HEALTH-RELATED QUALITY OF LIFE, CACHEXIA AND OVERALL SURVIVAL AFTER MAJOR UPPER ABDOMINAL SURGERY: A PROSPECTIVE COHORT STUDY

Short title: HRQOL and survival after abdominal surgery

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The authors declare that they have no conflicting interests

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Ethical considerations:

Inclusion into the original randomized controlled trial (1), as well as long-term follow-up was approved by the Regional Division of the National Committee for Research Ethics, Northern Chapter (REK V). All patients provided written consent.

The original trail was registered at ClinicalTrials.gov on August 23, 2005 (NCT00134407).

ABSTRACT

Background and Aims:

Major upper abdominal surgery is often associated with reduced health-related quality of life (HRQOL) and reduced survival. Patients with upper abdominal malignancies often suffer from cachexia, represented by preoperative weight loss and sarcopenia (low skeletal muscle mass) and this might affect both HRQOL and survival. We aimed to investigate how HRQOL is affected by cachexia and how HRQOL relates to long-term survival after major upper abdominal surgery.

Materials and Methods:

From 2001 to 2006, 447 patients were included in a Norwegian multicenter randomized controlled trial in major upper abdominal surgery. In the present study - six years later, these patients were analyzed as a single prospective cohort and survival data were retrieved from the National Population Registry. Cachexia was derived from patient-reported preoperative weight loss and sarcopenia as assessed from CT images taken within three months preoperatively. In the original trial, self-reported HRQOL was assessed preoperatively at trial enrollment and eight weeks postoperatively with the HRQOL questionnaire Short Form 36 (SF-36).

Results:

A majority of the patients experienced improved mental HRQOL and, to a lesser extent, deteriorated physical HRQOL following surgery. There was a significant association between preoperative weight loss and reduced physical HRQOL. No association between sarcopenia and HRQOL was observed. Overall survival was significantly associated with physical HRQOL both pre- and postoperatively, and with postoperative mental HRQOL. The

association between HRQOL and survival was particularly strong for postoperative physical HRQOL.

Conclusion:

Postoperative physical HRQOL strongly correlates with overall survival after major upper abdominal surgery.

Key words: Health-related quality of life, cancer, surgery, cachexia, sarcopenia, weight loss, recovery

INTRODUCTION

Patients undergoing major upper abdominal surgery are often weakened by weight loss (2;3) and sarcopenia (low skeletal muscle mass) (4;5), and major complications are relatively frequent (6;7). Weight loss in cancer patients has been associated with reduced health-related quality of life (HRQOL) (8) but the impact of sarcopenia is uncertain (9).

Survival after upper abdominal surgery for malignant diseases is often limited, even after operations with curative intent, and long-standing functional impairment is common (10;11). As cachexia, sarcopenia and reduced HRQOL have all been linked to reduced survival (3;12-14), these factors are potentially important in preoperative risk assessment and postoperative care.

Little is known about the relationship between *post*operative HRQOL and survival after abdominal surgery, although some studies have indicated a positive association (15). A possible correlation between postoperative HRQOL and survival would probably reflect both advanced disease and functional impairment. Self-reported HRQOL might then represent an important tool in postoperative follow up, both for indentifying patients at risk of reduced survival and to target functional impairment.

We have investigated the relationship between cachexia, sarcopenia and HRQOL and, furthermore, the relationship between HRQOL and long-term overall survival in a large cohort of patients undergoing major upper abdominal surgery.

MATERIAL AND METHODS

From 2001 to 2006, 447 patients were included in a Norwegian multicenter randomized controlled trial (RCT), which investigated how normal food at will after all kinds of major upper abdominal surgery was tolerated (1). Further analysis has not been performed on this dataset and it was now, six years later, treated as a single prospective cohort. We collected survival data from the Norwegian Population Registry. Survival data were collected during April 2012, six years after the last patient was included in the original trial. Patients without any preoperative or postoperative HRQOL data were excluded from further analysis.

In addition to general demographics and clinical characteristics, the prospective database included specifically: patient-reported preoperative weight loss, surgical procedures and major postoperative complications. Major complications, within eight weeks after surgery, were defined a priori and listed in the original publication (1), as were the operative procedures (1). Major complications were defined as major infectious, -pulmonary, -cardiac or -surgical, e.g. pneumonia, myocardial infarction or anastomotic leakage. Detailed criteria are listed in the original publication (1).

