

# Long-Term Quality of Life After Hepatic Resection: Health Is not Simply the Absence of Disease

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## Abstract

**Background** Due to advances in operative methods and perioperative care, mortality and morbidity following major hepatic resection have decreased substantially, making long-term quality of life (QoL) an increasingly prominent issue. We evaluated whether postoperative diagnosis was associated with long-term QoL and health in patients requiring hepatic surgery for benign or malignant disease.

**Methods** QoL was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 and the liver-specific QLQ-LMC21 module.

**Results** Between 2002 and 2006, 249 patients underwent hepatic surgery for malignant (76%) and benign (24%) conditions. One hundred thirty-five patients were available for QoL analysis after a mean of 26.5 months. There was no statistical difference in global QoL scores between patients with malignant and benign diseases ( $p = 0.367$ ). Neither the extent of the resection ( $\geq 2$  segments vs.  $< 2$  segments;  $p = 0.975$ ; OR = 0.988; 95% CI = 0.461–2.119) nor patient age had a significant influence on overall QoL ( $p = 0.092$ ).

**Conclusions** These results indicate that long-term QoL for patients who underwent liver resection for malignant disease is quite good and that a poor clinical prognosis does not seem to correlate with a poor QoL.

## Introduction

Quality of life (QoL) is a subjective multidimensional concept that is dynamic over time and encompasses a broad range of domains, including physical, functional, social, and emotional well-being [1]. The sum of these components does not necessarily equal the subjective assessment of general overall QoL [1, 2]. For example, there will be some cancer survivors who report a greater number of physical problems such as pain, restriction in physical activities, or sexual dysfunction (i.e., more specific problems than their healthy counterparts) who nevertheless report to have relatively good, general, subjective health, especially with regard to mental health and social and psychological well-being compared to their matched controls [3, 4]. Care needs to be taken, however, with regard to these findings and their consequent conclusions, as they certainly cannot be applied to all cancer patients. For health professionals and bystanders, there seems to be a discrepancy between reported health-related problems and the patient's judgment of his/her overall health status. The general question, "on the whole, how would you judge your health to be," gets answered more positively than would be expected.

Due to recent advances in operative methods and perioperative care, in specialized liver units postoperative mortality after major hepatic surgery has decreased from 20% to less than 5% and major morbidity has decreased proportionally. As a result, the indications for and extent of liver resection (LR) have been dramatically expanded [5–11]. Age no longer appears to be a contraindication to major hepatic surgery as recent studies have demonstrated favorable outcomes, even for elderly patients [12–14]. These facts, combined with increasingly prolonged survival following LR for hepatocellular carcinoma (HCC),

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cholangiocarcinoma, or colorectal metastases, have contributed to the establishment of new standards [15–20]. What was once considered experimental and extreme now represents standard procedure in high-volume hepatobiliary centers [21]. With this reduced morbidity and increased posthepatectomy survival, QoL has become a leading issue, as important as disease-free or overall survival [22].

Until now, no studies have addressed the potential differences in long-term QoL in patients who have undergone LR for benign versus malignant conditions. Our aim was to investigate whether postoperative diagnosis affected long-term self-estimated QoL and health in these patients.

## Materials and methods

This cross-sectional study included 249 consecutive patients who underwent liver resection for malignant or benign disease at our Department of Visceral Surgery and Medicine between January 2002 and June 2006. Exclusion criteria included death, undergoing only liver biopsy, or an incomplete medical file. Of the surviving 156 patients, 135 were available for QoL assessment by means of a telephone interview, with the questions and possible answers being read to them by an independent researcher.

Patients who at the time point of the interview had undergone LR less than half a year before were excluded from further analysis in order to avoid early specific postoperative problems (i.e., surgical complications) confounding QoL assessment. There was no limit regarding the maximum time postsurgery after which a patient was questioned.

To assess QoL, we used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30, version 3.0), which is a cancer-specific QoL instrument originally used in cancer clinical trials. It contains five functional scales, including physical, role, social, emotional, and cognitive functions, as well as questions specifically aimed at checking for symptoms often reported by cancer patients (fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation/diarrhea). The financial impact that the disease has on the patient is also taken into account. The questionnaire consists of 30 items of which 28 items have a 4-point scale and 2 items have a 7-point scale for the overall QoL and health measure [23].

