

Quality of Life in Locally Advanced Colorectal Cancer Patients - An Extremely Multi-Layered Problem - A Systematic Review

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Received: 02 May 2019

Accepted: 02 June 2019

Published: 08 Jun 2019

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1. Abstract

1.1. Introduction: There are quite more than dozens studies in world literature concerning the problems of the quality of life of patients with colorectal cancer in a wide variety of clinical and socio-individual aspects. It is significantly difficult any specific screening and stratified grouping of similar problems in patients with locally advanced cancer both of the colon and rectum to be implemented. Those kinds of patients, in turn, are extremely a heterogeneous group, but represent 1/5 to 1/4 of the primary presented and diagnosed as such by a colorectal cancer. The aim of this study is emphasis and displaying the forefront of specific problems of this group of patients among the diversity of published data.

1.2. Method: A systematic literature search of publications during the period 2001-2018 in certain electronic databases concerning issues of QUALITY of Life in patients with colorectal cancer was made. Studies were included in case they focused mainly on locally advanced colon cancer, primary advanced or recurrent rectal cancer and also included data on HRQoL. Out of all 337 potential publications 17 were set up as completely and sufficiently relevant to the purpose of the present study.

1.3. Results: Various studies aimed to identify the HRQoL themes that might be relevant to patients with locally advanced colorectal cancer. As far as there are studies aimed at certain aspects of HRQoL in locally advanced primary and recurrent rectal cancer, it lacks any targeted specifically at locally advanced colon cancer. Furthermore, various methodological deficiencies and limits in available publications are indicated there. There is no practice established to customize the complex approach in these patients.

1.4. Conclusion: Besides mere clinical and oncological outcomes in the treatment of patients with locally advanced CRC it is ultimately essential development of a comprehensive guideline concerning overarching in details all the aspects of their quality of life.

2. Key words: Health related quality of life; Locally advanced colon rectal cancer; Multivisceral resections; extensive surgery; Multidimensional instruments for measuring qol

3. Abbreviations: PBD: Percutaneous Biliary Drainage; ERCP: Endoscopic Retrograde Cholangiography; F: French; PTBD: Percutaneous Transhepatic Biliary Drainage

3. Introduction

Locally advanced colorectal cancer is defined initially by Cuthbert Dukes as radically incurable because of local tumor growth, derived from the mucosa, spreading through the layers of the intestine beyond the anatomical limits of the intestinal wall, with invasion of adjacent tissues and organs, and / or metastasis in regional lymph nodes [1]. At present, as locally advanced tumors (including the colorectal) are accepted those wherein the final evaluation of a multidisciplinary patient-management team, presented by the surgeons, pathologists, radiologists, medical oncologists, gastroenterologists and imaging diagnostics, is precisely such that it would not be able to be performed a standard (a single organ) resection, unlikely to remain (into the surrounding of the specimen tissue spaces) certain microscopic or macroscopic residual disease which is due to adhesion or fixation of the tumor to the surrounding structures [2].

Extensiveness of potentially curative multivisceral resections in locally advanced colorectal cancer varies widely according to location of either primary or loco-regional recurrent tumor. Generally locally advanced tumor in the left colon may infiltrate directly the left kidney, spleen, abdomen, stomach and distal pancreas. Sigmoid cancer may invade into the bladder, the ovaries and uterus. Right-sided colon cancer can affect liver, pancreas, duodenum, and the right kidney. Case of advanced right-sided colon cancer with involvement of the duodenum or pancreas, or both, constitutes a dilemma for the colorectal surgeon. Patients with limited impairment on the duodenal wall could be safely treated by partial resection and subsequent plastic while those with involvement of larger parts of the wall of the duodenum or pancreas require duodenopancreatic resection [3-28]. Literature data indicate that most often surrounding structures and organs have been affected by primary tumor location into the sigmoid colon and rectum - 66-89% of cases. The underlying reasons about that are the high incidence of cancer localization in these areas, mobility of the sigma and close spatial proximity of the structures into the pelvis [28-31].

Citation and mutual over-quoting of national and international cancer registries with respect to colorectal cancer in an extremely rich medical worldwide literature demonstrated that locally advanced colorectal tumors (T3 + / T4M0 tumors) constitutes up to about 22% of all colorectal cancers at the time of presentation. Some of these cases being AJCC stage II and III will undergo curative-intent multivisceral resections with 5-year survivals 58% and 43% similar to those undergoing conventional resections [3,5].

