Short-term outcome and survival after multiorgan resection for locally advanced colo-rectal cancer. Identification of risk factors

Ann. Ital. Chir., 2018 89, 3: 229-236
pii: S0003469X18027902

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INTRODUCTION: *Although multi-organ resections (MOR) are recommended by international guidelines for advanced colo-rectal cancer, the literature shows that the morbidity and mortality that accompanies these complex interventions limits the number of patients receiving this treatment.*
The purpose of our study was to analyse the immediate and remote results obtained after MOR and to identify potential factors that might influence the outcome.
MATERIAL AND METHOD: *Our study is a retrospective cohort which included patients surgically treated in our service for locally advanced colorectal cancer. We excluded patients with hepatic metastatic tumors and those who needed pelvic exenteration. Between 2006 and 2010, in our service, have been treated with MOR 146 patients, 107 being included in our study. We analysed morbidity, mortality and survival after MOR and the factors that could have influenced the postoperative course.*
RESULTS: *Identified risk factors that negatively influenced the postoperative outcome were: diabetes, personal neoplastic pathologies, associated cardiovascular disease, history of major surgeries, intraoperative blood loss, number of resected organs. Survival was negatively influenced by positive resection margins, the presence of lymph node metastases and the presence of complications in the postoperative period.*
CONCLUSIONS: *The data of this study support the indication for routine MOR for patients diagnosed with locally advanced colorectal cancer with the condition that R0 resection margins are achieved.*
All mentioned above underline the importance of the experience that the surgical team has in this type of surgeries, in order to achieve optimum results. This experience must concern the preoperative management, surgical technique and postoperative care.

KEY WORDS: Colo-rectal cancer, Multi-organ resections, Risk factors

Introduction. Background

Colorectal cancer (CRC) is a real public health problem, with an incidence of about 30 cases per 100,000 inhabitants and a mortality rate of 8.8, with which it classi-

Pervenuto in Redazione Ottobre 2017. Accettato per la pubblicazione Gennaio 2018
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fies itself as the second-largest cause of death by cancer, after broncho-pulmonary cancer [1].
The 5-year survival of CRC patients is variable, ranging from 8% to 93%, depending on the stage, co-morbidity and the followed treatment [2-4].
Local advanced CRC (LACRC) is characterized by the presence of T3-T4 tumors (after TNM staging), neoplasms that spread beyond the walls of the digestive tract (T4a), with the possibility of adherence, invasion or even penetration of the adjacent structures (T4b) [5-7]. In these situations, intraoperative differentiation between inflammatory adhesions or real neoplastic invasion is impossible to achieve, which is why surgical resection of the tumor "in block" with the affected organs is routinely indicated (multi-organ resections, MOR) [8-10].
MOR have been reported in literature since 1946 [11] and it was shown that even if the tumors are locally advanced, only 66.7% of them have been associated with lymph node metastases [12]. Moreover, the malignant nature of the adhesions between the colorectal tumor and adjacent structures was demonstrated in 60% of the diagnosed cases of locally advanced tumors [10,13]; in these cases, only the radical resection of neoplasia was associated with acceptable survival rate in between 36%- 46% [13-15]. All these highlights the feasibility and surgical indication of MOR for the treatment of LACRC. However, in clinical practice, only a few patients benefit from this curative treatment [16], most probably due to the technical complexity of these radical resections and the increased risk of complications and postoperative deaths [10,13,17].
This being said, literature states that MOR is performed in about 10% of the patients diagnosed with CRC, the most frequently resected organs being: bladder, internal genitalia, abdominal wall, small intestine and diaphragm [18-21]. Metastatic disease represents a contraindication for MOR, exception of the rule being represented by the carefully selected cases where serial multivisceral resections with radical intention are feasible in the context of a multidisciplinary approach. Also, in selected cases with peritoneal carcinomatosis, MOR associated with extensive peritonectomies and hyperthermic intraperitoneal chemotherapy (HIPEC) may bring an additional chance of survival for patients in such advanced stage of disease [22-24].
Due to the discrepancies between the clear indications for MOR and the relatively small number of patients who could benefit from them[16], we considered it appropriate to analyze the activity of our institution, a tertiary center in digestive surgery, with the purpose of identifying the risk factors that can influence the short and long outcome of these patients.

