10. The role of radiotherapy in colorectal cancer

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Abstract. The optimal management of CRC today requires a multidisciplinary approach that integrates gastroenterologists, radiologists, pathologists, surgeons, medical oncologists, and radiation specialists. Although surgery remains the mainstay of treatment, the rate of local recurrence in rectal and rectosigmoid junction cancer is more than negligible. Both EBRT and chemotherapy, therefore, play fundamental roles in increasing the rates of both local control and OS of this disease. This chapter attempts to clarify the current status of EBRT with or without chemotherapy in rectal and rectosigmoid junction cancer, based on scientific evidence.

Introduction

CRC is one of the most common cancers in Spain and also in the world, but this term includes two diseases that share aspects such as etiology, diagnosis, pathology, and treatment of metastatic disease, but that differs significantly in the treatment of localised disease, locally advanced disease, and locoregional recurrences rates.

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The rectum is considered to range from the last 12-15 cm of the most distal intestine to the anus, although no anatomic definition is uniformly accepted because of constitutional differences by age and sex. It is considered that the rectum ends at the dentate line, 1-2 cm below the anorectal ring.

The mainstay of treatment remains surgery, achieving cure rates of approximately 50% (1). The anatomical location, however, determines the natural history of the disease, with a greater propensity for local recurrence, which entails a different therapeutic approach than its counterpart in colon cancer.

Rectal cancer thus tends to present two patterns of recurrence after surgery with curative intent. One pattern, which is shared with colon cancer, is the appearance of distant metastases in 25% of cases, and the other pattern is pelvic-presacral recurrence (25-30%) (2) that is mostly exclusive to rectal cancer.

Rates of recurrence vary also according to the series evaluated; some studies report numbers of local recurrences of 10-20% in T3-T4 (3) and up to 50-60% in patients with positive nodes (N) (4). This pattern of recurrence is a serious problem because it has a negative impact on OS and also causes a significant deterioration in the quality of life (QOL). Approximately 70% of patients have symptoms of pelvic relapse resulting from the infiltration of vascular structures, nerve plexus, soft tissues, or bone structures. Most cases manifest as bleeding, neuropathic pain, infection, etc. The usefulness of cancer treatments in these patients is limited by the high morbidity associated with the treatments.

Numerous efforts have been made to prevent local recurrences. The root cause is postulated to be the lateral growth of malignant cells incompletely removed at surgery. The introduction of total mesorectal excision (TME) as a surgical technique has reduced rates of local recurrence up to 5% at 5 years (5). During the past decades different treatment modalities have been examined such as postoperative chemoEBRT with different 5FU based schedules, preoperative EBRT short course and long course alone or in combination with 5FU based regimens or even with new drugs and intraoperative radiation therapy (IORT). This chapter aims to update the treatment of rectal and rectosigmoid junction cancer by focusing primarily on treatment with EBRT.

1. Techniques and dose fractionation

External-beam radiation therapy (EBRT) in rectal cancer should include the primary tumour and regions of draining lymph nodes of the pelvis. Correct and optimal planning of treatment is required to minimise the dose to organs at risk, thus limiting toxicity to the patient.
The superior port edge is placed at the L4/L5 interspace usually in the mid-L5 vertebral body. The distal port edge should be 5 cm below palpable tumour for patients receiving preoperative treatment.

For postoperative cases the distal port edge is about 5 cm below the best estimate of the preoperative tumour bed and (if an abdomino-perineal has been performed) below the perineum. Anterior and posterior portals must have at least a 1.5-cm margin on the pelvic brim. Lateral treatment portals should encompass the entire sacrum posteriorly, 1.5-2 cm behind the sacrum anterior margin of the sacrum (6).

A radiopaque marker should be placed at the posterior aspect of the anus to ensure that blocks in the posterior-inferior aspect of the portal do not impinge on targeted portions of the anorectum. The anterior margin should be at least 4 cm anterior to the rectum, as determined by the rectal-contrast simulation. The use of intrarectal contrast simulation during portals ensures that the rectum will be at maximum distension. If the tumour has considerable extrarectal extension, then these guidelines should be modified to make certain that all macroscopic disease (determined by CT scan) is encompassed with about a 4-cm margin (7).

The definition of volumes of current planning with 3D techniques (8) are based on patterns of recurrence from the period before the introduction of TME surgery, and most provide references to RT in 2D. Following the guidelines of the International Commission on Radiation Units and Measurements (ICRU 50 and 62), the volumes planned are:

- **GTV (Gross Tumour Volume):** includes the gross rectal tumour
- **CTV (Clinical Target Volume):** includes the rectal mesentery and regions of lymph nodes at risk. Must include the presacral space, internal and distal common iliac nodes. The risk of lymph paraaortal is very low so irradiation is not needed. The area of the external iliac nodes should not be included either, only be performed for lesions that extend to the dentate line or in cases of affected structures with lymph drainage through them (vagina, uterus, prostate, bladder) and lymph inguinal nodes if there is involvement of the anal or distal third of the vagina.
- **PTV (Planning Target Volume):** includes the GTV and CTV with a margin of safety. This margin is not symmetric, because the movement of the rectum is anisotropic, i.e. movement is not the same on all axes and globally has been estimated at 1 cm for all margins (9).

In the event of amputation abdomino-pelvic surgery, postoperative RT irradiating the perineal region with a margin of 1.5-2 cm, and sometimes depending on the energy used in dosimetry, placing a bolus in the perineal incision will be necessary to optimise the dose. A study conducted at the Mayo Clinic from 1976 to 1984 showed a decrease in local recurrence and scarring,
when the scar is radiated following an intervention of abdomino-perineal type, but not in the anterior resections where this scar does not exist (10).

The technique of administration of radiation therapy should be precisely performed to avoid side effects as much as possible, because side effects can have an impact on survival. One example is the study of the Swedish group (11) in which preoperative EBRT with a dose of 25 Gy in 5 fractions of 5 Gy in two parallel opposed fields, anteroposterior and posteroanterior (AP and PA) to 849 patients, showing a mortality 8% at 30 days compared to 2% in nonirradiated patients ($p <0.01$). Mortality was secondary to infectious complications, cardiovascular complications, and progression of the disease. A Scandinavian study (12) using the same dose administered with a 3-field technique (AP, PA, and later) saw decreased mortality, at 4% in the RT group compared to 5% in the non-irradiated group ($p = 0.4$).

**Dose and fractionation**

Rectal cancer exhibits a dose-response relationship. A review of phase II studies at Princess Margaret Hospital observed higher rates of pathological responses in patients who had received a dose of 50 Gy compared to those who received 40 or 46 Gy (13). This is the reason why, recommended doses range from 46 to 50 Gy in 23-25 fractions of 2 Gy. When administered concomitantly, CT is performed at a fractionation of 1.8 Gy per session to a total of 50.4 Gy, with an overlay to 54 Gy in the primary tumour in postoperative RT (14). If the volume of small bowel included in the scope of treatment could be minimised, a boost of 9 Gy overlay is administered, which will be of 5.4 Gy in the case can not be excluded bowel.

A comparison of the fractions used in several studies found that Rt in 5 sessions of 5 Gy was less effective in stage III. A standard fractionation scheme of 46-50 Gy at 2 Gy per session is recommended to minimise toxicity. Intensity-modulated radiation therapy (IMRT) with image-guided systems did not confirm toxicity (15) and even if different doses and fractionation schemes have been compared, doses of 46-50 Gy (scheme long) is the standard recommended by all groups (16). Indeed, shorter fractionation RT combined to CT treatment is impossible. The two schemes have not been compared using current techniques.

