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Surgical Management of Hepatocellular Carcinoma Patients with Portal Vein Thrombosis: A United States Safety Net and Academic Center Collaborative Analysis

Emily L. Ryon, MD, MPH[1], **Joshua P. Kronenfeld, MD**[1], **Rachel M. Lee, MD, MSPH**[2], **Adam Yopp, MD**[3], **Annie Wang, MD**[4], **Ann Y. Lee, MD**[4], **Sommer Luu**[5], **Cary Hsu, MD**[5], **Eric Silberfein, MD**[5], **Maria C. Russell, MD**[2], **Neha Goel, MD**[1], **Nipun B. Merchant, MD**[1], **Jashodeep Datta, MD**[1]

[1.]Sylvester Comprehensive Cancer Center; Division of Surgical Oncology, Department of Surgery, University of Miami Miller School of Medicine, Miami, FL

[2.]Winship Cancer Institute, Division of Surgical Oncology, Department of Surgery, Emory University, Atlanta, GA

[3.]Division of Surgical Oncology, Department of Surgery, University of Texas Southwestern Medical School, Dallas, TX

[4.]Division of Surgical Oncology, Department of Surgery, New York University, Langone Health, New York, NY

[5.]Division of Surgical Oncology, Department of Surgery, Baylor College of Medicine, Houston, TX

Abstract

Background: Although consensus guidelines generally discourage any surgical management (ASM; i.e. resection and/or transplantation) in patients with hepatocellular carcinoma (HCC) and portal vein thrombosis (PVT), recent series from Asia have challenged this paradigm.

Methods: Patients from the US Safety Net Collaborative database (2012–2014) with localized HCC and radiographically-confirmed PVT were propensity-score matched based on demographic and clinicopathologic factors associated with receipt of ASM and overall survival (OS). OS was compared between patients undergoing ASM and those not selected for surgery.

Results: Of 1910 HCC patients, 207 (14.5%) had localized disease and PVT. The majority received either liver directed therapies (LDT; 34%) and/or targeted systemic therapies (36%). Twenty-one patients (10.1%) underwent ASM (resection [n=11], transplantation [n=10]); a third experienced any complication with no 30-day mortalities. Independent predictors of undergoing ASM were younger age, recent hepatology consultation, and lower MELD score. After matching for age, comorbidities, MELD, tumor size, receipt of LDT or systemic therapy, OS was

Address correspondence to: Jashodeep Datta, MD, Division of Surgical Oncology | Department of Surgery, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, 1120 NW 14th Street | Suite 410, Miami, FL 33136, Phone: (305) 243-4902, Fax: (305) 243-4907, jash.datta@med.miami.edu.

Data Availability Statement:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

significantly longer for patients selected for ASM versus non-ASM patients (median not reached vs. 5.8 months, p<0.001).

Conclusion: In a large North American multi-institutional cohort, a minority of HCC patients with PVT were selected for ASM. Resection or transplantation was associated with improved survival and may have a role in the multimodality management in selected patients.

Keywords

Outcomes; Hepatobiliary; Cancer

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide, accounting for approximately 700,000 deaths annually,[1] and also represents the fastest-rising cause of cancer-related death in the United States (US).[2] The latter development is driven in large part by the epidemic of obesity-related non-alcoholic fatty liver disease (NAFLD) as well as progression to cirrhosis in individuals born in the peak era of Hepatitis C virus (HCV) infection.[3] Regardless of HCC etiology, prognosis in HCC varies greatly by tumor stage. While curative options are available for patients diagnosed at early stages, with 5-year survival eclipsing 70% with any surgical management (ASM; i.e., surgical resection and/or liver transplantation),[4,5] patients presenting with locally advanced or metastatic HCC have dismal outcomes.[6]

In patients presenting with locally advanced HCC, portal vein thrombosis (PVT) is a relatively common occurrence, observed in 35–50% of patients at the time of diagnosis[7] and associated with hematogenous tumor dissemination.[8] Not surprisingly, PVT is associated with poor prognosis, likely due to the associated intra- and extra-hepatic tumor extension as well as the sequelae of elevated portal pressures resulting in portal hypertension in these patients. [9,10] Left untreated, median survival for HCC patients with PVT ranges from 2–4 months.[11] Moreover, several recent consensus HCC management guidelines (e.g., Barcelona Clinic Liver Cancer [BCLC], Hong-Kong Liver Cancer [HKLC], Liver Cancer Study Group of Japan, etc.) discourage surgical resection, liver transplantation, and/or transarterial liver-directed therapies (i.e., chemo- or radio-embolization, etc.) in HCC patients presenting with PVT.[12,13] The consensus recommended treatment according to these guidelines entails systemic therapy with tyrosine kinase inhibitors (e.g., sorafenib, lenvatinib, etc.).[14]

More recently, however, evidence from experienced centers in Asia treating high volumes of HCC patients with endemic viral hepatitis has challenged this relatively well-established paradigm. Several retrospective single-institution studies, as well as reasonably conducted meta-analyses, suggest that surgical resection is associated with nearly a three-fold higher median survival in HCC patients with PVT *without* main trunk or contralateral vein involvement.[15–17] Notwithstanding the careful selection of these patients for ASM, the applicability of these Asian data to Western/US populations—where the etiology and epidemiology of HCC vary substantially—remains uncertain. In this study, using the five-center US Safety Net and Academic Center Collaborative database, we sought to evaluate factors associated with selection of any surgical management (i.e., resection and/or

transplantation), as well as its association with overall survival (OS), in HCC patients with PVT in a large multi-institutional North American cohort.

