Radiotherapy for localized rectal cancer

E. Deutsch¹, P. Ezra¹, M. Mangoni² & M. Ducreux³

¹Department of Radiation Therapy Institut Gustave Roussy, Villejuif, France; ²Radiotherapy Unit, Department of Clinical Physiopatology, Firenze, Italy; ³Department of Medicine, Institut Gustave Roussy, Villejuif, France

Introduction

Surgical resection alone was the standard treatment modality for localized rectal cancer until the early 1990s. Total mesorectal excision (TME) has become the actual standard of care for patients with rectal cancer which greatly reduces local recurrences. Despite the introduction of TME, radiotherapy and chemotherapy have prevailed as integral components of modern treatment concepts. The management of localized rectal cancer requires a multi-disciplinary approach with specialist surgeons, gastro-enterologists, and medical and radiation oncologists. The sequence of treatments is more important than ever. Recent studies have highlighted the central role of radiation therapy associated with surgery to optimize local control, especially in stages II and III rectal cancer, and neo-adjvant radiochemotherapy (RCT) is now considered to be the standard. However, important questions about preoperative diagnosis, fractionation and dosing of short- and long-term radiation therapy, whether short- and long-term radiotherapy are comparable, and which chemotherapeutic drugs should be used in which combination and sequence remain to be answered. This article focuses on the indications of radiotherapy in the setting of rectal cancer, the benefits of concurrent chemoradiation and the integration of novel drugs into the strategy.

Radiation Therapy (Table 1)

The clinical target volume (CTV), estimated according to the International Commission on Radiation Units and Measurements report 50 (ICRU 50), includes the primary tumour, the mesorectum, and the posterior pelvis as well as the lateral lymph nodes which are at high risk for microscopic involvement [1]. The plan is to deliver treatment with three beams with the patient in a prone position or with a four-beam ‘box’ technique with the patient lying either supine or prone. The dose is defined as that delivered at the intersection of the central axes of the three or four beams. An improvement in survival by preoperative radiation was seen mainly in a trial conducted by Swedish investigators, in which non-TME surgery was performed [2]. Radiotherapy was given in five daily fractions of 5 Gray (Gy) followed by immediate surgery. Although long-term survival and local control benefits have been confirmed in irradiated patients, a very high local relapse rate was observed in the control arm, even in initial stages, indicating overall poor quality of surgery. Local relapse rate after rectal cancer surgery in centres that have adopted the TME technique went down from ~28 to 10%.

A similar trial was carried out by Dutch investigators, integrating TME into surgery and an extensive quality assurance program to assess surgery and radiotherapy [3]. Preoperative radiation significantly reduced local relapse rate at 5 years from 12% in the surgery alone arm to 6% in the group of irradiated patients. However, the trial was not able to detect differences in survival among patients allocated to surgery alone or to preoperative radiation. The impact of short-term preoperative radiotherapy on acute and late toxicity as well as on quality-of-life aspects and sexual functioning was also analysed in the Dutch trial [4]. Patients receiving preoperative radiation had more acute postoperative complications than patients allocated to surgery alone (48 versus 41%, P = 0.008). Most of these complications were perineal wound healing problems (29 versus 18%). Irradiated patients recovered more slowly from defecation problems than TME-only patients and irradiation had a negative effect on sexual functioning in males and in females. However, these side effects were reported not to affect health-related quality of life seriously. The analysis of long-term effects in the Swedish trial, involving the same type of preoperative radiation, showed that gastrointestinal disorders resulting in hospitalizations seem to be the most common adverse effect. Bowel obstruction was the most important complication and was more frequently observed in irradiated than in non-irradiated patients [5].

