

# MULTIVISCERAL RESECTIONS AS A TREATMENT OPTION FOR LOCALLY ADVANCED COLON CANCER WITH HEPATOPANCREATOBILIARY INVOLVEMENT

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**Background.** According to the data of National cancer registry colorectal cancer in 2012 obtains 1<sup>st</sup> place in morbidity and 3<sup>rd</sup> place in mortality among all adults malignancies. [1,2]. Each year there are 940 000 new cases and about 500 000 deaths, caused by this pathology. In 31 – 34% of cases primary diagnosed colon cancer appears to be locally advanced [3,4,5,6], and in 10-14% in unresectable, requiring only palliative or symptomatic care [5,6]. Intraoperative findings of tumor invasion into adjacent structures is not a quite rare entity, but it may crucially change a whole treatment strategy. Despite the advances in radiation diagnostic, preoperative detection of tumor adherence to adjacent structures is possible in only 11 – 28% of cases [17]. Locally advanced colonic cancer (LACC) as an intraoperative finding is not rare of a kind, however it may crucially determine the surgical tactic – either en-bloc multivisceral resection (MVR) or a symptomatic procedure. Tumor invasion in hepatopancreatobiliary zone (HPBZ) structures (liver, gallbladder, bile ducts, pancreas or duodenum) carries major confusion in choosing the strategy of surgical treatment [17]. This confusion is caused by a fact, that MVR performed in cases of HPBZ invasion are used to be accompanied by an increased rates of postoperative mortality, morbidity and a high rate of R<sub>1</sub> and R<sub>2</sub> – resections as well (11-13%) [10,11]. In these cases making a decision either to go for a MVR or to confine the operation to a symptomatic procedure as never lies on the surgeon's conscience and depends on his ability and skills. Despite the variety of publications, dedicated to surgical treatment of LACC, the information considering this type of pathology remains poor, hence, the patients cohorts described are quite small in number [14,15]. Now there is no common point of view in choosing the extent of surgery in cases of HPBZ tumor involvement. Atypical resection of pancreas or duodenum under the circumstances of colonic cancer invasion appears to be doubtful. Long-term outcomes of surgical treatment in a group of patients, who underwent R<sub>1-2</sub> resections are not evaluated as well.

**Aim of study.** To evaluate short and long-term outcomes of surgical treatment in a group of patients having LACC with HPBZ invasion.

**Patients and methods.** A retrospective analysis was performed in a group of 695 patients, who underwent surgical treatment of LACC (T<sub>4</sub>N<sub>0-2</sub>M<sub>0</sub>) in a period since 1982 and 2012 years. MVR took place in 237 cases (34%). Tumor staging had been processed according to AJCC TNM 7th ed., 2009. Inclusion criteria were histologically confirmed colonic adenocarcinoma, absence of distant metastases and peritoneal dissemination preoperatively and no data for unresectability. Study population consisted of patients having LACC with HPBZ invasion, who underwent R<sub>0</sub>, R<sub>1</sub> or R<sub>2</sub> resections of the colon. Short- and long-term treatment results were assessed. Only class III-V Clavien – Dindo complications were evaluated.

**Results.** An analyse of 276 patients, who underwent MVR for LACC was done. Among them tumor invasion into HPBZ organs was detected in 39 cases (16,5%). Additionally a subgroup of 32 patients, who received palliative surgery (R<sub>1-2</sub>) in cases of LACC with HPBZ involvement was analyzed. Cross-chart characteristics of subgroups are presented in table 1.

