

Research Article

Should we Operate on the Locally Advanced Colorectal Cancer at any Cost but When Should not Give Up Though?

Sokolov M^{1*}, Vasileva M¹, Goranov N¹, Atanasova MP², Vlahova A³ and Todorov G¹

¹Department of Surgery, Medical University of Sofia, Bulgaria

²Department of Anesthesiology and Intensive care, University Hospital Alexandrovska, Sofia

³Department of Pathology, University Hospital Alexandrovska, Sofia

***Corresponding author**

Manol Sokolov, Department of Surgery, University Hospital Alexandrovska, Medical University of Sofia, Georgi Sofiyanski str.1, Sofia 1431, Bulgaria, Tel: + 359 2 9230 540; Email:

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• Locally advanced colorectal cancer; Recurrent colorectal cancer; Combined multivisceral; En-block resection; Multidisciplinary approach in colorectal cancer

Abstract

Introduction: When T4 tumors infiltrated only the intestinal wall, survival and locoregional recurrence rates were similar in the case of T4a, while T4b tumors, with the participation of adjacent structures are associated with increased incidence of recurrence and decreased survival. Locally Advanced Colorectal Cancer (LACRC) may vary from visible intimately adhered to the surrounding tissue, i.e. marginal, "border" resectable tumor to one that directly macroscopic engages adjacent critical structures. The terms "unresectable", "inoperable" and "incurable" cancer / patient are widely used but not clearly defined, item of significant subjectivity. Where is the limit of "resectability" of locally advanced colorectal cancer? This report presents the experience of other foreign authors with their results in the determination of the tumor as resectable or unresectable and our own clinic experience in this area.

Materials and Methods: A retrospective, critical and comparative analysis of patients operated in our clinic with locally advanced primary and recurrent colorectal cancer in period of 10 years with the requirements for individualized "Team" approach of preoperative and intraoperative staging, planning and execution of multivisceral "en-block" resection with typical technical difficulties, complications and results.

Results: From 1105 surgeries on the occasion of colorectal cancer as advanced disease constitute 29.6 percent - 327 patients. 54.5% are localized in different parts of the colon and the others - 45.5% - in the rectum. Age between 61 and 80 years is the most affected. Males are 57.73% and females - 42.27%. There were performed 108 combined multivisceral resections - in 79 primary and 29 recurrent tumors as 17 of them (8 - recurrent tumors) are established pathologically as pR1, i.e. non radical result. 219 cases were assessed intraoperatively as non radical surgery suited and palliative procedures were performed - resections (with or without restoration of the intestinal passage, but in the case of M1), bypass anastomoses or simple interruption of the passage, including cryo-destruction. The overall survival rate is 34 months for pR0-resected and 12 months for pR1-cases (p<0.05).

Discussion: Many of the world's leading surgical centers adopt the tactics of "adequate aggressive behavior" for locally advanced primary and recurrent colorectal cancer. In determining a reasonable balance between aggressive approach and so called meaningless "surgical exorbitance" we strive to adhere to the view that failure to achieve R0-resection planned in such operation, as well as leading worse performance status of the patient or a combination of factors such as advanced age, severe co-morbidities, the presence of complicated forms of colorectal cancer, urgent intervention and data of generalization of the malignant process undermines the implementation of aggressively block removal of the tumor formation. However, adequate pre- and intraoperative assessment and surgical experience should avoid "exaggerated" on intraoperative status of locally advanced tumor and passively determination as "unresectable." It is justified the opinion that the adequate, in particular disease, reasonably aggressive pattern to LACRC securing the most favorable long-term survival prognosis.

