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Perioperative Patient Reported Outcomes Predict Serious Postoperative Complications: A Secondary Analysis of the COST Trial

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Abstract

Background—Decreased survival after colon cancer surgery has been reported in patients with deficient preoperative quality of life. We hypothesized that deficits in preoperative quality of life are associated with postoperative complications.

Patient and Methods—A secondary analysis of the Clinical Outcomes Surgical Therapy trial NCCTG 93-46-53 (INT 0146, Alliance) was performed. Quality of life deficit was defined as overall quality of life score < 50 on a 100 point scale and used for univariate and multivariate analysis.

Results—Of 431 patients enrolled in the quality of life portion of the trial, 81 patients (19%) experienced complications including two deaths (0.5%). Fifty-five patients (13%) had a preoperative quality of life score < 50. Patients with a preoperative deficit were more likely to have a serious early complication (16 vs 6%, p=0.023). Using stepwise logistic model, the variables significantly associated with having any early complications (yes/no) were age, ASA III and change in 'activity' from baseline to day 14. Patients with an early complication experienced a 3.5 day longer hospital stay (p=0.0001). Gender, race, tumor stage and laparoscopic or open approach were not associated with an increased frequency of complications. After adjusting for demographics, tumor stage, ASA and operative approach, significant predictors for readmission were preoperative pain (OR 1.61, CI 1.11–2.34, p=0.0125), and changes from baseline to day 2 in fatigue (OR 1.34, CI 1.03–1.74, p=0.032).

Conclusions—This study suggests that quality of life can provide an early indicator for patients at risk of complications. Further studies should evaluate how perioperative quality of life assessment may assist to improve outcomes.

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Keywords

Quality of life; outcomes; surgery; complication; colon cancer

INTRODUCTION

Patient reported outcomes, such as quality of life (QOL) scores, have recently been recognized as predictors for outcome in cancer patients. A clinically meaningful deficit in the QOL item fatigue at diagnosis was a sensitive predictor for increased mortality in lung cancer patients.[1] Deficient preoperative QOL scores have been reported to predict decreased survival after pancreatic cancer surgery. [2]

In the COST (Clinical Outcomes of Surgical Therapy) trial, a randomized clinical trial investigating the non-inferiority of laparoscopic versus open resection for colon cancer, postoperative QOL was compared as a patient outcome between the two operative approaches.[3–4] On a secondary analysis performed by Stucky et al,[5] preoperative QOL scores had a significant impact on the overall survival of patients in the trial and that clinically deficient global QOL scores (<50 on a 100 point scale) were consistently associated with worse individual QOL outcomes in the immediate postoperative period. A baseline QOL score <50 was the strongest predictor of QOL <50 at week 2 and at month 2. The authors of the study suggested that patients with particularly poor preoperative QOL may be at higher risk for a difficult postoperative course and might be candidates for enhanced ancillary services regardless of the surgery they will undergo.

We sought to investigate whether the patient's baseline QOL scores correlate with postoperative complications, which contribute significantly to a difficult postoperative course. Our hypothesis was that deficits in preoperative QOL scores are associated with surgical outcomes such as 30-day morbidity.

For this secondary analysis we had two aims: to determine if a clinically meaningful deficit at baseline is associated with postoperative complications, and to determine if the change in QOL from baseline to postoperative day 2 or day 14 (POD2, POD14) is associated with postoperative morbidity.

PATIENTS AND METHODS

A secondary analysis of the COST trial NCCTG 93-46-53 (INT 0146, Alliance) was performed. For the trial, each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Variables of 431 randomized patients from the COST trial who participated in the QOL portion of the trial were included. Patient demographics, composite and single item QOL scores and surgical complications were used for univariate and multivariate analysis. Risk modeling performed previously to assess the COST trial outcomes was reviewed to include other relevant covariates.

