

A Meta-Analysis of Quality of Life, Estimated by Questionnaires of the European Organization for Research and Treatment of Cancer (EORTC) after Rectal Cancer Surgery

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Rezumat

O metaanaliză a calității vieții după chirurgia pentru cancer rectal, estimată prin chestionarele Organizației Europene pentru Cercetarea și Tratamentul Cancerului (EORTC)

Date generale: carcinomul rectal este unul dintre cele mai frecvent întâlnite cancere la nivel mondial. Deși s-au făcut progrese majore în tratamentul cancerului în ultimele două decenii, chirurgia rămâne singura metodă curativă. Aceasta este însă adesea complicată și poate afecta diferite aspecte legate de percepția personală a pacienților asupra propriei sănătăți. Scopul acestui studiu a fost de a efectua o metaanaliză în vederea evaluării și comparării rezultatelor calității vieții după tratamentul pentru cancer rectal.

Metode: s-a efectuat căutarea articolelor relevante publicate între 2000 și 2015. Rezultatele rezecției abdominoperineale și anterioare au fost analizate cu ajutorul instrumentelor de măsurare a calității vieții furnizate de EORTC- chestionarele de evaluare a calității vieții C30 (QLQ-C30) și CR38 (QLQ-CR38). Scorul de evaluare, potrivit studiului, a fost stabilit la un an de la efectuarea intervenției radicale. Pachetul Statistical Package for Social Sciences (SPSS) furnizat de IBM Statistics, versiunea 19 a fost utilizat pentru analiza statistică.

Rezultate: 13 studii, publicate între 2001 și 2015, au fost incluse în această metaanaliză. Datele de la 1805 pacienți, cu o vârstă

medie de 64,7 ani, au fost analizate. La compararea extirpării Miles cu operațiile cu conservarea sfincterului anal, semnificație statistică a fost identificată în cazul următoarelor variabile: funcționalitate socială ($74,6 \pm 8,5$ vs. $83,4 \pm 8,6$, $P = 0,045$), constipație ($11 \pm 8,4$ vs. $22,6 \pm 8,3$, $P = 0,032$), și imagine corporală ($67,9 \pm 14$ vs. $82,5 \pm 9,1$, $P = 0,01$).

Concluzie: conservarea sfincteriană este o opțiune de tratament superioară ce ar trebui luată în considerare cu seriozitate. Date fiind diferențele subiective înregistrare, convingerea noastră este că în cazurile de cancer rectal este nevoie de individualizarea abordului chirurgical. Un aspect esențial este acela că evitarea rezecției pe cale abdominoperineală nu poate fi justificată strict pe baza rezultatelor calității vieții.

Cuvinte cheie: cancer rectal, calitatea vieții, EORTC, QLQ-C30, QLQ-CR38, rect

Abstract

Background: Rectal carcinoma is one of the most common cancers on a global scale. Although there were major improvements in its treatment during the last two decades, surgery is still the only curative method. However, is often complicated and can cause disorder of different aspects of the patients' self-perception of health. The aim of this study is performing of a meta-analysis for evaluation and comparison of the quality-of-life results after rectal cancer treatment.

Methods: Search of relevant articles, which were published between 2000 and 2015, was performed. The outcomes of abdominoperineal resection and anterior resection were

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analyzed with the EORTC's quality of life measuring instruments - quality-of-life questionnaire C30 (QLQ-C30) and quality-of-life questionnaire CR38 (QLQ-CR38). The assessment score, appropriate for the survey, was established at least one year after radical surgery. The Statistical Package for Social Sciences (SPSS) package of IBM Statistics, version 19 was used for the statistical analyses.

Results: 13 studies, published between 2001 and 2015, have been presented in this meta-analysis. Data from 1805 patients, with a mean age of 64.7 years, have been included. When comparing Miles extirpation and sphincter-sparing operations, statistical significance was detected for the following variables: social functioning (74.6 ± 8.5 vs. 83.4 ± 8.6 , $P = 0.045$), constipation (11 ± 8.4 vs. 22.6 ± 8.3 , $P = 0.032$), and body image (67.9 ± 14 vs. 82.5 ± 9.1 , $P = 0.01$).

