RESEARCH ARTICLE

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Efficacy and Safety of Liver Resection in Super Elderly Patients with Hepatocellular Carcinoma

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Abstract

Objective: Liver resection in the super elderly patients remains challenging because of comorbidities and operative tolerability. **Methods:** In this study, we compared postoperative complications and survival in patients aged ≥85 yr included five patients aged ≥90 yr with those aged 70-79 and 80-84 yr at a single institution. **Results:** Three hundred sixty-seven patients aged ≥70 yr underwent liver resection and were divided into three groups based on age at operation between 2010 and 2022; (a) 70-79 yr (median of 74 yr, n=245), (b) 80-84 yr (median of 82 yr, n=81), and (c) ≥85 yr (median of 87 yr, n=41). In the ≥85 yr group (90-yr-old group), twenty-five patients (four) had hypertension, fourteen (one) had diabetes mellitus, seven (one) had cardiovascular disease, and five patients (one) had dementia. The rate of comorbidities did not differ significantly among three groups. The rate of postoperative complications (Clavien–Dindo grade 3a≤) was 25% in the 70- to 79-yr-old group, 27% in the 80- to 84-yr-old group, and 17% in the ≥85-yr-old group (20% in the ≥90-yr-old group) (N.S.). The 1- and 5-yr patient survival rates in the ≥85-yr-old group were 90.1% and 48.5% respectively, compared with 86.7% and 60.9% in the 70- to 79-yr-old group and 83.8% and 66.3% in the 80- to 84-yr-old group, respectively (N.S.). **Conclusion:** Despite the management of comorbidities, liver resection for well-selected super elderly patients, such as those aged ≥85 yr included ≥90yr, has acceptable outcomes. The age of patient is not an absolute contraindication to liver resection.

Keywords: Postoperative complication- super elderly- survival

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Introduction

The longevity of the general population has increased worldwide. The proportion of elderly patients requiring liver surgery in malignant hepato-biliary-pancreatic tumors is increasing in tandem with the increase in average life expectancy (Kudo et al., 2021; Laconi et al., 2020). It is well known that the risk of developing HCC increases with age (Asahina et al., 2010; Cho et al., 2007). Liver resection is controversial because of the high incidence of comorbidities and poor functional status in the elderly patients (Tsujita et al., 2012). Age has been identified as a risk factor for complications and mortality in liver surgery. However, it has recently been reported in the literature that the prognosis of elderly patients after liver resection is similar to non-elderly patients (Kaibori et al., 2019; Oishi et al., 2009; Wu et al., 2019; Yamada et al., 2012). Many reports defined "elderly" as being 70, 75, and 80 yr old. To date, only a few groups have reported the outcomes following liver resection for super elderly patients ≥85 yr (Ishihara et al., 2021; Oishi et al., 2009). Many of these studies have not been demonstrated outcome of patients aged ≥90 yr in detail. The study aims to evaluate the postoperative complication, 30- and 90-day mortality, and survival after liver resection for hepatocellular carcinoma (HCC) in super elderly patients aged ≥85 yr included five patients aged ≥ 90 yr compared with 70-79 and 80-84 yr at a single institution.

Materials and Methods

Study cohort

Five hundred fifty-eight patients with HCC underwent initial hepatectomy at Kansai Medical University Hospital between January 2010 and March 2022. Three hundred sixty-seven patients aged more than 70 yr at the time of surgery were identified and reviewed retrospectively. Variables pertaining to the patient, surgery, and outcome (complication and survival) were extracted from the HCC database and supplemented where necessary by a review of clinical records.