Study parameters	Multivisceral resections (N = 237)	Multivisceral (R0) resections in cases of HPBZ involvement (N = 39)	Palliative colon resections in cases of HPBZ involvement (N = 32)
<b>Age and gender structure</b>			
Males	112 (45%)	12 (29%)	15 (47%)
Females	125 (55%)	27 (71%)	17 (53%)
Middle age	43 (24-63)	43 (24 – 63)	56 (26 - 82)
<b>Tumor localization</b>			
Caecum	57 (21%)	17 (44%)	4 (12,5%)
Ascending colon	24 (10,6%)		
Right colonic flexure	14 (7,6%)		
Transverse colon	16 (7,6%)	22 (56%)	8 (25%)
Left colonic flexure	10 (8%)		7 (22%)
Descending colon	7 (6,2%)	-	6 (18,5%)
Sigmoid colon	109 (39%)	-	-
<b>Tumor differentiation</b>			
G <sub>1</sub>	74 (27%)	10 (26%)	4 (12,5%)

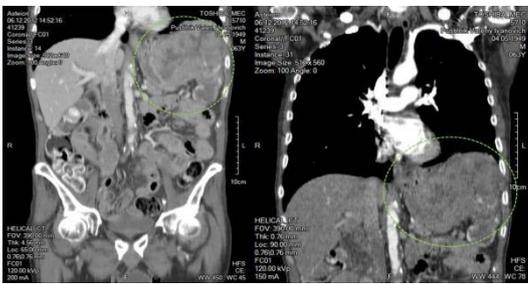
G <sub>2</sub>		154 (56%)	16 (55%)	19 (59%)
G <sub>3</sub>		47 (17%)	7 (24%)	9 (28,5%)
G <sub>4</sub>		2 (0,7%)	6 (21%)	-
Disease stage				
Stage I	T <sub>1-2</sub> N <sub>0</sub> M <sub>0</sub>	-	-	-
Stage IIА	T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>	-	-	-
Stage IIВ	T <sub>4a</sub> N <sub>0</sub> M <sub>0</sub>	111 (40%)	-	6 (19%)
Stage IIС	T <sub>4b</sub> N <sub>0</sub> M <sub>0</sub>	74 (36%)	26 (64%)	15 (46%)
Stage IIIА	T <sub>1-2</sub> N <sub>1</sub> M <sub>0</sub>	-	-	-
Stage IIIВ	T <sub>3-4a</sub> N <sub>1</sub> M <sub>0</sub> или T <sub>1-2</sub> N <sub>2</sub> M <sub>0</sub>	25 (14%)	-	5 (16%)
Stage IIIС	T <sub>4b</sub> N <sub>1-2</sub> M <sub>0</sub>	27 (10%)	13 (36%)	6 (19%)

Predominant symptoms, occurring in patients, were dyspepsia and anemia-related symptoms. Signs of tumor invasion in HPBZ were diagnosed preoperatively in 70.4% of cases.

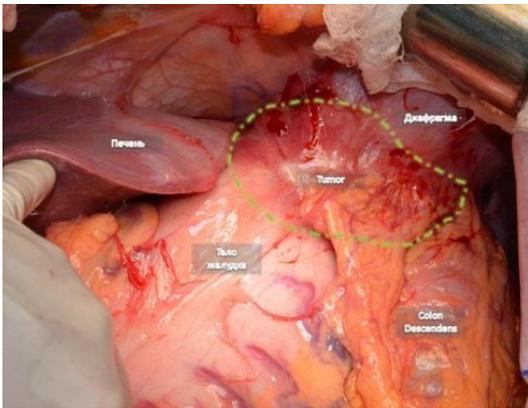
Among those patients, who underwent radical MVR for LACC with HPBZ organs invasion, left-side colonic tumors were prevalent (56%). Lymph node lesion was detected in 13 patients (36%).

Radical MVR included left upper abdominal exenteration procedure (left colectomy with splenectomy, gastric and pancreatic resection) in 17 cases (43%). Resection of pancreatic tail took place in 12 cases (31%), distal pancreatectomy – in 5 (13%). MVRs with diaphragm resection were in 5 cases (13%). Right hemicolectomy with partial hepatic resection and cholecystectomy was performed in 12 cases (31%). In one patient (3%) right hemicolectomy with gastropancreatoduodenectomy was performed due to ascending colon invasion into pancreatic head and a descending part of the duodenum. Right hemicolectomy with resection of the duodenum was done in 9 cases (23%). As a clinical example a set of photos illustrating a left colectomy with total gastrectomy, resection of pancreatic tail and diaphragm in a patient with locally advanced left colonic flexure cancer are represented (see pictures 1-5).

