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Hepatic resection of solitary HCC in the elderly: A unique disease in a growing population

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ABSTRACT

Background: Management of elderly patients with solitary hepatocellular carcinoma (sHCC) is challenging with perceived clinicopathologic differences driving treatment options. We sought to determine factors predictive of disease control and survival after hepatic resection of sHCC in elderly patients.
Methods: We identified n = 45 elderly patients ($^3\geq$65 yo) with sHCC treated with hepatic resection alone from our prospective database from 2003–16. Clinicopathologic data were analyzed and survival was assessed from the time of hepatic resection.
Results: The median age was 75-years-old. Less than half of patients (47%) had viral hepatitis. At resection, the median Child-Pugh score was A6, median tumor size 5 cm, and mean AFP of 1050 (ng/mL). Major hepatectomy was performed in 23 patients (51%) with R0 resection achieved in 96%. Two patients (4%) had Grade III complications with no mortalities at 30 days and one death (2%) at 90-days. After R0 resection 44% (n = 20) had intrahepatic recurrence at a median of 32 months (95% CI: 15–46) with 20% (n = 9) developing extrahepatic recurrence at a median of 78 months (95% CI: 78-.). The median survival was 72 months (95% CI: 30–108 months). For patients with at least 3 years of follow-up, the 1-, 3-, and 5-year overall survival was 74%, 59%, and 50%, respectively. Mortality was associated with higher AFP and lower Prognostic Nutritional Index (PNI).
Conclusion: Carefully selected elderly patients with sHCC appear to have unique disease that is amenable to hepatic resection with low morbidity and mortality with excellent overall and recurrence-free survival.

Introduction

Primary liver cancer is the sixth most common cancer worldwide with hepatocellular carcinoma (HCC) being the most prevalent. The incidence of this cancer has been on the rise over the last two decades with an estimated 42,220 new cases expected in 2018.[1] Along with this rise, there is a concomitant increase in the number of cancer deaths attributable to primary liver cancer.[2] Many centers have reported an increased proportion of elderly patients presenting with HCC[3] and analysis of the Surveillance, Epidemiology, End Results program (SEER) has revealed a steady increase in the incidence of HCC with age over time.[4] Cancer care of elderly patients is becoming a major topic of interest given the ageing population in the United States. Management of HCC in the elderly can be challenging given the variety of non-surgical treatment modalities available and the increasing use of less invasive therapies which include percutaneous procedures, such as *trans*-arterial chemoembolization (TACE) and radio-embolization (TARE) with agents like Yttrium-90. There is understandable apprehension regarding the impact of different liver-directed strategies on overall survival (OS), disease control, and peri-operative morbidity and mortality when considering non-resectional approaches compared to catheter-based procedures. Furthermore, many patients in this cohort may fall outside of transplant eligibility given their age, as well as the presence of concurrent but more indolent cancers (e.g., prostate cancer). The clinicopathologic characteristics of elderly patients with a solitary HCC (sHCC) raise the question if cancers in

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this cohort have a different biologic behavior compared to those in younger cohorts, which are often associated with underlying viral hepatitis or cirrhotic liver disease.[5]

The literature surrounding the management of the elderly patient population with resectable sHCC is sparse. We sought to analyze the peri-operative morbidity, mortality and clinicopathologic factors predictive of OS and disease-free survival (DFS) in elderly patients with sHCC managed with hepatic resection at our quaternary academic medical center. Ultimately, we hope this analysis lays the groundwork to define what we believe is unique cancer biology that deserves further study and to understand how to risk stratify elderly patients to better select those that can be managed with hepatic resection versus other liver-directed treatment modalities.

Methods

Data source

This is a retrospective analysis of prospectively collected data from the Oregon Health & Science University (OHSU) Knight Cancer Institute Liver Database maintained by the Divisions of Surgical Oncology and Liver Transplant Surgery. This database contains comprehensive information on patient demographics, etiology of liver disease, cancer and imaging characteristics including cancer size and number, treatment course, laboratory data at multiple time points, initial diagnosis information including presenting symptoms, operative details of the hepatic resection, perioperative outcomes including complications, final surgical pathology, and subsequent treatments until end of observation or death of patient, as well as date and cause of death if applicable.

The study was reviewed and approved by the Institutional Review Board of OHSU and the Knight Cancer Institute Clinical Research Review Committee.

