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Does Health-Related Quality of Life Improve for Advanced Pancreas Cancer Patients Who Respond to Gemcitabine?

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Analysis of a Randomized Phase III Trial of the Cancer and Leukemia Group B (CALGB 80303)

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Abstract

Context—Gemcitabine for advanced pancreas cancer (APC) is palliative and prognosis is poor, making health-related quality of life (HRQOL) particularly important.

Objectives—We evaluated HRQOL with the EuroQol EQ-5D™, in patients with APC participating in Cancer and Leukemia Group B (CALGB) 80303, a multicenter, double-blind, randomized trial comparing overall survival (OS) between two treatment arms, gemcitabine with bevacizumab, or gemcitabine with placebo.

Methods—A consecutive subsample of patients was invited to complete the EQ-5D surveys. Because neither clinical nor HRQOL outcomes differed based on study arm, analyses were pooled. Changes in mean scores from baseline to eight weeks and the prognostic value of the EQ-5D were evaluated.

Results—Mean index scores remained stable (0.78 at baseline [n=267], 0.79 at eight weeks [n=186], P-value=0.34, Wilcoxon signed rank test), attributable to a modest deterioration of physical function domain scores coincident with small improvements in pain and anxiety/depression scores. A small decline in visual analogue scale (VAS) scores was observed (70.7 vs. 68.2, P-value=0.026). HRQOL changes within chemotherapy response strata revealed stable index scores, but a trend of worsened physical function among patients with disease progression compared with those with stable or improved disease. VAS scores trended downward over time irrespective of chemotherapy response status, with a statistically meaningful deterioration in patients who progressed (68.9 vs. 64.4, P-value=0.029). Baseline scores from both EQ-5D scales were significant predictors of OS in Cox proportional hazard models.

Conclusion—Response to gemcitabine treatment in APC is not associated with appreciable improvement of global HRQOL. Small improvements in pain and mood are observed despite progressive functional decline. Those who respond to gemcitabine may experience a slight slowing of functional deterioration.

Keywords

Advanced pancreas cancer; gemcitabine; quality of life

Introduction

Advanced pancreas cancer (APC) is a lethal disease with median survival of four to nine months.[1-2] Gemcitabine-based chemotherapy is the current backbone of standard treatment for APC.[3-6] The approval of gemcitabine by the U.S. Food and Drug Administration for use

in APC was based on improvements in a composite endpoint called “clinical benefit response,” which combines pain palliation, analgesic reduction, weight gain, and clinician-reported performance status improvement. This efficacy endpoint did not account for the impact on patients of the toxicity of the drug. Therefore, because the goal of treatment is palliative. Subsequent efforts have focused on characterizing the overall effects of this drug on patients’ quality of life (QOL).

Previously, there has been conflicting evidence describing the impact of gemcitabine-based treatment on health-related quality of life (HRQOL). Although some clinical trials have suggested improvement in HRQOL,[7-8] others have reported no improvement or a decline in HRQOL among patients treated with gemcitabine.[4, 9-11] It has been posited that *response* to treatment is associated with HRQOL benefits.[4]

We sought to assess whether response to gemcitabine is associated with changes in overall and individual domains of HRQOL in the context of Cancer and Leukemia Group B (CALGB) 80303, a multicenter, double-blind clinical trial in which patients with APC were randomized to gemcitabine with bevacizumab (GB), or to gemcitabine with placebo (GP).[12] The clinical trial failed to demonstrate any difference in overall or progression-free survival between treatment arms.[12] The longitudinal HRQOL assessments, however, provided an important opportunity to evaluate HRQOL outcomes in patients with APC and their relationship to both treatment response and prognosis. We also evaluated the prognostic value of baseline scores from the EQ-5D index scale and the VAS in APC.

Methods

Patients

Patients were accrued to CALGB 80303 from June 2004 to April 2006 at CALGB sites and at other U.S. centers participating in the National Cancer Institute’s (NCI) Cancer Trials Support Unit (CTSU). Patients were eligible if they presented with APC and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Eligible patients had histologically or cytologically confirmed pancreas cancer that was not amenable to curative resection (advanced disease). This means that the cancer diagnoses were confirmed by biopsy, not by clinical criteria alone. This corresponds to American Joint Committee on Cancer (AJCC) clinical stage III-IV pancreas cancer. AJCC staging is not routinely used in pancreas cancer. Rather, pancreas cancers are routinely categorized on the basis of whether or not they are resectable (amenable to a Whipple procedure) or unresectable (not amenable to a curative intent surgical resection). Eligibility criteria for the parent trial stipulated that patients had to have disease that was not amenable to curative intent surgical resection.