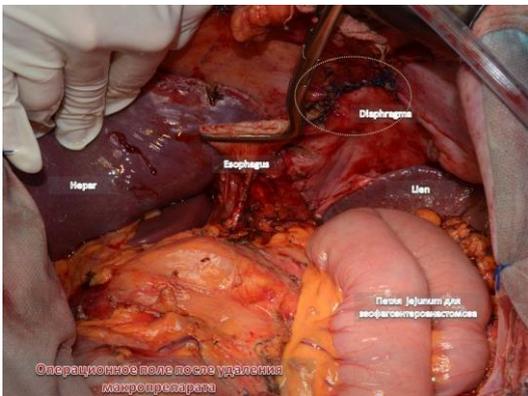
After pathohistological assessment tumor invasion was confirmed in all patients. Microscopic signs of residual tumor (R<sub>1</sub>) were detected in 3 cases (8%) – all of them after right colectomy with duodenal resection.



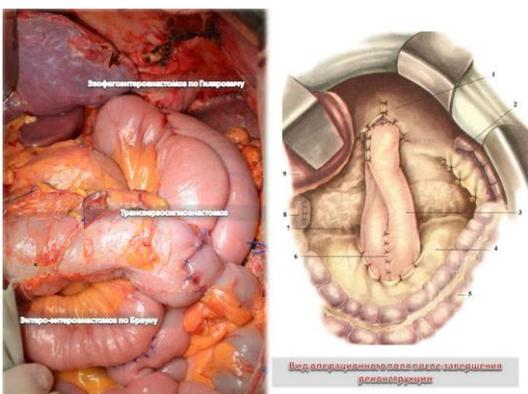
Picture 1. Computer tomography, frontal plane. Tumor is marked green.



Picture 2. Primary view of the operating field.



Picture 3. Operating field after gross specimen removal.



Picture 4. Reconstruction completed.



Microspecimen. Invasion of colonic adenocarcinoma into gastric submucosa. Hematoxylin-eosin staining X100.

In a group of radical MVR in cases of HPBZ organs invasion class III-IV Clavien-Dindo complications in a 30-days post-surgery term occurred in 39% of cases. Colonic anastomosis leakage was detected in 4 cases (9%), duodenal sutures leakage – in 1 (3%), external pancreatic fistula – in 6 (13%), gastrointestinal haemorrhage – in 1 (3%), reactive pleuritis – in 2 (6%) and left-side pneumothorax after resection of the diaphragm – in 1 (3%). No cases of postoperative mortality were observed.

In a group of patients, who underwent MVR due to invasion into other structures and organs (237 patients) class III-IV Clavien-Dindo complications in a 30-days post-surgery term occurred in 19%. Postoperative mortality rate was 3.3%.

During the first year after surgery disease progression in a group of patients who underwent radical MVR due to HPBZ organs involvement was diagnosed in 5 patients (13%): liver metastases - 3 (8%), peritoneal carcinomatosis – 1 (3%), lung metastases – 1 (3%). Local recurrences were not observed. All of 3 patients, who appeared to have R<sub>1</sub> resection developed local recurrence, causing their death in 3, 7 and 8 months after surgery.

In a subgroup of patients with LACC and HPBZ organs invasion who received palliative R<sub>1-2</sub> colonic resections the extent of surgery was distributed as follows: right hemicolectomy - 13 (41%), transverse colon resection - 5 (16%), left hemicolectomy – 14 (43%). Tumor invasion was histologically confirmed in

22 cases (69%), in other cases – inflammatory infiltration. Lymph node involvement was observed in 11 atients (34%). Postoperative class III-IV Clavien-Dindo complications were observed in 2 cases (6,25%) and were represented with postoperative peritonitis due to colonic anastomosis leakage after left hemicolectomy. Postoperative mortality was 3% (one patient died due to pulmonary artery embolysm).

