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Rectal cancer: Which patients benefit from radiotherapy

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The prognosis of patients with rectal cancer has improved in recent years, particularly as regards the lower probability of local recurrence. These positive results are obtained through correct preoperative staging and an adequate surgical resection of the affected lesion, as well as a multidisciplinary therapeutic approach. Based on the available scientific evidence, our aim is to clarify the framework in which options for the right therapy can be taken, especially in relation to the preoperative staging and its limitations, with regards to radiotherapy and its indications. We also emphasize the need of a tailor-made approach for each case.

Cáncer de recto: qué pacientes se benefician de la radioterapia

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R E S U M E N

El pronóstico de los pacientes con cáncer de recto ha mejorado en los últimos años, sobre todo en relación con la menor probabilidad de recidiva local. Estos resultados se consiguen con una correcta estadificación preoperatoria, una adecuada escisión quirúrgica de la lesión y un abordaje terapéutico multidisciplinar. Basándonos en la evidencia científica disponible, nuestro propósito es tratar de clarificar el marco en el cual se toman las decisiones terapéuticas, especialmente en relación con la estadificación preoperatoria y sus limitaciones y con el tratamiento con radioterapia y sus indicaciones, así como resaltar la necesidad de un enfoque individualizado en cada caso.

Rectal cancer and local relapse

In spite of sharing a similar biological behaviour with colon cancer, rectal cancer has always had the worse prognosis of the two.[1] This is based on the special anatomical characteristics of the area where these tumours occur and the difficulty that they present for R0 resection.

In recent years, considerable effort has been put into reducing the probability of local relapse in two different aspects: improving surgical technique by introducing the concept of total excision of the mesorectum[2] in order to

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obtain peripheral margins free of tumours,[3,4] and improving diagnostic methods in order to increase the precision of preoperative tumour staging.[5]

Optimal preoperative staging is the basis for successful treatment. The objective is to distinguish in which cases it is possible to achieve a R0 resection using only surgery and in which cases it is not. When the local extension of the tumour indicates that obtaining a surgical specimen with free margins would be impossible, patients must receive a preoperative treatment with the intent of achieving tumour regression, thereby facilitating an R0 resection and minimizing the risk of local relapse.[6,7]

Preoperative radiation therapy is the initial treatment of choice in cases of locally advanced rectal tumours,[8-10] generally accompanied by systemic treatment with chemotherapy.[11] Patients under this type of treatment have reduced probabilities of local relapse,[12,13] but irradiation of the pelvic area is not without its risks. Problems arise such as erectile dysfunction, loss of fertility, retroperitoneal fibrosis, and secondary urethrohydronephrosis, and even renal failure, radiation enteritis/cystitis, and decreased pelvic bone hematopoietic function, as well as decreased functionality in defecation and delayed healing of perineal injuries, among others, and are all related to the radiation dosage and techniques applied.[14,15] In the case of postoperative radiation therapy, efficiency is reduced and these problems are magnified as a consequence of the increased probability of small intestine loops affixed to the pelvis from surgical adherences, and thus included in the area exposed to radiation[16] (although some techniques do reduce this risk, they do not eliminate it). Without a doubt, these secondary effects of radiation therapy can determine the future of the patient.[17]

As a result, our obligation is to use radiation treatment in all patients that would benefit from it, and to avoid it when no improvements are foreseeable over the initial surgical results. However, this objective is currently difficult to achieve using the diagnostic methods presently available. We should present ourselves with the objective of reducing the minimum number of undertreated and overtreated patients using the available evidence in each case.

