

# A Prospective Longitudinal Study of Quality of Life After Resection of Hepatocellular Carcinoma

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**Hypothesis:** Hepatic resection improves quality of life (QOL) in patients with resectable hepatocellular carcinoma (HCC).

**Design:** A prospective longitudinal study.

**Setting:** A university teaching hospital.

**Patients:** Sixty-six consecutive patients undergoing resection of HCC, and 10 patients with unresectable HCC found after surgical exploration who were subsequently treated with transarterial chemoembolization (control group).

**Main Outcome Measure:** Serial measurements of preoperative and postoperative QOL using the Functional Assessment of Cancer Therapy–General (FACT-G) Questionnaire for up to 2 years after surgery (at 3, 6, 9, 12, 18, and 24 months).

**Results:** Among the 66 patients with resectable HCC, the mean postoperative QOL scores at 3 months after surgery were significantly higher than the mean preoperative QOL scores in domains related to physical, social, and emotional well-being and relationship with physicians. The mean total QOL score increased from 83.5 (SD, 9.4) before surgery

to 94.1 (SD, 7.7) at 3 months after surgery ( $P < .001$ ). No significant change of QOL scores at 3 months after surgery was observed in the control group. Twenty patients in the resected group died of early recurrence within 2 years after surgery, but their mean postoperative QOL scores remained higher than the preoperative QOL scores for most assessment times. In contrast, in the control group, the mean total QOL scores became significantly lower than the preoperative scores, starting 9 months after surgery. Forty-six patients in the resected group completed all QOL assessments. At all postoperative assessments, their mean QOL scores were higher than preoperative scores. Recurrence developed in 13 of the 46 patients within the 2-year study, and there was significant deterioration of QOL over time among these 13 ( $P < .001$ ), whereas no significant change in QOL over time was observed among the 33 recurrence-free patients. Of various clinicopathologic factors, only advanced pTNM stage was significantly predictive of deterioration of QOL over time after resection of HCC.

**Conclusions:** Hepatic resection results in significant enhancement of QOL in patients with HCC. Development of recurrence is the main factor leading to deterioration in QOL over time after resection of HCC.

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**H**EPATIC RESECTION is the mainstay of curative treatment of patients with hepatocellular carcinoma (HCC). Hepatectomy has become a safe operation with a low operative mortality rate as a result of recent advances in surgical technology and perioperative care.<sup>1,2</sup> However, the long-term results after hepatic resection remain unsatisfactory. A cumulative 5-year recurrence rate in the range of 75% to 100% has been reported from most centers.<sup>3</sup> In a strict sense, hepatic resection for HCC cannot be considered curative with such a high recurrence rate.<sup>4</sup> Hence, it is important to consider the quality of life (QOL) as a treatment outcome in addition

to the operative mortality and long-term survival rates. As most HCCs occur in patients with chronic liver diseases, hepatic resection could theoretically result in reduced QOL in these patients owing to a further compromise in liver function. Furthermore, early postoperative recurrence is a common event after resection of HCC and requires aggressive treatment with therapies such as transarterial chemoembolization (TACE) to prolong survival,<sup>5</sup> which could potentially lead to impairment in QOL.

During the 1990s, there has been a growing emphasis on the assessment of QOL in patients with cancer.<sup>6</sup> Quality of life is now regarded as a biologically and clinically meaningful outcome that is as

## PATIENTS AND METHODS

### PATIENTS

From January 1, 1996, through June 30, 1997, 66 consecutive patients undergoing hepatic resection for HCC in the Department of Surgery, University of Hong Kong, Hong Kong, China, were recruited for a prospective study of QOL before and after surgery. Informed consent was obtained from all patients. The criteria for resectability were absence of extrahepatic metastasis, absence of main portal vein thrombosis, anatomically resectable disease, and Child A or B liver function status. Indocyanine green retention at 15 minutes (ICGR-15) of 14% was considered the safety limit for major hepatectomy, but this was used as a general guideline rather than an absolute criterion.<sup>14</sup> Extent of hepatectomy was defined as *major* if 3 or more segments were resected, and *minor* if 2 or fewer segments were resected. None of the patients received any preoperative anticancer treatments. **Table 1** shows the demographic and clinical data of the 66 patients. The mean age of the patients was 52.8 years (SD, 11.0 years; range, 19-75 years), and the mean tumor size was 6.8 cm (SD, 4.3 cm; range, 1.5-20.0 cm). All patients had macroscopically complete resection of the tumor.