Clinical practice

Preoperative assessment

Routine tests (blood test: complete blood count, liver function test including indocyanine green retention

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measurement, renal function test, and clotting screen, electrocardiogram, respiratory function test, and chest X-ray) and computed tomography with three-phase liver contrast enhancement and/or ethxybenzyl (EOB) magnetic resonance imaging were performed during the preoperative examination. Moreover, the evaluation of liver function included whole and remnant liver prior to liver resection was performed by Tc-99m-GSA scintigraphy. In addition to routine work-up, especially elderly patients underwent echocardiogram. Nutritional status, frailty (grip strength and knee extension), performance status, and exercise performance by 6-minute walk test were assessed before operation and cognitive function in elderly patients was examined. A multidisciplinary team meeting determined the operation's indication and did the assessment of appropriate operative risk. Patients whose comorbidities were well treated and controlled were considered operable. Surgeons considered laparoscopic hepatectomy to be the best option for all patients. However, the main surgical concerns (whether laparoscopic or open hepatectomy) were finally preoperative liver function, type of liver resection, and severe adhesiolysis due to repeat surgery.

Surgical procedure

In operation, parenchymal transection was performed using the Cavitron ultrasonic surgical aspirator with soft-coagulation system in laparoscopic hepatectomy and with radiofrequency sealer (Aquamantys) in open hepatectomy. Intraoperative ultrasonography was routinely used to assess HCC lesions and determine the transection line. In both laparoscopic and open liver resections (OLRs), central venous pressure was reduced to less than 5-mmHg during liver resection. The Pringle maneuver was used to reduce intraoperative blood loss during parenchymal transection.

Postoperative management

Postoperative pain was controlled continuous intravenous fentanyl infusion and/or epidural analgesia. Physical rehabilitation was started with physical therapist from postoperative day 1 for all included elderly patients.

Study design

The 367 patients were divided into three age groups: 70-79 yr (n=245), 80-84 yr (n=81), and ≥85 yr (n=41). In terms of surgical complications by Clavien–Dindo grade 3a≤, postoperative delirium, 30- and 90-day mortality, HCC recurrence, and survival, the ≥85-yr-old group was compared with the 70- to 79-yr-old and 80- to 84-yr-old groups.

Statistical analysis

The numerical outcomes are represented by the median and range. Continuous data were analyzed using the Mann–Whitney U test, and categorical variables were evaluated using the χ^2 test and Fisher's exact test. Cumulative survival rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. A P value of < 0.05 was considered to be statistically significant. All statistical analyses were carried out using the JMP Pro version 16.0 statistical software program (SAS Institute, Cary, NC, USA).

Results

The comparison of patient's characteristics among the three groups is shown in Table 1. The median age of the 70- to 79-yr-old, 80- to 84-yr-old, and ≥85-yr-old groups were 74 yr (range, 70–79 yr), 82 yr (range, 80–84 yr), and 87 yr (range, 85–95 yr), respectively. Gender proportions significantly differ between 70- to 79-yr-old and ≥85-yr-old groups. There was no statistically significance in the prevalence of hepatitis B and C infection between the ≥85-yr-old, 70- to 79-yr-old, and 80- to 84-yr-old groups. There was no statistically significant difference in blood data except for platelet count, such as serum albumin, bilirubin, prothrombin activity, ICG 15, and tumor markers, including α-fetoprotein and PIVKA-II. The proportion of Child–Pugh grade was comparable

