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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

# Impact of interventions and tumor stage on health-related quality of life in patients with hepatocellular carcinoma

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## Abstract

**Purpose** This study aims to examine the health-related quality of life in patients with hepatocellular carcinoma.

**Methods** 181 patients attending a tertiary center outpatient clinic were interviewed and completed the short form 36 (SF36) questionnaire. The SF36 was used to assess health-related QoL. Cross-sectional analyses by group (age, gender, clinical scores, systemic, and local interventions) as well sequel questionnaires were conducted.

**Results** Participants included were 79% (143/181) men [mean age at first SF36: 63.8 (± 12.3; 18.4–85.8) years]. Barcelona Clinic Liver Cancer (BCLC) stadium C was associated with significantly lower SF36 total scores, and elevated initial alpha-fetoprotein (AFP) concentrations were associated with lower SF36 functional and mental health sum scores throughout the course of the third questionnaire. Patients treated with sorafenib had within the sub-dimension scores a significantly lower result for role limitations due to physical health compared to patients without sorafenib treatment. Patients who underwent a transarterial chemoembolization (TACE) had within the sub-dimension scores a significantly higher result for control of pain compared to patients without TACE. Kaplan–Meier analysis revealed significant survival benefits for patients who underwent any intervention at the first SF36 (mean survival in years 4.3 vs. 1.6; $P < 0.01$) as well as for patients who underwent hepatic resection (mean survival in years 6.3 vs. 2.7; $P < 0.0001$).

**Conclusion** Advanced tumor stages marked by BCLC stadium C and elevated initial AFP concentrations were associated with lower SF36 total scores and functional sum scores, respectively. During the course of sorafenib treatment, the sub-dimensional score for role limitations due to physical health decreased significantly, whereas TACE performance was associated with a significant improvement of the control of body pain.

**Keywords** Hepatocellular carcinoma · Quality of life · SF36 · Sorafenib · TACE

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## Introduction

In hepatocellular carcinoma (HCC), patients and healthcare professionals are confronted with a large variety of treatment options, and interdisciplinary tumor boards support the process of decision making. In clinical routine, HCC patients are categorized for evaluation of treatment by radiographic, laboratory, and clinical parameters as exemplarily done by BCLC status, Child–Pugh score, and ECOG performance status (Forner et al. 2009; Hinrichs et al. 2017). Along with overall survival and tumor response data, quality of life analysis of cancer patients has become important to the treatment selection process.

Notably, QoL data obtained by the general cancer questionnaire EORTC QLQ C30 and the additional liver cancer-specific HCC18 were prognostic for overall survival (Li and Yeo 2017; Sternby Eilard et al. 2018). Changes in quality of life can be related to disease progression (Kondo et al. 2007) as well as to side effects and therapeutic effects of HCC treatment. Less than 20% of newly diagnosed HCC patients are eligible for curative treatment (Salem et al. 2013). So far, potential curative interventions include radiofrequency ablation (RFA), liver resection (LR), and liver transplantation (LT), whereas TACE and—to a lesser extent—selective internal radiation therapy [also referred to as transarterial radioembolization (TARE)] assist downstaging HCC and bridging to transplantation (Couri and Pillai 2019).

Given the limited life expectancy, preserving QoL becomes a substantial therapeutic goal in HCC patients (Li and Yeo 2017; Van Cleave et al. 1999). The great spectrum of treatment options for locoregional and systemic control of HCC manifestations can complicate the process of finding the optimal intervention method for an individual patient. Outcome data comparing alternative interventions are limited not only for radiographic tumor response and survival rates, but especially also for the effects of treatments on QoL.

Hepatic resection in HCC significantly improved health-related quality of life evaluated by the SF36 questionnaire 3 months after the procedure (Chiu et al. 2018). There was a significant reduction in SF36 physical and mental sum scores at 1 month after hepatic resection and an even more significant reduction after TACE; however, in the long term, surgery led to significantly higher QoL scores than those for the TACE group after 24 months (Xie et al. 2015). Mental health scores improved after 4 months of TACE, whereas no significant change was present at 8 or 12 months in a single-center prospective study with SF36 assessment in 73 HCC patients. However, vitality scores worsened after the first TACE treatment in a subset of patients who underwent three or more chemoembolization procedures (Wible et al. 2010). Repetitive TACE procedures of four or more therapies did not significantly impact long-term health-related QoL after 6 and 12 months compared with patients who received three or fewer chemoembolizations (Xing et al. 2015).