Study population/patient data

The study population was comprised of elderly patients (as defined by age $\geq$ 65-years-old) diagnosed with sHCC that were managed with hepatic resection alone (no concomitant thermal ablations) from 2003 through 2016. The definition of "elderly" was based upon the World Health Organization (WHO) accepted definition.[6] All patients diagnosed with HCC are reviewed in our Multidisciplinary Liver Tumor Board with treatment recommendations rendered from a consensus opinion from representatives from hepatology, diagnostic radiology, medical oncology, surgical oncology, interventional radiology, transplant surgery, and radiation oncology.

The study inclusion criteria were patients with histologically confirmed HCC from final surgical pathology, with initial diagnoses as defined by diagnostic criteria using the International Classification of Disease (ICD) for Oncology, Third Edition.[7] Solitary HCC lesions were defined on the basis of pre-operative radiographic imaging and verified by post-operative pathologic examination. No subjects were excluded from the study based on gender, racial or ethnic origin.

Patients who were younger than 65-years-old were excluded from our study cohort. Patients with multifocal disease on pre-operative imaging or on final pathology were excluded. Patients managed with thermal ablation alone were excluded. Patients treated with pre-operative modalities directed at treating their HCC including systemic therapy, radioembolization (e.g., Y-90), TACE, or external beam radiation therapy were excluded from the study in order to establish the most uniform surgically managed sHCC elderly cohort as possible.

The Elixhauser Comorbidity Index[8] was used to stratify patients at higher operative risks with higher comorbidity index. This index categorizes patient comorbidities based on the International Classification of Disease (ICD) diagnosis codes in the datasets. Each comorbidity category is dichotomous (present or absent). This index is utilized to predict hospital resource use and in-hospital mortality. Twenty-six categories from the Elixhauser Comorbidity Index were used in the analysis of this dataset.[9] Patients were stratified based on their cumulative index value, where patients with index values of 1–3 were considered low risk, whilst those scoring 4 or higher were considered a higher operative risk.

Non-alcoholic fatty liver disease (NAFLD), which embodies the full spectrum of metabolic fatty liver disorders, was defined by liver steatosis appreciated on contrast-enhanced cross-sectional imaging studies prior to hepatic resection or identified on pathologic analysis of pre-operative biopsy specimen.[10,11] The liver resection specimen was also assessed for the presence NAFLD, defined as >5% steatosis.

Outcomes and predictor variables

Patient clinicopathologic information collected from our institutional dataset included: age, sex, race, year of treatment, cancer grade and stage, Child-Pugh classification,[12,13] Model for End-Stage Liver Disease-Sodium score (MELD-Na),[14,15] underlying liver disease, viral hepatitis, metabolic disorders, type of liver resection performed, and peri-operative outcomes. Operations were classified by type of hepatic resection and any non-surgically treated patients (e.g., ablations, TACE, TARE, etc.) were excluded from this analysis. When available, the types of operations were further divided to categorize the extent of resection according to the Brisbane consensus definitions[16] to include partial hepatectomy, central hepatectomy (4a/4b, 5, and 8), bi-segmentectomy, right hemi-hepatectomy, left hemi-hepatectomy, extended right and extended left hepatectomy. Major hepatectomy was defined as resection of >3 liver segments. Data regarding the operative approach—laparotomy versus laparoscopic liver resection—were collected and trends over time were assessed. Information regarding receipt of adjuvant systemic therapy was available in our database but was not included in our analysis.

We included several peri-operative laboratory parameters including pre-operative levels of the tumor marker alpha fetoprotein (AFP). In addition, serum inflammatory markers that have been reported as predictive of patient outcome were assessed, including neutrophil-to-lymphocyte ratio (NLR),[17,18] platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR),[19] prognostic nutritional index (PNI),[19,20] and aspartate aminotransferase-to-platelet ratio index (APRI).[17] Due to the known increased peri-operative risk in patients with portal hypertension undergoing hepatic resection, our institution checks transjugular hepatic venous pressure gradients in patients with concerning clinical criteria based on Child-Pugh scoring, serum chemistry, and platelet counts suggestive of underlying portal hypertension. Data regarding the hepatic venous pressures are not included in this analysis; however, our group uses a cut-off of <10 mmHg as a gradient considered safe to proceed with a major hepatic resection.

Given recent studies showing an association between overweight/obese patients and primary liver cancer,[21,22] body mass index (BMI) was used in the analysis to test for any associations.