INTRODUCTION

As "locally advanced" tumors represent 5-22 % of all colorectal carcinomas. According to the analyzed data in patients with tumor stage IIB, which extend through the intestinal wall and infiltrated the surrounding structures without lymph node metastases (T4 N0 M0) have a worse chance of survival than those with tumors in stage III, which remain within the intestinal wall, but had spread to the lymph nodes (T1- 3 N1- 2). Recent studies confirm that T4 stage is an important independent predictor of disease-free interval and overall survival [1,4,5]. The description of the importance of dissection in lymph nodes in locally advanced colorectal cancer is through related analogue of Total Mesorectal

Excision (TME) in rectal cancer. The lymphnode excision in locally advanced colon cancer being in sufficient volume is called "Complete Mesocolic Excision" (CME). There were not widely discussed the types of locally advanced primary tumors and recurrences with different ways of loco - regional involvement of surrounding structures and organs which make important the describing in detail the operational- tactical and technical aspects of the block R0- resection in primary and recurrent LACRC with type and severity of any complications and treatment outcomes. A priority is the concern on misunderstanding of the importance of an integrated "multi-team" approach in preoperative period as well as the complex implementing of neoadjuvant and adjuvant chemotherapy and radiotherapy.

Locally advanced primary and locally advanced recurrent cancer of the colon and the rectum are surgical challenging due to clinical presumption of tumor involvement of others structures and organs. The estimated need for extensive surgical resection, often with multivisceral en-bloc resection is crucial for preoperative surgical planning. As for the primary and the recurrent tumors, postoperative long-term survival is achievable, but only after complete R0- resection. The role of neoadjuvant and adjuvant therapy continues to be seen in this era of biological chemotherapies as in multimodality treatment provides an opportunity for the technical realization of resection and improve long-term survival.

Definition of locally advanced disease is necessary in order to achieve practical and theoretical clarity regarding not a small percentage of patients with colorectal cancer presented for treatment to the surgeon. Some patients with cancer of the colon or rectum, are represented with a different shape and extent of locally advanced primary or recurrent tumor, but in the stage of non-metastatic disease, which, despite the lack of generalization, it might be resected. Unresectable criteria are variable and not clearly defined. Locally advanced tumor, some authors define as such, visualized by endorectal ultrasound as T3/4 and N1 tumor, or one that is and / or clinically diagnosed with palpable on physical examination tumor mass but without a presence with distant metastases [1,2]. American Joint Committee on Cancer staging schema classify them as T4 lesions [3].

According to another contemporary definition as an advanced tumor (advanced cancer, advanced malignant disease) is considered malignant tumor at initial diagnosis or with clinical demonstration of relapse in stage of local development outside of the organ from which it originates which is limited or not allowed for radical resection or with distant metastasis [4].

In our opinion, proper working definition of locally advanced colorectal cancer is that the final evaluation of the patient from a multidisciplinary team presented by surgeons, pathologists, radiologists and medical oncologists, gastroenterologists and imaging diagnostics is to manage the patient's treatment precisely such that it could not be performed a standard resection - single-organ resection because it is quite likely to remain in the surrounding of the specimen tissues and spaces some of microscopic or macroscopic residual disease detectable due to adhesion or fixation of the tumor to the surrounding structures. Locally advanced lesion may range from visible intimately adhered to the surrounding tissue, i.e., marginal, "border" resectable tumor to one that directly macroscopic engages adjacent critical structures (e.g. main vessels, duodenum, pancreas, pelvic bones, lateral or anterior abdominal wall, the other parts of the colon or small intestine or its mesentery, internal genitalia or organs of the urinary system, nervous plexus, etc.). Literature data indicate that most surrounding structures and organs are affected in primary tumor location in the sigmoid colon and rectum - 66-89 % of cases. Reasons are the high incidence of cancer localization in these areas, the mobility of sigma and transversal colon and close spatial proximity of the structures in the pelvis [5-8].

Definition of locally advanced stage of the disease depends on an assessment of respectability clinically - preoperatively or intraoperatively. In some cases, the "inoperable" tumor, such as

assessed in a clinical examination or radiographic imaging, can subsequently, during intraoperative exploration, be susceptible to radical resection [2].