Definitions

In the COST trial, initiated in 1993, complications were defined as early (prior to hospital discharge) or late (after discharge, reported two months postoperatively). Complications were classified as: Grade 0= none, grade 1=non-life threatening and temporary, grade 2= potentially life threatening but temporary, 3=causing permanent disability (no grade 3 were reported), grade 4= fatal. Categories of complications included in the reporting were: fever, ileus, pulmonary infection, urinary tract infection or urinary retention, surgical site infection, abdominal sepsis, hemorrhage, return to the operating room, medical complications, anesthesia related complications and other.

Late complications included being readmitted to the hospital, being seen by a doctor for reasons other than chemotherapy or routine care, being prescribed antibiotics since hospital discharge, and incidence of any infection (wound, urinary, pulmonary, or other). Quality of life outcomes were collected using the validated 13 item symptom distress scale (SDS)[6] (e.g., pain, fatigue, nausea, cough), the validated 5-item quality of life index (QLI) (e.g., 'activity' = work related activities including job, household or volunteer work, daily living = eating, getting dressed, health, support, outlook) and a global QOL rating scale (1–100).[7] Each item was analyzed separately and as composite scores for SDS and QLI. Higher scores on the SDS and QLI indicate lower QOL. Patients with an overall QOL score <50 on the 100 point global rating scale were considered to have a QOL deficit. The SDS was collected at baseline, day 2, and week 2, while the other PRO measures were collected at baseline and week 2.

Statistical power considerations

The primary outcome of the COST trial NCCTG 93-46-53 (INT 0146) was oncologic non-inferiority. The target enrollment for the primary outcome was 1200 patients. As the entire study population was not needed to evaluate the QOL endpoints, a subgroup of patients was asked to fill out the QOL questionnaires. Target enrollment for the QOL endpoints was 416 patients with a power to identify a ± 5 point difference in the global QOL scale between the two surgical arms with a 95% confidence interval.[4]

An analysis performed by Stucky et al [5] demonstrated that the QOL subset had enough power to detect an association between QOL measures and mortality, a < 1% event. We estimated the overall complication rate to be at least 10%, thus our study would have enough power to detect an association, if present, between QOL and complications. Missing QOL or complication data were not included in the analysis. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

RESULTS

Of the 431 patients who were enrolled in the QOL portion of the COST trial, 81 patients (19%) experienced 101 early complications (Table 1). Of these, 42 complications (7%) were serious (grade 2–4) including two deaths (0.5%) prior to hospital discharge. Eighty-nine patients (24%) experienced a late complication. Patients experiencing an early complication tended to be about three years older than patients without complications and were more

likely to be ASA III (American Society of Anesthesiologists class)(Table 2). Gender, race, tumor stage and surgical approach (laparoscopic or open, intention to treat) were not associated with an increased frequency of complications. Patients with complications experienced a significantly longer mean hospital stay (8.9 vs 5.4 days, $p< 0.0001$).

Of the 431 patients, 338 had an overall QOL score ≥50 with the mean overall QOL scores at baseline were 78.9 (SD 18.7, median 80.5, range 20–100, Q1 70 Q3 90) for patients undergoing laparoscopic and 82.8 (SD 15.8, median 90, range 25–100, Q1 75,Q3 95) for patients undergoing open colectomy. 55 had a QOL score <50 and QOL scores from 38 patients were missing. A detailed report on the temporal change of the overall QOL and QLI and SDS items is presented in Stucky et al [5]. Of the patients with missing QOL scores, 35 had no complications and 3 had a grade 1 complication.

Patients with a preoperative QOL deficit were more likely to experience a serious (grade 2–4) early complication than patients without a QOL deficit (16 vs 6%, $p=0.023$) (Table 3).

Patients who experienced any, minor or serious, early complication recorded a statistically significant ($p=0.013$), however clinically very small (0.25 SD [standard deviation]), difference in ‘appearance’ on postoperative day 2. Similarly, patients with a complication exhibited a statistically significant ($p=0.033$), however clinically very small (0.3 SD), increase in ‘trouble breathing’ from baseline to postoperative day 2 (Table 4).