Therefore, their life-expectancy and quality of life, respectively,

will be different from those in which there is a generalization of the disease - distant metastases. Some of these patients will have received neoadjuvant radiotherapy or chemoradiotherapy while others will not, which is in dependence of the location and characteristics of the tumor and where the patients are being treated according to accepted practice and conducted national and international guidelines. It also would change their quality of life - different aspects of it, to some extent, in a variety of time interval. It is proved that a proportion of patients (30-40%) underwent curative-intent multivisceral resections will develop local or loco-regional recurrence and/or distant metastases approximately 1-3 years postoperatively [4], which further changes their quality of life anyway already been impaired - but how and to what extent? Furthermore, locally advanced non-metastatic colon cancers have the peculiarity of better outcomes compared to non-metastatic locally advanced rectal cancers. Quite a few of the literature sources have combined results of colon and rectal cancers. Some reports have combined locally advanced and recurrent cancers as well. As the tumor biology and the spatial relationships of these areas are different, the QoL after either the colon or rectum extensive surgery have to be considered separately. In addition, unlike standard Total Mesorectal Excision for rectal cancer in which anatomical approach in embryonic interfacial "plans de clivage" ensures protection of the autonomic innervation and surrounding pelvic organs and structures then in locally advanced rectal cancer (LARC), which penetrates through the mesorectal fascia and / probably invades neighboring tissues and organs (cT3 + / T4, no matter if subsequently it is confirmed as pT4a/b) requires expanded - en bloc resection out of the embryonic plans, which often results in damage to the autonomous nerves, pelvic supporting structures (pelvic bones, pelvic floor muscles), main vessels, nerves or organs [4]. Furthermore, the morbidity and mortality associated with multivisceral resections are different of these areas, and, respectively, the health-related quality of life (HRQoL) would be different [3]. The performance of the surgery as elective or in matter of urgency, the placement of bowel stoma (ileostomy or colostomy, malpositioning of the stoma, temporary or permanent stoma, early and / or late stoma-related complications or complications associated with restoration of intestinal continuity) further diversify HRQoL assessment. Last but not least, there is a different attitude to HRQoL, its assessment and its impact on the overall healing process depends on several factors: mere individual characteristics of the patient, some of which are interrelated (age, mental and intellectual level, premorbid life style, professional engagements, image and position into the micro- and macro society, level of self-esteem, social life, sexual activity and attitude to that, vision and prospects

for their future), religious background in the emergence of the disease; others are the level of economic development and health services in the country where the patient is being treated (accessibility to quality health care, national guidelines, health insurance and the established social insurance system, complexity of treatment, wound-care and ostomy-care professional specialists availability - inpatient, outpatient and at home), as well as participation in standard or experimental treatment.

There is a wide range of different validated or not multidimensional instruments being used in measuring QOL in colorectal cancer patients. All are characterized by varying level of specificity and internal consistency. They range from Karnofsky Performance Scale - not specific for cancer, through certain ad-hoc questionnaires and qualitative Interviews, Medical Outcomes Study (MOS) Short-Form Health Survey (SF-36) - measures of physical and mental health, European Organization for Research and Treatment of Cancer - EORTC - QLQ-CR29 / C30 / CR38, FACT-C (Functional Assessment of Cancer Therapy-colorectal) Questionnaire, Brief Pain Inventory (BPI), to Stoma Quality of Life Questionnaire, modified City of Hope Quality of Life Questionnaire Ostomy (mCOHQOLQO) and others.

All this makes the stratification of individual patient in terms of his individual HRQoL extremely difficult and complicated.

The aim of our study is a comprehensive review of existing data on HRQoL among the wide variety of different “types” of patients with colorectal cancer and extraction of data concerning patients with locally advanced primary and recurrent tumor in order to allow for individualized approach to improve their quality of life, in parallel with the serious complex treatment.

4. Method

A systematic literature search was made with language restrictions – only English-language papers about the period 2001-2018. Search amongst the following electronic databases was carried out: PubMed, Embase, Web of Science, UpToDate®, Cochrane database, Research Gate®, Chinahl. Different variations and combinations of medical terms and text words used in the searching process in aforementioned databases were as follows:

“Colorectal cancer” AND “Locally advanced colorectal cancer” AND “Quality of life” AND “Locally advanced colon cancer” AND “Locally advanced rectal cancer” AND “Primary” AND “Recurrent” AND “Multivisceral resection” AND “Extended OR Extensive surgery” AND “Pelvic exoneration” AND “Health related quality of life” AND “ HRQoL” AND “Colostomy” AND “Temporary versus permanent ostomy” AND “Ileostomy” AND “Stoma patients” AND “Quality of Life Questionnaire”

AND “Sexual dysfunction” AND “Treatment outcomes” AND “Complications”. Limits: Adult 18+, humans. NOT inflammatory bowel disease.