A more difficult situation arises when the combined resection involves higher risk procedures such as partial duodenectomy and / or duodeno-hemi-pancreatectomy. Koea et al. [9] reported eight cases of T4 tumor formations of the right colon, requiring pancreatic or duodenal resection. They had to perform right colectomy en block with duodenectomy (N = 4) or pancreatoduodenectomy (N = 4) to ensure complete (R0) resection. Reported only two non-serious complications and no deaths. Six patients remain "free" of the disease at an average follow-up of 26 months, and one - a "disease-free" period of 84 months. In another study published by Curley and others [10] 12 patients underwent partial en block duodenectomy (n = 5) or pancreatoduodenectomy (N = 7) for resection of colonic cancer. Eight patients were described as "free" of the disease at an average of 42 months follow-up. Such report Berrospi et al. [11] note "disease free survival" for a period of 10 to 113 months. These ranges provide evidence in support of aggressive behavior in resection of adjacent organs, including the pancreas, for locally advanced colon cancer, provided that it would be able to be performed with an acceptable range of morbidity and mortality. When a surgeon is not willing to take an extended resection is better patient being taken to a center with sufficient experience in multivisceral resections than to be allowed to conduct an incomplete (R1 or R2) resection.

Urgency of the surgery, often caused by complications typical for locally advanced colorectal cancer, has been identified as an independent risk factor for poor outcome in terms of long-term survival [12]. Possibility of conservative management of specific complications when it's real and is not associated with increased risk for the patient would allow conversion of the emergency procedure in elective surgery after assessment by a multidisciplinary team and with favorable conditions for the implementation of Complete Mesocolic Excision (CME) or TME including en block resection as a radical operation.

Primary anastomosis, in the case of tumor obstruction of locally advanced rectal or colon cancer in left-sided location can be performed only when the ileus dilation is in an initial stage, the walls of the proximal bowel part are not overstretched and with lack of any evidence for bacterial translocation and peritonitis, and also the risk profile (age, homeostasis, abnormalities, co-morbidities) is favorable. When there is an obstruction in advanced and a high risk then should be fulfill discontinuous resection - operation by Hartmann. Protective proximal stoma in case of a primary resection and anastomosis does not appear to provide any advantage, according to various authors. Data from the multicenter study Kolon / Rektum-Karzinome (Primärtumor) (primary colorectal carcinoma), published in 2010. by R. Kube, D. Granowski et al. [12] presented an assessment of the status of the surgical treatment of malignant obstruction of locally advanced cancer of the left colon in Germany and compare complications in different operational approaches in the emergency treatment, especially diversionary operations (Hartmann procedure) and primary anastomosis. 15911 of patients with cancer of the left colon reported between 2000. and 2004., a total of 743 patients

underwent emergency surgery for malignant obstruction caused by locally advanced cancer, who have received radical resection. These patients were compared with respect to their risk profile and post-operative results. In 57,9% (N = 430) in a single step is a radical surgery (Group I), 11,7% (N = 87) - with primary resection anastomosis, with outlets protecting stoma (Group II), and 30.4% (N = 226) - diversionary procedure Hartmann (III group). In Group III, most patients were male, overweight, in polymorbid status and more advanced tumors. Hospital morbidity and mortality (overall hospital mortality, 7,7% N = 57) did not differ significantly between the three groups. Preventive placement of temporary protective stoma did not influence the rate of anastomotic insufficiency (Group I, 7%, Group II, 8,0%).

Local recurrence after primary treatment of colorectal cancer, in itself, is also variable concept in respect of their acceptance by surgeons. It would appear as: Local recurrence with the same histological characteristics or negative grading progressed towards low differentiation, the site of anastomosis in previous comprehensive surgery - resection with subsequent reconstructive stage - anastomosis or - Locoregional recurrence - in the surrounding of the primary tumor removed - in incompletely R1 resection or inadequate removal of regional lymph-vessels or lymph-nodes, extensive perineural invasion, which were not covered in the removed specimen, iatrogenic implanted tumor cells in tumor bed (but not only failure to comply with No-Touch Turnbull's rules are responsible for both locoregional recurrence and the generalized organ metastasis through blood and lymph channels, but also implantation of metastasis throughout the operative field and surgical wound) [13].