After adjusting for demographics, none of the preoperative patient reported outcomes were significant predictors of early complication incidence or grade, in this analysis without grouping the complications into minor or serious. However, changes from baseline to day 2 in concentration (OR1.27 (1.00–1.61) $p =0.049$), appearance (OR 1.38 (1.02–1.87) $p=0.037$), and breathing (OR 1.50 (1.02–2.21), $p=0.038$) were significantly related to the incidence of early complications. Changes from baseline to day 14 in ‘activities’, ‘daily living’ and ‘total QLI’ were also associated with early complications. Using stepwise logistic model, the variables significantly associated with having any early complications (yes/no) were age, ASA III and change in ‘activity’ from baseline to day 14.

Changes in appearance and breathing from baseline to day 2 were significantly associated with the severity of the complication. Changes in ‘activities’, ‘daily living’, and ‘total QLI’ from baseline to day 14 were also associated with the complication grade (0–4). Using stepwise linear models, the variables significantly associated with the severity of early complications were age, change in ‘appearance’ and change in ‘daily living’ (Table 5).

Significant predictors for being readmitted to the hospital within 2 months were baseline pain distress severity and changes from baseline to day 2 in fatigue. Also associated with readmission were changes from baseline to postoperative day 14 in ‘daily living’ and outlook. These logistic models for predicting late complications are adjusted for age, gender, race, stage, ASA and operative approach (laparoscopic vs open). The final stepwise multivariate model for associations with readmission included only the baseline demographics and the change in ‘daily living’ from baseline to postoperative day 14, odds ratio 2.16 (1.30–3.59), $p=0.0029$.

DISCUSSION

The COST trial determined the oncologic non-inferiority of laparoscopic versus open resection for colon cancer.[3] Patients prefer the laparoscopic approach as reflected by better QOL scores for patients undergoing laparoscopic surgery compared to open procedures at 14 days postoperatively.[4] The trial data was later used to better understand factors predicting survival for patients undergoing colon cancer surgery. A secondary analysis by Mathis et al[8] reported that surgical factors such as number of lymph nodes harvested did not significantly predict survival when adjusted for age and tumor stage in this highly controlled environment where all trialists had to submit quality control data in the form of video footage from the operative procedures.

Attention has recently turned to better understanding the patient as the host of a disease and subject of treatment beyond the sum of age and comorbidities. Frailty, morphometric age and patient reported outcomes (QOL) have all been reported as predictors of mortality, including in the COST trial.[1,5,9–12] Patient reported outcomes can be more sensitive than physician reported outcomes in predicting mortality.[1]

Patient reported outcomes (outlook, support, QOL deficit at enrollment) were associated with survival in the COST trial analysis performed by Stucky et al.[5] In addition, slightly, but clinically meaningful better long-term QOL scores in favor of laparoscopy were noted. Here we further assess if perioperative QOL data are meaningful predictors of postoperative outcomes. We report that patients with a preoperative QOL deficit were more likely to experience a serious early postoperative complication than patients without a QOL deficit, independent of tumor stage. The overall QOL deficit describes a patient population with QOL scores < 50. For this tool with a score from 1–100, the population norms are calibrated as 50 or above, thus a score <50 is customarily defined as a QOL deficit. While a continuous score provides more granular information in the research environment, a dichotomous score is easier to use in clinical practice as it reduces the complexity of decision making to an actionable yes/no answer rather than a nuanced assessment of different scoring intervals. The patients with a complication also felt that their appearance had worsened by postoperative day 2 and they had a little more trouble breathing and could not concentrate as well. As the COST trial, which started in 1994, did not collect vital signs or clinician's impressions for the early postoperative period, a correlation with those data was not possible. Adjustment for demographics revealed that preoperative QOL deficits may not be an independent predictor for early complications (age is a significant confounder and ranged between 60– 95 years in this analysis); however, QOL data may provide information about which octogenarian with colon cancer may be at a higher risk for complications and permit a change in clinical pathways such as additional preoperative interventions or adjustment in level of postoperative care. QOL data should not be considered merely a proxy for comorbidities as patients in hospice care frequently have QOL scores comparable with the average population. In the hospice population patient needs are mostly met to their satisfaction. QOL data may provide thus an assessment of unmet needs, either in the physical, emotional, social or spiritual domain. Single item QOL data are easy to obtain, similar to the pain visual analog scale. Clinical oncology groups are now using QOL data

real time to adjust treatment, such as reducing the dose of a chemotherapeutic drug if the fatigue levels decrease more than 2 points on a 1–10 scale.