Material and Method

We conducted a retrospective cohort type study in which we targeted patients diagnosed with LACRC who had MOR at the Regional Institute of Gastroenterology and Hepatology Cluj-Napoca, Romania, between 2006-2010. We considered LACRC, tumors with tight adherence or invasion of at least one adjacent organ, without presence of metastases. MOR was defined as a surgery involving resection of at least one organ beside the one primarily affected by neoplasia. We excluded from our analysis patients with secondary liver metastasis, even if the MOR performed had a radical visa, considering that these patients had a systemic neoplastic disease at the time of surgery. Also, we did not include patients with advanced rectal tumors, for which, due to the significant local extension pelvic exenterations were performed, these ones considered to be palliative [25].
Thus, in our institution, during the above-mentioned period, from 1860 patients diagnosed with CRC, only 146 benefited from MOR. 39 patients were excluded from the study due to the presence of synchronous hepatic metastases, for which liver resections were performed on the same surgery with the colonic resection.
In the first phase of the study, on the remaining 107 patients, we analyzed the morbidity and mortality rates, as well as the factors that could have influence the results. Clavien-Dindo classification was used to stratify the postoperative complications [26]. The potential risk factors analyzed were those related to the patient: age, body mass index, comorbidity, serum hemoglobin (Hb) and total serum proteins (TP), whose values were preoperatively recorded. The associated pathologies taken in account were: diabetes, cardiovascular disease, other digestive and chronic renal diseases. We also analyzed the influence that personal cancer history or history of major abdominal surgeries have had on postoperatory outcome. The following possible risk factors related to the surgical procedure were taken in account: type of hospitalization (emergency or programed), tumor size (>5 cm), number of resected organs (2 organs versus >2 organs), the length of surgery (over 180 minutes) and intraoperative blood loss (over 180 ml). These values, used as a reference, were taken from the literature, from similar studies, which aimed to analyze individually, the impact of these factors on postoperative outcome [27-29].
In the second phase of the study, we analyzed the survival of patients who benefit from MOR and whether this was influenced by N stage (invasion of lymph nodes), degree of tumor differentiation (G), surgical resection margins (R), number of organs resected or the presence of postoperative complications. The staging in the N, G and R groups was done according to the 7th edition of UICC/AJCC [7,30] and was based on the surgical protocol and the anatomopathological result of the surgical resection piece. Some of the patients enrolled in the study were lost because of their lack of compliance with the follow-up visits, and therefore the recurrence status could not be determined. Mortality data was collected from the Population Evidence Register. The cause of death was unknown, and there for, the specific survival could not be calculated.

Statistical analysis was done to calculate the percentages and significance of certain values. In the study of possible associations between two nominal variables, contingency tables were used with: percentage frequency and frequencies correspond to absolute numbers, values arranged per line. The statistical significance of the association was tested using the Chi Square (Hi-square) test or Fisher's exact test if at least 20% of the theoretical frequencies were less than or equal to 5. In the case of a significant test, a quantification of the association effect was done by calculating OR (odd ratio, probability) and the associated 95% confidence interval.
The study of the differences related to the values of a quantitative variable on two independent groups was done by the Student (t test) with equal variants, given that the distribution of the variable considered in the two groups was a Gaussian distribution.
Alpha 0.05 was used as statistically significant for all the tests; the bilateral p value was taken in account in the tests that were providing it.
For statistical processing, the R version 2.15.0 for statistic calculations and graphics was used, with the Rcmdr version 1.8-3 graphical interface.
To compare the distribution of survival data between groups, the Kaplan Meier curves and the Log-rank test were used. The Cox regression was used to assess the existence and importance of the relationship between each predicted prognostic factor and survival. The statistical calculation software provided by StarSoft Inc., Tulsa, USA, version 7.0 was used.

