Quality of life after hepatic resection

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Original Article

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Footnote: The study was preregistered on ClinicalTrials.gov (NCT00681499).

Abstract

Background:

Long-term quality of life (QoL) after liver resection (LR) is becoming increasingly important, as improvements in operative methods and perioperative care diminished in morbidity and mortality. In this study, postoperative QoL after LR for benign or malignant tumors was evaluated.

Methods:

In this single center study, QoL was evaluated prospectively using the EORTC QLQ-C30 and the liver-specific QLQ-LMC21 module preoperatively and 1, 3, 6 and 12 months after open or laparoscopic liver surgery.

Results:

Between 06/2007 and 01/2013 n=188 patients (malignant n=130, benign n=58) requiring major LR were included. Global health status was equally bad in both groups preoperatively and one month after LR. All patients showed an improvement in global health status at 3, 6 and 12 months post operation. Patients with benign tumors had better global health status than those with malignant tumors during the same periods (p<0.001, p = 0.002, p = 0.006, respectively). Patients with benign disease had better physical functioning scores at 3, 6 and 12 months (p=0.011, p=0.025, p=0.041) and lower fatigue score at 3, 6 and 12 month compared to patients with malignant disease (p=0.001, p=0.002, p=0.002).

Conclusion:

This study confirms overall good QoL in patients undergoing LR for benign or malignant tumors which improved after surgery. Benign diseases were associated with better short and long-term QoL scores after LR.

Introduction

Advances in surgical technique, anesthesiology and perioperative care have resulted in a decrease in postoperative mortality and morbidity after major hepatic surgery in specialized liver units [1, 2]. As a result, the indications for and the extent of liver resections (LR) are being expanded [3-5] with "patient-tailored" medicine and individualized resection strategies becoming increasingly important [6]. Due to these developments, including advances in adjuvant therapies, survival following LR for colorectal metastases as well as hepatocellular carcinoma (HCC) and cholangiocarcinoma, have increased in the last decades [7-11]. With reduced morbidity and increased post-hepatectomy survival, quality of life (QoL) becomes a leading issue and, particularly from a patient's point of view, as important as disease-free or overall survival [12-14].

The term "Quality of life" (QoL) is used more frequently and tries to capture aspects of patient care and therapeutic goals previously not taken into account. QoL is subjective, multidimensional and dynamic over time, continuously fluctuating as it responds to life events. It includes a variety of domains and parameters, including physical, functional, social, and emotional well being. Interestingly, the sum of these components does not necessarily equal the subjective assessment of overall QoL [15]. Although patients with malignant diseases may more often complain about physical problems such as pain and restriction in physical activities compared to healthy individuals, they may nevertheless report a relatively good overall QoL. For health professionals and bystanders, there seems to be a discrepancy between reported health-related problems and the patient's personal judgment of overall health status.

A retrospective study evaluating postoperative QoL in patients undergoing LR for benign or malignant liver tumors was published previously. Interestingly, the study did not show a correlation between poor prognosis and postoperative QoL, a finding that may come as a surprise, considering the nature of certain illnesses [16]. However, the retrospective design of the study and missing preoperative baseline QoL scores may have formed an impediment to correct interpretation of the data. Until now, no prospective studies have addressed the potential differences in long-term QoL in patients who have undergone LR for benign compared to malignant diseases [17]. The aim of this study was to investigate the effect of LR on QoL in patients undergoing surgery for benign or malignant tumors.

Materials and Methods

This prospective study included patients who underwent open or laparoscopic LR for benign or malignant tumors at the Department of Visceral Surgery and Medicine at the Inselspital, University Hospital in Bern, Switzerland between 06/2007 - 01/2013. Major LR was defined as removal of ≥ 3 neighboring segments. Exclusion criteria were age under 18 years, hepatobiliary surgeries only involving a liver biopsy, failure to perform a liver resection due to unexpected intraoperative findings or declined informed consent. All participants had a detailed preoperative briefing of the study and questionnaires involved. All participants in the study received the questionnaires preoperatively and after 1, 3, 6 and 12 months post surgery.

Quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30, version 3.0). This cancer-specific QoL instrument was originally used in clinical trials involving patients with cancer. 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 have a 4-point scale; 2 items have a 7-point scale for the overall QoL and health measure [18]. In addition the QLQ-LMC21 was used. This questionnaire consists of 21 items, each of which has a 4-point scale. The QLQ-LMC21 was initially designed 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 [19].

Ethical considerations

Ethical approval was obtained from the University of Bern ethical committee (institutional protocol number KEK 18/08). The study was also registered on ClinicalTrials.gov (NCT00681499). 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 were 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

Primary and secondary outcomes based on multiply imputed data using repeated measures mixed-effects linear regression models adjusted for the baseline characteristics age, sex, jaundice, pruritus, weight loss, nausea, abdominal pain, lack of appetite, ASA Physical Status Classification System (used continuously), diabetes, cardiovascular disorders, pulmonary disorders and other disorders were analysed. The difference in scores between groups is presented with a corresponding 95% CI and p value.

Missing score data were accounted for by multiple imputation assuming missing data to be missing at random. Each score (i.e., global health status, physical functioning, emotional functioning, fatigue and pain) was imputed separately by linear regression

methods based on the tumor type and the following variables: patient age at inclusion, hospital stay in days, ASA Physical Status Classification System (all used continuous), number of resected liver segments, death, relapse, sex, jaundice, pruritus, weight loss, nausea, abdominal pain, lack of appetite, diabetes, cardiovascular disorders, pulmonary disorders, other disorders, (neo)adjuvant chemotherapy, adjuvant radiotherapy, superficial infection, bilioma, pneumonia and other complications (all used categorical). In two cases, the number of segments and in four cases, hospital stay duration was missing. These were imputed along with global health status. Due to the absence of a monotone missing data pattern, we performed multiple imputation by chained equation was performed. In total, twenty imputed data sets were generated and analyzed as described above using Rubin's rules (Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: J Wiley & Sons. 1987). Sensitivity analyses were based on complete data disregarding multiple imputation. All analyses were performed in STATA, release 13 (Stata Inc, College Station, TX).

Results

A total of 196 patients undergoing liver resection between 06/2007 – 01/2013 were initially included in the study. Eight patients were subsequently excluded due to unexpected, intraoperative findings resulting in no liver resection being performed. Thus 130 patients with malignant disease and 58 with a benign pathology were available for final analysis (Table 1 and Table 2). Patients with benign tumors were more often female (p=0.007) and younger (p=0.001) compared to patients with malignant tumors. Furthermore patients with benign disease presented more frequently with nausea (p=0.01), abdominal pain and a lower ASA score. Remaining baseline characteristics revealed no statistical differences between the groups (Table 1).

The amount of liver tissue removed was not different between the groups, with 53% of patients with benign tumors requiring major liver surgery compared to 65% of patients with malignant tumors (p=0.223). Hospital length of stay was significantly longer in patients with malignant disease (p=0.001), (Table 3).

The completeness of the EORTC questionnaires was analysed preoperatively and after 1, 3, 6 and 12 months (data not shown). The completeness 12 months after surgery dropped from 98% preoperatively in both groups to 69% in patients with malignant disease and remained high at 97% in patients with benign disease. Drop out in the early stages was mainly due to patients not willing to take part anymore (because filling in the two questionnaires was "too tedious"). At later time points other factors, such as patient death or loss to follow-up, played a more important role. Eight (6%) patients with malignant tumors deceased within the 12 month follow-up period. No postoperative mortality

occurred in the benign disease group. In n=68 patients, recurrence of the underlying disease was noted.

For the analysis of the QLQ-C30 and QLQ-LMC21 questionnaire, the individual parameters were summarized in the following 5 categories: global health status, physical functioning, emotional function, fatigue and pain.

