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Preoperative Radiotherapy in Rectal Cancer Treatment - is it Really a Golden Standard?*

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Rezumat

Radioterapia pre-operatorie în tratamentul cancerului rectal - indicație de principiu?

Iradierea pre-operatorie a tumorilor maligne ale rectului a fost considerată ca având o importanță similară cu excizia completă a mezorectului (TME) în managementul terapeutic al acestei afecțiuni. În ultimii ani, referitor la această strategie s-au formulat numeroase puncte de vedere critice. Am analizat cele 2 obiective ale iradierii pre-operatorii: posibila prezervare a sfincterului şi conversia unor tumori inițial nerezecabile într-unele posibil de rezecat, pe un material clinic constituit de 31 de pacienți consecutivi, operați în clinica noastră. La 20 dintre aceştia, s-a aplicat pre-operator radio- sau chimio-radioterapie; la ceilalți 11, atitudinea terapeutică a constat în intervenție chirurgicală inițială, urmată de iradiere post-operatorie. Tehnica a cuprins excizia completă a mezorectului la 30 de pacienți, în cadrul unei rezecții colo-rectale anterioare, în 13 cazuri sau a unei amputații de rect pe cale abdomino-perineală, la 17 bolnavi. Rezultatele au arătat că iradierea pre-operatorie reduce rata recidivelor locale, dar nu influențează rata de supraviețuire. Totodată, trebuie menționate numeroasele efecte adverse ale iradierii: enterite şi cistite radice, întârzierea vindecării plăgilor perineale şi creşterea incidenței fistulelor anastomotice. Concluzia la care am ajuns este în favoarea iradierii pre-operatorii selective, pentru tumori în stadiul T4 sau T3 - cu invazia fasciei mezorectului demonstrată de RMN, în cazurile cu posibilă invazie ganglionară, ca şi pentru tumorile localizate distal.

Cuvinte cheie: cancer de rect, iradiere pre-operatorie

Abstract

Preoperative radiotherapy in the treatment of rectal cancer was thought to be an achievement of similar importance to total mesorectal excision (TME), for the therapeutic management of rectal malignancies. However, numerous criticisms have been discussed in this field lately. We have analysed the two main purposes of preoperative radiation: possible sphincter preservation and the conversion of a non-resectable tumor into a resectable one in a series of 31 consecutive patients, operated in our clinic. In 20 of them, preoperative radio/chemoradiotherapy was applied, while 11 patients were firstly operated and then irradiated. The surgical procedure included total mesorectal excision in 30 patients, as part of a low anterior resection, in 13 cases and of an abdominal perineal resection, in the other 17 cases. We have found that preoperative radiotherapy improves the local recurrence rate but has no influence on the overall survival rate. However, we should not overlook the adverse effects of this method: toxicity of radiotherapy on the small bowel and the urinary bladder, the healing of the perineal wounds and the risk of anastomotic leaks. We concluded in favor of elective preoperative radiotherapy in selected cases: any T4 tumors, T3 tumors which threaten the mesorectal fascia on MRI, whenever there is a suspicion of nodal involvement and also for very low tumors.

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Key words: rectal cancer, preoperative radiotherapy

Introduction

Since 1979, the total mesorectal excision (TME) described by Heald (1) has become the golden standard of effective radical cancer surgery and it is unlikely that a significantly improved technique should be developed in the upcoming years.

Preoperative radiotherapy (RT) in the treatment of rectal cancer was thought to be an achievement of similar importance, but numerous criticisms have been mentioned in this field. The past two decades have brought significant changes to the practice of radiation oncology for rectal malignancies (2).

The question which we try to answer in the following article is if RT is really a golden standard in the management of rectal cancer or it should rather be considered an elective strategy.

Materials and Methods

We have retrospectively analysed a series of 31 consecutive patients with rectal cancer, which were admitted to the Surgical Clinic "I. Juvara" of the Clinical Hospital "Dr. I. Cantacuzino" from Bucharest, between 2009 and 2012. Among them, 20 patients (group 1) received preoperative chemoradiotherapy (CRT)/ RT alone, while the other 11 (group 2) were firstly operated and then irradiated. The age varied between 38 and 79 years in group 1 and from 50 to 72 years, in group 2.