Prior adjuvant chemotherapy and radiation therapy were permissible if patients had not received gemcitabine. Protocol therapy was delivered on days 1, 8 and 15 of a 28-day cycle and continued until disease progression. Patients were restaged every eight weeks and categorized as having progressive disease (PD), stable disease (SD), or complete response (CR) to protocol treatment, using pre-specified, established criteria.

Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

HRQOL Instruments

HRQOL data were planned and systematically collected during this trial in order to calculate the incremental cost per quality-adjusted life year for a planned economic analysis; the EuroQOL EQ-5D™ index and the EQ-5D visual analogue scale (VAS) are routinely used

for this purpose.[13] The Subjective Significance Questionnaire (SSQ) was included to anchor responses to the EQ-5D.[14]

EQ-5D Dimensions and Index—The EQ-5D instrument has well-established psychometric properties.[15] The index scale is a five-item, generic measure of HRQOL according to five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension is divided into three response levels from "no problems," "some problems" to "severe problems." The unique sets of scores across the five domains define a health state. The 243 possible health states have been weighted using population-derived valuations from a sample of the U.S. general population and can thus be expressed as a composite index score.[16] The plausible range of the index scores using U.S. weightings ranges from -0.11 to 1.0 on a scale where 0.0 = death and 1.0 = perfect health. The index score reflects *societal preferences* for a given health state. The index scale has demonstrated reliability and validity in patients with advanced cancer.[17] It is routinely included in economic analyses because it permits estimation of utilities based on societal valuations of particular health states, which are used to generate quality-adjusted life years, the denominator in calculations of incremental cost-effectiveness ratios.[18]

VAS—The VAS is represented by a 20-cm vertical thermometer, with values ranging from 0 (worst imaginable health state) to 100 (best). It is a single-item, self-rated assessment of global HRQOL that provides a snapshot of a person's health status "today," and reflects the *patient's own valuation* of his or her health state.

SSQ—The Subjective Significance Questionnaire (SSQ) overall QOL item was used as an external anchor to validate the responsiveness of the EQ-5D in our cohort to changes in HRQOL over time.[19] Respondents to the SSQ indicate if they feel they are very much worse to very much better compared to a prior assessment on a 7-point scale.

HRQOL Data Collection

HRQOL assessments were planned for a consecutive subsample of patients who first enrolled in the clinical trial and began protocol therapy. The sample size for the HRQOL surveys was governed by the economic endpoint of detecting a meaningful cost difference. Namely, it was determined that with an accrual of 240 patients, a moderate effect size of 0.363 in a cost-minimization analysis could be detected with an 80% power at a 0.05 significance level with a two-sided *t*-test. Although the planned economic analysis was rendered moot by the failure of bevacizumab to improve survival, the serial HRQOL assessments provided an important opportunity to evaluate HRQOL outcomes in patients with APC and their relationship to treatment response and prognosis. HRQOL was prospectively assessed in CALGB 80303 at baseline and at eight weeks, which corresponded with interval restaging.

At baseline, the EQ-5D and the VAS were administered in clinic prior to initiation of protocol therapy. Patients were instructed at that time by trained research assistants on the completion of the surveys. Patients who consented to participate in the economic companion study were invited to complete follow-up HRQOL assessments by telephone. The telephone EQ-5D survey administration is one of the possible modes of administration supported by the EuroQOL Group. Accordingly, patients were provided with paper copies of the original instrument in a notebook, which included the VAS for reference at the time of the telephone interview.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson.

Statistical Analysis

HRQOL analyses were conducted using a landmark analysis (conditioning upon survival at eight-week follow-up),[20] in a blinded fashion, on 186 patients who completed the HRQOL questionnaires both at baseline and again at eight weeks. To assess response bias, we compared the baseline characteristics and overall survival (OS) of the 186 patients who completed the HRQOL survey at follow-up (the analytic cohort for the HRQOL analysis) to the 64 who completed the baseline EQ-5D instrument but chose not to complete the 8-week survey. We also compared OS between the analytic cohort and the remaining 154 patients alive at eight weeks who began protocol therapy, but who, as planned, did not partake in the HRQOL assessments. A Kaplan-Meier analysis and the log-rank test were used to compare OS between groups.