The measured outcomes were post-operative complications and mortality at both 30- and 90-days.[23] Post-operative complications were categorized using the Clavien-Dindo classification.[24] Post-operative complications, including bile leak, liver abscess, pleural effusion, liver failure, respiratory compromise, cardiovascular events, cerebrovascular accidents, acute kidney injury, sepsis,

surgical site infection, and pulmonary embolism, were evaluated for up to 30-days post-operatively. At the outset of this study, every effort was made to update the last date of contact and survival status. Patients were contacted by phone and the date of their last follow-up and disease status were updated as appropriate.

All surgical pathology was staged and modified to reflect the 8th edition AJCC guidelines for patient with HCC.[25–27]

Statistical analyses

Data for patient demographic and clinical characteristics are reported as a count and percent for categorical variables, and as means for continuous variables. Data for associations with mortality and recurrence are reported as medians and interquartile ranges (IQR). AFP, NLR, PLR, LMR, PNI, and APRI, values were log-transformed to correct for non-normality, and differences in the log-transformed means were evaluated with t-tests. For categorical variables, associations with mortality and recurrence were evaluated with Fisher's Exact test or Fisher Freeman-Halton extension of the Fisher Exact test. Estimates for median survival within 30 days and 90 days following hepatic resection were evaluated with Kapan-Meier and univariate Cox Proportional Hazards, and differences between groups were evaluated with the Log-Rank or Chi-Square test. Sample size prohibited the construction of a multivariate model. Significance was set at $P < 0.05$. All statistical analysis was performed using JMP 13 and SAS 9.4 software (SAS Institute, Cary, NC).

Results

Patient, tumor, and operative details

We identified n = 45 elderly patients, as defined by ≥ 65 years of age, with sHCC diagnosed between 2003 and 2016 that met our inclusion criteria (Table 1). The median age at hepatic resection was 75-years-old (range 67–93) with most patients being men (n = 32; 71%). The BMI categorized n = 21 (46%) as overweight and n = 9 (20%) as obese. Most patients were non-Hispanic white (73%). The median distance patients traveled to our cancer institute was 95 miles with an IQR of 182 miles reflective of the wide catchment area of our quaternary academic medical center.

The median Child-Pugh score was A6, accounting for 83% of the resections while the other 17% were Childs-Pugh B. The median MELD-Na score was 8, with an IQR of 2. The median platelet count was 197,000/mm^3 (IQR; 146,500–232,500/mm^3). The mean AFP at the time of diagnosis was 1050 ng/mL (IQR; 3.9–382.2). Specific liver-related comorbidities were also investigated. Viral hepatitis was present in less than half of patients (n = 21; 47%) with 13% having hepatitis B, 27% with hepatitis C and 7% having both. Only 2% of patients had alcoholic hepatitis and 9% of patients had NAFLD (Table 1).

Comorbidities were further assessed using the Elixhauser index to differentiate high-risk patients (defined as cumulative cutoff criteria of ≥4). The median number of comorbidities per patient was four with 69% of patients having ≥4 comorbidities. Aside from cancer, the most common comorbidities were hypertension (71%), followed by uncomplicated diabetes mellitus (29%), and obesity (24%). Of note, none of the patients had coagulopathies, metastatic disease, pulmonary circulation disorders or peripheral vascular disorders (Table 1).

Over a 14-year period, all patients were treated with hepatic resection of their sHCC. The number of hepatic resections in this unique population increased throughout the years with 6 operations performed between 2003 and 2006, 18 operations between 2007 and 2011 and 21operations from 2012 to 2016. The majority of patients were treated via laparotomy while n = 5 (11%) underwent laparoscopic hepatic resection with an increase noted over the last several years of the study period.

Bi-segmentectomy (n = 12; 26.7%) was the most common hepatic resection followed by an equal number of patients requiring segmentectomy and right hemi-hepatectomy (10; 22% each). Overall, more than half of patients (n = 23; 51%) required major hepatectomy (>3 segments) for disease clearance. R0 resection was achieved in 96% (n = 43) with only two patients having an R1 resection (Table 2).

