Original Article

Surgical therapy and survival in young patients with stage I–II hepatocellular carcinoma: a retrospective cohort study

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Background: Hepatocellular carcinoma (HCC) is regarded as a high-mortality cancer, but the effectiveness of surgical strategies for young patients with early-stage HCC remains controversial. We aimed to analyze the survival in young patients with stage I–II HCC who underwent different kinds of surgical treatments.

Methods: Overall survival (OS) and cancer-specific survival (CSS) were compared among patients aged 18–45 years with stage I–II HCC from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2013) who underwent local tumor destruction (LTD), wedge or segmental resection (WSR), lobectomy resection (LR), liver transplantation (LT), or non-surgery. Univariate and multivariate analyses and Kaplan-Meier method were used to examine the OS and CSS of the patients. A stratification analysis of CSS was also conducted among the subgroups.

Results: Data from 664 patients were extracted. The median survival time was 46 months. In the multivariate analysis of OS, compared with non-surgery, LTD [hazard ratio (HR), 0.37; 95% confidence interval (CI): 0.25–0.54; P<0.0001], LR (HR, 0.29; 95% CI: 0.19–0.45; P<0.0001), and WSR (HR, 0.26; 95% CI: 0.17–0.39; P<0.0001) had better outcomes, and LT had the best survival benefit (HR, 0.24; 95% CI: 0.16–0.36; P<0.0001), which was similar to CSS. In the stratification analysis, compared with the non-surgery group, among patients with chemotherapy, LT reduced the risk of CSS by 64% (HR, 0.36; 95% CI: 0.19–0.66; P interaction=0.0004).

Conclusions: Surgery offers a survival benefit compared with non-surgery for young patients with stage I–II HCC. LT is associated with better survival than WSR, LR, and LTD.

Keywords: Hepatocellular carcinoma (HCC); young; surgery; resection; survival

Submitted Apr 06, 2022. Accepted for publication Oct 11, 2022.
doi: 10.21037/tcr-22-950
View this article at: https://dx.doi.org/10.21037/tcr-22-950

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Introduction

Hepatocellular carcinoma (HCC) is now the fifth most common cancer in the world (1) and the leading cause of death among patients with chronic liver disease (2). Although young patients have a better liver functional reserve, they usually have more aggressive tumors than older patients (3). It has been reported that the survival of HCC patients with American Joint Committee on Cancer (AJCC) stage I or II was superior to that with other stages (4). Although there are many well-known factors that affect survival, such as the selection of surgery modalities (5), for HCC, very few have been described in the early stages, especially among young people.

For young patients with stage I–II HCC, surgical treatment includes liver resection [wedge or segmental resection (WSR) and lobectomy resection (LR)], liver transplantation (LT), and local tumor destruction (LTD), which may offer curative treatment (6). The prognosis of patients with HCC depends on the stage of the disease as well as liver function at the time of diagnosis (7), and young patients tend to have better health conditions and stronger tolerance to curative treatment (3). A number of studies have focused on surgical options for HCC treatment. Liver resection is recommended for a single HCC when liver function is preserved, and it could also offer better long-term survival than transarterial chemoembolization (TACE) for patients with multiple HCCs (up to three tumors) (8). LT is recommended for those who are not good candidates for surgical resection and within Milan criteria (solitary tumor ≤5 cm or up to three nodules ≤3 cm) (9), but the scarcity of liver donors limits LT and patients drop out due to tumor progression while being in the waiting line (10). In addition, LTD with methods such as radiofrequency ablation (RFA) has gained popularity due to its ease of use, safety, and minimal invasiveness (11). Surgical resection is superior to RFA in terms of recurrence-free survival and local recurrence rate. In addition, LR shows better oncological results than RFA plus TACE (12). It remains a matter of debate which kinds of surgery are better for young patients with stage I–II HCC, and this aspect has rarely been elucidated systematically.

Hence, we sought to compare different surgery treatment outcomes among patients aged 18–45 years with stage I–II HCC who received LTD, WSR, LR, LT, or non-surgery in the Surveillance, Epidemiology, and End Results (SEER) database, which is an ideal data pool for oncologic studies. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-950/rc) (13).

Methods

Database introduction

The SEER database is one of the most comprehensive and authoritative public databases concerning cancer, which covers approximately 28% of the United States population. The SEER 18 registries include San Francisco-Oakland, Metropolitan Atlanta, Los Angeles, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, San Jose and Monterey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia. The SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and survival analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study was deemed to be exempt from institutional review board approval and the need for informed consent was waived.

Inclusion and exclusion criteria

All cases were diagnosed between January 1, 2004 and December 31, 2013, and collected using the International Classification of Diseases for Oncology Topography Codes, Third Edition. The inclusion criteria were as follows: (I) topography codes used were those for primary liver cancer (C22.0) (14), and morphology codes comprised the following histological types: 8170–8175 (i.e., not otherwise specified, fibrolamellar, scirrhous, spindle cell variant, clear cell type, pleomorphic-type HCC); (II) only patients who were defined as stage I–II (AJCC 6th) and aged 18–45 years (15) were included in the current study.

The exclusion criteria were as follows: (I) patients diagnosed before 2004 were excluded due to the use of prior histological coding systems; (II) patients who did not have a clear HCC diagnosis as their only or first of more than one tumor; (III) if the type of reporting source was autopsy only or death certificate only, patients were excluded to reduce bias; (IV) patients without evaluation of follow-up data, such as the survival time and tumor-specific mortality; (V) patients without complete data on ascertainment and definite information on some parameters, including specific surgery, tumor size, and grade of morphology.