Preoperative weight loss was calculated from patients' usual pre-morbid weight as they recalled it, with no time-limit, and current weight, which was scaled preoperatively at trial enrollment. It was dichotomized into >5% or ≤5% weight loss, according to international consensus (12).

Digitally stored computer tomography (CT) images for initial routine diagnostics and staging were analyzed using Slice-O-Matic software V4.2 (Tomovision, Montreal-Canada) which permitted specific tissue demarcation using Houndsfield unit threshold of -29 to +150 for

skeletal muscles (16), -150 to -50 for visceral adipose tissue (17), and -190 to -30 for subcutaneous adipose tissue (16). Cross-sectional areas (cm^2) were calculated for each tissue by summing tissue pixels and multiplying by the pixel surface area. A transverse CT image from the third lumbar vertebrae was assessed for each scan and tissue areas estimated (18). One single trained observer, who was blinded to all clinical and HRQOL data, analyzed all CT images. Cross-sectional area was normalized for stature (cm^2/m^2) and lumbar skeletal muscle index was calculated. CT images used for analysis were retrieved from routine images done within three months preoperatively. We used the cut-off for lumbar skeletal muscle index suggested by Mourtzakis et al (19), which corresponds to skeletal muscle mass two standard deviations from that of healthy young adults (39 cm^2/m^2 for women and 55 cm^2/m^2 for men).

Self-reported HRQOL was assessed preoperatively at trial enrollment and eight weeks after surgery in the original trial (1). The validated Norwegian translation (20) of the generic health-related quality of life instrument: Short Form 36 (SF-36), Norwegian version 1.2, was utilized. While SF-36 is not a disease-specific instrument, it has been used and validated in a wide range of malignant and non-malignant diseases (21). SF-36 contains thirty-six questions that produce eight scales. These scales are; physical functioning, role limitation (caused by physical problems), bodily pain, general health, vitality, social functioning, role limitation (caused by emotional problems) and mental health. These scales were aggregated to produce a summary physical HRQOL score (Physical Component Summary, PCS) and a summary mental HRQOL score (Mental Component Summary, MCS) (22). These norm-based scores have a mean of 50 and a standard deviation of 10 in general adult populations (22). Reduced HRQOL were defined as summary scores lower than 50.

Patients were divided into the following disease-categories: Gastroesophageal cancer, pancreatic cancer, other cancer (mainly malignant liver tumors and liver metastases) and non-cancer.

Statistics:

Statistical analysis was performed with SPSS statistics software, version 22 (IBM, New York -USA). A Cox proportional hazard regression analysis, stratified for disease-categories, was used for analysis of overall survival; the assumption of proportional hazards was visually inspected by log-log survival curves. Variables with a p-value <0.20 in the unadjusted analysis were included in the multivariable adjusted analysis. Pearson chi-square test and analysis of variance (ANOVA) were used for comparison of characteristics between different groups and categories. One-way t-test was used for analysis of two repeated measures. Linear regression analysis was used for analysis with HRQOL as outcome, adjusted for type of disease. The assumption of linearity and variance homogeneity was visually inspected. In all analysis, p-values <0.05 were considered statistically significant.

RESULTS

Selection and characteristics

The original study population comprised 447 patients. HRQOL data were missing for 53 (12.1%) patients, and survival data were not available in another nine (2.0%) patients. Thus, survival data and complete preoperative and/or postoperative HRQOL data were available in 385 (86.1%) patients of the original study population.

Information on preoperative weight loss was obtained in 87.2% (336/385) of these patients, and preoperative CT images of sufficient quality were available in 44.4% (171/385). Complete preoperative or postoperative HRQOL data were available in 82.1% (316/385) and 73.8% (284/385) of the patients, respectively. In 215 patients (55.8%), complete both preoperative and postoperative HRQOL data were available.

Sixteen patients (4.2%) died within 90 days after surgery. A total of 198 patients (51.4%) died within five years. A preoperative weight loss in excess of 5% was observed in 116 patients (116/336=34.5%). Sarcopenia was encountered in 69.0% (118/171=69.0%) of the patients with available CT images. One or more major postoperative complications occurred in 29.6% (114/385) of the patients.

Reduced physical HRQOL (PCS <50) was encountered preoperatively in 69.3% (219/316) and postoperatively in 78.5% (223/284) of the patients. Reduced mental HRQOL (MCS <50) was encountered in 65.8% (208/316) preoperatively and in 51.8% (147/284) of the patients postoperatively. Pre- and postoperative PCS and MCS values in the different disease categories are illustrated in Figure 1.