With respect to tumor characteristics, the median tumor size was 5 cm (SD = 3.14; IQR; 2.7–7.6 cm) at the time of resection, and negative margins were achieved in over 95% of the cases. On pathologic analysis, the majority of cancers (59%) were moderately differentiated while 25% were well differentiated. It is also important to note that vascular invasion was present in 39% (n = 17) of resected specimens. Overall, a minority of patients had evidence of hepatic steatosis (n = 10; 24%) as determined on final surgical pathology. Prevalence of vascular invasion was marginally higher for patients with extrahepatic recurrence compared to those who did not recur. Vascular invasion was far more prevalent in patients who had both extra-, and intrahepatic recurrence ($P < 0.001$). The majority of cases performed were AJCC stage I (n = 25; 56%); and stage II comprised 29% (n = 13) of cases. There were n = 5 patients classified as stage IIIA, one patient with stage IIIB, and one patient with stage IIIC.

Peri-operative outcomes

The median follow-up for patients was 32.5 months (IQR; 44.25 months). The median length of hospital stay was 6 days with an IQR of 4. The difference in hospital stay between patients managed with open and laparoscopic resections was not assessed given the low number of laparoscopic resections. Almost two-thirds of patients (n = 29; 64%) had no complications reported at 30 days post-operatively (Table 3). The one-third of patients (n = 16) that had peri-operative complications at 30-days were further classified with 88% (n = 14) being Clavien-Dindo Classification grades I and II. The most common complications were delirium (n = 3), urinary tract infection (n = 2), atrial fibrillation (n = 2), urinary retention (n = 2), and ileus (n = 2) (Table 3). No blood transfusions were administered to patients with grade II complications. Two patients (4%) had complications ≥ Grade III (Table 3).

There were six re-admissions within 90 days of discharge (14.3%), two of which were planned. Most patients were discharged to home except for n = 4 patients who were discharged to a skilled nursing facility (SNF). Only one of the SNF patients had a readmission. There were no postoperative deaths at 30-days and one death (2%) at 90-days, which was related to a pulmonary embolism discovered 68 days post-operatively.

Recurrence and predictors of survival

For patients followed for at least 3 years after their hepatic resection (n = 35), the overall survival at 1-, 3-, and 5-years was 74%, 59%, and 50%, respectively (Fig. 1). After R0 resection, 50% (n = 21) of patients had no recurrence with a median survival of 78 months. Twelve patients (29%) developed intrahepatic recurrence alone at a median of 32 months (95% CI: 15–46). Nine patients (20%) developed extrahepatic recurrence at a median of 78 months. Seven patients (17%) had both intrahepatic and extrahepatic recurrences. Of the patients with intrahepatic recurrences, n = 3 were at the prior resection margins and n = 2 were multifocal intrahepatic recurrences. Of the extrahepatic recurrences, n = 5 were in the lungs and the remaining tissue sites included peritoneal cavity, bone, and brain.

Table 1
Clinicopathologic characteristics for n = 45 elderly patients with resected solitary HCC.

Characteristic	Median (IQR) or n (%)
Demographics	
Age at resection (years)	75 (7.5)
Sex	
F	13 (28.9%)
M	32 (71.1%)
Race	
Asian	4 (8.9%)
Black/African American	2 (4.4%)
White	33 (73.3%)
More than one/unknown	4 (8.8%)
Body Mass Index (BMI) Categorization kg/m^2	26.13 (5.35)
Normal (18.5–24.9)	15 (34.1%)
Overweight (25–29.9)	20 (45.5%)
Obese (30 or more)	9 (20.5%)
American Society of Anesthesiologists (ASA) Classification	
2	5 (11.6%)
3	34 (79.1%)
4	3 (7.0%)
5	1 (2.3%)
Underlying Liver Disease	
Hepatitis	
Hepatitis B	6 (13.3%)
Hepatitis C	12 (26.7%)
Hepatitis B and C	3 (6.7%)
Alcoholic Hepatitis	1 (2.2%)
NAFLD	4 (8.9%)
None	15 (33.3%)
Unknown/missing	4 (8.9%)
MELD-Na	8 (2)
Child-Pugh Score	5.6 (0.77)
Child-Pugh A	38 (82.6%)
Child-Pugh B	8 (17.4%)
Pre-operative Laboratory Values	
AFP	11.30 (378.30)
Total bilirubin	0.90 (0.50)
Albumin (plasma)	3.60 (0.50)
INR	1.05 (0.12)
Elixhauser Comorbidities Index Total	
<4	13 (31%)
≥4	32 (47%)
Elixhauser Comorbidities	
Congestive Heart Failure	1 (2.2%)
Valvular disease	1 (2.2%)
Hypertension	32 (71.1%)
Other neurologic disorders	5 (11.1%)
COPD	5 (11.1%)
DM uncomplicated	13 (28.9%)
Diabetes Mellitus, complicated	1 (2.2%)
Hypothyroidism	6 (13.3%)
Renal Failure	5 (11.1%)
Liver disease	45 (100%)
Peptic ulcer excluding bleeding	1 (2.2%)
Lymphoma	1 (2.2%)
Solid tumor without metastasis	45 (100%)
Rheumatoid arthritis, collagen vascular disease	5 (11.1%)
Obesity	11 (24.4%)
Blood loss anemia	1 (2.2%)
Deficiency anemia	5 (11.1%)
Alcohol abuse	6 (13.3%)
Depression	6 (13.3%)

