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Health related quality of life as a prognostic in advanced cancer patients

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Abstract

Background and Aims—Evidence continues to accumulate regarding the association between health related quality of life (HRQL) and survival across chronic diseases. The aims of the present study were to investigate the prognostic value of HRQL in patients with hepatocellular carcinoma and cholangio carcinoma after adjusting for sociodemographic, disease-, and treatment-related factors.

Methods—A total of 321 patients diagnosed with hepatocellular or cholangio carcinoma were administered the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) instrument. Cox regression and Kaplan Meier survival analyses were performed to test the association between the five domains of HRQL and survival.

Results—Using Cox regression, overall HRQL was found to be significantly associated with survival (p=0.003), after adjusting for demographic, disease-specific factors and treatment. Subscales of the FACT-Hepatobiliary, including the physical well-being (p=0.02) and the Symptoms and Side Effects subscale (p=0.05), were also found to be significantly associated with survival after adjusting for demographic, disease specific factors, and treatment.

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Conclusion—Health related quality of life was found to be prognostic of survival in patients with hepatocellular and cholangio carcinoma while covarying for demographic, disease-specific factors, and treatment. Stratifyng patients based on HRQL when testing novel treatments may be recommended.

Introduction

Evidence is accumulating in regard to the prognostic value of health related quality of life (HRQL) across chronic illnesses.[1–25] The value of HRQL in predicting survival has been most extensively studied in oncology.[6–25] With a single published exception,[1] studies consistently show that higher HRQL is associated with longer survival across cancer types.[3–24] In addition to overall HRQL, specific symptoms such as anorexia, nausea, weakness, and appetite have been found to be significant predictors of survival in advanced cancer.[2–4]

It is unclear whether HRQL holds similar prognostic value for survival in patients diagnosed with advanced cancer such as hepatocellular (HCC) and cholangio carcinoma (CCC) as these cancer types present at diagnosis at advanced stages and often with a poor prognosis. Poon and colleagues began to address the association between HRQL and survival in patients with *resectable* HCC, which have a better prognosis than those who cannot undergo surgical interventions.[5] The majority of cases of HCC and CCC in the U.S. present at advanced stages and are unresectable (≥80%). No study to date has tested the link between HRQL and survival in patients who are unresectable and who do undergo surgical intervention to treat HCC and CCC. This is an important omission in the literature, as it is expected that the incidence of hepatocellular carcinoma will double in the next decade due to the increased incidence of hepatitis C and the majority of patients will be those who cannot undergo surgical resection or transplantation.[6] Moreover, quality of life is of particular importance in this cancer population due to the modest survival benefits reported with available treatments.[7, 8]

Limitations of previous research concerning the HRQL as a prognostic indicator for survival in cancer has (1) assumed that the relationship between HRQL and survival is linear, (2) has not included all the data in the analyses (e.g., only used data in upper and lower quartiles of overall HRQL scores), (3) utilized general HRQL instruments rather than disease-specific instruments,[2–4,9–14] and/or (4) specific to this patient population only included patients who were eligible for surgical intervention and, as a result, had better prognosis. The study will also examine whether each of the domains of a disease-specific instrument measuring HRQL is associated with survival. It was expected that overall HRQL would remain a prognostic indicator of survival, despite the poor prognosis associated with HCC and CCC. The symptom and side effect domain of the FACT-Hep was also expected to be associated with survival. All available data were analyzed and linear and non-linear relationships between HRQL subscale scores and survival were explored.

Methods

Design

The study was prospective in design and data was collected between August 2000 and September 2009.

Participants

Three hundred and twenty-one patients diagnosed with hepatocellular (HCC) or cholangio carcinoma (CCC) were recruited from the University of Pittsburgh Medical Center. Inclusion and exclusion criterion specified that (1) the patient was diagnosed with radiographic or biopsy proven HCC or CCC, (2) was 18 years or older, and (3) fluent in English; (4) no evidence of suicidal or homicidal ideation, hallucinations, or delusions; or (5) patient did not undergo orthotopic liver transplant. Patients included in this study were recruited as part of ongoing psychosocial research (NCIK07CA118576; NCIR21CA127046; American Cancer Society) and inclusion was not based on treatment.

Sociodemographic, Disease-Specific Factors, and Treatment

Sociodemographic, disease, and treatment-specific information was collected from medical records. Survival was assessed from the data of diagnosis until death and then recorded in days. If the patient was lost to follow-up, the patient's date of death was obtained through the Social Security Death Index.