Only one randomized trial has addressed the issue of comparing short-term radiation versus conventional chemoradiation [6]. In the conventional chemoradiation arm, radiotherapy was given in daily fraction of 1.8 Gy for 3–6 consecutive days to a total dose of 45–50.4 Gy. No differences in sphincter-saving surgery were detected between the two arms, but local control or survival data have not yet been reported. Short-term preoperative radiation trials were conducted when staging with magnetic resonance imaging (MRI) was not routinely used in localized rectal cancer. This means that patient populations might be heterogeneous and consist of T2 and limited extension T3 tumours as well as locally advanced cancers. For patients with locally advanced tumours this strategy cannot be recommended due to the absence of down-staging. With the Swedish schedule, chemotherapy cannot be integrated into these large fractions of radiation without excessive toxicity. Furthermore, radiation of...
the anal sphincter with the same schedule is associated with poor bowel function. Another disadvantage is that high doses per fraction may increase the incidence of late effects such as injury to the small bowel. Furthermore, with a short interval between radiotherapy and surgery, neither tumour regression nor an increased ability to perform sphincter sparing surgery was achieved. In the Swedish study, however, the regimen was associated with a substantial reduction in local recurrence (27–11%; \( P < 0.001 \)), and also improved the 5-year survival rate (48–58%; \( P = 0.004 \)). The findings of this study have been confirmed by a meta-analysis of 8507 patients comparing preoperative radiotherapy with surgery alone [12]. Overall survival was only marginally better in patients who were allocated to radiotherapy than in those allocated to surgery alone (62 versus 63% died; \( P = 0.06 \)). Rates of apparently curative resection were not improved by preoperative radiotherapy (85% radiotherapy versus 86% control). Yearly risk of local recurrence was 46% lower in those who had preoperative radiotherapy than in those who had surgery alone (\( P = 0.00001 \)), and 37% lower in those who had postoperative treatment than those who had surgery alone (\( P = 0.002 \)). Fewer patients who had preoperative radiotherapy died from rectal cancer than did those who had surgery alone (45 versus 50%, respectively; \( P = 0.0003 \)), but early (<1 year after treatment) deaths from other causes increased (8 versus 4% died; \( P < 0.0001 \)). This analysis demonstrated that preoperative radiotherapy reduces risk of local recurrence and death from rectal cancer and substantially decreased local failure rates and, unless counterbalanced by increased postoperative mortality seen in some trials [16], it slightly improved overall survival (OS) [7–9]. According to these results, this approach has been adopted widely in clinical practice. Systemically active chemotherapy synchronously with preoperative radiation has also been tested to improve OS.

postoperative chemoradiation (Table 2)

In the USA, a series of randomized trials clearly demonstrated that adjuvant 5-fluorouracil (5-FU)-based chemotherapy administered with postoperative radiotherapy significantly reduced rates of local recurrence and improved overall survival compared with surgery alone or surgery plus postoperative radiotherapy [10–12].

A randomized trial [13] conducted in 660 patients with TNM stage II or III rectal cancer, demonstrated that continuous infusion of 5-FU (225 mg/m²/d) for the 5-week duration of radiotherapy (total dose 45 Gy plus a 5.4 Gy boost) resulted in significantly improved overall survival (\( P = 0.005 \)) and disease-free survival (\( P = 0.01 \)) compared with bolus 5-FU administration (500 mg/m² on days 1–3 during weeks 1 and 4 of radiotherapy). Patients in the two groups received identical pre- and postradiation therapy, consisting of i.v. bolus 5-FU 500 mg/m² (or 350 mg/m² plus semustine 130 mg/m² on day 1) on days 1–5 and 36–40, and i.v. bolus 5-FU 450 mg/m² (or 400 mg/m² plus semustine 100 mg/m² on day 134) on days 134–138 and 169–173. The incidence of distant metastases was also significantly decreased with infused versus bolus 5-FU. Moreover, the treatment was well tolerated. There was more grade 3/4 diarrhoea associated with infused 5-FU (24 versus 14%) but less grade 3/4 leukopenia (2 versus 11%). This study was very influential in the USA, where postoperative chemoradiotherapy with infusional 5-FU has been considered as the standard of care. A National Surgical Adjuvant Breast and Bowel Project (NSABP) [14] study, protocol R-02, confirmed that at the 5-year follow-up, postoperative radiotherapy plus 5-FU/LV achieves a small but significant reduction in the rate of local relapse from 13 to 8% in comparison with post-operative 5-FU/LV alone (\( P = 0.02 \)). In the USA, this has become the standard for patients with rectal cancer.