METHODS

Data Source

The United States Safety Net and Academic Center Consortium (USSNC) comprises five tertiary referral academic institutions with affiliated safety-net hospitals. The collaboration was started initially to extend the demographic base for cancer research, as well as to understand the effects of social determinants of health on cancer outcomes. The HCC database includes patients diagnosed with HCC at both academic and safety-net centers, and comprises data on patient demographics, screening and healthcare access, clinical characteristics, treatment modalities and cancer-related outcomes. Retrospective review of patient medical records and sharing of de-identified data was approved by the Institutional Review Boards at all collaborating institutions.

Patient Selection

Patients over 18 years of age with hepatocellular carcinoma were identified in the USSNC database from 2012 to 2014 (n=1910). Patients with regional lymph node involvement, distant metastases, missing data or incomplete follow-up were excluded from the analysis (Figure 1). Patients with documented radiographically confirmed PVT of any portal venous branch (i.e., Liver Cancer Study Group of Japan portal vein thrombosis types Vp1–4[18] and AJCC 8th Edition Stage IIIB[19]) were included in this study.

Variables

Patents were stratified into a “no surgery” cohort and an “any surgical management” (ASM) cohort. The ASM cohort included patients who underwent liver transplantation, major hepatectomy (i.e., ≥3 contiguous Couinaud segments) and minor or non-anatomic hepatectomy. We included demographic (i.e., age, gender, race, ethnicity, median income, insurance status) and clinical (i.e., body mass index [BMI], Charlson Comorbidity Index [CCI], functional status, hepatology visit within 1 year of diagnosis, treatment at an academic center, presentation at tumor board, previous hepatitis or cirrhosis, Model of End Stage Liver Disease [MELD] Score, Child-Pugh Score, radiographic tumor size, tumor number (i.e., dichotomized at solitary or multiple) and alpha fetoprotein level [AFP]) variables for analysis. Treatment variables included liver-directed therapies (LDT)—e.g., radio frequency ablation (RFA), transarterial chemoembolization (TACE), and Yttrium-90 radioembolization (Y90)—as well as systemic therapies (e.g., tyrosine kinase inhibitors sorafenib, lenvatinib, or regorafenib). The primary endpoint was overall survival, which was defined as time of diagnosis to date of death or last follow-up. Secondary endpoints included predictors of ASM as well as clinical outcomes such as postoperative complications, reoperation, 90-day readmission and 30-day mortality.

Statistical Analysis

Descriptive statistics were computed for demographic factors, clinical characteristics and treatment modalities. Frequencies (percentage) were reported for categorical data and mean

(standard deviation) or median (interquartile range) for continuous data. Differences in percentages were compared across groups using chi-squared (X^2) test for categorical variables and means of continuous variables were compared using Student's t-test for parametric data or the Mann-Whitney U test for non-parametric data. Binomial logistic regression was performed to identify independent predictors of undergoing ASM and odds ratios were calculated.

Propensity score matching was performed in order to reduce selection bias among the treatment cohorts in this study. "Control" (i.e., no surgery) and "case" (i.e., ASM) sets were matched on a set of accrued variables that would otherwise confound comparisons between them. Once a matched sample was formed, the treatment effect could be estimated by directly comparing outcomes (e.g., overall survival) between control and case subjects in the matched sample.

Factors identified as predictors of undergoing ASM on multivariate regression, as well as factors known to affect overall survival were used to match the cohorts. The nearest neighbor matching algorithm was used with caliper width set at 0.2.[20] The final propensity score model was based on a 1:3 case-to-control ratio, and patients were ultimately matched by age, comorbidities, tumor size, MELD score, receipt of liver directed therapy (LDT) and receipt of chemotherapy.

Kaplan-Meier survival analyses using the Klein-Moeschberger methodology[21] were performed in the propensity-matched cohorts, and the log-rank test compared differences in overall survival between treatment groups. Statistical significance was determined at an alpha level of <0.05. Statistical analyses were carried out using statistical software SPSS v25, (SPSS Inc. Chicago, 2017) and Rv3.6.1, (The R Foundation, 2016).