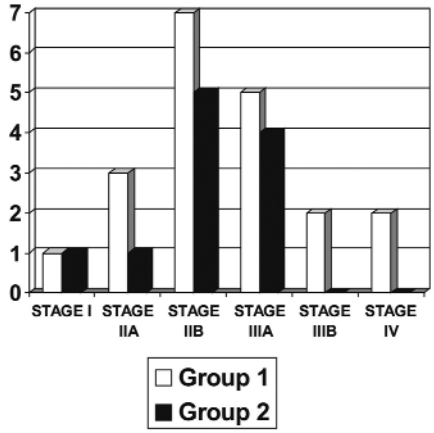
Preoperative assessment included abdominal ultrasonography, standard chest radiography, colonoscopy and MRI/CT.

The tumoral staging was different for the 2 groups, as expected. The patients in group 1 were mainly stage II or III (17 of 20 patients), while those included in group 2 were stage I or II (7 of 11 patients) and only a few of them (4 of 11 patients) were stage IIIA. The tumoral staging is presented in *Graphic 1*.

In the first group of patients, which received neoadjuvant therapy, 8 of them were irradiated, with doses of 25 x 2Gy, then 5-FU was administrated. In the other 12 patients RT alone was selected; in 10 cases long course RT, 20-28 x 2 Gy and in 2 cases short-course RT, 5 x 5 Gy. The decision of whether patients should receive or not additional chemotherapy was according to the oncologist's clinical judgement.

The interval between neoadjuvant therapy and surgery was 4 to 9 weeks, after long-course RT and 10 to 12 days, after short-course RT. As an exception, one patient with stage IV rectal cancer was operated only after 2 years.

The results of neoadjuvant treatment were encouraging. Among the 20 patients from group 1, in 17 cases we noticed a significant or moderate downsizing of the tumor, while 1 patient had complete clinical remission. In 2 patients, both with stage IV disease, no noticeable effect was obtained.



Graphic 1. *Tumoral staging*

The technical procedure included a total mesorectal excision (TME) in all but one of all the patients. In 17 cases an abdominal perineal resection was performed, while in 13 cases a low anterior resection followed by an anastomosis was possible. In the 31st case, a Hartmann procedure was done (3). Among the 13 patients with anastomoses, these were protected in 8 cases, using virtual colostomy, in 2 cases, lateral ileostomy in other 2 cases, while in 4 cases a transanal decompressive tube was maintained for 4 or 5 days after surgery.

Results

There were no anastomotic leaks among the 13 patients who underwent a low anterior resection, followed by an anastomosis. Postoperative complications included 2 cases of postoperative small bowel obstruction after abdominal perineal resection, one for each group and 1 case of prolonged perineal wound dehiscence (group I), after long-course RT (*Fig. 1 A,B*).

Follow-up included only 18 of the 31 patients; this is one of the most important limits of our study. Among the 20 patients in group 1, 13 patients were followed for different periods of time, which varied from 6 to 37 months; the median was 14 months. In group 2, 5 of the 11 patients were followed for 9 to 65 months, with a median period of 49 months. We did not notice any local recurrences in both groups, according to these available data.

In group 1, multiple hepatic and pulmonary metastases were diagnosed in 1 patient, who received palliative chemotherapy. Pulmonary metastases which occurred in another patient, from group 2, were surgically resected.

We found no significant differences between the two groups regarding postoperative and long-term evolution, according to our available data. Preoperative RT/CRT achieved the aim of downsizing the tumor in 18 of 20 patients, who had a significant or moderate therapeutic response. Surgical procedure thus became possible or was facilitated, but no sphincter-saving procedure was made possible by preoperative RT/CRT itself.

