

Therapeutic Approach in Locally Advanced Colon Tumours (T4NxM0) - Clinical Experience in 18 Consecutive Cases

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Rezumat

Conduita terapeutică în tumorile de colon avansate local (T4NxM0) - experiența clinică în 18 cazuri consecutive

Introducere: Chirurgia ocupă un loc central în tratamentul cancerului de colon având drept scop rezecția R0. Chimioterapia și o urmărire oncologică corectă completează tratamentul.

Scopul: Stabilirea unei conduite terapeutice adecvate pentru pacienții cu tumori de colon avansate, fără metastaze hepatice.

Material și metodă: studiu retrospectiv pe un lot format din 150 de pacienți cu neoplasm de colon tratați în Clinica Chirurgie I a Institutului Oncologic București în perioada 01.01.2008 -01.03.2013.

Rezultate: 18 pacienți au prezentat tumori de colon extinse local care au necesitat rezecții multiviscerale. Din studiu au fost excluși pacienții cu metastaze hepatice. Viscerele cel mai frecvent implicate au fost: intestinul subțire și organele genitale interne, apoi vezica urinară, splina, duodenul și diafragma. Pacienții au fost urmăriți oncologic conform protocoalelor actuale și supuși chimioterapiei. La atingerea maximumului de răspuns la chimioterapie la pacienții R2 sau la apariția recidivei la cei R0 și R1 s-a intervenit chirurgical. La nevoie, operația s-a desfășurat în echipe multidisciplinare. Au decedat 5 pacienți prin recidive locale, continuare de evoluție, boala metastatică, dar și prin co-morbidități.

Concluzie: Tratamentul în comisiile oncologice și în echipe chirurgicale multidisciplinare, alături de urmărirea oncologică corectă cu reintervenție chirurgicală realizată după răspunsul maxim la chimioterapie la pacienții R2 sau la apariția recidivei la pacienții R0 și R1 reprezintă conduita terapeutică adecvată la pacienții cu tumori de colon avansate local.

Cuvinte cheie: cancer de colon avansat, rezecție multiviscerală

Abstract

Introduction: Surgery holds a central seat in the treatment of colon cancer, its objective being R0 resection. Chemotherapy and an appropriate oncological follow-up complete the treatment.

Aim: To establish an adequate therapeutic conduct in patients with advanced colon tumours, with no hepatic metastases.

Material and Method: retrospective study on a group of 150 patients with colon neoplasm treated in the First Surgery Clinic of the Bucharest Oncology Institute in Bucharest, between 01/01/2008 -01/03/2013.

Results: 18 patients presented locally extended colon tumours which required multivisceral resections. Patients with hepatic metastases were excluded from the study. The most frequently affected organs were: the small bowel and the internal genital organs, followed by the urinary bladder, spleen, duodenum and diaphragm muscle. Patients were oncologically followed-up according to current protocols and submitted to chemotherapy. When a maximum response was reached in R2 patients or when recurrence occurred in R0 and R1 patients, surgical intervention was required. When necessary, the operation was performed by multidisciplinary teams. 5 patients died due to

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local recurrence, disease progression, metastatic disease, and also due to comorbidities.

Conclusion: Treatment applied by oncological committees and multidisciplinary surgical teams, along with correct oncological follow-up and surgical reintervention when maximum response to chemotherapy was reached in R2 or when recurrences occurred in R0 and R1 patients represents the adequate therapeutic conduct in patients with locally advanced colon tumours.

Key words: advanced colon cancer, multivisceral resection

Introduction

Locally advanced colon cancer is represented by those forms of colon neoplastic disease in which the tumour invades the neighbouring organs. In approximately 50% of cases adherence to neighbouring organs is due to an inflammatory peritumoral process, and in the remaining 50% there is a real extension into the adjacent organs.

The invaded intraperitoneal organs differ depending on the affected segment of the colon. In tumours of the right colon the right kidney and the duodenum are frequently involved, in tumours of the transverse colon the stomach and great omentum, those of the left colon flexure affect the spleen, tail of the pancreas, diaphragm and left kidney, while those of the sigmoid colon extend to the internal genital organs in women and the urinary bladder. Small bowel loops and structures of the abdominal wall can be affected in any localisation of the colon cancer. (1).