In addition, some patients notice within the first 48 hours after surgery that their appearance may have worsened, which is often earlier than clinicians are able to diagnose a complication. The change in early postoperative QOL data may be a tool to quantify the 'eyeball test' from the patient's perspective. However, given the limited effect size in this report, further research to target this timeframe should be undertaken to provide information about the utility of this information.

Changes in QOL at 2 weeks after surgery are most likely the consequence of an early postoperative complication rather than a predictor. They remind us, however, that complications affect patients' quality of life and their ability to pursue their normal activities beyond the fact that they underwent an operative procedure.

Similarly to early complications, re-admission to the hospital was associated with pre- and early postoperative patient reported outcomes, such as pain and fatigue. Preoperative pain is now a metric that is collected for every patient prior to surgery as a Joint Commission requirement. Beyond addressing the immediate pain issue, surgical teams might evaluate if high preoperative pain scores should trigger adjustments in discharge planning and early post-hospital support to preempt the need for readmission.

CONCLUSION

Adverse outcomes continue to affect patients negatively. Many risk factors, such as age and comorbidities are not modifiable. Preoperative QOL data are relatively easily obtained and can be early markers for serious complications. Interventions to achieve improved QOL preoperatively, including stakeholders such as the primary care teams, should be investigated to understand if that can reduce the risk for complications.

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Appendix

Discussant

Dr. Vassiliki Li Tsikitis (Portland, OR):

I would like to congratulate you and your team on an interesting, well-written, study demonstrating that a clinically meaningful preoperative deficit of QOL is associated with

early post-op complications. The authors also show that changes in QOL from baseline to POD#2 and #14 are associated with overall increased post-op morbidity. What makes the study significant, compared to other QOL studies, is that there is large patient cohort examined to provide the power to identify +5 points difference in the QOL scale with a 95% confidence interval.

Comments:

1. I am intrigued on how the patient's subjective appreciation of lack in appearance, decreased concentration, and difficulty in breathing on POD#2 was not correlated with the resident/surgeon perception of early morbidity. Were there any correlations with objective findings, such as fluctuation in the pulse ox or change in the vital signs?
2. Could you comment on whether or not the perceived low QOL is a surrogate of comorbidities/health issues that have gone un/or under-diagnosed? I understand that you use ASA in your analysis, but this is still a rudimentary measure of health.
3. Poor outlook and overall mental health issues are clearly under-appreciated factors that negatively affect longevity and specifically cancer survival. How do you propose working up patients before a cancer operation, which is a time sensitive issue (i.e. should PCP do global QOL assessment before surgery)?

Closing Discussant

Dr. Bingener:

Thank you very much for your comments and questions. As this was a legacy trial started in 1994 we unfortunately we do not have granular data on vital signs or pulse oximetry. We also don’t have the clinical impression of the treating team at the time for this early postoperative period available for our analysis.

To you second question: Comorbidities and health issues certainly influence QOL. However, we know that patients who are terminally ill and in hospice care often had near normal QOL as their current needs are being met. So QOL and comorbidities while certainly confounding each other, are probably not just surrogates of each other.

Your third question poses the most interesting challenge, how do we intervene now. An early preoperative QOL assessment paired with possible interventions (e.g. providing information on financial or social assistance) may indeed be of benefit. Surgical teams are likely not the most efficient providers of this type of intervention and close collaboration with all other stakeholders in the patients care may be necessary.