EQ-5D scores between groups were compared using the Wilcoxon rank sum test. Paired comparisons of HRQOL change scores from baseline to week eight were analyzed using the Wilcoxon signed rank test.

The baseline, eight-week and change scores of the index and VAS scales were comparable between arms (Table 2). Based on the similarity of HRQOL scores, subsequent analyses were based on pooled scores.

We used multivariate Cox proportional hazard models to assess the independent prognostic value of the EQ-5D scales for OS with prognostic factors for survival including age, extent of disease (locally advanced, metastatic) and ECOG PS, and potential confounders (race/ethnicity, and gender) included in the models.[22]

Statistical significance was set at a two-sided *P*-value of 0.05. Domain-specific level of functioning at baseline and at eight weeks was summarized descriptively using frequencies of patient-reported problems in each domain of the EQ-5D.

The sensitivity of the EQ-5D scales to change in HRQOL was assessed by comparing changes of the EQ-5D responses to the SSQ QOL item.[15] “Moderate” and “little” change categories of the SSQ item were combined because of the modest number of patients in each category. We calculated nonparametric Spearman rank correlations between SSQ QOL and the index and VAS score changes from baseline to eight weeks to assess the usefulness of the SSQ as an external anchor.[22] We also evaluated the ceiling and floor effects of change scores for the index and VAS scales.[16] All analyses were conducted using SAS, v.9.1 (SAS Institute, Cary, NC). Statistical analyses were performed by CALGB statisticians.

Results

Patients

Of 602 patients randomized, 544 patients began protocol therapy (Fig. 1). Follow-up EQ-5D survey completion was planned for a subset of consecutively enrolled patients who began protocol treatment. Of 366 who consented to HRQOL telephone interviews, 267 (73%) patients completed the baseline EQ-5D survey and 186 (70%) patients completed the eight-week follow-up EQ-5D telephone interview. Seventeen patients who responded to the baseline EQ-5D died prior to the eight-week assessment, and 64 either refused or could not be reached for follow-up. Both the baseline and follow-up EQ-5D surveys were completed by 186 patients, who constitute the analytic cohort.

The baseline patient and disease characteristics for this analytical cohort were comparable to the remaining patients in the study who were not part of the HRQOL assessments but who were followed through eight weeks (*n*=154, data not shown). These two groups also had similar OS (Fig. 2).

Baseline characteristics for the economic companion participants are shown in Table 1. Patients who did (*n*=186) and did not (*n*=64) provide follow-up EQ-5D surveys had similar demographic and clinical characteristics. The index and VAS scores at baseline did not differ between these two groups (data not shown). However, a higher proportion of patients who completed eight-week EQ-5D surveys (*n*=186) responded to chemotherapy or had stable disease compared to the group that did not complete the follow-up survey (*n*=64, *P*-value <0.0001). The follow-up survey group also had a significantly longer OS compared to the no follow-up group (*P*-value=0.0189).

EQ-5D and Overall Survival

Baseline EQ-5D scores were prognostic for OS in unadjusted analyses (Fig. 3). In a Cox proportional hazard model, baseline EQ-5D scores remained a statistically significant predictor of OS (EQ-5D index: adjusted hazard ratio [HR]=0.98, 95% confidence interval [CI] 0.97-0.99; VAS: adjusted HR=0.99, 95% CI 0.98-0.99) after adjusting for age, race, ethnicity, gender, ECOG PS and extent of disease at baseline.

HRQOL

Overall Scores—The mean baseline index score was 0.78 for patients who completed the survey, a value similar to that reported by a representative sample from the U.S. general population, 0.79 (Table 2).[17] The mean index score at follow-up was essentially unchanged (*P*-value=0.3409, paired comparisons from baseline to eight weeks).

A different pattern emerged for self-rated valuations of global HRQOL. First, the mean baseline VAS score was markedly lower than general population norms (70.7 vs. 84.2). Second, a modest but statistically significant decrement in VAS scores was noted at eight-week follow-up (mean VAS change score=−2.81, *P*-value=0.0259, Table 2).