A study in 2010 concluded that the biological effective dose (BED), the actual dose at the cellular level taking into account cell division, must be greater than 30 Gy. Data from this study demonstrate that preoperative RT with a BED $>30$ Gy (17) is more efficient in reducing local recurrence and mortality than preoperative RT with a BED $<30$ Gy and is independent of the scheme of fractionation used (short or long course). A phase III trial is currently under way in Stockholm (18) in which patients are randomised to 3 arms: EBRT in 5
fractions of 5 Gy with immediate surgery, 5 fractions of 5 Gy with delayed surgery, and 50 Gy with standard fractionation and delayed surgery. Determining the best regimen of treatment must await the results of this study.

**Immobilisation**

Historically, EBRT patients with rectal cancer were placed in the prone position to reduce the volume of irradiated small bowel (19). Combined with proper planning using non-coplanar beams, a combination of different energies, and the Belly-Board system, consisting of a table with a central opening for the patient's abdomen, this positioning allows better tolerance of the RT on the pelvis with lower acute and late toxicities (20). Currently, however, the use of EBRT multileaf collimators, 3D and IMRT (Intensity Modulated Radiation Therapy), and CT imaging systems (computerised tomography), and MRI (magnetic resonance imaging) to plan treatments (21) and several studies have noted that the prone position is so difficult to maintain in many patients, and irreproducible (22). There is a small bowel volume included in the planned volume similar in the two positions in both prone and supine so some authors recommend the use of supine tolerance for the best when planning the treatments (23). See Figures 1, 2, 3, and 4.

**Figure 1.** Definition of structures in preoperative rectal cancer in supine position. GTV: gross tumour in red, yellow ganglion chains, CTV and PTV in blue. Small intestine: orange. MasterPlan Oncentra Planner version 3.2.
Figure 2. Definition of structures in preoperative rectal cancer in the prone position. CTV: node chains in red and PTV in blue. Small intestine in yellow.

Figure 3. Planning for preoperative rectal cancer with 3 shaped fields MLC 80, side impact and rear wedge.
The advent of IMRT systems and image-guided RT (IGRT) has allowed a decrease in intestinal toxicity with good coverage in the PTV (24).

In planning a course of radiotherapy in rectal cancer, we must consider other factors such as margins and volumes. In 2009, a Dutch study observed 28 patients for variation of the mesorectum prior to treatment during daily imaging by image-guided systems, CT, and Cone Beam CT (CBCT). The mesorectum can vary in a heterogeneous and anisotropic inter-fraction, which differs between women and men (25). Changes in organs at risk in prone and supine positions are scarce.

**Special techniques of radiation therapy**

a. **Intraoperative Electron Radiotherapy (IORT)**

Rectal cancer after curative surgery has a high local recurrence rate of 10-15% depending on the stage, surgical technique, and risk factors. Unresectable recurrence or palliative resection has a poor prognosis with a median survival of 7-12 months (26). Many patients will have breakthrough bleeding, ulcers, perineal or pelvic pain, ureteral obstruction, and secondary sepsis. Some patients develop distant disease and die of complications from local recurrence. If we study the topography of local recurrence observed in
the presacral space, the perineum is the predominant anatomical site of relapse: 67% presacral, perineal 13%, 4% perianastomotic or pelvic side wall, 0.5% in the posterior wall of the vagina, 2% in the prostate or bladder, and 14% in the anastomotic line (27). No equivalent detailed information on patterns of relapse in the pelvic area after preoperative RT-CT and radical surgery (28) have been published. Local recurrences usually occur with fixing organs or structures and if there was an option for surgery, it must be very radical or resection margins would be positive, so that surgery would become palliative. This situation coupled with the majority of patients having been previously submitted to EBRT, limits the possibility of resectability.

EBRT as a unique tool get very good results in pain control from 70% to 100% in recurrences (29) but with a cure rate of less than 5% so that the patient will die within 2 years (30).

EBRT dose has to exceed 60 Gy for microscopic residual disease and further to reach a tumouricidal dose to the gross tumour (31). However, the small intestine as the target organ of the administered dose limits risk to EBRT. Since both surgery and EBRT as rescue treatments for pelvic local recurrences have a major constraint, it appears the possibility of increasing the radiation dose and the capacity of drawing better the RT field with IORT. Thus IORT is indicated for locally advanced tumours to deliver a boost and in cases of tumour recurrences, where surgery cannot eradicate the tumour (32). IORT mainly benefits patients with very low margins of resection or with minimal residual disease. When in doubt, we can use the surgical margins or the IORT boost on small volumes by postoperative EBRT (33). Small institutions with IORT programmes reported high rates of local control in both adjuvant RT (34) and in preoperative RT-CT (35-37).

IORT can be administered by two techniques:

- IORT with electron accelerator
- Intraoperative High Dose Rate (IOHDR) brachytherapy.

Although the potential advantage of brachytherapy is the flexibility of the applicators that allow a more composed treatment, it is a lengthy procedure, and IORT is most often used. During IORT, after the surgeon removes the tumour, the radiation oncologist defines the area to be irradiated, and then the radiation physicist selects the prescribed dose and sets the depth ranging from few millimeters to 4 cm. The area of the tumour is irradiated, excluding risk organs and tissues. The main difficulties with the use of IORT are the problems associated with transporting the patient from the operating room to the radiation-therapy bunker. The two rooms are generally in different locations due to the physical risks to the patient and the time required for
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anesthesia. Recent decades have seen the emergence of accelerators, designed exclusively to run IORT, the MEVATRON, MOBETRON, and NOVAC, that may be located in the operating room, thus avoiding transport of the patient.

Patients are treated during surgery in a prone or supine position. The dose is calculated as the 90% isodose line depending on the characteristics of the disease (38):

- close but negative margins: 7.5-12.5 Gy
- microscopic margin: 10-12.5 Gy
- macroscopic residual disease, 2 cm or less: 15 Gy
- macroscopic residual disease, 2 cm or more: 17.5-20 Gy

If the dose of the EBRT is limited by problems of the disease, the IORT dose is increased to achieve an equivalent dose of 50 Gy for resection with negative margins and of 60 Gy for patients with residual disease.

EBRT vs conventional pre- or postoperative IORT could present some potential advantages such as:

1) Direct action in the tumour bed.
2) Exclusion in the irradiated field structures with less toxicity to healthy organs at risk
3) Combination with EBRT
4) The biological equivalent dose delivered to the IORT is 2-3 times higher than the same dose administered with conventional fractionation (39).

Many studies have retrospectively compared the results of the EBRT and EBRT with IORT as boost with promising results (Table 1), although there are no randomised trials to provide standard instructions. Also, very few centers currently have the facilities for IORT. The University Hospital of Navarra has researched the long-term effects of IORT over 5 years of follow-up (40).

**Table 1.** IORT studies compared with other techniques.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Treatment</th>
<th>n</th>
<th>Survival 3 years</th>
<th>Survival 5 years</th>
<th>local relapse</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong 1998 (41)</td>
<td>EBRT</td>
<td>519</td>
<td>5%</td>
<td>93%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Guiney 1997 (42)</td>
<td>surgery + EBRT</td>
<td>39</td>
<td>9%</td>
<td>82%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mannaerts 2001 (43)</td>
<td>EBRT only vs EBRT + surgery vs EBRT + surgery + IORT</td>
<td>146</td>
<td>14%</td>
<td>11%</td>
<td>60%</td>
<td>3 years 90%</td>
</tr>
</tbody>
</table>
b. Brachytherapy

Although endocavitary brachytherapy data from 1914 when using the endocavitary Radium was not until the time of Papillon (44) when he showed the utility as contact RT boost after EBRT or as exclusive treatment. High dose rate (HDR) brachytherapy is used as treatment in three situations (45):

1. T1N0 polypoid tumours: small, up to 3 cm, exophytic, with minimal penetration of rectal wall without lymph node and less than 10-12 cm from the anal margin
2. smaller T2 and T3 tumours: used as an overlay or after surgery or boost EBRT, with doses of 20-30 Gy
3. presacral recurrences: HDR brachytherapy has not been evaluated in phase III trials, but its use is justified in phase II trials or treatment protocols.