Web of Science (Web of Knowledge) database has been sought out about the studies that cited the articles already found.

Inclusion criteria were comprehensive range of studies and systematic reviews concerning the problems of the locally advanced colon and/or rectal cancer both in the primary and in the relapsed form with regard to the parameters associated with the QUALITY of life of the patients operated on. Case reports and letters were excluded. Studies concerning the quality of life in surgical patients with either non-locally advanced disease (NLA) or locally advanced (LA) plus systemic advanced disease and palliative procedures are included only if they are compared with a separate group of patients with locally advanced non-metastatic tumor undergone curative intent surgery. Studies concerning the quality of life in stoma patients both LA and NLA were included due to the fact that this is a common point in elective or emergency surgery of patients with locally advanced colorectal cancer, and is also established an independent factor influencing the quality of life.

According to the adapted Mols` et col. 13-item version checklist for systematic reviews about QOL (the original is about breast cancer), just like other authors have done, a point for each item is given in case of overlapping with these criteria but zero points if there is not [6-9]. All studies finally collected have had score > 75%.

5. Data Collection and Analysis Process

Studies were included in case they focused mainly on locally advanced colon cancer, primary advanced or recurrent rectal cancer and also included data on HRQoL. They also had to give information about the surgical treatment, design of the study and multidimensional instruments for measuring QoL, as well as the number of patients included. Studies on palliative treatment or those that assessed function only but HRQoL directed were included as well.

All the titles and abstracts identified from the literature were 337. Out of these, 47 were allocated as relevant to the topic under consideration and meeting the inclusion criteria. As a final step 17 studies have been allocated. Of these, 7 are systematic review, and the remaining 10 are publications that are not included in the described systematic reviews, but contain essential information relevant to the subject matter (**Figure 1**).

Figure 1 Flowchart of studies retrieved from literature search.

Full text copies of all studies of possible relevance included were obtained and analyzed (**Table 1**).

Table 1: Summary findings of the studies included.

1	2	3	4	5	6	7
N	Author(first +year)	Topic (QoL in...)	Type of study	QoL categories and themes identified	Patients included (n)	multidimensional instruments for measuring QoL
1	Vonk Klaassen SM,2016 [10]	colorectal cancer ostomates	systematic review – 14 studies	accord. to column 7	range n: 22–517	<ul style="list-style-type: none"> • EORTC C30/CR38(n=10) • MCOHQOLQO (n=3) • Stoma QoL Quest. (n=1)
2	Liao C, 2014[11]	colorectal cancer underwent stoma	Cross-sectional study	accord. to column 7	n=76	<ul style="list-style-type: none"> • Stoma-QOL(SQOL) • Stoma self-care agency scaleHerth Hope Index (HHI)
3	Ciorogar G,2016[12]	colorectal cancer underwent colostoma/ ileostoma	Prospective Longitudinal observ. study	<p>The degree of skin irritation around the stoma.</p> <ul style="list-style-type: none"> - The degree of stoma leakage - Availability of family support and care of the stoma patient. - Patient's optimism regarding the changes brought by the stoma appliance. - Patient's comfort regarding the location of the stoma appliance 	n=56	<ul style="list-style-type: none"> • Nursing Research • Education City of Hope National Medical Center, in California, USA
4	Neuman, H.B, 2011 [13]	temporary stoma after sphincter-preserving surgery in rectal cancer	Prospective, single-institution longitudinal study	work/social function, sexuality/body image, stoma function – (/+column 7)	n=60 (46 completely responsive)	<ul style="list-style-type: none"> • EORTC QLQ C-30 • EORTC CR-38 • Stoma-QOL
5	Silva MA, 2003[14]	temporary ileostomy versus colostomy (incl. CRC patients)	Cross-sectional cohort study	<ul style="list-style-type: none"> -Ability to purchase stomal appliances -Stoma effluent -Appetite impairment -Travel by public transport impairment -Dress impairment -Daily activities impairment -Hygiene impairment -Abstaining from sexual activity 	n=50(25-ileostomy & 25-colostomy)	<ul style="list-style-type: none"> • A self-administered structured questionnaire
6	Canova C, 2013[15]	ileostomy & colostomy (incl. CRC patients)	Cross-sectional multicentre study	accord. to column 7,validated using a Rasch model	n=251(70% CRC)	<ul style="list-style-type: none"> • Stoma Care QoL scale(SQOL)