Preoperative staging

We have pointed out the importance of a preoperative assessment of the local extent of the tumour in order to decide whether or not an R0 resection is feasible. As we mentioned before, the problem lies in the reliability of imaging methods available for tumour staging. Endorectal ultrasound allows for a higher precision in evaluating the level of penetration of the rectal wall, discriminating between T1, T2, and T3.[18] However, in the case of T3 tumours, this method does not allow for an evaluation of the distance of the tumour from the mesorectal fascia. NMR imaging facilitates a clear picture of the difference between tumour and muscle tissue, as well as the distance between the tumour and the mesorectal fascia with high precision (in the study by Mercury, the anatomopathological exams produced a 92.5% of positive correlation with T).[19,20]

The prediction provided by NMR for damage to the rectal circumferential margin caused by the tumour has been related to a higher probability of relapse.[21] Following the recommendations by Quirke et al,[3] any specimen with a tumour 1 mm or less from the circumferential margin is considered a positive margin. However, recent data from a randomized prospective study[10] widened this “positive margin” group (that is, those with an elevated risk of local relapse) to include all those in which a tumour is identifiable (primary tumour or lymph nodes with metastasis) within 2 mm of the rectal circumferential margin. Thus the ability to reliably evaluate this state using NMR with anticipation is a key management tool in these patients.

However, as the previous mention of lymph nodes with metastases asserts, one factor distorts the decision making process, making the evaluation more difficult: the N factor. The reliability of radiological tests for identifying affected lymph nodes does not compare with the reliability in T assessment. A recent study[22] indicated that the use of specific contrasts could increase the capacity of NMR for discrimination between mestasized lymph nodes and non-tumour lymph nodes. However, although it is probable that substantial advances in this field will be made in the future, thereby creating ever more precise preoperative staging, we must say that currently, the clinical applicability of these advances must be ascertained through additional studies. For example, another study[23] estimated that around 22% of patients treated with neoadjuvance and preoperatively staged as T3N0 presented affected lymph nodes in the postoperative anatomopathological study. This is an excessively high rate, which puts in doubt the convenience of making a therapeutic decision based on NMR results.

However, these data would need to be qualified. Perhaps a considerable portion of these 22% would have received neoadjuvant treatment due to other factors. The deeper the penetration of the tumour into the rectal wall, the higher the risk of metastasized lymph nodes. Although this study does not specifically mention such information, the extrapolation of data from other studies[24] indicates that up to 50% of T3 could have positive margins according to the previously mentioned criteria, and this subgroup will have a higher risk of lymph node metastasis. Thus, of these 22% patients with preoperatively undetected affected lymph nodes, probably over half are treated with neoadjuvance based on T: thus the patients would not be undertreated. Similarly, another study[10] indicates that of all stage III patients, 25% of positive margins are determined by the damaged lymph nodes in relation to the mesorectal fascia. In the study we have made reference to, the position of the affected lymph nodes with relation to the mesorectal fascia was not described. Considering this factor, perhaps an important percentage of these lymph nodes are over 2 mm from said fascia, with the consequent low risk of local relapse that these cases produce, as well as the poor results from radiation therapy.

Although it is true that the application of new diagnostic techniques will increase performance and reduce the number of under-staged patients,[25,26] we currently cannot aspire to achieve the same results in detecting affected lymph nodes as far as T. In any case, we must be conscious of the fact that

under-staging, and thus under-treating, are ever-present risks. It is our obligation to reduce them to a minimum. However, the opposite risk is also real: as we have seen, radiation therapy has severe, and often lethal, secondary effects. As such, avoiding over-treatment should also be a major preoccupation. We might never achieve a complete reduction of either extreme.

The role of radiation therapy in rectal cancer treatment

We have no other option but to use the available evidence for making the most favourable decision for the patient, and this information has its limits.

Between 1980 and 1993, the Stockholm I and II projects were developed. They demonstrated a reduced probability of local relapse when conventional surgery without TME was used in addition to preoperative radiation therapy.[27] When the same study was continued later, the TME technique was included, and results improved with respect to local relapse and the group receiving conventional surgery.[28]