Data extraction

Data were extracted from the SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying). The National Cancer Institute's SEER*Stat software (Version 8.3.8) (www.seer.cancer.gov/seerstat) was used to identify the database. We collected demographic variables, including age at diagnosis, race, sex, marital status, insurance status, and year of diagnosis (16,17). The marital status was classified as "married," "non-married," or "unknown". "Non-married" included single, unmarried, separated, divorced, widowed, and domestic partners (16). Therapy information included surgeries, radiotherapy, and chemotherapy. Patients were divided into five surgery groups: non-surgery, LTD, WSR, LR, and LT (6,18). LTD comprised RFA, cryosurgery, alcohol [percutaneous ethanol injection (PEI)], and photodynamic therapy (PDT). WSR referred to surgeries with removing one, two, or three wedges or segments of the liver. Lobectomy and extended lobectomy in the original data were merged into the LR group. Radiotherapy and chemotherapy information was converted into two levels (Yes and No). Pathological information included the tumor size, stage, tumor grade, alpha-fetoprotein (AFP) levels, and fibrosis score (6). AFP was categorized as positive, negative, or unknown (borderline, test not done, not applicable, and unknown) (19). The AJCC 6th staging criteria were used. Age was treated as a continuous variable, and others were categorical variables. Patients were divided into two groups with 35 years as the cutoff value in the stratified analysis (14).

Study endpoint

In this retrospective cohort study, patients were evaluated by clinical variables such as overall survival (OS) and cancer-specific survival (CSS). OS was defined as the time between the surgery and death or the last follow-up, while CSS was defined as the period between the surgery and death due to cancer to reduce the impact of life-threatening comorbidities (20). Deaths from any other causes were calculated as censored cases.

Statistical analysis

We first compared the data distribution of each covariate between different surgery types using the *t* test (normal distribution) or the Kruskal-Wallis rank-sum test (non-normal distribution) for continuous variables and chi-square test for categorical data. Next, univariate and multivariate Cox proportional hazard ratio models were used to examine OS and CSS rates of stage I–II young patients. Interaction and stratified analyses were conducted according to selected covariates to reduce the impact of confounding factors. The effect of surgery categories on OS and CSS was evaluated using Kaplan–Meier curves (log-rank test). All statistical results were considered significant if the two-tailed P value was below 0.05, and 95% confidence interval (CI) risk ratios were also presented. Data were analyzed using the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y Solutions, Inc., Boston, Massachusetts).

Results

Patients' characteristics

In this retrospective cohort study, data from 46,852 patients with HCC were extracted from the SEER database. Furthermore, our selection criteria identified 664 patients aged 18–45 years with an affirmative diagnosis of stage I–II HCC. The flowchart in *Figure 1* shows the overall scheme of our research design; 394 patients received surgical therapies, including LTD, WSR, LR, or LT, while 270 cases did not. The baseline demographic characteristics are summarized in *Table 1*. The median survival time was 46 months [interquartile range (IQR), 15–88 months]. The median age of the participants was 42 years; 376 (56.63%) were White; 482 (72.59%) were male; 328 (49.40%) were married; and 435 (65.51%) were insured. Most patients had a well-differentiated or moderately differentiated tumor (n=269, 40.51%). There were 253 (38.10%) patients who had tumors of <3 cm in size, and the others had tumors of ≥3 cm in size. Most patients (50.75%) presented an elevated AFP level, and 151 (22.74%) patients showed severe liver fibrosis or cirrhosis (fibrosis score, 5 or 6). Only 18 (2.71%) patients received radiation, and 247 (37.20%) received chemotherapy. There were no significant differences (P>0.05) between different surgery groups in stage, sex, AFP, and radiation, while statistical differences were observed with respect to other variables.

Univariate and multivariate analysis of HCC

The univariate analysis identified that age, sex, stage, grade, tumor size, AFP, surgery, and chemotherapy were associated with OS, while marital status, stage, grade, tumor size, AFP,

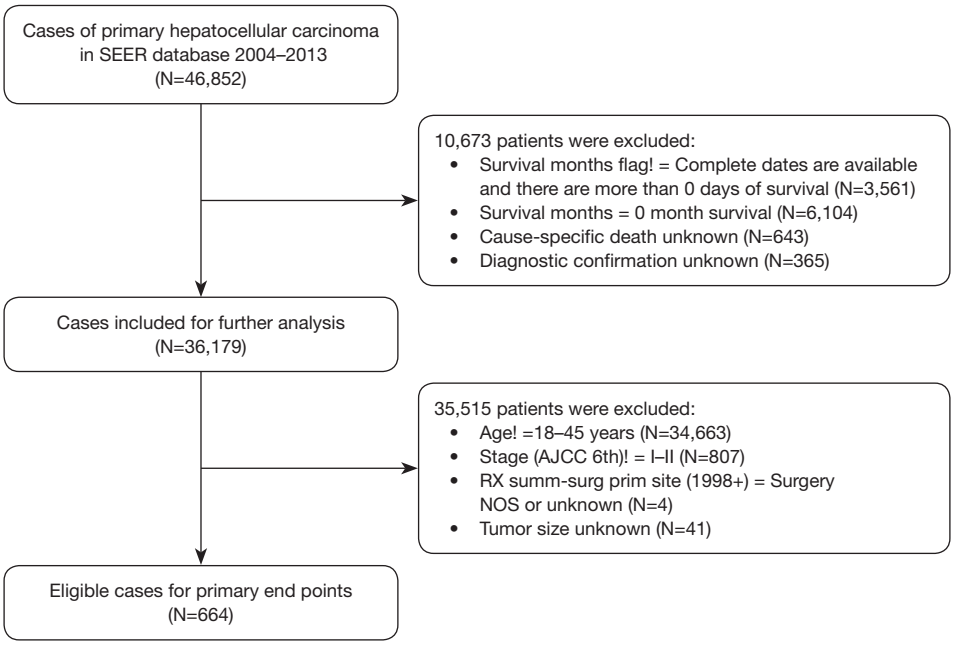

Figure 1 Flowchart of patient selection. SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

Table 1 Demographic and clinicopathologic characteristics of young patients with stage I–II HCC from SEER database

