introduction

The management of rectal cancer requires a multidisciplinary approach with individual treatment based on a careful assessment of tumour location, stage and resectability. Early identification of the patients that are candidates for combined modality treatment is crucial. After showing less acute and long-term toxicity along with an improved local control in a randomized study, pre-operative combined chemoradiation has in fact recently replaced post-operative radiochemotherapy as standard treatment for locally advanced rectal cancer [1]. Multimodality treatment and the optimization of single treatment components [surgery in particular with the introduction of total mesorectal excision (TME)] have concurred to improve the prognosis of locally advanced rectal cancer with local recurrences decreasing from 40 to <10% and overall survival increasing from 50 to 75% in the last 40 years [2]. In addition, low anterior resection (LAR) has progressively replaced abdomino-perineal resection (APR) with rates of sphincter preservation that have moved from <10% in the 1970s to >80% in the 2000s [3]. Of note, the substantial improvement in local control has not been paralleled by a similar decrease in distant metastases that represent the site of failure for up to 30% of patients, despite optimal surgery and pre- or post-operative radiation with concomitant, radiosensitizing, and sequential, adjuvant, 5-fluorouracil (FU)-based chemotherapy (Figure 1) [1, 4, 5]. The role and limits of the chemotherapy regimens used in the standard combined-modality treatment programs for rectal cancer and the ongoing research to improve these regimens will be reviewed in this article in the light of the specific aims and current indications of adjuvant/neoadjuvant treatment.

definition of rectal cancer

The first task of a multidisciplinary team facing a patient with a cancer in the distal portion of the large bowel is discriminating between colon and rectal cancer. This is particularly important from a medical oncologist’s viewpoint. Combination chemotherapy represents in fact the standard adjuvant treatment for radically resected colon cancer, at least in the presence of involved regional lymph nodes [6], while radiation, combined with FU-based chemotherapy, is routinely used for extraperitoneal rectal tumours [7] and preferentially administered before surgery [8].

Anatomically, the upper boundary of the rectum is located at the rectosigmoid junction, slightly below the sacral promontory. On clinical grounds, the peritoneal reflection is a more important landmark. The anterolateral wall of the upper third of the rectum is in fact lined by the peritoneum and tumours located above the peritoneal reflection have the same clinical behaviour and, therefore, clinical management of colon cancer. The risk of local recurrence increases, and overall prognosis worsens, moving towards the ano-rectal junction [9]. Combined modality treatment, including radiation therapy, is thus warranted for tumours with an extraperitoneal component.

This distinction is easy in the post-operative setting as the location of the tumour relative to the peritoneal reflection is part of the surgical and pathological report. A tentative identification of extraperitoneal rectal tumours prior to surgery is generally obtained measuring the distance between the inferior edge of the tumour and the anal verge. Although rigid rectoscopy eliminates the variability due to the possible folding of a flexible scope, the optimal cut-off distance remains to be defined. Several trials of pre-operative radiation have included patients with tumours located up to 16 cm from the
anal verge [1, 4, 10, 11]. This measure may not correspond to the extraperitoneal rectum, potentially resulting in inclusion of intraperitoneal tumours that would thus be over-treated with unnecessary radiotherapy. A more conservative 12-cm limit has been used in other trials [12–14]. The rates of local failure for tumours located in the upper-third of the rectum that are 3–5-fold lower compared with more distal tumours, and thus similar to those reported for colon cancer [15], provide an argument in favour of this more conservative approach. Moreover, the benefit of radiotherapy on local control has been shown to fade-off in tumours located in the upper-third of the rectum [4, 16]. Constitutional factors that may influence the distance of the peritoneal reflection from the anal verge, including age, sex, height, weight and parity, also need to be considered. Pelvis magnetic resonance imaging (MRI) may overcome these pitfalls directly showing the peritoneal reflection and the tumour on high resolution images [17, 18].