Conclusion: Preservation of the sphincter is a better treatment option that should be carefully considered. Dependently registered differences, our conviction for the rectal cancer care concern needs individualization of the approach in this surgery. It is essential that the policy of avoidance of abdominoperineal resection (APR) cannot currently be justified on the grounds of quality-of-life (QoL) results alone.

Key words: rectal cancer, quality of life, EORTC, QLQ-C30, QLQ-CR38, rectum

Introduction

Colorectal carcinoma is one of the most common neoplasms. 1 360 602 new cases in the world and 447 136 new cases in Europe are established every year according to Globocan 2012 data (1). Improvement of the treatment results in increase of the number of patients, who survive with the consequences of this disease. Although there were major improvements in its treatment during the last two decades, surgery is still the only curative method. Last few decades have been marked by advances in rectal cancer treatment, in particular the widespread adoption of total mesorectal excision (TME), which now is a gold standard in this surgery (2). New neoadjuvant chemoradiotherapy (CRT) improved local control and long-term results. Rectal cancer surgery, however, is often complicated and it may change different aspects of QoL. There are particularly disorders of social and emotional aspects, body image, sexuality, and symptomatology aspects like bowel movements or pain. The decision whether to perform sphincter-sparing operation or abdominoperineal resection is affected by these variables. QoL is an individual subjective feeling of each patient concerning different aspects of his/her life (3). One of the main factors, which specify it, is the operative technique used. Being a traumatic procedure, dissection of the pelvis could compromise functional outcome with defecation, micturition and sexual problems. Performing of a stoma as in APR also disturbs the psychological well-being. This is a procedure of choice when a

distal margin of clearance cannot be achieved or the sphincter complex is involved by the tumor. Otherwise, anterior resection (AR) is indicated for the rest of cases (4).

Sphincter-preserving surgery more often allows better QoL results as compared to APR. Other factors that can influence the postoperative results are gender, age, tumor location, stage of disease, comorbidity, and period of time passed after surgery (5). Many authors, like Cornish, suggested as an aim the follow-up of patients for a period longer than a year after the operation (6). We also reckon that this should be the earliest moment of detecting the "clear" effects of the intervention. The aim of this study was collecting of QoL data published after rectal carcinoma surgery. QoL was compared in patients that have undergone AR or APR. The selected articles were searched, based on at least one year follow-up period after the surgery. The insufficient data for estimating QoL about rectal cancer surgery was the main reason to perform this study.

Material and Method

For identification of articles related to our study we searched the major medical databases such as MEDLINE, Excerpta Medica dataBASE (EMBASE), Science Citation Index, Scopus, Science Direct, and Trail Government Register. The EORTC QLQ-CR38 was selected for assessment of QoL, because it demonstrates widespread validity regardless of the stage of disease and primary tumor site (7). Basic keywords that we used in all related articles were "quality of life", "rectal cancer", "rectal carcinoma", "EORTC QLQ-C30" and "EORTC QLQ-CR38". Our interest was focused on studies published between 2000 and 2015. Furthermore, the search in references was limited to studies comparing APR and AR, and studies including a period of minimum a year follow-up after the surgery. We reviewed 49 studies and found that the data from 13 of them were appropriate for the aims of this meta-analysis. Researcher's team extracted information from each article and entered it into a database, using a structured sheet on Microsoft Excel package 2010. Meta-analyses were performed for the aspects of quality of life aspects estimated by the EORTC QLQ-C30 and EORTC QLQ-CR38 (7). All studies estimating QoL by other metrical systems and shorter than one-year follow-up period were excluded. Breakdown of the selected groups according to operative procedure (APR vs. AR) was observed by the original source. There were also present merging results from the whole cohort, year of publishing, tumor location, gender and age of participants, stoma or non-stoma patients, time after surgery and adjuvant therapy, if any. The study uses 26 components of EORTC methodology, separated in symptom and functional scales that form the subjective term QoL. The authors of the original studies were contacted for obtaining of additional information. For statistical analyses we used SPSS statistical package of IBM Statistics, version 19. We introduced $P \leq 0.05$ for the rejection of null hypothesis. Confidence interval (CI) was established at 95%. Descriptive statistics, explorative analysis, χ^2 test, Mann Whitney U test, and multiple regression analyses were used for the present study.