adding chemotherapy to radiotherapy

Despite important advances in local therapy for rectal cancer, metastases will appear in a significant number of patients, especially in those with locally advanced tumours, nodal involvement or positive circumferential resection margin (CRM). Chemotherapy has been used to eradicate micrometastases and therefore reducing distant relapses. Chemotherapy has also been integrated in radiation schedules trying to enhance the effect of radiotherapy and resulting in better local control.

5-fluorouracil

5-FU is one of the most commonly used chemotherapeutic agents for colorectal cancer. Phase II studies have shown higher rates of complete pathological responses after chemoradiation compared with radiation alone. Complete pathological response rates after chemoradiation (45–50.4 Gy pelvic radiation with various 5-FU-based chemotherapy regimens) have now increased 20–26% compared with only 6–12% with radiation alone [15]. The European Organization for the Research and Treatment of Cancer conducted a randomized trial investigating concurrent and/or maintenance 5-FU chemotherapy combined with preoperative radiation therapy [16]. This trial used a factorial plan evaluating the addition of chemotherapy to preoperative radiotherapy pre- and postoperatively resulting in four groups of patients RT alone, preoperative RT + preoperative CT, preoperative RT + postoperative CT, preoperative RT + pre- and postoperative CT. There was no significant difference in OS among the groups that received chemotherapy preoperatively and those that received it postoperatively. The 5-year cumulative incidence rates for local recurrences were 8.7, 9.6 and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy (\( P = 0.002 \)). This suggests that adding 5-FU-based chemotherapy preoperatively or postoperatively to preoperative radiotherapy, has no significant effect on survival. However, chemotherapy, regardless of whether it is administered before or after surgery, confers a significant benefit with respect to local control. In a trial comparing preoperative and postoperative combined-modality therapy (NSABP R-03 trial), 23% of patients undergoing preoperative chemoradiation had a complete clinical response of which 44% had a complete pathological response. Forty-four percent of patients underwent sphincter-sparing surgery in the preoperative treatment arm versus 34% in the postoperative...
treatment arm. This underscores the fact that preoperative chemoradiation, increases the likelihood of a sphincter-sparing resection with a colo-anal anastomosis as an alternative to abdomino-perineal resection (APR). Although the sphincter may be affected by low anterior resection, the majority of patients have acceptable ano-rectal function [17]. There has been increasing interest in using neo-adjuvant chemoradiation with 5-FU-based regimens to enhance sphincter-conserving surgical approaches as an alternative to APR for the treatment of distal rectal cancers (tumours with a distal edge located up to 6 cm from the anal margin).

**pre-versus postoperative strategies (Table 2)**

A randomized phase III trial from the German Rectal Cancer Study Group showed that preoperative fluorouracil-based chemoradiation administered in the conventional way over 5 weeks is more effective in local control than when the same treatment is given postoperatively [18]. Local relapse rate estimates at 5 years were 13% for the postoperatively treated patients and only 6% for the pre-operatively treated group (P = 0.006). The incidence of acute and long-term toxicity, mainly gastrointestinal, also favours preoperative treatment.

Therefore, preoperative chemoradiation with its better tolerability and improved local control may be considered as the new standard treatment of rectal cancer although no differences in distant metastases or survival were observed.

Another recent phase III trial from the Fédération Francophone de Cancérologie Digestive (FFCD), FFCD 9203, confirmed the advantages of preoperative 5-FU-based chemoradiotherapy over radiotherapy alone with respect to local control rates, but failed to detect any survival significantly improvement [19]. The addition of chemotherapy resulted in significant higher rates of complete tumour eradication in pathological analysis of the surgical specimen (11.4% for chemoradiation versus 3.6% for radiation alone). Systemic chemotherapy not only induced down-staging and downsizing of treated tumours, but also reduced the rate of tumour vascular and lymphatic invasion. Local failure rate for radiation alone arms was 16.5%, but went down to 8.1% in patients treated in the combined modality arms. However, although the addition of chemotherapy was able to increase local control, no effect was observed in distant metastases or OS.

