≥ 3)						
No	295 (93.9)	47 (78.3)	**<0.001**	105 (87.5)	47 (78.3)	0.110
Yes	19 (6.1)	13 (21.7)		15 (12.5)	13 (21.7)	
HCC median size on pathology (mm), SD	70 (45.2)	80 (37)	0.250	70 (50)	80 (37)	0.429
WHO tumor differentiation[a]						
Well	46 (17)	20 (35.1)	**<0.001**	27 (27)	20 (35.1)	0.302
Moderately	184 (68.1)	35 (61.4)		64 (64)	35 (61.4)	
Poor	40 (14.8)	2 (3.5)		9 (9)	2 (3.5)	
Tumor number						
Solitary	271 (83.6)	43 (71.7)	**0.027**	97 (80.8)	43 (71.7)	0.163
Multiple	53 (16.4)	17 (28.3)		23 (19.2)	17 (28.3)	
Microvascular infiltration						
No	159 (49.1)	39 (65)	**0.023**	69 (57.5)	39 (65)	0.333
Yes	165 (50.9)	21 (35)		51 (42.5)	21 (35)	
Capsular invasion						
No	261 (80.6)	56 (93.3)	**0.017**	103 (85.8)	56 (93.3)	0.140
Yes	63 (19.4)	4 (6.7)		17 (14.2)	4 (6.7)	
Satellites nodules						
No	242 (74.7)	45 (75)	0.960	93 (77.5)	45 (75)	0.709
Yes	82 (25.3)	15 (25)		27 (22.5)	15 (25)	
Margin status						
Negative	296 (91.4)	55 (91.7)	0.938	111 (92.5)	55 (91.7)	0.844
Positive	28 (8.6)	5 (8.3)		9 (7.5)	5 (8.3)	

PSM, propensity score matching; TACE, transarterial chemoembolization; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; PVE, portal vein embolization; PVL, portal vein ligation; PHLF, post hepatectomy liver failure; PHH, post hepatectomy hemorrhage; CD, Clavien–Dindo; WHO, World Health Organisation.
[a] 57 cases missing for the whole cohort and 23 values after PSM.

any improved outcomes (DFS: p = 0.431; OS: p = 0.952). Analysis of huge HCC (n = 79, 20.6%), by contrast, revealed a prolonged survival in the 19 cases (24.1%) pre-treated with TACE (p = 0.045) with a similar trend in case of single lesion (Fig. 2), although of borderline significance (p = 0.052).

Discussion

One of the most important lacks in the therapeutic algorithm of HCC is undoubtedly the absence of any effective pre- and post-operative treatment. As it happens in large unresectable diseases converted to surgery thanks to the shrinkage obtained by TACE,[22] this technique has been proposed as well in large upfront resectable HCC with the aim of down-staging the tumor and improving long-term outcomes. Although several series have been published, results are far from being promising with only a few authors reporting a benefit when performing this procedure before liver resection in specific subgroups of patients.[11–14] However, conclusions are difficult to be drawn. The majority of the evidence comes from retrospective heterogeneous cohorts while randomized control-trials are rather dated with limited inclusions.[23–26] Furthermore, some series present evident selection bias as patients included after tumor down-staging in initially unresectable disease, several TACE sessions or cases with non-anatomic resection, which are known to be associated with a higher risk of disease recurrence.[17,18] To our knowledge, this study represents the largest experience of western centers comparing patients undergoing surgical resection with or without preoperative TACE for upfront resectable HCC larger than 5 cm. Our results suggest that neoadjuvant TACE is a safe procedure with no increased perioperative morbi-mortality, but long-term outcomes analysis showed no associated benefit when