	Total (n=664)	Non-surgery (n=270)	LTD (n=77)	WSR (n=103)	LR (n=97)	LT (n=117)	P value[a]
Median age (IQR), year	42.00 (18.00–45.00)	43.00 (18.00–45.00)	43.00 (21.00–45.00)	38.00 (18.00–45.00)	39.00 (19.00–45.00)	42.00 (21.00–45.00)	<0.001
Stage (AJCC 6th)							0.544
I	412 (62.05%)	169 (62.59%)	51 (66.23%)	68 (66.02%)	58 (59.79%)	66 (56.41%)	
II	252 (37.95%)	101 (37.41%)	26 (33.77%)	35 (33.98%)	39 (40.21%)	51 (43.59%)	
Race							<0.001
White	376 (56.63%)	163 (60.37%)	39 (50.65%)	45 (43.69%)	47 (48.45%)	82 (70.09%)	
Black	90 (13.55%)	45 (16.67%)	10 (12.99%)	8 (7.77%)	12 (12.37%)	15 (12.82%)	
Other	195 (29.37%)	62 (22.96%)	28 (36.36%)	49 (47.57%)	38 (39.18%)	18 (15.38%)	
Unknown	3 (0.45%)	0 (0.00%)	0 (0.00%)	1 (0.97%)	0 (0.00%)	2 (1.71%)	
Sex							0.475
Male	482 (72.59%)	205 (75.93%)	53 (68.83%)	70 (67.96%)	68 (70.10%)	86 (73.50%)	
Female	182 (27.41%)	65 (24.07%)	24 (31.17%)	33 (32.04%)	29 (29.90%)	31 (26.50%)	
Marital status							0.022
Unmarried	309 (46.54%)	133 (49.26%)	44 (57.14%)	43 (41.75%)	35 (36.08%)	54 (46.15%)	
Married	328 (49.40%)	120 (44.44%)	31 (40.26%)	57 (55.34%)	58 (59.79%)	62 (52.99%)	
Unknown	27 (4.07%)	17 (6.30%)	2 (2.60%)	3 (2.91%)	4 (4.12%)	1 (0.85%)	

Table 1 *(Continued)*

Table 1 *(Continued)*

	Total (n=664)	Non-surgery (n=270)	LTD (n=77)	WSR (n=103)	LR (n=97)	LT (n=117)	P value[a]
Insurance							0.001
Uninsured	17 (2.56%)	12 (4.44%)	2 (2.60%)	3 (2.91%)	0 (0.00%)	0 (0.00%)	
Insured	435 (65.51%)	195 (72.22%)	51 (66.23%)	63 (61.17%)	59 (60.82%)	67 (57.26%)	
Unknown	212 (31.93%)	63 (23.33%)	24 (31.17%)	37 (35.92%)	38 (39.18%)	50 (42.74%)	
Year of diagnosis							0.001
2004–2008	337 (50.75%)	112 (41.48%)	41 (53.25%)	55 (53.40%)	56 (57.73%)	73 (62.39%)	
2009–2013	327 (49.25%)	158 (58.52%)	36 (46.75%)	48 (46.60%)	41 (42.27%)	44 (37.61%)	
Grade							<0.001
Well	148 (22.29%)	31 (11.48%)	13 (16.88%)	30 (29.13%)	29 (29.90%)	45 (38.46%)	
Moderately	121 (18.22%)	15 (5.56%)	8 (10.39%)	31 (30.10%)	35 (36.08%)	32 (27.35%)	
Poorly	67 (10.09%)	9 (3.33%)	7 (9.09%)	22 (21.36%)	19 (19.59%)	10 (8.55%)	
Undifferentiated	3 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	2 (1.71%)	
Unknown	325 (48.95%)	215 (79.63%)	49 (63.64%)	20 (19.42%)	13 (13.40%)	28 (23.93%)	
Tumor size							<0.001
<3 cm	253 (38.10%)	95 (35.19%)	48 (62.34%)	27 (26.21%)	8 (8.25%)	75 (64.10%)	
≥3 cm	411 (61.90%)	175 (64.81%)	29 (37.66%)	76 (73.79%)	89 (91.75%)	42 (35.90%)	
AFP							0.106
Negative	205 (30.87%)	75 (27.78%)	23 (29.87%)	29 (28.16%)	39 (40.21%)	39 (33.33%)	
Positive	337 (50.75%)	152 (56.30%)	43 (55.84%)	50 (48.54%)	37 (38.14%)	55 (47.01%)	
Unknown	122 (18.37%)	43 (15.93%)	11 (14.29%)	24 (23.30%)	21 (21.65%)	23 (19.66%)	
Fibrosis score							<0.001
0–4	67 (10.09%)	13 (4.81%)	7 (9.09%)	18 (17.48%)	19 (19.59%)	10 (8.55%)	
5–6	151 (22.74%)	69 (25.56%)	19 (24.68%)	14 (13.59%)	4 (4.12%)	45 (38.46%)	
Unknown	446 (67.17%)	188 (69.63%)	51 (66.23%)	71 (68.93%)	74 (76.29%)	62 (52.99%)	
Radiation							0.504
None	646 (97.29%)	260 (96.30%)	74 (96.10%)	101 (98.06%)	95 (97.94%)	116 (99.15%)	
Yes	18 (2.71%)	10 (3.70%)	3 (3.90%)	2 (1.94%)	2 (2.06%)	1 (0.85%)	
Chemotherapy							<0.001
None	417 (62.80%)	132 (48.89%)	50 (64.94%)	85 (82.52%)	80 (82.47%)	70 (59.83%)	
Yes	247 (37.20%)	138 (51.11%)	27 (35.06%)	18 (17.48%)	17 (17.53%)	47 (40.17%)	

[a], based on the *t*-test (normal distribution) or the Kruskal-Wallis rank-sum test (non-normal distribution) for continuous variables and χ^2 tests for categorical data. HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results Program; LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation; IQR, inter quartile range; AJCC, American Joint Committee on Cancer; AFP, alpha fetal protein.

