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 postterapeutic 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
of the progress of the disease, according to the current treat-
ment protocols.

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

a) “Short course” preoperative radiation therapy, in
which 25Gy are administered, with 5 Gy during a
one-week period, immediately followed by surgery.

b) “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.

c) “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

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 differentia-
  tion 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 respounse to radio-
therapy, 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**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>20-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
<th>81-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>27</td>
<td>27</td>
<td>22</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. The distribution of the group according to sex**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>35</td>
</tr>
</tbody>
</table>

Graphic 1.

---

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

Graphic 2.

The largest number in the group under examination is represented by men
Table 3. The distribution of the group according to the preoperative stage of the disease

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2 N0 M0</td>
<td>T3-4 N0 M0</td>
<td>T1-4 N1-2 M0</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>28</td>
<td>12</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
<td>67</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

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.

Figure 1. Complete macroscopic regression

Figure 2. Partial macroscopic regression

Graphic 3.

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

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>42</td>
<td>15</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

- 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 4.

Graphic 5.
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 6. Surgical interventions

<table>
<thead>
<tr>
<th>Rectal amputation</th>
<th>Rectal-sigmoidal resection</th>
<th>Pelvectomy</th>
<th>Palliative interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>19</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 7.

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R2</td>
<td>3</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>R3</td>
<td>2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>R4</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>R5</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 8.

<table>
<thead>
<tr>
<th>Favorable progress</th>
<th>Metastases</th>
<th>Local recurrence</th>
<th>Continuous progress</th>
<th>Non-monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1G1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R1G2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R3G1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R3G2</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>R3G3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>R4G2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>R4G3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 9.

<table>
<thead>
<tr>
<th>Stage II</th>
<th>Stage III</th>
<th>Total no. of patients treated with radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>R2</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>R3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>R4</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>R5</td>
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<tr>
<td>Total</td>
<td>45</td>
<td>28</td>
</tr>
</tbody>
</table>
and obliterating arteritis by hyalinosis. 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 preoperative 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 process 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.

Discussions

Oncogenesis begins with the alteration 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.

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However, besides the above mentioned benefits of preoperative 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.

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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 radiochemotherapy. The period of time between the diagnosis 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 must be determined in the post-operative angiogenic score, and subsequent studies will enable the correct use of antiangiogenic medication.

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.

References