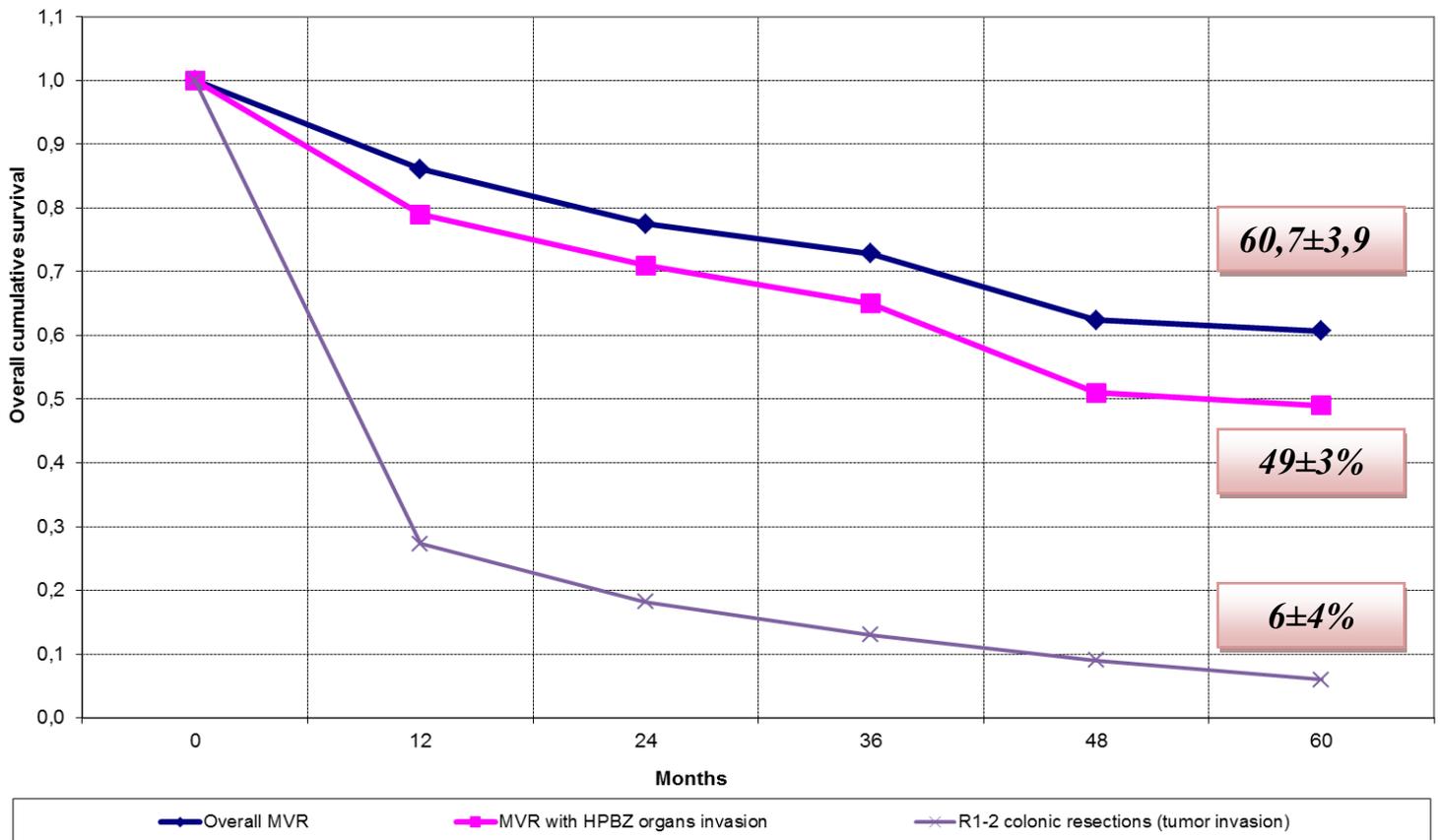
Overall 5-year survival rate was evaluated for patients, who received radical MVR due to HPBZ organs involvement (39), other organs and structures involvement (237) and also for those, who underwent palliative R<sub>1-2</sub> colonic resections (32). Overall 5-year survival was 49±3%, 60,7±3,9% and 6±4% respectively (see table 2, picture 6). For both MVR-groups statistical difference was insignificant (p=0,067). Overall survival rates for patients, who received palliative resections of the colon was significantly lower comparing to both MVR groups (p<0,05).