The QLQ-LMC21 consists of 21 items, each of which has a 4-point scale. The QLQ-LMC21 was initially devised to be used for patients with colorectal liver metastases because the general EORTC QLQ-C30 questionnaire did not adequately address problems specifically associated with hepatic metastases. Question categories include items on food intake, weight loss, pain, jaundice, fatigue, social

problems, anxiety, and the influence of the disease on sexual activity [24]. Because approximately one-third of our patients required LR for metastatic colorectal disease, we used the QLQ-LMC21 questionnaire to better address hepatobiliary symptoms. Official validation of the QLQ-LMC21 is still required, although an international validation study is complete and data analyses are underway. The provisional scoring system provided by the EORTC (very similar to the already validated QLQ-C30, version 3.0) was used in this study.

## Ethical considerations

Ethical approval was obtained from the University of Bern ethical committee (institutional protocol number 18/08). Written permission was obtained from all study participants. All eligible patients were given details of the study, including contact information of the researcher. Patients were informed about the aim of the study and guaranteed anonymity and confidentiality with regard to the information given to the researcher. A licensing agreement was obtained from the EORTC for use of QLQ-C30, version 3.0 and the LMC21 questionnaires.

## Statistical analysis

All statistical analyses were performed using SAS 9.1 and R 2.5. The scoring method of the EORTC was applied to the QLQ-C30 and the QLQ-LMC21 with mandatory recoding, summing, and transforming of the 30 and the 21 items, respectively.

For distributional analysis, the  $\chi^2$  test or Fisher's exact test was applied for categorical data and the MannWhitney *U* test was used for continuous data. Regarding model fitting, the ordinary least-squares criterion was used for linear regression analysis between two variables, the significance of which was quantified by analysis of variance (ANOVA). Estimated odds ratios (OR) and their confidence intervals (CI) were derived by fitting an ordered logistic regression model to the data and checking the proportional odds assumption adequacy with the score test. A two-tailed *p* value of less than 0.05 was considered statistically significant. All statistical analyses were carried out with professional help from the Institute of Mathematical Statistics and Actuarial Science, University of Bern, Bern, Switzerland.

## Results

Of the 249 complete patient files, all but 7 patients (2.8%) could either be tracked down directly or their postoperative course be accounted for with the help of the family

physician or the treating oncologist. Of these 242 patients, 86 patients had died in the interim, mostly due to the underlying disease for which hepatic resection was initially required. Nine patients died during the initial hospitalization. Of these, five died of multiorgan failure, one of liver failure, two of acute cardiac failure, and one patient died intraoperatively due to extensive hemorrhage in the setting of a severe polytrauma. Of the surviving 156 patients, 135 (86.5%) could be contacted by phone for further evaluation. All of these 135 patients consented to answering the EORTC QoL questionnaire. The mean interval between the initial surgical intervention and completion of the QoL questionnaire was 26.5 months (standard deviation [SD] = 16.2). Patient demographics are summarized in Table 1.

Table 2 summarizes the indications for hepatic surgery for all 249 patients, for the 135 patients participating in the QoL survey, and the 21 surviving patients who could not be reached for the QoL analysis. Of the initial study population, most resections were done for malignant diseases ( $n = 189$ , 76%), and approximately one-quarter of the patients underwent hepatic surgery for benign diseases ( $n = 60$ , 24%). Of the 135 patients who completed the QoL questionnaire, 89 patients (66%) suffered from

malignant disease and 46 patients (34%) had benign disease.

Of the patients who completed the QoL survey, 110 required resection of two or more segments and 25 had minor resections (less than two complete segments according to Couinaud) [25]. Most patients had a laparotomy and three patients (2.2%) had laparoscopic surgery. Figure 1 summarizes the extent of the hepatic resections performed.

