

Clinical and Paraclinical Criteria of Patient Selection for the Non-operative Treatment in Completely Responsive Rectal Cancer (after Neoadjuvant Radiochemotherapy)

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Rezumat

Criterii de selecție a pacienților pentru tratamentul non-operator în cancerul de rect remis complet după radiochimioterapia neoadjuvantă

Introducere: Radioterapia neoadjuvantă este inclusă în protocoalele de tratament pentru tumorile de rect începând cu stadiile $\geq T3$. La unii pacienți, după radioterapie, tumorile dispar complet. Utilizarea radioterapiei neoadjuvante a permis și coborârea limitei inferioare de siguranță oncologică la 1-2 cm, precum și restrângerea indicației amputației de rect la tumorile aflate la 4 cm de orificiul anal. Această modificare de atitudine terapeutică a crescut realizarea de anastomoze joase, ultrajoase și colo-anale.

Scopul: Analizând complicațiile acestor tipuri de anastomoze, precum și dezavantajele amputației de rect, ne-am propus identificarea unor criterii care să permită selectarea pacienților cu răspuns complet la radiochimioterapia neoadjuvantă pentru tratamentul nonoperator în condiții de siguranță oncologică.

Material și metodă: Am efectuat un studiu retrospectiv pe un număr de 171 pacienți cu cancer de rect tratați în Clinica I de Chirurgie a Institutului Oncologic București între octombrie 2007 și decembrie 2013.

Rezultate: 141 pacienți au fost iradiați. 9 pacienți au avut un răspuns complet la radioterapie. 5 dintre ei nu au fost

operați și, după monitorizări clinice și paraclinice pe perioade variabile (2-6 ani), nu au prezentat recidive locale.
Concluzii: Renunțarea la intervenția chirurgicală la pacienții cu tumori de rect cu răspuns complet la radioterapie este o soluție bună și trebuie luată după o corectă informare a pacienților privind complicațiile chirurgiei rectului, cu condiția respectării cu strictețe a unor criterii de selecție a pacienților.

Cuvinte cheie: cancer rect, radioterapie neoadjuvantă, regresie postradioterapie

Abstract

Introduction: Neoadjuvant radiotherapy is included in the treatment protocols for rectal tumors in stages $\geq T3$. The use of neoadjuvant radiotherapy allowed the limit of surgical oncologic safety margin to decrease with 1-2 cm and the abdominoperineal resection to be able to be performed in tumors situated at 4 cm from the anal verge. This modification of the treatment strategy increased the use of low, ultra low and colo-anal anastomoses.

Goal: Through the analysis of these types of anastomoses and of the disadvantages of the abdomino-perineal resection, we aimed at performing a study on the patients which responded completely to radiotherapy by taking into account the criteria of oncologic safety and the sparing of the patients from surgical complications.

Material and method: We performed a retrospective study on 171 patients with rectal cancer treated in the 1st Clinic of Surgery from the Bucharest Oncology Institute between October 2007 and December 2013.

Results: 141 patients received radiotherapy, out of which 9

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responded completely. 5 of those 9 were not operated on and after variable clinical and paraclinical follow up (2-6 years), they did not present with local recurrence.

Conclusions: Not performing surgery in the patients with rectal cancer with a complete response to radiotherapy is a good solution and must be taken after a correct information of the patient about rectal surgery with the condition of strictly observing the selection criteria of the patients.

Key words: rectal cancer, neoadjuvant radiochemotherapy, post radiotherapy regression

Introduction

The destructive effect of radiotherapy on tumours is produced through the generation of cell apoptosis secondary to the alteration of DNA of the tumour cell and through the cellular hypoxia secondary to the destruction and the hyalinisation of the neo-formation vessels (1). The rectum, an anatomically fixed organ, situated in the pelvis sub-peritoneal space creates optimal condition for the irradiation as it allows the realisation of the irradiation field with the protection of the small bowel and the application of the maximal irradiation dose on the tumour. Applied preoperatively, radiotherapy allows the decrease in the inferior margin of oncological safety from 4-5 cm to 1-2 cm under the macroscopic tumour limit, thus increasing the number of patients which could benefit from low or ultra low rectal anastomoses. Postoperative radiotherapy predisposes to the irradiation of the small bowel, which in the post op period occupies the space previously held by the rectum, and, likewise, the risk of post-radiation enteritis is very high in those patients. Under these conditions, the majority of the studies sustain the indication of preoperative radiotherapy in rectal tumours which have a $T \geq T3$ and without metastases (stages II and III).