During the study period, 10 other patients who initially intended to undergo resection were found to have unresectable tumors after exploratory laparoscopy or laparotomy, and subsequently received TACE. The mean age of these patients was 61.1 years (SD, 8.1 years; range, 51-77 years), and the mean tumor size was 6.9 cm (SD, 4.1 cm; range, 2.7-14.7 cm). The TACE was given every 3 months until evidence of progressive disease or deterioration of liver function precluded further treatment. The QOL evaluations were performed with the same schedule in these 10 patients as in those undergoing tumor resection, and they served as a control group.

### STUDY PROTOCOL

Patients were asked to complete a Chinese translation of the Functional Assessment of Cancer Therapy-General (FACT-G) Questionnaire<sup>16</sup> before surgery and at 3, 6, 9, 12, 18, and 24 months after surgery. Patients were requested to complete the questionnaires during follow-up visits at our outpatient clinic, and a research assistant (B.K.L.) was present to encourage the completion of all questionnaires during each outpatient session, which optimized compliance and minimized volunteer bias.<sup>9</sup> All QOL data were collected by the research assistant. Patients were informed that their responses in the questionnaire would not be made known to the attending surgeons, and hence would not affect their treatment. For those patients who survived less than 2 years after surgery, QOL assessment was performed with the same scheme till the last follow-up in the outpatient clinic.

All patients who had undergone tumor resection had serial assessments of liver function after hepatectomy by means of ICG clearance test before surgery and at 3, 6, 9, 12, 18, and 24 months after surgery. The ICG clearance test provides the best estimate of liver function reserve among other laboratory variables in patients undergoing hepatectomy for HCC.<sup>14</sup> Patients underwent regular monitoring for

recurrent disease by means of monthly measurement of serum  $\alpha$ -fetoprotein level and ultrasonography or computed tomography every 3 months. Diagnosis of recurrent disease was based on elevated  $\alpha$ -fetoprotein level and typical imaging findings, and if necessary, results of percutaneous fine needle aspiration cytologic study. Recurrent disease confined to the liver was treated with TACE. For extrahepatic recurrence, systemic chemotherapy or symptomatic treatment alone was offered, depending on the patient's general status.

### INSTRUMENT FOR QOL ASSESSMENT

The FACT-G Questionnaire is one of the most widely used instruments for QOL assessment of patients with cancer and has been found to be applicable to patients from diverse cultural backgrounds.<sup>17,18</sup> Results of a study from our institution<sup>19</sup> have validated the use of the FACT-G Questionnaire after Chinese translation as a measure of QOL among Chinese patients with cancer. The FACT-G Questionnaire is a self-report instrument that measures multidimensional QOL using a total of 29 items in the following 5 specific life domains: (1) physical well-being (7 items), (2) social well-being (7 items), (3) emotional well-being (6 items), (4) functional well-being (7 items), and (5) relationship with physicians (2 items).<sup>16</sup> For each item, a statement regarding the specific domain was given (eg, "I have a lack of energy" in physical well-being, "I feel distant from my friends" in social well-being, "I feel sad" in emotional well-being, "I am able to work" in functional well-being, and "I have confidence in my doctors" in relationship with physicians). The patients were asked to indicate how true each statement was for them during the past week on a 5-point ordinal scale where 0 indicates not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. The score of each domain (possible range, 0-28 for physical well-being, 0-28 for social well-being, 0-24 for emotional well-being, 0-28 for functional well-being, and 0-8 for relationship with physicians; higher scores indicate better QOL) and the total score of all domains (possible range, 0-116) were computed for each assessment.

### STATISTICAL ANALYSIS

All clinicopathologic data, ICG clearance test results, FACT-G scores of each assessment, and recurrence status after resection were prospectively entered into a computerized database. A commercially available statistical package (SPSS version 9.0 for Windows; SPSS Inc, Chicago, Ill) was used for all statistical analyses. Comparison of categorical variables was performed using the  $\chi^2$  test. Continuous variables (QOL scores or ICGR-15) at 2 time points were compared by means of the *t* test. Correlation between QOL scores and ICGR-15 was assessed by means of the Spearman correlation coefficient. Multivariate analysis of variance (MANOVA) for repeated measures was used to compare serial measurements of postoperative QOL scores. The influence of clinicopathologic factors on the change of postoperative QOL over time was studied by entering the variables as between-subject factors in the MANOVA procedure. A *P* value of less than .05 was considered statistically significant.