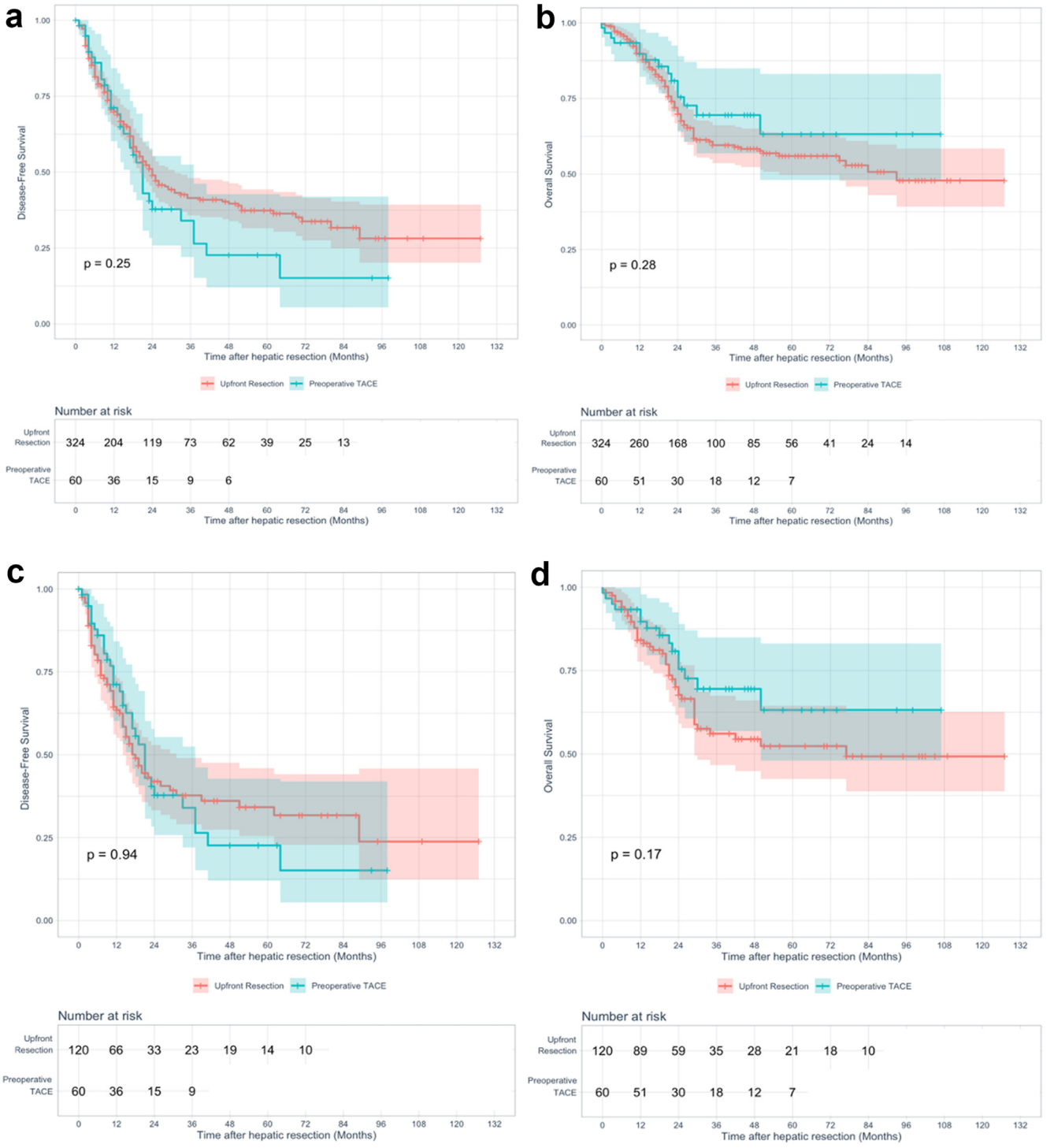

Figure 1 Kaplan–Meier curves of disease-free survival and overall survival in patients undergoing upfront resection or preoperative TACE before (a and b) and after (c and d) the propensity score matching

combining this treatment prior to surgery even after PSM, neither in terms of disease recurrence nor of overall survival. These findings are not far from those reported in literature. Indeed, several series already concluded that systematic use of TACE before surgery was not recommended because of a lack of real oncologic benefit.[27,28] Similarly, results from three meta-

Table 2 Univariate and multivariate cox regression analysis of prognostic factors for disease-free survival in the whole cohort and after propensity score matching