Brachytherapy can be performed with permanent seed called Seed Mini-Mick and can be performed using intraoperative or perioperative high dose rates. The techniques and applicators may be of several types:

- Technical Papillon applicator and needles
- Implant technique with "fork"
- Technical Créteil
- Technical cylindrical applicator.

According to the studies shown in Table 2, brachytherapy obtained good results in OS, with excellent preservation of the anal sphincter and without major genitourinary or gastrointestinal toxicity. Maignon et al. (46) observed late rectal effects grade 3 in 3.8% and sphincter preservation in 82% of the included patients. Gerard observed no grade 3-4 toxicity in any of the patients, only acute rectal proctitis, which was not the cause of the discontinuation of treatment, and anal sphinter preservation was 92%.

Centres with more experience are the French, (Léon Bérard in Lyon) with major retrospectives publications (49) and several placed in Spain such as ICO (Catalan Oncology Institute), University of Navarra, or Hospital Gregorio Maranon, but with few publications.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>OS at 5 years</th>
<th>Sphincter preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillón (47)</td>
<td>90 (T1-2)</td>
<td>77,8%</td>
<td>95,7%</td>
</tr>
<tr>
<td>Maignon (46)</td>
<td>151 (T1-3)</td>
<td>59,6%</td>
<td>98%</td>
</tr>
<tr>
<td>Gérard (48)</td>
<td>63 (T1-2)</td>
<td>65,4%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Table 2. Studies of survival with brachytherapy.
c. Photodynamic therapy

Photodynamic therapy (PDT) involves systemic or topical administration of a photosensitising compound that preferentially accumulates in tumour tissues. The subsequent irradiation of these tissues with visible light causes the formation of highly reactive oxygen species, which are responsible for the selective destruction of tumour cells.

PDT has a number of advantages over other local or systemic treatments of cancer such as:

- low systemic toxicity, because the photosensitiser is activated only in the presence of light
- ability to selectively destroy tumours, with a consequent reduction of side effects on other tissues, and
- may be given alone or in combination with other therapies such as chemotherapy, EBRT, immunotherapy, or surgery. The results of its application are many, from the delay in tumour growth in advanced cancers to a complete destruction of the tumour.

The study of the photodynamic reaction has advanced in the last decade, extending its spectrum of activity to other diseases such as inflammatory and infectious diseases. Approved PDT indications are actinic keratoses, superficial and nodular basal cell carcinomas, and Bowen's disease, but PDT has also been applied to cases of recurrence and colorectal, gastric, pancreatic, and other gastrointestinal tumours in the last few decades. It is used in CRC recurrences and anal tumours after failure of radical treatment, with good long-term results and in obstructions caused by recurrences (50). Allison et al. (51) used PDT in recurrence of anal cancer after radical treatment with EBRT and chemotherapy. Follow-ups 18-48 months later indicated good control of local disease and retention of sphincter function (52). All published studies are out of testing and protocols are performed within each center.

2. Adjuvant and neoadjuvant radiotherapy with or without chemotherapy

EBRT has become an essential therapeutic tool in the treatment of cancer of the rectum both as a single modality and combined with chemotherapy. Concurrent use is supported by the evidence that chemotherapy acts as a radiosensitiser at the cellular level (2) so that both treatments synergise their activities for the eradication of residual, subclinical micrometastases after surgery with radical intent. Although surgery alone remains the mainstay of treatment, the rate of local recurrence is 25% with OS of 40-50% for stage
T3-4 N1-2 (53), while surgery combined with EBRT-chemotherapy reduces local relapse to 10-15% and increases survival to 50-60%.

**Early localized tumours**

Early tumours are neoplasms limited to the rectal wall (c/p T1 and T2). These tumours represent 3-5% of rectal cancers.

Cases underwent standard surgery for an early tumour do not need further therapy. However, patients after a local surgical procedure are at risk for disease recurrence in the rectal wall or the local nodes. At stage T1, tumours without adverse pathologic factors have a low rate of local failure of approximately 5% and usually do not need adjuvant therapy but there is not an evidence to show that the outcome would be equivalent to radical surgery (54).

Favourable histological (55) features include well or moderately differentiated tumours, absence of perineural and lymphovascular invasion, location of injury from 8 to 10 cm from the anal margin, with less than 4 cm and less than one third of the circumference of the rectum affected.

On the contrary, pT1 with unfavourable pathological factors have to undergo a radical resection and if patients refuse surgery or if general conditions are compromised, adjuvant radiation therapy with or without chemotherapy could be considered.

On the other hand, whenever adverse pathologic factors are present or the tumour invades into or through the muscularis propria (T2), the local failure rate increases to 17% and the incidence of positive nodes is about 10% (56). In all these cases local excision seems to be insufficient and a radical surgery is recommended, but in cases in which this procedure cannot be performed or it is refused, adjuvant therapy should be considered.

Preoperative short-course EBRT in T2 operable tumours results in an even lower risk of local recurrence but it is not indicated since the absolute risk is very low providing a very high quality surgery has been performed (57).

Cases with medically inoperable or who refuse surgery could receive preoperative radiation followed by local excision. It is usually administered with 5FU based concurrent chemotherapy. In cases of patients not fit for prolonged EBRT with or without chemotherapy can receive short course EBRT alone and delayed surgery. This management must be limited to only this subset of patients.

**Intermediate stage tumours**

These stages include T3, T4, and/or N (+) resectable tumours. There are two approaches for these patients. One of them is initial radical surgery
followed by adjuvant combined treatment. The other is preoperative EBRT with or without chemotherapy followed by surgery and then adjuvant chemotherapy could be considered, although there is insufficient evidence on the benefit of adjuvant chemotherapy after preoperative chemoradiation (58).

Exploratory analyses of this topic suggest that only patients who are downstaged from T3-4 to ypT0-2 benefit from 5FU based adjuvant chemotherapy. These data supports a significant survival benefit of 3-4% with 5FU based chemotherapy. Bolus and continuous infusion 5FU and capecitabine have been combined in several phase II studies with oxaliplatin or irinotecan plus preoperative EBRT and have also been delivered alone as adjuvant treatment after surgery. However, the compliance of 5FU/LV in the adjuvant setting in two large randomized phase II trials was suboptimal. We expect that ongoing phase III studies will help clarify the role of the combination of these drugs (59, 60).

As a conclusion, the role of adjuvant treatment strategy after preoperative chemoradiation is still being investigated (61).

a. Adjuvant and neoadjuvant treatments

In general, radical surgery has a lower rate of local recurrence of 7%. However, adjuvant or neoadjuvant treatments are needed for these stages to better control the disease (62).

The characteristics of rectal cancer with a high rate of local recurrence and evidence of the palliative effect of EBRT in unresectable tumours led to studies with postoperative EBRT. Most of these studies were non-comparative, or compared modern with historical groups, and showed reductions in the number of relapses (<10%) and improvements in survival in stage II, reaching 65-75% at 5 years (63,64).

In 1979, Ghossein et al. (65) demonstrated that postoperative EBRT decreased the rate of local recurrence in patients with intermediate stages rectal cancer (T3-4 N0 or Tx N 1-2). Since then, many studies in this field have addressed the benefits of this treatment (66, 67).

A study at the MD Anderson Cancer Center published in 1977 included 62 patients treated with a EBRT dose of 50 Gy 3-6 weeks after surgery without total mesorectal excision. A local control of 92% and a disease-free survival of 79% at 48 months were achieved, but at the cost of significant gastrointestinal toxicity (68).