important as disease-free and overall survival with regard to anticancer treatment.<sup>7,8</sup> Surgeons have been relatively slow in adopting QOL assessment in the manage-

ment of cancer, partly as a result of the misperception that clinical judgment is more reliable than QOL data.<sup>9</sup> In recent years, however, awareness of the importance

of assessing QOL after major surgery for cancer resection has increased. Various authors have reported the QOL results after resection of malignant neoplasms of the gastrointestinal tract such as esophageal,<sup>10</sup> gastric,<sup>11</sup> colorectal,<sup>12</sup> and pancreatic cancer.<sup>13</sup> To our knowledge, there has been no previous report on the QOL outcome after hepatic resection for HCC. Recognizing the importance of QOL as a surgical outcome in cancer resection, we conducted a prospective longitudinal study to evaluate the QOL of patients undergoing resection of HCC.

## RESULTS

### PERIOPERATIVE AND SURVIVAL OUTCOMES

There was no hospital mortality among the 66 patients in the resected group. Postoperative morbidity occurred in 25 patients (38%), including wound infection (n=9), chest infection (n=8), pleural effusion (n=3), cardiac arrhythmia (n=3), wound dehiscence (n=1), and intraperitoneal sepsis (n=1). There was no perioperative morbidity or mortality in the control group who underwent exploratory laparoscopy or laparotomy only.

Follow-up was complete in all patients. Recurrent disease developed in 33 (50%) of the 66 patients in the resected group (25 intrahepatic, 8 extrahepatic) within 2 years after surgery (median interval from surgery to recurrence, 9 months; range, 3-23 months). Of these 33 patients, 23 with intrahepatic recurrence were treated with TACE, 2 with extrahepatic recurrence were treated with systemic chemotherapy, and the other 8 patients received symptomatic treatment alone. Twenty of these 33 patients with recurrence died before the completion of the 2-year QOL assessment. A total of 46 patients, 13 with recurrent disease and 33 without recurrent disease, completed the 2-year QOL assessments.

Of the 10 patients who had unresectable HCC treated with TACE, only 4 patients survived for more than 2 years. The other 6 patients died before 2 years after 2 to 6 sessions of TACE.

### EARLY POSTOPERATIVE QOL

All 66 patients in the resected group completed the first postoperative QOL assessment at 3 months after surgery. To evaluate the immediate effect of surgery on QOL, the first postoperative QOL scores at 3 months after surgery were compared with preoperative QOL scores (**Table 2**). There was significant improvement in physical, social, and emotional well-being and in relationship with physicians after the surgery. The most remarkable improvement was noted in physical well-being. The mean total QOL score increased from 83.5 to 94.1 ( $P<.001$ ).

There was a significant deterioration of liver function in terms of ICGR at 3 months after surgery, with a mean postoperative ICGR-15 of 18.8% (SD, 14.8%) compared with a mean preoperative ICGR-15 of 11.4% (SD, 7.8%) ( $P<.001$ ). However, 58 patients remained in the Child A class and the other 8 patients were in the Child B class; ie, there was a deterioration from Child A to B class in only 4 patients at 3 months after surgery. There was a trend toward a negative correlation between total QOL

**Table 1. Demographic and Clinical Data of 66 Patients With Hepatic Resection for HCC\***

	No. of Patients
Sex	
Male	55
Female	11
Age, y	
≤65	52
>65	14
Comorbid illness†	
Absent	48
Present	18
Hepatitis B infection	
Absent	9
Present	57
Underlying cirrhosis	
Absent	39
Present	27
Child grade	
A	62
B	4
ICGR-15, %	
≤10	35
>10	31
Tumor size, cm	
≤5	33
>5	33
pTNM stage‡	
I/II	2/29
IIIA/IVA	31/4
Extent of hepatectomy§	
Major	44
Minor	22

\*HCC indicates hepatocellular carcinoma; ICGR-15, indocyanine green retention at 15 minutes.

†Includes diabetes mellitus and chronic cardiovascular and respiratory diseases, but excludes underlying chronic liver disease.

‡Described in Sobin and Wittekind.<sup>15</sup>

§Described in the "Patients" subsection of the "Patients and Methods" section.