RESULTS

Descriptive statistics

Of 1910 patients reviewed, 207 non-metastatic patients with PVT were identified (Figure 1). The median age was 59.8 [IQR: 55.6, 64.5] with 38 (18.4%) female, 80 (38.6%) black, and 33 (15.9%) Hispanic. Over a third of patients received liver-directed therapies—five patients (2.4%) underwent RFA, 42 (20.3%) underwent TACE and 33 (15.9%) underwent Y90 radioembolization. Seventy-five patients (36.2%) received targeted systemic therapy (i.e., either sorafenib or regorafenib) (Table 1).

Twenty-one patients (10.1%) were submitted for ASM; of these, 10 (47.6%) underwent liver transplantation, 7 (33.3%) underwent major hepatectomy, and 4 (19.0%) underwent minor or non-anatomic hepatectomy. In the perioperative period, 7 (33.3%) experienced any complication with 4 (19.0%) requiring additional procedures, 6 (28.6%) were readmitted within 90 days, and there were no 30-day mortalities. Of patients undergoing hepatectomy, 8 of 11 (88.9%) were R0 resections (Table 2).

Predictors of Treatment Receipt

On univariate analysis, patients who underwent ASM were younger (55 vs. 61 years old), less often black (25% vs. 47%), more often had independent functional status (100% vs. 79%) and more often had a hepatology visit prior to diagnosis (52% vs. 15%). Moreover, patients submitted for ASM had lower MELD scores (10.3±3.4 vs.13.5±6.7), smaller tumors (median 7.9 [4.8,11.8] vs. 4.5 [3.0,10.0] cm) and lower initial AFP levels (median 30 [9,307] vs. 1100 [62, 7900] ng/mL). More ASM patients received any form of liver-directed therapy (52% vs. 32%), but not targeted systemic therapy (33% vs. 37%, p=0.77). Notably, there was no statistical differences between cohorts when comparing gender, ethnicity, median income, type of insurance, BMI, or comorbidities. Furthermore, patients treated at the academic university hospital were not more likely to undergo ASM compared with those treated at affiliated safety net hospitals (Table 1).

On multivariate analysis, after accounting for sociodemographic factors (i.e., age, gender, race, income, insurance status and previous hepatology visit), clinicopathologic factors (i.e., presence of cirrhosis, Child-Pugh Class, MELD Score, tumor size, tumor number, and AFP level), and previous therapy (i.e., receipt of any LDT or systemic therapies), patients who were older (OR 0.75, 95% CI 0.62–0.93, p=0.008) and had higher MELD scores (OR 0.55, 95% CI 0.32–0.95, p=0.031) were less likely to be selected for ASM. Conversely, patients who had hepatology consultation within one year of diagnosis (OR 27.6, 95% CI 1.94–342, p=0.029) were more likely to be submitted for ASM (Table 1).

Propensity score matching

To better control for the confounding inherent in the selection and/or completion of surgical management in this cohort of HCC patients with PVT, patients were matched 3:1 based upon the likelihood of either undergoing surgical management or factors associated with survival in the unmatched cohort (Tables 1 and 3). The propensity score-matched cohort comprised 64 patients – 18 (28.1%) ASM and 46 (71.9%) no surgery; 3 patients in the ASM cohort could not be successfully matched (Supplementary Figure S1). Table 4 lists the covariate imbalance between cohorts before and after matching. Previously observed covariate imbalances between ASM and no surgery cohorts with respect to age, comorbidities, MELD score, tumor size, receipt of liver targeted therapies and chemotherapy were alleviated following matching (Supplementary Table S1).

Survival analysis

With a median follow up of 52 months [95% CI 37.7–66.3], median overall survival in the unmatched cohort was 6.5 months [95% CI 4.8, 8.2] compared with 15.5 months [95% CI 5.7, 25.3] in the matched cohort. Kaplan-Meier survival estimates (using Klein-Moschberger methodology) comparing the ASM and no surgery groups in the unmatched and propensity score-matched cohorts are illustrated in Figures 2A and 2B, respectively. Median OS of patients who underwent ASM was significantly improved compared with patients not selected for surgery (median not reached vs. 5.8 months, p<0.001). When stratified by type of surgical management (i.e., liver transplantation vs. resectional hepatectomy), median OS was improved for patients undergoing liver transplantation compared with resection (not reached vs. 19.0 months, p=0.037), and for patients undergoing resection versus no surgery

(19.0 vs 5.80, p=0.033) (Figure 2C). On multivariate survival modeling, selection for ASM remained a significant predictor of improved survival in the propensity score-matched cohort (HR 0.01, 95% CI 0.00, 0.10; p<0.001; Table 3).

DISCUSSION

This is the first study, to our knowledge, to describe factors influencing selection of surgical management (i.e., hepatectomy or liver transplantation) in a contemporary *multi-institutional North American* cohort of HCC patients presenting with portal vein thrombosis. In this multi-institutional cohort comprising five tertiary referral academic medical centers affiliated with safety net hospital networks, a significant minority of HCC patients with PVT (10%) were selected for surgical management. Not surprisingly, factors associated with receipt of surgical management in this heavily pretreated population—such as younger age, prior hepatology consultation, and lower MELD scores—suggested careful surgical selection. In such patients, resection and/or transplantation was independently associated with improved survival after controlling for confounding via propensity score matching, suggesting that surgical strategies may have a role in the multimodality management of North American HCC patients presenting with PVT.