*Table 2. Overall 5-year survival and median survival in patients groups*

<b>Patient group</b>	<b>Overall 5-year survival, %</b>	<b>Median survival, months</b>
Overall MVR (N=237)	60,7±3,9	23
MVR due to HPBZ organs invasion (N=39)	49±3	19,6
Palliative R <sub>1-2</sub> colonic resections (N=32)		
- inflammatory infiltration (N=10)	32±6	22,7
- tumor invasion (N=22)	6±4	7,6

In a subgroup of patients, who received palliative R<sub>1-2</sub> colonic resections in cases of HPBZ organs invasion (32) residual tumor elements were observed in the duodenum (20 cases – 62,5%), in the pancreas (9 – 28%) and in both pancreas and stomach (3 cases – 9,5%). Disease progression was observed in 22 patients (68%): local recurrence – 11 (34%), distant metastases – 11 (34%). Median time to progression was 4,2 months. In 10 patients (32%) during 2 years after surgery no signs of disease progression were observed.

**Picture 6. Overall 5-year survival of patients, who underwent overall MVR, MVR for LACC with HPBZ organs invasion and palliative surgery**



This condition regards to the presence of inflammatory infiltration, but no tumor invasion because of a wrong intraoperative assessment of tumor spreading.

After comparing long-term results in patients, who underwent palliative surgery and had either tumor invasion or inflammatory infiltration, overall 5-year survival rates differed quite significantly -  $6\pm 4\%$  and  $32\pm 6\%$  respectively (see table 2). Median survival turned out to be 7,6 and 22,7 month respectively.

**Discussion.** Local tumor spread on adjacent structures is not a rare entity for colorectal cancer. It is quite difficult to identify a tumor invasion into HPBZ organs preoperatively using radiologic methods due to its low sensibility [8]. However, in our study tumor invasion into adjacent HPBZ organs was defined with computer tomography preoperatively in 70.4% of cases.

Defining tumor invasion and inflammatory infiltration is a complicated procedure. According to data, elucidated in the majority of studies, the rate of tumor invasion in LACC hesitates from 50 to 75% [9-11], causing plenty of doubt in performing such an extensive surgical procedures, especially when dealing with HPBZ organs invasion.

It is well known, that MVR are always accompanied by increases in postoperative morbidity and mortality, comparing to standard colorectal cancer surgery procedures (20-40%) [10,11]. In cases of HPBZ organs invasion the number of postoperative adverse events arises tremendously comparing to standard operations and to overall MVR as well. For example, in a study of Won-Suk et al., postoperative morbidity rate was 22% with no cases of postoperative mortality [14]. In our study postoperative complications took place in 39% of cases. For comparing, after standard surgery for colonic cancer in our institution we observed postoperative complications in 8% with mortality less than in 1%.

It is well-known, that with patients, presented with LACC, an en-bloc R<sub>0</sub> – MVR is a “golden standard” of treatment, because only this treatment option is capable to gain the best long-term outcomes. This argument is totally supported by our institution, remaining to be a point of view of the most prominent authors, studying this pathology, and is confirmed by the obtained results of the present study. An overall 5-year survival rate in a group of patients, who underwent curative R<sub>0</sub> MVR for LACC with HPBZ organs invasion turned up to be 49%, what’s in a couple of times greater comparing to those, who underwent palliative surgery – median survival in this subgroup was only 7,6 months.

According to data, presented by Eldar S. et al., the level of local recurrences after palliative surgery for LACC with pancreatic head or duodenal invasion was 75 – 100% [12]. In our series all patients, who underwent R<sub>1-2</sub> procedures developed local recurrences.