**selection of patients for adjuvant treatment**

Rectal tumours with extramural penetration and/or involvement of the regional lymph nodes are candidates to receive adjuvant or neoadjuvant chemoradiation [7, 8]. Since preoperative treatment recently proved superior to post-operative chemoradiation [1], the identification of these patients prior to surgery is crucial. Trans-rectal ultrasound or pelvic computed tomography scan (CT) with an appropriate technique to enhance wall resolution may be alternatively used based on tumour location and expertise available at each centre. MRI may complement these techniques in the definition of T and N stage and provide additional information important for patient selection [18]. In particular, high-resolution MRI allows identification of the mesorectal fascia that will correspond to the lateral margin of the resection specimen after TME [17, 19]. If the tumour reaches, or closely approaches, the mesorectal fascia, a radical resection with a negative circumferential resection margin will not be feasible unless adequate tumour shrinkage is obtained before surgery. In this case, pre-operative treatment with an active chemoradiation regimen becomes the only treatment option. Penetration into the perirectal fat may also be accurately measured helping to refine the prognosis within the group of patients with T3N0 tumours [18].

Efforts are being made also to develop more conservative treatment approaches for selected groups of patients. The omission of radiotherapy has been proposed for T1–T3 tumours without, or with just a minimal, lymph node involvement based on low rates of local failures reported in retrospective analyses of post-operative trials comparing different chemoradiation regimens [5, 20, 21]. In one of these series, however, local failures for T3N+ tumours reached 18% [20]. This may depend on the existence of subgroups with a different prognosis within the T3 category underlining the importance of quantitatively assessing the degree of penetration into the perirectal fat. In particular, rates of local failures similar to that of T1–T2 tumours have been reported when this measure does not exceed 5 mm [22]. A further limitation is that almost all patients in these studies received post-operative chemoradiation making it impossible to rule out a contribution of post-operative treatment to the favourable outcome.

In addition, these analyses were based on patients treated in the post-operative setting and the results cannot be immediately extrapolated to preoperative treatment. In the Dutch TME trial, a significant reduction of local failures with
preoperative radiation has indeed been reported even for stage II patients [4]. Given the substantial reduction of acute and, more important, long-term toxicity achieved with neoadjuvant compared with post-operative chemoradiation [1], the search of less aggressive treatment programs may then be less compelling when pre-operative chemoradiation is considered. A final note of caution on the use of selective treatment approaches comes from a Medical Research Council (MRC) study presented at the last ASCO meeting. Selective post-operative chemoradiation, based on pathologic findings, and, specifically, on the detection of a positive circumferential resection margin, resulted in fact in thrice higher rates of local failure at 5-years compared with routine administration of short-course pre-operative radiation to all patients [23]. A distance between the tumour and the mesorectal fascia of at least 5 mm measured on high-resolution MRI, a <5 mm tumour penetration into the perirectal fat, the lack of pathological lymph nodes on preoperative imaging and a tumour location allowing restorative surgery without a coloanal anastomosis are the necessary prerequisites to consider initial surgery in selected patients. Radiation could then be omitted even in the adjuvant setting if the pathologic findings confirm an intact mesorectum with an adequate radial clearance (≥22 mm) and a minimal tumour penetration into the perirectal fat with an adequate number of negative lymph nodes (≥12) and a well to moderately-well-differentiated tumour.

**chemotherapy concomitant to radiation**

Radiotherapy is used in rectal cancer to sterilize local foci of microscopic disease and, therefore, decrease the risk of local failure. When administered before surgery, radiation therapy has the additional effect of inducing an objective tumour shrinkage with potential benefits in terms of resectability and/or salvage of the anal sphincter for large or low-lying tumours. Concomitant radiosensitizing chemotherapy is required to maximize both of these effects. In the post-operative setting, chemoradiation consistently halved the rates of local failure compared with surgery alone in a series of randomized clinical trials [24–27]. Chemotherapy plays an important role in determining this effect. Post-operative radiation alone has in fact been shown to reduce local recurrences by only one-third in a metaanalysis of randomized studies with a surgery alone control arm [28]. In addition, a statistically significant reduction was observed in only one of these studies. Direct evidence of the importance of adding chemotherapy to post-operative radiation in order to optimize local control was then provided in a head-to-head comparison with post-operative radiotherapy [26]. In these studies, chemotherapy was generally administered both concomitantly and sequentially to radiation with a various number of additional chemotherapy courses delivered either before or after concurrent treatment [24–26]. The contribution of a direct cytotoxic effect of chemotherapy to the observed gain in local control cannot thus be excluded. The significant reduction of local recurrences compared with surgery alone obtained even with chemotherapy administered exclusively during radiation underlines the importance of radiosensitization with concurrent administration [27].

