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The Survival Paradox of Elderly Patients After Major Liver Resections

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Abstract

Objective The objective of this study is to assess the outcome of liver resections in the elderly in a matched control analysis.
Patients and Methods From a prospective single center database of 628 patients, 132 patients were aged 60 years or over and underwent a primary major liver resection. Of these patients, 93 could be matched one-to-one with a control patient, aged less than 60 years, with the same diagnosis and the same type of liver resection. The mean age difference was 16.7 years.
Results Patients over 60 years of age had a significantly higher American Society of Anaesthesiologists (ASA) grade. All other demographics and operative characteristics were not different. In-hospital mortality and morbidity were higher in the patients over 60 years of age (11% versus 2%, $p=0.017$ and 47% versus 31%, $p=0.024$). One-, 3-, and 5-year survival rates in the patients over 60 years of age were 81%, 58%, and 42%, respectively, compared to 90%, 59%, and 42% in the control patients ($p=0.558$). Unified model Cox regression analysis showed that resection margin status (hazard ratio 2.51) and ASA grade (hazard ratio 2.26), and not age, were determining factors for survival.
Conclusion This finding underlines the important fact that in patient selection for major liver resections, ASA grade is more important than patient age.

Introduction

Liver resection is the preferred treatment for a wide range of primary and secondary liver tumors. Advances

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in preoperative assessment, surgical techniques, anesthesiology, and postoperative care have progressively lowered the perioperative risk of liver resections and thereby widened operative indications.[1–3] This has markedly increased the number of patients evaluated for liver resections.[4]

Besides this, increased life expectancy and improved general health status lead to an increase in the number of elderly patients eligible for liver resection.

These developments stress the need to determine the influence of advanced age on the outcome after liver resection. Age-associated decline in liver volume, hepatic blood flow, and regenerative capacity might be responsible for higher risks associated with liver resections in elderly patients.[5] Nevertheless, several observational cohort studies addressed this issue and have failed to show age to be an independent risk factor influencing short- and long-term survival after liver resections.[6–11] These observational

cohort studies included a mix of wedge, minor, and major liver resections, and retrospectively compared study groups based on patient age at the time of liver resection. This study design may include a selection bias in terms of diagnosis and magnitude of liver resection.

The aim of this study is to assess the short- and long-term outcome of liver resections in the elderly in a matched control analysis. In order to address the shortcomings of the earlier mentioned studies, a homogeneous cohort of patients undergoing major liver resections for primary or secondary tumors in otherwise normal liver parenchyma was chosen.

Patients and Methods

Between December 1978 and December 2006, 628 consecutive patients underwent a primary liver resection in our institution. Their medical data were collected in a database. The patient variables included patient demographics, operative data, pathology data, and follow-up data concerning morbidity and survival. Follow-up was completed until December 31, 2006.

From this database, 236 patients (37.6%) were over the age of 60 at the time of liver resection. Of these patients, 74 underwent a resection of less then three Couinaud's segments[12] and were therefore excluded. A further 30 patients, treated for Klatskin tumors, were also excluded as this aggressive type of tumor tends to result in a different short- and long-term outcome compared to other primary or secondary hepatic malignancies.[13,14] Another argument to exclude patients treated for Klatskin tumors was the prolonged preoperative cholestasis resulting in parenchymal changes.

Therefore, the study group consisted of the remaining 132 patients over 60 years of age. Of these patients, 93 could be matched with a control group of patients aged less than 60 years at the time of liver resection. Patients were matched on a one-to-one basis with control patients with the same type of tumor and the same type of liver resection according to Couinaud segments. In case of more than one potential match, the control patient who underwent the liver resection at a date closest to the operation date of the match was selected in order to minimize any potential historical bias. All included patients had non-cirrhotic parenchyma.

An exact match could not be found for 39 patients. The demographic data of these 39 unmatched patients were compared with the data of the matched patients to assess a potential selection bias.

Data about pre- and postoperative treatment protocols and techniques of liver resections have been published in earlier reports by this group.[13,15]

Study Variables

Study variables were age, gender, American Society of Anaesthesiologists (ASA) score, type of tumor, type of resection, intraoperative blood transfusions, and resection margin status. Type of tumor was divided in colorectal metastasis, hepatocellular carcinoma, or other malignant or benign tumors. In concordance with recent literature,[10] intraoperative blood transfusions were noted as less than three packed cells or three or more packed cells transfused peroperatively. Resection margin status was defined as R0 resection when all surgical margins were microscopically free of tumor cells, R1 resection when tumor cells were identified on light microscopy in one or more of the margins, and palliative resection when macroscopic tumor was left behind in one or more of the margins or outside the liver. R0 resections were considered radical, and R1 and palliative resections were considered irradical.