7	Harji DP,2016 [16]	pelvic exenteration(incl. CRC patients – LARC/LRRC)	systematic review – 24 studies	<p>=physical, =psychological =social domains: - body image, -sexual function, -communication, -relationships, -work -finance</p>	n=374 primary rectal cancer and locally recurrent rectal cancer(out of 976 pelvic exenterations due to gynaecological, urological or colorectal malignancy)	<ul style="list-style-type: none"> • Qualitative Interview • Symptom scales • Sexual Function Vaginal Changes Questionnaire (SVQ) • EORTC QLQ-C30/EORTC-QLQ CR38/EORTC QLQ-BLM30/BFI/BPI-SF IADL/CES-D/IES-R • FACT-C/SF36 II <ul style="list-style-type: none"> • Cancer Rehabilitation Evaluation System (CARES)/Preoperative Anxiety (STAI) • Strauss-Appelt Body Image Symptom Checklist-90/Beck Depression Inventory/Katz Social Adjustment Scales/Marital Adjustment/Derogatis Sexual Functioning Inventory/Heterosexual Behaviour Hierarchy/Sexual Arousal Inventory • Australian Quality of Life/Distress Thermometer • International Prostate Symptom Score (IPSS)/Urogenital Distress Inventory (UDI-6)
8	Yang, T X,2013 [17]	pelvic exenteration outcomes (incl. QoL)for primary advanced and locally recurrent rectal cancer	systematic review – 23 studies (3 studies - Esnaola et al86;Guren et al87; Austin et al88, devoted to HRQoL)	<p>-mean QoL scores, -SF-36v2, -levels of pain, -extended hospital stays, -complication rates, -long rehabilitation process, -potentially disfiguring nature of the operation</p>	n=1049	<ul style="list-style-type: none"> • SF-36v2 • mean QoL scores
9	Choy, I, 2015[18]	Baseline QoL as a significant, independent predictor of QoL after pelvic exenteration for LRRC	Prospective cohort study	<p>-age, sex, -baseline QoL score,- R0 margins, -ASA score, -extent of surgery (three or more compartments involved), -bone resection, -excision of the major sacral nerve, -formation of an ileal or colonic conduit</p>	n=117	<ul style="list-style-type: none"> • Assessment of Quality of Life (AQOL) • SF6D

10	Quyn AJ, 2016[19]	clinical and patient-reported quality of life outcomes over 12 months for patients having pelvic exenteration for locally advanced primary rectal cancer(LARC)	Prospective cohort study	-physical component summary (PCS) and mental component summary (MCS) scales -bowel function, appetite, digestion and stoma concerns	n=64	<ul style="list-style-type: none"> • SF-36v2 • Functional Assessment of Cancer Therapy – Colorectal (FACT-C)
11	Harji DP, 2015[20]	HRQOL themes relevant to patients with LRRC	systematic review – 14 studies	accord. to column 7	n=505	<ul style="list-style-type: none"> • EORTC QLQ-BLM30s/QLQ-C30/QLQ-CR38 • SF36 II • BPIFACT-C • Symptom scales • Qualitative Face-to-Face Interview
12	Thaysen, H. V., 2012 [21]	HRQoL after surgery for LARC/LRRC	systematic review – 7 studies	accord. to column 7	n=173	<ul style="list-style-type: none"> • Face-to face interview Open-ended • Face-to face semi-structured interview • EORTC QLQ-C30 • EORTC QLQ-CR 38 • EORTC QLQ BLM-30 • FACT-C • BPI • SF-36
13	Thaysen, H. V., 2014 [22]	HRQoL after complex surgery for LARC/LRRC (COMP-RCS) compared with standard rectal cancer surgery(STAN-RCS) and NORM-data group-extracted from the Danish Colorectal Cancer Group (DCCG) database	nationwide prospective longitudinal comparative study	accord. to column 7: -global quality of life, physical, social, role and emotional function, pain and fatigue -body image, future perspective and sexual functioning	n=80COMP-RCS (compared with 48 patients treated with STAN-RCS)	<ul style="list-style-type: none"> • EORTC QLQ-C30 • EORTC QLQ-CR38 • SF-36
14	Guren, M G, 2001 [23]	QoL in disease-free patients with urinary diversion after extensive surgery LARC	Retrospective case-control cross-sectional study	accord. to column 7	n=12 (compared to drawn randomly drawn 133 LARC/LRRC without urinary diversion)	<ul style="list-style-type: none"> • EORTC QLQ-C30 • EORTC QLQ-CR38 • EORTC QLQ-BLM30