A randomised study conducted at the Mayo Clinic on patients with these intermediate stages of rectal cancer or unresectable local recurrence showed that the combination of EBRT and 5FU improved symptoms control rate and duration and increased survival and the number of responses.
All the studies from this period included few patients and short follow-ups. Therefore, subsequent randomised studies were needed to assess the effectiveness of adjuvant treatment.

A Dutch multicenter prospective trial published by Treurniet-Donker (69) et al. studied 172 patients randomised to two arms. The experimental arm consisted of an EBRT dose of 50 Gy in five weeks (standard fractionation of two Gy per fraction), while the control group received no adjuvant treatment after surgery. The adjuvant EBRT showed a decrease in the rate of local recurrence but without statistical significance (24% vs 33%, p < 0.1) or an increase in disease-free or OS.

These results were similar to those obtained in other studies in Europe and USA; then postoperative EBRT alone was accepted as routine treatment after surgery in resectable rectal cancer.

a.1. Preoperative radiation therapy alone

A study by the Medical Research Council Rectal Cancer Working Party compared a control arm with surgery alone to the experimental arm with surgery preceded by EBRT dose of 40 Gy with standard fractionation. The study included 479 patients with recruitment between 1981 and 1989 from over 20 regional centres in the UK (70). The patients were followed up for a minimum of 5 years or to death. 217 patients died, 114 of 140 allocated surgery alone and 103 of 139 allocated preoperative EBRT with median survival times of 24 months and 31 months, respectively. The hazard ratio (HR) for OS was 0·79 (95% CI 0·60—1·04, p=0·10).

At 5 years' follow-up 65 patients allocated surgery alone and 50 who received preoperative EBRT had local relapse (HR 0·68 [0·47—0·98], p=0·04); the corresponding numbers of patients with distant recurrence were 67 and 49 (HR 0·66 [0·46-0·95], p=0·02). There was a significant benefit of EBRT on DFS (HR 0·76 [0·58-1·0], p=0·05). There was no increase in postoperative or late complications in the EBRT group.

The authors interpreted these results as providing further evidence that preoperative EBRT reduces the rate of local recurrence of rectal cancer in patients with locally advanced disease. The results concerning survival, however, are still equivocal, and we must await the results of a meta-analysis of all trials that may provide definitive results, particularly for rates of survival.

a.2. Preoperative versus adjuvant EBRT

A systematic overview (71) of more than 8000 patients from 28 randomised, controlled trials compared the outcomes of surgery for rectal
cancer combined with preoperative or postoperative EBRT with those of surgery alone. Data from individual patients were analysed from 22 randomised comparisons between preoperative (6350 patients in 14 trials) or postoperative (2157 in eight trials) EBRT and no EBRT. OS in patients receiving EBRT was only marginally better than in those allocated to surgery alone (62% vs 63% mortality, \( p = 0.06 \)), and preoperative EBRT failed to improve rates of curative resection (85% EBRT vs 86% control). The yearly risk of local recurrence was 46% lower in patients receiving preoperative EBRT, and 37% lower in patients receiving postoperative EBRT, compared to those who had surgery alone (\( p = 0.00001 \) and \( p = 0.002 \), respectively. Fewer patients who had preoperative EBRT died from rectal cancer than did those who had surgery alone (45% vs 50%, respectively, \( p = 0.0003 \)), but early (\( \leq 1 \) year after treatment) deaths from other causes increased (8% vs 4% died, \( p < 0.0001 \)).

The authors concluded that preoperative EBRT (at biologically effective doses ≥ 30 Gy) reduced the risk of local recurrence and death from rectal cancer. Postoperative EBRT also reduces local recurrence, but short schedules appeared to be at least as effective as longer ones. If the safety of preoperative EBRT could be improved without compromising effectiveness, then OS would moderately improve, especially for young, high-risk patients.

a.3. Combined treatments

Concomitant treatments involve the administration of systemic drugs producing cellular radiosensitisation that increases the destructive effect of radiation therapy. The most commonly used radiosensitisers in rectal cancer include intravenous fluoropyrimidines such as 5-fluorouracil (5-FU), oral fluoropyrimidines such as capecitabine and UFT, and antifolates such as raltitrexed. Oral fluoropyrimidines are an alternative to 5-FU. Pharmacokinetic studies have found no differences between oral and intravenous fluoropyrimidine 5-FU (72). Oral treatment during the course of irradiation is more comfortable for the patient than the continuous intravenous administration of 5-FU combined with EBRT.

The Fisher Group trial (73), National Surgical Breast and Bowel Project R-01 (NSABP R-01), evaluated 555 patients treated by curative resection between 1977 and 1986. Patients were randomised to three arms, one with surgery alone compared to a second arm with surgery followed by postoperative EBRT, and a third arm with surgery followed by postoperative chemotherapy with 5-FU, vincristine, and semustine (MOF). The EBRT dose was 46-47 Gy in 26-27 fractions, with a later overlay in the perineal area of 51-53 Gy.
Local relapse decreased in the adjuvant EBRT group compared to the surgery-alone control group (25% vs 16%, \( p = 0.06 \)). DFS (\( p = 0.4 \)) or OS (\( p = 0.7 \)) did not differ significantly with the use of EBRT.

The chemotherapy group compared to the control group, though, showed a statistically significant improvement in OS (\( p = 0.05 \)) and DFS (\( p = 0.006 \)). When evaluated according to sex, the benefit for chemotherapy at 5 years, both in DFS (29% vs. 47%, \( p <.001 \); relative odds, 2.00) and in OS (37% vs. 60%, \( p = 0.001 \), relative odds, 1.93), was restricted to males. When males were tested for age trend with the use of a logistic regression analysis, chemotherapy was to be more advantageous found in young patients.

The global test for interaction to identify heterogeneity of response to radiation within subsets of patients was not significant.

This investigation has demonstrated the benefit of adjuvant chemotherapy (MOF) for the management of rectal cancer. The observed advantage was restricted to males but postoperative EBRT reduced the incidence of local and regional recurrence but failed to affect OS and DFS.

The North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic (74) conducted a trial comparing adjuvant EBRT at a dose of 45-50.4 Gy after surgery with a combination of adjuvant EBRT and chemotherapy with 5-FU preceded and followed by a cycle of systemic treatment with 5-FU and semustine (methyl-CCNU). The 204 patients in the combined-therapy arm demonstrated superior results. The relative reduction in recurrence was 34% (the 95% confidence interval was 12-50%). Combined therapy significantly reduced the length of time to recurrence (\( p = 0.0025 \)) and reduced the death rate by 29% (\( p = 0.043 \), the 95% confidence interval was 7-45%). The combination of postoperative local radiation and systemic therapy with a fluorouracil-based regimen substantively improved treatment of rectal carcinomas having a poor prognosis, as compared to postoperative EBRT alone.

In a trial by the Gastrointestinal Tumour Study Group (GITSG) (75) in 1975, 202 patients at stages B2 and C were randomised to 4 arms, (1) surgery alone, (2) Adjuvant chemotherapy with 5-FU, (3) EBRT (40-48 Gy split course, or two courses), and (4) Chemotherapy and adjuvant EBRT (40-44 Gy). This study was criticised for its small number of patients and the use of interrupted EBRT. After nine years, the combination of EBRT and chemotherapy provided an increased OS of 54% compared to 27% in the surgery-alone arm.

The combined arm had a longer time to recurrence, and the local recurrence decreased compared with surgery alone, 11% vs 24% respectively, and distance recurrence was also improved 26% vs 34%.
This study thus concluded that the combined-arm increased OS almost double than in surgery alone arm. Following the publication of these two trials, the American National Institutes of Health (NIH) recommended, in 1990, the use of adjuvant treatments after surgery for rectal cancer in stages II and III (76).