Outcome Parameters

Outcome parameters were patient survival, disease-free survival, in-hospital mortality, and postoperative morbidity and reinterventions. Patients with benign tumors and patients with palliative resections were excluded when computing disease-free survival. Patient survival was defined as time between the operation date and the date of patient death. Surviving patients at the end of the study period were censored. Disease-free survival was defined as the time between the operation date and the date of tumor recurrence. Recurrence was proven histological by imaging studies or by compelling clinical suspicion. Patients without evidence for recurrence were censored after the end of the study period. Mortality was defined as in hospital mortality during the initial hospitalization for the liver resection. Postoperative morbidity was assessed by analyzing the incidence of bleeding, hepatic, biliary, lung, wound, and infectious complications. Postoperative morbidity was expressed as the proportion of patients with any of these complications. The length of postoperative intensive care unit (ICU) stay, as well as the length of hospital stay, was recorded.

Study Design and Statistical Methods

In order to assess differences in baseline characteristics between the matched patients and the control patients, study variables were compared. Since not all patients over 60 years of age could be matched, a potential selection bias existed. Therefore, the 93 matched patients and the 39

unmatched patients were also compared. To assess a potential historical bias, the difference in operation date between the matched patients and the control patients was assessed.

In order to assess differences in outcome between the matched patients and the control patients, outcome parameters were compared. The influence of the study variables on overall outcome was assessed in a univariate analysis in a unified model of matched and control patients. Parameters with a p value <0.10 as well as age, being the parameter of paramount interest in this study, were entered into a Cox regression analysis in a backward likelihood manner for multivariate analysis.

Categorical and continuous variables were compared using the Pearson chi-square test and the Mann–Whitney U test where appropriate. Survival analyses were performed by the Kaplan–Meier method, and comparisons were made using the log-rank test.[16] A significant difference was defined as a p value <0.05.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 14.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Demographics

Patient demographics and operative characteristics are shown in Table 1. Mean age difference between the matched and the control patients was 16.7 years (SD, 9.2 years). The operation date of the matched patients was on average 1.2 years (SD, 3.4 years) later, compared to the operation date of the control patients. The difference between operation dates was below 5 years for 95% of the matches.

As expected, significant differences between the matched and the control patients were found regarding age but also regarding ASA status $p<0.001$. Since only two patients were ASA grade 4, grades 3 and 4 were combined in one group. Of the matched patients, 24% were ASA grade 3 or 4 versus 8% of the control patients. Of the control patients, 49% were ASA grade 1 versus 22% of the matched patients.

Significant differences between the matched and the unmatched patients were found regarding the type of tumor

Table 1 Patient Demographics and Operative Characteristics

	Matched elderly, $n=93$	Control group, $n=93$	p value matched versus control	Unmatched elderly, $n=39$	p value matched versus unmatched
Median age range, years	66 (60–82)	52 (19–59)	<0.001[a]	68 (61–78)	n.s.[a]
Gender, n %					
Male	49 (53)	55 (59)	n.s.[a]	24 (62)	n.s.[a]
ASA grade, n %			<0.001[b]		n.s.[b]
Grade 1	21 (23)	47 (51)		11 (28)	
Grade 2	48 (52)	39 (42)		15 (39)	
Grade 3 or 4	24 (26)	7 (8)		12 (31)	
Type of disease			n.s.[b]		0.010[b]
Colorectal metastasis	70 (75)	70 (75)		25 (64)	
Hepatocellular Carcinoma	15 (16)	15 (16)		3 (8)	
Other malignant disease	3 (3)	3 (3)		7 (18)	
Benign disease	5 (5)	5 (5)		4 (10)	
Type of resection			n.s.[b]		0.002[b]
Right trisectionectomy S 4, 5, 6, 7, 8±1	19 (20)	19 (20)		4 (10)	
Left trisectionectomy S 2, 3, 4, 5, 8±1	4 (4)	4 (4)		1 (3)	
Left hemihepatecomy S 2, 3, 4±1	21 (23)	21 (23)		10 (26)	
Right hemihepatecomy S 5, 6, 7, 8±1	49 (53)	49 (53)		18 (46)	
Other 3 or more segments	0	0		6 (15)	
Resection margin status			n.s.[b]		n.s.[b]
R0	75 (81)	74 (80)		30 (77)	
R1 or R2	9 (10)	12 (13)		3 (8)	
Benign disease	5 (5)	5 (5)		4 (10)	
Missing	4 (4)	2 (2)		2 (5)	
Intraoperative blood transfusion			n.s.[a]		n.s.[a]
Three or more RBCs	29 (31)	24 (26)		9 (23)	