There is a substantial body of evidence from Asia—where viral hepatitis is endemic and the dominant contributor to HCC pathogenesis[22]—suggesting that surgical management may play a role in the multimodality management of select patients presenting with PVT. A retrospective review in over 6,000 Japanese Child-Pugh A patients with PVT (*without* main trunk or contralateral vein involvement) revealed an almost 3-fold higher median survival in patients undergoing resection compared with those not selected for resection.[15] On similar lines, in a cohort of 172 Korean patients with segmental or main branch PVT, survival was nearly 3-fold higher with resection compared with transarterial chemoembolization (TACE) or sorafenib only.[16] Furthermore, a recent meta-analysis pooling 7 retrospective studies from high-volume centers in Asia revealed an association with improved survival in 4,810 HCC patients with PVT selected for ASM.[17] However, there are no clear data supporting this paradigm in North American patients, where the epidemiology is starkly different.[23] A bi-institutional retrospective review by Pawlik and colleagues in 2005 reported sobering outcomes following surgical resection in HCC patients with major vascular invasion—median and 5-year survival was 11 months and 10%, respectively.[24] The present study, therefore, represents not only the first *multi-institutional* North American series exploring this paradigm, but also provides a contemporary reappraisal of this controversial treatment approach in this patient population.

The comparative effectiveness of ASM with non-surgical therapies in this locally advanced HCC cohort, however, must be interpreted with a clear understanding of the careful selection inherent in submission for surgical management—either liver transplantation or resection—in the ASM cohort. Factors involved in this selection ranged from younger age, better medical fitness, less advanced liver disease, favorable socioeconomic status, and improved access to care. Other biologic and anatomic factors, not captured in this analysis, were likely contributory as well. It is impossible, for instance, to determine if radiographic PVT in the ASM cohort was indicative of tumor or bland thrombus. Moreover, it is plausible that

patients selected for ASM were enriched for Vp1/Vp2 (or short-segment Vp3) PVT compared with patients not selected for surgery; these data cannot clarify these details. Conversely, it is unclear if the selection of ASM was intended to alleviate the deleterious consequences of portal hypertension from Vp3/Vp4 PVT in ASM patients. Notwithstanding, this study potentially outlines a paradigm whereby surgically fit HCC patients with PVT who *initially* receive liver-directed and/or systemic therapies may be considered for ASM if anatomic and biologic considerations allow.

Limitations of this retrospective study warrant discussion. First, despite a rigorous propensity score matching algorithm, our study cannot control for confounding from unaccrued covariates that account for the undoubted selection of patients with more favorable tumor biology for ASM. This is exemplified in the improved overall survival of patients undergoing hepatectomy despite near-universal recurrence of disease. Moreover, this study lacked data on treatments offered for salvage of recurrent disease, which undoubtedly contribute to survival. Second, only 8 of 21 patients undergoing ASM had macrovascular tumor invasion noted on final pathology. From these data, it is unclear whether is related to lack of tumor thrombus initially (i.e., bland thrombus manifesting as radiographic PVT) or tumor downstaging as a result of liver-directed or systemic treatments. There was no difference in survival, however, between patients who had or did not have PVT on final pathology (5-year survival 71% vs. 63%, respectively, p=0.721; Supplementary Figure S2). Finally, the outcomes following ASM in selected patients from the high-volume tertiary referral institutions included herein may not be generalizable to other practice settings nationally. As such, these findings warrant validation in larger national cancer registries. Notwithstanding, these data mirror findings from high-volume Asian centers expanding indications for ASM in locally advanced HCC patients, and provide a compelling rationale for a prospective randomized trial investigating the role of surgical management in HCC patients presenting with PVT. Indeed, the relatively small number of patients selected for resection or transplant in this contemporary patient sample suggests that surgical management may be underutilized in Western populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 3 1;136(5):E359–86. [PubMed: 25220842]
2. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology. 2019 1;156(2):477–491. [PubMed: 30367835]
3. Rotman Y B, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology. 2015 1;61(1):191–9. [PubMed: 25142309]
4. Nathan H, Hyder O, Mayo SC, et al. Surgical therapy for early hepatocellular carcinoma in the modern era: a 10-year SEER-medicare analysis. Ann Surg. 2013;258(6):1022–1027. [PubMed: 23299519]
5. Shah C, Mramba LK, Bishnoi R, et al. Survival differences among patients with hepatocellular carcinoma based on the stage of disease and therapy received: pre and post sorafenib era. J Gastrointest Oncol. 2017;8(5):789–798. [PubMed: 29184682]
6. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2016, National Cancer Institute. Bethesda, MD; 2018.
7. Chan SL, Chong CC, Chan AW, et al. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. World J Gastroenterol. 2016 8 28;22(32):7289–300. [PubMed: 27621575]
8. Connolly GC, Chen R, Hyrien O, Mantry P, et al. Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. Thromb Res. 2008;122(3):299–306. [PubMed: 18045666]
9. Jiang JF, Lao YC, Yuan BH, et al. Treatment of hepatocellular carcinoma with portal vein tumor thrombus: advances and challenges. Oncotarget. 2017 5 16;8(20):33911–33921. [PubMed: 28430610]
10. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol. 2006;12(47):7561–7567. [PubMed: 17171782]
11. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999 1;29(1):62–7. [PubMed: 9862851]
12. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–38. [PubMed: 10518312]
13. Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014 6;146(7):1691–700.e3. [PubMed: 24583061]
14. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34. [PubMed: 19095497]
15. Kokudo T, Hasegawa K, Matsuyama Y, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016; 65: 938–943. [PubMed: 27266618]
16. Lee JM, Jang BK, Lee YJ, et al. Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. Clin Mol Hepatol. 2016 3;22(1):160–7. [PubMed: 27044767]
17. Liang L, Chen TH, Li C, et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB. 2018 12;20(12):1119–1129. [PubMed: 30056066]
18. Ikai I, Kudo M, Arii S, et al. Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatol Res. 2010;40:1043–1059.
19. Kamarajah SK, Frankel TL, Sonnenday C, et al. Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with Hepatocellular Carcinoma (HCC): A Surveillance, Epidemiology, EndResults (SEER) analysis. J Surg Oncol. 2018 3;117(4):644–650. [PubMed: 29127719]