and surgery were associated with CSS (P<0.05) (*Table 2*). In the multivariate analysis of OS, OS was significantly better in patients receiving surgery compared with patients who did not receive surgery after adjusting for stage, age, race, sex, marital status, grade, tumor size, AFP, fibrosis score, and chemotherapy (*Table 3*). It was also demonstrated that compared with non-surgery, LTD [hazard ratio (HR), 0.37; 95% CI: 0.25–0.54; P<0.0001], WSR (HR, 0.26; 95% CI: 0.17–0.39; P<0.0001), and LR (HR, 0.29; 95% CI: 0.19–0.45; P<0.0001) had better outcomes, and LT (HR, 0.24; 95% CI: 0.16–0.36; P<0.0001) had the best survival after adjusting for the aforementioned variables. Meanwhile, WSR showed better survival than LR (HR, 0.26 *vs.* 0.29). The multivariate analysis of CSS showed results similar to the OS results (*Table 4*). The non-surgery group had a lower survival curve than the surgery groups, and LT showed the highest survival curve (P<0.0001) with respect to both OS and CSS (*Figure 2*).

Stratification analyses

In the stratification analyses of the CSS Cox model (*Table 5*), the association between the surgery types and CSS was robust for most strata (P=0.0943–0.8499). There was a significantly better CSS in patients receiving WSR (HR, 0.18; 95% CI: 0.04–0.87) with normal to moderate liver fibrosis (fibrosis score 0–4) and in patients receiving LT (HR, 0.17; 95% CI: 0.07–0.44) with severe liver fibrosis or cirrhosis (fibrosis score 5–6). Only chemotherapy was significantly associated with the effects of surgery type on CSS (P interaction=0.0004). Compared with the non-surgery group, LT reduced the risk of CSS by 64% (HR, 0.36; 95% CI: 0.19–0.66) among patients with chemotherapy.

Discussion

The population of young patients with HCC is increasing globally each year (5). However, few studies have elaborated on the relationship between surgical treatments and prognosis of HCC, especially in these patients with early-stage HCC (14). Currently, surgical treatment is the primary option for HCC treatment, and advances in surgery for HCC over several decades have expanded the range of surgical options (21). The results of the present study showed that surgery could offer better long-term survival than non-surgery for patients with HCC, which is consistent with several previous studies (21-26). Yu *et al.* reported that the main treatments for early HCC included liver resection, LT, and other operations such as LTD (24,27).

LT is generally considered the best surgical option both in older and younger patients (23), as it can extirpate both the tumor and the underlying liver disease to inhibit the relevant comorbidities (28), thereby increasing survival rates. LT may be a better choice for HCC patients with severe cirrhosis (fibrosis score 5–6) but not superior to liver resection for patients with none to moderate fibrosis (fibrosis score 0–4) (8), which was observed in the stratification analysis in our study. Unfortunately, the use of LT is limited due to the shortage of liver donors. Awareness of the importance of organ donation needs to be promoted to solve the mismatch between supply and demand and to make better use of the limited transplantation resources. Our study supported the principle of LT priority in early-stage young HCC patients with cirrhosis. However, due to the lack of relevant data in the SEER database, the etiology of liver fibrosis or cirrhosis was not analyzed.

In the meantime, liver resection might be considered when LT is not applicable. Currently, the American Association for the Study of Liver Diseases (AASLD) guidelines advocate for liver resection in patients with Child–Pugh A cirrhosis and resectable stage I or II HCC. With the improvement of surgical technology and perioperative management, the safety, feasibility, and availability of surgical resection for patients with stage I–II HCC have been widely improved (21,24). In terms of liver resection, our study showed that LR was not associated with better survival than WSR, which is similar to several previous studies (6,29). When determining whether a patient is eligible for surgical resection, one must consider tumor burden, liver function, presence of portal hypertension, and comorbidities, as well as the extent of hepatectomy and the expected volume of the future liver remnant. It has been reported that a remnant liver volume of approximately 25–30% of the total liver volume for patients without cirrhosis is required before the main hepatectomy to reduce the risk of postoperative liver failure, and for patients with cirrhosis, the remnant liver volume must be up to 40% (30). Extended hepatectomy for large HCC from one lobe to the other or central HCC critically related to the hepatic veins is justifiable in patients with cirrhosis but preserved liver function and adequate liver remnant (31). Young patients always have a better liver functional reserve to receive extended hepatectomy. However, they tend to have more aggressive tumors and an increased risk of hepatic decompensation (32). Extended hepatectomy results in the loss of more liver tissue, possibly

Table 2 Univariate analysis of factors associated with OS and CSS

Characteristics	OS		CSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.02 (1.00, 1.04)	0.0470	1.02 (1.00, 1.04)	0.1090
Race				
White	1		1	
Black	1.30 (0.95, 1.77)	0.0959	1.49 (1.06, 2.09)	0.0210
Other	0.90 (0.70, 1.16)	0.4284	1.01 (0.76, 1.34)	0.9320
Unknown	0.48 (0.07, 3.43)	0.4641	-	-
Sex				
Male	1		1	
Female	0.76 (0.59, 0.98)	0.0333	0.81 (0.61, 1.07)	0.1394
Marital status				
Unmarried	1		1	
Married	0.68 (0.55, 0.86)	0.0009	0.73 (0.57, 0.94)	0.0150
Unknown	1.00 (0.59, 1.69)	0.9949	0.77 (0.39, 1.51)	0.4501
Stage (AJCC 6th)				
I	1		1	
II	1.29 (1.03, 1.60)	0.0247	1.39 (1.09, 1.78)	0.0078
Insurance				
Uninsured	1		1	
insured	0.74 (0.39, 1.39)	0.3426	0.74 (0.36, 1.51)	0.4092
Unknown	0.78 (0.41, 1.50)	0.4624	0.80 (0.39, 1.65)	0.5475
Year of diagnosis				
2004–2008	1		1	
2009–2013	0.89 (0.71, 1.11)	0.2982	0.85 (0.66, 1.09)	0.2017
Grade				
Well	1		1	
Moderately	1.56 (1.04, 2.33)	0.0331	2.01 (1.26, 3.21)	0.0034
Poorly	2.56 (1.67, 3.95)	<0.0001	3.44 (2.12, 5.60)	<0.0001
Undifferentiated	12.07 (3.72, 39.19)	<0.0001	16.97 (5.13, 56.18)	<0.0001
Unknown	2.73 (1.96, 3.80)	<0.0001	3.03 (2.03, 4.52)	<0.0001
Tumor size				
<3 cm	1		1	
≥3 cm	1.79 (1.41, 2.27)	<0.0001	2.24 (1.69, 2.96)	<0.0001
AFP				
Negative	1		1	

