

Postradiotherapy regression - a prognostic factor in rectal neoplasm

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Rezumat

Regresia postradică - factor de prognostic în neoplasmul rectal

Radioterapia preoperatorie este procedura standard în protocoalele de tratament a cancerului rectal. Experiența acumulată și analiza clinico-paraclinică a rezultatelor acestei proceduri au stabilit faptul că răspunsul la radioterapie, în sensul reducerii volumului tumoral și a adenopatiilor din stațiile I și II este foarte variabil, de la dispariția completă a masei tumorale, până la lipsa de răspuns. Răspunsul la radioterapie coroborat cu datele anatomopatologice și imunohistochimie ar putea permite aprecierea prognosticului în cancerul de rect. În acest scop ne-am propus efectuarea unui studiu clinic, care să analizeze grading-ul tumoral, markerii imunohistochimici, precum și eventuale modificări genetice care să permită aprecierea gradului de regresie postradică precum și prognosticul postterapeutic. Pe baza acestor criterii ar fi posibil să se stabilească grupa de regresie în care se situează pacientul încă din faza preterapeutică. În acest fel s-ar nuanța tipul de radioterapie prechirurgicală, uneori aceasta efectuată standard fiind inefectivă. Venim cu o statistică de lot preliminar, cu valoare de ipoteză de lucru.

Cuvinte cheie: neoplasm rectal, radioterapie, angiogeneză

Abstract

Preoperative radiotherapy is standard procedure in rectal cancer treatment protocols. Experience and analysis of clinical and laboratory features of the results of this procedure have established that the response to radiotherapy, in order to reduce the volume of tumor and adenopathies of stations I and II is highly variable, from complete disappearance of the tumor mass, to the lack of response. The response to radiotherapy in conjunction with pathological and immunohistochemical data could allow assessment of prognosis in the rectal cancer. For this purpose we have proposed conducting a clinical trial to examine the tumor grading, immunohistochemical markers, and possible genetic changes that allow assessment of the degree of post-radical regression and the posttherapeutic prognosis. Based on these criteria would be possible to establish a group of regression in which the patient stands still from the pretherapeutic phase. In this way the type of the presurgical radiation would shade, sometimes this standard being made ineffective. We come with a lot preliminary statistics, with the value of working hypothesis.

Key words: rectal neoplasm, radiotherapy, angiogenesis

Introduction

The treatment protocol for rectal cancer includes preoperative radiation therapy for rectal tumors, classified T3+ invasion until the muscularis propria or until the serous membrane, for the segments covered by the serous layer, but which do not go beyond it. Consequently, stage II and III tumors (T3N0M0 and T3-4N1-2) benefit from preoperative radiation therapy. Pre and post-operative radiation therapy in combination with chemotherapy is also useful in stage IV

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of the progress of the disease, according to the current treatment protocols.

The types of irradiation treatment for rectal cancer are divided into:

- "Short course" preoperative radiation therapy, in which 25Gy are administered, with 5 Gy during a one-week period, immediately followed by surgery.
- "Long course" preoperative radiation therapy, in which, in phase I 45-50 Gy are administered, in 25 fractions, while in phase II, 5,4 Gy are administered in three fractions, followed by surgery after 4-8 weeks.
- "Long course" preoperative chemotherapy, which differs from the previous one in that in weeks 1 and 5, 20 mg/sqm of folic acid and 5FU, 350mg/sqm(1) are administered.

Thus, in "long course" preoperative radiation therapy, the patient undergoes irradiation for approximately 5 weeks and is operated after approximately 6 weeks. Consequently, the surgical treatment is applied after 11-12 weeks from the moment of the diagnosis.

While rigorously applying the above mentioned treatment protocol, we noticed differences in terms of the response to radiation therapy, as well as in the post-therapeutical progress of the patients. Taking into account the fact that so far there does not exist any genetic, biological, or histopathologic marker to enable us to predict the response of the rectal tumor to radiation therapy and to chemotherapy, we set out to determine to what extent the response to radiotherapy is a prognostic factor, as well as the value of applying two new criteria, which are known but not used, in order to assess the post-therapeutical prognosis: the angiogenetic score and the post radiotherapy tumor regression, established by pre and post-irradiation histopathologic exams.