Within this category of colon tumours there are situations in which, despite advanced local evolution, patients do not present metastases at a distance. Numerous tumour, invasion and metastasis markers are under study at present, which will allow timely identification of these patients.

These forms of colon tumours with advanced local evolution and no metastases at a distance present, at the moment the patient addresses to the clinician at least, a particular clinical evolution, as the morbidity and mortality rates are not influenced by the evolution of metastases, and a particular therapeutic conduct is required in these cases. Experience in our clinic has however also recorded patients which presented themselves for locally advanced colon cancers, with no metastases, which were beyond resection limit and in whom palliative interventions were performed instead: colostomies, biopsies, exploratory laparatomies.

Material and Method

We conducted a retrospective study on a group of 150 patients admitted to and treated for colon neoplasm in the First Surgery Clinic of the "Alexandru Trestioreanu" Oncology Institute, in Bucharest, between 01/01/2008 – 01/03/2013.

The oncological data were obtained from the database of

the Oncology Institute in Bucharest. We were interested in data regarding: local extension of the colon cancer, organs adjacent to the cancer which were invaded, type of R0, R1, R2 resection, correlation between types of resection, number of surgical interventions submitted to, along with the degree of tumour differentiation, complications, mortality rate. The type of resection in terms of oncological surgical margins, R0 – no tumour tissue remaining, R1 – microscopic tumour tissue remaining and R2 – macroscopic tumour tissues remaining, was established according to the anatomo-pathological exam result. We excluded from our study patients who already had metastases at their first presentation, as they represent an additional factor influencing the evolution and prognosis, as well as the surgical approach in terms of the amplitude of the local intervention. From the group of 150 patients treated for colon tumours, a subgroup of 18 patients presented with locally advanced tumours and no metastases at a distance. As it was only a small lot, we did not perform a statistical analysis. Our aim was to establish a therapeutic conduct applicable to patients with colon tumours which meet the selection criteria presented above.

Results

In the study group we analysed the following parameters:

1. Distribution of the group of patients according to the degree of extent of the disease (*Fig. 1*). Out of the 150 patients included in the study group, 18 presented locally advanced colon tumours, with no metastases at a distance at first presentation, representing 12% of the entire lot.

2. Tumour invaded organs adjacent to the colon (*Table 1*). Tumoral invasion of the small bowel was the most frequently encountered situation, followed by that of the abdominal wall, of the internal genital organs in women and the urinary bladder, but there were other types of organs invaded as well, as according to *Table 1*. We also noted patients with invasion of more than one organ. It must be highlighted that the small bowel was involved, in the majority of cases, in stenosing-occlusive form, as a first manifestation of the disease.

3. Type of resection performed (R0, R1, R2) (*Table 2*). The aim of the surgical intervention in these patients with locally

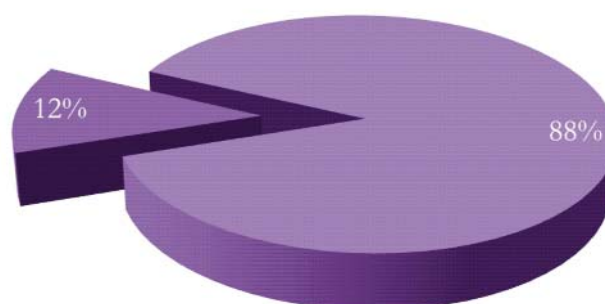


Figure 1. Disease distribution according to degree of local extension

Table 1. Adjacent organs with tumour extension from the colon

Organs	No. of patients
Small bowel	5
Internal genital organs	3
Urinary bladder	3
Spleen	2
Duodenum and pancreas	1
Abdominal wall	4
Diaphragm	1
Sacrum	1
Iliac bone and muscle	1

advanced tumours was radical oncologic resection (R0), which was however possible, due to regional conditions, in only 8 patients. To this purpose we sometimes resorted to surgical interventions performed by multidisciplinary teams (thoracic surgeon, urologist) and to the use of other associated ablative methods, such as radioablation. Given the locoregional invasion, multivisceral resections or resections of other anatomical structures were required, which were associated to colostomy, as mentioned in *Table 3*.

4. The correlation between type of resection (R0, R1, R2) and number of surgical interventions performed (*Table 4*).

The number of reinterventions was larger in patients with initial R1 and R2 resections, and were decided for depending on the response to the adjuvant chemotherapeutic treatment undergone.