**Optimisation of chemotherapy**

The following studies were conducted to optimise the different patterns of chemotherapy. One study showed that 5-FU was better than methyl-CCNU being this more toxic and without any kind of benefit in local recurrence and OS.

The administration of continuously infused 5-FU during EBRT was better than a bolus, with a risk of distant metastases of 31% vs. 41% and DFS at 4 years of 70% vs. 60%, although the rates of local recurrence did not differ. One of the most significant studies was that of Intergroup INT 0144 (77) that evaluated the benefits of continuous infusion during EBRT and then after completion.

After resection of T3-4, N0, M0 or T1-4, N1, 2 M0 rectal adenocarcinomas, 1,917 patients were randomly assigned to arm 1, with bolus 5-FU in two 5-day cycles every 28 days before and after radiotherapy plus 5-FU via protracted venous infusion (PVI) (dose of 225 mg/m2/d during EBRT; arm 2 (PVI-only arm), with PVI 42 days before and 56 days after EBRT + PVI; or arm 3 (bolus-only arm), with bolus5-FU + LV in two 5-day cycles before and after EBRT, plus bolus 5-FU + LV (levamisole was administered each cycle before and after EBRT).

Differences in DFS, local recurrence, or OS were not observed after a median follow-up of 5 years, and hematologic toxicity was lower in the group treated with 5-FU in continuous infusion. Despite these results, continuous infusion is considered effective and is the most widely used scheme in many institutions.

The optimal time for administering EBRT, however, is not well defined and remains an important question. Most studies start after one or two cycles of chemotherapy. One study randomised 308 patients who received EBRT after the first or after the third cycle of adjuvant chemotherapy (5-FU/LV). DFS after four years was better in the patients who received early EBRT (81% vs 70%, \( p = 0.043 \)), but OS in the two groups was essentially the same (84% vs 82%, \( p = 0.387 \)). The group receiving EBRT after the first cycle had 23 recurrences (78), compared to 38 recurrences in the group receiving EBRT after the third cycle. Although no consensus exists, postoperative EBRT should start 3-6 weeks after surgery according to institutional protocols.
**T3N0 favourable cases**

Several studies show that a subgroup of patients do not need adjuvant treatment for the low risk of recurrence after surgery. In 1999, researchers at the Memorial Sloan-Kettering Cancer Center (MSKCC) (79) evaluated 95 patients with T3N0 rectal adenocarcinoma treated with surgery alone. The aim was to investigate whether favourable T3N0 cases could forgo additional treatment. Seventy-nine patients underwent low anterior resection, ten to coloanal anastomosis, and 6 to abdomino-perineal resections with total mesorectum excision (TME). At a follow-up after 53.5 months, 6% had local recurrence, distant metastasis 13% and 3% local and distant recurrence. Of the risk factors analysed, the presence of lymphovascular invasion was the most important histological factor for local recurrence. No other factors such as surgical technique, type of resection, tumour location, or extent of the margin were important in determining recurrence. This study showed that the TME anterior resection of abdominoperineal T3N0 tumours result in low rates of local tumour recurrence (<10%) without adjuvant therapies. Other groups have supported this result, but even if a limited subset of T3N0 patients get excellent results (80) with surgery alone, no randomised study has yet supported the omission of adjuvant therapies in these patients.

**a.4. Neoadjuvant radiation therapy**

Preoperative, or neoadjuvant, treatments have some important advantages over postoperative, or adjuvant, treatments. They have the potential to reduce the tumour to facilitate surgery, reduce the risk of tumour spread eliminating micrometastases, and reduce the problems of hypoxia that increase after surgery. The patient is in good physical condition, and treatments are usually administered at full dose with a better tolerance reducing the toxicity of treatment and tumour seeding that occurs during surgery. The administration of concurrent preoperative EBRT and chemotherapy increases efficiency providing a better resectability and therefore allowing the performance of sphincter-sparing surgery (81).

Despite these advantages, neoadjuvant treatment also has a number of drawbacks. One of the main problems is the delay in surgical treatment, because patients must wait one month after completion of EBRT, and the side effects of EBRT increase the difficulties of surgery (81). The occurrence of postoperative perineal infections, delayed healing, and the overtreatment of patients with early-stage (T1-T2 N0) or disseminated tumours at diagnosis, despite the use of high-definition imaging techniques, are the main
Radiotherapy in colorectal cancer

The disadvantages of preoperative EBRT (82,83). The selection of the best treatment strategy is based on a good initial staging. In this context diagnostic tests such as MRI, helical Computed Tomography, endorectal ultrasound, and PET could help to decide which cases could benefit more with neoadjuvant therapy than with adjuvant.

Preoperative EBRT has a number of physical and biological advantages compared to postoperative EBRT. Preoperative EBRT is less toxic, and the absence of adhesions or other complications secondary to pelvic surgery is beneficial for the small intestine, which is very radiosensitive (84). Tumour cells are well oxygenated and so are more radiosensitive. A decrease in tumour mass and therefore a decrease in the resected cancer stage (down-staging) allows an increased curative resection at a lower cost compared to postoperative EBRT. Preoperative EBRT and first treatment are about six times less costly, are easier to complete, and are less toxic than equivalent doses after surgery (85).

The first randomised studies with preoperative EBRT were performed with the aim of making unresectable lesions resectable. In 1914, Symonds (86) reported the first use of preoperative EBRT as a treatment for rectal cancer. Symonds used radium in a patient with a tumour in a low rectal location, with good results three months after surgery. Several studies have used moderate-dose preoperative EBRT, observing a consistent local control with or without a minimal increase in OS (87, 88).

In 1960, a study was conducted at MD Anderson Cancer Center (92) with 126 patients, 52 of whom received only EBRT with a fractionation of two Gy per session and a total of 50 Gy prior to surgery for rectosigmoid tumours, resectable or unresectable. The objective was to evaluate the tolerance of patients to preoperative EBRT. 50% (8 of 16) unresectable lesions were operated. No tumour was found in pathology samples in 10 of 52 patients, and preoperative EBRT was well tolerated with few complications after treatment. Later clinical trials of the Medical Research Council among others, showed a significant decrease in local recurrence after preoperative EBRT (89).

Rouanet et al. (90) administered 40 Gy preoperatively to 27 T2-T3 patients who were evaluated three weeks later. When the response was good (30%), patients received an additional 20 Gy, achieving anterior resection in 63% of patients and transanal local excision in four patients (15%). In all, 78% of the patients underwent sphincter-preserving surgery. In a later study by Mohiuddin et al (91), 70 patients with tumours 2 cm from the anal margin received 40-45 Gy at 1.8-2 Gy/session, and the worst cases continued with a boost of 10-15 Gy. Surgery was performed at 5-10 weeks, and the results were very promising: 48 patients received radical resection, and 22 received full thickness local excision. At a mean follow-up of four years, 60 patients (86%)
had succeeded in maintaining sphincter function, with local failure in nine patients (13%) and distant metastases in 12 (17%) without presenting gastrointestinal toxicity grade III-IV. These data led to many studies designed with preoperative EBRT fractionation schemes and standards, but in 1960, the MSKCC (93) designed a study that was administered in a hypofractionated EBRT, i.e. the dose per fraction increased, with the intention of reducing treatment time and preventing a delay to surgery. The trial was randomised to evaluate the usefulness of preoperative, low-dose EBRT (to 20 Gy in 8 fractions of 2.5 Gy) for operable tumours and was aimed at increasing OS. The study included 800 patients and found that the EBRT did not increase OS in patients with tumours or those who were node-positive or negative. This study was criticised because a large number of the non randomised patients were included and they received a very heterogeneous radiobiological doses and fractionations. Thus, with these methodological flaws, this study showed no advantages of preoperative EBRT for local control or survival compared to surgery alone.