Pre-operative radiation is more efficacious than post-operative radiotherapy. A significant reduction of local recurrences compared with surgery alone has been reported in eight randomized clinical trials [29] with a proportional reduction in the rates of local recurrence that compares favourably with that obtained with post-operative chemoradiation [28]. The need to add concomitant chemotherapy to radiation in the pre-operative setting has indeed been questioned for a long time [30]. In addition, the large daily fractions of radiation preclude the incorporation of concurrent chemotherapy when short-course radiation is used [30]. An improved anti-tumour activity with the addition of concurrent chemotherapy to pre-operative radiation has been initially suggested in retrospective studies with historical controls [31, 32]. Recently, two large randomized clinical trials have provided formal proof of the superior anti-tumour activity of pre-operative chemoradiation compared with pre-operative radiation alone, with a significant 3–4-fold increase in the rates of pathological complete responses (pCRs) (11–16 versus 3–5%, respectively) [11, 33]. More importantly, the addition of chemotherapy to radiation also reduced local recurrences, which were observed in 17.1 and 16.5 versus 7.6 and 8.6% of patients, in the radiation-alone and chemoradiation arms, respectively [11, 33]. Although standard fractionation regimens were used as control arms in these studies, the biologically effective dose of radiation is predictable and manageable allowing a >80% compliance to chemotherapy administration and not impairing the delivery of full radiotherapy doses [11, 33].

**chemotherapy sequential to radiation**

In the standard combined-modality treatment programs for locally-advanced rectal cancer, chemotherapy is administered both concomitantly and sequentially to radiation. Additional chemotherapy courses are in fact delivered either before or after concurrent treatment for a total of ~6 monthly cycles [8]. The aim is to complement the reduction of local failures achieved through radiosensitization with a reduction of metastases at distant sites and, thereby, increase survival. Decreased rates of distant metastases and improved survival were indeed obtained, along with an improved local control, when concomitant, radiosensitizing, and sequential, adjuvant, chemotherapy was added to post-operative radiation [24, 26]. Conversely, local control and overall survival were improved but no effect on distant metastases was obtained when chemotherapy was administered exclusively during radiation [27]. Strong support
for the use of adjuvant chemotherapy in rectal cancer is provided by a recent pooled analysis of five randomized studies that showed a 20% absolute survival benefit with post-operative chemotherapy, administered for 6–18 months with or without post-operative radiotherapy, compared with observation or post-operative radiation alone following surgery [21].

Since the benefit of adjuvant chemotherapy added to chemoradiation has not been directly established in randomized studies, the use of chemotherapy sequential to radiation has long been debated. Given the greater efficacy of pre-operative compared with post-operative radiation (with an increased survival compared with surgery alone in a randomized study) [10], the need of a formal proof of efficacy for the use of adjuvant chemotherapy has been advocated particularly for patients that receive radiation or chemoradiation pre-operatively. Various recent European studies in patients treated with pre-operative chemoradiation, or even radiation alone, do include in fact an observation only arm after surgery [3, 30]. On the other hand, the standard duration of adjuvant chemotherapy in colon cancer and the total duration of chemotherapy in the post-operative trials that have demonstrated the superiority of combined modality treatment compared with surgery alone support the contention that approximately 6 months of chemotherapy are required to optimize the adjuvant treatment of rectal cancer. Of note, 6 months of chemotherapy were given in both arms of the German study that has shown the equivalent efficacy of pre-operative compared with post-operative chemoradiation [1].

Given the convincing data and quality of this study, this regimen of pre-operative chemoradiation with surgery followed by four additional adjuvant chemotherapy cycles represents a reference program for the treatment of rectal cancer and should be taken into account even for the interpretation of other studies. Extrapolating from these data would allow to side-step the question concerning the benefit added by adjuvant chemotherapy after pre-operative chemoradiation and to concentrate research efforts on more relevant questions (as the search of new strategies to reduce distant metastases). Only small differences may in fact be expected when comparing active chemoradiation regimens using exactly the same radiation schedule and chemotherapy agent and leaving the different number of chemotherapy cycles as the only variable. Lack of adequate statistical power may thus result in inconclusive studies wrongly interpreted as negative [13, 35].

Of note, even a large study as the recently reported EORTC chemoradiation study [38] and of an MD Anderson single institution series [39] appear indeed to show that patients responding to pre-operative chemoradiation are also those achieving more benefit from adjuvant post-operative chemotherapy.