Scores by Response to Chemotherapy—At week 8, index scores remained stable in the SD, CR and partial response (PR) groups, but declined from 0.77 at baseline to 0.73 at week 8 (*P*-value=0.2377, Table 2) among patients with PD. Unlike the index scale results, VAS scores declined irrespective of response status to treatment at eight weeks. The decrement was greater for the PD group (mean VAS change score=−5.78, *P*-value=0.0289) than the SD group (mean VAS change score=−1.49, *P*-value=0.2231). In the CR/PR group, the VAS scores declined (mean VAS change score=−2.76, *P*-value=0.4790).

EQ-5D Responsiveness in APC—We found the SSQ QOL item was correlated with the index (r=0.30, P-value=<0.0001) and VAS change scores (r=0.34, *P*-value=<0.0001), suggesting it was an acceptable external anchor for evaluation of responsiveness alongside both scales. As depicted in Fig. 4, the SSQ responses corresponded to the magnitude and the direction of the EQ-5D change scores.

We found no floor effects in the index scale since no patients reported a “worst” health state at baseline and at eight weeks. Five percent (10/186) of participants had a maximal index score at both baseline and follow-up, suggesting a negligible ceiling effect.

EQ-5D Domains—Compared to the U.S. general population, a larger proportion of patients in the analytic cohort reported problems in each index domain (Fig. 5), with pain/discomfort and anxiety/depression domains most pronounced.

Longitudinally, symptoms of anxiety/depression and pain/discomfort improved, whereas scores in all three domains of physical functioning worsened. Problems were most frequently reported in the usual activities domain, with 60% of patients reporting problems at eight weeks. A third of the participants had difficulty with mobility at follow-up and the number of patients with problems in the self-care domain more than doubled over time from 6% to 14% (Fig. 5).

An analysis of index domains by treatment response found that anxiety/depression and pain/discomfort improved or remained stable at eight weeks, irrespective of chemotherapy response, whereas scores in all three domains of physical functioning declined. In the PD group, despite improvement from baseline, 73% of patients reported problems with pain at eight weeks, with a bigger decline in physical functioning than among patients with stable or responsive disease.

Discussion

We relied on two widely used, easily administered metrics of the EQ-5D instrument to evaluate HRQOL in patients with APC treated with gemcitabine in the context of a large NCI cooperative group randomized trial. Our findings based on the brief EQ-5D instrument provided a snapshot of global HRQOL from both a patient (VAS) and an objective (societal, EQ-5D Index) perspective. Furthermore, our results provided insights about differing trajectories of the physical, emotional, and symptom components of HRQOL during treatment, which may explain conflicting results of prior HRQOL studies in advanced pancreas cancer.

We found that pre-treatment EQ-5D index scores in APC were not substantially different from scores derived from a sample of the U.S. general population, whereas VAS scores were considerably lower than those from the general population (mean of 71 versus 84). When we examined changes in scores from baseline to eight weeks, we found a statistically meaningful 2.8 mean decline in VAS scores, while index scores remained stable. Furthermore, changes in EQ-5D index scores did track with response to treatment, although the magnitude was modest. Specifically, patients with progressive disease had worse HRQOL at eight weeks compared to baseline, whereas those with stable or responsive disease experienced a slight mean improvement in HRQOL. In domain-specific reports, we found the proportion of patients reporting problems with pain/anxiety generally decreased, whereas mobility, self-care and ability to perform usual activities deteriorated. The decline in physical functioning was most pronounced in the PD group. Based on the VAS scores, patients typically had deterioration over eight weeks irrespective of response to gemcitabine. The decline, however, was double in magnitude for patients with disease progression compared to those with disease stabilization or response.

The VAS and index scales measure different constructs and provide complementary and useful information about HRQOL. The index scale reflects societal valuation of a health state according to five predefined dimensions, rendering them useful in cost-effectiveness analyses for policy decision making. The VAS, on the other hand, is a self-rating approach of global HRQOL. It allows patients to incorporate subjectively important domains into their valuation of HRQOL. For example, loss of appetite and fatigue may be factored into the VAS ratings, which are not confined to predefined (albeit important) domains. Given that

HRQOL is a highly individualized concept, the VAS scores provide valuable HRQOL data for clinical decision making on an individual patient level.