15	Mosher, C E, 2016 [24]	Mental HRQoL in CRC (incl. LACRC)	systematic review – 12 studies	-Anxiety and depressive symptoms -Emotional functioning =during the acute and the long-term survivorship period	n=234-1892	<ul style="list-style-type: none"> • SI, Brief Symptom Inventory; • CES-D, Center for Epidemiologic Studies Depression Scale; • EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core30; • HADS, Hospital Anxiety and Depression Scale; • MDD, major depressive disorder; • MHOS, Medicare Health Outcomes Survey; • PANAS, Positive and Negative Affect Scale; • SF-36: MCS, Medical Outcomes Study 36-Item Short Form • Health Survey: Mental Component Summary; • VR-12: MCS, Veterans RAND 12-Item Health Survey: Mental Component Summary
16	Stephenson LE, 2009 [25]	in CRC patients receiving chemotherapy (incl. LACRC)	cross-sectional study	-Physical Activity Behaviour -Diet Behaviour -Social Support	n=67	<ul style="list-style-type: none"> • Godin's leisure score index (LSI) • 3-day diet record • Social Provisions Scale (SPS)
17	American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA: A Cancer Journal for Clinicians, 2015[26]	Evidence based recommendations to CRC survivors (incl. LACRC)	systematic review – 226 studies+RCT,prospective studies, population-based, case-control studies; large studies of more than 200 cancer cases + recommendations with relevant Level of evidence	Assessment and Management of Physical acute and Psychosocial Long-Term and Late Effects of CRC and its Treatment	Not identified	<ul style="list-style-type: none"> • All of aforementioned

6. Results

Extensive surgery impacts upon a large number of HrQoL essentials as physical, psychological and social functioning, i.e. body image, sexual function, communication, relationships, work and finance status. The impact on each of these domains is quite variable, with a considerable reduction in initial HrQoL, however this could be transitory process following treatment trajectory and a certain period of adjustment. Multivisceral resection, including pelvic exenteration, is the only available option aimed to achieve curative intent of the treatment in a range of advanced pelvic malignancies, including not only locally advanced primary

and recurrent rectal cancer but also gynaecological and urological malignancy.

Harji et al., 2016 [16] give a summary of the explanations concerning the categories and themes characterizing HrQoL as Body image; Social impact; Sexual function; Treatment expectations; Symptoms; communication; Psychological impact; Relationships; Work and finance.

7. Locally Advanced Colon Cancer

There is lack of distinctively allocated clinical studies concerning quality of life after extensive multivisceral resections with

advanced tumor located explicitly into the colon by itself. Unlike the locally advanced rectal tumor, with the exception of certain cases of pelvic structures impairment by a tumor originating from a mobile sigma or mobile caecum, in most of the cases the advanced colon cancer resection are not so mutilate and disabling and do not violate functional, sexual and mental aspects of quality of life so directly. However, it is quite different when it appears demand for temporary or permanent colostomy/ileostomy or some kind of urostoma to be placed, mostly due to complicated carcinoma (most often intestinal obstruction or peritumoral abscess and fistula formation – external or internal). Many authors describe the injurious impact of the stoma on the quality of life, even more so in 30% of the cases of temporarily placed stomas eventually they remain constant [10-15]. Those authors have used a range of scores for ostomy-specific QOL measurement and the results pointed that about 70 % of the patients stated to be dissatisfied in terms of the ‘sexual activity’ and ‘depression feelings.’ Factors such as the type of ostomy (temporary/permanent), the underlying disease that had led to the stoma, depression, problem with location of ostomy, change in clothing had significant effects on overall QOL and its subscales ($p < 0.05$) but most of the studies have not described the outcomes in stratifying manner as afraid about stoma, noise, afraid about smell of stools, worry about possible leakage, caring for stoma, irritated skin, embarrassment, feeling less complete [10]. Reported that women described more specific psychological and social issues than men. Regarding the type of stoma McMullen et al. reported the greatest challenges in cases of long-term colorectal cancer survivors with ostomies as those who have a permanent colostomy or ileostomy, require significant and permanent physical changes in bowel functioning which require daily care adjustments and challenging psychological and social adaptations[10]. The results also established that young people are experiencing much greater damage on social life, but also mental and sexual problems, in contrast to the adults presented with permanent stoma[10,12,14].