Changes in health-related quality of life

There was a statistically significant decrease in PCS postoperatively for patients in all disease categories except for patients without cancer (increase in PCS, p=0.056) and patients with pancreatic cancer (decrease in PCS, p=0.058) (Table 1). Mean decrease in PCS after surgery for the entire cohort was -2.3 (p=0.002) (Table 1). There was a statistically significant increase of postoperative MCS in all disease categories except for patients with gastroesophageal cancer (increase in MCS, p=0.058). Mean increase in MCS after surgery for the entire cohort was 3.9 (p<0.001) (Table 1).

Risk factors, postoperative complications and HRQOL

Patients older than 65 years had higher preoperative MCS as compared to patients younger than 65 years (Estimated difference (ED) = 5.2, p>0.001). Patients with preoperative weight loss >5% had a significantly lower preoperative PCS when compared to patients with preoperative weight loss ≤5% (ED=-3.3, p=0.012) (Table 2). Patients who suffered postoperative complications had significantly lower postoperative PCS (ED= -3.1, p=0.023), with no difference in postoperative MCS (p=0.149), compared to patients without complications.

There was no association between sarcopenia (low skeletal muscle mass) (19), and pre- or postoperative HRQOL (Table 2). There were no association between the continuous variable lumbar skeletal muscle index (adjusted for age and gender) and pre- or postoperative HRQOL.

HRQOL and overall survival

Pre- and postoperative PCS and postoperative MCS were all significantly associated with survival when analyzed as continuous variables.

Preoperative PCS <50 was associated with a worse overall survival (HR=1.38, p=0.048) (Table 3), but no association was observed after adjustment for preoperative weight loss (p=0.362).

Postoperative PCS <50 (HR=1.98, p=0.005) and MCS <50 (HR=1.41, p=0.041) were associated with reduced overall survival, also when adjusted for age and postoperative complications (PCS<50: HR=1.98, p=0.05) (Table 3). The association between PCS and overall survival was similar in all disease categories, including patients without cancer (PCS <50: HR=2.99, p=0.08).

DISCUSSION

We have demonstrated a strong association between postoperative health-related quality of life (HRQOL) and overall survival after major upper abdominal surgery, particularly for physical HRQOL. A majority of patients in our cohort experienced improved mental HRQOL and, to a lesser extent, deteriorated physical HRQOL following surgery. This study is, to our knowledge, the first multicenter investigation of HRQOL in relation to cachexia and sarcopenia together with long-term survival after major upper abdominal surgery. This adds to our investigation of sarcopenia and morbidity in the same study population (23).

An association between reduced *pre*operative HRQOL and overall survival is well documented (14). While this association was confirmed in our study, the strong association between *post*operative HRQOL and overall survival was more evident. The physical HRQOL as an *outcome* after major upper abdominal surgery is important as such. In addition, this quality of life measure appears to be a sensitive predictor for overall survival.

Patients with gastroesophageal cancer experienced the largest deterioration in physical HRQOL after surgery and these were the only patients in whom an improvement in mental HRQOL after surgery could not be shown. Surgery for gastroesophageal cancer (esophagectomy, gastrectomy) can cause especially severe functional impairment (24) which might explain these findings.

Upper abdominal malignancies are often associated with a poor prognosis (23). Younger cancer patients appear to be more predisposed to anxiety and depression when faced with the

possibility of a huge reduction in lifespan or long-lasting functional impairment (25). This might in part explain why younger age was associated with worse preoperative mental HRQOL in our study.

Little is known about the impact of sarcopenia on HRQOL in patients with upper abdominal malignancies. Our results on weight loss and sarcopenia are consistent with the results in a study on patients with advanced colorectal carcinoma, where no association between sarcopenia and HRQOL was found, but where an association between weight loss and deteriorated HRQOL was indeed observed (9). The association between weight loss and HRQOL in cancer-patients is well documented (8) and reduced preoperative HRQOL has been associated with advanced disease in pancreatic cancer (26). Preoperative weight loss might be a more global indicator of advanced disease than the amount of skeletal muscle measured at a single time-point (23), and hence be more directly linked to preoperative HRQOL.

Some limitations of our study should be addressed. For one, 14% of the patients in the original cohort were excluded because survival and/or HRQOL data were not available. Furthermore, we lacked complete pre- and postoperative HRQOL data in 18% and 26% of these patients respectively. The percentage of patients with available CT images, to assess sarcopenia and HRQOL was only 44%. Stage of disease was not included in our study, as our database lacked information on this variable.