First, when counseling patients and assisting in decision making, it is important to recognize that, irrespective of response to gemcitabine, overall HRQOL does not typically improve, largely because of a decline in mobility and ability to participate in usual activities that overshadows any improvements in pain and anxiety scores. Of the five domains in the EQ-5D index score, pain and anxiety appear to be the most amenable to palliation. The high proportion of patients with problems in these domains is an important reminder of the need to focus on symptom management in APC. Further, patients' HRQOL scores at baseline are good prognostic indicators independent of ECOG PS.

Our results using a generic QOL instrument parallel findings from disease-specific instruments in APC. Using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 PAN-26, Reni et al.,[4] found patients with APC receiving gemcitabine reported stable or worse scores in global QOL and in functional scales (worse physical, emotional, social, role, cognitive functioning) at two months compared to baseline.[4] Improvement in some symptoms was noted (pain, dyspnea, sleep, appetite, constipation, pancreatic pain, digestive, hepatic, bowel habit, sexuality), while others remained stable or deteriorated over time (nausea, vomiting, fatigue, diarrhea, flatulence, cachexia). In another phase III trial, no significant changes on EORTC QLQ-C30 were noted over time for patients treated with gemcitabine.[9] There is mounting evidence that, although some symptoms improve, gemcitabine does not improve overall HRQOL scores in APC. Whether the pace of decline is slower with gemcitabine than with best supportive care cannot be ascertained from CALGB 80303.

We found that baseline scores for both the index and the VAS EQ-5D scales are predictive of OS in patients with APC. These findings corroborate QOL research in other cancers in which an independent association between baseline EQ-5D index scores and OS in terminal cancer patients has been identified.[23]

Our study should be interpreted in the context of several limitations. Because the randomized trial did not contain a control arm lacking gemcitabine, we cannot compare HRQOL for patients treated with gemcitabine to those treated either without chemotherapy or with combination regimens such as gemcitabine with erlotinib or gemcitabine with oxaliplatin. We also did not routinely collect information on supportive care interventions, which precluded us from analyzing the extent to which, for example, opioid analgesics or anxiolytics influenced the domain scores. Patients enrolled in randomized controlled trials tend to be healthier than the source population. Second, while respondents to the baseline EQ-5D survey were representative of the study population, we were not able to interview all patients at follow-up, evidencing some response bias. Based on analysis of survival curves, sicker patients were less likely to complete the follow-up. We mitigated response bias by analyzing changes in HRQOL for patients who provided estimates both at baseline and eight weeks later. We employed two modes of EQ-5D survey administration -- an in-person interview at baseline, and a telephone interview at follow-up. Although the EQ-5D is suitable for administration by either method, there is some potential for bias when the two methods are interchanged.

We found that, in APC, EQ-5D was quite responsive to longitudinal changes in HRQOL when anchored against SSQ. Further, we did not observe floor or ceiling effects in EQ-5D responses. These findings support the use of the EQ-5D to measure HRQOL changes in APC and corroborate the findings of other studies that demonstrate the responsiveness of the EQ-5D. For example, the EQ-5D index and VAS were equal in responsiveness to the global

health status scale of the EORTC QLQ C-30 for patients with liver metastases.[24] When compared to the Functional Assessment of Cancer Therapy-General scale, a disease-specific HRQOL instrument, the EQ-5D was shown to be sensitive to changes over time in patients with advanced cancer.[18] In addition, the EQ-5D provides complementary and informative data for clinical and policy decision making, including information on objective functioning and the patient's own global HRQOL assessment.

In conclusion, based on a large national cohort of patients with APC treated with gemcitabine, we did not find an improvement in global HRQOL even for patients who responded to treatment. A subtle benefit was observed among patients with gemcitabine-responsive disease in terms of a reduced functional decline compared to those who did not respond. These results underscore the urgent need to identify better treatment and palliative care strategies for advanced pancreas cancer.