By our results, in the predominant number of cases (62,5%) the reason to decline a curative MVR was tumor invasion into the duodenal wall and a necessity to perform pancreatoduodenectomy. The leading points that influence the decision to perform such an extended surgical procedure are the absence of clear information considering tumor invasion or inflammatory infiltration and the level of surgeon’s personal experience. In this aspect the question of atypical duodenal resection possibility demonstrates interest. Right hemicolectomy with atypical duodenal resection in our series was performed in 9 cases (23%). Among them anastomotic leakage was observed in 1 case (conservative treatment successful). No signs of local recurrence in these patients were observed in terms of 12 months post surgery.

As mentioned above, because of small patients cohorts in most studies, the evaluation of long-term results of such patients category is quite complicated. According to the data of Won-Suk et al., who evaluated long-term outcomes of 9 patients, who underwent right hemicolectomy with pancreatoduodenectomy, median overall survival was 23,5 months [14]. According to other author's data, median overall survival after similar operations represents from 22 to 68,4 months [13, 15, 17]. These results are mostly explained by low frequency of lymph nodes involvement. In studies of Saiura et al., and Fielding et al., metastatic lesion of regional lymph nodes was detected in 20 – 30% of cases [15-16]. In our study lymph node involvement took place in 36%. In th study of Won-Suk et al., this level was 33%. Under these circumstances we suppose that local spread is a specific quality of these tumors, unlike tumors with more active lymphatic and hematogenous spreading, what creates more profitable oncological background for developing exactly surgical treatment methods.

**Conclusion.** In all cases of LACC with adjacent organs invasion performing an MVR should be considered as justified and acceptable option, because despite the increased level of postoperative adverse events long-term treatment results significantly benefit. Decision concerning the extent of surgery in every patient should be taken individually. Multivisceral resections for LACC with HPBZ organs involvement is strongly associated with increased rate of postoperative adverse events, the most frequent of which are external pancreatic fistulas. These circumstances should be kept in mind while planning the optimal surgical treatment, adequate postoperative care and recovery.

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## *SUMMARY*

En-bloc multivisceral resection (MVR) is a commonly considered “golden standard” treatment option for locally advanced colonic cancer. Invasion into hepatopancreatobiliary zone (HPBZ) organs remains to be an underevaluated form of this morbidity, leaving plenty of surgical strategy questions unsolved. The aim of this study was to assess short- and long-term outcomes of locally advanced colonic cancer with HPBZ structures involvement treatment. A total of 625 patients were studied. Among them MVR were performed in 237 cases (34%), 39 (16,5%) – because of HPBZ structures involvement. Additionally an analyze of 32 locally advanced colonic cancer with HPBZ structures invasion patients, who underwent standard palliative (R<sub>1</sub> or R<sub>2</sub>) colonic resections. Class III – IV Clavien-Dindo complications and postoperative mortality in groups of all MVR, MVR with HPBZ structures invasion and in a group of patients with palliative resections appeared to be 19% and 3,3%, 39% and 0%, 6,25% and 3% respectively. The main types of complications were septic and purulent ones, among patients after MVR with HPBZ structures invasion – external pancreatic fistula. Overall 5-year survival in a group of all MVR patients was 60,7±3,9%, median survival – 23 months, in a group of MVR with HPBZ structures invasion - 49±3%, median survival – 19,6 months. In a subgroup of patients, who underwent palliative colonic resections with cases of inflammatory infiltration overall 5-year survival rate was 32±6%, median survival – 22,7 months, but in cases of tumor invasion - 6±4% with median survival 4,2 months. Performing of MVR in patients with locally advanced colonic cancer with HPBZ structures invasion should be considered as justified and favorable treatment options. However, the rate of overall surgical complications appears to be significantly higher, this treatment option has the capability to strongly improve long-term treatment outcomes.

Key words: locally advanced colonic cancer, hepatopancreatobiliary zone invasion, multivisceral resections.