### standard regimens

Infused regimens are generally used for the administration of FU concomitant to radiation [40]. Extensive pre-clinical data have in fact shown that radiosensitization is a post-irradiation phenomenon and, based on FU pharmacokinetics, sensitization is more likely to be achieved with prolonged infusions [41].

In the pre-operative setting, the use of infused regimens has indeed been found to be significantly associated with higher rates of pCR in a retrospective pooled analysis of phase II–III trials including a total of 3157 patients [42]. Although comparative data on different infused regimens are not available, prolonged infusions, protracted all through radiation or for at least 5 days during the first and last radiotherapy week, are generally used.

Post-operative data are less clear-cut. The superiority of continuous infusion compared with bolus FU during radiotherapy shown in a North Central Cancer Treatment Group (NCCTG) trial [43] could not be confirmed in a successive US intergroup study that showed statistically identical survival outcomes with infused FU or leucovorin-modulated bolus FU concurrent to radiation [5]. Similarly, attempts to increase the efficacy of FU-based chemotherapy with biochemical modulation have been unsuccessful [20]. In the post-operative setting, various bolus or infused regimens, with or without leucovorin, are thus currently used in the clinical practice as well as in control arms of clinical studies [30].

### future developments

All the new drugs approved for use in colorectal cancer in the last 10 years (irinotecan, oxaliplatin, capecitabine, cetuximab and bevacizumab) have radiosensitizing properties. Several trials are thus investigating the incorporation of these agents in the chemotherapy and chemoradiation programs for locally advanced rectal cancer with the main aim of increasing treatment efficacy, particularly in the control of metastases at distant sites, and/or tolerance and patient convenience (Tables 1 and 2). Given the increasing number of potentially active agents becoming available, efforts are also being made...
to tailor the treatment to specific individual patient and tumour characteristics and to develop new treatment strategies.

**treatment simplification**

The ability of oral fluoropyrimydines (FPs) to maintain protracted plasma levels of FU without the need for intravenous accesses and infusion pumps makes them an attractive alternative in regimens combining chemotherapy and radiation. Both capecitabine and uracil/tegafur (UFT) have demonstrated radiosensitizing properties in pre-clinical models and initial clinical studies have confirmed the feasibility of their administration concomitant to radiation with promising activity.

The recommended dose (RD) of capecitabine for combination with standard radiotherapy (50.4 Gy in 1.8-Gy daily fractions) identified in the initial phase I studies is 825 mg/m² twice daily using a continuous schedule (7 days/week for 6 weeks) or 900 mg/m² twice daily when a Monday through Friday schedule is used (5 days/week for 6 weeks) [44, 45]. Phase II trials have been performed mainly with the continuous schedule. Toxicity was generally mild and well manageable, with a low rate of grade 3–4 events mainly consisting of diarrhoea, which occurred in 4–13% of patients. Other grade 3–4 toxicities were radiation dermatitis (2–6%), hand–foot syndrome (2–11%) and leuko-neutropenia (4–10%). Overall, downstaging rates ranging from 49 to 84% were observed with 4–31% of patients achieving a pCR [46]. Given these promising results, the value of capecitabine as a substitute for infused FU concurrent to pre-operative radiation, either as a single agent or in combination with oxaliplatin, is being evaluated in the ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP R04) randomized study.

UFT was also safely combined with pelvic radiotherapy at doses similar to those commonly used in the treatment of advanced colorectal cancer. A RD of 300 mg/m²/day Monday through Friday all during radiation has in fact been identified in the initial phase I study [47]. Activity and safety results in phase II studies were comparable with those obtained with FU-based chemoradiation (pCR rates 9–25%; overall down-staging 54–75%; grade 3–4 diarrhoea 9–23%) [48, 49].

Given the favourable toxicity profiles and promising activities observed in these studies, combination regimens incorporating either oxaliplatin or irinotecan have been developed with both capecitabine and UFT and are actively investigated in multiple phase I and II clinical trials [50–52].