The median recurrence-free survival was 16.3 months (95% CI: 9–17). The 1-, 3-, and 5-year recurrence-free survival differed based on recurrence sites. For patients with both extrahepatic and intrahepatic recurrence, 30% remained alive after 1 year and only 14% were alive at 3 years. Fifty percent of patients with extrahepatic recurrence were alive at 1 year while 68% of patients with intrahepatic recurrence remained alive at 1 year. The prevalence of vascular invasion was marginally higher for patients with extrahepatic recurrence (n = 6, 67%, $P = 0.06$). Underlying liver disease was marginally different between patients who recurred compared to those who did not recur (n = 6, 75%, $P = 0.07$). The prevalence of HCV was slightly higher in patients who recurred (43% vs. 26% $P = 0.07$) and NAFLD was marginally higher in patients who did recur (75% vs. 25%; $P > 0.05$) although neither achieved statistical significance. While tumor size was not associated with intrahepatic recurrence ($P = 0.83$), it was associated with extrahepatic recurrence ($P = 0.05$, median 7.3 cm, IQR; 5.6).

Univariate survival analysis evaluated both intrahepatic and extrahepatic recurrence between the following groups: age group (≥75-years-old), tumor size (≥5 cm), gender, BMI (≥30),

Table 2
Operative and pathologic characteristics of elderly patients with resected solitary HCC.

	Median (IQR) or n (%)
Operative Details	
Major hepatic resection (> = 3 segments)	23 (51.1%)
Type of hepatic resection	
Central hepatectomy (4a, 4b, 5, and 8)	4 (8.9%)
Mono-segmentectomy	11 (24.4%)
Bi-segmentectomy	12 (26.7%)
Right hemi-hepatectomy	10 (22.2%)
Left hemi-hepatectomy	4 (8.9%)
Extended right hepatectomy	4 (8.9%)
Extended left hepatectomy	1 (2.2%)
Total Operative Time (minutes)	279.5 (160.5)
Tumor Characteristics	
Size (cm)	5 (5.05)
Margin Status	
R1	2 (4.4%)
R0	43 (95.6%)
Steatosis	
N	34 (75.6%)
Y	11 (24.4%)
Vascular invasion	
N	27 (61.4%)
Y	17 (38.6%)
Stage According to AJCC 8th edition	
I	25 (55.6%)
II	13 (28.9%)
IIIA	5 (11.1%)
IIIB	1 (2.2%)
IIIC	1 (2.2%)

underlying liver disease (hepatitis status), Elixhauser Comorbidity Index (≥4), APRI and PNI. Of these comparisons, overall survival was associated with lower PNI ($P = 0.04$; 95% CI; 0.81–0.99) and larger tumor size ($P = 0.02$; 95%CI 1.16–4.27). A multivariate analysis was not performed given the small sample size and preliminary statistical model characteristics indicating that an analysis was not appropriate.

Following hepatic resection, the median overall time to death/follow-up was 72 months (95% CI: 30–108 months). For patients with at least 3 years of follow-up, the 1-, 3-, and 5-year overall survival was 74%, 59%, and 50%, respectively (Fig. 1). Mortality was