Approximately 40% of patients with resected colon cancer develop recurrence, and most of them exhibit initially distant spread of the disease. Locoregional recurrence is much less common and accounts for 10% to 20% of recurrent cases. Causes of local recurrence include incomplete resection of transmural or lymphatic spread of the disease, violation of the integrity of the tumor or implantation of tumor cells. Surgery remains the primary treatment method, but it is clear that (R0)-resection can only achieve long-term survival.

MATERIAL AND METHODS

Retrospective analysis of patients with proven colorectal cancer operated at the Clinic of Surgery at the University Hospital "Alexandrovska" for the 10-year period (2002-2012), using documentary evidence from history, operative reports, operational logs and data from the Clinical Center of pathology at the same university hospital where they performed histological examinations, pathologic staging and protocols for specialized oncology hospital committees with final staging of patients and decisions of oncology committee. Statistical data processing was performed with IBM SPSS Software. The total number is 1105 patients, providing representation of the groups and the high reliability of results. Type of study is a retrospective cohort with a degree of evidence 4 of 5-point scale for level of evidence and grade of recommendation, in accordance with EBM - evidence based medicine.

RESULTS

There is an established operational activity in the clinic by

an average of 1100 operations per year, so that for the analyzed 10-year period there is a total of 1105 surgical patients with histologically verified colorectal cancer. Out of them the cases of colorectal cancer as advanced disease constitute 29.6 percent - 327 patients. 54.5% are localized in different parts of the colon and the others - 45.5% - in the rectum. Age between 61 and 80 years is the most affected. Males are 57.73% and females - 42.27%. There were performed 108 combined multivisceral resections - in 79 primary and 29 recurrent tumors as in 17 of them (8 - recurrent tumors) is established pathologically as R1, i.e. nonradical result. 219 cases were assessed intraoperatively as non radical surgery suited caused by pre- and intraoperative discovery of a generalization of the cancer process - bilobar unresectable multiple liver metastases and / or diffuse carcinosis on peritoneum. Different palliative procedures were performed in those cases - resections (with or without restoration of the intestinal passage, but in the case of M1), bypass anastomoses or simple interruption of the passage, including cryo-destruction. 19 patients out of all the group (17.6%) have developed local recurrences in 2-5 years after initial resection for locally advanced tumor. 11 of them undergone "radical" enblock multivisceral resection - 3 established pathologically as pR1, but in 8 patients we achieved pR0-result.

As expected, the morbidity after block resection is larger than that of a standard single-organ resection in terms of complexity of the procedure and excessive blood loss. Values vary according to the source, but Lopez (2001) gives an average aggregate value of approximately 30% [14] while Gannon (2007) notes the total amount of complications by 43% as some of them are serious (fistula enterocutanea, respiratory disorders - pneumonia, urinary insufficiency conduit) [15]. The rate of complications in our survey is 46% and some of the patients have had more than one complication.

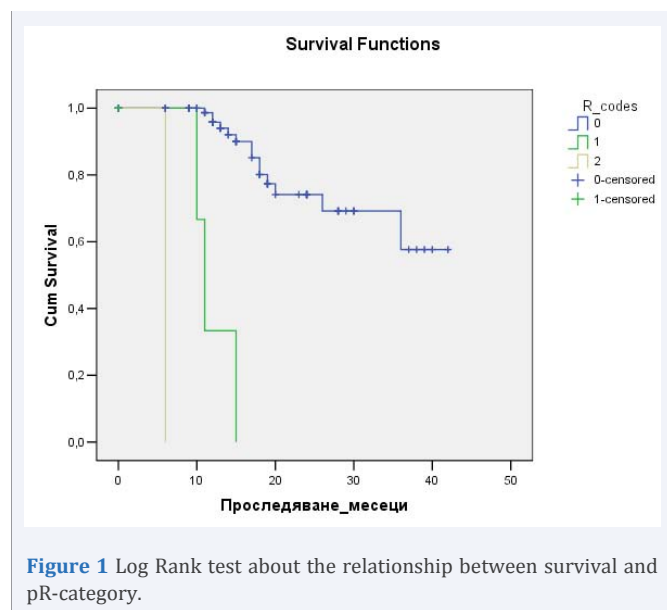
With an exact preoperative planning, precisely executed operation and wide anatomic resection it would be able to achieve curative effect of 5 years survival near 50% [1,16]. The overall survival rate is as follows - in group R0 median survival is 33,858 (30,252 ÷ 37,463); In the R1 group median survival was 12,000 (9,006 ÷ 14,994). Here we can calculate the median - it was 11 months with 95% confidence interval (9,400 ÷ 12,600). Median of 11 means that the half of the people to this month including the deceased are alive and the others are dead - for pR0-resected and pR1-cases $p < 0.05$ (Figure 1).