**Table 2. Comparison of Preoperative and First Postoperative Assessment of QOL Using FACT-G Questionnaire Among 66 Patients\***

FACT-G Domain	Preoperative Score	Postoperative Score	P
Physical well-being	22.6 (2.4)	26.6 (1.4)	<.001
Social well-being	19.6 (3.9)	22.1 (2.9)	<.001
Emotional well-being	14.3 (3.3)	16.5 (2.4)	<.001
Functional well-being	20.4 (5.1)	21.7 (4.3)	.12
Relation with physicians	6.6 (1.6)	7.2 (1.2)	.02
Total score	83.5 (9.4)	94.1 (7.7)	<.001

\*QOL indicates quality of life; FACT-G, Functional Assessment of Cancer Therapy-General. Values are expressed as mean (SD). High scores indicate high QOL.

score and ICGR-15 at 3 months after hepatectomy, but the correlation coefficient was not statistically significant ( $r=-0.23$ ;  $P=.07$ ).

**Table 3** shows comparisons between the preoperative and 3-month postoperative total QOL scores in subgroups of patients categorized by 10 host, tumor, and treatment factors that could potentially influence the QOL

outcome after resection of HCC. Significant improvement in QOL after surgery was observed in all subgroups.

In the control group with unresectable HCC, no significant differences were observed between the QOL scores in individual domain or the total QOL score at the 3-month assessment compared with the preoperative assessment (**Table 4**). The mean preoperative total QOL score was not significantly different between the re-

sected and unresected groups (82.7 vs 83.5;  $P=.54$ ), whereas the mean 3-month total QOL score was significantly higher in the resected than in the unresected group (94.1 vs 81.7;  $P<.001$ ).

### CHANGES IN QOL OVER TIME AFTER SURGERY

The QOL results of the resected group over time were separately depicted for the 20 patients who died before completion of the 2-year QOL assessment (**Table 5**) and the 46 patients who completed 2 years of QOL assessment (**Table 6**). For the 20 patients who died within 2 years as a result of early recurrence, QOL data were available up to the last follow-up in the outpatient clinic. The mean postoperative QOL score of these patients remained higher than the preoperative QOL score in each domain during most of the assessments after surgery, and the mean total QOL scores were also higher than the preoperative score at all assessment times except at 18 months after surgery (Table 5).

For the 46 patients who completed 2 years of QOL assessment, the QOL score in each domain appeared to peak at 6 months after surgery, followed by a trend toward a slight decrease in the scores afterward, but there was no significant change of QOL in each domain from 3 to 24 months after surgery (Table 6). There was a significant decrease in the total QOL score from 6 to 24 months ( $P=.04$ ). However, even at 24 months after surgery, the mean postoperative total QOL score (88.5) was higher than the mean preoperative total QOL score (86.9). When patients were subdivided into groups with and without recurrent disease within the 2-year study (13 and 33 patients, respectively), there was a significant decrease in the total QOL score over time in the group with recurrence ( $P<.001$ ), whereas no significant change was observed in the QOL in the recurrence-free group (**Figure 1**). Overall, there was no significant change in the liver function assessed by means of ICGR-15 during the 2 years (**Figure 2**). There was no significant correlation between ICGR-15 and total QOL score at any assessment time after surgery.

When the 10 factors listed in Table 3 were entered as between-subject factors in the MANOVA analysis for the 46 patients who completed 2 years of assessment, only pTNM stage was a significant factor influencing the QOL outcome over time ( $P=.005$ ), with worse results among patients with pTNM stage IIIA or IVA disease compared with those with stage I or II disease. The frequency of recurrence within 2 years was significantly higher in pa-

**Table 3. Comparison of Preoperative and First Postoperative QOL Assessment in Subgroups\***

Subgroup	Total QOL Score		P
	Preoperative	Postoperative	
Sex			
Male	85.8 (9.4)	94.2 (7.3)	<.001
Female	83.1 (9.6)	93.8 (10.0)	.01
Age, y			
≤65	85.0 (9.6)	94.6 (7.6)	<.001
>65	86.7 (8.8)	92.4 (8.1)	.008
Comorbid illness			
Absent	85.5 (8.2)	94.0 (7.5)	<.001
Present	85.1 (12.7)	94.7 (8.4)	.003
Hepatitis B infection			
Absent	90.3 (8.9)	94.8 (7.5)	.048
Present	84.7 (9.4)	94.0 (7.9)	<.001
Underlying cirrhosis			
Absent	86.5 (9.3)	95.3 (8.6)	<.001
Present	83.8 (9.6)	92.6 (6.1)	<.001
ICGR-15, %			
≤10	86.6 (9.4)	94.7 (7.6)	<.001
>10	83.8 (9.4)	93.5 (7.9)	<.001
Tumor size, cm			
≤5	85.5 (9.9)	93.5 (7.3)	<.001
>5	85.3 (9.0)	94.9 (8.2)	<.001
pTNM stage†			
I or II	87.2 (8.3)	94.2 (7.9)	<.001
IIIA or IVA	83.5 (10.2)	94.1 (8.1)	<.001
Extent of hepatectomy‡			
Major	85.7 (8.5)	94.6 (7.8)	<.001
Minor	84.8 (11.3)	93.3 (7.7)	<.001
Postoperative morbidity			
Absent	83.8 (9.3)	94.7 (7.7)	.001
Present	86.8 (9.3)	92.4 (7.8)	.03