For patients in stage IV disease, the indication is established in oncological tumour sessions (oncological committees), according to the predominant symptomatology, radiotherapy not being excluded from the treatment of these patients.

The introduction of neoadjuvant chemoradiotherapy in the treatment protocol of rectal neoplasm (from $T \geq 3$) has produced a series of changes in the surgical approach, all with the goal to improve the quality of life, but without renouncing at the oncological safety criteria (2). The technical progress has contributed much to this aspect, with: the long scale introduction of mechanical sutures which allow the performance of low and ultra low anastomoses, and also the importance of total mesorectal excision extended inferiorly until 1 cm from the distal tumour margin. All matters have lead to the conclusion that the security limit distally to the tumour can be accepted to 1-2 cm from the macroscopic tumour limit, as such that the inferior limit of the resection in which one practices abdominoperineal resection may be limited to 4 cm. Under these conditions, a number increasingly high of patients

benefit from rectal resections with low, ultra-low, and coloanal anastomoses. Unfortunately, these anastomoses are not without complications or impact on the patient's quality of life. Certain patients have completely responsive tumours to radiochemotherapy, that is, in those cases, the tumours completely disappear. By analysing the complications of the anastomoses and the disadvantages of abdominoperineal resection, one asks themselves whether in these patients the surgical protocol should be followed up or if they should be only under oncological surveillance.

Material and Method

We performed a retrospective study on a batch of 171 patients operated on for rectal cancer in the 1st Clinic of General Surgery of the Bucharest Oncology Institute from October 2007 - 31st of December 2013. 7 patients in stage I (with $T < T3$) were initially operated on and then received adjuvant treatment, while in 24 patients in stage IV the attitude was variable, and, 141 patients with a T more or equal to T3, in stages II and III, with tumours located either on the superior, medium and low rectum were given neoadjuvant radiochemotherapy the long schedule of 45 GY given in 25 sessions and folic acid 20 mg/m² and 5 fluorouracil 350 mg /m² in weeks 1 and 5.

9 patients from the total of 141 treated with long course neoadjuvant radiotherapy responded completely (6.38%).

The patients were re-evaluated after radiochemotherapy at 4-8 weeks through rectal examination, colonoscopy, pelvis MRI and/or transrectal ultrasound and were further divided in two groups:

- Group I - 5 patients without lesions at the mucosal level, but with mesorectal increased lymph nodes in a patient. This patient had a rectal tumour at 7 cm from the anal verge and he was in stage III of the disease (T3 N1 M0). The patient was operated on, the procedure performed was recto-sigmoid resection with total mesorectal excision of and low mechanical anastomosis. The pathology exam confirmed the tumour invasion of a lymph node at the level of the mesorectum without any tumour infiltration of the rectal wall. Two patients out of the 4 with a complete response to neo adjuvant radiochemotherapy and without increased lymph nodes had the rectal tumour situated at 6 cm from the anal verge and the other two at less than 4 cm from the anal verge. All these 4 patients were in stage II of disease (T3N0M0).
- Group II - 4 patients with a persistent lesion at the mucosal level (anything from scar tissue to different grades of stenosis). Three patients were in stage II of the disease (T4N0 M0) and one was in stage III (T3N1M0). In all these patients the lesion was situated in less than 4 cm from the anal verge and they were given abdominoperineal resection. The pathology exam of the resected specimen did not identify any tumour cells. After radiotherapy, the patients did not receive any biopsy, as in the 5 patients with restitutio ad integrum one could not

establish the area which would be most adequate, and in the other 4 patients, with a remaining scar lesion it was considered that they present with a remaining tumour after radiochemotherapy and given those facts they were operated on.

- The other four patients without a lesion at the mucosal level and without any increased lymph nodes after a complete information on the risks of the low, ultra-low and colo-anal anastomoses, and also on the disadvantages of abdominoperineal resection and on the risks of evolution of the tumour progression, decided to remain under clinical surveillance, denying surgical intervention. In a patient, one year after the conclusion of radiotherapy, and after 6 months from chemotherapy, hepatic metastases appeared which were treated through radio-frequency ablation and chemotherapy series with a good 4 year clinical outcome. The other 3 patients had a positive clinical outcome at 3, 4 respectively 5 years after radiotherapy and diagnostic, they received a follow up periodically at 3 months in the first two years and in 6 months in the following years.