ASA American Society of Anaesthesiologists

[a] Pearson chi-square test

[b] Chi-square test

$p=0.01$. Of the matched patients, 16% had hepatocellular carcinoma HCC versus 8% of the unmatched patients. Of the unmatched patients, 18% had non-colorectal, non-HCC malignancies versus 3% of the matched patients. Gender, resection margin status and intraoperative blood transfusion were not significantly different between the matched patients and the unmatched patients.

Short-term Outcome

Matched Versus Control Patients

Short-term outcome parameters are shown in Table 2. In-hospital mortality was 6.5%. In-hospital mortality was significantly higher in the matched patients compared to the control patients 11% versus 2%, $p=0.017$. Four matched patients versus one of the control patients died because of sepsis. Four matched patients died because of liver insufficiency, compared to one of the control patients. One matched patient died of massive pulmonary embolism and another of pulmonary aspiration.

Unified Model Analysis

Patients with ASA grade 1, 2, or 3/4 had an in-hospital mortality rate of 2.5%, 6.9%, and 14%, respectively $p=0.101$. Gender, type of disease, type of resection, intraoperative blood transfusion, and resection margin status also showed no significant influence on in-hospital mortality.

Overall postoperative morbidity was 39%. Morbidity was significantly higher in the matched patients compared to the control patients 47% versus 31%, $p=0.024$. Morbidity was significantly higher after resections of five or more

Couinaud segments compared to resections of three or four Couinaud segments 59% versus 33%, $p=0.002$, after three or more preoperative transfusions compared to less than three 53% versus 34%, $p=0.017$, and after radical resections compared to irradical resections 62% versus 38%, $p=0.039$. ASA grade, gender, and type of disease showed no significant influence on morbidity.

The overall reintervention rate was 22%. Overall median length of stay in the ICU and hospital were 1 range, 0–45, and 16 range, 5–116 days, respectively. The reintervention rate and length of stay in the ICU and hospital were not significantly different between the matched and the control patients. The reintervention rate was significantly higher in male patients compared to female patients 27% versus 15%, 0.043, in patients undergoing resection of five or more Couinaud segments compared to resections of three or four Couinaud segments 41% versus 15%, $p<0.0005$, and in patients with three or more intraoperative transfusions compared to patients with less than three 32% versus 17%, $p=0.027$. ASA grade, type of disease, and resection margin status showed no significant influence on morbidity.

Long-term Outcome

Matched Versus Control Patients

One-, 3-, and 5-year survival in the matched patients was 81%, 58%, and 42%, respectively. One-, 3-, and 5-year survival in the control patients was 90%, 59%, and 42%, respectively $p=0.558$; Fig. 1. At the end of the study period, 49 53% of the matched patients and 45 48% of the control patients were still alive.

Table 2 ICU/Hospital Stay, Mortality, and Morbidity

	Matched elderly, $n=93$	Control group, $n=93$	p value[a] matched versus control	Unmatched elderly, $n=39$	p value[a] matched versus unmatched
ICU stay, days, mean ± SD	3.6±5.7	3.4±8.7	n.s.[b]	2.5±2.7	n.s.[b]
Total hospital stay, days, mean ± SD	20±12	22±17	n.s.[b]	18±11	n.s.[b]
Mortality, n %	10 (11)	2 (2)	0.017	3 (8)	n.s.
Postoperative morbidity, n %					
Overall	44 (47)	29 (31)	0.024	17 (44)	n.s.
≤4 segments resected	27/70 (39)	19/70 (27)	n.s.	14/34 (41)	n.s.
>4 segments resected	17/23 (74)	10/23 (44)	0.036	3/5 (60)	n.s.
Reinterventions, n %					
Overall	22 (24)	18 (19)	n.s.	8 (21)	n.s.
≤4 segments resected	10/70 (14)	11/70 (16)	n.s.	6/34 (18)	n.s.
>4 segments resected	12/23 (52)	7/23 (30)	n.s.	2/5 (40)	n.s.