Global health status (as measured by the QLQ-C30 questionnaire) was equally low in patients with malignant and benign tumors in the preoperative setting and dropped similarly at one month after LR. Global health status improved over time in both groups, with the score gradually increasing again at 3, 6 and 12 months postoperatively. However, patients with benign disease showed a better global health status after 3, 6 and 12 months than to patients with malignant tumors (p<0.001, p=0.002, p=0.006). Also, in both patient groups, global health status was better 12 months after surgery compared to preoperative values (p<0.001 benign, p=0.042 malignant). Patients with recurrent disease did not present with worse global health status (p=0.961) (Figure 1a). Similar results were found in the QLQ-C30 category physical functioning. Both patient groups recovered after an initial drop one month after surgery. Patients with benign disease presented with better physical functioning scores at 3, 6 and 12 months (p=0.011, p=0.025, p=0.041) compared to patients with malignant diseases (Figure 1b). Emotional function according to the QLQ-C30 score was similar in both groups at baseline. Unlike the global health score and physical functioning score, there was no initial decrease in the emotional function score. The emotional functioning score continuously increased up to 12 months after LR, being identical in both groups at the 12-month time point. At 3 and 6 months, patients with benign disease presented with a slightly better emotional functioning score compared to patients with malignant disease (p=0.005, p=0.019) (Figure 1c). Fatigue as a symptom was

identical in both groups at baseline. Fatigue scores increased to a similar extent one month after surgery in all patients and decreased to preoperative values in patients with malignant tumors. However, in patients with benign tumors fatigue was less pronounced at 3, 6 and 12 month compared to the patients with malignant disease (p=0.001, p=0.002, p=0.002) but also lower compared to baseline (Figure 1d). Mean scores for pain were identical in both groups at baseline, 1, 6 and 12 months. One month after LR, pain scores were still increased in all patients compared to preoperatively, with patients with malignant tumors having a significantly higher pain score, 3 months postoperatively compared to patients with LR for benign tumors (p=0.005), (Figure 1e).

Discussion

In this prospective study covering a longer time period quality of life in patients undergoing liver resection for benign or malignant tumors was evaluated. Liver resection was found to be safe and showed an acceptable morbidity and low mortality as previously reported [1]. As might be expected, self-reported overall quality of life, as measured by the global health status, showed a drop in the first month after surgery for both patient groups. It is essential that patients are informed preoperatively about this, reassuring them that QoL improves for the majority of patients after the first month. Already at the 3-month postoperative time-point, QoL increased substantially and continued to do so during the entire study period. For patients with benign pathologies, this finding is in line with the high percentage of symptom relief after liver resection previously demonstrated [20]. Parallel to what can be observed in many specialized liver units worldwide [21, 22], minimally invasive

liver resections are increasingly becoming gold standard in the present authors' unit, making up the majority of hepatic resections in the currently. However, during the study period, patients still mainly underwent open hepatic surgery. Too low patient numbers concerning laparoscopic LR precluded statistical analyses, but the drop in self-reported QoL at one month postoperative may be expected to be less in patients undergoing laparoscopic resections [23].

Some of the patients not answering the one month questionnaire were still in hospital at the given time point. It may seem fair to assume, that their self-reported overall QoL might be worse than the one actually reported. However, and surprisingly, patients suffering from postoperative complications who answered the questionnaires at the one month time period showed QoL scores that were not statistically different from those patients with an unproblematic postoperative course. This goes against what treating surgeons and physicians might expect. However, as has been shown by others [24, 25], self-reported QoL remains subjective, taking into account a multitude of equations. There are not solely based on measurable factors such as disease entity (malignant versus benign) or the presence or absence of physical restrictions and limitations.