**impact of tumour downstaging**

Recent reports showed that improved downstaging of cancer after neo-adjuvant therapy also leads to improved survival of patients. Patients downstaged to pT0 or T1–T2 tumours have a 5-year survival of 100% compared with 78% in patients who remain T3 or N positive after neo-adjuvant therapy [31]. Similar results have also been reported by others [32, 33]. Radiation dose is a significant factor in the degree of downstaging of disease. Mohiuddin found that patients treated to a dose of ≤50 Gy even in the presence of chemotherapy had a downstaging rate of 67% and a pathological complete response (pCR) rate of 3%, compared with a downstaging rate of 89% and a pCR rate of 45% at doses of ≥55 Gy (P = 0.05).

The degree of histological tumour regression after preoperative chemoradiation has been assessed in the German study [18]. Complete and intermediate primary tumour (not including nodal) response was associated with improved disease-free survival (P = 0.006), although in multivariate analyses, only pathologic nodal staging predicted disease-free survival, local recurrence and distant metastasis rates [34].

**capecitabine**

Capecitabine is an oral fluoropyrimidine that imitates the pharmacokinetics of a continuous 5-FU infusion and is preferentially converted to the active metabolite within tumour cells by exploiting the higher activity of the enzyme thymidine phosphorylase in tumour tissue compared with normal tissue [20]. This tumour-selective activation of capecitabine is improved further when combined with radiotherapy, which upregulates thymidine phosphorylase in tumour cells but not in healthy tissues [21].

Preoperative chemoradiation with capecitabine and radiotherapy appears to be effective in locally advanced resectable rectal cancer phase II trials. The favourable safety profile of the combination might warrant the use of capecitabine and radiotherapy with other effective new drugs. A two arms comparative trial between bolus injection of 5-FU and leucovorin versus capecitabine [22] in the preoperative setting did not reveal significant differences in tumour responses rates. Although long-term results and a prospective randomized trial are needed, these data strongly suggest that either 5-FU or capecitabine might be used during radiotherapy [23].

**oxaliplatin**

Oxaliplatin is a platinum derivative which has substantial activity in colorectal cancer. Used alone, it gives ~20% objective response rates in patients with metastatic disease [24]. In combination with 5-FU and folinic acid, the overall response rate can be >50%, leading to a significant progression-free survival advantage over 5-FU with folinic acid alone [25].

Moreover, like all platinum derivatives, oxaliplatin is a radiosensitizer [26] and may therefore improve preoperative chemoradiation results, both in terms of local control and prevention of distant metastasis.

Also, it is a reasonable candidate for combined-modality programs because of its relative lack of acute dose-limiting adverse effects when added to radiotherapy. A phase I study with oxaliplatin combined with 5-FU on weeks 1 and 5 of radiotherapy recommended 130 mg/m² oxaliplatin for phase II studies [27]. Interestingly at this dose level, no toxicity was observed concurrently with radiation. A phase II study found that weekly oxaliplatin at doses potentially active systemically can be combined with full-dose radiotherapy [28]. A phase I/II study evaluated the feasibility and efficacy of preoperative radiotherapy (total dose, 50.4 Gy) with concurrent capecitabine and oxaliplatin (XELOX-RT) in patients with rectal cancer. T-category downstaging was achieved in 17 (55%) of 31 operated patients, and 68% of patients had negative lymph nodes. A pCR was found in 19% of the resected specimens. Radical surgery with free margins could be performed in 79% of patients with...
<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Outcomes</th>
<th>Reported toxicities</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **RADIATION THERAPY**

Swedish Rectal Cancer Trial [2]

Preoperative short-term RT (5 × 1 × 5) followed by immediate non-TME (total mesorectal excision) surgery versus surgery alone