Randomised trials have subsequently shown benefits of preoperative EBRT. Cedermark et al., in a series of 847 patients (94), obtained an increase in local control by decreasing the rate of recurrence using a preoperative dose of 25 Gy in 5-7 days (hypofractionation). The EBRT arm, however, experienced more toxicity than the group that only underwent surgery. Other randomised trials have reported a significant reduction in local recurrence. Such a reduction, compared to surgery alone (p < 0.05), was found by a group of the Imperial Cancer Fund (1) in a randomised set of 468 patients receiving preoperative EBRT doses of 5 Gy in 3 sessions. The European Organisation for Research and Treatment of Cancer (EORTC) (2), and others, later showed a trend towards increased OS after preoperative EBRT.

The most consistent data, however, were obtained in the Swedish Rectal Cancer Trial (1) that randomised 1168 patients to receive preoperative EBRT hypofractionated into doses of 25 Gy in 5 sessions or to receive surgery alone. Both local control (89% vs 73%) and OS (58% vs 48%, p < 0.05) increased with preoperative EBRT. A Dutch trial (2) with 1861 patients failed to demonstrate improvement in local control with the best surgery (TME). Patients received high-dose EBRT followed by surgery or surgery alone with TME in the two arms. Preoperative EBRT reduced the rate of local recurrence at 2 years (2.4% vs 8.2%) but failed to increase OS (82% in both arms). Patients in the EBRT arm also experienced problems such as poor healing of wounds after abdominal-perineal surgery, sexual dysfunction, and fecal incontinence (p = 0.008). The rates of local relapse after 6 years were 10.9% vs 5.6% with statistical significance (p < 0.001) favoring the preoperative EBRT group, with equivalent survival rates in both groups.
Two meta-analyses of approximately 6000 patients each explored the benefit of preoperative EBRT. One analysis included 14 randomised, controlled trials and found that neoadjuvant EBRT was associated with significantly fewer local recurrences, improved version-specific survival, and improved OS. The second meta-analysis, provided by the CRC Collaborative Group, included 22 randomised, controlled trials and concluded that preoperative EBRT significantly reduced the risk of local recurrence and death from rectal cancer (3).

a.5. Neoadjuvant combined treatments

Two fundamental strategies were developed to improve the results of preoperative EBRT: increasing intraoperative doses and adding chemotherapy to EBRT to increase the radiosensitivity of the tissues. The second of these strategies was tested in the EORTC 22921 (1) trial that randomised 1011 patients receiving preoperative EBRT doses of 45 Gy with standard fractionation or receiving hypofractionated EBRT with preoperative chemotherapy (5-FU/LV). Total excision of the mesorectum was performed in 40% of the patients. The rates of pathological complete response (pCR) were 13.7% vs 5.3% for the combined arm. The sizes of tumours decreased, but survival at 5 years and the rate of preservation of the anal sphincter in the two arms remained unchanged. The FFCD 9203 trial by the Fédération Francophone de la Canérologie Digestive obtained similar results. This study included 773 patients with T3-4 Nx M0 in the distal rectal region randomised to receive EBRT or EBRT-chemotherapy preoperatively. The EBRT group received 45 Gy with standard fractionation, and the EBRT-chemotherapy group received concomitant chemotherapy (5-FU/LV). The patients subsequently underwent surgery. The primary endpoint was OS. No differences between the groups were seen in sphincter preservation, but the group with preoperative EBRT-chemotherapy had a higher rate of pCR (11.4% vs 3.6%, p < 0.05) and a lower rate of local recurrence (8.1% vs 16.5%, p < 0.05) compared to the group with preoperative EBRT. No differences in OS between groups were observed (2).

a.6. Neoadjuvant versus adjuvant combined treatments

To determine which of the two therapies was better, three phase III trials were designed that compared EBRT and chemotherapy prior to or after surgery. The first trial (RTOG 94-01/intergroup (INT) 0417) compared 5-FU/LV + preoperative EBRT (50.4 Gy) versus the same pattern after
surgery. This study included 53 patients and was closed for poor recruitment of patients.

The second trial (NSABP-RO3) (95) had a design similar to the INT 0147 trial and compared the administration of EBRT (45 Gy) + CT (5-FU/LV) before or after surgery. The trial began in 1993 and recruited 267 of the 900 patients originally planned (due to low enrollment). The objectives of the study were to monitor sphincter preservation rate and both DFS and OS. Few data were published, but the study showed a similar toxicity in both groups, and no patients progressed during preoperative treatment. Sphincter preservation was higher in the preoperative treatment group (50% vs 33%), which had an 8% pCR. No significant differences in disease-free survival at 3 years (70% vs 65%) or OS (85% vs 78%) were observed. A subsequent analysis reported that patients who had achieved a pCR showed an OS at 3 years of 100%, while those with partial response had 95% OS and in cases with stable disease OS was of 83% (96). The third and final study (CAO/ARO/AIO-94 by the German Rectal Cancer Group) (97) in favor of preoperative EBRT randomised 823 patients with stage T3-4 or a node-positive diagnosis to receive EBRT (50.4 Gy at 1.8 Gy per fraction) + 5-FU in continuous infusion (weeks 1 and 5). In all cases of resection of the mesorectum, surgery was followed by adjuvant chemotherapy. The postoperative group received a boost of 5.4 Gy. In a follow-up after 5 years, neoadjuvant therapy was associated with a lower rate of local recurrence (6% vs 13%). A significant downstaging after pretreatment was seen with a pCR of 8%. Disease-free or OS did not differ between groups. Both acute and chronic toxicities were lower in patients receiving the neoadjuvant.

The results of these randomised studies show that the scheme of preoperative EBRT-chemotherapy for locally advanced rectal cancer is well tolerated, with no contribution to surgical mortality and morbidity, disregarding technical difficulties after surgery.

Preoperative EBRT-chemotherapy (or even EBRT alone are able to decrease the rate of recurrence (98). Together with meticulous surgical techniques, preoperative EBRT-chemotherapy today is improving the risk-benefit of combination therapy for locally advanced carcinoma. Multidisciplinary approach can achieve good oncologic results at an equally good QOL.

a.7. Neoadjuvant and adjuvant radiation therapy

This technique, called the "Sandwich technique", has the advantage of a preoperative low dose (5-15 Gy) followed immediately by surgery, preventing the cells from spreading. A full-dose EBRT is given after surgery, as high as
45-50 Gy in the worst cases. The RTOG (Radiation Therapy Oncology Group) (1) trial administered 5 Gy preoperatively to 350 patients and then an adjuvant 45 Gy after surgery for T3 or N-positive patients. No therapeutic benefit was demonstrated as there were no differences in local or distant failure.

3. Palliative radiation therapy

Locally advanced and/or unresectable stage tumours represent very heterogeneous diseases, and the definition of resectability differs among schools and authors. From the surgical point of view, resectability is when a tumour can be resected without leaving residual tumour material, either microscopic or macroscopic. In this context, we find that different clinical and multidisciplinary approaches are essential to the patient.