Table 2 *(Continued)*

Table 2 *(Continued)*

Characteristics	OS		CSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Positive	2.58 (1.95, 3.41)	<0.0001	2.71 (1.96, 3.74)	<0.0001
Unknown	1.64 (1.15, 2.35)	0.0069	1.78 (1.19, 2.67)	0.0051
Fibrosis score				
0–4	1		1	
5–6	1.63 (1.02, 2.62)	0.0411	1.34 (0.80, 2.26)	0.2622
Unknown	1.88 (1.23, 2.89)	0.0038	1.72 (1.08, 2.72)	0.0215
Surgery				
None	1		1	
LTD	0.35 (0.24, 0.52)	<0.0001	0.39 (0.26, 0.60)	<0.0001
WSR	0.31 (0.22, 0.44)	<0.0001	0.38 (0.26, 0.55)	<0.0001
LR	0.34 (0.24, 0.49)	<0.0001	0.40 (0.27, 0.58)	<0.0001
LT	0.23 (0.16, 0.33)	<0.0001	0.20 (0.13, 0.32)	<0.0001
Radiation				
None	1		1	
Yes	1.43 (0.78, 2.61)	0.2447	1.62 (0.86, 3.04)	0.1368
Chemotherapy				
None	1		1	
Yes	1.32 (1.06, 1.65)	0.0127	1.26 (0.99, 1.62)	0.0627

OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; AFP, alpha fetal protein; LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation.

Table 3 Multivariate analysis of factors associated with OS

Surgery	Non-adjusted		Adjust I		Adjust II	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
None	1		1		1	
LTD	0.35 (0.24, 0.52)	<0.0001	0.35 (0.24, 0.51)	<0.0001	0.37 (0.25, 0.54)	<0.0001
WSR	0.31 (0.22, 0.44)	<0.0001	0.33 (0.23, 0.49)	<0.0001	0.26 (0.17, 0.39)	<0.0001
LR	0.34 (0.24, 0.49)	<0.0001	0.38 (0.26, 0.55)	<0.0001	0.29 (0.19, 0.45)	<0.0001
LT	0.23 (0.16, 0.33)	<0.0001	0.23 (0.16, 0.34)	<0.0001	0.24 (0.16, 0.36)	<0.0001

Adjust I model of P values adjusts for: age, race, sex, marital status. Adjust II model of P values adjusts for: Stage (AJCC 6th), age, race, sex, marital status, grade, tumor size, AFP, fibrosis score, chemotherapy. OS, overall survival; HR, hazard ratio; CI, confidence interval; LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation; AJCC, American Joint Committee on Cancer; AFP, alpha fetal protein.

Table 4 Multivariate analysis of factors associated with CSS

Surgery	Non-adjusted		Adjust I		Adjust II	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
None	1		1		1	
LTD	0.39 (0.26, 0.60)	<0.0001	0.38 (0.25, 0.58)	<0.0001	0.40 (0.26, 0.62)	<0.0001
WSR	0.38 (0.26, 0.55)	<0.0001	0.41 (0.27, 0.62)	<0.0001	0.28 (0.18, 0.44)	<0.0001
LR	0.40 (0.27, 0.58)	<0.0001	0.44 (0.30, 0.66)	<0.0001	0.29 (0.18, 0.46)	<0.0001
LT	0.20 (0.13, 0.32)	<0.0001	0.21 (0.13, 0.33)	<0.0001	0.19 (0.11, 0.32)	<0.0001

Adjust I model of P values adjusts for: age, race, sex, marital status. Adjust II model of P values adjusts for: Stage (AJCC 6th), age, race, sex, marital status, grade, tumor size, AFP, fibrosis score, chemotherapy. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation; AJCC, American Joint Committee on Cancer; AFP, alpha fetal protein.