\*Abbreviations are described in the first footnotes to Tables 1 and 2. Values are expressed as mean (SD). High scores indicate high QOL.

†Described in Sobin and Wittekind.<sup>15</sup>

‡Described in the "Patients" subsection of the "Patients and Methods" section.

**Table 4. QOL in Patients With Unresectable Tumors Treated With Transarterial Chemoembolization\***

FACT-G Domain	QOL Scores						
	Preoperative (n = 10)	3-mo (n = 10)	6-mo (n = 9)	9-mo (n = 7)	12-mo (n = 7)	18-mo (n = 6)	24-mo (n = 4)
Physical well-being	22.4 (1.4)	22.2 (2.0)	22.0 (1.6)	19.0 (1.8)	18.2 (1.4)†	17.4 (2.4)†	17.6 (0.9)†
Social well-being	19.6 (3.7)	21.6 (2.0)	20.4 (2.2)	19.4 (3.2)	18.2 (2.4)	17.4 (2.2)	17.4 (1.2)
Emotional well-being	14.5 (1.7)	12.4 (1.7)	10.6 (1.2)†	9.4 (1.9)†	9.2 (2.1)†	9.0 (2.4)†	9.0 (2.1)†
Functional well-being	19.4 (2.7)	18.6 (3.8)	17.2 (1.9)†	17.7 (1.2)	17.4 (2.3)	17.0 (1.3)†	17.3 (2.0)
Relation with physicians	6.8 (1.3)	6.9 (0.6)	7.1 (0.4)	7.0 (1.2)	6.8 (1.0)	6.8 (1.2)	7.0 (1.2)
Total score	82.7 (6.2)	81.7 (5.1)	77.3 (6.2)	72.5 (5.8)†	69.8 (6.1)†	67.6 (4.5)†	68.3 (4.4)†

\*Abbreviation is described in the footnote to Table 2. Values are expressed as mean (SD). High scores indicate high QOL.

† $P<.05$ , lower postoperative score compared with preoperative score.



**Table 5. QOL After Surgery in Patients Who Survived Less Than 2 Years\***

FACT-G Domain	QOL Scores					
	Preoperative (n = 20)	3-mo (n = 20)	6-mo (n = 17)	9-mo (n = 15)	12-mo (n = 10)	18-mo (n = 6)
Physical well-being	22.0 (2.9)	26.5 (0.9)†	26.3 (1.7)†	25.2 (0.9)†	24.8 (0.9)†	22.2 (5.5)
Social well-being	20.2 (3.5)	21.9 (2.3)†	21.5 (2.7)	21.5 (2.8)	21.3 (2.5)	18.7 (3.1)
Emotional well-being	14.4 (4.0)	16.3 (3.1)†	16.1 (2.0)†	16.7 (2.3)†	15.7 (2.2)	14.2 (3.5)
Functional well-being	20.2 (6.3)	21.6 (4.8)†	20.5 (5.9)	20.4 (3.5)	20.3 (3.1)	15.0 (3.6)‡
Relation with physicians	5.9 (2.0)	6.9 (1.1)†	6.6 (0.9)	6.9 (8.0)	6.7 (1.4)	6.1 (1.1)
Total score	82.7 (10.6)	93.2 (7.6)†	91.0 (12.2)†	90.7 (5.8)†	88.8 (5.9)	76.2 (10.2)

\*Abbreviations are described in the footnote to Table 2. Values are expressed as mean (SD). High scores indicate high QOL.

†P<.05, higher postoperative score compared with preoperative score.