Types of visceral exeresis performed during reintervention are listed in *Table 5*: reinterventions were aimed to solve some postoperative complications, recurrence or progression of local neoplastic remnants.

5. Correlation between resection type (R0,R1,R2) and degree of tumour differentiation (*Table 6*).

It is difficult to establish a correlation between tumour differentiation grade and type of resection – out of the group of patients with R0 resection there were 2 patients with G1 degree of differentiation, and in patients with R1 and R2 resections all patients presented a G2 differentiation grade.

6. Evolution and complications (*Table 7*).

Out of the 6 patients with R2 type of resection, 2 patients, after several reinterventions for completion of surgical exeresis and after several chemotherapeutic cures, had favourable evolution, with positive 4-year survival.

7. Mortality rate (*Table 8*):

- 2 patients from the R2 subgroup died due to progression of disease, initially having presented with inoperable tumours;
- 2 patients from the R2 subgroup died due to inoperable tumour recurrences;
- 1 patient from the R1 subgroup died due to metastatic disease.

Discussions

The aim of surgical treatment in locally advanced colon

Table 2. Types of resection performed

R	R0	R1	R2
No. of patients	8	4	6

Table 3. Visceral exeresis performed during the first surgery

Surgical interventions	No. of cases
Enterectomy and adnexectomy	1
Enterectomy and histerectomy	1
Colostoma	2
Enterectomy	3
Partial cystectomy and abdominal wall resection	2
Partial cystectomy	1
Resection and radioablation of the iliac bone	1
Duodenopancreatectomy	1
Histerectomy and anexectomy	1
Splenectomy	1
Partial resection of the diaphragm and modelling resection of the stomach	1
Abdominal wall resection	2
Splenopancreatectomy	1

Table 4. Correlation between type of resection and number of interventions

Type of resection	0 interventions	2 interventions	3 interventions
R0 (8)	7	1	0
R1 (4)	1	3	0
R2 (6)	2	2	2

Table 5. Visceral exeresis performed during reintervention

Type of intervention	No. of cases
Abdominal wall resection and partial cystectomy	1
Partial cystectomy and resection of the rectal-sigmoidal junction	1
Explorative laparotomy	2
Iliac muscle resection and enterectomy and iliac bone tumour radioablation	1
Hepatic metastasis radioablation	3

Table 6. Correlation between intervention type and tumour differentiation grade. Tumour degree of differentiation

	G1	G2	G3	G4
R0	2	6	0	0
R1	0	4	0	0
R2	0	6	0	0

Table 7. Evolution and complications

Intervention type	Recurrence	Disease progression	Metastasis
R0 (8)	-	-	2
R1 (4)	-	-	1
R2 (6)	2	2	-

Table 8. No. of deaths compared to total no. of patients

No. of patients	Deaths
18	5

tumours is negative margin R0 resection (resection with no remaining tumour tissues). To this purpose multivisceral resections are required. Along with first-line surgical treatment, chemotherapy plays an important role in this matter.

In our study we included patients with locally advanced colon tumours with no metastases at a distance at presentation, in order to eliminate a factor which highly influenced the evolution and prognosis, meaning metastases. Thus, we intended to analyse the optimal therapeutic conduct in the case of preponderantly local evolution of the disease.

It is a known medical fact that there are colon tumours with local evolution and low tendency towards metastases, while there are other small sized tumours which are associated with metastases very early on in the progression of the disease. There are a series of tumoral invasion and metastasis markers which are being studied at present. Matrix metalloproteinases (MMPs) are secreted in latent form by tumour cells, but also by fibroblasts and by the cells of the inflammatory infiltrate, and are activated by proteolytic cleavage of the terminal amino acid. These enzymes play a part in the solubilisation of the intercellular matrix, so that there is a correlation between the degree of MMPs expression and the risk of recurrence and metastasis, and MMPs inhibitors have proven effective against malignant tumours in preclinical studies. (2). Cellular adhesion molecules in colon cancer, such as cadherin E (CDH1), epithelial adhesion molecule (Ep.CAM) and β cadherin (CTNNB1), play a part in the organization of the intercellular cytoskeleton. A lowered expression leads to progression of the neoplastic disease and metastasis. Unfortunately, up until present, we do not possess the means to analyse these markers and establish the aggressiveness and potential of metastasis of colon tumours.