- Reduction in local recurrence: 27% in surgery arm versus 11% in RT arm ($P < 0.001$)
- 5 years local survival rate: 48% in the surgery alone arm versus 58% in RT arm ($P < 0.004$)
- Very high local relapse rate in control arm: overall poor quality of surgery

Gastrointestinal disorders

CT cannot be integrated without excessive toxicity

Bowel obstruction most frequent in RT arm [5]

Radiation of the anal sphincter is associated with poor bowel function

High doses per fraction increase the incidence of injury to small bowel

With a short interval between RT and surgery neither tumor regression nor an increased ability to perform sphincter sparing surgery were achieved

Dutch trial [3]

Preoperative short-term RT combined TME versus TME alone

5 years local relapse rate: 12% in the surgery alone arm versus 6% in the preoperative RT arm

More acute postoperative complications in the preoperative RT arm (48 versus 41%; $P = 0.008$), mostly perineal wound healing problems (29 versus 18%)

More slow recovery from defecation problems in RT arm

The side effects were reported not to affect quality of life seriously

Bujko K et al. [6]

Randomized trial comparing short-term preoperative RT versus conventionally fractionated RT–CT (1.8 × 1 × 5–6 total dose 45–50.4 Gy) bolus 5-FU LV

No difference in sphincter saving surgery

Data on local control or survival not yet reported

Holm T et al. [7]

RT versus surgery alone

OS only marginally better in patients who were allocated to RT (62 versus 63% died $P = 0.06$)

Early deaths from other causes increased in preoperative RT (8 versus 4%; $P < 0.0001$)

Preoperative RT reduces risk of local recurrence and improves OS

Camma C et al. [8]

Rates of apparently curative resection not improved by preoperative RT (85 versus 86%)

Krook JE et al. [12]

Yearly risk of local recurrence was 46% lower ($P = 0.00001$) in preoperative RT and 37% lower ($P = 0.002$) in postoperative RT versus surgery alone

Bosset JF et al. [16]

Less death for cancer in preoperative RT versus surgery alone (45 versus 50% $P = 0.0003$)
## Table 2. Postoperative chemoradiotherapy and pre- versus post-operative strategy

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Outcomes</th>
<th>Reported toxicities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSTOPERATIVE CHEMORADIOThERAPY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Tumor Study Group [10]</td>
<td>Adjuvant 5-FU-based CT with postoperative RT versus surgery alone or surgery + postoperative RT</td>
<td>Significantly reduced rates of local recurrence</td>
<td></td>
</tr>
<tr>
<td>NSABP protocol R-01 [11]</td>
<td></td>
<td>Improved OS versus surgery alone or surgery + postoperative RT</td>
<td></td>
</tr>
<tr>
<td>Krook JE et al. [12]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Connell MJ [13]</td>
<td>5-FU c.i. (225 mg/m²/d) for the 5-week duration of RT (45 + 5.4 Gy boost) versus 5-FU bolus (500 mg/m²) on days 1–3, during weeks 1 and 4 of RT</td>
<td>Significantly improved OS (P = 0.003) and disease free survival (P = 0.01)</td>
<td>More grade 3/4 diarrhoea associated with 5-FU c.i. (24 versus 14%) but less grade 3/4 leukopenia (2 versus 11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP protocol R-02 [14]</td>
<td>Postoperative RT+ 5-FU/LV versus postoperative 5-FU/LV alone</td>
<td>Decreased incidence of distant metastases with 5-FU c.i.</td>
<td></td>
</tr>
<tr>
<td><strong>5-Fluorouracil</strong></td>
<td></td>
<td>Reduction in rate of local relapse in RT arm (8 versus 12%; P = 0.02)</td>
<td></td>
</tr>
<tr>
<td>Minsky et al. [15]</td>
<td>CT–RT (45–50.4 Gy with 5-FU-based regimens) versus RT alone</td>
<td>Complete pathological response rates increased 20–26% versus 6–12% with RT alone</td>
<td></td>
</tr>
<tr>
<td>EORTC [16]</td>
<td>RT alone, versus preop. RT + preop. CT, versus preop. RT + postop. CT, versus preop. RT + pre- and postop. CT</td>
<td>5 years cumulative incidence rates for local recurrence: 17.1% RT alone, 8.7% CT preop, 9.6% CT postop, 7.6% both OS: no significant differences between CT pre or postop</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No significant difference between CT pre- or postoperative, but benefit in local control with CT versus RT preoperative alone</td>
</tr>
<tr>
<td>NSABP R-03</td>
<td>Preoperative neoadjuvant to postoperative adjuvant CT–RT</td>
<td>Patients with preop. CT–RT: 23% complete clinical response, of which 44% complete pathological response</td>
<td>Preoperative CT–RT increases the likelihood of sphincter-sparing resection [17]</td>
</tr>
<tr>
<td><strong>PRE- VERSUS POST-OPERATIVE STRATEGY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>German Rectal Cancer Study Group [18]</td>
<td>Preop. versus postop. CT–RT</td>
<td>5 years local relapse rate 6% in preop. versus 13% in postop. (P = 0.006)</td>
<td>Less incidence of acute long term toxicity in preop. arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No differences in distant metastases or survival</td>
<td></td>
</tr>
<tr>
<td>FFCD 9203 [19]</td>
<td>Preop. RT with concurrent 5-FU and LV versus RT preop. alone (phase III)</td>
<td>Addition of CT increases local control (local failure 8.1 versus 16.5%)</td>
<td>Systemic CT induces downstaging and downsizing of tumor and reduces the rates of tumor vascular and lymphatic invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not differences in OS</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. (Continued)