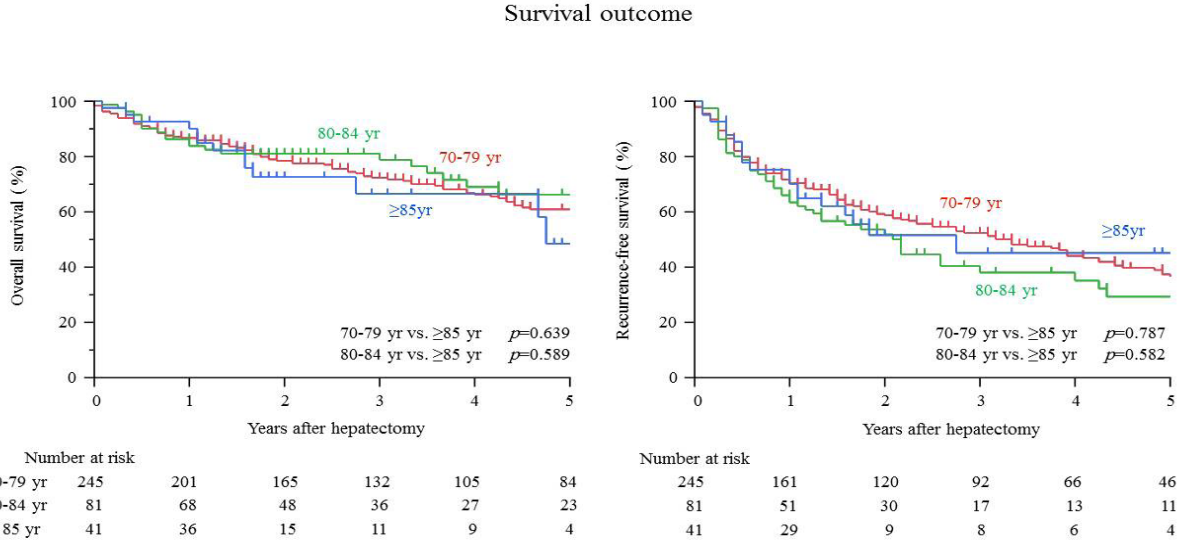

Figure 1. The Survival Rates

Table 1. Characteristics of the Patients According to Age

Variable	70–79 yr (n=245)	80–84 yr (n=81)	≥85 yr (n=41)	p value 70–79 vs. ≥85 yr	p value 80–84 vs. ≥85 yr
Age (yr)	74 (70–79)	82 (80–84)	87 (85–95)	<0.001	<0.001
Gender (male/female)	192/53	58/23	26/15	0.037	0.356
HBs ag (+)	18 (7)	4 (5)	1 (2)	0.2428	0.5107
HCV ab (+)	101 (41)	37 (46)	14 (34)	0.3923	0.223
Serum albumin (g/dL)	3.9 (1.3–5.2)	3.8 (2.4–5.1)	3.9 (2.9–4.8)	0.7037	0.236
Serum bilirubin (mg/dL)	0.8 (0.2–1.9)	0.8 (0.3–3.3)	0.7 (0.4–1.5)	0.521	0.671
Prothrombin activity (%)	88 (43–124)	88 (64–125)	87 (43–117)	0.753	0.917
Platelet count (104/μL)	15.5 (2.4–48.4)	15.1 (6.1–47.9)	19.9 (6.6–61.7)	<0.05	0.073
ICGR 15 (%)	15 (2–62)	16 (3–47)	15 (6–39)	0.484	0.958
α-fetoprotein (ng/mL)	10 (2–1212,370)	11 (2–261,351)	8 (2–29806)	0.99	0.7
PIVKA-II (mAU/mL)	102 (2–173,137)	128 (9–75,000)	153 (12–134821)	0.603	0.727
Child–Pugh grade (A/B/C)	220/25/0	8/1/1972	38/3/0	0.565	0.689
Comorbidities					
Diabetes mellitus	105 (43)	25 (31)	14 (34)	0.295	0.714
Hypertension	130 (53)	44 (54)	25 (61)	0.347	0.484
Cardiovascular	39 (16)	18 (22)	7 (17)	0.852	0.506
Cerebrovascular	23 (9)	4 (5)	1 (2)	0.138	0.511
Dementia	12 (5)	4 (5)	5 (12)	0.067	0.148
History of abdominal surgery	59 (24)	24 (30)	9 (22)	0.767	0.367

Note. HBs ag, hepatitis B surface antigen; HCV ab, hepatitis C virus antibody; ICGR 15, indocyanine green retention; rate at 15 min; PIVKA-II, protein induced by vitamin K absence-II; The data are presented as the median (range) or n (%).

across all three groups. The prevalence of comorbidities, including diabetes mellitus, hypertension, cardiovascular disease, and cerebrovascular disease in ≥85 yr old was similar to that in 70- to 79-yr-old and 80- to 84-yr-old groups. The rate of dementia tended to be more in ≥85 yr old than 70- to 79-yr-old group. Two of the five patients in the ≥90-yr-old group had a history of abdominal surgery. They both had laparoscopic surgery for transverse colon cancer. There was no significant difference between the groups of ≥85 yr old, 70- to 79 yr old, and 80- to 84 yr old in terms of the history of abdominal surgery.