Material and Method

We performed a retrospective study on a group of 89 patients, hospitalized and treated for rectal neoplasm at the "Al. Trestioreanu" Oncological Institute of Bucharest during the

period comprised between 1 October 2007 – 31 December 2010.

In order to assess the postradiotherapy regression of rectal tumors we used the classification into 5 degrees of regression established by Bazzetti in 1996 (2):

- "R1 – total regression – absence of neoplastic cells;
- R2 – almost complete regression – with rare residual neoplastic cells;
- R3 – partial regression – the postradiotherapy fibrosis is more severe than the residual tumor;
- R4 – insufficient regression (non-responsive tumors) - the residual tumor is larger than the postradiotherapy fibrosis;
- R5 – absence of regression."

(Table 1, Graphic 1, Table 2, Graphic 2, Table 3, Graphic 3, Table 4, Graphic 4, Table 5, Graphic 5, Figures 1-5)

The rectal amputation was performed for the tumors of the lower rectum, as well as for those of the medium rectum if, following radiotherapy, sufficient regression was not achieved so as to enable the decrease of the lower level of oncological security to 2 cm. (Table 6, Graphic 6)

The analysis of the response to radiotherapy according to the tumor grading (Table 7):

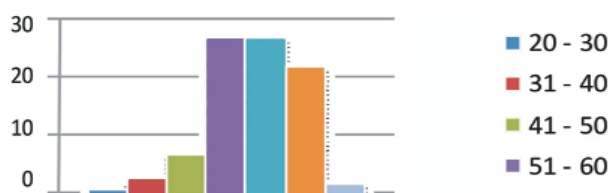
- Patients with well differentiated G1 tumors or moderately differentiated G2 tumors presented with total regression (R1) or almost complete regression (R2) at a ratio of 67.69% (44 patients out of the 73 treated with radiotherapy);
- Patients with a reduced degree of tumoral differentiation G3 presented with almost complete regression (R2) 37.5% (3 out of the 8 patients in group G3), most of whom falling into the non-responsive group;
- The response to radiotherapy was influenced by the tumor grading.

The analysis of the ratio between the response to radiotherapy, the tumor grading and the post-therapeutical progress (Table 8):

- A good R1+R2 response to radiotherapy controls the local progress, but does not prevent metastasis.
- The absence of R4+R5 response to radiotherapy or a

Table 1. The distribution of the group according to age

Age (years)	20 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	81 - 90
No. of patients	1	3	7	27	27	22	2

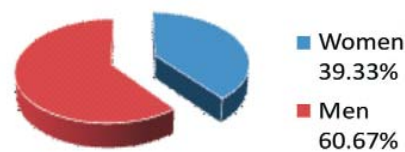


The largest number is represented by the patients aged 50-80

Graphic 1.

Table 2. The distribution of the group according to sex

Men	Women
54	35



The largest number in the group under examination is represented by men

Graphic 2.

Table 3. The distribution of the group according to the preoperative stage of the disease

Stage 1 T1-2 N0 M0	Stage 2 T3-4 N0 M0	Stage 3 T1-4 N1-2 M0	Stage 4 Any T Any N M1
4	45	28	12

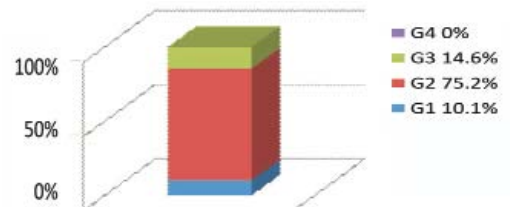


Out of the total number of 89 patients, only those in stages II and III of progress (81.9%) were subject to pre-operative radiotherapy

Graphic 3.

Table 4. The distribution of the group according to the histological type and grading

Adenocarcinoma			
G1	G2	G3	G4
9	67	13	0



The largest part is represented by patients with moderately differentiated tumors

Graphic 4.

Table 5. Postradiotherapy regression according to the criteria established by Bazzetti in 1996

R1	R2	R3	R4	R5
5	42	15	8	3



- patients with no response to radiotherapy (R5) or with insufficient response (R4) represented 15%.
- 6.8% of the patients experienced total regression (R1) after radiotherapy.
- 64.3% of the patients experienced complete or almost complete regression (R1+R2).