Discussions

The destructive effect of radiotherapy on tumours is produced through the generation of cell apoptosis secondary to the alteration of DNA of the tumour cell and through the cellular hypoxia secondary to the destruction and the hyalinisation of the neo-formation vessels (2). The rectum, an anatomically fixed organ, situated in the pelvis sub-peritoneal space creates optimal condition for the irradiation as it allows the realisation of the irradiation field with the protection of the small bowel and the application of the maximal irradiation dose on the tumour. Applied preoperatively, radiotherapy allows the decrease in the inferior margin of oncological safety from 4-5 cm to 1-2 cm under the macroscopic tumour limit, thus increasing the number of patients which could benefit from low or ultra low rectal anastomoses. Postoperative radiotherapy predisposes to the irradiation of the small bowel, which in the post op period occupies the space previously held by the rectum and, likewise, the risk of post-radiation enteritis is very high in those patients. Under these conditions, the majority of the studies sustain the indication of preoperative radiotherapy in rectal tumours which have a T $\geq$ T3 and without metastases (stages II and III).

For patients in stage IV disease, the indication is established in oncological tumour sessions (oncological committees), according to the predominant symptomatology, radiotherapy not being excluded from the treatment of these patients.

Once neo-adjuvant radio-chemotherapy was included in the treatment protocols it was established that in a number of patients irradiated with the long course schedule of 45 Gy given in 25 sessions the tumour disappears after radiochemotherapy. The number of these patients progressively increased with the improvement of the radiotherapy techniques which currently allow the administration of targeted conformational radiotherapies.

The decrease in the inferior limit of safety after neo-adjuvant radiotherapy has made that the abdominoperineal resection be indicated only in tumours situated under 4 cm from the anal verge. It has now been noticed the situation according to which an increasing number of patients benefit from recto-sigmoid resections, followed by transit reposition with the help of low and ultra-low and colorectal anastomoses. Unfortunately, clinical observations and studies made have lead to the conclusion that more than 60% of the patients with ultra low anastomoses after anterior rectal resections present with anal incontinence of different grades and approximately 30% have very severe forms. These complications are much more intense after neo-adjuvant radiotherapy (3). The risk of anastomotic leakage increases with performing the total mesorectal excision associated with lowering of the anastomotic site and neo-adjuvant radiotherapy. The risk of anastomotic leakage in colorectal anastomosis is 7.8% and perioperative morbidity 33.74% (4). In coloanal anastomoses, 22% of the patients present with 4 or more bowel movements a day, 21% with gas incontinence and 23% with low grade incontinence and 5% with high grade incontinence (5). We also mention that protection ileostomy lowers the severe consequences of the fistulae, but does not lower their incidence.

Starting from those presented above, the complete response to radiotherapy in some patients with rectal cancer and the significant complications of the surgical treatment in rectal cancer, a dilemma has appeared regarding the treatment protocol after neo-adjuvant radiotherapy in rectal cancer.

The first study regarding the non operative approach in patients with completely responsive rectal cancer was performed in 2004 in Sao Paulo, Brazil, by Habr-Gama et al (6). From this study on, which showed good evolution of the patients that did not receive surgical treatment, other studies (2010) (7) were done in the recent years in the intent to establish clinical and paraclinical criteria which would allow efficient patient selection between the group which should receive surgery and between the group which should not, without any negative impact on oncologic safety.