The survival benefit from upper abdominal surgery is often limited (10;11), and patients frequently suffer complications (6;7) which again have been associated with reduced HRQOL (27). This is sometimes used as an argument against surgery in borderline cases. Interestingly, the patients in our study, even those who suffered postoperative complications, experienced improved mental HRQOL after surgery. Furthermore, the deterioration in physical HRQOL was less severe. These findings might be useful to consider when benefits of upper abdominal surgical procedures are evaluated.

Structured oncologic follow-up after surgery for gastric and pancreatic cancer has not improved long-term outcomes (10). Research has indicated that oncologic follow-up including routine imaging can cause increased anxiety (28) but many patients welcome regular visits to a physician (29). Postoperative physical HRQOL is probably influenced by many factors and stage of disease might be the most important. Nevertheless, postoperative HRQOL is also influenced by factors which are not necessarily directly related to stage of disease, including functional impairment, pain and nutritional depletion. Identifying patients with reduced postoperative HRQOL and paying more attention to their functional impairments may improve long-term HRQOL, and even survival, with few unwanted side-effects. Further research could investigate the benefit of intervention on functional impairment after major upper abdominal surgery.

LIST OF ABBREVATIONS

HRQOL = Health-related quality of life

PCS = Physical Component Summary

MCS = Mental Component Summary

WL = Weight loss

AUTHORS CONTRIBUTIONS

EKAa and KL: Performed the data analysis.

NJ: Calculated the body composition indices, blinded to all clinical data.

EKAa, GT, JAS, KCF, AR, KL: Participated in study conception and design.

All authors participated in data acquisition and interpretation, manuscript preparation, editing and final approval.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare that they have no conflicting interests

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FIGURE LEGENDS

Figure 1: Pre- and postoperative Health-related quality of life (HRQOL) in the different disease categories.

Box-and-whisker plot of the physical HRQOL (PCS) and mental HRQOL (MCS) in different disease categories. Boxes represent median values and interquartile range. Whiskers represent the top and bottom 25%. Outliers are indicated by (o). Dotted horizontal lines represent mean PCS and MCS in the general adult population.

Panel A = Physical HRQOL

Panel B = Mental HRQOL

Preoperative; n=316, postoperative; n=284

Table 1. Change in health related quality of life (HRQOL) from preoperative to postoperative in all patients and in the different disease categories.

	Physical HRQOL (PCS)			Mental HRQOL (MCS)		
	Mean change	95% CI	P-value	Mean change	95% CI	P-value
Gastroesophageal cancer (n=92)	-4.4	-6.4/-2.2	<0.001	2.6	-0.1/5.3	0.058
Pancreatic cancer (n=49)	-3.0	-6.1/0.1	0.058	4.6	0.9/8.3	0.015
Other cancer (n=27)	-2.8	-7.0/1.4	0.186	6.1	1.8/10.4	0.007
Non cancer (n=47)	2.8	-0.1/5.6	0.056	4.5	0.7/8.4	0.021
All patients (n=215)	-2.3	-3.7/-0.9	0.002	3.9	2.2/5.6	<0.001

Negative changes are indicated with (-)

Table 2. The association between age, weight loss, sarcopenia and health-related quality of life (HRQOL) pre- and postoperatively. Multivariable linear regression analysis adjusted for type of disease.

	Physical Component Summary				**Mental Component Summary**			
	Preoperative		Postoperative		Preoperative		Postoperative	
	Estimated difference	P-value	Estimated difference	P-value	Estimated difference	P-value	Estimated difference	P-value
Age >65y	-2.5	0.032	-2.0	0.089	5.2	<0.001	1.2	0.385
WL >5%	-3.3	0.012	-1.1	0.402	-1.6	0.262	-1.2	0.433
Sarcopenia	-0.7	0.701	-1.0	0.588	2.1	0.278	-1.2	0.550

Estimated differences in physical and mental HRQOL compared to patients with age ≤65 years, weight loss ≤5% or no sarcopenia respectively. Negative estimated differences are identified with (-). In the total study population, 187 (48.6%) patients were above 65 years old, 116 (116/336=34.5%) had suffered preoperative weight loss and 118 (118/171=69.0%) patients were sarcopenic on preoperative CT examinations.