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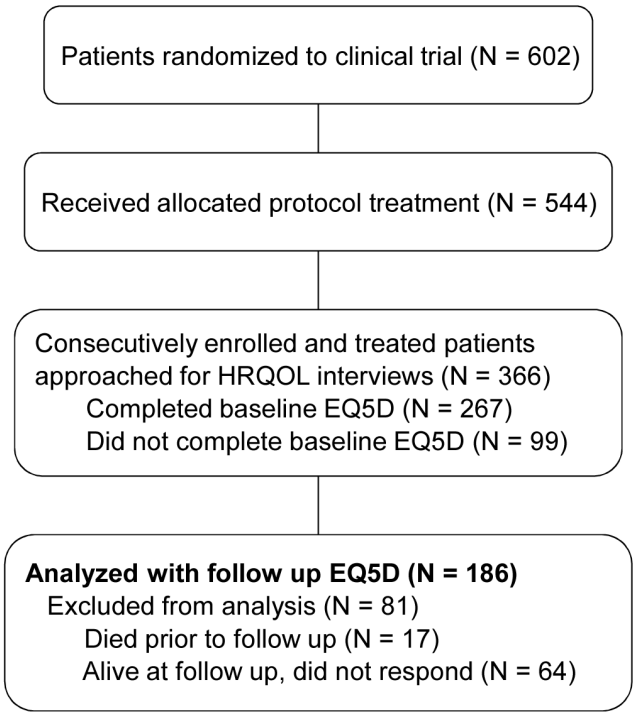
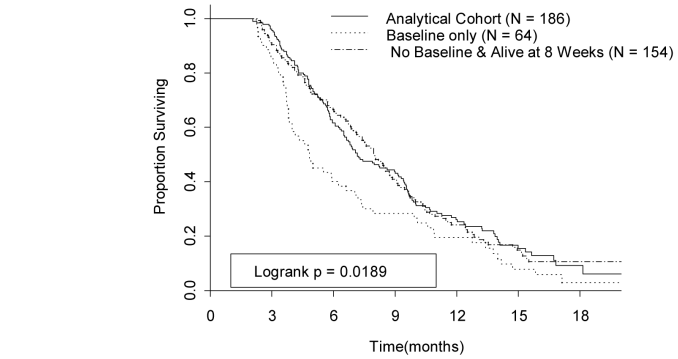


Figure 1.
CONSORT diagram of patient enrollment and EQ5D survey completion in the study.



Number of Patients at Risk							
Analytical Cohort	186	174	106	68	33	12	3
Baseline only	64	51	24	16	10	4	1
No Baseline & Alive at 8 Weeks	154	131	94	54	28	14	6

Figure 2.
Overall survival by EQ5D completion status.

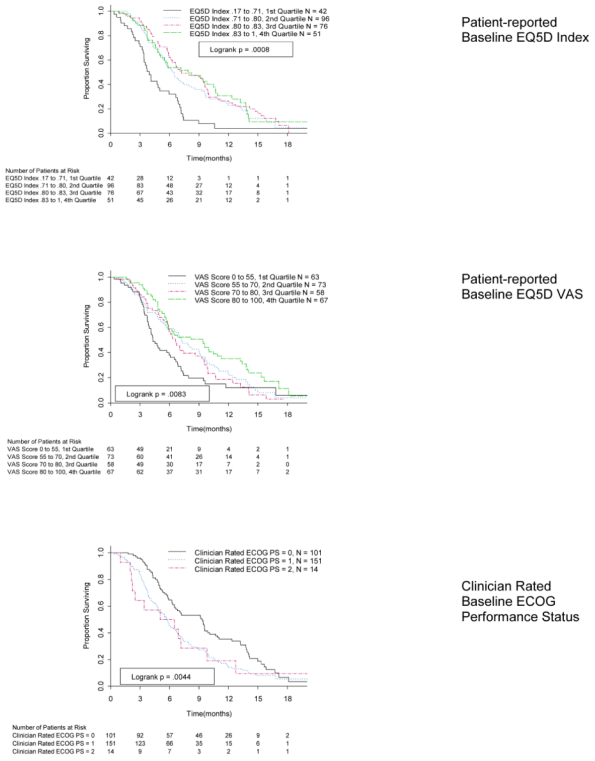


Figure 3.

Kaplan-Meier survival curves for overall survival for patients who responded to baseline EQ5D surveys (n=267). A: Overall survival by baseline EQ5D Index score. B: Overall survival by baseline EQ5D VAS scores. C: Overall survival by baseline ECOG PS.