Results

On the analyzed group, the incidence of MOR was 7.84%.
The average age was 64 years. By dividing patients into 2 groups: under 70 and over 70, we did not find significant differences between the rates of complications and postoperative deaths. Statistical calculations have shown that patients with at least one associated pathology are significantly older than those without comorbidities (median = 65.32±10.01 vs 58.10±10.15, p= 0.005, t-test). Also, the patients who died in the postoperative period were significantly older (median = 71.25±8.77 vs. 63.05±10.24, p= 0.009, T-test).
22 patients had a body mass index (BMI) greater than 30. These patients were more susceptible to develop postoperative complications (OR=1.32).
The most frequent localization of the tumors was in the sigmoid colon (40 cases), followed by the rectum (n= 21) and the descending colon with 16 cases. In 5 cases, synchronous tumors were present. In terms of additional resected organs, the small intestine was mostly resected (n= 30), followed by uterus and appendix, other colorectal segments and spleen.
Overall morbidity after MOR was 26%. The most common complications were anastomotic fistula and wound infection (Table I). The rate of postoperative deaths was 11.11%.
From the 28 patients who developed postoperative complications, 25 (89%) had comorbidities (Table II). Patients with a personal history of neoplastic disease had a higher probability of developing anastomotic fistula (OR= 14,250) and pulmonary complications (OR= 9,600). Also, these patients had a greater probability for association of septic complications (OR= 5.380) and postoperative deaths (OR= 1.340). Clearly, the presence of cardiovascular pathology was associated with an increased rate of postoperative cardiac complications (p= 0.048; Fisher's Exact Test). Overall, the association of cardiac pathology did not influence the rate of complications. Patients with diabetes had a higher risk of wound infections (p=0.035; Fisher's Exact Test) and a greater probability of developing pulmonary complications (OR=6.769). Personal history of major surgeries has increased the probability of septic postoperative complications (OR=12,450). We have not found a link between personal history of digestive or renal disease and the incidence of postoperative complications.
The results of our study do not show a clear influence that Hb and TP might have on the rate of occurrence of anastomotic fistula (p = 0.258 and p = 0.054; Fisher's Exact Test). In this idea, from the group of patients with Hb<10 mg/dl (n=42), only 12% developed anastomotic fistula. This complication occurred in 5% of the patients with Hb>10 mg/dl (n=65).
22 patients had low TP values (<6 g). Of these, 18% developed anastomotic fistula. In contrast, only 5% of patients with normal serum protein levels developed this complication.
With respect to postoperative deaths (n=12), 11 had cardiac pathologies associated when admitted in the hospital. However, the association was not validated by the statistical analysis (p=0.271; Fisher's Exact Test), probably due to the reduced number of patients and the inclusion of all cardiovascular diseases, some with low mortality (e.g. essential arterial hypertension).
16 patients were admitted for acute symptoms and required emergency procedures; from these, 4 died in the postoperative period. Due to the low number of

TABLE I - *Postoperative complications after MOR (after Bartos A et al [21])*

Complications	**N (%)**
Anastomotic fistula	11 (10.18%)
Wound infection	16 (14.81%)
Postoperative hernia/ Evisceration	3 (2.77%)
Postoperative complications	8 (7.40%)
Intraabdominal hemorrhage	2 (1.85%)
Intraabdominal abscesses	2 (1.85%)
Cardiac complications	7 (6.48%)
Sepsis	4 (3.70 %)

TABLE II - *The influence of personal history over postoperative morbidity and mortality (after Bartos A et al [21])*

Pathological history	Postoperative complications	p*	OR**
Diabetes mellitus	Wound infection	0.035	-
	Pulmonary complications	-	6.769
Personal cancer history	Anastomotic fistula	-	14.250
	Pulmonary complications	-	9.600
	Sepsis	-	5.380
	Postoperative deaths	-	1.340
History of cardiovascular disease	Cardiac complications	0.048	-
History of major abdominal surgeries	Sepsis	-	12.450

* Fisher's Exact Test
** OR=odds ratio (chance), calculated for contingency tables with cells that contain values < 5

TABLE III - *The influence of intraoperative factors over postoperative morbidity and mortality (after Bartos A et al [21])*

Intraoperative factors	Postoperative complications	p	OR***
Number of resected organs (more than 2)	Complications(at least 1)	0.032*	-
	Deaths	0.288*	-
Length of surgery (over 180 minutes)	Complications(at least 1)	0.586*	-
	Deaths	-	1.529
Intraoperative blood loss (over 500 ml)	Complications(at least 1)	0.007**	-
	Deaths	0.009**	-
Tumor size (> 5cm)	Complications(at least 1)	0.785*	-
	Deaths	0.922*	-