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Outcomes</th>
<th>Reported toxicities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impact of tumor downstaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobiuddin M et al. [31]</td>
<td>Preop. CT–RT</td>
<td>CT–RT with doses ≤50 Gy had downstaging rate of 67% and pCR rate of 3% versus a downstaging rate of 89% and pCR rate of 45% at doses ≥55 Gy ($P = 0.05$)</td>
<td>Improved downstaging after neoadjuvant therapy leads to improved survival</td>
</tr>
<tr>
<td><strong>Capecitabine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machiels JP et al. [22]</td>
<td>Bolus injection of 5-FU and LV versus capecitabine preoperative (phase I/II)</td>
<td>Not significant differences</td>
<td>Good tolerance</td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becouarn Y et al. [24]</td>
<td>OXA monotherapy</td>
<td>20% objective response rates in patients with metastatic disease</td>
<td></td>
</tr>
<tr>
<td>GERCORD [25]</td>
<td>OXA in combination with 5FU and folinic acid</td>
<td>Significant progression-free advantage versus LV5-F-U2 alone (overall response rate &gt;50%)</td>
<td></td>
</tr>
<tr>
<td>McMullen et al. [26]</td>
<td>CT–RT preop. with OXA</td>
<td>OXA improves local control and prevention of metastases</td>
<td>No acute dose-limiting adverse effects when added to RT</td>
</tr>
<tr>
<td>Lyon R0-04[27]</td>
<td>Preop CT–RT with high dose RT and OXA-regimen (phase I) on weeks 1 and 5</td>
<td>No toxicity</td>
<td>Recommended 130 mg/m² for phase II study</td>
</tr>
<tr>
<td>Aschele C et al. [28]</td>
<td>Weekly OXA, 5-FU c.i. and preop. RT (phase I–II)</td>
<td></td>
<td>Weekly OXA at doses active systemically can be combined with full-dose RT</td>
</tr>
<tr>
<td>Rodel C et al. [29]</td>
<td>Preoperative RT 50.4 Gy with concurrent capecitabine and OXA (XELOX-RT)</td>
<td>T-category downstaging achieved in 55% of patients 19% of pathologic complete response</td>
<td>Evidence of clinical potential of OXA-based preoperative CT–RT regimens</td>
</tr>
<tr>
<td>Chau I et al. [30]</td>
<td>Neoadjuvant capecitabine and OXA follow by synchronous CT–RT</td>
<td>PCR rate 24%</td>
<td>Randomized phase III trials result are awaited to demonstrate superiority of OXA to 5FU-based CT-RT</td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navarro M et al. [35]</td>
<td>Irinotecan + 5-FU or CPT11 + capecitabine</td>
<td>Efficient: pCR rate 13–22%</td>
<td>Good tolerance in CT–RT</td>
</tr>
<tr>
<td>Hofheinz RD [36]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voelter V [37]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
T4 disease, and 36% of patients with tumours ≤2 cm from the dentate line had sphincter-saving surgery [29]. In a recent study evaluating neo-adjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation the pCR rate was 24%, and another 48% of patients had only microscopic tumour foci seen in the resected specimen, with clear pathologic CRM observed in all but one patient. The pathological downstaging rate was 76% [30].