20. Randolph JJ, Falbe K, Manuel AK, Balloun JL. A Step-by Step Guide to Propensity Score Matching in R. Practical Assessment, Research, and Evaluation. 2014. 11: 19(18):1–6.

21. Klein JP and Moeschberger ML. Survival Analysis: Techniques for censored and truncated data. 2nd ed. Springer-Verlag, New York. 2003.

22. Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006 10;45(4):529–38. [PubMed: 16879891]

23. Choo SP, Tan WL, Goh BKP, et al. Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer. 2016 11 15;122(22):3430–3446. [PubMed: 27622302]

24. Pawlik TM, Poon RT, Abdalla EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery. 2005 4;137(4):403–10. [PubMed: 15800485]

Synopsis

In a multi-institutional North American cohort of hepatocellular cancer (HCC) patients with portal vein thrombosis, selection for resection or transplantation involved biologic and physiologic factors. When controlling for such factors, surgical management was associated with improved survival in this cohort.

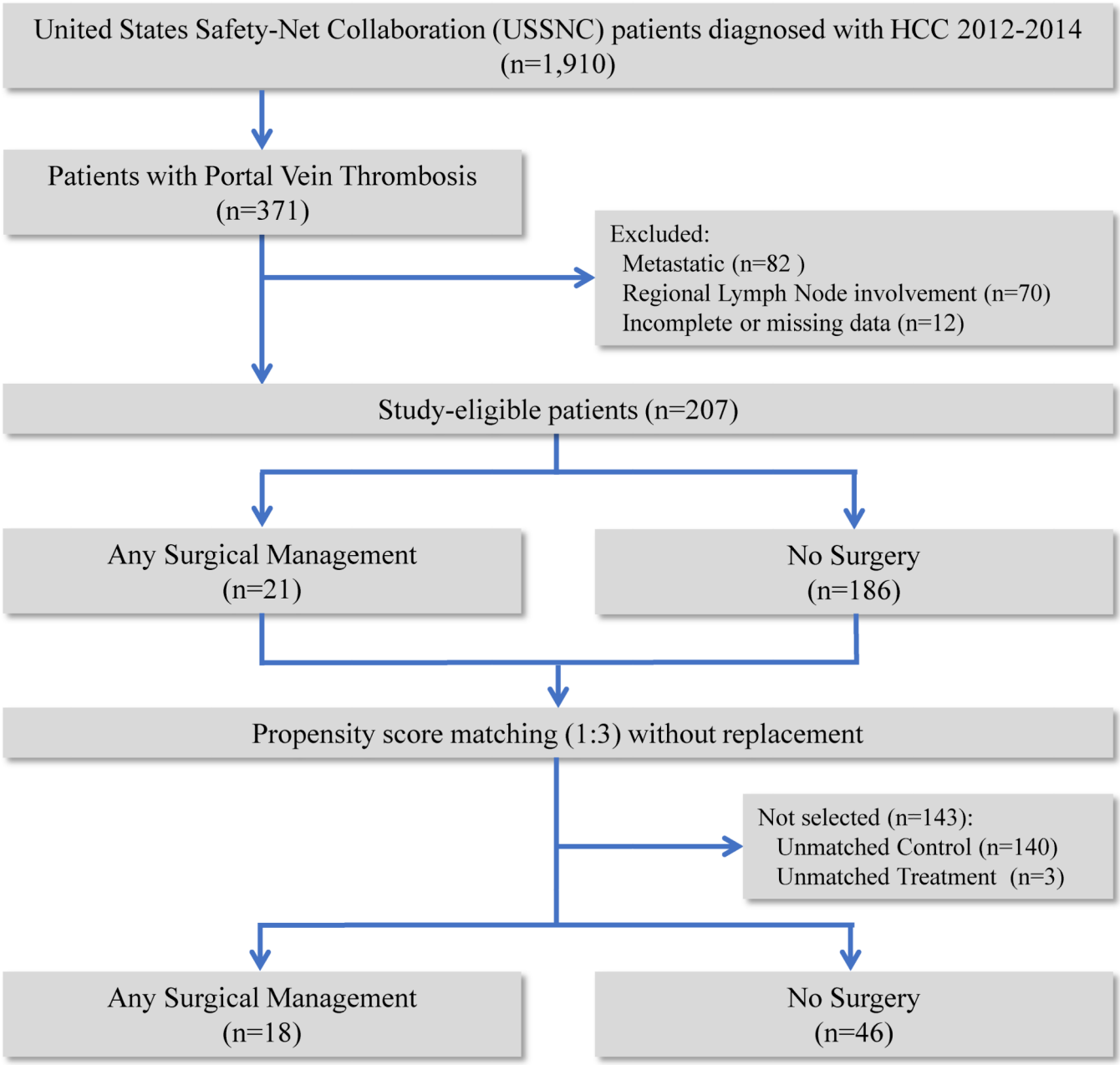

Figure 1:
Patient selection criteria diagram

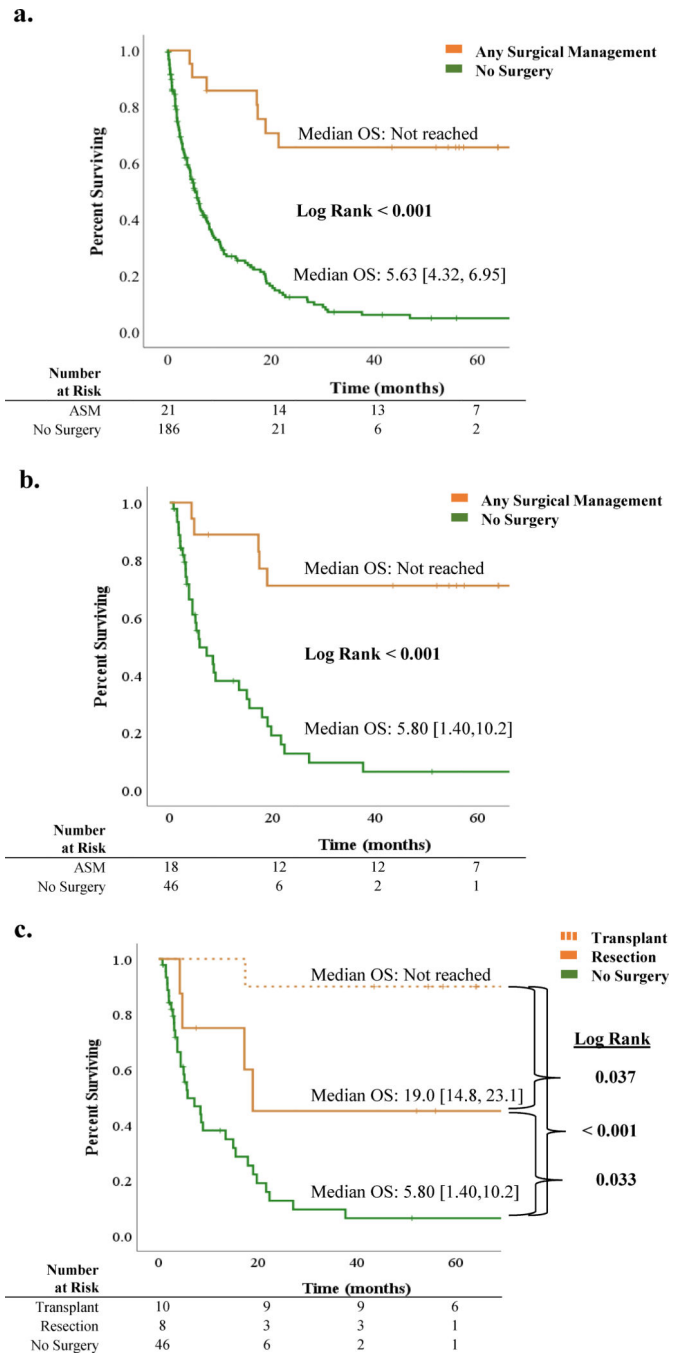

Figure 2:

Overall survival (OS) in hepatocellular patients with portal vein thrombosis: **A.** *Unmatched cohort*: OS in patients undergoing any surgical management (ASM) versus no surgery; **B.** *Propensity score-matched cohort*: OS in patients undergoing ASM versus no surgery; **C.** *Propensity score-matched cohort*: OS in patients undergoing transplant versus resection versus no surgery.