With the advent of the total mesorectal excision technique, truly low levels of local relapse were achieved. Local relapse rates following resections as low as 9% have been described in past studies using the marginal form of preoperative radiation therapy, and this in a time when the common experience with preoperative staging lacked the reliability of current methods.[29] The experience from Norway has provided the idea that these levels can be obtained by minimizing the use of radiation therapy, reserving it for those patients with severe risk of presenting positive margins following surgery.[24] A study performed by the Dutch Colorectal Cancer Group[30] attempted to clarify the role of radiation therapy in this context. Candidate patients with rectal cancer were randomly assigned to different treatment groups without discriminating based on functional state: one included preoperative radiation therapy, and the other was exclusively surgery. The group that received preoperative radiation therapy followed by TME showed consistently better results on a long-term basis (mean follow-up period of 6 years) for local relapse than the group that only received surgery. The presence of an incompletely extirpated mesorectum in almost 24% of the patients in this study may have influenced these results.[31] The authors suggest that this difference is produced at the expense of stage III patients, finding no significant differences between stage I and II patients. It remains unclear whether or not this last piece of information could be affected by the small sample size in each subgroup. As such, T3 and T4 patients with no affected lymph nodes, under this data set, would not benefit from preoperative radiation therapy. From this point of view, the recommended practices from treatment guides[32-34] do not follow the evidence from this study, given that the norm in this subgroup of patients is to apply preoperative radiation therapy. On the other hand, if we consider the global dataset, without differentiating by stage, and apply its conclusions, we would be administering preoperative radiation therapy to T1 and T2 patients without affected lymph nodes, which is not recommended nor in line with normal practice. The absence of data on the different levels of tumour penetration in patients with positive lymph nodes impedes the evaluation of differences in local relapse rates between the two arms of the study, as applied to T1, T2, or T3 (and, even more, to the distance between the tumour and the mesorectal fascia, further subdividing the T3 cases). The MRC CR07[35] study shows results that are superimposable with the previous study and that advocate the use of postoperative radiation therapy in previously untreated patients with appreciable positive margins. At the same time, the majority of these patients with positive margins could have been identified before surgery, and thus could have perhaps taken benefit from the more effective preoperative radiation therapy. For the rest, the same considerations with respect to discrimination based on T that worried us in the previous study apply in this case as well. In a separate prospective study,[36] radiation therapy (in this case postoperative) did not improve the results of corrective surgery in patients with T1 and T2 tumours with affected lymph nodes, although the subgroup of patients with T3 tumours separated from the fascia was not analyzed.

In the same context, we must point out that postoperative radiation therapy is the recommended practice in cases of patients that have previously been classified as stage II (and as such have not received neoadjuvant treatment) but that the postoperative exam shows to be stage III. However, the MRC state is not taken into account in these cases. There is no evidence that radiation therapy provides a positive effect that cannot be achieved using corrective surgery in T1, T2, or even T3 cases with positive margins. Only if the affected lymph nodes reside in the mesorectum (although habitual discrimination in anatomopathological reports between lymph nodes in the mesorectum, mesosigma, or root does not prove to be practical) and close to the margin the use of radiation therapy would be justified, given the increased risk of local relapse in these cases.[10] As we previously indicated and as has been presented in both prospective and retrospective studies,[10,37] when the affected lymph node is greater than 2 mm in distance from the fascia, the risk of local relapse is low.

When the tumour affects the lymph nodes, it appears that we must not only trust in a surgical approach, given that the disease has a systemic component that must be treated with chemotherapy. However, in light of the previous arguments, we must conclude that the presence of affected lymph nodes does not always require a radical local excision. Given that the objective of radiation therapy is to reduce the probability of local relapse,[38] it is improbable that these patients would benefit from its application.

Based on this information, the work of the attending pathologist is key. The effort put into localizing the lymph nodes, specifying whether they are lymph nodes situated in the meso-interperitoneal space or mesorectum (lymph nodes above or below the peritoneal reflex), and, in this last case, affirming its relation with the mesorectal fascia have the reward of a more precise evaluation of the risks the patient must run.