The use of current paraclinical exploring methods allows for establishing the degree of local extension and stage of the disease. A complete clinical and paraclinical evaluation of the patient is important in order to identify any associated pathologies as well. Preoperative knowledge of the grade of local invasion, the stage of the disease and of the associated pathology allows the selection of the correct therapeutic approach, meaning of comprising a surgical team that includes surgeons from other specialties as well. Thus, for a tumour of the left colonic flexure, in a patient which has undergone a

**Figure 2.** Colon tumour extended in the diaphragm muscle

splenectomy according to his/her history, with wide extension of the tumour in the left hemidiaphragm, which required diaphragmatic resection and prosthetic repair with textile mesh, we performed the operation divided in 2 teams, one of thoracic surgery and one of general surgery (Fig. 2).

Treatment protocol includes surgical treatment as a first-line therapeutic conduct, having as a purpose radical resection, with negative margins (R0) and, in order to accomplish that in patients with locally extended tumours, multivisceral resections are necessary as well (3).

Multivisceral resection is defined as the resection of at least one organ other than that of the primarily affected one, which in this case is represented by a segment of the colon (3). Adjuvant chemotherapeutic treatment is mandatory in all patients, and is of greater importance in patients with R1 resections (with remaining microscopic tissue) or R2 (with remaining macroscopic tissue), as the goals are a slowdown of the disease progression in R1 patients and a stimulation of chemical cytoreduction in R2 patients. Thus, we surgically reintervened at the occurrence of local recurrence or metastasis in patients with R0 or R1 resections, or when the effect of chemotherapy was considered to have reached a maximum in R2 patients and paraclinical investigations indicated the possibility to complete the exeresis. This leads to the conclusion that an oncological follow-up is highly important in these patients according to current protocols, with examinations every 3 months in the first postoperative year, by screening the values of CEA and CA19-9 tumoral markers and by performing thoracic, abdominal and pelvic CT every 6 months.

The most frequently invaded organs are the small bowel, followed by the internal genital organs, the urinary bladder and the abdominal wall. There are situations with multiple organ extension. The number of organs to which the disease has extended to does not influence the chances of survival (4).

In order to perform R0 resection we made use of ablation through radiofrequency in a patient with extension to the iliac bone, with very good results, proved by the PET-CT scan performed due to increase of tumoral markers under the

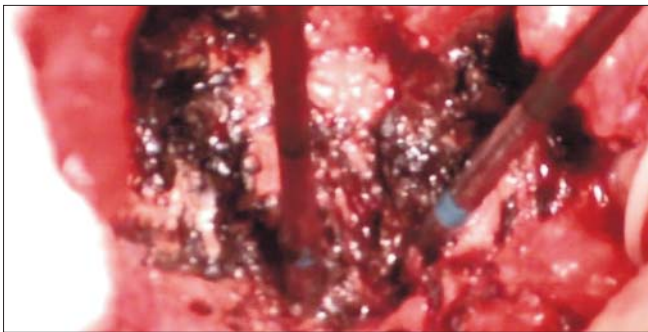


Figure 3. Intraoperative aspect of the tissues submitted to radiofrequency ablation – tumour of the psoas muscle

circumstance in which CT scan did not identify the recurrence of the tumour. PET-CT scan showed an area of intake with inflammatory characteristics in the region of the right iliac bone, with neoplastic features at the level of the rectosigmoid junction, where a large polyp which had had malignant evolution was detected and surgically treated (Fig. 3, 4)

In our study group the majority of patients was represented by patients with G2 moderately differentiated tumours, in an almost equal ratio among the 3 types of resection (R0, R1 and R2). This fact does not allow for the establishing of a correlation between grade of differentiation and local evolution of colon tumours. However, the role played by the grade of differentiation in providing a prognosis is known, meaning that patients with highly malignant tumours have a greater mortality risk compared to the control group (5). In order to simplify the repartition in groups corresponding to the differentiation degree of tumours, the American Committee on Cancer recommends the following division, in 2 types: tumours with low malignant degree, and tumours with high malignant degree (5).

The prognosis of patients with locally advanced colon tumours if influenced by the type of resection, therefore R0 patients having a net superior prognosis (6).