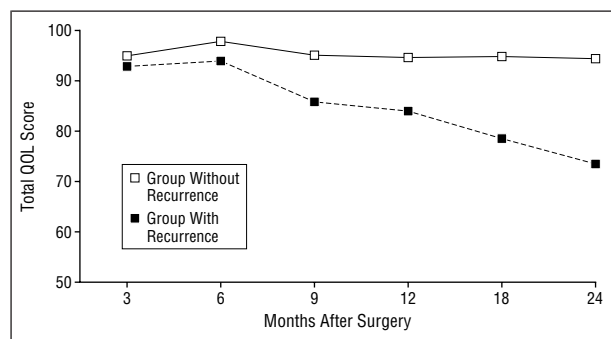
‡P<.05, lower postoperative score compared with preoperative score.

**Table 6. QOL After Surgery in 46 Patients Who Completed 2 Years of Assessment\***

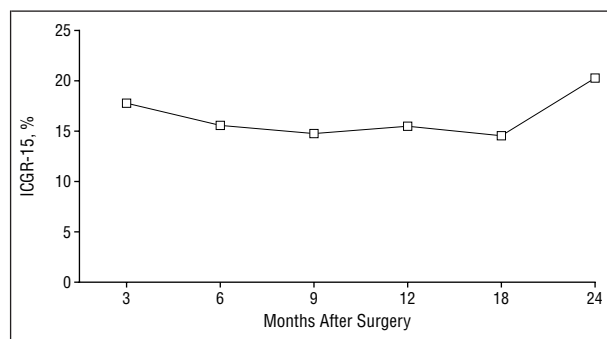
FACT-G Domain	QOL Scores							P†
	Preoperative	3-mo	6-mo	9-mo	12-mo	18-mo	24-mo	
Physical well-being	22.9 (2.1)	26.7 (1.2)	27.1 (1.3)	26.1 (1.4)	26.2 (1.0)	26.0 (0.9)	25.7 (1.1)	.18
Social well-being	19.9 (4.1)	21.8 (3.1)	22.1 (2.8)	21.2 (2.6)	20.6 (3.3)	19.8 (3.1)	19.6 (3.0)	.10
Emotional well-being	14.3 (2.9)	16.7 (2.1)	17.0 (2.0)	16.5 (1.5)	16.3 (1.6)	16.5 (1.2)	16.0 (1.4)	.14
Functional well-being	22.9 (2.1)	21.9 (4.1)	23.4 (4.4)	21.6 (3.4)	21.7 (2.9)	21.0 (2.4)	20.2 (3.5)	.09
Relation with physicians	6.9 (1.3)	7.3 (1.2)	7.2 (1.4)	7.1 (0.9)	6.9 (1.0)	7.0 (0.4)	7.0 (0.6)	.20
Total score	86.9 (8.2)	94.4 (7.7)	96.8 (7.6)	92.5 (7.4)	91.7 (6.5)	90.3 (5.8)	88.5 (6.0)	.04

\*Abbreviations are described in the footnote to Table 2. Values are expressed as mean (SD). High scores indicate high QOL.

†Comparison of the mean score of each domain and total score at all time points from 3 to 24 months after surgery by multivariate analysis of variance.



**Figure 1.** Mean postoperative total quality-of-life (QOL) scores from 3 to 24 months in 46 patients who completed all QOL assessments. There was no significant change in scores of the 33 patients without recurrent disease during the 2-year study ( $P = .32$ ), in contrast to a significant decrease in scores of the 13 patients in whom recurrent disease developed within 2 years after surgery ( $P < .001$ ). Cumulative number of patients with recurrence at 3, 6, 9, 12, 18, and 24 months were 1, 3, 7, 9, 11, and 13, respectively.



**Figure 2.** Mean postoperative indocyanine green retention at 15 minutes (ICGR-15) from 3 to 24 months in 46 patients who completed all quality-of-life (QOL) assessments. No significant change over time was observed ( $P = .17$ ).

tients with stage IIIA or IVA disease (9/19) compared with those with stage I or II disease (4/27) ( $P = .02$ ).

For the unresected group, significantly lower QOL scores compared with preoperative scores were observed in domains such as physical, emotional, and functional well-being at some assessments from 6 to 24 months after surgery, and the total score was significantly lower at the 9-, 12-, 18-, and 24-month assessments.