Table 1.

Sociodemographics, clinical and treatment characteristics of hepatocellular carcinoma patients with portal vein thrombosis undergoing any surgical management versus no surgery

		No Surgery n = 186 N (%)	Any Surgical Management n = 21 N (%)	Uni-variate p-value	Multi-variate OR	Multi-variate p-value
Age, years (mean ± SD)		**61.2 (±8.46)**	**55.2 (±9.38)**	**0.002**	**0.75**	**0.008**
Gender	*Female*	35 (18.8)	3 (14.3)	0.611	Ref	0.525
	Male	151 (81.2)	18 (85.7)		0.37	
Race*	*White*	68 (42.5)	11 (55.0)	0.143	Ref	0.290
	Black	75 (46.9)	5 (25.0)		4.75	0.261
	Asian	17 (10.6)	4 (20.0)		10.3	0.623
Hispanic Ethnicity		30 (16.1)	3 (14.3)	1.00	1.27	0.915
Income (median, IQR)		46,300 (36,900, 62,300)	47,000 (42,600, 66,000)	0.832	1.00	0.535
Insurance*	*Private*	45 (26.3)	7 (35.0)	0.610	Ref	0.618
	Medicare/Medicaid	90 (52.6)	11 (55.0)		0.39	0.523
	Hospital Card	6 (3.5)	0 (0)		--	--
	Uninsured	30 (17.5)	2 (10.0)		--	--
BMI (mean ± SD)		26.2 (±7.46)	26.0 (±4.16)	0.870	1.13	0.277
Charlson Comorbidity Index	*0*	32 (26.4)	7 (35.0)	0.410	Ref	0.801
	1	42 (34.7)	4 (19.0)		0.38	0.498
	2	25 (20.7)	6 (28.6)		0.41	0.658
	≥ 3	22 (18.2)	3 (14.3)		6.1	0.329
Functional Status*	*Independent*	137 (78.7)	21 (100.0)	0.064	--	--
	Partially Dependent	32 (18.4)	0 (0)		--	--
	Totally Dependent	5 (2.9)	0 (0)		--	--
Hepatology visit within 1 year of Dx		**28 (15.1)**	**11 (52.4)**	**<0.001**	**27.6**	**0.029**
Treated at academic center		96 (51.6)	10 (47.6)	0.729	0.83	0.897
Presented at tumor board		85 (46.4)	13 (61.9)	0.159	8.86	0.083
Hepatitis		143 (83.1)	17 (81.0)	0.802	1.95	0.750
Cirrhosis		150 (87.2)	17 (81.0)	0.428	0.01	0.095
Radiologic Tumor Size, cm (median, IQR)		7.9 (4.8,11.8)	4.5 (3.0,10.0)	0.153	0.80	0.315
Solitary tumor (vs. > 1 tumor)		71 (38.2)	12 (57.1)	0.093	5.60	0.245
AFP, ng/dL (median, IQR)		**1100 (62, 7900)**	**30.3 (9.0, 307)**	**0.027**	1.00	0.930
MELD Score (mean ± SD)		**13.5 (±6.70)**	**10.3 (±3.35)**	**0.030**	**0.55**	**0.031**
Child-Pugh Class	*A*	67 (36.4)	12 (57.1)	0.171	Ref	0.377
	B	85 (46.2)	6 (28.6)		0.45	0.602
	C	32 (17.4)	3 (14.3)		9.41	0.389
Any Liver-Directed Therapy		59 (31.7)	11 (52.4)[§]	0.058	0.22	0.405
	*RFA**	**2 (1.1)**	**3 (14.3)**	**<0.001**	--	--
	TACE	**35 (18.8)**	**7 (38.1)**	**0.039**	5.03	0.192
	*Y90**	31 (17.0)	2 (10.0)	0.397	--	--

	No Surgery n = 186 N (%)	Any Surgical Management n = 21 N (%)	Uni-variate p-value	Multi-variate OR	Multi-variate p-value
Targeted Systemic Therapy [°]	68 (36.6)	7 (33.3)	0.771	0.11	0.113

OR=Odds Ratio, SD=Standard deviation, IQR=Interquartile Range, BMI=Body Mass Index, Dx=Diagnosis, AFP=Alpha fetoprotein, MELD=Model of End Organ Dysfunction, RFA=Radiofrequency ablation, TACE=transarterial chemoembolization, Y90=Yttrium-90;

[*] Covariates with fewer than 3 patients not included in multivariate analysis;

[°] Sorafenib or Regorafenib;

[§] All liver-directed therapy in the ASM cohort was utilized *prior to* surgery (i.e., neoadjuvant setting)

Table 2.