*The Pearson Chi-Square
** Fisher's Exact Test
*** OR=odds ratio, calculated for contingency table with cell frequency less than 5

patients, we cannot determine whether postoperative mortality was or not influenced by this parameter.
The average size of the tumors was 7.91±5.52 cm, with minimum and maximum sizes ranging from 3 to 25 cm. By dividing the patients into two subgroups (tumors smaller than 5 cm and tumors larger than 5 cm), we found no statistical significance between rates of postoperative complications and deaths among these patients (p=0.785 and p=0.922; The Pearson Chi-Square) (Table III).
25% of the patients had surgeries in which more than 2 organs were resected. By dividing the patients into two subgroups (2 resected organs and more than 2 resected organs), we found an increased risk of at least one more complication in patients with more than 2 resected organs (p=0.032; The Pearson Chi-Square) (Table III).
The average length of surgery for patients receiving MOR was of 161 minutes (ranging between 60 to 330 minutes). We divided the group into patients whose surgery lasted less than 180 minutes and in patients whose surgery exceeded 180 minutes. Postoperative complications occurred in 30% (n=6) of the patients with surgery length more than 180 minutes and 24% (n=21) of the patients with less than 180 minutes surgery. The statistical analysis indicated the presence of a higher risk of death in patients with longer surgical time (OR=1.529) (Table III).
Average blood loss was 346 ml, with a maximum of 1200 ml. Taking the 500 ml blood loos as the reference value we divided the group into patients with less than 500 ml intraoperative blood loss and in patients with more than 500 ml loss. Postoperative complications occurred in 8 patients (57%) with blood loss of at least 500 ml per surgery and in 20% (n = 19) of patients with minimal blood loss. Statistical analysis indicated that blood losses greater than 500 ml could be considered as a risk factor for complications and postoperative deaths (p=0.007 and p=0.009; Fisher's Exact Test) (Table III).
From the anatomopathological point of view, most tumors were intestinal adenocarcinomas (79.2%), followed by mucinous carcinomas (17.82%) and signet ring-cell carcinomas (2.97%). Regarding the degree of tumor cell differentiation, 16.8% of patients had well differentiated tumors and 32.7% moderately differentiated. 18 patients had poorly differentiated tumors (16.8%). The rest of the patients (n=36) were staged as Gx (the degree of differentiation could not be specified).

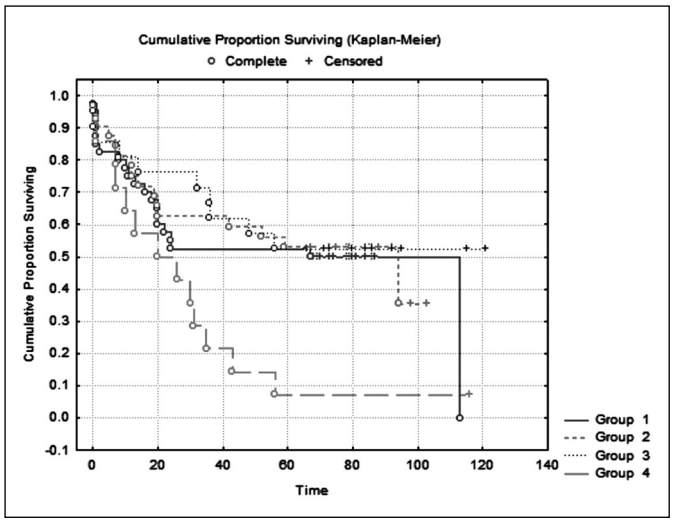

Fig. 2: 5-years survival rates depending of the presence of postoperative complications. (Group 1=without complications; Group 2=with complications).