DISCUSSION

Many global acknowledged surgical centers promote the idea of "adequate aggressive behavior" for locally advanced primary

Table 1: Complications in surgeries of LACRC.

Complications in/after block-resections	Rectal tumor	Colon tumor	Total
Hemorrhage	6	1	5
Lickage	10	4	14
Sepsis	5	2	7
Pneumonia	5	4	9
SSI	12	9	21
Total	38	20	58



and recurrent colorectal carcinomas [17]. But this inevitably requires individualized and comprehensive assessment of each case based on the use of the full resources of diagnostic methods for preoperative staging, as well as a broad discussion of the results by a multidisciplinary team before undertaking the operation. Our vision largely overlaps with the opinion of most of the published authors on the circumstances that determine the decision about the possibility for resectability of locally advanced cancer of the colon or rectum. In our practice, the performance of a combined removal of colon tumor and duodeno-pancreatic resection because of infiltration of sections of the duodenum or the head of the pancreas is relatively reticent about the results of the balance: the benefits of long-term survival and disease-free interval/intra- and postoperative complications. Although the reported results Koea et al., Curley and Berrospi [9-11], the small number of patients operated on and followed not guarantee representativeness of the sample. Along with assessing the status of all vital organs and systems, evidence or lack of generalization of the process, the presence of complicated forms of colorectal cancer and urgent or planned order of operation, macroscopic features of malignancy must be assessed with intraoperative exploration. This is proved decisive for their assessment of resectability, which depends very much on the experience of the operating surgeon responsible for the patient. In 219 of our patients factors such as distant unresectable metastases, the extent of the estimated gross infiltration engagement of critical structures and / or worsening performance-status, because of severe comorbidities are heavy in favor of the decision, that end in itself "aggression" would be unnecessary and even harmful to short-term and long-term prognosis for the patient. Opinion of all authors, including ours, to consolidate the idea that failure to achieve R0-resection undermines the performance of aggressively block removal of tumor formation, while simultaneously removal of synchronous or metachronous oligometastases in the liver remains controversial. In 17 of locally advanced (8 of them - recurrent) tumors was performed a block-resection with intraoperative macroscopic presumption of radical surgery, but the final histological results showed microscopic infiltration in

some areas of the excision of infiltration. Since it was a massive infiltration made the "edge" of technical ability and poor general condition of patients, some of them elderly, has not reached the re-Redo surgery to attempt to achieve histological, i.e. real radicality. All authors emphasize the adequate consensus, called "team"-preoperative approach. In our practice, unfortunately, is not perceived patients to be presented and reported to Cancer Committee in the phase before any operation. Especially in recent years, a limitation and complex use of the full range of highly specialized and high-tech diagnostic imaging methods (such reasons from subjective and objective nature) by economic reasons are leading. Most authors have adopted the view to hold, in indications, of combined preoperative chemoradiotherapy in order to increase the possibility of planning the operation as "potentially curative."

It is imperative to validate a standardized strategy for management of patients with advanced (locally or generalized) colorectal cancer, delineating and clearer criteria for resectability and, respectively, unresectability of the primary or recurrent tumor, and the prospects of neoadjuvant therapy.

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