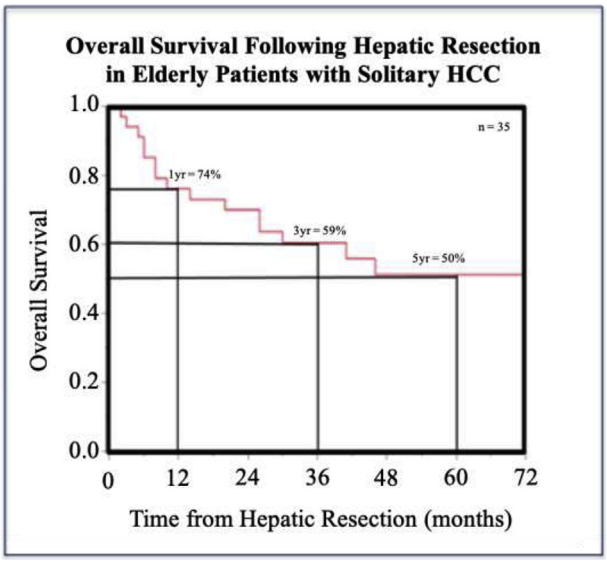

Fig. 1. Overall survival of elderly patients with solitary HCC after hepatic resection. A total of n=35 patients were followed for a minimum of 3 years after resection demonstrating an overall survival at 1-, 3-, and 5-years of 74%, 59%, and 50%, respectively.

associated with higher AFP, NLR, and PLR, and with lower PNI and LMR (Table 4) (all $P < 0.05$). T-stage and increased tumor size were associated with extrahepatic recurrence ($P = 0.01$).

Discussion

Hepatocellular carcinoma carries a poor prognosis and its incidence is on the rise both in the United States and worldwide,[1] especially in the elderly population. As the safety of liver resections and peri-operative management continues to improve, more elderly patients with HCC are being managed with hepatectomy.[28] Our primary objective in this study was to assess the use of hepatic resection in our carefully selected elderly patient population with solitary HCC at our institution. The data we collected

Table 3
Post-operative morbidity and mortality for n = 45 elderly patients with resected solitary HCC.

	n	Median (or %)
Length of hospital stay (days)	45	6 (4)
Complications 30-days		
No	29	64.40%
Yes	16	35.60%
Clavien-Dindo grade of complications at 30-days post-operatively	16	
I	5	31.25%
II	9	56.25%
III	1	6.25%
IV	1	6.25%
Mortality 30-days		
No	45	100.00%
Mortality 90-days		
No	44	97.78%
Yes[a]	1	2.22%
Intrahepatic Recurrence		
No	23	52.27%
Yes	19	43.18%
Unknown	2	4.55%
Extrahepatic Recurrence		
No	33	73.33%
Yes	9	20.00%
Unknown	3	6.67%

[a] One patient died of complications secondary to pulmonary embolism on POD68.

Table 4
Tests for Association between overall survival in elderly patients with resected solitary HCC.

	Alive (n = 26)			Deceased (n = 19)			
	N	Median	IQR	N	Median	IQR	*P*-value
AFP	25	845.21	2845.88	17	6067.46	19,553.55	0.0234
NLR	20	3.1	3.62	17	5.94	3.17	<.0001
PLR	20	133.14	102.94	17	221.26	120.48	0.0071
LMR	20	2.92	1.33	17	2.13	1.22	0.0473
PNI	20	46.8	6.55	17	40	3.93	0.0004
APRI	26	0.71	0.74	19	1.4	1.9	0.2501

Note. Comparisons between groups were evaluated with t-tests. Values were log-transformed for analysis.
AFP alpha-fetoprotein, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *PNI* prognostic nutritional index, *APRI* aspartate aminotransferase-to-platelet ratio index.

reflects the unique characteristics of this population in a high-volume academic hospital. Importantly, this study brings to light the distinctive nature of this aging population and their overall suitability for surgical interventions when carefully selected and managed by an experienced anesthesia, surgical, and nursing team.

The median age of our patients with sHCC undergoing hepatic resection was 75-years-old. It is important to note that none of these patients were eligible for transplant—likely a combination of several factors including: the median tumor size of 5 cm (SD 3.1 cm), which is the upper limit of standard Milan criteria for a solitary HCC, the prevalence of other concomitant cancers, and multiple medical comorbidities. The survival data we report are consistent with outcomes for hepatic resection reported by Shah and colleagues[29] in their retrospective analysis of n = 140 patients with early-stage HCC managed with resection or liver transplant despite their cohort being more than 15 years younger with tumors over 1 cm smaller (mean tumor size of our cohort was 5.3; IQR 4.4–6.3 cm). In thelderly patient cohort we report, with more than 50% managed with a major hepatectomy, our 90-day mortality was 2% with a median survival of 72 months after resection. Based on the median age at resection and 50% of patients surviving to 5 years, a large majority of patients reached their early 80s. Our study confirms reports from several recent studies throughout Asia demonstrating low 90-day mortality rates for elderly patients undergoing hepatic resection for HCC.[30–32] However, the majority of patients from those studies have HCC arising in the background of hepatitis B, which is a distinct entity compared to hepatitis C or alcoholic cirrhosis that's often seen in the United States. Again, less than half of the patients in this elderly cohort had HCC arising in the background of viral hepatitis or cirrhotic liver disease.