Besides the role of the stoma itself on the altered quality of life, also other factors, for example risks associated with a subsequent operation to restore the passage, complications of primary and subsequent operations, as well as fear of recurrence or metastasis of the disease affect the overall quality of life of the patients [26]. Most of these patients undergo adjuvant systemic chemotherapy, which further complicates their quality of life[25]. Stephenson et al. having assessed current dietary and physical activity behaviour in the CRC population undergoing systemic chemotherapy have found that lower BMI, older age, and greater provisions of attachment, social integration, guidance, and reliable alliance were significantly associated with overall QOL. Moreover, there was no significant differences on any QOL scales founded between

patients treated in the adjuvant or metastatic setting, which implies that QOL is no worse when treated with palliative intent as compared to adjuvant therapy in this population[25].

8. Locally Advanced Primary Rectal Cancer LARC

Despite the improved survival in colon cancer and more pronounced prevention of occurrence of that cancer, in general, and its advanced type, in particular, by prevention of intestinal polyposis, the evidence suggests that locally advanced cases of cancer of the rectum increase progressively in recent years, especially in younger patients[17]. The only way to reach potential curative effect of the treatment of locally advanced primary rectal tumors or loco-regional recurrence is the pelvic multivisceral resection executed in order to achieve free tumor resection margins - R0. It is technically complex surgery to be performed; it is by the domain of the “genuine great surgery” as the most commonly it requires neo-adjuvant radiotherapy or chemoradiotherapy and multidisciplinary team consisted of colorectal surgeons, onco-gynecologist, urologists, orthopedists, plastic surgeons. In many cases this in fact poses performing of a real pelvic evisceration/exenteration. Pelvic exenteration is described as implementation of radical extirpation of the all pelvic malignant disease in order to achieve tumor-free margins which requires involvement into the operative en bloc-resection specimen the pelvic tumor itself, as well as, part or all of the invaded pelvic viscera, including the rectum, distal colon, bladder, lower ureters, internal reproductive organs, draining lymph nodes, main blood vessels, and pelvic peritoneum. In some instances, the resection of stabilizing structures such as muscles, ligaments, and parts of the pelvic bone might be necessary. Given its extensiveness, pelvic exenteration has been associated with a high rate of intra- and postoperative morbidity and mortality[17]. Quin et al. [19] gives a precise definition of pelvic exenteration for primary rectal cancer, as well as, terms as complete soft tissue exenteration and extended resections as different volume variations of multivisceral resection bearing varying complexity of implementation, varying degrees of complexity and mutilating effect and therefore varying degrees of influence on quality of life. Of course, this interesting interpretation concerning the degree of the extensiveness of resection may be applied to the rectal recurrence surgery. Treatment of the locally advanced rectal cancer affects to varying degrees four different areas of functioning as follows: physical functioning (e.g., defecation and/or micturition urgency, frequent/irregular bowel movements, gas/fecal leakage, altered urinary and bowel habits etc.), social functioning (e.g., due to urgency and/or frequency of their bowel or urinary movements), and sexual functioning (erectile dysfunction, failure of ejaculation or retrograde ejaculation, and incapability of orgasm in men whereas in females it causes

dyspareunia, destroyed orgasm and less frequent intercourse), and as a result of the all of that – the entire mental and psychosocial acute and long-term functioning. Moreover those patients who also have a colostomy (and often two type ostomies – colo and urinary diversion) are significantly in risk for considerably high level of distress and suffer from the so-called “double stigma” due to both the cancer and ostomy[19,21].

As it has been mentioned above, in pelvic exenteration patients generally end up with both a colo/ileostomy and urinary diversion which, for sure, interfere considerably with their quality of life (QOL)[17]. Moreover, commonly these patients are characterized by postoperative pelvic instability and pelvic floor defects, although somehow or other plastic rebuilt. This applies, for example, over largely to populations as Dutch and Scandinavian, who are extremely accustomed to cycling and are almost dependent on it in their daily lives. In his own systematic review Yang and col,2013 [17] cited studies found that, although resected patients had levels of pain nearly similar to those underwent palliation in the first 3 years, long-term survivors beyond 3 years had a good QOL and minimal pain. He mentioned also the Guren`s at al study[23] found that the mean QOL scores of disease-free patients underwent both pelvic exenteration in case of locally advanced rectal cancer and had urinary diversion did not differ significantly from patients who had surgery without urinary diversion or the general population. This was corroborated recently by other authors suggested that although patients had lower physical wellbeing scores in comparison with the general population on the generic QOL, the mental well-being was as good and comparable to the general population[17,21,22].