Although there was no statistical difference in the overall self-estimated global QoL and health scores between patients with malignant and benign diseases ( $p = 0.367$ , Table 3), of the 26 scales and items assessed, patients with malignant diseases fared significantly worse in 9 points. In detail, analysis of the EORTC functional scales (ordered logistic regression) revealed that patients with malignant diseases fared worse in three of the five scores, with statistically significant worse results regarding social function ( $p = 0.014$ ), physical function ( $p = 0.007$ ), and role function ( $p = 0.046$ ). Patients who required resection for malignant lesions also had worse symptom scores for fatigue and pain ( $p = 0.007$  and 0.010, respectively). Evaluation of the liver-specific LMC21 score revealed worse pain scores ( $p = 0.042$ ),

**Table 1** Patient demographics and comorbidities

Demographics	Malignant ( $n = 89$ )	Benign ( $n = 46$ )	Alive but not reached <sup>f</sup> ( $n = 21$ )
Median age (years) (range)	62 (36–81)	51.5 (19–77)	<b>59 (35–82)*</b>
Gender ratio (male: female)	1.34 (51:38)	0.59 (17:29)	2:1 (14:7)
ASA (I:II:III)	2:46:41	7:27:12	0:11:10
Mean BMI ( $\text{kg}/\text{m}^2$ )	23.6	22.9	24.7
Cardiovascular disease <sup>a</sup> (%)	35 (39.3)	12 (26.1)	10 (47.6)
Pulmonary disease <sup>b</sup> (%)	17 (19.1)	4 (8.7)	4 (19.0)
Diabetes mellitus <sup>c</sup> (%)	8 (9.0)	3 (6.5)	1 (4.8)
Chronic renal disease <sup>d</sup> (%)	3 (3.4)	0 (0.0)	1 (4.8)
Other debilitating comorbidities <sup>e</sup> (%)	10 (11.2)	3 (6.5)	5 (23.8)
Number of patients with comorbidities (%)	50 (56.2)	17 (37.0)	15 (71.4)
Median hospital stay in days (range)	13 (7–43)	11 (3–47)	<b>17 (9–37)**</b>
Resection $\geq 2$ segments (%)	77 (86.5)	33 (71.7)	13 (61.9)
Resection $< 2$ segments (%)	12 (13.5)	13 (28.3)	8 (38.1)

<sup>a</sup> Cardiovascular disease was defined as the presence of a disorder of the heart or vessels, such as arrhythmia or arterial hypertension, that required medication, the presence of a pacemaker, cardiac valve disease, coronary heart disease, peripheral arteriosclerosis

<sup>b</sup> Pulmonary disease was defined as the presence of abnormal lung-function tests and included asthma, COPD

<sup>c</sup> Diabetes mellitus as defined by the World Health Organization criteria

<sup>d</sup> Chronic renal disease requiring regular dialysis

<sup>e</sup> Other comorbidities include severely debilitating diseases resulting in a reduced health status, such as severe depression requiring constant medication or intermittent in-hospital or ambulatory treatment, severe polyarthritis, advanced stages of Parkinson's disease

<sup>f</sup> Statistically significant differences in sociodemographic values are in bold. \*  $p < 0.05$  when comparing the age of patients with benign diseases to that of patients with malignant diseases and to the 21 patients alive but who had not completed the QoL questionnaire. \*\*  $p = 0.019$  when comparing median hospital stay of patients with benign diseases to that of the 21 patients alive but who had not completed the QoL questionnaire. All other intergroup comparisons do not show any significant differences

**Table 2** Indications for hepatic surgery

Hepatic lesion <sup>a</sup>	All patients <sup>b</sup> [n (%)]	QoL patients <sup>c</sup> [n (%)]	QoL patients not reached <sup>d</sup> [n (%)]
Metastatic colorectal cancer	77 (30.9)	37 (27.4)	7 (33.3)
Other metastatic disease	40 (16.1)	22 (16.3)	3(14.3)
Neuroendocrine tumor	11	7	
Pancreatic cancer	6	1	1
Adrenal gland	5	4	
Leiomyosarcoma	3	3	
Breast cancer	3	2	
Melanoma	3	1	
GIST <sup>d</sup>	2	1	1
Gastric cancer	2	1	1
Uterine cancer	2	1	
Teratoma	1	1	
Thyroid cancer	1	0	
Cholangiocarcinoma	34 (13.7)	15 (11.1)	3 (14.3)
Hepatocellular carcinoma	24 (9.6)	9 (6.7)	3 (14.3)
Other malignancies	14 (5.6)	6 (4.4)	0
Gallbladder carcinoma	4	2	
Liposarcoma	3	2	
Hepatoblastoma	1	1	
Angiosarcoma	1	0	
Local invasion of gastric cancer, renal cancer, mesothelioma, squamous cell carcinoma, GIST	1 each	1 GIST	
Trauma	6 (2.4)	4 (3.0)	0
Echinococcus	17 (6.8)	15 (11.1)	1 (4.8)
Benign tumors	37 (14.9)	27 (20)	4 (19)
Cysts	11	9	1
Hemangioma	7	4	1
Focal nodular hyperplasia	6	6	
Adenoma	3	1	1
Abscess	2	1	
Chronic hepaticolithiasis	2	2	
Pseudolipoma, epitheloid tumor, hilar stricture, sarcoidosis, Caroli's disease, insulinoma	1 each	1 Hilar stricture 1 Sarcoidosis 1 Pseudolipoma 1 Epitheloid tumor	1 Insulinoma