In comparison, patients who underwent liver transplantation or resection and patients treated by RFA had higher SF36 scores for body pain, general health, and vitality at 6 and 36 months after surgery (He et al. 2018). In patients treated by selective internal radiation therapy (SIRT) with Yttrium-90 for infiltrative hepatocellular carcinoma (including portal vein thrombosis), a significant decrease in the SF36 physical sum score at 1 month post-treatment was an independent predictor of poorer overall survival and time to progression (Xing et al. 2018). Studies comparing patients after stereotactic ablative radiotherapy for primary and metastatic liver cancer did not show significant QoL decline in any domain (Mutsaers et al. 2017).

In addition to locoregional treatment procedures, higher SF36 physical and social functioning scores at baseline predicted longer treatment duration for the systemic antineoplastic drug sorafenib (Shomura et al. 2016). Patients treated with sorafenib had no significant QoL changes compared to the respective placebo group, as documented in the Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia–Pacific studies (Cheng et al. 2009; Llovet et al. 2008). Nevertheless, applying the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, a significant QoL decrease and higher rates of treatment withdrawal due to adverse events were revealed in patients treated with sorafenib (Brunocilla et al. 2013). Kondo et al. (2007) reported, for the SF36, a significantly lower physical function score in the sum analysis for women compared with men. In addition, subscales were significantly worse in females for the hepatobiliary cancer designed FACT-Hep questionnaire (Gmur et al. 2018). The aim of this study was to evaluate health-related QoL in HCC affected patients and to compare the influence of various interventional options upon dimensional and summarized SF36 scores. An additional goal of the study was to identify factors influencing QoL over the course of three sequel questionnaires. We performed a prospective, cross-sectional study of patients diagnosed with HCC attending a tertiary center liver cancer unit in Heidelberg University Hospital between 2010 and 2014 using the SF36 questionnaire.

## Methods

A prospective, cross-sectional study was conducted at our tertiary care HCC outpatient center. All included patients had histologically or radiographically confirmed diagnosis of HCC and were 18 years of age or older. Initial clinical

presentation and laboratory assessments of liver function at the time of diagnosis of HCC were used for the calculation of clinical scores. Diagnosis of cirrhosis was based on histology, transient elastography, and imaging (CT, MRI, ultrasound). Patients were asked to complete the SF36 questionnaire version 2.0 (Bullinger 1995; Morfeld et al. 2005) in German, before their regular medical visit at the HCC outpatient clinic. Interventions before completion of the first SF36 health questionnaire were analyzed in this cross-sectional study. The SF36 questionnaire contains 36 questions with normalized scores ranging from 0 (absence of QoL) to 100 (optimal QoL) in 8 dimensions: physical function (PF), role limitations due to physical health (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). For the analyses, we used the standardized SF36 dimensional scores, SF36 physical and mental health sum scores, and total SF36 score. These scores were calculated as described previously (Ellert and Bellach 1999; Ellert and Kurth 2004; Stewart et al. 1988).

### Ethical standards

Collecting data for this study was approved a priori by the ethics committee of the medical faculty of the University of Heidelberg. The study complies with the Declaration of Helsinki of 1975, as revised in 2000. The appointed ethics approval number was S-204/2010. Written informed consent was obtained from every patient or legal representative included in this study.

### Statistical analysis

Statistical analyses were performed with GraphPad Prism version 5 software (GraphPad Software, San Diego, CA, USA). The Kruskal–Wallis test followed by Dunn's test was used for the comparison of more than two subgroups. Data are presented as mean ± standard error of mean (SEM), unless otherwise noted. For the Kaplan–Meier analysis, the Mantel–Cox log-rank test was applied. A $P$ value $< 0.05$ was considered statistically significant.