A more recent study performed by Monique Moos et al and published in the Journal of Clinical Oncology in 2011 has done a retrospective analysis between 2004-2009 of a lot formed by 192 patients, out of which 21 (11%) have completely responded to neo-adjuvant radiotherapy. Those 21 patients were not operated on and were on a follow up of around 25 $\pm$ 19 months. The patients were correctly informed on the risks of the evolution of the disease and under these conditions they agreed with this non-surgical approach. Out of this group only one patient presented with local recurrence after 22 months of follow up and needed a recto-sigmoid resection with low anastomosis. In the control group, formed by 20 patients after neo-adjuvant radiotherapy, 5 patients were considered to have completely responded and 15 had residual tumour. All of them were operated on and all of them presented with a series of specific complications, but no patient presented with local recurrence. The conclusion of the study was that in those patients in which the non operative surgery was adopted the oncologic control was similar to that of those who did receive

surgery, but the functional effect was significantly better (8). The inclusion criteria in the group of non operated patients were the following:

- a) Disappearance of the tumour which was initially palpated at the rectal examination
- b) Without any residual tumour or with a small erythematous ulcer or small residual scar at the colonoscopy, but with negative biopsy
- c) Without any suspicion of lymph node invasion at the MRI examination (8)

The results of this study are also mentioned in the NCCN guideline version 2/2015 where there is established as a possible attitude the clinical follow up of the patients with a complete response, but also mentions that neither PET CT, nor MRI could certify the complete response to radiotherapy of the increased lymph nodes from the mesorectum and mentions that this approach cannot be applied routinely. A study which appeared in 2014, authored by Habr-Gama and co., showed that 49% of the patients with distal rectal cancer (T2-4N0-2M0)-which had been previously treated with radio-chemotherapy-presented with a complete response. Those patients were not operated on and were put under clinical follow-up. Out of these, only 31% developed local recurrence, most of them in the first 12 months. Those patients were put under organ preservation treatment with good results (9). Out of this study, one can infer that a consistent number of patients with a distal rectal cancer benefited from complete organ preservation.

In the study performed by us, 9 patients out of the 141 which were given neo-adjuvant treatment have completely responded to radiotherapy which represents 6,38%, a percent relatively small in comparison to the data from other similar studies where the complete response to radiotherapy is more than 25% (10). We have divided these 9 patients into two groups. In the first group we have included the 5 patients, out of which in 4 no tumour was seen after radiotherapy, either through rectal examination, proctoscopy, pelvis MRI and the transrectal ultrasound have not identified any lesions of the rectal wall and neither increased lymph nodes detectable at the MRI examination or transrectal ultrasound. In the second group we have included other 4 patients in which after radiotherapy there were persistent lesions at the mucosal level represented by scars and stenosis. These 4 patients were treated surgically, as they had tumour persistence and they were not further investigated after radiotherapy. As the rectal tumour was at 4 cm or less from the anal verge, they were given abdominoperineal resection. The patients from the first group were not re biopsied because they did not present any mucosal lesion, but, as we have mentioned they received proctoscopy, pelvic MRI and transrectal ultrasound. The patient with increased lymph node in the mesorectum was operated on and the pathology examination confirmed the neoplasm in a lymph node from the mesorectum but without the identification of a remaining tumour at the level of the rectal wall. The other 4 patients, out of which 2 would have needed abdominoperineal resection and the other 2 anterior rectal low resection, after a correct information regarding the possible complications and the possibili-

ties of evolution of the cancer, they chose to renounce at the surgical treatment and to go under clinical and paraclinical follow up.

The most delicate problem in the establishment of this treatment approach is how we manage to evaluate and describe a complete response to radiotherapy. There are studies which state that after radiotherapy, tumour cells were identified in 49% of the patients at 4 cm outside the area of the primary lesion (10). When a small area of ulceration or a scar zone exists after radiotherapy, a biopsy from these areas is compulsory, but when the lesion completely disappears the targeted biopsy is no longer possible. Under these conditions the clinical and paraclinical imagery is very helpful. The CT scan has a 50% specificity due to the difficulties to distinguish between fibrosis and recurrence. MRI has a 73% specificity and the method of MRI-DW (diffusion weighted) has reached a specificity of 90%. PET-CT has an accuracy of 85% in determining the residual tumour and of 65% in identifying the remaining increased lymph nodes (10). Practically, none of the imagistic explorations has a 100% specificity in identifying the tumour, or the remaining lymph nodes. In the study performed by us in a patient which completely responded with a full disappearance of the parietal lesions, MRI has identified a remaining increased lymph node in the mesorectum, which was histologically confirmed postoperatively. The clinical staging is a preoperative evaluation based on clinical and laboratory finding and the information are used for correctly treatment but the pathological staging made after examining the surgical specimen permit the postoperative assessment that brings prognostic information (11). In the 4 patients from the second group, which were operated on without a repeated biopsy the pathology exam did not identify any tumour cells on the surgical specimens. In all these 4 patients abdominoperineal resection was performed.