Instruments/Assessment

The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)[15] was used to assess changes in symptoms and side effects of treatment. The FACT-Hep includes both the FACT-General[16] (a 27-item instrument that measures four dimensions of quality of life) and a module with 18 items specific to hepatobiliary disease[15]. The FACT-G has four subscales including a physical (PWB), social and family (SFWB), emotional (EWB), and functional well-being (FWB). The hepatobiliary module includes items that pertain to symptoms of the disease as well as side effects of the treatment. The FACT is one of the most widely utilized quality of life questionnaires in clinical trials for new cancer treatments and both the FACT-G, as well as the FACT-Hep, have been demonstrated to be valid and reliable instruments.[15,16]

Procedure

The study received Institutional Review Board approval and patients provided written informed consent prior to their participation. Upon receiving written consent, patients were administered a battery of questionnaires including the FACT-Hepatobiliary by a clinical psychologist. The patient's HRQL was assessed at the time of diagnosis and patients were followed until death or until lost to follow-up.

Data Analysis

The data were analyzed using SPSS v.21. Descriptive statistics were performed to describe sociodemographic, disease, and treatment specific characteristics of the sample. Cox

Regression analyses was employed and all available sociodemographic (i.e., age, gender); disease-specific variables (i.e., Model End Stage Liver Disease [MELD] score, tumor size, number of lesions, vascularity of lesion, vascular invasion); and treatment were entered into the equation followed by the overall HRQL score, as well as the five domains of the FACT-Hep (e.g., physical well-being, emotional well-being).

Results

Three hundred and forty-five patients were approached for participation in the present study. Of the 345 patients, 321 (93%) patients agreed to participate in the study. There were no significant differences between those patients who agreed to participate versus those who refused to participate on sociodemographic, disease or treatment-related factors. The majority of the sample was male (76%), which is relatively consistent with the 2:1 ratio often observed in this cancer type in North America and Europe.[30] The mean age was 65 years (range 27 to 94 years). The median survival was 268 days and 71% of the patients had died at the time of analyses. Further details of the sociodemographic, disease, and treatment-related characteristics of this sample can be found in Table 1.

Cox regression analyses were performed to test a model that included all available sociodemographic, disease-specific variables, treatment type, and HRQL on survival. None of these significantly predicted survival in the present study. Overall HRQL was found to be significantly associated with survival after adjusting for demographic, disease-related, and treatment type (p=0.03). See Table 2 and Figure 1.

Additional subscales of the FACT-Hepatobiliary were also found to be associated with survival including the physical well-being (p=0.02) and symptoms and side effects (HepCS) subscale (p=0.03) after adjusting for demographic and disease specific factors. See Table 3–4.

Discussion

Consistent with prior research, overall HRQL was found to be associated with survival in patients diagnosed with HCC. Using all available data, a linear relationship was found between overall HRQL and survival. Patients reporting the highest level of overall HRQL were found to have the longest survival followed by those in the middle and lowest tertile of overall HRQL. A similar pattern was observed between symptoms and side effects subscale of the FACT-Hepatobiliary with high levels of symptoms and/or side effects being associated with decreased survival. Recent research has begun to explore the association between symptom clusters (e.g., sickness behavior) and associated biomarkers such as cytokines.[17] Although further research is needed to understand the possible association between symptoms, underlying biological mechanisms and disease progression; the results of the present study reflect a possible association between symptoms and side effects of treatment for HCC and survival.

As would be expected, trends toward significance were observed, where patients who had low levels of physical and functional well-being also experienced increased mortality. Consistent with prior research including studies performed our team, [28,31,42–47] a trend

toward significance was observed between emotional well-being and survival, in which low levels of reported emotional well-being were found to be associated with increased mortality. One possible explanation to explain the association between depression and survival may include immune system dysregulation, which has been previously reported by this team.[45]

The present study addressed the limitations of prior research including adjusting for sociodemographic (e.g., age, gender), disease (e.g., tumor size, vascular invasion), and treatment-related predictors in the model that tested the association between HRQL and survival. The investigators used all available data and analyzed linear and non-linear relationships between HRQL and survival. A disease-specific HRQL instrument was also employed in the present study and the sample included patients who were not recommended for treatment as well as those who received surgical and nonsurgical intervention for hepatocellular carcinoma.

The limitations of the present study included the small number of patients treated with surgical interventions. However, Poon and colleagues only included patients who underwent resection and reported similar results in that HRQL was predictive of survival in a cohort of resectable HCC patients.[24] The large confidence intervals observed in the Cox regression analyses for the treatment variables may reflect a less precise hazard ratio. However, secondary to the multiple studies across cancer types as well as the results reported by Poon and colleagues, we have confidence that the association between HRQL and survival is likely accurate across treatment types.[24] The MELD score was included in the model as this is the staging system used at our center. If a different staging system was included in the model (e.g., TNM, CLIP) it may have resulted in differential findings. Finally, we did not include those patients who underwent liver transplantation due to the small number of patients (<10%) and significant difference in survival rates between those who undergo liver transplantation versus those who undergo resection, radiofrequency ablation and/or regional chemotherapy or radiation. It is possible that the findings may be different if these patients were included in the analyses.