## Results

### Patient characteristics

Patient characteristics are given in Table 1, including patients' demographics, initial clinical scores, and etiology of liver cirrhosis. There were 143 (79%) male patients and 38 (21%) female patients. The mean age (± standard deviation; range) at the time of completing the first SF36 questionnaire was 63.8 (± 12.3; 18.4–85.8) years. Causes of liver

**Table 1** Patients' characteristics of the studied HCC patients

| Patients' characteristics at first questionnaire | Number | Percent (%) |
|---|---|---|
| Total patients | 181 | 100 |
| General | | |
| Sex, male | 143 | 79.0 |
| Sex, female | 38 | 21.0 |
| Age at first questionnaire (years) | 63.8 (± 12.3) | |
| Death | 91 | 50.3 |
| Metastatic disease | 28 | 15.5 |
| Lung metastases | 13 | 7.2 |
| Lymph node metastases | 12 | 6.6 |
| Bone metastases | 4 | 2.2 |
| Other location[a] | 7 | 3.9 |
| Synchronous tumor | 17 | 9.4 |
| Cholangiocellular carcinoma | 4 | 2.2 |
| Upper gastrointestinal tract | 3 | 1.7 |
| Renal cell carcinoma | 3 | 1.7 |
| Breast cancer | 2 | 1.1 |
| Lung cancer | 2 | 1.1 |
| Other malignoma[b] | 3 | 1.7 |
| Clinical status | | |
| Child A | 133 | 73.5 |
| Child B | 37 | 20.4 |
| Child C | 11 | 6.1 |
| BCLC initial A | 48 | 26.5 |
| BCLC initial B | 69 | 38.1 |
| BCLC initial C | 53 | 29.3 |
| BCLC initial D | 11 | 6.1 |
| ECOG initial 0 | 112 | 61.9 |
| ECOG initial 1 | 44 | 24.3 |
| ECOG initial 2 | 8 | 4.4 |
| ECOG[c] initial 3–4 | 0 | 0.0 |
| Liver cirrhosis | 121 | 66.9 |
| Cause of liver cirrhosis | | |
| Alcoholic | 53 | 29.3 |
| Hepatitis B | 25 | 13.8 |
| Hepatitis C | 44 | 24.3 |
| Non-alcoholic fatty liver disease | 7 | 3.9 |
| Autoimmune hepatitis | 2 | 1.1 |
| Primary biliary cholangitis | 1 | 0.6 |
| Cryptogenic[d] | 15 | 8.3 |

[a]Other location of metastatic disease included cutaneous, peritoneal, splenic, adrenal, and gastric

[b]Other malignomas included prostate, colon, and ovarian cancer

[c]ECOG status was not available in 17 patients

[d]Patients with cryptogenic cirrhosis had negative clinical and laboratory parameters to exclude alcoholic, viral, and autoimmune-related cirrhosis as well as non-alcoholic fatty liver disease

cirrhosis were alcoholic liver disease (29.3%), viral hepatitis C (24.3%), viral hepatitis B (13.8%), non-alcoholic steatohepatitis (3.9%), autoimmune hepatitis (1.1%), primary biliary cholangitis (0.6%), and cryptogenic cirrhosis (8.3%). Patients with cryptogenic cirrhosis had negative clinical and laboratory parameters to exclude etiologies mentioned above. Metastatic HCC was present in 28 patients (15.5%), with pulmonary and lymphatic metastasis representing the most common localizations. At the time of last follow-up, 90 patients were still alive (49.7%). The mean follow-up after the first SF36 was 547 days (± standard deviation; ± 580). Table 2 summarizes the distribution of patients receiving interventions in subjection to the first SF36. Throughout the whole observational period, 21 patients (11.6%) did not receive any of the following interventions: sorafenib (SOF), chemotherapy (CHT), transarterial chemoembolization (TACE), radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), radiotherapy (RT), hepatic resection (RS). The mean interval of initiation of an intervention was 387 ± 484 days prior to completion of the first SF36.