GIST gastrointestinal stromal tumor

<sup>a</sup> All diagnoses were based on postoperative pathology reports

<sup>b</sup> Includes the initial study population of 249 patients

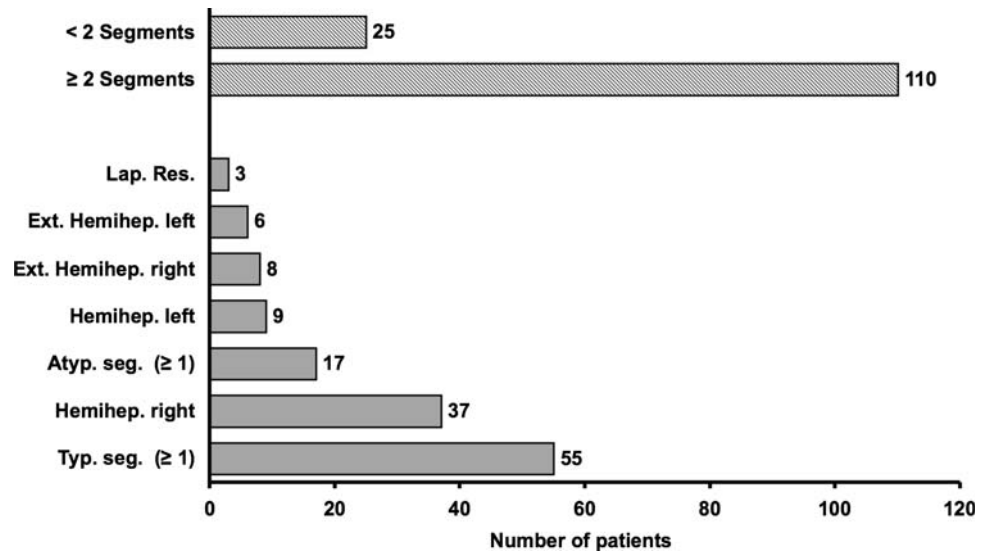
<sup>c</sup> Includes the subpopulation of 135 patients who completed the QoL assessment

<sup>d</sup> Includes the 21 patients who are known to still be alive but who could not be reached for QoL analysis

increased worries regarding weight loss ( $p = 0.035$ ), and more taste problems ( $p = 0.007$ ) and peripheral neuropathy ( $p = 0.018$ ) for patients with malignant diseases. For two items in the QLQ-C30 questionnaire (diarrhea, financial problems) and three items in the LMC21 questionnaire (fatigue, social relations, and anxiety scale), there was a tendency toward patients with malignant diseases having worse scores, although not statistically significant. Neither the extent of the resection ( $\geq 2$  segments vs.  $< 2$  segments;  $p = 0.975$ ; OR = 0.988; 95% CI = 0.461–2.119; Table 3) nor patient age significantly influenced overall QoL and health ( $p = 0.092$ ; Fig. 2a).

Subgroup analysis of patients with extended ( $\geq 2$  segments) versus limited surgery ( $< 2$  completed segments) revealed that patients who underwent extended resection had a significantly decreased social function score ( $p = 0.020$ ), a worse symptom item (constipation,  $p < 0.001$ ), and an impaired eating scale as defined using the LMC21 questionnaire ( $p = 0.031$ ). Not surprisingly, older patients had significantly lower physical and cognitive scores than younger patients ( $p < 0.001$  and  $p = 0.032$ , respectively; Fig. 2b, c); however, emotional ( $p = 0.704$ ), social ( $p = 0.271$ ), and role function ( $p = 0.051$ ) scores were not significantly different.