Graphic 5.

Figure 1. Complete macroscopic regression

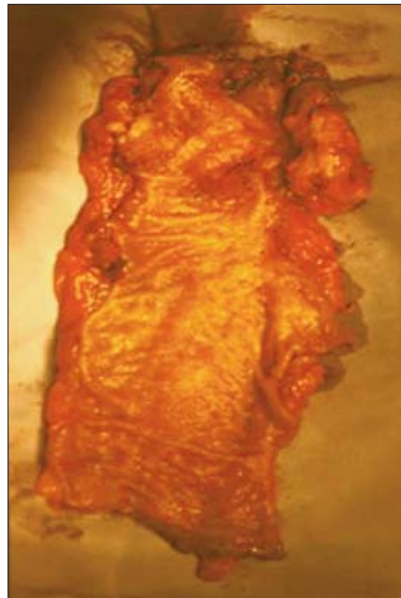


Figure 2. Partial macroscopic regression

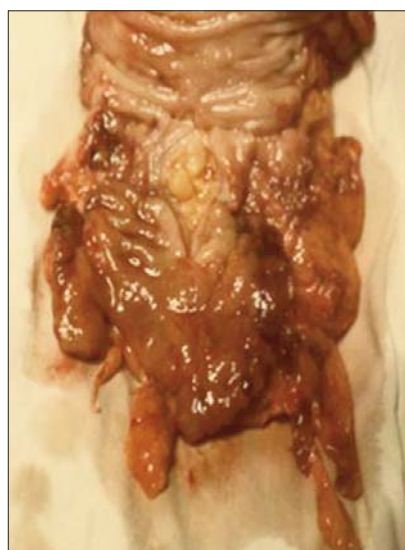


Figure 3. Partial macroscopic regression



Figure 4. Intense process of postradiotherapy parietal sclerosis

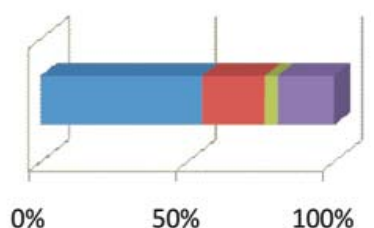


Figure 5. Absence of regression



Table 6. Surgical interventions

Rectal amputation	Rectal-sigmoidal resection	Pelvectomy	Palliative interventions
49	19	4	17



■ Rectal amputation 55.05%
 ■ Rectal-sigmoidal resection 21.34%
 ■ Pelvectomy 4.49%
 ■ Palliative interventions 19.1%

Graphic 6.

partial R3 regression is correlated with an unfavorable local progress.

- The response to radiotherapy is an essential prognostic factor in the local progress of the neoplastic disease, but it does not influence secondary distance determinations.

The analysis of the relation between the response to radiotherapy and the initial stage of the neoplastic disease (Table 9):

- R1+R2 response to radiotherapy was obtained in 86.66% of the patients in stage II, while R3 (partial regression) in 13.34% of the cases.
- A good R2 response to radiotherapy (almost complete regression) was obtained in only 28.57 % of the patients in stage III, whereas the other 71.43% of the patients

Table 7.

	G1	G2	G3	G4
R1	2	3	0	0
R2	3	36	3	0
R3	2	11	2	0
R4	0	8	0	0
R5	0	0	3	0

Table 8.

	Favorable progress	Metastases	Local recurrence	Continuous progress	Non-monitored
R1G1	1	1	0	0	0
R1G2	2	1	0	0	0
R2G1	3	0	0	0	0
R2G2	33	2	0	0	1
R2G3	1	0	1	0	1
R3G1	2	0	0	0	0
R3G2	5	3	2	0	1
R3G3	2	0	0	0	0
R4G2	1	0	2	4	1
R4G3	0	0	0	0	0
R5G2	0	0	0	3	0
Total	50	7	5	7	4

Table 9.

	Stage II	Stage III	Total no. of patients treated with radiotherapy
R1	5	0	5
R2	34	8	42
R3	6	9	15
R4	0	8	8
R5	0	3	3
Total patients S. II and III	45	28	73

obtained insufficient regression or no regression.

- The response to radiotherapy is directly correlated with the initial stage of the disease.