[a] Pearson chi-square test
[b] Mann–Whitney U test
ASA, American Society of Anaesthesiologists

Figure 1 Patient survival.
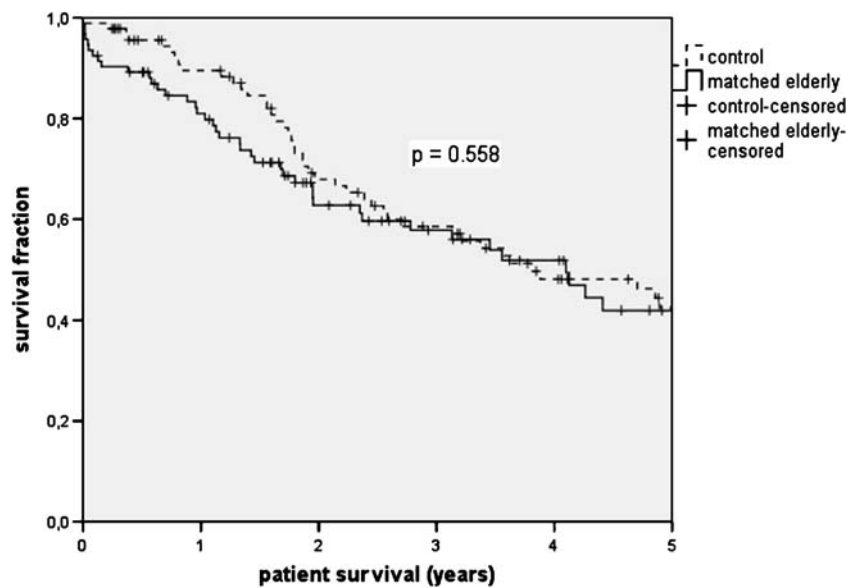
One-, 3-, and 5-year disease-free survival in the matched patients was 63%, 45%, and 39%, respectively. One-, 3-, and 5-year disease-free survival in the control patients was 67%, 35%, and 31%, respectively $p=0.468$; Fig. 2.

Unified Model Analysis

Patient age, ASA grade, gender, and intraoperative blood transfusions showed no significant influence on patient survival. In univariate analysis, colorectal metastatic tumor or hepatocellular carcinoma, resection of five or more Couinaud segments, and irradical resection all significantly correlated with worse patient survival (Table 3).

Patient survival was further analyzed by entering patient age, ASA grade, type of disease, type of resection, and resection margin status as covariables in a multivariate analysis. In Cox regression analysis, resection margin status and ASA grade proved to be independent predictors of patient survival (Table 4).

Univariate analysis of disease-free survival in patients undergoing a radical resection for malignant disease showed that none of the study variables met the conditions to be entered in a multivariate analysis.

Discussion

Demographic studies have indicated a marked increase in life expectancy leading to 19% of the population aged 60 years or over at this moment in Europe and Northern
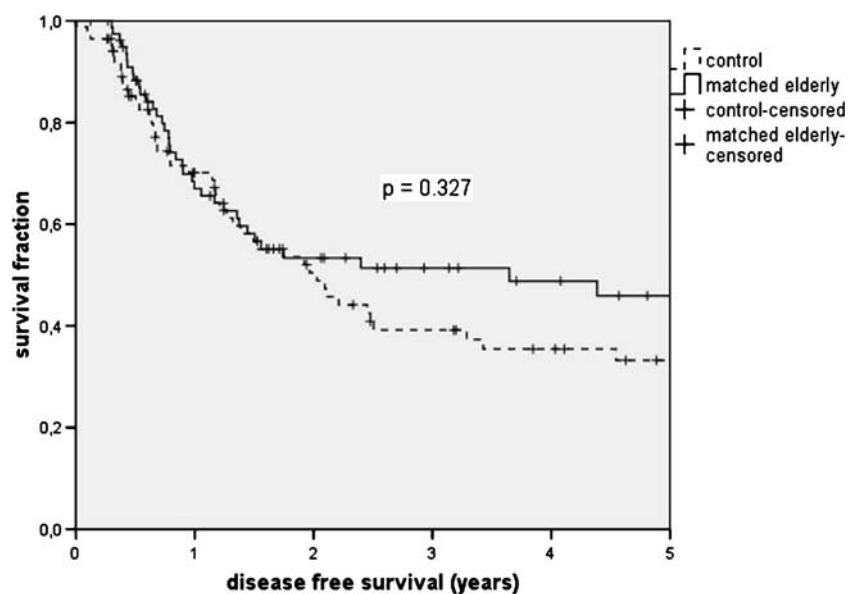
Figure 2 Disease-free survival.