WL = Weight loss

Table 3. The association between pre- and postoperative health-related quality of life (HRQOL) and overall survival. Multivariable Cox proportional hazard regression analysis, stratified for type of disease.

Preoperative HRQOL and overall survival (n=316)						
	Unadjusted			Multivariable adjusted		
	HR	95% CI	P-value	HR	95% CI	P-value
Age >65y (n=150)	1.28	0.96-1.71	0.098	1.25	0.93-1.68	0.157
PCS <50 (n=219)	1.41	1.02-1.93	0.036	1.38	1.00-1.90	0.048
MCS <50 (n=208)	1.00	0.74-1.35	0.977			

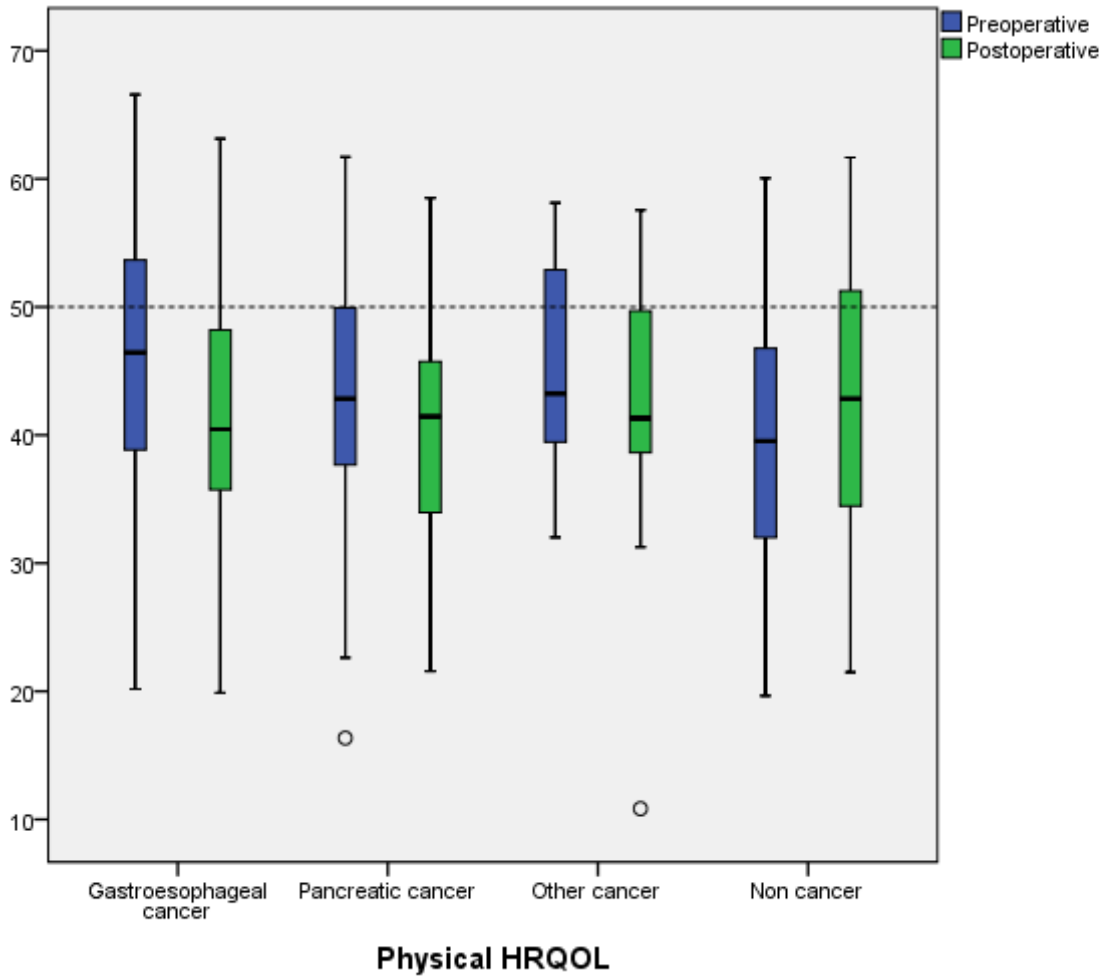
Postoperative HRQOL and overall survival (n=284)						
	Unadjusted			Multivariable adjusted		
	HR	95% CI	P-value	HR	95% CI	P-value
Age >65y (n=130)	1.29	0.94-1.78	0.119	1.30	0.93-1.79	0.108
Complications (n=70)	1.36	0.97-1.91	0.078	1.27	0.89-1.79	0.184
PCS <50 (n=223)	2.21	1.38-3.55	0.001	1.98	1.23-3.21	0.005
MCS <50 (n=147)	1.57	1.14-2.16	0.006	1.41	1.01-1.95	0.041