Quin et al. [19] demonstrated good short term clinical and oncological outcomes with a rapid return to baseline quality of life following pelvic exenteration in a selective group of patients with locally advanced primary rectal cancer.

Thaysen and al during 2012 in theirs systematic review [21] concerning HRQoL after surgery for both LARC / LRRC sets various limitations of the cited studies resulted in considerably difficulties in study-results interpretation, for example small sample size, small number of prospective longitudinal studies, the different points of time for assessment of HRQoL, the use of different HRQoL questionnaires and the lack of matching between control and study groups. So the same team published in 2014 a nationwide prospective longitudinal comparative study based on HRQoL after complex surgery for LARC / LRRC (introduced the term COMP-RCS) compared with standard rectal cancer surgery (introduced the term STAN-RCS) and (normal) NORM-data group - extracted from the national database - the Danish colorectal Cancer Group (DCCG) database in 2 years

follow-up period [22]. Avoiding the drawbacks of previous studies cited they compared the results with preoperative reported level of HRQoL topics. Thus, they found that the majority of the HRQoL scales improved or remained stable during the first postoperative year with decrease observed only for body image. Furthermore, a year after surgery, HRQoL in patients treated with COMP-RCS was comparable to that for patients treated with STAN-RCS with lower levels were found for physical and emotional role functioning, compared with NORM-data.

9. Locally Advanced Recurrent Rectal Cancer LRRC

Harji and col. in 2015 [20] presented a comprehensive systematic review including meta-analysis and synthesis of qualitative and quantitative studies focused on HRQOL themes relevant to patients exclusively with LRRC. The authors present again synthesized definitions of categories and themes identifying HRQoL by specifically relevant measuring-scale instruments. They discussed in detail the problems of the physical, psychological and social impact, financial and occupational impact, relationships with others, communication with healthcare professionals and sexual function following surgery for LRRC as well as a variety of symptoms as: pain, gastrointestinal, genitourinary and musculoskeletal symptoms in patients with LRRC being the most commonly reported in patients after extensive surgery. The authors indicate the limitations in the methodology in cited studies, as well as the necessity of a disease-specific, validated and reliable outcome measure through well designed, prospective study measuring HRQoL outcomes across a range of management strategies. It would contribute to the valuable information gained regarding the benefits conferred by individual treatments to patients in improving HRQoL outcomes. Furthermore, Choy and col. 2015 in their prospective cohort study attach importance to the baseline QoL as a significant and independent predictor of patients' QoL after pelvic exenteration for recurrent rectal cancer [18].

10. Discussion

Various studies aimed to identify the HRQOL themes that might be relevant to patients with locally advanced colorectal cancer. We have not found any of them that dealt explicitly and independently with locally advanced colon cancer. Eight of the studies considered by us are dedicated to colorectal cancer involving a group of locally advanced colorectal cancer, which in turn comprises a group of locally advanced colon cancer [10-15, 24-26]. Of these, 3 were systematic review [10,24,26]. Locally advanced primary rectal cancer (LARC) in combination with locally advanced recurrent rectal cancer (LRRC) are considered in 8 studies [16,17,19,21,22,24,25,26], out of which 5 are systematic review [16, 17,24,26]. Additional are the studies

concerning HRQoL in ostomy-patients with CRC, including locally advanced type [10,11,12,13,14,15]. LARC is regarded as a particular problem in one prospective cohort study [19] and one retrospective case-control cross-sectional study [23] while LRRc as directed subject is addressed in a systematic review [20] and one prospective cohort study [18]. In some of the studies devoted to the HRQoL in patients after pelvic exenteration, except primary or recurrent locally advanced rectal cancer, are also examined groups of patients with primary urological or gynecological pelvic malignancy. However, models and principles of extensive surgery as well as its mutilating effect on the external image, physical and social wellbeing, sexual and mental / psychological normal balance can be attributed to patients with locally advanced primary / recurrent rectal cancer with the same level of significance .