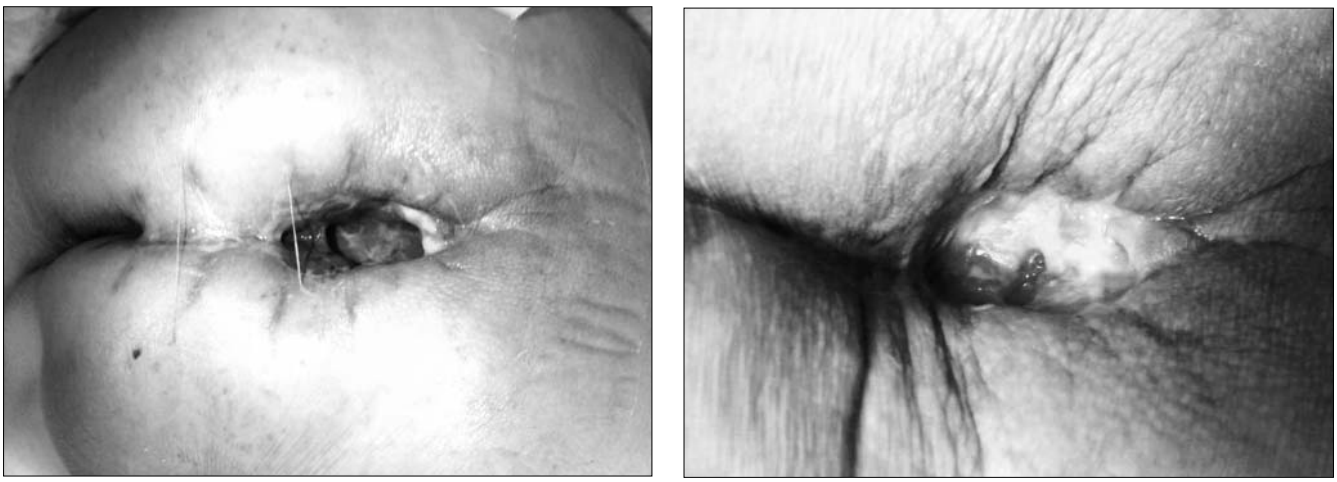


Figure 1. ***(A, B)*** *Perineal wound dehiscence after APR with resection of the coccyx, following long-course RT- 2 months and 5 months after surgery*

Figure 2. ***(A, B)*** *Radiation enteritis: intra-operative aspect and the surgical specimen*

We did not notice any adverse events of radiation in this series of 31 consecutive patients. Still, 1 patient, who was not included in the study, developed a severe radiation enteritis, which led to a perforation and generalized peritonitis (*Fig. 2 A,B*).

Discussions

According to Keighley and Williams, RT is indicated in the therapeutic management of rectal cancer in 5 circumstances: as a primary treatment - endocavitary radiation; as neoadjuvant /adjuvant therapy; for downsizing the tumor in order to facilitate surgery; as intraoperative RT and as a palliative technique (4).

The main advantage of endocavitary therapy is the fact that radiation is delivered mainly to tumor tissue in higher dose. The disadvantages and limits are related to the need of a careful selection of patients: the tumor must not be too large, as each field of irradiation is only 3 cm in diameter; it should be well-differentiated and the surrounding rectal wall must be intact. Tumors projecting into the lumen are more suitable for this method. These are mainly the same patients who could be satisfactorily treated by local excision, so the advantages of endocavitary radiation are not so obvious (5).

Neoadjuvant or adjuvant RT represents the main issue of this paper. In the past two decades, a large number of opinions and indications have been stated, which have been changed or adjusted many times. In 1990, the NIH Consensus Statement noticed that there appeared to be a significant decrease in local recurrence rates in patients receiving moderate to high dose (>35 Gy) preoperative irradiation, usually without any impact on survival. The necessity of RT for survival benefits was not convincingly demonstrated. Thus, adjuvant treatment of stage II rectal cancer was recommended, while no adjuvant therapy was recommended for stage I patients (6).

Ten years after, an important clinical experience had been accumulated and analysed. It became clear that pelvic recurrences arise from tumor clonogens residual beyond the

surgical margins. After a dose of more than 44 Gy, there appeared to be little chance that the surviving tumor clonogens could regrow to a metastasis-yielding volume (7).