Variable	Category	Before matching ($n = 384$)		After PSM ($n = 180$)	
		Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Univariate analysis					
Age	Continuous data	1.003 (0.989–1.017)	0.685	0.978 (0.956–1)	0.055
Sex	Female vs male	0.851(0.602–1.202)	0.352	0.896 (0.479–1.676)	0.727
BMI	Continuous data	1.011 (0.982–1.042)	0.465	0.978 (0.935–1.023)	0.332
ASA	III–IV vs I–II	1.350 (1.026–1.778)	**0.029**	0.856 (0.581–1.261)	0.423
Preoperative cirrhosis	Yes vs no	0.977 (0.744–1.284)	0.864	0.924 (0.626–1.363)	0.684
Normal platelets count	Yes vs no	0.962 (0.701–1.320)	0.807	0.723 (0.454–1.152)	0.163
History of viral infection	Yes vs no	1.165 (0.883–1.536)	0.272	1.268 (0.845–1.904)	0.242
AFP level at diagnosis	>400 vs ≤ 400	2.081 (1.295–3.343)	**0.002**	1.807 (1.020–3.202)	**0.036**
HCC size at diagnosis	Continuous data	1.002 (1–1.004)	0.055	1.003 (0.999–1.006)	0.106
Preoperative TACE	Yes vs no	1.236 (0.859–1.779)	0.246	1.017 (0.676–1.530)	0.935
PVE/PVL performed	Yes vs no	1.371 (1.003–1.875)	**0.044**	1.128 (0.764–1.667)	0.537
Approach	MI vs open	0.565 (0.420–0.759)	**<0.001**	0.634 (0.360–1.115)	0.105
Extension of hepatectomy	Major vs minor	1.579 (1.2–2.077)	**0.001**	1.573 (0.894–2.768)	0.107
Severe post-operative complications	Yes vs no	2.221 (1.381–3.572)	**0.001**	1.938 (1.149–3.270)	**0.010**
HCC tumor size on pathology	Continuous data	1.003 (1.001–1.005)	**0.008**	1.005 (1.001–1.008)	**0.012**
WHO tumor differentiation	Moderately vs well Poor vs well	1.057 (0.720–1.553) 1.106 (0.647–1.893)	0.776 0.712	1.192 (0.722–1.968) 1.623 (0.689–3.824)	0.492 0.268
Tumor number	Multiple vs solitary	1.715 (1.229–2.392)	**0.001**	1.819 (1.168–2.831)	**0.006**
Microvascular infiltration	Yes vs no	1.640 (1.247–2.158)	**<0.001**	2.115 (1.432–3.125)	**<0.001**
Capsular invasion	Yes vs no	1.199 (0.852–1.687)	0.299	1.618 (0.948–2.761)	0.070
Satellites nodules	Yes vs no	1.760 (1.313–2.357)	**<0.001**	2.335 (1.543–3.532)	**<0.001**
Margin status	R1 vs R0	1.549 (0.986–2.435)	0.052	2.135 (1.108–4.113)	**0.018**
Multivariate analysis					
ASA	III–IV vs I–II	1.211 (0.902–1.625)	0.204	–	–
AFP level at diagnosis	>400 vs ≤400	1.645 (1.008–2.684)	**0.046**	1.904 (1.049–3.456)	**0.034**
PVE/PVL performed	Yes vs no	0.967 (0.669–1.398)	0.857	–	–
Approach	MI vs open	0.725 (0.530–0.994)	**0.045**	–	–
Extension of hepatectomy	Major vs minor	1.434 (1.075–1.914)	**0.014**	–	–
Severe post-operative complications	Yes vs no	1.551 (0.943–2.552)	0.084	1.529 (0.888–2.633)	0.126
HCC tumor size on pathology	Continuous data	1.002 (1–1.004)	0.120	1.004 (1–1.008)	0.056
Tumor number	Multiple vs solitary	1.507 (1.073–2.116)	**0.018**	1.955 (1.234–3.098)	**0.004**
Microvascular infiltration	Yes vs no	1.683 (1.269–2.233)	**<0.001**	1.887 (1.259–2.828)	**0.002**
Satellites nodules	Yes vs no	1.584 (1.175–2.136)	**0.003**	1.961 (1.277–3.013)	**0.002**
Margin status	R1 vs R0	–	–	1.504 (0.753–3.006)	0.248