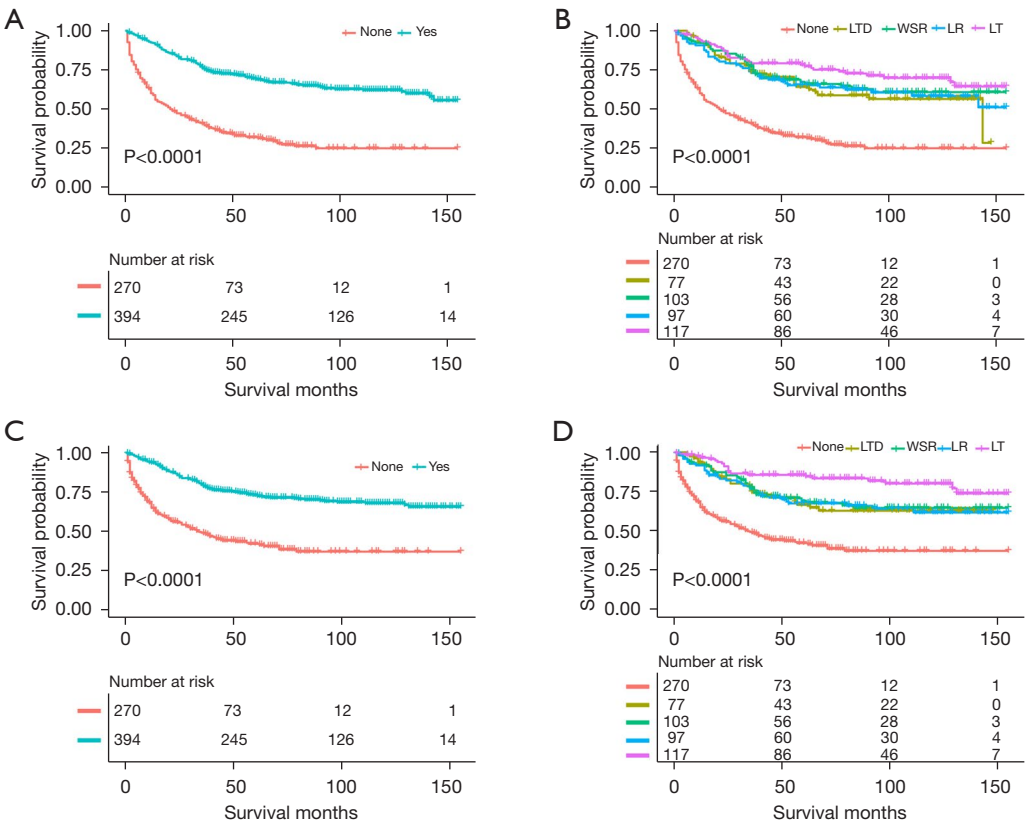

Figure 2 Kaplan-Meier survival estimates. (A) Overall survival for patients stratified by surgery. (B) Overall survival for patients who underwent non-surgery, LTD, WSR, LR, or LT. (C) Cancer-specific survival for patients stratified by surgery. (D) Cancer-specific survival for patients who underwent non-surgery, LTD, WSR, LR, or LT. LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation.

Table 5 Stratification analysis for the impact of surgeries on CSS

Strata	No.	Reference	HR (95% CI)				P interaction[a]
		Non-surgery	LTD	WSR	LR	LT	
Age							0.0943
18–35 years	122	1	0.15 (0.02, 1.10)	0.46 (0.22, 0.95)	0.21 (0.08, 0.53)	0.38 (0.13, 1.12)	
36–45 years	542	1	0.42 (0.27, 0.65)	0.35 (0.22, 0.55)	0.51 (0.34, 0.77)	0.18 (0.11, 0.30)	
Race							0.7173
White	376	1	0.46 (0.26, 0.81)	0.41 (0.23, 0.71)	0.32 (0.18, 0.58)	0.21 (0.12, 0.36)	
Black	90	1	0.52 (0.20, 1.34)	0.24 (0.06, 1.00)	0.41 (0.16, 1.07)	0.11 (0.03, 0.47)	
Other	195	1	0.29 (0.13, 0.66)	0.42 (0.23, 0.76)	0.52 (0.28, 0.96)	0.33 (0.13, 0.86)	
Unknown	3	–	–	–	–	–	
Sex							0.1803
Male	482	1	0.45 (0.28, 0.71)	0.32 (0.20, 0.51)	0.39 (0.25, 0.61)	0.16 (0.09, 0.28)	
Female	182	1	0.27 (0.10, 0.71)	0.57 (0.29, 1.11)	0.45 (0.21, 0.94)	0.37 (0.17, 0.82)	
Marital status							0.1391
Unmarried	309	1	0.40 (0.24, 0.66)	0.30 (0.17, 0.54)	0.23 (0.12, 0.46)	0.18 (0.09, 0.33)	
married	328	1	0.36 (0.17, 0.76)	0.48 (0.28, 0.81)	0.64 (0.40, 1.04)	0.22 (0.11, 0.43)	
Unknown	27	1	–	0.56 (0.07, 4.57)	–	2.38 (0.28, 20.15	
Grade							–
Well	148	1	0.27 (0.06, 1.23)	0.32 (0.11, 0.92)	0.12 (0.03, 0.55)	0.34 (0.14, 0.83)	
Moderately	121	1	0.23 (0.05, 1.04)	0.37 (0.16, 0.88)	0.50 (0.23, 1.09)	0.14 (0.05, 0.41)	
Poorly	67	1	0.90 (0.27, 2.95)	0.41 (0.15, 1.12)	0.56 (0.21, 1.53)	0.36 (0.10, 1.28)	
Undifferentiated	3	–	–	–	–	–	
Unknown	325	1	0.42 (0.25, 0.69)	0.34 (0.15, 0.78)	0.17 (0.04, 0.69)	0.08 (0.02, 0.31)	
Tumor size							0.6207
<3 cm	253	1	0.53 (0.28, 1.03)	0.56 (0.25, 1.27)	0.57 (0.14, 2.36)	0.27 (0.13, 0.55)	
≥3 cm	411	1	0.44 (0.25, 0.77)	0.29 (0.19, 0.45)	0.29 (0.19, 0.43)	0.22 (0.12, 0.40)	
AFP							0.8499
Negative	205	1	0.37 (0.13, 1.06)	0.43 (0.18, 1.06)	0.30 (0.12, 0.74)	0.28 (0.11, 0.69)	
Positive	337	1	0.35 (0.21, 0.58)	0.38 (0.24, 0.61)	0.51 (0.31, 0.83)	0.20 (0.11, 0.37)	
Unknown	122	1	0.54 (0.21, 1.42)	0.26 (0.11, 0.64)	0.42 (0.19, 0.93)	0.12 (0.04, 0.42)	
Fibrosis score							0.1316
0–4	67	1	0.48 (0.10, 2.37)	0.18 (0.04, 0.87)	0.55 (0.18, 1.71)	0.67 (0.19, 2.38)	
5–6	151	1	0.85 (0.40, 1.78)	0.61 (0.24, 1.58)	0.93 (0.22, 3.92)	0.17 (0.07, 0.44)	
Unknown	446	1	0.30 (0.17, 0.51)	0.39 (0.25, 0.60)	0.35 (0.23, 0.54)	0.20 (0.11, 0.35)	
Chemotherapy							0.0004
None	417	1	0.21 (0.12, 0.40)	0.27 (0.17, 0.43)	0.27 (0.17, 0.43)	0.12 (0.06, 0.23)	
Yes	247	1	0.82 (0.46, 1.46)	0.67 (0.32, 1.40)	0.86 (0.43, 1.73)	0.36 (0.19, 0.66)	

[a], stratified by Surveillance, Epidemiology, and End Results (SEER) registry data among all patients. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; LTD, liver tumor destruction; WSR, wedge or segmental resection; LR, lobectomy resection; LT, liver transplantation; AFP, alpha fetal protein.

explaining why WSR is the first choice for early-stage HCC compared with LR. Furthermore, WSR, which is associated with relatively low invasiveness and a faster postoperative recovery, would be a better choice leading to longer survival. Considering the inconsistent recommendations, the efficacy of different surgical strategies for treating HCC patients needs to be further clarified.