In our study, more than 50% of our elderly patients required a major hepatectomy with 50% having no recurrence after R0 resection. In our study, the median number of comorbidities was four, but contrary to other studies, we show that pre-operative comorbidities alone do not appear to portend a poor post-operative outcome. Likely, there are uncaptured operative fitness characteristics (e.g., the “eyeball test”, the get-up and go test, etc.) that are not reflected in the Elixhauser comorbidity index and are better predictors of outcome. The most common peri-operative complications was delirium, which is not surprising and underscores the importance of engaging gerontologic medicine services pre-emptively in the elderly population as has been reported elsewhere.[33,34] Given the large median tumor size and that major hepatectomy was required in half of our patients, the low utilization of minimally-invasive liver resections (i.e., laparoscopic, laparoscopic hand-assisted, and robotic-assisted) is not surprising. However, our group routinely performs laparoscopic and robotic-assisted hepatic resections, including major hepatectomy, for both primary liver cancers and colorectal liver metastases. Improved peri-operative outcomes and equivalent oncologic control has been previously reported with minimal-access hepatic resections[35] and we would expect similar benefits in the elderly population.

The patients reported in this study achieved good disease control at 5 years with a median survival of 72 months, which is remarkable given the median age 75 years at resection. However, with a median recurrence-free survival of 16 months, improved patient selection and a better understanding of this cancer is undoubtedly needed. Patients with sHCC are not reported as a distinct group in the interventional radiology literature, so it is difficult to assess the impact of selective internal radiation therapy (e.g., Y-90) and other catheter-directed therapies on long term survival. The SIRveNIB trial[36] randomized Asian patients with locally advanced HCC not amenable to resection or transplant to treatment with either Y-90 or sorafenib and revealed an overall survival of 8.8 and 10 months, respectively. The median age in the trial was 60-years-old whereas the patients in our study had an older median age by 15 years. The reported tolerance of tyrosine-kinase inhibitors (TKIs), including sorafenib, in patients with HCC, has been reported to be less than 50%,[37–39] with research suggesting that patients are hesitant to actually report to their physicians if they miss doses or do not take the medication.[40] We would expect this to be even more pronounced in the elderly population. Therefore, given the limited effective treatment options without a chance of long-term survival, hepatic resection remains an effective modality in select elderly patients. As our population ages and the incidence of primary liver cancers continue to rise, it will be important to assess management strategies—resection versus palliative catheter-directed therapy or systemic therapy—to maximally benefit patients in terms of both disease control and quality of life.

Our study has several important limitations. First, our patient cohort included only elderly patients aged 65 years and older, limiting the generalizability of this study to a different population. Second, this study is a single institution experience and has a limited number of patients; exploration of a larger cohort is needed to make more generalizable observations in the elderly population. Third, and perhaps most importantly, the patients included in this study are highly selected, reflective of our median patient age of 75-years-old and excellent outcomes after major hepatectomy, which was required in more than 50% of cases. Similar to other major referral centers, our group focuses on extensive nutritional prehabilitation and medical optimization prior to taking elderly patients to the operating room for a major hepatic resection. Lastly, this study is retrospective in nature and subject to biases inherent in data collection even with a well-maintained database.

In summary, in this single institutional prospectively collected study spanning 14 years, we demonstrated excellent short- and long-term outcomes after hepatectomy in a cohort of elderly patients with solitary HCC in the North Pacific region of the United States. Elderly patients with solitary HCC were able to achieve a significant disease-free and long-term survival that far exceeds the reported disease control and overall survival afforded with

radioembolization or systemic treatment. We believe these data will help us investigate larger cohorts and better select elderly patients for resection. Undoubtedly, hepatic resection is still plagued by intra-hepatic recurrence, even in margin-negative and carefully selected patients. This study has already been expanded into larger administrative datasets to help further identify factors associated with improved outcomes for hepatic resection in elderly patients with HCC. Ultimately, we hope to be to continue our study in this population as we believe solitary HCC represents a unique disease biology that warrants further scientific investigation.

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Appendix A. Supplementary data

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