PSM, propensity score matching; BMI, body mass index; ASA, American Society of Anesthesiologists; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PVE, portal vein embolization; PVL, portal vein ligation; MI, minimally-invasive; WHO, World Health Organization.

analysis and a RCT revealed comparable OS and DFS between hepatic resection with or without preoperative TACE in large resectable HCC.[14,24,29,30]

In theory, principle behind the benefit of the use of this technique before liver resection lies in the necrosis of a large portion of tumor cells, the destruction of any possible satellite nodules and a consequent reduction in MVI and R1/R2 rates. TACE may additionally limit tumor cell dissemination during surgery and inhibit metastasis of HCC.[31,32] Following these assumptions, Yang *et al.* recently analyzed HCC cases undergoing liver resection with or without neoadjuvant TACE with the aim of assessing any possible correlation between this

Table 3 Univariate and multivariate cox regression analysis of prognostic factors for overall survival in the whole cohort and after propensity score matching

Variable	Category	Before matching (n = 384)		After PSM (n = 180)	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Univariate analysis					
Age	Continuous data	0.990 (0.973–1.008)	0.275	0.976 (0.949–1.004)	0.094
Sex	Female vs male	0.868 (0.560–1.345)	0.522	0.708 (0.304–1.650)	0.417
BMI	Continuous data	1.017 (0.979–1.056)	0.385	1.011 (0.952–1.073)	0.721
ASA	III–IV vs I–II	1.432 (1.009–2.034)	**0.042**	1.1 (0.661–1.831)	0.711
Preoperative cirrhosis	Yes vs no	1.521 (1.069–2.163)	**0.018**	1.249 (0.753–2.073)	0.384
Normal platelets count	Yes vs no	0.699 (0.480–1.020)	0.063	0.591 (0.337–1.037)	0.061
History of viral infection	Yes vs no	1.446 (1.020–2.052)	**0.036**	1.158 (0.680–1.970)	0.586
AFP level at diagnosis	>400 vs ≤400	1.251 (0.634–2.466)	0.514	1.348 (0.608–2.986)	0.457
HCC size at diagnosis	Continuous data	0.999 (0.995–1.003)	0.699	1 (0.994–1.006)	0.956
Preoperative TACE	Yes vs no	0.744 (0.434–1.275)	0.276	0.670 (0.373–1.202)	0.172
PVE/PVL performed	Yes vs no	1.012 (0.665–1.539)	0.956	0.845 (0.502–1.423)	0.522
Approach	MI vs open	0.756 (0.520–1.101)	0.140	0.946 (0.479–1.870)	0.873
Extension of hepatectomy	Major vs minor	1.266 (0.893–1.795)	0.180	1.353 (0.642–2.849)	0.420
Severe post-operative complications	Yes vs no	2.327 (1.395–3.880)	**0.001**	2.340 (1.303–4.201)	**0.003**
HCC tumor size on pathology	Continuous data	1 (0.977–1.004)	0.953	1.002 (0.997–1.007)	0.485
WHO tumor differentiation	Moderately vs well Poor vs well	1.237 (0.762–2.007) 0.948 (0.457–1.966)	0.390 0.885	1.023 (0.547–1.911) 0.948 (0.272–3.302)	0.944 0.934
Tumor number	Multiple vs solitary	1.492 (0.980–2.272)	0.059	1.923 (1.115–3.317)	**0.016**
Microvascular infiltration	Yes vs no	1.967 (1.370–2.826)	**<0.001**	2.022 (1.201–3.337)	**0.006**
Capsular invasion	Yes vs no	0.914 (0.577–1.447)	0.698	1.383 (0.681–2.812)	0.364
Satellites nodules	Yes vs no	1.527 (1.055–2.212)	**0.023**	2.098 (1.240–3.550)	**0.004**
Margin status	R1 vs R0	1.555 (0.920–2.628)	0.134	2.3 (1.131–4.673)	**0.017**
Multivariate analysis					
ASA	III–IV vs I–II	1.379 (0.952–1.997)	0.089	–	–
Preoperative cirrhosis	Yes vs no	1.405 (0.977–2.021)	0.067	–	–
History of viral infection	Yes vs no	1.277 (0.884–1.844)	0.193	–	–
Severe post-operative complications	Yes vs no	2.151 (1.279–3.618)	**0.004**	2.043 (1.131–3.691)	**0.018**
Tumor number	Multiple vs solitary	–	–	1.859 (1.071–3.228)	**0.028**
Microvascular infiltration	Yes vs no	2.074 (1.439–2.989)	**<0.001**	2.024 (1.211–3.382)	**0.007**
Satellites nodules	Yes vs no	1.288 (0.873–1.899)	0.202	1.581 (0.903–2.770)	0.109
Margin status	R1 vs R0	–	–	1.564 (0.747–3.273)	0.236