**Fig. 1** Types of liver resections performed. A summary is given of all the liver resections performed in the 135 patients taking part in the QoL study. The patients are divided into extent of resection ( $<2$  segments vs.  $\geq 2$  segments) and then into the exact anatomical resection performed. Lap. Res. = laparoscopic resection; Ext. Hemihep. left = extended hemihepatectomy left; Hemihep. left = hemihepatectomy left; Atyp. seg. = atypical segment resection; Hemihep. right = hemihepatectomy right; Typ. seg. = typical segment resection



## Discussion

Our data show that patients who underwent LR for malignant disease fared no worse than their counterparts with benign disease as far as general, global, self-assessed QoL and overall self-assessed health were concerned despite significantly worse results in nine items/scales. Not unexpectedly, however, patients with malignant diseases fared worse with regard to physical function scores, specifically reporting more pain and also having worse social function scores, suggesting a certain social isolation due to the underlying disease and the often long therapies involved.

Similar to our global QoL findings, a recent study compared health-related QoL for liver cirrhosis patients with and without HCC [26] and found no difference in QoL for patients with HCC compared to patients suffering from cirrhosis alone. This could have been due to the extensive preoperative information provided to patients that mentally prepared them for possible malignancy and to the minimally invasive, less-stressful nature of the therapies used for treating HCC. One might assume that once patients have come to terms with their diagnosis, their attitude toward life in general, and with it their self-assessed QoL, might improve. This is reflected by the fact that the patients who underwent resection for malignant diseases in our study population still judge their overall health as being good despite having more pain, more fatigue, more symptoms associated with chemo-/radiotherapy (problems with taste and peripheral neuropathy), and worse social and role function. There seems to be a certain discrepancy between the significantly lower subscores, which imply increased patient discomfort and suffering, and the quite high global QoL scores. This also contrasts with how physicians estimate the QoL of the patients they treat. A

study assessing QoL in patients with chemotherapy-resistant colorectal cancer revealed that the scores judged by the treating physician, using the visual analog scale, were 12% lower than the patients' ratings [27]. Other studies, including palliative-care evaluations, also showed a great discrepancy between patient-assessed and physician-assessed QoL [28–30].

The concept of hope, an aspect rarely talked about or taken into account by physicians, is an important notion that makes most patients willing to accept toxic chemotherapy for minimal benefit in terms of overall survival [31]. Perez et al. [32] studied patients with metastatic cancer to determine how many of their patients were willing to trade survival time in order to gain QoL. Astonishingly, only 37% of patients were prepared to trade quantity for quality. The willingness to trade was independent of whether the cancer was progressing, the length of time since the diagnosis of metastatic cancer was made, age, education, or religious beliefs.

Extended LR ( $\geq 2$  segments) versus limited LR ( $<2$  segments) did not result in a worse overall QoL, although subset analysis of different symptoms did reveal a reduced symptom score and more problems with eating for patients who underwent extended resection. Because most of our patients had undergone surgery more than two years before the administration of the QoL questionnaire, it might seem reasonable to expect similar overall QoL scores regardless of the extent of the initial surgery. A recent study compared QoL and return to baseline for patients who underwent major and minor LR [33] and found, as one might expect, that there was a quicker return to baseline QoL for patients who underwent minor surgery. Nevertheless, patients who needed extensive surgery returned to their individual preoperative QoL within 6 months of surgery. Our data fit nicely with these results, illustrating the need to reassure