**Table 1.** Planned/ongoing randomized studies testing FU replacement and/or combination with new drugs in the combined modality treatment programs for locally advanced rectal cancer

<table>
<thead>
<tr>
<th>Setting</th>
<th>Study</th>
<th>Control arm</th>
<th>Experimental arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative</td>
<td>E3201b</td>
<td>FU + LV</td>
<td>FOLFIRI/FOLFOX</td>
</tr>
<tr>
<td></td>
<td>E5204</td>
<td>FOLFOX</td>
<td>FOLFOX + bevazumb</td>
</tr>
<tr>
<td></td>
<td>CHRONICLE</td>
<td>Observation</td>
<td>CAPE + OXA</td>
</tr>
<tr>
<td>Pre-operative</td>
<td>STAR</td>
<td>PVI FU</td>
<td>PVI FU + OXA</td>
</tr>
<tr>
<td></td>
<td>NASBP R-04</td>
<td>PVI FU</td>
<td>PVI FU + OXA/CAPE ± OXA</td>
</tr>
<tr>
<td>Pre- and post-operative</td>
<td>PETACC 6</td>
<td>CAPE</td>
<td>CAPE + OXA</td>
</tr>
</tbody>
</table>

*Following pre- or post-operative fluoropyrimidine-based chemoradiation. Study accrual closed on April 2005. FU, 5-fluorouracil; LV, leucovorin; FOLFIRI, fluororacil + leucovorin + irinotecan; FOLFOX, fluororacil + leucovorin + oxaliplatin; CAPE, capecitabine; OXA, oxaliplatin; PVI, protracted venous infusion. *Concomitant to radiation. *Concomitant to pre-operative radiation and as adjuvant post-operative treatment.

**Table 2.** Early studies testing FU replacement and/or combination with new drugs in pre-operative chemoradiation regimens for locally advanced rectal cancer

<table>
<thead>
<tr>
<th>Aim</th>
<th>Regimen*</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>pCR (%)</th>
<th>Grade III–IV toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplification</td>
<td>CAPE</td>
<td>14</td>
<td>668</td>
<td>4–31</td>
<td>6–40</td>
</tr>
<tr>
<td></td>
<td>UFT</td>
<td>11</td>
<td>538</td>
<td>8–25</td>
<td>6–32</td>
</tr>
<tr>
<td></td>
<td>Eniluracil</td>
<td>1</td>
<td>22</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td>Potentiation</td>
<td>FU + OXA</td>
<td>15</td>
<td>450</td>
<td>7–36</td>
<td>6–39</td>
</tr>
<tr>
<td></td>
<td>CAPE/UFT + OXA</td>
<td>14</td>
<td>616</td>
<td>6–29</td>
<td>6–33</td>
</tr>
<tr>
<td></td>
<td>RTX + OXA</td>
<td>4</td>
<td>160</td>
<td>14</td>
<td>7–23</td>
</tr>
<tr>
<td></td>
<td>FU + IRI</td>
<td>6</td>
<td>300</td>
<td>14–26</td>
<td>2–32</td>
</tr>
<tr>
<td></td>
<td>CAPE/UFT + IRI</td>
<td>10</td>
<td>221</td>
<td>9–33</td>
<td>8–66</td>
</tr>
<tr>
<td></td>
<td>FP ± OXA/IRI + cetuximab</td>
<td>4</td>
<td>93</td>
<td>5–25</td>
<td>8–27</td>
</tr>
<tr>
<td></td>
<td>CAPE + gefitinib</td>
<td>1</td>
<td>6</td>
<td>NR</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>FU + bevacizumab</td>
<td>1</td>
<td>9</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

*Concomitant to pre-operative radiation. pCR, pathologic complete response; CAPE, capecitabine; UFT, uracil/tegafur; NR, not reported; FU, 5-fluorouracil; OXA, oxaliplatin; RTX, raltitrexed; IRI, irinotecan; FP, 5-fluorouracil or capecitabine.
treatment potentiation

Multiple studies are testing the incorporation of new agents in the chemotherapy regimens for rectal cancer. The high rates of metastases at distant sites with FU-based chemoradiation provide a strong rational for this approach. Based on the results obtained in colon cancer where the combination of oxaliplatin and fluorouracil has become the standard adjuvant treatment following radical resection [6], American and European trials are currently comparing FP monotherapy with a FP-oxaliplatin doublet as post-operative adjuvant treatment in patients who have received chemoradiation either pre- or post-operatively.