Table 3 Univariate Analysis of Predictors of Patient Survival

	p value
Age <60/60+	0.558
Gender	0.484
ASA grade	0.054
Type of disease	0.041
Type of resection minor/major	0.022
Intraoperative blood transfusion <3/3+ RBCs	0.085
Resection margin status	0.002

America, Australia/New Zealand, and Japan. This figure is expected to increase to 33% in 2050 (http://www.un.org/esa/population/publications/aging99/fa99.htm). Epidemiologic surveys show over 50% of primary and secondary hepatic malignancies to occur in patients over 65 years (http://seer.cancer.gov), and liver surgery is the mainstay of curative treatment for these tumors.[17] It is therefore important to assess the influence of age on outcome after liver surgery. Previous studies addressing this issue have compared cohorts of elderly patients with younger patients treated in the same time period (Table 5).[6–11,18] However, comparing cohorts introduces a potential selection bias due to heterogeneity of patients and operative characteristics. In order to maximally reduce selection bias in this study, a matched control analysis was performed to ensure comparison of elderly and younger patients with the same diagnosis and the same extent of liver resection. Only noncirrhotic patients undergoing a primary liver resection of three or more Couinaud segments were included.

A cutoff point at 70 years of age at the time of liver resection would allow for only 31 patients to be matched one-on-one to a control patient with the same type of liver resection for the same diagnosis. Including such a small number of patients would lead to an underpowered study. With a cutoff point for elderly and younger patients at 60 years of age at the time of liver resection, 93 of the patients over 60 years of age could be matched, which is over 70% of the patients over 60 years of age from this series. This was an important argument in an always arbitrary choice of a cutoff point for elderly and younger patients. The matched patients were not different from the unmatched patients with regard to age, gender, ASA grade, resection margin status, and intraoperative blood transfusions.

Hepatocellular carcinoma was more common in the matched patients, whereas non-colorectal, non-hepatocellular carcinoma was more common in the unmatched patients. This difference results from the fact that these non-colorectal, non-hepatocellular carcinoma have their peak incidence in patients over 60 years of age, so only for a minority of these patients a matching younger control patient could be found.

Mean age difference between the matched patients and the control patients was over 16 years, indicating a clinically relevant age difference. The mean difference in operation date was only 1.2 years, and for 95% of the matches, this difference was below 5 years, showing that no relevant historical bias was introduced.

Besides the obvious difference in age between the matched and the control patients, a significant difference regarding ASA grade was found. A higher proportion of matched patients were ASA grade 3 and a higher proportion of control patients were ASA grade 1. This was the only significant difference in baseline characteristics between the matched and the control patients. However, higher ASA grade could not be significantly correlated to a worse short-term outcome in terms of postoperative morbidity or in-hospital mortality, whereas age above 60 years was related to worse short-term outcome. Patients in ASA grade 3 are particularly represented among the subgroup of patients aged less then 60 years, since a patient over 60 years of age with ASA grade 3 will be more often deemed inoperable compared to a younger patient with ASA grade 3. This selection bias regarding ASA grade might explain the fact that a relation between ASA grade and short-term outcome could not be found in these series.

Short-term outcome was worse in matched patients compared to the control patients. Matched patients had a significantly higher in-hospital mortality rate (11%) compared to control patients (2%) in this study. In both of the control patients and in eight out of ten matched patients, the in-hospital mortality was due to liver insufficiency and sepsis.

The key to explaining the difference in in-hospital mortality might be a slower regeneration rate in patients over 60 years of age, making these patients more prone to liver insufficiency and sepsis. Liver regeneration occurs by inducing hyperplasia in the remnant liver volume. The initiation and synchronization of this regeneration response depends on the extent of liver resection. A substantially higher cellular replication rate is seen after major liver resection compared to minor liver resection.[19,20] An

Table 4 Multivariate Analysis of Predictors of Patient Survival

	p value	Hazard ratio 95% CI
Resection margin		
Radical		
Irradical	0.002	2.44 (1.34–4.42)
ASA		
Grade 1		
Grade 2	0.084	1.61 (0.97–2.66)
Grades 3 or 4	0.016	2.21 (1.16–4.22)
Age		
<60 years		
≥60 years	0.213	1.01 (0.99–1.04)