Interestingly, preoperative, that is "base-line" QoL was very similar in both patient groups, as were some of the main parameters analyzed by the QLQ-C30 and QLQ-LCM21 (physical function, emotional functioning, fatigue and pain). This too seems contra-intuitive, as one might expect patients with malignant diagnoses to fare worse. However, this may in part be explained by the fact that patients with benign tumors more frequently reported nausea and abdominal pain at the time point of their first consultation. It also may be explained by the patient's general attitude and expectations towards the planned surgical intervention in case of a malignant diagnosis. Patients with a malignant tumor will

be aware of the fact, that surgery may be the only potentially long-term curative treatment strategy. Knowing that they qualify for surgery may thus result in an improved, self-reported overall QoL. Similar findings have been reported by others [26].

The findings of this study are limited by its single center design, restricting generalisation of the results. Also, patients with malignant diseases not responding to the survey may have had poor QoL, potentially adding a bias to the results presented. Finally, the sample size for this study was calculated for the overall, self-reported QoL but not for every sub-analysis performed.

Acknowledgments

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Figure Legends

Table 1: Baseline characteristics of included patients (N=188) for each tumor type

Table 2: Baseline table of tumor entities

Table 3: Procedural characteristics and complications of included patients (N=188) for each tumor type

Figure 1a-e: Scoring results of the QLQ-C30 and the QLQ-LMC21

Table 1: Baseline characteristics of included patients (N=188) for each tumor type

	All tumor groups (n=188)	Patients with malignant tumors (n=130)	Patients with benign tumors (n=58)	p value
Sex (female)	88 (47%)	52 (40%)	36 (62%)	0.007
Age	58.0 ± 13.4	61.7 ± 10.6	49.8 ± 15.2	<0.001
Jaundice				0.778
No	164 (87%)	114 (88%)	50 (86%)	
Yes	24 (13%)	16 (12%)	8 (14%)	
Pruritus				0.099
No	171 (91%)	115 (88%)	56 (97%)	
Yes	17 (9%)	15 (12%)	2 (3%)	
Weight loss				0.513
No	140 (74%)	95 (73%)	45 (78%)	
Yes	48 (26%)	35 (27%)	13 (22%)	
Nausea				<0.001
No	159 (85%)	118 (91%)	41 (71%)	
Yes	29 (15%)	12 (9%)	17 (29%)	
Abdominal pain				<0.001
No	128 (68%)	101 (78%)	27 (47%)	
Yes	60 (32%)	29 (22%)	31 (53%)	
Loss of appetite				0.096
No	147 (78%)	106 (82%)	41 (71%)	
Yes	41 (22%)	24 (18%)	17 (29%)	
ASA Physical Status Classification System				<0.001
Normal healthy patient	17 (9%)	6 (5%)	11 (19%)	
Patients with mild systemic disease	101 (54%)	65 (50%)	36 (62%)	
Patients with severe systemic disease	67 (36%)	57 (44%)	10 (17%)	
Patients with severe systemic disease that is a constant threat to life	3 (2%)	2 (2%)	1 (2%)	
Moribund patients who are not expected to survive without the operation	0 (0%)	0 (0%)	0 (0%)	
A declared brain-dead patient whose organs are being removed for donor purposes	0 (0%)	0 (0%)	0 (0%)	
Diabetes				0.820
No	163 (87%)	112 (86%)	51 (88%)	
Yes	25 (13%)	18 (14%)	7 (12%)	
Cardiovascular disorders				0.109
No	113 (60%)	73 (56%)	40 (69%)	
Yes	75 (40%)	57 (44%)	18 (31%)	
Pulmonary disorders				0.177
No	161 (86%)	108 (83%)	53 (91%)	
Yes	27 (14%)	22 (17%)	5 (9%)	
Kidney disease				0.440
No	181 (96%)	124 (95%)	57 (98%)	
Yes	7 (4%)	6 (5%)	1 (2%)	
Other disorders				0.266
No	108 (57%)	71 (55%)	37 (64%)	
Yes	80 (43%)	59 (45%)	21 (36%)	

Data are n (%) or mean ± SD. P value: Fisher's exact test or t-test as appropriate. * American Society of Anesthesiologists.