Taking into account the lack of clinical and paraclinical criteria able to certify the complete response to radiotherapy, one tries to find supplementary laboratory criteria. Therefore, one considers that the decrease in CEA under 0,5 ng/dl after RT would be an important predictor for the complete response (10). The genetic analysis of the biopsied tumour material is important as it identifies genetic mutations in the KRAS and BRAF systems which allow the description of the tumour aggressiveness and also of the treatment possibilities (10).

If we must treat a patient with a KRAS mutation, we cannot use monoclonal antibodies against EGFR and BRAF mutation, which appears in 8-10% of the cases of colorectal cancer, indicates a weak response to chemotherapy (10). Under these conditions, due to the tumour aggressiveness surgical treatment is preferable even in patients with a complete clinical and paraclinical response.

The four patients which were treated without an operation have received chemotherapy for 6 months after radiotherapy and were followed up through controls made every 3 months in the first 2 years and every 6 months in the following 3 years. A patient presented with hepatic metastases 6 months after the completion of chemotherapy and he was given radio-frequency ablation and chemotherapy with a favouring evolu-

tion after 3 years and after that new hepatic metastases appeared for which chemotherapy is currently performed. The other 3 patients had a favouring evolution for 5, 4 and 3 years. Clinical follow up for the patients treated without surgery is very important, the risk for recurrence being bigger in the first 14 months after neo-adjuvant radiotherapy (12). Recurrences occur more frequently inside the lumen, but they may appear as pelvic increased lymph nodes or distance metastases. Likewise, in these patients, every three months, a full clinical evaluation must be completed with the inclusion of the rectal digital examination and CEA every 3 months, and every 6 months colonoscopy, pelvic MRI and transrectal ultrasound, and also thoracic and abdominal CT, must be also performed. The follow up lasts at least 5 years, but practically for any cancer patient, follow up must last during all the patient's life. We did not include in the group of patients treated non-operatively anyone except the patients that after radiotherapy, did not have any lesion at the level of the mucosa, and those that at the MRI and/or transrectal ultrasound did not come with any parietal lesions or remaining increased lymph nodes. There are studies-as we previously mentioned- which included in this group also patients with small remaining lesions (superficial ulceration and induration zones), but with negative biopsies. In which regards the presence of increased lymph nodes before radiotherapy, they could be a contraindication to the non operative attitude, even if after radiotherapy they disappear. The motive is the lack of paraclinical explorations of high specificity in the identification of lymph node recurrence under the conditions in which an endoluminal recurrence is more easily identified (12).

After the analysis of the existing studies out of which some claim the implementation of the non-operative attitude and others claim that there is not enough clinical evidence for that (13), we consider that, in order to apply that non surgical treatment method, the patient must meet the following criteria:

- a) the absence of the lesion at the mucosal level after radiotherapy or the presence of a small ulceration with a negative biopsy;
- b) the patient must not present with increased lymph nodes of a malignant aspect in the mesorectum before radiotherapy;
- c) CEA <0,5 ng/dl after radiotherapy, a useful aspect in patients in which CEA was greater before radiotherapy;
- d) the lack of KRAS and BRAF mutations;
- e) the absence of the wall lesions and increased lymph nodes at the MRI examination and transrectal ultrasound.

Conclusions

1. Clinical follow-up in patients with a complete response to radiotherapy is a good option, as it protects the patients from the frequent complications of low, ultralow and coloanal anastomoses and also from the disadvantages of abdominoperineal resection.
2. In order to apply this attitude, it is compulsory to respect the selection criteria of the patients-as it was

presented above-in order to perform a more correct and aggressive follow up.

3. The follow up must include: clinical examination, rectoscopy and biopsy in patients with small ulcerations or small scars at the level of the mucosa, pelvic MRI and transrectal ultrasound performed periodically in the first 5 years at the same time with the rest of the biological and imagistic explorations included in the follow up protocols of the patient with rectal neoplasms.
4. The decision to establish this attitude must be made by taking into account the patient's opinion, as he must be correctly informed regarding the complications of the surgical treatment, but also on the possibilities of evolution of the neoplasm.

Conflict of interest and source of funding

No conflicts of interests are declared.

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