Overall, a second and third questionnaire was completed by 74 (40.9%) and 32 (17.7%) patients, respectively. The second and third questionnaires were obtained after a mean of 125 (± 113) and 199 (± 114) days following the first questionnaire, respectively. The first, second, and third questionnaires were completed by 48, 19, and 10 patients staged BCLC A, by 69, 32, und 15 patients staged BCLC B, and by 47, 18, and 6 patients staged BCLC C, respectively. The first, second, and third questionnaires were completed by 57, 28, and 14 patients with initial AFP concentrations < 8 IU/ml, by 63, 33, und 16 patients with initial AFP concentrations 8–400 IU/ml, and by 38, 8, and 1 patients with initial AFP concentrations > 400 IU/ml, respectively. The first, second, and third questionnaires were completed by 143, 61, and 25 male patients, and by 38, 13, and 7 female patients, respectively.

## Quality of life

Patients who underwent at least one intervention ($n = 119$; sorafenib, chemotherapy, TACE, RFA, SIRT, radiotherapy, resection) had similar dimensional scores compared to patients without any intervention ($n = 62$) when they completed the first SF36 questionnaire (Fig. 1a). However, in the Kaplan–Meier analysis, a significant survival benefit for patients who underwent any intervention could be shown (mean survival in years 4.3 vs. 1.6; $P < 0.01$, Suppl. Figure 1). Systemic interventions such as sorafenib and chemotherapy resulted in lower scores for role limitations due to physical health (RP), significantly for sorafenib-treated

**Table 2** Performed interventions of the studied HCC patients were analyzed according to the time point prior or after completion of the first SF36 questionnaire

| | Number of completed questionnaires independent of 1. SF36 | Percentage (%) of completed questionnaires independent of 1. SF36 | Number of patients with interventions prior to 1. SF36 | Percentage (%) of patients with interventions prior to 1. SF36 | Mean interval (days) of intervention prior to 1. SF36 | Mean duration (days) of intervention |
|---|---|---|---|---|---|---|
| Individual patients | 181 | | 181 | | | |
| Patients with TACE | 68 | 37.6 | 53 | 29.3 | 386 ± 456 | 296 ± 356 |
| Patients with SOF | 101 | 55.8 | 53 | 29.3 | 277 ± 321 | 348 ± 473 |
| Patients with SIRT | 25 | 13.8 | 11 | 6.1 | 137 ± 141 | NA |
| Patients with resection | 61 | 33.7 | 53 | 29.3 | 716 ± 722 | NA |
| Patients with CHT | 11 | 6.1 | 5 | 2.8 | 258 ± 113 | 117 ± 76 |
| Patients with RFA | 24 | 13.3 | 12 | 6.6 | 299 ± 175 | NA |
| Patients with radiatio | 14 | 7.7 | 6 | 3.3 | 223 ± 214 | NA |
| Patients with any intervention | 160 | 88.4 | 119 | 65.7 | 387 ± 484 | |
| Patients with multiple interventions ($n \geq 2$) | 93 | 51.4 | 54 | 29.8 | | |
| Patients with no intervention | 21 | 11.6 | 62 | 34.3 | | |

For patients after SIRT, hepatic resection, RFA, and radiation therapy, no date of the last procedure was obtained