Research continues to mount regarding the prognostic value of HRQL. Accordingly, future research in the area of HRQL and survival should explore possible mediating and moderating variables between HRQL and survival. Only until recently have randomized controlled trials become possible due to the modest benefits many previous treatments offered to this patient population. With the advent of Nexavar and combinations of drugs using TACE, the increase in randomized controlled trials testing the efficacy of novel treatments in patients with hepatocellular carcinoma may rise. Baseline HRQL may facilitate the stratification of patients to treatment arms in clinical trials or the interpretation of results of clinical trials testing the efficacy of novel treatment strategies for this patient population. Outside the context of a clinical trial, baseline HRQL may also facilitate clinical decisions regarding treatment options for patients diagnosed with hepatocellular carcinoma.

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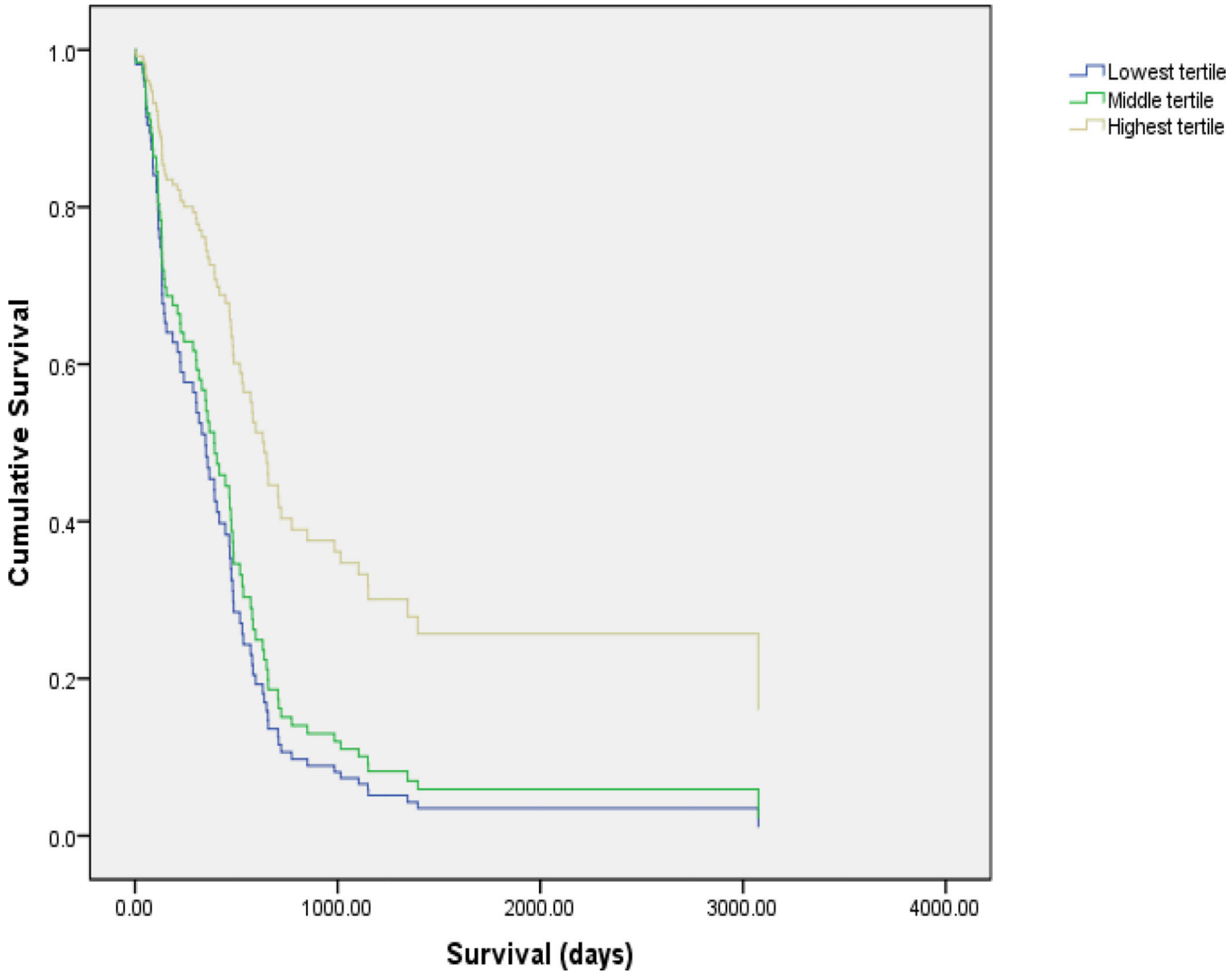

Figure 1.