Table 2. Tumor types

	All patients	Malignant	Benign
	N = 196	N = 138	N = 58
Diagnosis	n = 196,	n = 138,	n = 58,
Benign (excl. echinococcosis)	38 (19%)	0 (0%)	38 (66%)
Cholangiocarcinoma (incl. hilar cholangiocarcinoma)	17 (9%)	17 (12%)	0 (0%)
Colorectal liver metastases	57 (29%)	57 (41%)	0 (0%)
Echinococcosis	20 (10%)	0 (0%)	20 (34%)
Hepatocellular carcinoma	32 (16%)	32 (23%)	0 (0%)
Other liver metastases (excl. colorectal)	25 (13%)	25 (18%)	0 (0%)
Other primary malignant liver tumors	5 (3%)	5 (4%)	0 (0%)
Colorectal liver metastases & Hepatocellular carcinoma	2 (1%)	2 (1%)	0 (0%)

Table 3: Procedural characteristics and complications of included patients (N=188) for each tumor type

	All tumor groups	Patients with malignant tumor	Patients with benign tumor	p Value
	N = 188	N = 130	N = 58	
Number of resected liver segments				0.223
<3 segments (minor liver surgery)	71 (38%)	44 (34%)	27 (47%)	
≥3 segments (major liver surgery)	115 (61%)	84 (65%)	31 (53%)	
Missing	2 (1%)	2 (2%)	0 (0%)	
Hospital stay (days)	15.6 ± 13.0	18.1 ± 14.4	10.0 ± 6.4	<0.001
(Neo)adjuvant chemotherapy				<0.001
No	126 (67%)	69 (53%)	57 (98%)	
Yes	62 (33%)	61 (47%)	1 (2%)	
Adjuvant radiotherapy				0.010
No	175 (93%)	117 (90%)	58 (100%)	
Yes	13 (7%)	13 (10%)	0 (0%)	
Superficial infection				0.128
No	168 (89%)	113 (87%)	55 (95%)	
Yes	20 (11%)	17 (13%)	3 (5%)	
Deep infection				1.000
No	180 (96%)	124 (95%)	56 (97%)	
Yes	8 (4%)	6 (5%)	2 (3%)	
Bilioma				0.515
No	160 (85%)	109 (84%)	51 (88%)	
Yes	28 (15%)	21 (16%)	7 (12%)	
Hemorrhage/ hematoma				1.000
No	178 (95%)	123 (95%)	55 (95%)	
Yes	10 (5%)	7 (5%)	3 (5%)	
Thrombosis				0.523
No	186 (99%)	129 (99%)	57 (98%)	
Yes	2 (1%)	1 (1%)	1 (2%)	
Pulmonary embolism				1.000
No	186 (99%)	128 (98%)	58 (100%)	
Yes	2 (1%)	2 (2%)	0 (0%)	
Pneumonia				1.000
No	177 (94%)	122 (94%)	55 (95%)	
Yes	11 (6%)	8 (6%)	3 (5%)	
Other complications				0.001
No	139 (74%)	87 (67%)	52 (90%)	

Yes	49 (26%)	43 (33%)	6 (10%)	
Surgical reintervention				0.119
No	170 (90%)	114 (88%)	56 (97%)	
Yes	17 (9%)	15 (12%)	2 (3%)	
Missing	1 (1%)	1 (1%)	0 (0%)	