Discussions

Oncogenesis begins with the alteration of the cellular cycle, but without the involvement of the angiogenic phenomenon, tumoral growth would not be possible. (3). Angiogenesis – the formation of new blood vessels is not only specific to the neoplastic processes, but also to the physiological healing process of the wounds, to the restoration of the endometrium after the menstrual bleeding, to benign tumors and to other non-neoplastic pathological processes. The formation of new vessels ensures the intake of oxygen and nutrients in the tumoral mass, the elimination of the metabolic products, and at the same time represents the means of distance dissemination and formation of metastases. The process of angiogenesis is mediated by the cytokines produced in the tumoral cells by the macrophages attached to the tumors and to other stromal cells. From the group of cytokines involved in this process, the followings have been identified: angiogenin, interleukin 8, the fibroblastic growth factor (FGF), the endothelial growth factor (EGF), haptoglobin, hyaluronic acid, ganglioside. The macrophages and the tumoral cells produce urokinase (a plasminogen activator, which favors angiogenesis (4). There is evidence that the level of angiogenesis in colorectal tumors is correlated with the tumoral behavior in terms of distance metastasis, the risk of local recurrence, as well as with survival in the sense that the patients who survived 5 years after the treatment had a much lower angiogenic score than those with shorter survivals (4). Tumoral angiogenesis is also conditioned by the metastasized organ. In the hepatic metastases caused by the colorectal tumors lower angiogenic scores were found than in the primary tumor. These differences are also present in pulmonary metastases, compared to the hepatic ones. Survival is directly proportional with the angiogenic score in the metastatic lesions in the sense that a higher score is associated with better survival. “Metachronous liver metastases had a significantly higher score than synchronous metastases” (4). The explanation for this fact is that synchronous metastases are detected during the surgery for the primary tumor and have a smaller size than the metachronous metastases, which have to reach a larger size, and consequently more new vessels, in order to be detected based on the appearance of the symptoms (5). Thus, in order to assess the tumoral behavior, besides the determination of the stage of the tumor, of the degree of differentiation and of the lymphatic status, it would be necessary to establish an angiogenic score, which is represented by the number of new vessels / field unit.

The effects of radiotherapy are cellular apoptosis and tumoral hypoxia. Cellular apoptosis is produced through the occurrence of disruptions at the level of the DNA of the tumoral cell and through the production of free oxygen radicals (3).

Tumoral hypoxia is due to the destruction of the micro-angiogenic network, by the obstruction of the promoter cells and obliterating arteritis by hyalinosis.

The anatomical position of the rectum as a fixed organ situated in the pelvic-peritoneal cavity makes it a good target for radiotherapy. To this contribute the relations it has with the neighboring organs as these make it possible to obtain an irradiation field which avoids affecting the small intestine and allows the application of the maximum dose of rays on the tumor. The irradiated segment is largely removed during surgery, leaving behind only the inferior anastomotic stump in the case of rectosigmoidal resections with low colorectal or colo-anal anastomosis. Preoperative irradiation also enables the reduction of the inferior margin of oncological security to 2 cm below the macroscopic limit of the tumor, which leads to the increase of the number of patients who benefit from such resection with anastomosis.

However, besides the above mentioned benefits of pre-operative irradiation, it also has a series of disadvantages related to the risk of tumoral dissemination during radiation therapy, to the delay of the surgical treatment and to the inability to know exactly the stage in which radiotherapy is applied to patients with tumors smaller than T3 or to those with unknown metastases.

Postoperative irradiation does not have these disadvantages, but it also has drawbacks related to the irradiation of the small intestine, which drops into the pelvis after surgery, to the impossibility of accurately determining the target area which should be the “bed” of the previous tumor, as well as to the irradiation of the anastomosis and of the neighboring colon and rectal segments, followed by the development of fibrosis and of the functional failures specific to postradiation lesions.

The positive effects of radiotherapy are proved by the clinical data in the literature, showing that in patients with T3 and N1 tumors, the risk of pelvic recurrence is up to 20% if case only surgery is performed (6). In patients with T4 tumors, the risk of local recurrence is of 50% if only surgery is performed (6). Other factors which predispose local recurrence are circumferential tumors with obstruction and an increased level of CEA.