PSM, propensity score matching; BMI, body mass index; ASA, American Society of Anesthesiologists; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PVE, portal vein embolization; PVL, portal vein ligation; MI, minimally-invasive; WHO, World Health Organization.

procedure and incidence of MVI.[33] Although an initial association with a lower rate of MVI was found in the initial cohort of the TACE group, after PSM this correlation was not confirmed. In this series, neoadjuvant TACE was associated with a lower incidence of MVI and capsular invasion, whereas no differences in satellite nodules and positive margin was observed. Nevertheless, these results come from the initial cohort without covariates balancing. The aim of this study was, in fact, rather prognostic and these pathological variables were later included in the propensity score model in order to create two groups as homogeneous as possible and thus compare long-term outcomes.

As above mentioned, different issues limit the possibility of drawing consistent conclusions regarding the oncologic benefit of preoperative TACE and literature analysis provides cases in which this procedure was successfully used before surgery.[11,12] Some authors even reported biologic predictive indicators which can filter patients who may benefit from the use of

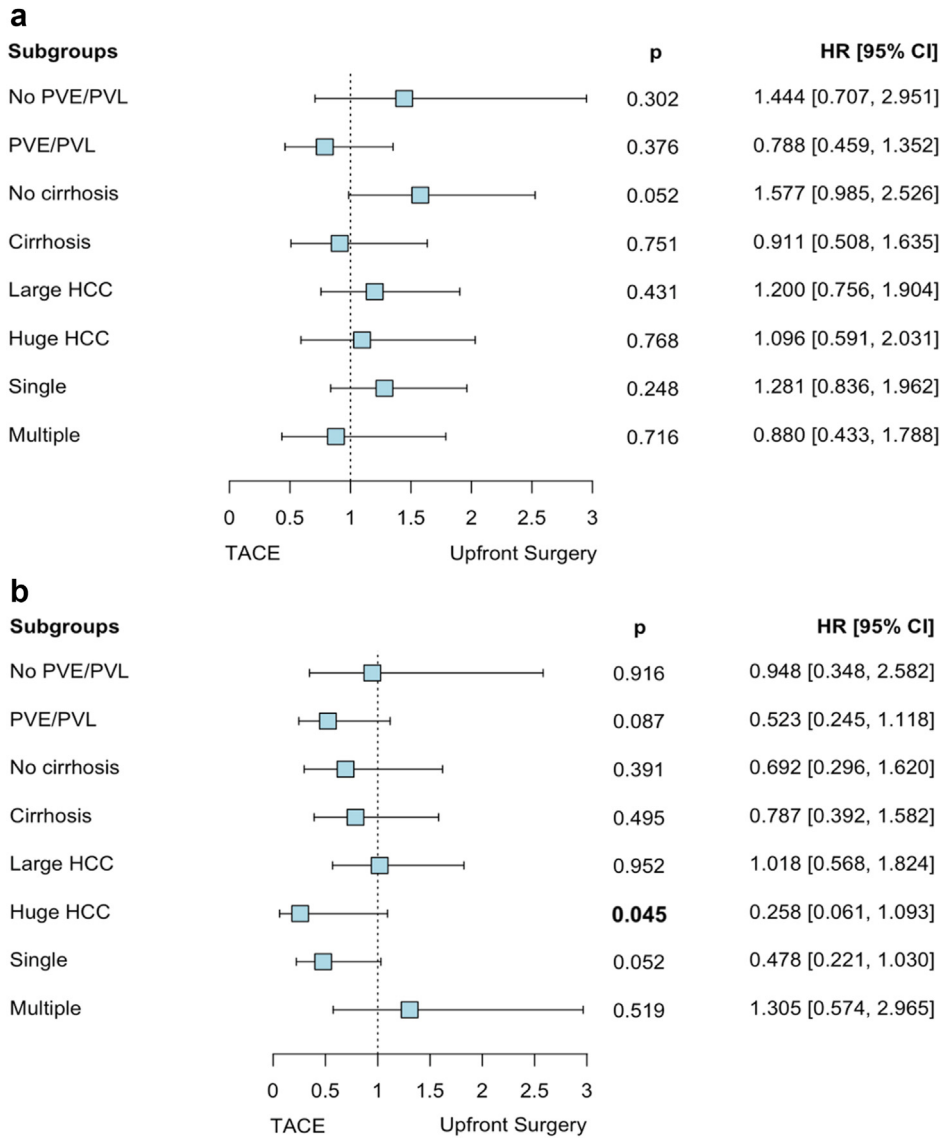

Figure 2 Forest-plot representing subgroup analysis for disease-free survival (a) and overall survival (b)

neoadjuvant TACE.[34,35] This means that solution could be found in a possible advantage in selected cases or in specific situations. One of these may be the necessity of increasing FLR by preoperative PVE. Time required to obtain a sufficient FLR vary from 4 to 6 weeks which means a delayed resection with a consequent higher risk of tumor progression. In this context, TACE is used in some centers prior to PVE to induce necrosis and reduce the risk of tumor cells dissemination. This association was already corroborated by a few series in terms of oncologic outcomes,[36–38] but only one study focused on large HCC with an intention-to-treat analysis.