Locally advanced cases are rare and have a poor prognosis for survival and QOL of the patients. After completing a perfect staging, the indication is to perform preoperative chemotherapy + EBRT at a dose of 45-50 Gy with concurrent chemotherapy schemes, provided that the patient can tolerate them. Responses can be achieved in 50-70% of patients with pCR rates of 10-30%, depending on the series, with increased gastrointestinal toxicity. Four to six weeks after surgery, the type of resection needed will depend on the location and extent of the disease (1). Once excised, the tissue is examined, and the surgical field must be examined to identify areas where residual disease and the presence of microscopic or macroscopic positive margins may occur. In cases in which residual disease is possible and the technology is available, IORT at doses of 10-20 Gy could be administered over the area of risk of relapse, to improve local control. Subsequent chemotherapy (4-6 cycles) gives significant rates of control of local disease. For patients with only local recurrence after a radical treatment with preoperative EBRT + chemotherapy, total or posterior pelvic exenteration can produce prolonged disease-free survival. IORT for patients with locally recurrent disease who previously received RT may improve local control with acceptable levels of morbidity. The symptoms that accompany both locally advanced colorectal and presacral recurrences are varied: bleeding, pain, infiltration of the sacral plexus, bone destruction, intestinal obstruction, etc. Metastases of colorectal origin occur, in order of frequency, in the liver, lung, and bone and also display the symptoms described above. Surgical resection of lung and liver metastases can be performed in selected patients with survival to five years. Palliative treatments improved symptoms in 70% (5) of patients with bone metastases. RT has an analgesic effect widely known since the 1960s. Pain is relieved in 70% of cases and disappears in 20-60%, beginning 3-10 days after treatment, depending on the fractionation used (99).
The treatment of bone metastases has no standard time frames or dose rates. Many schemes have been analysed with different doses and fractionations, number of locations, onset of symptoms, histology of the primary tumour, and volumes of irradiation. None have shown significant differences in strength and response to pain (1). A meta-analysis in 2003 and the Cochrane review (Sze et al.) (100) reported no differences between single and standard subdivisions in response to pain (2,3).

For liver metastases many therapeutic options have been studied and described, and all are palliative. The liver palliative RT is a great unknown in the palliation of symptoms. But some studies such as RTOG, in his study 76/05, communicate schemes with total doses of 20 to 30 Gy in 7 to 16 fractions over the entire liver, with or without superimposition of single lesions (20 Gy). The rates of improvement of signs and symptoms evaluated after four weeks of EBRT were: 55% for abdominal pain (1), 49% for nausea and vomiting, 45% for sweating and fever, 49% for ascites, and 39% for alkaline phosphatase levels (2). We must not forget, however, that the average survival of patients undergoing EBRT for liver metastases is only 4 months (3).

4. Reirradiation

Irradiation in patients treated for rectal cancer is a major problem because of the risk of damage to organs involved in the treatment and the toxicity that occurs with EBRT and chemotherapy. This was long the thinking of many radiation oncologists, but recent years have seen a change in the management of irradiated patients. Oncologists should consider the previous radiotherapy, dose, fractionation, technique, and length of interval between treatments, the first of which is sometimes enough to repair cell damage. Even though we have different techniques, we should use for reirradiation cautiously and be conscious of possible complications to the patient. Different techniques include: 3D radiotherapy, IMRT, stereotactic RT, IORT, particle and proton therapy, and brachytherapy with both high and low rates. All these techniques are in clinical trials or treatment protocols.

Studies, reviewed by Mohiuddin et al. (91), have shown good long-term outcomes in patients with local pelvic recurrence. In one study, 103 patients with presacral recurrence received a combined treatment with chemotherapy and EBRT (50.4 Gy) and subsequent surgery, then EBRT (reirradiation) with chemotherapy (5-FU continuous infusion). Patients were irradiated with doses of 30 Gy (1.2 Gy Twice a day) or 30.6 Gy (1.8 Gy Every Day) Followed by a boost of 6 to -20 Gy to gross tumour volume with a 2 cm margin) with Opposed laterals or a three-field technique with a posterior field and two laterals to the presacral area and gross tumour volume with 2 - to 4-cm
margin. Forty-one patients were subsequently explored surgically, 34 of whom received surgery that preserved the anal sphincter. OS at 5 years was 19%. Patients receiving surgery had better survival with acceptable acute and late toxicities. The palliation of symptoms such as bleeding was achieved in 100% of patients.

Another study, by Haddock et al. from the Mayo Clinic and Mayo Medical School (101), highlighted a series of 51 previously irradiated patients who underwent IORT with a mean reirradiation dose of 20 Gy. The results revealed a tendency to local control but a short OS time due to the development of distant metastases. Peripheral neuropathy and ureteral obstruction were among the toxicities seen with IORT. Glimelius et al (102), at the Uppsala University Hospital, reported that patients who suffered recurrence after receiving pelvic EBRT at a dose of 50 Gy could be treated with doses of at least 30 Gy with the new technologies described above. All strategies that succeed in increasing the dose in recurrences can bring short-term benefits but do not change survival. All treatments with reirradiation should be considered when treatment options are minimal.

5. Toxicity of radiation therapy

The toxicity of EBRT is of two types: acute and chronic. According to the criteria of the RTOG and the National Cancer Institute published in the Common Toxicity Criteria (CTC) is considered acute toxic to all the changes that occur during treatment and 90 days and chronic or delayed toxicity complications that occur after the 3 months to years after EBRT (103). The acute toxicity of EBRT in rectal cancer appears as intestinal (2) and genitourinary symptoms as are the parts that are included in the treatment volume.

Symptoms of acute gastrointestinal toxicity (80-90% of patients) include: nausea and vomiting, fullness, anorexia, and fatigue, all of which may appear from the first session of EBRT; proctocolitis: increased bowel movements, diarrhea, rectal urgency, tenesmus, and rectal bleeding; and radiation enteritis, which appears in the second to third week of EBRT and consists of watery diarrhea, frequent bulky stools, and abdominal cramping. Radiation enteritis usually subsides within 2-3 weeks after the completion of EBRT (1).

Symptoms of chronic gastrointestinal toxicity (60-90%) (104) include: complications such as intestinal obstruction that is often preceded by acute colitis; drilling with acute abdominal pain, rectal bleeding, altered bowel ulceration, thickening of folds, narrowing of bowel segments, and mesenteric adhesions that cause malabsorption; chronic proctitis with rectal urgency, abdominal pain, mucous discharge, and bleeding; and ulceration, fistulation, and rectal stenosis, which is more common in patients who
received vaginal brachytherapy. Symptoms of acute genitourinary toxicity (80-90%) include acute cystitis from bladder toxicity, clinically characterised by dysuria, and increased urinary frequency and urgency. Symptoms of chronic genitourinary toxicity (10-20%) usually appear within 12-20 months of EBRT and include reduced bladder capacity, hematuria by telangiectasias, hemorrhagic cystitis, chronic irritation, or the formation of vesicovaginal fistulas.

All these symptoms depend on the total dose, fractionation used, and above all, the treatment volume and planning. Hypertension, diabetes, previous abdominal surgery, and pelvic inflammatory disease have been described as predisposing factors for the development of radiation-induced intestinal toxicity. Diarrhea (1-3) is the most common symptom of acute toxicity in these patients, which is increased by the concomitant administration of chemotherapy (5-FU and capecitabine) (105-107).