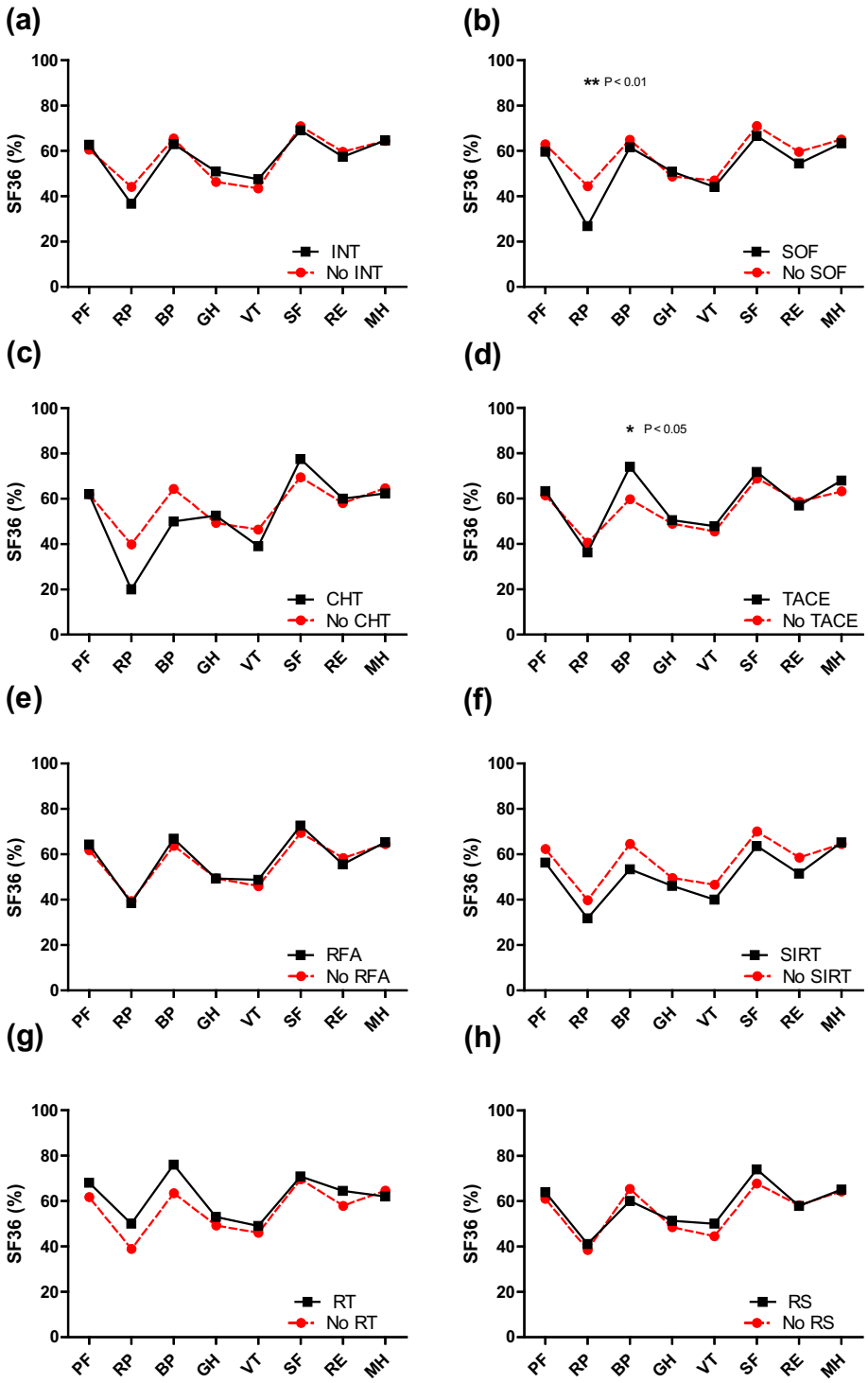


**Fig. 1** SF36 eight dimensions in relationship to intervention. The SF36 questionnaire contains 36 questions with normalized scores ranging from 0 (absence of QoL) to 100 (optimal QoL) in eight dimensions: physical function (PF), role limitations due to physical health (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Following comparisons are shown of patients who underwent the stated intervention prior to the first SF36: **a** patients with and without intervention (INT, $n=119$; no INT, $n=62$), **b** patients with and without sorafenib treatment (SOF, $n=53$; no SOF, $n=128$), **c** patients with and without chemotherapy (CHT, $n=5$; no CHT, $n=176$), **d** patients with and without transarterial chemoembolization (TACE, $n=53$; no TACE, $n=128$), **e** patients with and without radiofrequency ablation (RFA, $n=12$; no RFA, $n=169$), **f** patients with and without selective internal radiation therapy (SIRT, $n=11$; no SIRT, $n=170$), **g** patients with and without radiotherapy (RT, $n=6$; no RT, $n=175$), **h** patients with and without hepatic resection (RS, $n=53$; no RS, $n=128$)

patients after having completed the first SF36 questionnaire (26.9 vs. 44.1; $P<0.01$; Fig. 1b). The performance of a TACE was associated with a significantly higher result for control of pain (74.1 vs. 59.7; $P<0.05$; Fig. 1d). Dimensional scores did not differ between patients who had undergone RFA treatment and those who had not (Fig. 1e). Although not significant, patients had lower SF36 scores after SIRT throughout all dimensions, whereas patients who underwent radiotherapy appeared to have higher post-interventional scores (Fig. 1f, g). No significant change in dimensional scores was observed in hepatic resected patients (Fig. 1h). Furthermore, Kaplan–Meier analysis

showed a significant survival benefit for patients who underwent hepatic resection (mean survival in years 6.3 vs. 2.7; $P < 0.0001$, Suppl. Figure 1).