Following the treatment guide for colorectal carcinomas, all the patients in the group we studied, who were in stage II or III of the progress of the disease, underwent preoperative radiotherapy, starting with T3 tumors. We noticed a complete post-radiotherapy regression in 6.8% of the patients. The data in the literature indicate that the ratio of complete response to radiotherapy (R1 – according the Bazzetti’s 1996 classification) reach up to 10% (7) and may be increased if it associated with chemotherapy, which, however, raises perioperative morbidity (8).

We obtained a good response to radiotherapy (R1+R2), complete or almost complete regression, in 64.3% of the patients in the group under examination.

The response to radiotherapy was favored by a good or moderate degree of tumor differentiation. The patients in groups G1 and G2 displayed complete regression R1, or almost complete regression, R2, in a ratio of 67.69%, in comparison with those with grade G3, who showed a response ratio of 37.5% in R2.

In terms of the local control of the neoplastic progress, the data we obtained are in agreement with those in the literature. A good response to radiotherapy (R1 + R2) is accompanied by a significant decrease of local recurrences, in comparison with the patients with insufficient response or non-responsive patients, in whose case the local recurrences and the continuous progress of the disease were significant.

In terms of metastasis, we found that a good response to radiotherapy (R1, R2) does not influence distance determinations, even if it provides good control of the local progress of the disease. These findings have also been reported by other authors. (2)

Mention should be made of the fact that the patients in the group we studied were irradiated postoperatively according to the "long course" plan, some of them being treated with radio-chemotherapy. The period of time between the diagnostication and the surgery was of 12 weeks. This delay in the administration of other treatments (surgery, chemotherapy) does not represent an advantage for the non-responsive patients or for the responsive ones who develop early metastasis. It could, therefore, be useful to determine pre-therapeutically which patients respond to radiotherapy and which do not, as well as those at risk for early metastasis. The likely answer to this question will come from the numerous genetic studies which analyze the genetic implications in rectal tumors. It is known that the mutations of the p53 suppressor gene can lead to cellular production of apoptosis inhibitors, which make tumoral cells resistant to radiotherapy.

The assessment of the status of the p53 gene would enable the determination of the aggressive behavior of an apparently localized tumor, the response to polichemotherapy, the survival after the curative resection, as well as the prognosis (9,10,11). Furthermore, the mutations of the K-ras gene are associated with a higher recurrence rate and an increased mortality in rectal tumors. Unfortunately, so far, the data of the genetic studies are inconsistent and do not allow the identification of a genetic marker as a predictor of rectal tumor response to radio-chemotherapy.

Starting from this current state, we consider that the analysis of the angiogenic score and of the postradiation tumoral regression would be useful so as to determine the post-therapeutical prognosis in rectal tumors.

We also consider that, for the patients with T3 small size tumors, the application of the short radiotherapy course of 25 Gy, with 5 Gy per fraction, for a week, followed by immediate surgery, is a more correct attitude than the application of a long course radiotherapy, which places the surgical intervention after 12 weeks from the moment of diagnosis.

Conclusions

1. Rectal tumor response to radiotherapy is clearly dependent on the stage and grading of the tumor.
2. The association of a good response to radiotherapy, R1 and R2, and a G1 or G2 level of differentiation between rectal tumors imply favorable local development, but do not influence distance determinations (metastasis).
3. The response to radiotherapy is an obvious prognostic

factor of local development, but does not influence or worsen distance development (metastasis) by delaying the administration of other treatments – the beginning of chemotherapy or the performance of surgery with the avoidance of useless radiotherapy.

4. Since, at the moment, we do not have any biological, histological or genetic marker as a predictor of rectal tumor response to radio-chemotherapy, we consider the following to be necessary:

- the quantification of angiogenesis according to pre-therapeutic histopathologic criteria by establishing an angiogenic score correlated with tumoral regression, taking into account the volume of the tumor, the depth of the invasion, the incidence of local and distance metastases.
- tumoral regression must be determined in the post-irradiation phase, according to histological and angiogenic score criteria.
- the place of chemotherapy in this new context has to be re-evaluated in accordance with the pre and post-operative angiogenic score, and subsequent studies will enable the correct use of antiangiogenic medication.

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