**Table 3** EORTC QLQ-C30 and LMC21 questionnaire - results

	Benign	Malignant	<i>p</i>	<2 seg.	≥2 seg.	<i>p</i>
<b>EORCT QLQ-C30</b>						
Global health status/QoL	71.7(17.4)	65.4(16.2)	0.367	67.7	67.5	0.975
<i>Functional scales<sup>a</sup></i>						
Emotional function	70.8	66.6	0.529	63.6	69.0	0.512
Cognitive function	67.6	68.2	0.927	74.1	66.6	0.299
Social function	78.3	62.7	<b>0.014</b>	82.8	64.6	<b>0.020</b>
Physical function	80.3	61.6	<b>0.007</b>	76.9	66.0	0.201
Role function	76.8	63.5	<b>0.046</b>	71.1	67.3	0.642
<i>Symptom scales/items<sup>b</sup></i>						
Fatigue	55.6	74.4	<b>0.007</b>	62.1	69.4	0.389
Nausea and vomiting	63.9	70.1	0.213	70.2	67.5	0.659
Pain	62.4	78.8	<b>0.010</b>	58.0	70.3	0.114
Dyspnea	64.7	69.7	0.395	64.0	69.0	0.492
Insomnia	65.2	69.5	0.500	71.8	67.1	0.547
Appetite loss	63.4	70.4	0.162	69.7	67.6	0.724
Constipation	71.6	65.4	0.255	62.9	87.5	<b>&lt;0.001</b>
Diarrhea	61.5	71.4	0.085	67.0	68.2	0.862
Financial problems	72.6	65.6	0.085	65.0	68.7	0.458
<b>LMC21</b>						
<i>Symptom scales<sup>b</sup></i>						
Eating scale	70.8	66.6	0.501	54.5	71.1	<b>0.031</b>
Pain scale	63.3	77.2	<b>0.042</b>	64.6	68.8	0.622
Fatigue scale	59.6	72.4	0.066	58.5	70.2	0.171
Social relations scale	60.0	71.3	0.080	64.0	68.3	0.580
Anxiety scale	59.2	71.7	0.075	66.9	67.7	0.926
<i>Single items<sup>b</sup></i>						
Worry about weight loss	63.0	70.6	<b>0.035</b>	61.5	69.5	0.072
Problems with taste	59.3	71.6	<b>0.007</b>	67.1	67.6	0.936
Dry mouth	62.5	70.0	0.199	61.6	68.8	0.313
Sore mouth/tongue	67.0	68.5	0.750	65.2	68.7	0.531
Peripheral neuropathy	58.0	72.3	<b>0.018</b>	57.7	69.8	0.101
Jaundice	66.4	68.9	0.414	63.5	69.0	0.140

Values are mean ranks (SD of the ranks), *p* < 0.05 is considered significant and in bold

<sup>a</sup> Higher scores indicate better function

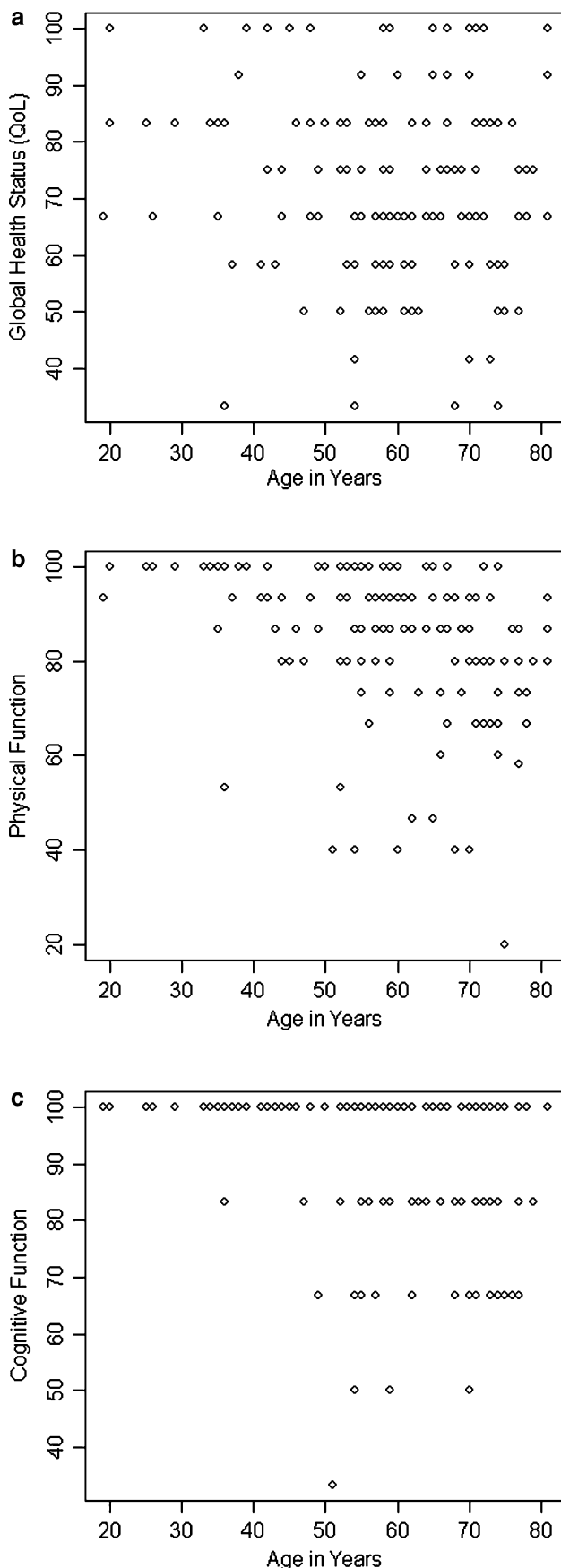
<sup>b</sup> Higher scores indicate more symptoms