**Fisiopathology of radiation toxicity**

The pathophysiology of toxicity begins early in EBRT, with an inhibition of mitosis, depletion of intestinal mucosal cells with high proliferative capacity, degenerative changes, and necrosis of the deep cells of the intestinal glands (crypts of Lieberkühn). Capillary conjunctival hyperemia and swelling develop later. Congestion of the vessels appears and hyalinisation begins. Mitosis resumes but starts late and programmed cell death (apoptosis) occurs. All these effects result in malabsorption of fats, carbohydrates, proteins, and bile salts. The intestinal mucosae usually recover within 1-3 months after completion of EBRT. In the connective tissues of the mucous membranes, submucosal and subserosal thickening of vascular adventitia appears and mucohialino tissue with the formation of collagen. Symptoms during the late phase of EBRT are more serious and irreversible. EBRT can cause atrophy of the mucosa and thickening and proliferation of endothelial lipid deposition, and endoarteritis obliterans with anoxia and subsequent necrosis may occur later (108). Many of these symptoms can be controlled with a low-fat diet, iron supplements, and vitamins B12, A, and D, but sometimes surgery is necessary, which is complicated by extensive multiple injuries. The distinction between tumour recurrence and radiation-induced toxicity is difficult to discern, and in some cases both can coexist. Prevention is the most important measure and avoid treating of the small intestine is a priority. Proper treatment, especially the choice of technique, is essential to minimise side effects.
Emami (109) tolerance doses to the small intestine and bladder are specified in Table 3, with the volumes of organ at risk receiving more than the written dose are the following: Volume rectal V72 <30%, V60 <50%, V40 <60%. In the case of the bladder, V70 <10%, V60 <40% (see Table 3 to better understanding).

**Table 3.** Normal tissue tolerance to therapeutic irradiation.

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD5/5 volume</th>
<th>TD5/50 volume</th>
<th>complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Small intestine</td>
<td>50Gy ---</td>
<td>40Gy 60Gy</td>
<td>45Gy</td>
</tr>
<tr>
<td>Colon</td>
<td>55Gy ---</td>
<td>45Gy 65Gy</td>
<td>55Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>--- 80Gy 65Gy</td>
<td>--- 85Gy 80Gy</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>50Gy 30Gy 23Gy</td>
<td>--- 40Gy 28Gy</td>
<td></td>
</tr>
</tbody>
</table>

TD 5/5: tolerance dose of 5 years, 5% complications

For the assessment of possible acute and late complications, various scales have been developed to standardise terms for the various symptoms/signs in EBRT:

- **CTC (Common Toxicity Criteria) Scale:** In 1982, the National Cancer Institute developed criteria for assessing the toxicity of treatment with chemotherapy, for use in clinical trials. The last scale was published in December, 2003 (CTCAE version 3.0 (common Terminology Criteria for Adverse Events)) and is used for both chemotherapy and EBRT (110).
- **RTOG/EORTC (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer):** In 1983, these two organisations differentiated between acute and chronic toxicity (103). This scale assesses organ toxicity and is commonly used in used in clinical practice in Radiation Oncology (111,112).
- **SOMA/LENT:** In 1995, the consensus conference of late effects in normal tissues introduced a new scale for late toxicity, also developed by the RTOG and EORTC, called SOMA/LENT (subjectivism, objectivism, Management, and Analytic/The Late Effects on Normal tissue) (113). The main objective of this scale was to create a classification system of late toxicity to vital organs as a result of different oncological treatments. This
scale is used for each organ included in the radiation field, and consists of four aspects:

1. Subjective: description of symptoms
2. Objective: signs, such as edema or weight loss, can be detected on physical examination
3. Management: possible treatment and reversibility of toxicity
4. Analysis: special laboratory tests or imaging techniques (Computed tomography, MRI), and measurable procedures.

In general, toxicity is lower in groups receiving preoperative EBRT + chemotherapy, compared to those receiving postoperative EBRT + chemotherapy. Minsky et al. (56) compared the toxicity of EBRT + chemotherapy applied preoperatively and postoperatively and found less grade 3-4 toxicity in preoperative treatment (13% vs 48%, p = 0.045). Two patients had grade 3 gastrointestinal toxicity in the preoperative group and postoperative group had toxicities grade 3-4 gastrointestinal and 2 genitourinary in 7 and 2 patients respectively. In the NSABP study (95), toxicity was similar in both treatments. Diarrhea was worse in the preoperative group, and complications of surgery were related to the type of surgery. Frequent complications of anastomosis arose in the preoperative group, and the postoperative group experienced perineal complications.

In the CAO/ARO/AIO-94 study (114), rates of grade 3-4 gastrointestinal toxicity were significantly lower in the preoperative treatment group (acute: 12% vs 18%, p = 0.04; late: 9% vs 15%, p = 0.07). With chemotherapy, the incidence of diarrhea is higher for continuous infusion of 5-FU than for bolus 5-FU. Hand/foot syndrome is also more common in infusional therapy (1). Late complications are less frequent but more serious. Late symptoms typically appear 6-18 months after the end of EBRT and frequently involve the intestine: persistent diarrhea, proctitis, and obstructive symptoms and/or intestinal perforation. Urinary symptoms such as incontinence and cystitis can appear but are less common. The incidence of intestinal obstruction in patients who received postoperative pelvic EBRT and surgery is 4-12%, and some authors found no differences in the frequency of occurrence of this complication when compared with patients who did not receive EBRT (1).

A very debilitating late side effect of postoperative EBRT is described in patients undergoing low anterior resection: rectal urgency with very frequent bowel movements. These patients usually have 10 or more bowel movements a day, increasing at night, and are occasionally incontinent. These symptoms are involved in the development of anastomotic stricture
and fibrosis neorectum (115). Several studies have attempted to minimise testing the effects of pelvic EBRT using Octreotide (a somatostatin analogue), but results were poor: some symptoms worsened in the group treated with Octreotide (116).

In general, data from randomised EBRT + chemotherapy trials indicate that preoperative therapy is less toxic than postoperative therapy (7% vs 14%) (1). In studies of postoperative combination treatment, severe acute toxicity vary between 24-40% (2,3), however, the numbers of acute grade 3 to 4 in phase II studies of preoperative EBRT + chemotherapy are between 15-20% (2,5) so it is generally accepted that combined preoperative treatment does not appear to increase postoperative morbidity. Special techniques such as brachytherapy or IORT are not without morbidity. Some well-described symptoms are sensory neuropathy (16%), ureteral stenosis (23%) (117), and particularly anovaginal fistulae. As reirradiation there is no long-term studies showing low toxicity and effectiveness of these treatments, so they are performed in centers with good protocols and advanced technology experience that may cause little toxicity, ie IMRT.

The treatment of CRC must consider both acute and chronic toxicity, the patient's general condition, status of disease, and the chances of a cure. Medical care should be provided using a multidisciplinary approach, offering the patient all the best treatment options for CRC.

6. Future of radiation therapy and combined treatments in colorectal cancers

Several trials are studying ways to increase doses in rectal cancer for obtaining better local control. An Italian trial is comparing a pattern of accelerated hyperfractionation with concomitant boost and Capecitabine to conventional EBRT with Oxaliplatin and Capecitabine. This is the INTERACT-LEADER trial. Additionally, this test hopes that cT3N0-1 patients can skip the subsequent surgery if it is achieved pCR. The optimal schedule for RT, whether short or long course, must be, and is being, addressed. as we said earlier the Stockholm phase III trial will have short term results early. On the other hand, how could we administer chemotherapy in cases of short RT (5 fractions 5 Gy). To resolve this question we must await the results of the SCRIPT (Simply capecitabine in rectal cancer after irradiation plus TME) trial. All these studies will influence the way we work in the future. They will contribute to the prevention of colorectal tumours, better diagnosis, and better control at both the local and systemic scale.
Conclusion

Currently, neoadjuvant therapy, consisting of 5-FU based chemotherapy and long-course radiation therapy, is the standard of treatment for locally advanced rectal cancer. Local recurrence rates of 6-8% are consistent in randomised clinical trials. There does not appear to be a benefit in OS with preoperative chemoradiation. However, these regimens are nearing the point of tumour eradication, although the surgical resection of rectal cancer continues being necessary. Future randomised controlled trials will need to determine markers of complete response and the most effective combination of chemotherapy and radiation therapy to optimize outcomes in rectal cancer. The promising new therapies may have a role in selected patients although the research has to continue.

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