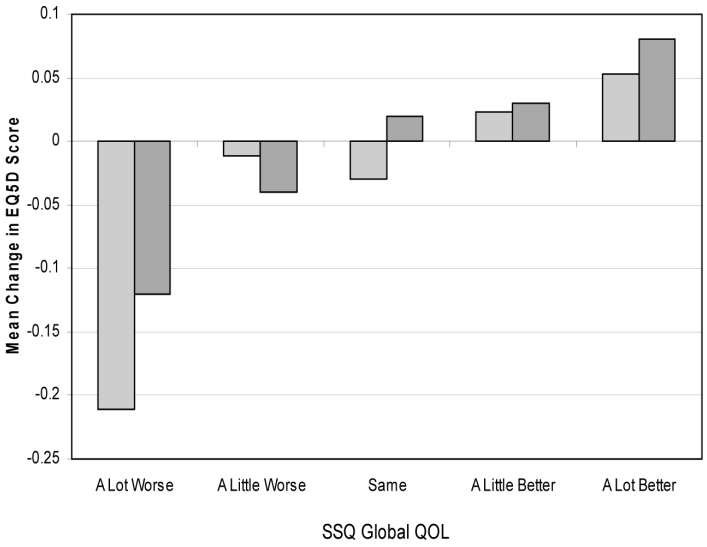


Figure 4.
Responsiveness of EQ5D Index (dark bars) and VAS Scale (light bars). EQ5D change scores (y-axis, x100 for VAS scale), at 8 weeks from baseline, compared to SSQ responses (x-axis) at 8 weeks.

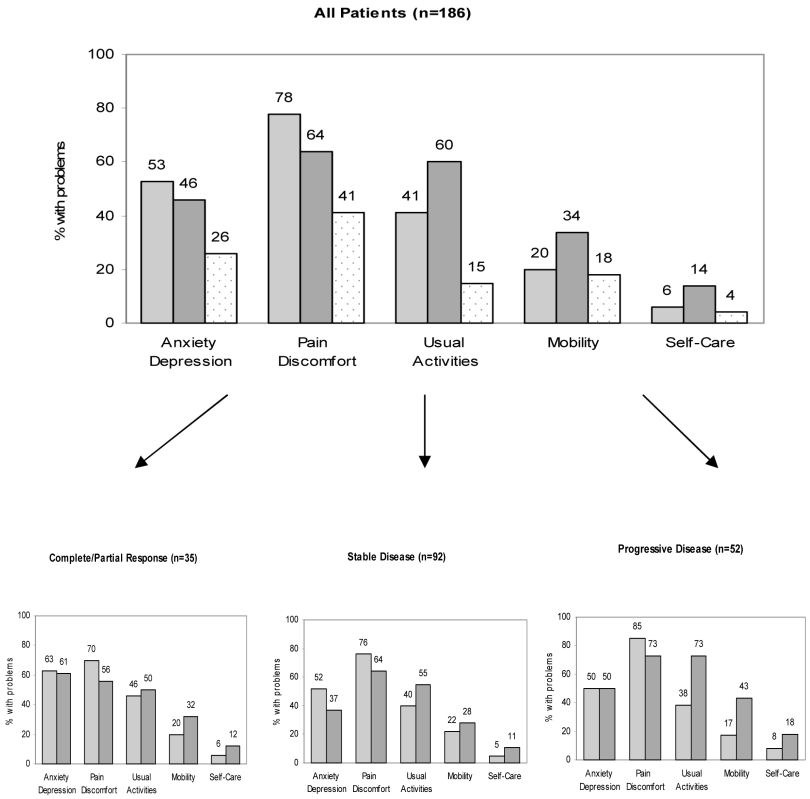


Figure 5.

EQ5D domain specific responses. Panels depict percentages of patients reporting any problem at baseline (lightly shaded bars) and at 8 weeks (darkly shaded bars) in each listed domain. Percentages of respondents from a sample of the US general population who reported any problems are also shown (dotted bars).