The mean total SF36 score deteriorated significantly throughout the third sequel questionnaires between patients initially staged as BCLC C and those staged as BCLC A (66.9 vs. 34.3; $P < 0.05$). Although not significant, a similar relation between these groups was observed for summary score of the physical function and mental health. BCLC stadium D was excluded from analysis due to the limited number of patients who completed sequel questionnaires (Fig. 2a–c). Elevated initial AFP concentrations above 8 IU/ml were associated with a greater loss of physical function and mental health in the sum analysis compared to patients with an initial AFP below 8 IU/ml. Even lower SF36 scores were registered for patients with very high initial AFP concentrations exceeding 400 IU/ml (Fig. 2d–f). Analysis of SF36 results revealed lower values for the total SF36, the sum of the physical function, and sum of the mental health score for women compared to men. However, this association was not significant and did not change over time during the course of sequel questionnaires (Fig. 2g–i).

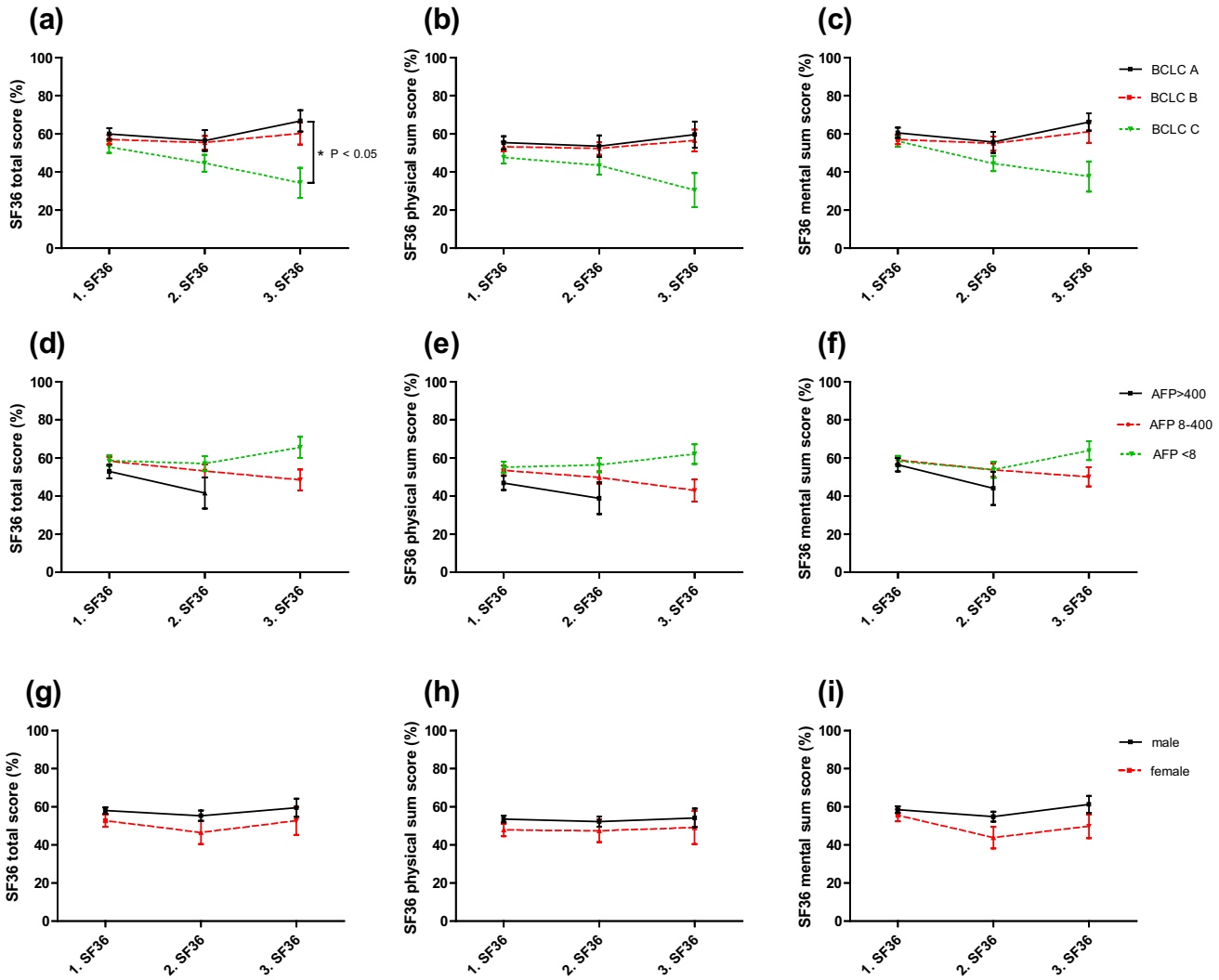


**Fig. 2** SF36 summary scores along sequel questionnaires. SF36 physical function and mental health summary scores, and total SF36 score were analyzed along three sequel questionnaires (1., 2. and 3. SF36). Patients are stratified by Barcelona Clinic Liver Cancer (1. SF36; BCLC; A, $n=48$; B, $n=69$; C, $n=47$) stadium in the figures (**a**), (**b**) and (**c**) and results of total, physical function, and mental health sum score are depicted, respectively. Elevated AFP concentrations (1. SF36; AFP; < 8 IU/ml, $n=57$; 8–400 IU/ml, $n=63$; > 400 IU/ml, $n=38$) correlate with deterioration of SF36 total score, physical function, and mental health sum, respectively, for figures (**d**), (**e**) and (**f**). Female sex (1. SF36; female, $n=38$; male, $n=143$) is associated with lower, although not significant total, physical function, and mental health sum score, demonstrated in figures (**g**), (**h**) and (**i**), respectively

## Discussion

Preserving quality of life in cancer patients has become an important therapeutic goal and is considered to be equal