We found that LTD resulted in inferior survival benefits compared with other surgical strategies. Over the past decades, LTD has been introduced and clinically used for its low invasiveness, low perioperative risk, and minor deteriorative effects on liver function compared with surgical resection (21). Yu *et al.* (24) suggested that for solitary HCC of 3–5 cm in diameter, RFA can achieve better outcomes than resection, and similar long-term outcomes. However, several previous studies (23,32,33) concluded that LTD resulted in a worse survival than surgical resection and LT. Although LTD is now regarded as an alternative to surgical resection for certain patients who are poor surgical candidates or refuse surgery (33), it should be noted that RFA has an obvious drawback of limited ablative margins, leading to a higher risk of recurrence (21).

Our stratification analysis results were similar to our multivariate analysis results, indicating that our results were robust. Also, we found an interaction between LT and chemotherapy (P interaction=0.0004). Although chemotherapy, such as the FOLFOX regimen, was more commonly used in patients with advanced HCC, we estimated the effect of chemotherapy in our early-stage patients. In the stratification analysis, young patients with early-stage HCC who received LT combined with chemotherapy had a superior survival (HR, 0.36; 95% CI: 0.19–0.66; P interaction=0.0004) compared with non-surgery patients. Previous studies have shown that after LT, adjuvant chemotherapy such as the FOLFOX regimen for HCC significantly prolongs patients' survival (34-36). However, few studies have focused on the association of other chemotherapy regimens and LT; hence, more randomized controlled clinical trials are needed for further validation.

Our study has some strengths. To obtain meaningful variables that can convincingly describe young patients with stage I–II HCC, it is important to have strict inclusion criteria for patients, such as age between 18 and 45 years, and the confirmed clinical diagnosis of HCC. Patients without HCC as the only primary cancer or as the first of more than one tumor and those without available clinical data (such as follow-up time, morphological information, and surgery) were excluded. We also eliminated patients whose report sources were autopsy only and death certificate only to reduce selection bias. Moreover, the nodal points of the research interval were also very significant. We ensured that more balanced and rational data were available by choosing from those methods (6,14). Moreover, we conducted subgroup analysis and performed an interaction test to eliminate variables that affected the relationship between surgical therapy and patients' survival.

Limitations

We are aware of several limitations of our study. The SEER database does not provide sufficient data on postoperative survival, such as laboratory examination (including prothrombin time, alanine aminotransferase, albumin, and bilirubin levels), surgery details, and performance status. Also, the staging was performed based on the tumor, node, metastases (TNM) system (AJCC), and data about the Milan criteria or the Barcelona Clinical Liver Cancer (BCLC) staging system were incomplete or lacking. Although some important factors were not recorded in the data, we used CSS as a secondary outcome to separate the impact of surgical type on HCC specific outcome to reduce the impact of comorbidities on the survival differences. All surgical treatments, including LTD, WSR, LR and LT, were analyzed in our study by using comprehensive statistical methods. Moreover, details with respect to chemotherapy such as TACE are not available in the SEER database. It is generally believed that surgery provides a better survival benefit for HCC patients. Nevertheless, to the best of our knowledge, this is the first study to report that LR does not result in better long-term survival than WSR in young patients with stage I–II HCC, based on an authoritative source of cancer data in the United States. Our results may provide guidance to clinicians when making treatment decisions for young patients with early-stage HCC.

Conclusions

In summary, compared with non-surgery, surgeries offer better long-term survival in young patients with stage I–II HCC. Moreover, LT results in the best survival, and WSR is recommended if liver donors are not available. More randomized controlled clinical studies with a large number of patients are needed for further validation to obtain more objective, reasonable, and convincing results to facilitate decision-making for HCC treatment in young patients and improve the survival rates.

Acknowledgments

We sincerely thank all the staff in the National Cancer Institute and every member's contributions to the SEER Program. We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Funding: This work was supported by grants from the Beijing Xisike Clinical Oncology Research Foundation (grant No. Y-2020Sciclone/zb/qn-0005), the National Natural Science Foundation of China (grant No. 81873147) and "Double first-class" and high-level university construction discipline (Integrated Traditional Chinese and Western Medicine) reserve talent cultivation project of Guangzhou University of Chinese Medicine (grant No. A1-2601-22-415-014).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-950/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-950/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50.
2. Song P, Cai Y, Tang H, et al. The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines from 2001 to 2017. Biosci Trends 2017;11:389-98.
3. Zhang ZY, Guan J, Wang XP, et al. Outcomes of adolescent and young patients with hepatocellular carcinoma after curative liver resection: a retrospective study. World J Surg Oncol 2022;20:210.
4. Park S, Choi S, Cho YA, et al. Evaluation of the American Joint Committee on Cancer (AJCC) 8th Edition Staging System for Hepatocellular Carcinoma in 1,008 Patients with Curative Resection. Cancer Res Treat 2020;52:1145-52.
5. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
6. Zhang QQ, Wu PY, ALBahde M, et al. Do Elderly Patients With Stage I-II Hepatocellular Carcinoma Benefit From More Radical Surgeries? A Population-Based Analysis. Front Oncol 2020;10:479.
7. Seehofer D, Petrowsky H, Schneeberger S, et al. Patient Selection for Downstaging of Hepatocellular Carcinoma Prior to Liver Transplantation-Adjusting the Odds? Transpl Int 2022;35:10333.
8. Wu Z, Chen W, Ouyang T, et al. Management and survival for patients with stage-I hepatocellular carcinoma: An observational study based on SEER database. Medicine (Baltimore) 2020;99:e22118.
9. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
10. Fukami Y, Kaneoka Y, Maeda A, et al. Liver Resection for Multiple Hepatocellular Carcinomas: A Japanese Nationwide Survey. Ann Surg 2020;272:145-54.
11. Zhou C, Zhang X, Peng Y, et al. Surgical Resection plus Radiofrequency Ablation versus Radical Surgery for Hepatocellular Carcinoma: A Propensity Score Matching Analysis. J Cancer 2019;10:3933-40.
12. Shin SW, Ahn KS, Kim SW, et al. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. Ann Surg 2021;273:656-66.
13. Agha R, Abdall-Razak A, Crossley E, et al. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. Int J Surg 2019;72:156-65.
14. Han SS, Kelly SP, Li Y, et al. Changing Landscape of