## COMMENT

Hepatocellular carcinoma is one of the most common malignant neoplasms worldwide. Unfortunately, for most pa-

tients with HCC, only palliative treatment is possible because of advanced disease on presentation or severe underlying cirrhosis. Even after surgical resection with a curative intent, the natural course of the disease is such that the outcome is palliative in most cases. Although never assessed in a randomized trial, it is widely accepted that hepatic resection is effective in prolonging the survival of patients, despite a high recurrence rate. However, it is important to ask, "Does hepatic resection produce prolonged life of improved quality?" To our knowledge, this study is the first attempt to address this issue. In fact, a MEDLINE search of the English-language literature did not find any report that specifically addressed the issue of QOL in patients with HCC. The lack of data on QOL in patients with HCC may be because HCC is mainly a disease of Asian and African countries, and the QOL of patients in these countries has

received much less attention compared with that of patients in Western countries.

The FACT-G Questionnaire used in this study is a QOL instrument that was initially developed by investigators in the United States.<sup>16</sup> In recent years, it has been used extensively in studies of QOL in patients with cancer worldwide.<sup>17,18</sup> The various domains in the FACT-G Questionnaire allow evaluation of a patient's QOL in several important aspects of life, and the total score is a good reflection of the overall QOL of a patient with cancer.<sup>16</sup> Ideally, in the evaluation of QOL of patients with any cancer, a disease-specific subscale focusing on the special symptoms and problems related to the cancer is desirable in addition to a general QOL measurement. Such a subscale has been developed for several cancers in conjunction with the FACT-G Questionnaire (eg, FACT-B for breast cancer and FACT-E for esophageal cancer),<sup>18</sup> but not yet for HCC. The physical well-being domain of the FACT-G Questionnaire, however, has encompassed some of the common symptoms of HCC, such as malaise, pain, and nausea.<sup>16</sup> Before the availability of a specific QOL assessment module for patients with HCC, the use of the FACT-G Questionnaire alone should provide a reasonable evaluation of the QOL for patients with HCC.

This study demonstrated significant improvement of QOL at 3 months after hepatectomy for HCC in almost all domains of life. Removal of the tumors not only improved the physical well-being of the patients, but also enhanced their social and emotional well-being. The improved relationship with physicians reflected the patients' satisfaction with the surgical treatment. Regardless of the tumor size or stage, underlying liver status, or extent of resection, there was an elevation in the total QOL score after surgery. The role of surgical resection for large or advanced HCC has been controversial despite documentation in the literature of a reasonable survival outcome.<sup>20</sup> The gain of QOL after hepatic resection in patients with large or advanced HCC helps justify the role of hepatic resection in such patients, for whom no other available treatment modalities seem to be effective. Also, QOL was significantly improved after hepatectomy, even in elderly patients. There has been a reluctance among some surgeons to perform hepatic resection in elderly patients with HCC because of the concern about the surgical risk and the doubt about the benefit of such a major surgical procedure in the elderly. A previous study from our department has shown that the perioperative and survival outcomes among elderly patients who underwent hepatectomy for HCC were comparable to those among younger patients, provided they underwent careful screening for operative risk.<sup>21</sup> The results of the present study should further reduce the age-related bias in the treatment of the increasing number of elderly patients with HCC expected in the future.

Particular attention has also been paid to the QOL outcome after surgery in patients who had postoperative morbidity. The morbidity rate of hepatic resection for HCC has remained high, despite a low mortality rate.<sup>1,2</sup> In our study design, the first assessment was performed 3 months after hepatectomy to allow time for recovery from the surgery. At the time of the first assessment, there was improved QOL, even among patients with postoperative morbidity, suggesting that postoperative morbidity did not have a lasting adverse effect on the QOL of patients.

The scheduling of the first postoperative assessment at 3 months after surgery also allowed time for regeneration of the liver remnant before measuring the first postoperative ICGR results. There was an overall deterioration in ICGR-15 after surgery, which is expected, as patients with cirrhosis have limited capacity in liver regeneration. However, there was no significant correlation between QOL and ICGR-15 outcomes at 3 months after surgery, suggesting that the liver function status was not a significant factor influencing the QOL outcome in these patients. In fact, only 4 patients had deterioration of Child liver function status, whereas most of the patients remained in the Child A class. With careful preoperative assessment and selection, major deterioration of liver function status after hepatectomy can be avoided in most patients.