Results

Table 1 presents general information of all studies included into the meta-analysis. The total number of patients included was 1 805, with questionnaire filled in more than 12 months after the operation. The male sex prevailed (58.4%), which responds to the global deviation of disease. In approximately two thirds of selected patients sphincter-sparing operations were performed. According to the chief aim of the meta-analysis, the data of patients with low and the high rectum were merged. The presence of stoma after APR was the cornerstone for holding the following debate.

The distributions were normal, excluding the following indices: fatigue, pain, sexual enjoyment, and side effects of CRT. Our study did not show normal distribution in AR cases according to the following scales: dyspnea, appetite loss, financial problems, sexual functioning, and gastrointestinal problems. The same results were found in APR for nausea and vomiting, sleep disorder, future perspective, and urinary problems. 13 included studies, which were published in original articles between 2001 and 2015, are shown on the Table 2. The table presents the year, type of study, number of patients enrolled, and number of references used. Our interest was focused on surveys with high quality and level of proof. Methodologically comparable single-center, cross-sectional, prospective and randomized studies were enlisted, all of them having level 3 to level 5 of evidence proved.

Comparing analysis from different studies by EORTC QoL in relation to operative procedure is shown on Table 3. In multiple regression analyses we found that the type of operation is a predictor of quality of life. Physical functioning ($P=0,049$), social functioning ($P=0,023$), constipation ($P=0,009$), and body image ($P=0,004$) are EORTC's indices presenting significant difference between the group scores of AR and APR survival.

Discussions

The studied sample is large enough in number, with sufficient stratification of groups that reflect age, sex, location, and type of

Table 1. General study information

General information	N (%)
Patients include into analysis	1805
Time after surgery	>12 months
Publications between	2001-2015
Gender: Males/Females	1099/783
Age Mean \pm SD	64,7 \pm 4,1
Patients undergo CHRT	877
APR	370
AR (total number)	1318
LAR (low AR)	366
HAR (high AR)	952
Stoma	405
Non-Stoma	1019
Localization (in rectum)	
Low	262
Middle	511
Upper	221

NB. There were missing values in different parameters in some studies.

surgery. The usage of verified and validated in practice EORTC's instrument allows combination and interpretation of very wide range of database (7). Based on the decision to perform a parallel of results at least a year after the operation, we searched for the earlier moment of detecting the "clear" effects of the operation. Our initial hypothesis of reduced QoL in patients with APR was subjected of critical debate (8,9,11).

The data of Global Health Status do not present evidence of overall impaired score in the group with extirpation. This generic index reflects the most essential self-esteem changes, demonstrating the affected psychology of these patients (11). There was a clear tendency of decreased values of this indicator, but no obvious significance was observed (11,12,13). In the cases with different level of anterior resection the permanent fear of relapse affected the self-perception of health. Otherwise, all previous doubts about dealing with a new anatomical structure offered in advance with APR and with results related to the modern colostomy, which supplied a surprisingly easy service (13,14). This naturally increases their QoL rating.

Table 2. Baseline characteristics of meta-analysis

Study	Year of publishing	Study Design	Size (N)	Number of reference
M. Grumann et al.	2001	Single center, Prospective	73	33
J. Engel et al.	2003	Prospective, Cross-sectional	299	36
V. Arndt et al.	2004	Cross-sectional	119	37
L. Sideris et al.	2005	Cross-sectional	122	28
M. Guren et al.	2005	Cross-sectional	319	25
A. Tsonuda et al.	2007	Prospective, Single center	47	18
O. Zajac et al.	2008	Single centre, retrospective	50	13
S. Pucciarelli et al.	2008	Randomized, Multicenter	117	36
S. Maslyankov et al.	2012	Single center, Prospective	162	36
J. Arraras et al.	2013	Single center Prospective	84	37
P. Neto et al.	2013	Single center Prospective	72	34
X. Li et al.	2014	Cross-sectional	266	40
Y. Kinoshita et al.	2015	Single center Prospective	75	30