As we can see, the problem that is presented upon attempting to reach a precise preoperative diagnosis and indications for an effective treatment does not have a simple

answer. Faced with this situation, the goal is not so much to create a whole new proposal, but rather to bring into our environment the experience that, throughout the years and in a very consistent way, has shown that obtaining good results in local relapse and survival is possible.[39] Thus we can avoid the use of radiation therapy in T1 and T2 tumours, since a corrective surgery should be enough to obtain an R0 resection. Experience indicates that the same results can be reached in T3 patients where the tumour is at least 2 mm from the fascia[39] (this being highly reliable information). In the rest of T3 patients and in all T4 patients, the application of preoperative radiation therapy appears to be required, with the goal of reducing the size of the tumour, avoiding the presence of positive circumferential margins, and increasing the probability of obtaining an R0 resection.[40]

When we speak of stage III patients, the level of lymph node involvement complicates the decision-making process. Firstly, as we have already discussed, identification presents a difficulty. Secondly, radiation therapy could have a positive impact on lateral pelvic lymph nodes that are not included in the TME resection,[41] which could sterilize them, explaining the improved results from this type of treatment as opposed to the results without radiation therapy (although the experience with results from lateral pelvic lymphadenectomy in Japan is distinct from the European one). However, with respect to T, it is doubtful that in patients with affected lymph nodes and T1/T2 tumours, and as we have seen, even T3 removed from the fascia at least 2 mm, the use of radiation therapy will provide real benefits, except for those cases in which the lymph node is dangerously close to the fascia. The capacity to measure the presence of affected lymph nodes with precision is a key diagnostic tool. However, as we have already indicated, the percentage of patients in which this is the determining factor for affected circumferential margins and thus, indicates the need for radiation therapy, is probably quite low.

On the other hand, as we have already pointed out, even at centres with specific specializations, it is not always easy to obtain a complete excision of the mesorectum.[31]

In this sense, perhaps radiation therapy could compensate for such difficulties. Each centre should continually review these aspects of their practice and decide through their analysis how to maintain a minimal risk of under-treatment.

Radiation therapy in conservative treatment of rectal cancer

Another specific field of rectal cancer surgery exists in which radiation therapy plays an important role. With the development of transanal endoscopic microsurgery in early stages, the indications for conservative surgery have increased. Local excision of even T2 and T3 tumours implicates a certain risk of the presence of lymph nodes affected by the tumour that may not be surgically removed. The recommendation for select cases is the application of pelvic radiation therapy, which in this context could contribute to improved surgical results, even more evident if used preoperatively.[42,43]

The existence of complete clinical responses to chemo/radiation therapy is well known.[44] This fact has opened the door for the "wait and see" mentality, in the sense of not performing surgery on the subgroup of patients that have responded positively to treatment. This is an attitude that is little accepted today for most patients, but that, in any case, opens possibilities to those who refuse intervention or are not in any condition to withstand it. Perhaps the more efficient radiation and chemotherapy techniques developed in the future will expand the options available under this attitude.

The future of staging

It is possible that in the near future, data that differ from those presented (T) will contribute to the decision-making process with these patients. In this sense, efforts are being made in various fields. One of these is the use of PET/CT for measuring metabolic activity in relation to the response to neoadjuvant treatment, and the ability to discern which patients would benefit from treatment and which would not.[45] Another is molecular marker analyses that allow for the identification of patients that present tumours with higher aggressiveness and risk of relapse, or of those tumours that might respond better to radiation therapy.[46] However, the clinical applicability of these efforts is not well developed, and no clear course of action is available yet based on the criteria that arise from these efforts.

It is also likely that the techniques for administering radiation therapy will also evolve in the future. The role of intraoperative radiation therapy, as well as endorectal brachytherapy at high doses will undoubtedly play a role in this development.

After our analysis of the preceding information, we have compiled some doubts as to the suitability of current practices for radiation therapy, hoping to perhaps limit its use to those cases with high risk of positive margins in order to better treat our patients. Without a doubt, new studies are needed to resolve doubts that currently arise as to which the ideal treatment is based on the characteristics of each patient. As we have insinuated, new tools will aid in this process. However, today we must appreciate the limitations of the studies currently available and be conscious of the decisions we make, as there will always be a margin of error. Our objective will be to minimize this margin, and we hope that the analysis of our data and reflection on the subject will help us to do so.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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