Table 5 Literature Reports

	Group	Year	Country	Number of patients	3-year survival %		5-year survival %	
					<70 years	>70 years	<70 years	>70 years
CRM	Mazzoni et al.	2007	Italy	144 versus 53			38	30
	Nagano et al.	2005	Japan	150 versus 62			53	34
HCC	Ferrero et al.	2005	Italy	177 versus 64			32	49
	Hanazaki et al.	2001	Japan	283 versus 103			40	42
All indications	Menon et al.	2006	UK	390 versus 127	57	59		
	Cescon et al.	2003	Italy	99 versus 23	54	64		

CRM colorectal metastasis, *HCC* hepatocellular carcinoma

excellent summary of the molecular basis of this process has recently been described by Clavien et al.[21] Animal studies show the process of regeneration to be dependant of mediators similar to those found in acute inflammation. Mediators identified in the process of initiating the cell cycle are cytokines derived from Kupfer cells like tumor necrosis factor α and interleukin-6. After activation of the cell cycle, growth factors like epidermal growth factor, hepatocyte growth factor, transforming growth factor α and β, and other factors like platelet-derived serotonin and bile acids induce, maintain, and finally, terminate a full and synchronized regeneration phase. Lower expression of these mediators in patients over 60 years of age might impair the process of liver regeneration and thereby increase the risk of inadequate recovery of liver volume and lead to higher risks of clinical signs of liver failure after liver resection.

A previous study already showed a correlation between patient age and the risk of liver failure after primary liver resection.[22] Shimada et al. more recently showed a correlation between higher patient age and slower regeneration rate after right hemihepatectomy in humans.[23] In humans, no comparative studies regarding regeneration rate after hepatectomy in elderly versus younger patients have been performed, but Biondo-Simoes et al. recently showed a relevant delay in regeneration rate after major hepatectomy in elderly compared to younger rats.[24] Slower regeneration rates might well explain the higher in-hospital mortality, mostly due to liver insufficiency and sepsis, in patients over 60 years of age.

Despite significantly higher in-hospital mortality in the matched patients, 5-year patient survival was 42% in both groups, and 5-year disease-free survival was 39% in the matched and 31% in younger patients, respectively. These figures are concordant with recent studies showing 5-year patient survival rates of 30% to 49% in elderly patients compared to 32% to 53% in younger patients. This means that, despite the difference regarding short-term outcome, patients over 60 years of age show no difference in long-term outcome compared to younger patients. This suggests

a relatively worse long-term prospect for younger patients surviving the hospitalization phase of a liver resection compared to patients over 60 years of age surviving this phase. While from previous literature it might already been known that long-term outcome is not different between elderly and younger patients, a new observation from this study is the paradox in survival patterns. Younger patients may show a far better in-hospital survival, but in the end, it still leads to the same prospects in terms of long-term survival compared to patients over 60 years of age. In return, the patient over 60 years of age has a higher risk of in-hospital mortality, but this is compensated by a relatively better prospect in terms of long-term survival, which might be due to less aggressive tumor biology in these patients. However, survival analysis showed no difference in patient survival or disease-free survival between younger patients surviving the hospitalization phase of a liver resection compared to patients over 60 years of age surviving the hospitalization phase of a liver resection in our population (data not shown).

Multivariate analysis shows the resection margin status and ASA grade to be independent predictors of long-term patient survival. As indicated in Table 4, ASA grades 3 or 4 patients have an increased chance of long-term mortality compared to ASA grade 1 patients with a hazard ratio of 2.21. Age itself was not an independent predictor of long-term survival.

This finding underlines the obvious statement to strive for tumor-free margins, but it also urges those involved in preoperative patient selection for major liver resections rather to consider the ASA grade than patient age as a predictive factor for long-term survival.

Conclusion

The influence of advanced age on the outcome after liver resection has never been explored in a matched control study. The current study paradoxically shows a worse short-term outcome in patients over 60 years of age in terms of in-

hospital mortality and morbidity, while their overall long-term survival is not different from control patients. This observation confirms the clinical observation that patients over 60 years of age have higher risks after liver resections, while at the same time, this does not result in a difference in long-term outcome. Multivariate analysis shows tumor-free resection margins and lower ASA grade to be independent predictors of long-term patient survival, while age itself was not associated with long-term patient survival.

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