Characteristics and outcomes of patients undergoing any surgical management

		Any Surgical Management n=21 N (%)	Resection n=11 N (%)	Transplant n=10 N (%)	P value
Surgical Approach	*Open*	20 (95.2)	10 (90.9)	10 (100.0)	0.279
	Laparoscopic	1 (5.3)	1 (11.1)	0 (0)	
EBL, Liters (median, IQR)		0.55 (0.4, 2.1)	0.40 (0.3, 0.7)	1.0 (0.45, 3.0)	1.00
Margin Status *	*R0*	18 (94.7)	8 (88.9)	10 (100.0)	0.279
	R1	1 (5.3)	1 (11.1)	0 (0)	
PVT on Final Pathology		8 (38.1)	5 (45.4)	3 (30.0)	0.260
Any Complication		7 (33.3)	2 (12.1)	5 (50.0)	0.210
Additional Operation		4 (19.0)	**0 (0)**	**4 (40.0)**	**0.023**
LOS, Days (median, IQR)		7 (6,13)	7 (6, 8)	10 (6,13)	0.370
Discharged Home		18 (85.7)	8 (72.7)	10 (100.0)	0.279
90-Day Readmission		6 (28.6)	1 (0.1)	5 (50.0)	0.069
30-Day Mortality		0 (0)	0 (0)	0 (0)	1.00
Recurrence		11 (52.4)	**9 (81.8)**	**2 (20.0)**	**0.005**

EBL=Estimated Blood Loss, PVT=Portal Vein Thrombosis, LOS=Length of Stay

*Patients with missing data not included in comparison

Table 3.

Cox proportional hazard model predicting mortality among unmatched and propensity score-matched cohorts

		Unmatched Cohort (n=207)		Propensity Score-Matched Cohort (n=64)	
		HR	**p-value**	**HR**	**p-value**
Older age		0.98 [0.95, 1.01]	0.126	1.05 [0.93, 1.17]	0.454
Male Gender		1.46 [0.83, 2.57]	0.194	0.52 [0.07, 3.77]	0.521
Race	*White*	Ref	0.022	Ref	0.052
	Black	1.54 [0.97, 2.45]	0.065	0.36 [0.08, 1.56]	0.171
	Asian	**2.87 [1.28, 6.42]**	**0.010**	6.84 [0.72, 64.8]	0.094
Hispanic		0.82 [0.34, 1.97]	0.658	0.12 [0.014, 1.06]	0.057
BMI		1.03 [0.99, 1.08]	0.990	1.02 [0.91, 1.14]	0.770
Charlson Comorbidity Index	*0*	Ref	0.551	Ref	0.540
	1	1.20 [0.61, 2.36]	0.650	0.63 [0.14, 2.81]	0.558
	2	1.16 [0.55, 2.41]	0.701	2.31 [0.52, 10.3]	0.277
	≥3	0.78 [0.33, 1.86]	0.585	0.39 [0.038, 4.06]	0.431
Hepatology visit within 1 year of Dx		1.38 [0.76, 2.48]	0.297	1.86 [0.42, 8.22]	0.427
Treated at academic center		1.02 [0.64, 1.63]	0.937	2.95 [0.49, 17.8]	0.244
Presentation at tumor board		0.69 [0.45, 1.06]	0.093	**0.15 [0.04, 0.67]**	**0.013**
MELD Score		**1.11 [1.07, 1.16]**	**<0.001**	1.18 [0.94, 1.49]	0.166
AFP		1.0 [1.0, 1.0]	0.862	1.0 [1.0, 1.0]	0.354
Radiologic Tumor Size		1.02 [1.00, 1.03]	0.058	0.97 [0.84, 1.11]	0.660
Any Liver Directed Therapy		**0.43 [0.25, 0.73]**	**0.002**	**0.10 [0.01, 0.85]**	**0.035**
Targeted Systemic Therapy		**0.61 [0.37, 0.99]**	**0.048**	1.02 [0.27, 3.88]	0.985
Any Surgical Management		**0.05 [0.02, 0.18]**	**<0.001**	**0.01 [0.00, 0.09]**	**<0.001**

HR=Hazard Ratio, BMI=Body Mass Index, Dx=Diagnosis, MELD=Model of End Organ Dysfunction, AFP=Alpha fetoprotein

Table 4.

Covariate balance in unmatched and propensity score-matched cohorts

	Unmatched Cohort (n=207)			Propensity Score-Matched Cohort (n=64)		
	No Surgery	**ASM**	**p-value**	**No Surgery**	**ASM**	**p-value**
Age, years	61.2±8.5	55.2±9.4	0.002	59.1±7.0	57.8±5.8	0.520
CCI	1.5±2.1	1.2±1.2	0.571	0.96±1.5	1.1±1.2	0.283
MELD Score	13.5±6.7	10.3±3.4	0.030	11.4±4.9	10.7±3.4	0.621
Tumor Size, cm	9.6±10.7	6.2 ±4.4	0.153	7.7±5.3	6.2±4.7	0.335
Any Liver Directed Therapy	33.3%	52.4%	0.083	58.7%	61.1%	0.862
Receipt of Chemotherapy	36.6%	33.3%	0.770	37.0%	38.9%	0.890

CCI= Charlson Comorbidity Index, MELD=Model of End Organ Dysfunction