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30, version 3.0) is a cancer-specific QoL instrument. The QLQ-LMC21 was initially used in patients with colorectal liver metastases. The QLQ-C30 consists of 30 items, of which 28 have a 4-point scale and two have a 7-point scale for the overall QoL and health measure. In analog, the QLQ-LMC21 consists of 21 items, each item being made up of a 4-point scale. The scoring method of the EORTC was applied with mandatory recoding, summing, and transforming of the 30 respective 21 items

patients that although initial QoL will deteriorate postoperatively, longer-term outcomes are very encouraging. Indeed, Chen et al. [34] showed that not only did the QoL of patients who underwent LR for primary liver cancer recover after surgery, but QoL was better 9 months post-surgery than before the LR.

Certain aspects of the study design might limit interpretation and merit further discussion. For example, there

is the potential for patients to rate their QoL better than reality when answering a QoL questionnaire. Self-administered questionnaires can be a disadvantage to patients with limited literacy and the information gathered may be incomplete [35]. Because the “need to please” is likely to affect all patients similarly, artificial differences within the subgroup analyses seem unlikely. In addition, because we did not have a preoperative, pretherapy QoL questionnaire



◀**Fig. 2** **a** Scatterplot with the EORTC QLQ-C30 overall global health status, respectively, the self-judged QoL. Age does not influence overall QoL assessment. This is true for all age categories, ranging from very young to very old patients. **b** Scatterplot with the EORTC QLQ-C30 physical score as a function of age. The older the patient, the more restricted his or her physical abilities are. **c** Scatterplot with the EORTC QLQ-C30 cognitive score as a function of age. As might be expected, the cognitive function is reduced with age ( $p = 0.032$ )

with which to compare, it is difficult to deduce which patients might have had a low baseline QoL that was largely independent of the liver resection, influenced more by concomitant diseases or other nonclinical factors. We are currently conducting a study in which all patients who are to undergo hepatic surgery are administered the EORTC QoL questionnaire preoperatively and at defined intervals postoperatively. This will allow us to compare preoperative QoL with short-term postoperative QoL, and it will allow us to follow the evolution of postoperative QoL over time. Ultimately, these data might enable us to provide more patient-tailored postoperative follow-up and care in the future.

Good health is a state of physical, mental, and social well-being and not merely the absence of disease or infirmity. Because a person’s expectations with regard to his/her health and ability to cope with disabilities and restrictions can dramatically affect the perception of health and overall satisfaction with life, two patients with the same objective health status may have truly different QoLs. Likewise, patients whose health statuses are objectively different may rate their QoLs similarly. Healthier patients are not necessarily happier patients.

Our results demonstrate that irrespective of their underlying malignant diseases, patients who have undergone hepatic resection for primary or secondary malignancies will judge their overall QoL as being similar to that of their peers who were treated for benign diseases, despite faring substantially worse in a significant amount of subitems according to the two EORTC questionnaires used. However, care needs to be taken regarding the interpretation of these global QoL scores, because although patients with benign disease and patients with malignant disease may have similar scores, the exact interpretation of these findings is uncertain and does not automatically imply equal findings. The global QoL score should therefore not be interpreted in isolation of the other subscores. Our results, however, suggest that carefully selected patients might benefit from more aggressive surgery.

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