Liver Cancer in California: A Glimpse Into the Future of Liver Cancer in the United States. J Natl Cancer Inst 2019;111:550-6.
15. Li X, Bi X, Zhao J, et al. A nomogram to predict prognosis after surgery for young patients with hepatocellular carcinoma. Transl Cancer Res 2021;10:1773-86.
16. Bai DS, Zhang C, Chen P, et al. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep 2017;7:12870.
17. Xu RB, Kong X, Xu BP, et al. Longitudinal association between fasting blood glucose concentrations and first stroke in hypertensive adults in China: effect of folic acid intervention. Am J Clin Nutr 2017;105:564-70.
18. Hatzidakis A, Müller L, Krokidis M, et al. Local and Regional Therapies for Hepatocellular Carcinoma and Future Combinations. Cancers (Basel) 2022;14:2469.
19. El-Fattah MA, Aboelmagd M, Elhamouly M. Prognostic factors of hepatocellular carcinoma survival after radiofrequency ablation: A US population-based study. United European Gastroenterol J 2017;5:227-35.
20. Wu C, Ren X, Zhang Q. Incidence, risk factors, and prognosis in patients with primary hepatocellular carcinoma and lung metastasis: a population-based study. Cancer Manag Res 2019;11:2759-68.
21. Lee J, Jin YJ, Shin SK, et al. Surgery versus radiofrequency ablation in patients with Child- Pugh class-A/single small (≤3 cm) hepatocellular carcinoma. Clin Mol Hepatol 2022;28:207-18.
22. Jianyong L, Lunan Y, Dajiang L, et al. Comparison of open liver resection and RFA for the treatment of solitary 3-5-cmhepatocellular carcinoma: a retrospective study. BMC Surg 2019;19:195.
23. Zhang EL, Cheng Q, Huang ZY, et al. Revisiting Surgical Strategies for Hepatocellular Carcinoma With Microvascular Invasion. Front Oncol 2021;11:691354.
24. Yu B, Ding Y, Liao X, et al. Radiofrequency ablation versus surgical resection in elderly patients with early-stage hepatocellular carcinoma in the era of organ shortage. Saudi J Gastroenterol 2018;24:317-25.
25. Kim GA, Shim JH, Kim MJ, et al. Radiofrequency ablation as an alternative to hepatic resection for single small hepatocellular carcinomas. Br J Surg 2016;103:126-35.
26. Jiang YQ, Wang ZX, Deng YN, et al. Efficacy of Hepatic Resection vs. Radiofrequency Ablation for Patients With Very-Early-Stage or Early-Stage Hepatocellular Carcinoma: A Population-Based Study With Stratification by Age and Tumor Size. Front Oncol 2019;9:113.
27. Zhao WJ, Zhu GQ, Wu YM, et al. Comparative Effectiveness of Radiofrequency Ablation, Surgical Resection and Transplantation for Early Hepatocellular Carcinoma by Cancer Risk Groups: Results of Propensity Score-Weighted Analysis. Onco Targets Ther 2019;12:10389-400.
28. Mironov O, Jaberi A, Kachura JR. Thermal Ablation versus Surgical Resection for the Treatment of Stage T1 Hepatocellular Carcinoma in the Surveillance, Epidemiology, and End Results Database Population. J Vasc Interv Radiol 2017;28:325-33.
29. Morise Z. Developments and perspectives of laparoscopic liver resection in the treatment of hepatocellular carcinoma. Surg Today 2019;49:649-55.
30. Allaire M, Goumard C, Lim C, et al. New frontiers in liver resection for hepatocellular carcinoma. JHEP Rep 2020;2:100134.
31. Poon RT, Fan ST, Lo CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? Ann Surg 2002;236:602-11.
32. Xu J, Noda C, Erickson A, et al. Radiofrequency Ablation vs. Cryoablation for Localized Hepatocellular Carcinoma: A Propensity-matched Population Study. Anticancer Res 2018;38:6381-6.
33. Yang A, Ju W, Yuan X, et al. Comparison between liver resection and liver transplantation on outcomes in patients with solitary hepatocellular carcinoma meeting UNOS criteria: a population-based study of the SEER database. Oncotarget 2017;8:97428-38.
34. Liu M, Xu M, Tang T. Association between chemotherapy and prognostic factors of survival in hepatocellular carcinoma: a SEER population-based cohort study. Sci Rep 2021;11:23754.
35. Liu Y, Wang Y, Guo X, et al. Comparative Effectiveness of Adjuvant Treatment for Resected Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis. Front Oncol 2021;11:709278.
36. Huang D, Shen Y, Zhang W, et al. A preoperative nomogram predicts prognosis of patients with hepatocellular carcinoma after liver transplantation: a multicenter retrospective study. BMC Cancer 2021;21:280.

Cite this article as: Zhang C, Jiang Z, Huang X, Zuo J, Zhai L. Surgical therapy and survival in young patients with stage I–II hepatocellular carcinoma: a retrospective cohort study. Transl Cancer Res 2022;11(11):3951-3963. doi: 10.21037/tcr-22-950