Table 3. Meta-analysis results comparing APR and AR

Scales	Number of studies included	APR (mean \pm SD) (CI)	AR (mean \pm SD) (CI)	P value
Global Health Status	13	65,78 \pm 6,85 (60 - 71,5)	69,87 \pm 9,59 (62,24 - 74,5)	0,262
Physical Functioning	12	80,1 \pm 9,8 (70,9 - 89,2)	87,8 \pm 7,4 (89,2 - 91,6)	0,061
Role Functioning	12	78,81 \pm 12,7 (67 - 90,5)	82,66 \pm 12,5 (76 - 89,3)	0,384
Emotional Functioning	11	77,26 \pm 9,8 (66,9 - 87,6)	80 \pm 11,2 (74 - 86)	0,685
Cognitive Functioning	11	84,90 \pm 3,8 (81,2 - 93,2)	86,5 \pm 5,8 (82,9 - 90)	0,650
Social Functioning	13	74,56 \pm 8,5 (67,5 - 81,6)	83,4 \pm 8,6 (79,1 - 87,6)	0,045*
Fatigue	10	31,80 \pm 26,4 (11 - 64,6)	28,7 \pm 19,6 (18,3 - 39,2)	0,869
Pain	11	28 \pm 19,8 (3,4 - 52,6)	25,8 \pm 29,4 (4,7 - 46,8)	0,178
Nausea and Vomiting	8	4,7 \pm 5,1 (8 - 17,3)	3,8 \pm 4,2 (1,1 - 6,4)	0,713
Dyspnea	8	4,33 \pm 4,2 (-6-14,7)	9,1 \pm 10,1 (2,7 - 15,5)	0,512
Sleep disorder	8	27,7 \pm 6,5 (17,4 - 38)	27,2 \pm 11,2 (20 - 34,3)	0,855
Appetite loss	8	15,43 \pm 19,1 (32 - 62,9)	9,5 \pm 10,8 (2,6 - 16,4)	0,659
Constipation	11	11 \pm 8,4 (2,2 - 19,8)	22,6 \pm 8,3 (18,2 - 27,1)	0,032*
Diarrhea	11	12,1 \pm 8,4 (3,3 - 20,9)	23,5 \pm 13,6 (16,2 - 30,7)	0,071
Financial Problems	10	19,08 \pm 14,5 (1,1 - 37,1)	24,7 \pm 27,4 (10,1 - 39,4)	0,868
Body image	11	67,9 \pm 14 (77,9 - 87,2)	82,5 \pm 9,1 (56,1 - 79,6)	0,010*
Sexual Functioning	9	15 \pm 9,4 (5,2 - 24,9)	27,7 \pm 16,5 (18,2 - 37,3)	0,090
Sexual Enjoyment	7	30,2 \pm 3,2 (25,1 - 35,3)	42,5 \pm 20 (29,1 - 55,9)	0,280
Future Perspective	7	60 \pm 13,8 (38 - 89,1)	61,7 \pm 14,6 (52,9 - 70,5)	0,954
Urinary Problems	9	35,18 \pm 18,2 (16,1 - 54,3)	33,6 \pm 21,1 (22,3 - 44,9)	0,685
Side effects from CRT	4	52,1 \pm 52,1 (41,6 - 52)	32,3 \pm 38,4 (8,6 - 31,8)	0,513
Gastrointestinal Problems	9	32,8 \pm 28,7 (2,7 - 63)	25,5 \pm 24,9 (11,1 - 39,9)	0,409
Male Sexual Problems	8	35,6 \pm 23,7 (10,7 - 60,6)	25,4 \pm 17,4 (14,3 - 36,5)	0,398
Female Sexual Problems	5	20,2 \pm 12,1 (1 - 39,5)	29,5 \pm 20,3 (10,8 - 48,3)	0,345
Defecation Problems	9	-	22,2 \pm 2,6 (-1,6 - 46,1)	-
Weight loss	5	10,7 \pm 9,2 (-3,9 - 25,4)	15,9 \pm 14,3 (5,6 - 26,1)	0,520

SD – Standard Deviation; CI – Confidence Interval; * - statistically significant

The present analysis demonstrated the advance of QoL results of patients who had undergone AR in terms of social functioning, constipation, and body image. The presence of stoma is the most important factor decreasing the score for social functioning scale. J.Engel in his four-annual prospective trial demonstrated the same increase of social functioning over time for patients with spared sphincter (15). O. Zajac et al., who analyzed only stoma patients, registered significant influence of all functional scales in comparison with the general population (16,17). The conclusion of the most influenced QoL parameter social functioning reflects in the same way findings of our database of all included into meta-analysis centers. The similar interference tend to be registered in all functional scales of QLQ-C30, but in using multiple regression analyses physical functioning was also set as a significant predictor (P = 0,049). Emotional functioning retains high scores in APR group which confirm their high sensation of health. In general, the trend of the most of generic instruments' functional scales is to interfere with the factors as younger age, low education, marital status, etc. (6,16).