The analysis of our group proves that some R2 patients can have the chance of a favourable evolution as well, if the treatment and clinical follow-up protocol is respected. Thus, out of the 6 patients with R2 resection, 2 benefited from palliative interventions, as the tumours were unresectable, 2 presented with progression of the disease after multivisceral resections, despite chemotherapeutic treatment, but the other 2, after 3 interventions each for completion of exeresis of first recurrence, and after several chemotherapeutic cures, presented favourable evolution.

Patient survival after multivisceral resections is similar to that after standard surgeries (76.6% at 5-year follow-up), but the risk of intra- and postoperative complications is higher (7,8). Both survival and complication rates are influenced by the type of resection, and the amplitude of the anatomical exeresis. Old age and comorbidities influence the mortality rate in a negative manner, both by the component imputable to associated disease and by limiting the amplitude of the surgical act.

For an improvement of prognosis and survival it is recommended that these patients, once correctly diagnosed, be guided towards treatment in services that benefit from a varied array of surgical specialties, from appropriate technical equipment and from a chemotherapy department.

Conclusions

1. In locally advanced colon cancers the objective of the operation is radical resection from an oncological point of view. The operative indication must be solidly argued for from an imaging, oncological and biological point of view.
2. Accomplishment of this objective sometimes leads to the necessity of the intervention to be performed by multidisciplinary teams (thoracic surgeon, urologist) and of association of ablative methods (tumour ablation through radiofrequency).

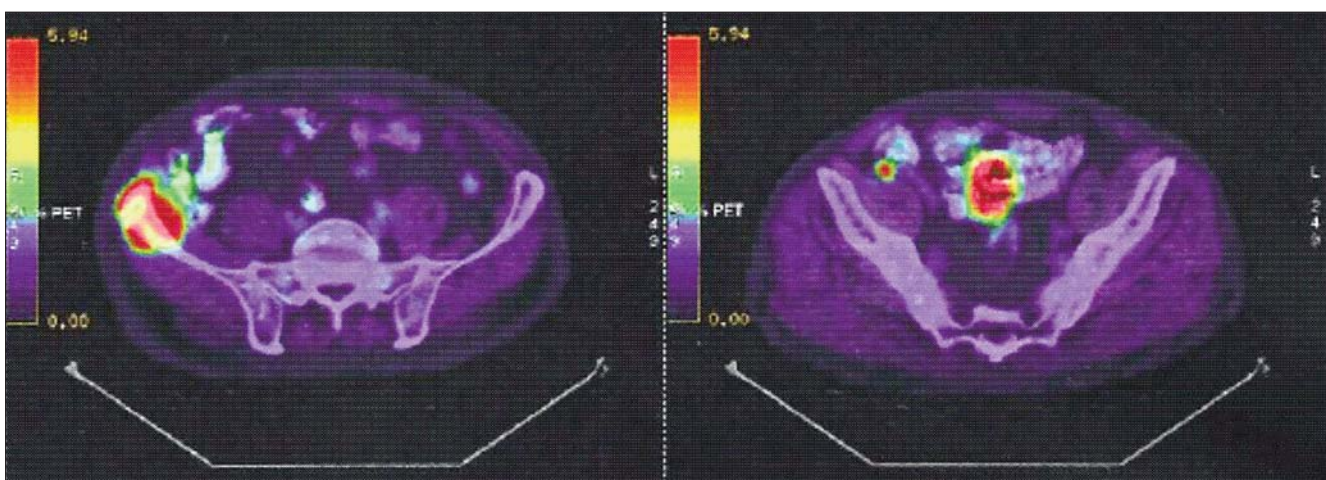


Figure 4. PET-CT scan revealing tumour recurrence – polyp of the sigmoid colon with malignant evolution and right iliac tumour mass

This standpoint may seem aggressive, but over the last decade the indications for exeresis in cancers with multiple organ extension have broadened.

3. Postoperative chemotherapy brings major therapeutic benefits in terms of local evolution in R1 and R2 patients.
4. Correct oncological follow-up results in surgical reintervention in case of recurrence or detection of evolution of the malignant tissues remaining. Reintervention in R2 patients may be indicated when a maximum response to chemotherapy is reached.
5. Deaths were caused by local recurrence, disease progression or metastatic disease, and mortality was significantly influenced by the patients' age and comorbidities.
6. The genetic markers submitted to study at present will allow in the future the identification of patients with tumours with low tendency towards metastasis and predominantly local evolution.

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