These results clearly suggest the clinical potential of oxaliplatin-based pre-operative chemoradiation regimens. Randomized phase III trials results are awaited to demonstrate their superiority to 5-FU-based chemoradiation. An ongoing randomized phase III trial from the French gastrointestinal cancer study group (FFCD) comparing two concurrent preoperative chemotherapy regimens namely capecitabine versus capecitabine + oxaliplatin should also contribute to the assessment of the benefit of concurrent oxaliplatin.

**irinotecan**

Several clinical trials found that Irinotecan +5-FU [35] or capecitabine [36] [37] [38], was safe and efficient in combination with radiation with tumour pCR rates ranging from 13 to 22%. The Radiation Therapy Oncology Group [39] undertook a randomized study to compare a radiotherapy dose-intensification approach (55–60 Gy) using a hyperfractionated radiotherapy schedule with continuous venous infusion of 5-FU and a chemotherapy dose-intensification approach using irinotecan and 5-FU, with conventional once-daily radiotherapy (50–54 Gy). The rate of tumour downstaging was high (80%) with either radiotherapy dose intensification or with chemotherapy dose-intensification. The pCR rate was 28% with either radiotherapy or chemotherapy dose-intensification. This pCR might be higher than many studies indicate and may be the consequence of the increase in radiation dose. Although no differences could be observed between both arms, this study suggests a high efficacy of irinotecan-based chemoradiation preoperative regimens.

**EGF and VEGF receptors inhibitors**

The development of molecular targeted therapies in colorectal cancer offers opportunities for new drug–radiation combinations. Among the many pathways and potential new drugs, agents targeting the epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) receptors, which are already approved in colorectal cancer, are to-date the most likely to be combined with radiotherapy in the near future. Two phase I trials have shown that preoperative radiation combined to cetuximab and capecitabine + irinotecan is feasible with some patients achieving pathological downstaging [22]. Whether this approach improves local control and survival will be the object of subsequent phase II–III evaluation. In contrast, combination of gefitinib, capectabine and radiation in pancreatic and rectal cancer patients resulted in significant toxicity. This suggests that combination of radiotherapy and gefitinib should be approached with caution [40].
The use of the anti-vascular EGFR antibody bevacizumab in combination with pre-operative radiochemotherapy for the treatment of rectal cancer has been evaluated in a phase I setting. This study not only assessed the tolerance of this regimen but also the validation of the concept of endothelium normalization under vascular endothelial growth factor receptor modulation in humans.

**Conclusion**

The management of localized rectal cancer requires a multidisciplinary approach with specialist surgeons, gastroenterologists, medical and radiation oncologists. As evidence of the usefulness of neo-adjuvant chemoradiation is increasing, clinical trials will have to define the best drugs regimen to be combined to radiotherapy beyond 5-FU. Future challenges will be to incorporate imaging and molecular tumour characteristics into the TNM staging to choose the optimal treatment. The integration of imaging refinements, especially MRI to allocate patients-at-risk to more choose the optimal treatment. The integration of imaging refinements, especially MRI to allocate patients-at-risk to more

**References**