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Table 1

Early Complications Prior to Hospital Dismissal

Complications											
Grade	**Fever**	**Ileus**	**Pulmonary Infection**	**[a]UTI/Uret[b]**	**[c]SSi**	**Abdominal Sepsis**	**Hemorrhage**	**[d]ROR**	**Medical**	**Other**	**Total**
1	17	8	2	11	4	0	0	0	9	8	**59**
2	2	1	3	3	2	1	5	5	15	3	**40**
4	0	0	0	0	0	0	0	0	2	0	**2**
Total	**19**	**9**	**5**	**14**	**6**	**1**	**5**	**5**	**26**	**11**	**101**

Grade 0 = none
Grade 1 = non-life threatening and temporary
Grade 2 = potentially life threatening but temporary
Grade 3 – causing permanent disability (no grade 3 were reported)
Grade 4 = fatal

[a]UTI = urinary tract infection

[b]Uret – urinary retention

[c]SSI = surgical site infection

[d]ROR = return to the operating room

Table 2

Demographics by Complications

Demographics by Complications				
	No Complication (N=350)	**Complication (N=81)**	**Total (N=431)**	**p value**
Surgery Hours/Operative duration				0.863
N	315	81	396	
Mean ([a]SD)	2.4 (1.3)	2.3 (1.1)	2.3 (1.2)	
[b]**ITT Laparoscopic**				0.226
Laparoscopic colectomy	177	47	224	
Open	173	34	207	
Gender				0.15
Female	178	34	212	
Male	172	47	219	
Race				0.601
Asian	5 (1.4%)	0 (0.0%)	5 (1.2%)	
Black	30 (8.6%)	6 (7.4%)	36 (8.4%)	
Hispanic	6 (1.7%)	3 (3.7%)	9 (2.1%)	
Other	1 (0.3%)	0 (0.0%)	1 (0.2%)	
White	308 (88.0%)	72 (88.9%)	380 (88.2%)	
Age				0.031
N	350	81	431	
Mean (SD)	68.4 (11.3)	71.7 (10.3)	69.0 (11.2)	
Stage				0.746
1	128	29	157	
2	128	27	155	
3	94	25	119	
[c]**ASA**				0.003
I or II	311 (88.9%)	62 (76.5%)	373 (86.5%)	
III	39 (11.1%)	19 (23.5%)	58 (13.5%)	
Length of Stay (Days)				<0.0001
N	350	81	431	
Mean (SD)	5.4 (2.5)	8.9 (6.3)	6.0 (3.8)	
Median	5.0	7.0	5.0	
[d]Q1, Q3	4.0, 6.0	6.0, 9.0	4.0, 7.0	
Range	(2.0–34.0)	(2.0–40.0)	(2.0–40.0)	

[a]SD = standard deviation

[b]ITT = intention to treat

[c]ASA = American Society of Anesthesiologists class

[d]Q = quartile

Table 3

COST Trial Quality of Life and Surgical Outcomes Secondary Analysis Risk for major postoperative complications in patients with preoperative QOL < 50

		Baseline QOL < 50			
Complications	**Grade**	**Yes (%)**	**No (%)**	**Missing**	**P-value**
Early	0–1	46 (84)	317 (94)	36	0.023
	2–5	9 (16)	21 (6)	2	
Late	No	35 (71)	249 (77)	27	0.472
	Yes	14 (29)	75 (23)	4	