A longitudinal evaluation of the QOL outcome over time demonstrated that the improved QOL after surgical resection of HCC was well maintained during a 2-year study. Even among the 20 patients who died of early recurrence within 2 years after surgery, the mean QOL scores were higher than the preoperative values for most of the assessment times after surgery, except at 18 months. Hence, benefits in terms of QOL may be accrued from resection of HCC, even when the outcome is palliative. For those who survived for more than 2 years, the QOL scores were above the preoperative values for all assessment times, although there was a gradual decrease in the total QOL scores from 6 to 24 months after surgery. The deterioration of the QOL over time appeared to be largely the result of the development of recurrent disease. The liver function status did not seem to have an important influence on the QOL outcome. Additional analysis revealed no significant decrease in the total QOL scores among patients without recurrent disease within the 2-year study, whereas a significant decrease in QOL over time was observed among those in whom recurrence developed. The appearance of recurrent disease is often deemed as a treatment failure by the patients, and it is understandable that the patients' emotional well-being and relationship with physicians would be compromised by the development of recurrence. Most patients with recurrent disease were treated with TACE, which is considered effective in prolonging survival after the development of intrahepatic recurrence, but is also associated with significant morbidity that may reduce physical well-being.<sup>22</sup> Hence, postoperative recurrence is not only the limiting factor of patients' survival, but also the main culprit in the deterioration of QOL over time after surgical resection of HCC. The significant adverse influence of advanced pTNM stage on the QOL over time further corroborates the negative impact of recurrent disease on the QOL outcome. A previous study from our department has shown that advanced pTNM stage was the most important factor predictive of postoperative recurrence among various clinicopathologic factors in patients undergoing hepatectomy for HCC.<sup>23</sup>

The QOL outcome in the control group treated with TACE was worse than that of the resected group. The QOL scores did not improve in the 3-month postoperative assessment, and scores worsened in some of the domains after 6 months. Although the control group was not exactly comparable to the resected group, the different outcome in this group helps eliminate the possibility that the improvement in the resected group resulted from any learn-

ing curve effect in responding to the questionnaires or any effect of repetition of the same instrument. This also suggests that it is unlikely for the improvement in QOL scores in the resected group to be related to the patients' wish to satisfy their attending clinicians as they got to know them better. To minimize such a possibility, the patients were informed beforehand that their responses to the questionnaires would not be revealed to their attending clinicians.

The QOL outcome is becoming an obligatory aspect in evaluating any treatment of patients with cancer, and it is going to play an increasingly important role in treatment decisions. The management of HCC is featured by the availability of a number of treatment modalities that have not been fully evaluated by randomized controlled trials, making it difficult to assess their true impact on patient survival and QOL.<sup>24</sup> Apart from surgical resection, liver transplantation,<sup>25</sup> TACE,<sup>22</sup> percutaneous ethanol injection therapy,<sup>26</sup> and other local ablative therapies such as radiofrequency thermal therapy<sup>27</sup> are all being used to treat patients with HCC. To enable a comprehensive evaluation of the relative roles of these treatment modalities, the QOL outcome associated with each of these modalities should be studied and compared in addition to survival outcome. Whether hepatic resection or liver transplantation is the surgical treatment of choice for HCC has been much debated in recent years.<sup>28,29</sup> It is essential to evaluate the QOL outcome when comparing these 2 treatments. Previous studies have evaluated the general QOL results after liver transplantation,<sup>30,31</sup> but the QOL outcome after transplantation for HCC demands a specific assessment, as it is complicated by the issue of tumor recurrence. Similarly, to clarify the relative benefits of surgical resection and percutaneous ethanol injection therapy for patients with small HCC, it is important to compare the QOL outcome associated with each of these treatment modalities, as survival results appear to be comparable for either treatment.<sup>26,32</sup>

## CONCLUSIONS

This study demonstrates an improvement in the QOL of patients after resection of HCC, hence supporting the role of hepatic resection as an effective treatment of HCC. Our data suggest that disease recurrence is the main factor leading to deterioration in the QOL over time after resection of HCC. In this respect, the search for an effective adjuvant therapy to reduce postoperative recurrence after resection of HCC is important not only to improve long-term survival, but also to preserve the QOL of patients. Final conclusions regarding the QOL benefits of surgical resection for HCC need verification from further studies with a larger number of patients, and future studies should incorporate a QOL assessment module that is specifically developed for evaluating QOL in patients with HCC in addition to a general QOL instrument such as the FACT-G Questionnaire. It is hoped that the preliminary results of this first study of QOL outcome in patients undergoing resection of HCC will generate further interest in the research of QOL outcome associated with other treatment modalities for HCC. To clarify the optimal strategies in the treatment of patients with HCC, it is imperative that QOL be included as an end point in future trials of any treatment modalities for HCC.

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