in significance to radiographic tumor response and survival rates by patients and clinicians (Heffernan et al. 2002; Li and Yeo 2017; Van Cleave et al. 1999). In this cross-sectional study, our findings show a greater loss of physical role in patients with HCC receiving to those not receiving systemic treatments. Our studied HCC population represents predominantly male patients (79%) with a median age of 63.8 years, and most frequently with a history of viral hepatitis followed by alcoholic liver disease. These patients' characteristics comply with previously published cohorts (Brunocilla et al. 2013; Hartrumpf et al. 2018; Kirstein et al. 2017). In consistency with Kondo et al. (2007), female sex appeared to be a predictor for lower QoL scores throughout sequel questionnaires, although it is not significant in our analysis.

Deterioration of QoL during sorafenib treatment can be partially explained by systemic side effects such as diarrhea, nausea, and fatigue (Gill et al. 2018), which hamper daily physical activities and, therefore, should be critically evaluated in this palliative setting. Under everyday conditions, drug-related adverse events resulted in one-third of patients with HCC (12/36) in permanent sorafenib treatment discontinuation, representing the most frequent cause of sorafenib withdrawal (Brunocilla et al. 2013). Brunocilla et al. (2013) found that throughout weeks 1, 4, and 8, sorafenib treatment significantly reduced the physical wellbeing score in the FACT-Hep questionnaire. This was confirmed by our results showing a significantly lower SF36 physical role score for sorafenib-treated patients compared to those HCC patients not receiving sorafenib. Patients receiving sorafenib reported similar scores for controlling body pain as patients without sorafenib; however, patient control of body pain appeared to be lower for those treated by a chemotherapy regimen. Whether this observation is related to drug-related adverse events such as polyneuropathic pain mediated by platinum-based regimens (Zedan et al. 2014), remains uncertain due to the limitation of unbalanced patient numbers within the interventional sub-groups in our cross-sectional analysis.