Two important rectal cancer trials have been published. Swedish Rectal Cancer Trial stated that preoperative RT reduced rates of local recurrence and significantly improved survival among patients with resectable rectal cancer (8), while according to Dutch TME Trial, preoperative RT reduced the risk of local recurrence in patients with rectal cancer who underwent a standardized total mesorectal excision (9). Both trials found the same results regarding local recurrence rate; the survival improvement was noticed only by the Swedish Trial, while the Dutch Trial did not mention it. The latter seemed to be more believable, because it was more homogenous, as it included only those patients who actually underwent a total mesorectal excision (TME).

In 2008, there seemed to be strong evidence that in patients treated by preoperative radiation, both the size of the primary tumor and the number of involved lymph nodes decreased. The downgrading varied with the dose of radiation used. It was also accepted that preoperative treatment reduced the rate of pelvic recurrence and was more dose efficient than the postoperative one. However, there was little evidence of any improvement in survival, with the exception of patients with involved lymph nodes, in whom the survival rate was higher after irradiation (4).

Nowadays, it is accepted that outcomes vary significantly according to the stage of disease. All patients should be stratified into low, moderate and high-risk disease, according to high-resolution MRI findings. The aim is to reduce overtreatment of patients at moderate risk and also to intensify procedures for those with high-risk disease, in order to reduce distant failure rates and improve survival (10).

Patients with low-risk tumors are those with no evidence of either extramural spread or nodal involvement and with proximal location in the rectum. They should be operated at once, because a R0 resection is almost always possible and immediate surgery is often reasonable. When unanticipated lymph node involvement is detected at surgical pathology, postoperative radiation is indicated.

Patients with high-risk tumors are those with distal tumor location, requiring an abdominal perineal resection, threatened radial margins or T4 tumors. In these cases, preoperative chemoradiation is essential. Also, some high-risk patients are those with bulky T4 or nodal disease, in whom preoperative systemic therapy followed by preoperative chemoradiation and then surgery may be the optimal approach (11).

One of the main disadvantages of RT is the large number of severe adverse events, which may occur many years after the procedure. Wound infections and perineal wound dehiscence are more common in irradiated patients (12), as well as skin reaction (with an incidence of up to 86.7%), radiation cystitis (34.6%), proctitis (89.2%) and enteritis (33.6%) (13). The development of nonantibiotic-associated pseudomembranous colitis, caused by Clostridium difficile, which represent nowadays a serious public health problem in hospitalized patients, has also been diagnosed (14).

One of the main disadvantages of neo-adjuvant therapy is that it represents one of the strongest risk factors for anastomotic dehiscence. Anastomotic leakage after colorectal resection is a serious complication, which is reported to have a significant mortality (6%-22%) (15).

There are many data in the medical literature and some of them are quite divergent. We tried to summarize the facts and we found that 4 issues seem to be of a certain importance.

First of all, the interval between neoadjuvant RT and surgery should be greater than or equal to 8 weeks. This delay has decreased postoperative complication rate and it also significantly increased rate of nodal downstaging, which is associated with a higher rate of pathologic complete response and decreased local recurrence (16,17).

An exciting question is the choice between pre- or postoperative RT. It has been noticed that in patients with clinical stage T3 or T4 or node-positive disease, postoperative CRT, as compared with preoperative CRT, reduced local control, increased toxicity and had no significant difference regarding overall survival (18). Another study, which was based on a follow-up period of 11 years, has found persisting improvement on local control after pre- versus postoperative CRT (19). The conclusion is that pre-op CRT is more efficient, less-toxic and more dose-efficient than the postoperative method.

A significant exception is represented by lymph node-positive patients, in whom overall survival was higher among those receiving postoperative chemoradiation, compared to the preoperative one. This is the reason for which stage III rectal cancer patients with persistent pathologic lymph nodes represent a high-risk group, in which postoperative chemoradiation is strongly recommended (20).

The question of short-course (5×5 Gy) versus long-course conventional RT (1.8–2.0 Gy×25–28) has not yet been settled. There seems to be no difference in local recurrence rates and disease-free overall survival. Both options, short-course and long-course, are considered valid (21).