Table 1

Sociodemographic, disease-, and treatment-related characteristics of sample

Male (n, %)	217 (76)
Age (years)	
Mean (range)	65 (27–94)
Model for End Stage Disease (MELD)	
Mean (range)	10 (6–26)
Tumor Size (cm)	
Mean (range)	6.6 (1–20)
Number of Lesions	
Mean (range)	3.4 (1–6)
Vascular invasion (n, %)	104 (41)
Vascularity (n, %)	
Hypovascular	46 (20)
Hypervascular	177 (76)
Mixed	11 (5)
Treatment	
No Treatment	15 (5)
TACE	153 (54)
90-Yttrium	82 (29)
Radiofrequency Ablation	9 (3)
Resection	26 (9)

Table 2

Cox regression analyses of health related quality of life and survival after adjusting for demographic, disease-, and treatment -related predictors

	B	p-value	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
AGE					
Ref: <50 years	.055	.892	1.056	.480	2.325
GENDER					
Ref: male	.451	.164	1.570	.832	2.962
MELD	.020	.504	1.020	.963	1.080
TUMOR SIZE					
Ref: <5cm	.507	.035	1.660	1.036	2.660
LESION NUMBER					
Ref: <2	-1.010	.000	.364	.225	.590
VASCULARITY					
Ref: hyper		.214			
Mixed	−.963	.080	.382	.130	1.122
Hypo	−.935	.121	.393	.120	1.281
VASCULAR INVASION	.817	.001	2.264	1.380	3.713
TREATMENT					
Ref: TACE		.626			
90 Yttrium	.071	.897	1.074	.365	3.157
No treatment	−.242	.671	.785	.257	2.397
RFA	1.145	.329	3.143	.315	31.371
Resection	−.098	.904	.906	.184	4.457
HRQL					
Ref: Lowest tertile		.009			
Middle tertile	.904	.003	2.469	1.351	4.514
Highest tertile	.734	.018	2.084	1.135	3.824

Table 3

Cox regression analyses of Physical Well-Being Scale of the FACT-Hepatobiliary and survival after adjusting for demographic, disease-, and treatment-related predictors

Variable	B	p-value	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
AGE					
Ref:<50 years	−.097	.800	.907	.428	1.926
GENDER					
Ref: male	.448	.123	1.566	.886	2.768
MELD	.035	.199	1.036	.982	1.093
TUMOR SIZE					
Ref: <5cm	.580	.014	1.787	1.124	2.840
LESION NUMBER					
Ref: <2	−.857	.000	.424	.265	.678
VASCULARITY					
Ref: hyper		.267			
Hyper	−.894	.116	.409	.134	1.245
Mixed	−.958	.117	.384	.116	1.270
VASCULAR INVASION	.688	.005	1.991	1.225	3.236
TREATMENT					
Ref: TACE		.245			
90 Yttrium	.275	.575	1.316	.503	3.443
No treatment	−.216	.688	.806	.280	2.316
RFA	−1.083	.338	.338	.037	3.105
Resection	−.459	.564	.632	.133	3.011
Physical Well-Being					
Ref: lowest tertile		.015			
Middle tertile	.730	.008	2.075	1.210	3.560
Highest tertile	.068	.809	1.070	.616	1.859

Table 4

Cox regression analyses of Hepatobiliary Module (symptoms and side effects) of the FACT-Hepatobiliary and survival after adjusting for demographic, disease-, and treatment-related predictors

Variable	B	p-value	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
AGE					
Ref: <50 years	.037	.925	1.038	.479	2.249
GENDER					
Ref: male	.406	.177	1.501	.833	2.706
MELD	.006	.849	1.006	.949	1.066
TUMOR SIZE					
Ref: <5cm	.481	.043	1.617	1.016	2.574
LESION NUMBER					
Ref: <2	−.786	.001	.456	.289	.719
VASCULARITY					
Ref: hypervascular		.248			
Mixed vascularity	−.854	.120	.426	.145	1.251
Hypovascular	−.966	.099	.381	.121	1.201
VASCULAR INVASION	.815	.001	2.259	1.402	3.641
TREATMENT					
Ref: TACE		.244			
90 Yttrium	.655	.189	1.924	.725	5.107
No treatment	.240	.659	1.271	.439	3.679
Radiofrequency Ablation	1.661	.160	5.265	.518	53.492
Resection	.145	.857	1.156	.238	5.622
HepCS					
Ref: lowest tertile		.043			
Middle tertile	.686	.028	1.986	1.075	3.668
Highest tertile	.678	.025	1.970	1.088	3.568