In contrast, our study reveals significantly higher control of body pain QoL scores for patients after TACE compared to patients without TACE. Wible et al. (2010) described consistent improvement in SF36of body pain scores 4 months after the initial TACE procedure. Increased control of body pain after TACE may represent a long-term effect occurring after 2 weeks, as Hinrichs et al. (2017) reported controversial results showing increased symptom severity of pain comparing individual pre- and 2 weeks post-TACE treatment using QlQC30 and HCC18 questionnaires. According to Toro et al. (2012) the FACT-Hep questionnaire at 24 months after intervention shows that hepatic resection provided the best QoL data, followed by RFA. TACE was superior to no intervention; nevertheless, performing a TACE was inferior to both hepatic resection and RFA. Repetitive TACE interventions did not result in a significant change in QoL including parameters for Global Health, Physical Functioning, fever, pain, nausea, and vomiting (Hartrumpf et al. 2018). In the same study, a higher than average Physical Functioning score at baseline as well as a higher initial Global Health score proved to be independent risk factors for a greater decrease of these scores after TACE (Hartrumpf et al. 2018).

In our cohort of patients treated by RFA, no difference in all eight SF36 dimensions was seen and even appeared to line up with patients not having been ablated. The enhancing effect on QoL scores by RFA treatment in contrast to patients after liver transplantation and hepatic resection (He et al. 2018) could not be reproduced in our cohort, which can be partially explained by including additional systemic and locoregional interventions in the reference cohort. Furthermore, Toro et al. (2012) reported no significant change of QoL data over a period of 24 months after RFA, yet an overall deterioration in QoL over time was observed in contrast to a beneficial effect of hepatic resection. On the contrary, Huang et al. (2014) attribute better clinical outcome to RFA compared to hepatic resection based on QoL analysis. For our cohort of patients who underwent hepatic resection, no significant difference was found in any of the dimensional scores compared to patients without hepatic resection. As both RFA and hepatic resection appear in our cohort not to worsen QoL, this encourages the choice of these methods with curative intention.

Albeit not significant, the performance of SIRT appeared to be associated with lower QoL score throughout all eight dimensions. A similar negative trend was reported 3 months after Yttrium-90 therapy for the General Health dimension, whereas overall no significant change of QoL could be evaluated by the SF36 questionnaire (Xing et al. 2018). In addition, no significant worsening of any FACT-Hep subscale could be documented for the 13 patients treated by SIRT in a pilot trial (Kolligs et al. 2015).

No statistic QoL difference was seen in patients receiving stereotactic ablative radiotherapy, consistent with the results of Mutsaers et al. (2017). Radiotherapy for HCC was associated with a significant decline in Child–Pugh score; however, low rates of late adverse events and minimal overall toxicity have been attributed to this treatment modality (Wahl et al. 2016).

Our study identified a predictive value of the BCLC status C in association with a greater total SF36 score deterioration over the period of sequel questionnaires compared to BCLC status A. In addition, initially normal concentration (< 8 IU/ml) of the tumor marker AFP was a predictor for preserving physical function and mental health in the sum

analysis as initially elevated AFP concentrations (> 8 IU/ml) correlated with a greater loss of sum scores over time. AFP concentrations initially exceeding 400 IU/ml were associated with even lower SF36 total and physical function and mental health sum scores; however, our study shows limitations due to the low number of patients completing the second and third questionnaire. For this population in the REACH trial—patients treated with ramucirumab as second-line treatment following sorafenib—Qol deterioration as measured by the FHSI-8 questionnaire at the end of treatment was significantly reduced compared to the placebo group (Chau et al. 2017).

The scarcity of QoL data available from randomized clinical trials about individuals with early- and intermediate-stage HCC has been emphasized in Cochrane analyses in 2017 by Majumdar et al. (2017) and Roccarina et al. (2017), respectively. In line with this, our findings highlight the need for further research due to limited data available comparing QoL in HCC patients subject to different locoregional and systemic antineoplastic interventions as well as with regard to gender-related differences in QoL. Our analyses prove advanced disease—as defined by higher BCLC stage and elevated AFP concentrations—to predict greater deterioration of QoL over time. Due to the low patient numbers in some interventional subgroups, we see the need for the study of a larger cohort, preferably multicenter based. Despite these limitations, in our study, systemic treatment correlates with lower physical role, whereas the performance of TACE was associated with better control of body pain. These findings may assist the future pursuit for the selection of systemic and locoregional interventions accounting also for the impact upon QoL.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interest.

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