Finally, the association of chemotherapy has been widely analysed. It has been proved that preoperative CRT improves local control, but it also moderately increases acute toxicity and has no significant impact on overall survival rate (22). Another study noticed that chemotherapy, administrated before or after surgery, has an important benefit with respect to local control, but no significant effect on long-term survival, neither on sphincter-preservation rate (23). We may conclude that the gains from the chemotherapy addition are limited and come at a rather high price.

RT is also indicated for tumor downsizing to facilitate surgery. The main objective is to convert a non-resectable tumor to a resectable one, by achieving non-involved circumferential margins, thus making a sphincter preservation procedure possible. A much narrower margin distally is accepted nowadays: a 5-10 mm margin is considered a curative procedure, if a stapled anastomosis is performed (24). The current view is that CRT should be given to all T3 tumors

which threaten the mesorectal fascia on MRI and also to all T4 tumors (25).

The results that have been obtained are quite encouraging. In locally advanced rectal cancer, preoperative CRT induces significant tumor downstaging. T downstaging was mentioned in up to 44% of the patients, N downstaging in up to 68% of cases, while the percentage of global downstaging (T or N) was up to 82%. The conclusion was that CRT significantly increases the rate of sphincter preservation, although the rate of surgical complications such as anastomosis stenosis and fistula formation is relatively higher (26).

Preoperative RT improves local disease control and possibly overall survival in rectal cancer. Still, predictive markers for a positive response are currently unavailable. A solution may be provided by genetic diagnosis. Not only rectal cancer, but also its radiation sensitivity may be determined by protein encoding genes. A key-role may be held by microsatellite instability in the DNA damage response pathways. It has been suggested that the assessment of microsatellite instability in tumor biopsies from colonoscopy may hold the answer not only to the patient prognosis, but also to their sensitivity to radiotherapy (27).

Intraoperative RT is highly indicated, especially in patients with primary or recurrent tumors that are difficult to resect due to severe invasion into adjacent organs. It allows precise application of a high radiation dose with minimal exposure of the surrounding organs at the time of an operation. Adding this technique to preoperative or postoperative CRT, it will increase the local control rate, without major complications. The main target is clinical T3-T4Nx rectal cancer, in which the method significantly reduces local recurrence and improves prognosis, also improves the feasibility of sphincter-preservation, in combination with preoperative RT and oral chemotherapy (28).

RT is indicated as a palliative technique, in patients who present with locally advanced or recurrent disease with bleeding or pelvic pain, secondary to involvement of nerve structures within the pelvis, or from involvement of the sacrum. RT (from 20 to 60 Gy) can provide relief of pain and bleeding in 75% of patients, for a median duration of 6-9 months. The method does not confer a survival benefit and should be used for palliation of symptoms in patients with short life expectancy (6 months) (29).

In patients with a pelvic mass (recurrence of rectal cancer) who underwent radiotherapy, symptom palliation was obtained in 80% of the cases; the median symptom control duration was five months. Improvement of symptom control rate and duration requires a dose higher than 40 Gy. Considering the low morbidity and the improved symptom palliation, palliative RT might be considered a safe and efficient method (30).

Conclusions

Preoperative RT or CRT significantly decrease recurrence rate, but have no influence on overall survival. Prolonged CRT and delayed surgery may facilitate sphincter saving procedures. However, the incidence of anastomotic leakage is also higher in these patients, so the protection of these anastomoses is mandatory.

Acute and late adverse events of RT can be severe and may appear many years after the procedure. It is essential that every patient should be assessed individually.

All these taken into consideration, our option is in favor of an elective preoperative RT in selected cases. These are: T3 tumors which threaten the mesorectal fascia on MRI, all T4 tumors and also those cases in which there is a suspicion of nodal involvement, according to the findings of endo-rectal ultrasound, CT or MRI. Very low tumors are also highly indicated for RT, because they do have a significant therapeutic response. The advantages and disadvantages of RT should be further considered.

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