Table 4

Symptom Changes by Early Complications

	No Complication (N=350)	Complication (N=81)	Total (N=431)	p value
FATIGUE-PRE-OP				0.1211
N	325	80	405	
Mean (SD)	2.0 (0.9)	2.2 (1.1)	2.0 (1.0)	
Median	2.0	2.0	2.0	
Q1,Q3	1.0, 2.0	1.0, 3.0	1.0, 3.0	
Range	(1.0–5.0)	(1.0–5.0)	(1.0–5.0)	
FATIGUE- DAY 2				0.8151
N	312	79	391	
Mean (SD)	2.5 (1.1)	2.6 (1.1)	2.5 (1.1)	
Median	2.0	2.0	2.0	
Q1, Q3	2.0, 3.0	2.0, 3.0	2.0, 3.0	
Range	(1.0–5.0)	(1.0–5.0)	(1.0–5.0)	
Fatigue: day 2-base				0.2288
N	303	78	381	
Mean (SD)	0.6 (1.2)	0.4 (1.5)	0.5 (1.3)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0	
Range	(−4.0–4.0)	(−3.0–4.0)	(−4.0–4.0)	
APPEARANCE-PRE-OP				0.3042
N	325	81	406	
Mean (SD)	1.3 (0.7)	1.3 (0.6)	1.3 (0.7)	
Median	1.0	1.0	1.0	
Q1, Q3	1.0, 1.0	1.0, 2.0	1.0, 1.0	
Range	(1.0–4.0)	(1.0–4.0)	(1.0–4.0)	
APPEARANCE- DAY2				0.0126
N	310	77	387	
Mean (SD)	1.5 (0.8)	1.7 (0.8)	1.6 (0.8)	
Median	1.0	2.0	1.0	
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	
Range	(1.0–4.0)	(1.0–5.0)	(1.0–5.0)	
Appearance: day2-base				0.0626
N	301	77	378	
Mean (SD)	0.2 (0.8)	0.4 (1.0)	0.3 (0.9)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0	
Range	(−3.0–3.0)	(−3.0–4.0)	(−3.0–4.0)	
BREATHING-PRE-OP				0.9211
N	326	81	407	

	No Complication (N=350)	Complication (N=81)	Total (N=431)	p value
Mean (SD)	1.2 (0.5)	1.2 (0.4)	1.2 (0.5)	
Median	1.0	1.0	1.0	
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0	
Range	(1.0–5.0)	(1.0–3.0)	(1.0–5.0)	
BREATHING- DAY2				0.0616
N	311	79	390	
Mean (SD)	1.3 (0.6)	1.4 (0.7)	1.3 (0.6)	
Median	1.0	1.0	1.0	
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	
Range	(1.0–5.0)	(1.0–4.0)	(1.0–5.0)	
Breathing: day2-base				0.0333
N	303	79	382	
Mean (SD)	0.1 (0.6)	0.3 (0.7)	0.1 (0.6)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 0.0	0.0, 1.0	0.0, 0.0	
Range	(−3.0–4.0)	(−2.0–3.0)	(−3.0–4.0)	
OUTLOOK-PRE-OP				0.6403
N	325	81	406	
Mean (SD)	1.9 (1.0)	1.9 (1.0)	1.9 (1.0)	
Median	2.0	2.0	2.0	
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	
Range	(1.0–5.0)	(1.0–5.0)	(1.0–5.0)	
OUTLOOK-DAY2				0.6633
N	309	79	388	
Mean (SD)	1.9 (1.0)	1.8 (0.9)	1.9 (1.0)	
Median	2.0	2.0	2.0	
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0	
Range	(1.0–5.0)	(1.0–5.0)	(1.0–5.0)	
Outlook: day2-base				0.9012
N	300	79	379	
Mean (SD)	−0.1 (1.1)	−0.1 (1.3)	−0.1 (1.1)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 0.0	−1.0, 0.0	0.0, 0.0	
Range	(−4.0–3.0)	(−3.0–3.0)	(−4.0–3.0)	

Table 5

Final Multivariate Model for Association of Any Complications From Stepwise Models		
Independent Variable	**p-value**	**Odds Ratio**
Age	0.045	1.03 (1.00–1.05)
[a]ASA III	0.023	2.24 (1.12–4.49)
Change in activity from baseline to day 14	0.004	1.56 (1.15–2.11)

Final Multivariate Linear Model for Association Complication Grade From Stepwise Models		
Independent Variable	**p-value**	**Estimate**
Age	0.015	0.00704
Change in appearance from baseline to day 2	0.012	0.09650
Change in daily living from baseline to day 14	0.011	0.15661

[a]ASA = American Society of Anesthesiologists class