Table 1

Baseline and Disease Characteristics Among Patients with Advanced Pancreas Cancer (*n*=267)

Characteristic	Completed EQ5D at Baseline and 8 Weeks *n*=186	Completed EQ5D at Baseline but Not 8 Weeks *n*=64	Died Before 8 Weeks *n*=17	Comparison of EQ5D vs. No EQ5D at 8 Weeks
	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**
Age				
< 65	96 (52)	31 (48)	14 (82)	
65-74	54 (29)	19 (30)	2 (12)	0.8813
75+	36 (19)	14 (22)	1 (6)	
Race				
White	172 (93)	51 (80)	15 (88)	
Black	11 (6)	8 (13)	2 (12)	0.0249
Other	1 (1)	2 (3)	0 (0)	
Unknown	2 (1)	3 (5)	0 (0)	
Ethnicity				
Hispanic	7 (4)	4 (6)	0 (0)	
Non-Hispanic	154 (83)	54 (84)	14 (82)	0.5173
Unknown	25 (13)	6 (9)	3 (18)	
Gender				
Male	103 (55)	35 (55)	12 (71)	0.9239
Female	83 (45)	29 (45)	5 (29)	
ECOG Performance Status				
0	76 (41)	25 (39)	1 (6)	
1	102 (55)	36 (56)	13 (76)	0.9649
2	8 (4)	3 (5)	3 (18)	
Arm				
Gemcitabine/Placebo	82 (44)	30 (47)	8 (47)	0.6988
Gemcitabine/Bevacizumab	104 (56)	34 (53)	9 (53)	
Extent of Disease				
Metastatic	160 (86)	57 (89)	16 (94)	
Locally Advanced	23 (12)	6 (9)	1 (6)	0.3960
Unknown	3 (2)	1 (2)	0 (0)	
Prior Radiation				
No	172 (92)	55 (86)	15 (88)	
Yes	13 (7)	9 (14)	2 (12)	0.2960
Unknown	1 (1)	0 (0)	0 (0)	
Prior Cancer				
No	158 (85)	58 (91)	13 (76)	
Yes	26 (14)	5 (8)	3 (18)	0.5480
Unknown	2 (1)	1 (2)	1 (6)	
Response to Chemotherapy				

Characteristic	Completed EQ5D at Baseline and 8 Weeks *n*=186	Completed EQ5D at Baseline but Not 8 Weeks *n*=64	Died Before 8 Weeks *n*=17	Comparison of EQ5D vs. No EQ5D at 8 Weeks
	***n* (%)**	***n* (%)**	***n* (%)**	***P*-value**
CR/PR	35 (19)	7 (11)	0 (0)	
SD	92 (50)	17 (27)	3 (18)	
PD	52 (28)	26 (41)	11 (65)	<0.0001
Unknown	5 (3)	10 (16)	3 (18)	
Missing	2 (1)	4 (6)	0 (0)	

Table 2

EQ5D Index and VAS Scores for Advanced Pancreas Cancer Patients with Baseline and 8 Week Follow-Up EQ5D by Response to Chemotherapy [a]

	QOL Cohort All	Progressive Disease	Stable Disease	Complete /Partial Response	Gemcitabine/ Bevacizumab	Gemcitabine/ Placebo	Normative Data for US General Population (26)
Index Score (Mean, Standard Deviation)							
N patients	186	52	92	35	104	82	4,048
Baseline	0.78 (0.13)	0.77 (0.13)	0.79 (0.14)	0.79 (0.14)	0.80 (0.12)	0.77 (0.15)	0.79 (0.01)
8-week	0.79 (0.16)	0.73 (0.18)	0.81 (0.15)	0.81 (0.15)	0.80 (0.15)	0.77 (0.18)	
Change	0.0002 (0.182)	−0.0441 (0.221)	0.0198 (0.158)	0.0258 (0.179)	−0.001 (0.17)	0.001 (0.20)	
VAS Score (Mean, Standard Deviation)							
N patients	186	52	92	35	104	82	4,048
Baseline	70.7 (19.5)	68.9 (22.2)	73.1 (17.5)	71.6 (18.1)	72.1 (17.9)	69.0 (21.4)	84.2 (0.4)
8-week	68.2 (20.2)	64.4 (21.5)	71.6 (18.7)	68.7 (17.4)	69.5 (20.4)	66.5 (19.9)	
Change	−2.81 (18.95) [b]	−5.78 (21.23) [b]	−1.49 (17.12)	−2.76 (19.18)	−2.84 (16.9)	−2.78 (21.3)	

[a] Mean baseline Index and VAS scores were identical between the treatment arms; similarly, change scores did not differ by treatment randomization. All HRQOL analyses were based on pooled data for both treatment arms.

[b] Paired-test, *P*-value <0.0300; all other *P*-values >0.0500.