[13] Other possible scenario with favorable results reported in literature concern huge HCC,[11] intermediate BCLC stage,[30,39] portal vein invasion[40] or cirrhotic patients,[14] although mechanisms are not always clear and results usually not statistically robust with possible selection bias. Larger HCC for example may exhibit a richer arterial blood supply which translates into a massive necrosis and a more effective TACE. In order to confirm a possible benefit in these specific cases, a subgroup analysis was therefore performed which found an improved OS when performing neoadjuvant TACE in case of huge HCC, single lesion (corresponding to early stage BCLC) and in association with PVE, although reaching a statistically significance only in tumor $\geq$10 cm.

Some limitations have to be reported. Although a strict and well-focused study design, the retrospective and multicenter nature of the study represent undoubtedly a limit of our study. TACE, for instance, was not standardized in terms of technique (more or less selective procedure), type and dose of drug administrated (doxorubicin or idarubicin), with a consequent

heterogeneity and a possible different effect on tumor necrosis. Another drawback was the impossibility of accurately gather some variables, as portal venous invasion, tumor response after TACE or degree of tumor necrosis, which were therefore excluded from the analysis. Furthermore, an intention-to-treat analysis could not be performed and some patients could have progressed after performing TACE or PVE. Finally, it must be considered that some of the criteria used for the PSM are histological and therefore influenced by a possible downstaging by the TACE. Consequently, upfront resected cases were matched with a group which actually contained originally more aggressive tumors.

In conclusion, TACE represents a safe and well-tolerated technique with no increased risk of morbidity and mortality after liver resection. However, our results do not support the indiscriminate use of this procedure in all patients with a large HCC in which surgical resection is validated. Selected cases could benefit from a neoadjuvant TACE, as patients with a huge and single tumor or those with an insufficient FLR necessitating of a PVE.

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Conflict of interest

None.

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