PCS <50 = Reduced physical HRQOL

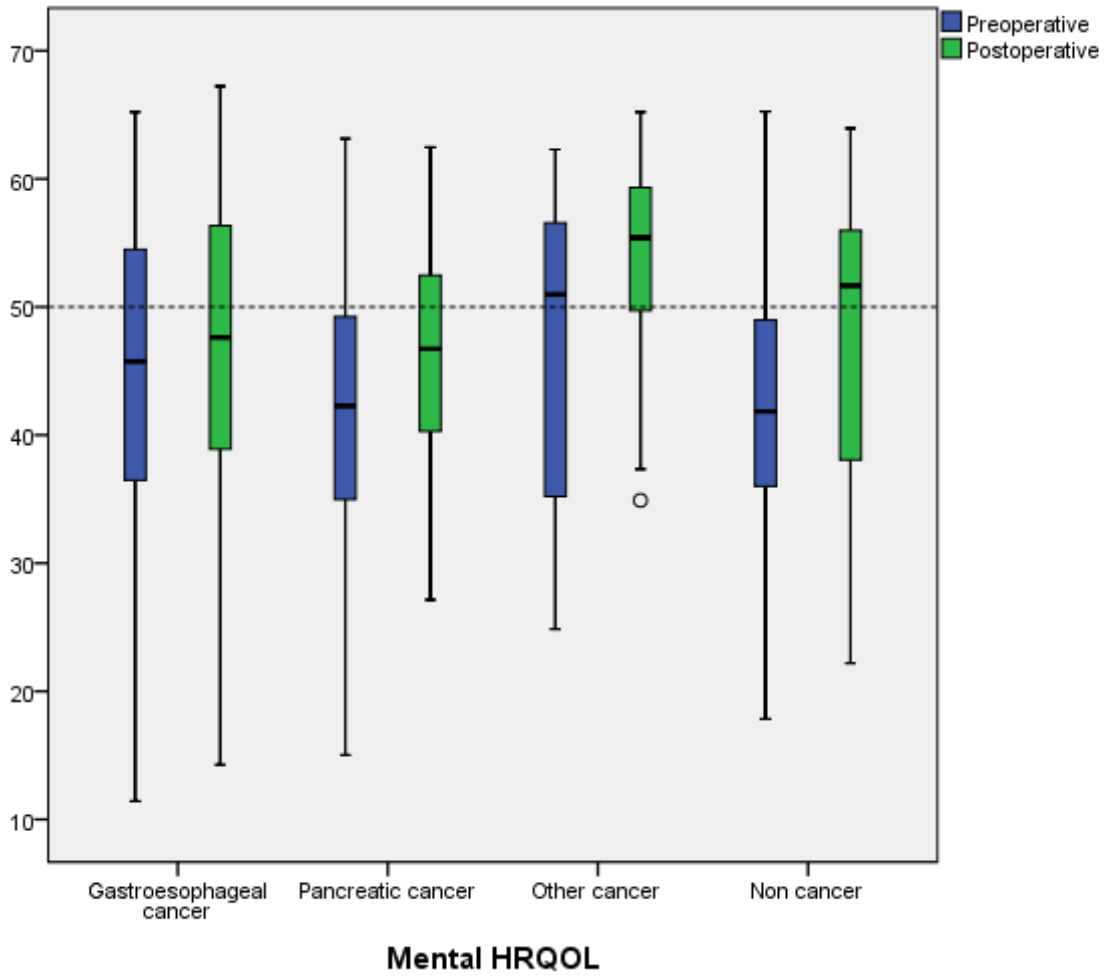
MCS <50 = Reduced mental HRQOL

Figure 1. Pre- and postoperative Health-related quality of life (HRQOL) in the different disease categories.

A)



B)



Box-and-whisker plot of the physical HRQOL (PCS) and mental HRQOL (MCS) in different disease categories. Boxes represent median values and interquartile range. Whiskers represent the top and bottom 25%. Outliers are indicated by (o). Dotted horizontal lines represent mean PCS and MCS in the general adult population.

Panel A = Physical HRQOL

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Preoperative; n=316, postoperative; n=284