In terms of operative factors, half of the patients aged ≥85 yr, particularly 80% of those aged ≥90 yr, underwent laparoscopic hepatectomy (Table 2). There was

Table 2. Surgical Factors of the Patients According to Age.

Variable	70–79 yr (n=245)	80–84 yr (n=81)	≥85 yr (n=41)	p value 70–79 vs. ≥85 yr	p value 80–84 vs. ≥85 yr
Laparoscopy	66 (27)	39 (48)	21 (51)	<0.05	0.749
Tumor number	1 (1–5)	1 (1–3)	1 (1–3)	0.27	0.504
Tumor size (cm)	3.7 (0.5–18.5)	3.7 (0.3–14)	3.5 (1.2–13)	0.709	0.806
Type of resection				0.191	0.454
Partial resection	56 (23)	22 (27)	7 (17)		
Subsegmentectomy	58 (24)	21 (26)	12 (29)		
Segmentectomy	46 (19)	20 (25)	13 (32)		
Left hepatectomy	22 (9)	6 (7)	5 (12)		
Right hepatectomy	40 (16)	8 (10)	1 (2)		
Central bisegmentectomy	17 (7)	3 (4)	3 (7)		
Left trisegmentectomy	1 (0.4)	0 (0)	0 (0)		
Right trisegmentectomy	5 (2)	1 (1)	0 (0)		
Operative time (min)	329 (119–721)	320 (123–668)	333 (138–517)	0.129	0.452
Blood loss (mL)	611 (10–5,778)	559 (12–3,032)	553 (26–5,628)	0.321	0.976
RBC transfusion (+)	47 (19)	16 (20)	14 (34)	0.259	0.081

Note. RBC, red blood cell; The data are presented as the median (range) or n (%).

Table 3. Postoperative Outcomes of the Patients According to Age

Variable	70–79 yr (n=245)	80–84 yr (n=81)	≥85 yr (n=41)	p value 70–79 vs. ≥85 yr	p value 80–84 vs. ≥85 yr
Postoperative stay (day)	15 (4–146)	18 (8–132)	16 (10–189)	0.511	0.52
Postoperative delirium	32 (13)	15 (19)	13 (32)	<0.05	0.102
Clavien-Dindo grade 3a≤	61 (25)	22 (27)	7 (17)	0.276	0.216
30-day mortality	4 (2)	0 (0)	0 (0)	0.41	–
90-day mortality	7 (3)	1 (1)	1 (2)	0.881	0.621
Recurrence	104 (42)	41 (51)	15 (37)	0.556	0.092

Note. The data are presented as the median (range) or n (%).

statistically significant difference between of ≥85-yr-old and 70- to 79-yr-old groups. There was no statistically significant difference in the type of resection among the three groups. In the ≥90-yr-old group, one had a partial resection, three had a subsegmentectomy, and one had an anterior segmentectomy. Furthermore, operative time and intraoperative blood loss was no significant difference among the three groups.

Incidence of complications and survival

Table 3 compares postoperative complications, 30- and 90-day mortality, and recurrence rates in the ≥85-yr-old group with the 70- to 79-yr-old and 80- to 84-yr-old groups. Table 4 also includes a detailed list of postoperative complications and prognosis of the ≥90 yr old. There was statistically significant difference in postoperative delirium between the 70- to 79-yr-old and ≥85-yr-old groups. There were no significant differences in postoperative complications expressed by Clavien–Dindo grade 3a≤ among the three groups. The 30- and 90-day mortality rates in 70- to 79 yr old were 2% and 3%, respectively, 80- to 84 yr old were 0% and 1%, respectively, and ≥85 yr old were 0% and 2%, respectively. The cause of death within 30 days after liver resection was heart failure (n = 2, 4 days and 18 days postoperative), multi-organ failure (n = 1, 17 days postoperative), and liver failure (n = 1, 30 days postoperative) in the 70- to 79-yr-old group. One patient aged 80–84 yr died of an unknown cardiac arrest (36 days postoperative), and another aged 85–89 yr died of liver failure (51 days postoperative). In the ≥90-yr-old group, no patient died within 90 days of surgery. In terms of 30- and 90-day mortality, there was no significant difference among the three groups. There was no significant difference in recurrence among the three groups. Two patients in the 90-yr-old group had HCC recurrence. One 90-yr-old patient had a single HCC recurrence and underwent a repeat laparoscopic hepatectomy 18 months later (case 2). The other patient aged 93 yr had multiple HCC at 14 months after surgery and was treated with atezolizumab/bevacizumab (case 4). Six times for five patients including recurrence were performed liver resection in more than 90 yr. Two of the five patients had an abdominal infection. One was used to replace the abdominal drain (case 4), and the other was given antibiotics (case 5).