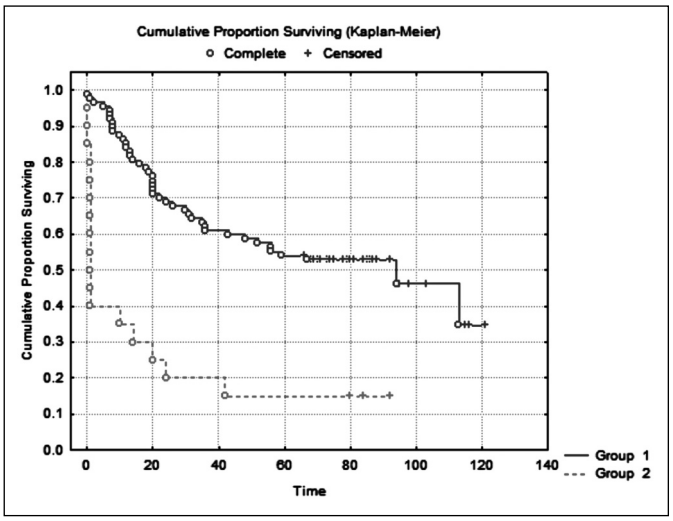

Fig. 1: 5-years survival depending on the N stage of disease. (Group 1= Nx; Group 2 = N0; Group 3 = N1; Group 4 = N2)

The radical-resection rate was achieved in 94.4% of the cases. The resection margins were without microscopic tumor invasion (R0) in 101 cases of MOR. In 2 cases, the resection edges had microscopic invasion (R1) and in 4 cases the tumor infiltration was visible macroscopically (R2).

The 5-year survival rate of patients in group A was 43.9%, with an estimated median survival of 52 months (95% confidence interval for the median; 14.95-89.05). Statistical analysis indicated that differences in survival time in patients with R1/R2 margins tend to have statistical significance (Log Rank (Mantel-Cox), 2 (1)=2.57, p=0.109).

Depending on the N stage of disease, there were significant statistical differences in survival time (Log Rank (Mantel-Cox), 2(3)=8.52, p=0.036), meaning that there are differences between at least 2 groups of patients; for their identification, we performed a post-test analysis (Bonferroni correction). From the post-test analysis, we discovered that there are significant statistical differences in survival time in N0 versus N2 patients (Log Rank (Mantel-Cox), 2=7.16, p=0.007 <0.008) and in N1 versus N2 ((Log Rank (Mantel Cox), 2=7.16, p= 0.003<0.008 (Fig. 1).

The presence of complications has significantly influenced the survival length (Fig. 2).

We have not found a statistical link between the degree of tumor differentiation, number of resected organs and distal survival.

Discussions

Comparing the results after MOR with the ones after conventional colorectal surgeries, literature reports indicate a significantly higher incidence of complications and postoperative deaths for the first category [10,13,14,21,31,32], findings sustained by the retrospective and prospective studies done in our institution [21,31,33].

Anastomotic fistula and wound infection represent the most common postoperative complications after colorectal surgery [5,6,34,35]. In case of MOR, we found that these complications have a significantly higher risk of occurrence. Also, the rate of cardiovascular and pulmonary complications was significantly higher after MOR [21].

Although some authors indicate emergency surgeries as risk factors for an increased rate of complications and postoperative deaths, in our study we did not find an influence of this parameter on postoperative outcome. This assertion can be limited by the small number of patients in this situation in our group, the statistical analysis being irrelevant [18,36].

Age over 64 is considered by the literature as an independent prognostic factor for the occurrence of complications and postoperative deaths [18]. In our study, age over 70 did not significantly affect mortality and morbidity after MOR. Obviously, older age was more commonly associated with the presence of associated pathology and a consequent higher risk of postoperative deaths, which underlines that postoperative risks after MOR increase with age.

Associated diseases of patients receiving MOR may adversely affect postoperative outcome[14,37]. Our study indicates the presence of diabetes mellitus, personal history of neoplasia, the association of cardiovascular pathology and major surgical history as having a significant influence on the rate of postoperative complications.

Low values of hemoglobin and serum proteins are indicated by the literature as being risk factors for the devel-

opment of anastomotic fistula [38]. In our study, these factors did not significantly affect the occurrence of anastomotic fistula, most likely due to the elective character of the surgery and to a proper preoperative preparation. Based on the statistical analysis, we found that increased intraoperative blood loss was associated with an increased incidence of complications and postoperative deaths, a conclusion similar to the data presented in the literature [18]. Morbidity was influenced by the number of resected organs, being higher in patients who had at least two organs resected. These conclusions highlight the importance that the experience of the surgical team has on postoperative outcome.