Many authors working on QoL problems after rectal surgery emphasize the relation of its impairment to the worsened function (10,12,14). Patients with very low anastomosis suffer from the following bad consequences: frequency, urgency, incontinence, etc. The functional score of these groups often decreases and the symptom scales have higher values. This

evidence changes the profile of overall QoL data. Groups' comparison of AR and APR rarely detect advance in the sphincter-spared patients. However, the idea of this meta-analysis includes the influence of unfavorable bad functional effects on the whole anterior resection group. Thus, we could derive clear juxtaposition via EORTC methodology of two completely different techniques.

Another affected functional scale, which was detected and significantly changed in the study, was the QLQ-CR38's parameter body image. APR patients apparently suffer from their new abdominal wall appearance (15,18,19). This influence tends to persist during time, which is the reason of Fucini et al. to conclude that five years later patients operated for very distal rectal cancer have a better QoL, if a definitive abdominal stoma could be avoided (20). Meanwhile, a major number of patients need a temporary osteotomy during low AR (21). These patients have a tendency to improve the values of the indices after an initial drop. This is an expression of their suspense. The unexpected problem of reduced to lacking control of continence, even in a normal healing process, results in decreased long-term score, especially for body image. It is obvious that the role of factors as adequate postoperative volume of rectum, nerve-sparing surgery, complications, etc. influence the specialized questionnaire data (13,22,23). There is a place for bigger, prospectively organized, randomized trial that could clarify the exact importance of

each surgical detail and healing disorders on QoL.

In our compilation of meta-analysis groups, constipation was the only significantly influenced symptom scale ($P=0,032$). It has remarkably changed in the most of the surveys, but, as may be observed, the absolute score for APR group has decreased twice than the AR ($11 \pm 8,4$ vs. $22,6 \pm 8,3$). Otherwise, these symptoms mostly disturb QoL of sphincter-spared patients (24). This is especially and manifestly observed for intersphincteric resections, like a final possible opportunity to preserve rectum distally (25). Plenty of studies confirm the high level of adverse symptoms that negatively affect the condition of self-perception of health (16,26,27). Similar advances for APR technique suggested many authors' conclusions of the lack of a principal advantage of sparing the sphincter by all means (13,28). This is, however, a relative base for changing the tactics, because of the unfavorable consequences after low resections, which have the tendency to improve function and the following QoL score (24,25,29). And what is more, there are no adequate data how using the mini-invasive approach would change the degree of anterior resection syndrome and related scores. Most author collectives conclude that laparoscopic, preserving resection for rectal cancer is associated with a better quality-of-life result (28,30).

None of the studies, included into this meta-analysis, can definitely conclude whether the quality of life of people after anterior resection is surpassing that of people who underwent APR. A well-observed tendency of a change of QoL values early after the operation determined our approach of groups' juxtaposition. Obviously, the best self-perception of health after treating the rectal carcinomas is found in tumors of high location. But in cases with low resections, which have poor function, the quality of life in some aspects is frequently lower than in patients with extirpation. However, the principal difference of both techniques makes adequate comparison very arduous. Thus, the choice of patients becomes much more related to the experienced surgeon discussion, and finally, it is quite personally dependent.

Conclusions

Aggressive approach and definitive stoma seem to have a negative impact on some QoL domains. Preservation of the sphincter is a better treatment option that should be carefully considered and used sparingly. All the patients should be fully informed of the potential impact of the consequences of this surgery to the following health perception. No matter of the definitely decreased functional scales social functioning and body image, we reckon that overall quality of life in patients, who survived APE, is comparable to all AR. The advantage for the stoma group for the symptom scale constipation more than a year after the surgery, confirms the insufficiency to assert which group have better perception. Our conviction for the rectal cancer care is in favor of the individualized approach. It is essential that the policy of avoidance of APR cannot currently be justified on the grounds alone of QoL.

Conflict of interests

The authors have declared that there was no conflict of interests.

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