The survival rates are shown in Figure 1. The 1-, 3-, and 5-yr patient survival rates were 86.7%, 72.3%, and 60.9% in the 70- to 79-yr-old group, 83.8%, 78.8%, and 66.3% in the 80- to 84-yr-old group, and 90.1%, 66.5%, and 48.5% in the ≥85-yr-old group, respectively (log rank: 70–79 vs. ≥85 yr, p = 0.639; 80–84 vs. ≥85 yr, p = 0.589). The causes of death were HCC-related (n = 8), liver-related (n = 3), and others (n = 2) in the ≥85-yr-old group. The causes of death were HCC recurrence (n = 1) and dissected abdominal aortic aneurysm (n = 1) in the ≥90-yr-old group. The 1-, 3-, and 5-yr recurrent free survival rates were 70.3%, 52.4%, and 36.5% in the 70- to 79-yr-old group, 63.4%, 38.0%, and 29.3% in the 80- to 84-yr-old group, and 70.1%, 45.1%, and 45.1% in the ≥85-yr-old group, respectively (log rank: 70–79 vs. ≥85 yr, p = 0.787; 80–84 vs. ≥85 yr, p = 0.582).

Table 4. Postoperative Complications and Prognosis in ≥90-yr Patients

Case	Age (yr)	ASA-PS	Operative type	Type of resection	Postoperative complications and treatment	Recurrence and treatment	Postoperative Stay (day)	Prognosis (time from operation, m) and cause of death
1	90	2	Laparoscopy	Segmentectomy	—	—	16	Alive (20)
2	90	2	Laparoscopy	Subsegmentectomy	—	Single → operation	13	Alive (18)
3	92	2	Open	Partial	—	—	11	Alive (84)
4	93	2	Laparoscopy	Subsegmentectomy	Abdominal infection → Abdominal drain Delirium →Medication	Multiple → chemotherapy	23	Dead (21), HCC recurrence
5	95	2	Laparoscopy	Subsegmentectomy	Abdominal infection →Antibiotics	—	16	Dead (4), dissected AAA

ASA-PS, American society of anesthesiologists-Physical status; AAA, abdominal aortic aneurysm; HCC, hepatocellular carcinoma

Discussion

This study found that the prognosis of the patients aged ≥85 yr included five patients aged ≥90 yr after liver resection is not significantly different from that of the patients aged 70-79 and 80-84 yr. Furthermore, there was no significant difference in postoperative complications between the ≥85-yr-old and 70- to 79-yr old groups or between ≥85-yr-old and 80- to 84-yr-old groups.

Most previous studies found that elderly and non-elderly patients with HCC had similar long-term survival rates (Famularo et al., 2019; Oishi et al., 2009; Yamada et al., 2012). However, other studies have refuted this observation (Huang et al., 2009; Kaibori et al., 2019). In the literature, the 5-yr survival rates in elderly patients aged ≥80 yr ranged from 26% to 43% (Hatanaka et al., 2023; Kinoshita et al., 2016; Yamada et al., 2012). Wu et al. showed that the 5-yr overall survival rate in ≥85-yr-old patients was 35.5% (Wu et al., 2019). The present study found the superior result after ≥85 yr, with a 5-yr overall survival rate of 48.5%. In our study, the cause of death ≥85 yr was HCC-related in eight cases, liver-related in three, and non-liver or non-HCC-related in two. The cause of death ≥90 yr was HCC-related in one case and non-liver or non-HCC-related in the other. According to the literature, the incidence of HCC-related or liver-related death in elderly patients was nearly identical to that of non-elderly patients; however, the other cause of death in elderly patients was higher than that of non-elderly patients (Kaibori et al., 2019; Wu et al., 2019). Hatanaka et al., 2022 found that age was strongly associated with non-liver-related death. In the literature, vascular invasion, tumor size, pTNM stage, AFP level, and the Geriatric 8 (G8) score, but not age itself, were predictive factors for poor prognosis of patients with HCC (Huang et al., 2009; Kaibori et al., 2021; Yeh et al., 2002; Zhou et al., 2006).