The assertion in the literature that tumor size did not significantly influence post-operative outcome [38] was also supported by the results of our study, indicating that tumor size over 5 cm was not associated with an increase morbidity and mortality rate.

Regarding the 5-year survival of patients receiving MOR, this is similar to the overall survival of patients operated for colorectal cancer, regardless of stage (43.9% vs 42%) [11,31]. In addition, survival is comparable to that of the patients who received a radical surgical treatment for lower-grade colon cancers: stage IIIC (30%), stage III B (56%), stage III A (50%) [31].

The statistical analysis showed that the 5-year survival of patients operated with MOR could be adversely affected by the status of surgical resection margins (R1/R2) and by the presence of lymph node metastases (N1/N2), as it is in the conventional colo-rectal resections [11,18,20,31,39]. Particularly, the survival of patients with MOR is negatively influenced by the presence of postoperative complications.

The results of our study fall within the survival values reported in literature [11,20,40,43].

Conclusions

MOR represents complex surgical procedures that offer a real chance of survival to patients diagnosed with locally advanced colorectal cancer, the results of our study highlighting the benefits that these surgeries can bring to patients.

The risk factors identified as having a negative impact on the postoperative outcome were: diabetes mellitus, history of personal neoplasia, associated cardio-vascular pathology, major surgical history, intraoperative blood loss, number of resected organs.

5-year survival was influenced by positive resection margins, presence of lymph node metastases and the presence of postoperative complications. All emphasize the importance of the surgical team's experience in achieving optimum results. This experience should be of interest in preoperative conduct (patient selection, preoperative preparation), surgical technique (minimal blood loss, R0 resection margins) and postoperative management.

Our study data, along with those in the literature, support the routine indication of MOR for patients diagnosed with locally advanced colorectal cancer, with the condition of R0 resection margins and careful patient selection to ensure optimal immediate and long-term outcome.

Acknowledgement

Adrian Bartoş, Dana Bartoş, Raluca Stoian and Bianca Szabo have contributed equally for the realisation of this paper; for that they occupy the same position as main authors in this paper.

The results and conclusions of the study presented in this paper are part of the first author's PhD thesis, entitled "Optimizing the prognosis in advanced colon cancer", publicly sustained in December 2016 in Cluj-Napoca, Romania. Intermediate results, regarding only the immediate outcomes after MOR, were first published in 2012, by the same first author [21].

Riassunto

Nonostante che la resezione multiorgano (MOR) sia raccomandata nelle line guida internazionali per il carcro colon-rettale avanzato, la letteratura mostra che l'elevata morbilità e mortalità che si accompagna a questi interventi complessi rappresenta un limite al numero dei pazienti sottoposti a tale trattamento.

Lo scopo del nostro studio era quello di analizzare i risultati immediati e remoti ottenuti con MOR e di analizzare i fattori potenzialmente in grado di influenzare i risultati.

Si tratta di uno studio retrospettivo su una casistica comprendente pazienti trattati nella nostra struttura per cancro colon rettale avanzato, escludendo pazienti con metastasi epatiche e quelli destinati ad exenteratio pelvica.

Si tratta di una casistica globale di 146 pazienti trattati tra il 2006 ed il 2010 di cui 107 sono stati utilizzati per questo studio.

È stata analizzata morbilità, mortalità e sopravvivenza dopo MOR ed i fattori che potrebbero aver influenzato il decorso postoperatorio.

Ebbene i fattori di rischio che hanno influenzato negativamente il decorso postoperatorio sono stati il diabete, patologie neoplastiche personali, malattie cardiovascolari associate, pregressa chirurgia maggiore, perdita ematica intraoperatoria, numero degli organi asportati. La sopravvivenza è stata influenzata negativamente dalla positività dei margini di resezione, la presenza di metastasi linfonodali e la presenza di complicazioni nel periodo postoperatorio.

In conclusione i dati di questo studio confermano la indicazione di base alla esecuzione della MOR nei pazien-

ti affetti da cancro colon-rettale avanzato a condizione di raggiungere la condizione di R0. Tutti questi dati sottolineano l'importanza dell'esperienza della squadra chirurgica in questo tipo di chirurgia per ottenere i risultati ottimali. Questa esperienza deve comprendere il trattamento preoperatorio, la tecnica chirurgica e le cure postoperatorie.

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