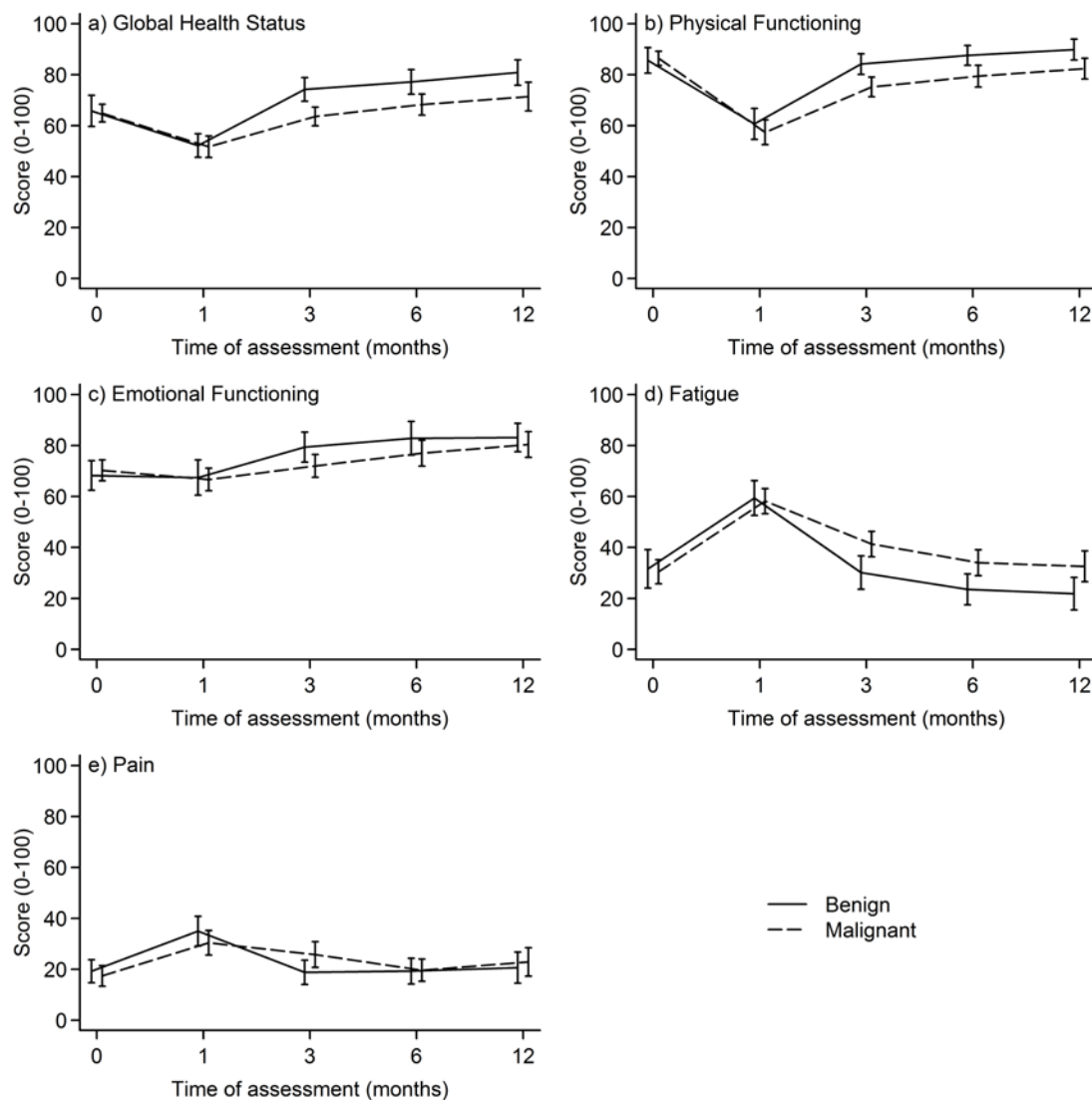Data are n (%) or mean ± SD. P value: Fisher's exact test or t-test as appropriate.

Figure 1 a-f: Mean scores with 95% confidence intervals based on imputed data.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for the global health status / QoL represents a high QoL, a high score for a functional scale (e.g., physical functioning, emotional functioning) represents a high / healthy level of functioning, but a high score for a symptom scale / item (e.g., fatigue) represents a high level of symptomatology / problems.