In terms of postoperative complication, a large cohort study found no difference between elderly and non-elderly patients in terms of liver-specific complications (e.g., bile leakage and liver failure) (Elfrink et al., 2021; Okinaga et al., 2018). When compared with younger patients, elderly patients had more complications, primarily due to increased cardiac disease, pulmonary disease, and delirium (Elfrink et al., 2021; Nozawa et al., 2015; Okinaga et al., 2018; Zhou et al., 2006). Some studies have found that increasing age is associated with postoperative delirium (Ishihara et al., 2021; Muzzana et al., 2022). In this study, there was no significant difference in postoperative complications between patients aged ≥85 yr and those aged 70–79 or 80–84 yr. Fortunately, no patients aged ≥90 yr were found to have cardiac or pulmonary complications. Postoperative delirium significantly increased in ≥85 yr. compared with 70- to 79-yr old group. Preoperative dementia complicated postoperative delirium in one patient aged ≥90 yr.

In the present study, more than half of the patients were aged ≥80 yr and underwent laparoscopic liver resection (LLR). LLR was performed on four of five patients aged ≥90 yr. LLR was significantly performed in ≥85 yr. compared with 70- to 79-yr old group. When compared with OLR, LLR is considered a safer approach due to lower intraoperative blood loss, shorter hospital stay, and lower postoperative morbidity (Cauchy et al., 2016; Nomi et al., 2020). Some studies have found that LLR has a lower risk of postoperative pulmonary complications than OLR (Fuks et al., 2016; Nomi et al., 2020). There are no postoperative pulmonary complications in our super elderly patients. One of the main advantages of laparoscopic surgery is the lack of large incisions, which results in less pain and faster recovery. Under postoperative pain management, most elderly patients undergoing LLR could sit and walk according to postoperative rehabilitation protocol. If possible, a laparoscopic approach could be beneficial for patients, particularly the elderly.

Additionally, elderly patients were more likely to have comorbidities, such as cerebrovascular disease, dementia, and chronic pulmonary disease. Okinaga et al., 2018 found that multiple comorbidities increased significantly in patients aged 70 yr. In our study, hypertension was the most common comorbidity in each group. Because the majority of elderly patients have comorbidities, their management is more complicated and requires more attention than that of younger patients.

The retrospective nature of our study and the small sample size merit further discussion. Prospective and multicenter studies are required to clarify the long-term clinical outcomes of super elderly patients. Despite these limitations, we believe that this study provides useful information about the clinical outcomes of super elderly patients because, to the best of our knowledge, it includes the largest number of super elderly patients.

In conclusion, liver resection for well-selected super elderly patients, such as aged ≥85 yr included 90 yr has acceptable outcomes despite having more comorbidities than non-elderly patients. Liver resection for super elderly patients may be a key to paying more attention to comorbidities and performing minimally invasive surgery, such as a laparoscopic approach, if possible. The age of patient is not an absolute contraindication to liver resection.

Author Contribution Statement

Hidekazu Yamamoto: acquisition and analysis of data, study design, and drafting of the manuscript. Masaki Kaibori: critical review of the manuscript and supervision of the project. Hideyuki Matsushima: acquisition of data. Hisashi Kosaka: acquisition of data. Kosuke Matsui: acquisition of data. Mitsugu Sekimoto: critical review of the manuscript and supervision of the project.

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Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki after approval from Institutional Review Board (IRB) of Kansai Medical University, Osaka, Japan (IRB approval number 2022211).

Conflict of Interest

The authors have no conflict of interest to disclose regarding this article.

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