An interesting phenomenon is the lack of significant difference in HRQoL between patients with locally advanced disease and patients with non-advanced disease in several publications [34] which indicate that HRQoL after extensive surgery is not directly linked neither with the type of surgery nor the type of the tumor .This might be explained by a shift in expectations, the so-called “response shift” in those patients. This probably due to the ability of patients to cope with their QoL damages inasmuch as they are certain part of their curative treatment[4].

Mosher and col, 2016 [24] in their systematic review about adults' mental health outcomes during acute and long-term colorectal cancer (CRC) survivorship found clinically meaningful levels of anxiety and depressive symptoms or reduced mental well-being across the trajectory of the illness. Certain demographic, medical, and psychosocial predictors of mental health outcomes have been identified but the authors present existing gaps in understanding of risk and protective factors according to the mental health outcomes, especially during long-term CRC survivorship[24].

The importance of the problem of personalizing the measures to improve the quality of life of patients with locally advanced colorectal cancer arises from the heterogeneity of this group of patients who are relatively large proportion of all patients with colorectal cancer. Wong et al. in their longitudinal study concerning association between HRQOL with OS, all-cause death or CRC recurrence found the HRQoL as not a significant prognostic factor for CRC recurrence, but the HRQoL, by itself, provided independent prognostic value about mortality in patients with advanced stage of CRC[32].

Velikova and col. [33] examine the feasibility of the proposed by them a computer-based model aimed to assess specific HRQoL, including patients with locally advanced colorectal cancer. That approach would contribute to improve the doctor-patient

interactions both in preoperative and postoperative short / long term period in order to achieve a maximal timely and effectively resolution of specific problems in one of the areas of Quality Management Systems of life. As useful issues in the process of optimizing and personalizing measures concerning QUALITY of life in patients with locally advanced colorectal cancer could be differ some publications related to the activity of The National Comprehensive Cancer Network® (NCCN®) of the American Cancer Society. Strict consensus-based guidelines for the treatment of patients with colon and rectal cancers are developed there, in addition with straightforward recommendations regarding follow-up care after completion of treatment [26]. The recommendations with a certain level of evidence are enshrined in the guidelines for the primary care management of CRC survivors about the following topics: surveillance for CRC recurrence, assessment and management of physical and psychosocial long-term and late effects of CRC and its treatment, health promotion and care coordination and practice implications. In the proposed Guidelines for the Assessment and Management of Physical and Psychosocial Long-Term and Late Effects are assessed the potential long-term and late effects of colorectal cancer with appropriate recommendations targeting specific bowel / gastrointestinal issues, cardiovascular effects, cognitive function, dental / oral problems , distress, depression and anxiety, fatigue, neuropathy, pain, ostomy-related problems, urinary / bladder related issues, sexual function and fertility. These recommendations could be used as a basis for building up an individualized approach to the management of QUALITY of life of the distinguished group of patients with locally advanced primary or recurrent cancer of the colon or rectum.

Optimizing the quality of life in patients with locally advanced tumor is related to the need for standardized application of certain multidimensional instruments for measuring QoL not only in general topics for this but also as particular measuring instruments specifically targeted at this group of patients. The purpose of this is particular recommendations to the individual patient in the particular period of its follow up and multidisciplinary treatment to be created and codified . These recommendations should be addressed accordingly also to the appropriate team of medical professionals who are responsible for conducting the complex treatment of patients with advanced (local and / or systemic) disease in curative intent or palliative appearance.

The limitations of this study are failure to carry out meta-analysis, lack of protocol for a systematic review in order to minimize the potential for bias in the review process, and also the lack of registration in Cochrane Database of Systematic Reviews (CDSR). The lack of a meta-analysis could be explained

by the inability for the formation of relevant comparable groups because of the diversity and heterogeneity of patients with locally advanced colorectal cancer. The lack of protocol and registration in CDSR we explain that this study draws on certain high quality production as Systematic reviews with relevant protocols that although treated the problem heterogeneous and mixed are already listed in the Cochrane Library - CDSR. However, further studies are needed to commit with HRQoL data meta-analysis conducting on the basis of stratified consideration of patients with locally advanced colorectal cancer.

11. Conclusion

This study shows the existing variability and heterogeneity in the available literature concerning the quality of life of patients with locally advanced colorectal cancer. It is necessary specifically directed towards those kind of patients protocol of action to be created; a protocol engaged on customized approach to QUALITY of Life of these patients from the time of the diagnosis throughout the perioperative period and in the immediate postoperative period towards the long-term follow-up.

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