An alternative strategy is to potentiate the chemoradiation regimens used pre-operatively. Both irinotecan and oxaliplatin have been combined with preoperative radiation and either FU or capecitabine with acceptable toxicities rates and preliminary evidence of increased local tumour response [50, 51, 53–55]. While gastrointestinal toxicity may be a limitation for the use of irinotecan in combination with a FP and pelvic radiation, the low mucosal toxicity of oxaliplatin reduces the risk of overlapping toxicities. Fully active doses of oxaliplatin, with potential systemic activity, have indeed been combined with FU and radiation with increased but manageable toxicity and without affecting the delivery of the planned radiotherapy dose and the ability to perform surgery [14]. Combination chemotherapy delivered concurrently with pre-operative radiation may thus result in early exposure to a systemic active treatment with the potential additional advantage of an increased local anti-tumour activity. This may be particularly important for large tumours reaching the mesorectal fascia, where tumour shrinkage is necessary to make an R0 resection possible, and for low-lying tumours, where downsizing may allow to pursue sphincter preserving surgery or to convert a coloanal into a colorectal anastomosis with favourable functional implications. Finally, the prognostic value of response to preoperative chemoradiation represents a further argument supporting the intensification of the preoperative regimens for the treatment of locally advanced rectal cancer. The impact of this strategy is specifically investigated in the STAR-01 study in Italy and NSABP R04 study in the US that compare a FP-alone pre-operative chemoradiation regimen (infused FU and infused FU or oral capecitabine, respectively) with the same regimen with the addition of weekly oxaliplatin [14].

Potentially, the maximum increase in treatment efficacy, coupling enhanced local anti-tumour activity with improved control of micrometastases at distant sites, may be awaited from the incorporation of the new active agents both pre-operatively concurrent to radiation and in the post-operative adjuvant setting. This strategy will be tested in the PETACC 6 study, which will compare capecitabine-based pre-operative chemoradiation followed by post-operative capecitabine alone to a capecitabine–oxaliplatin doublet given both concurrent to pre-operative radiation and as adjuvant treatment following surgery.

Incorporation of biological agents may represent a further step towards the improvement of rectal cancer treatment. Epidermal growth factor receptor (EGFR)-inhibition in particular may result in radiosensitization [56, 57] along with synergy with chemotherapy in determining tumour shrinkage [58]. In addition, the toxicity profile of these agents appears to be favourable for their use in combination with chemotherapy and radiation. Both tyrosine kinase inhibitors (TKIs) and monoclonal antibodies targeting the EGFR have indeed been combined with pre-operative radiation and various chemotherapy drugs. While adverse events appear to limit the use of TKIs combined to pelvic radiation [59], preliminary reports have shown a good safety profile with promising anti-tumour activity for monoclonal antibodies [60, 61].

Angiogenesis is another important, recently identified, therapeutic target in colorectal cancer [62]. Radiosensitizing properties have been described in pre-clinical models and a promising anti-tumour activity has been observed in a small series of patients with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab combined to fluorouracil and pre-operative radiation [63]. However, important safety concerns may be raised for the use of this anti-angiogenetic agent prior to surgery with an unreated primary rectal tumour. Less safety problems are expected incorporating the VEGF antibody in the post-operative adjuvant treatment. This also allows a longer treatment time, in line with advanced disease data suggesting a benefit after prolonged treatment. An intergroup US study is indeed comparing a bevacizumab/FU/oxaliplatin (FOLFOX) combination versus FOLFOX alone as post-operative treatment in radically resected locally advanced rectal cancer treated with pre-operative chemoradiation.

An alternative strategy to potentiate pre-operative treatment is induction chemotherapy. The initial pilot studies of this strategy have reported that three to four courses of induction chemotherapy may be administered before chemoradiation with a negligible risk of disease progression and without affecting compliance to the subsequent chemoradiation treatment [64]. Induction chemotherapy also appeared to be active with high rates of tumour response before starting radiation paralleled by a rapid relief of symptoms in affected patients [65]. pCR and R0 resection rates after completing all the planned pre-operative treatment were also high, particularly for the populations of locally advanced high-risk rectal cancer included in these studies [65]. An additional benefit of this strategy is that induction chemotherapy may, at least partially, reduce patient anxiety during the waiting time before starting radiotherapy. This strategy may acquire further importance with the introduction in the treatment armamentarium for rectal cancer of new biological agents that require a longer treatment time to achieve the maximum tumour shrinkage compared with classical chemotherapy drugs. Although promising, this remains, however, an experimental approach without any comparative supporting evidence. Concerns have also been raised mainly related to the delay in definitive local treatment and risk for development of resistance [66].

Finally, tailored treatment programs are being developed based on patient and/or tumour biological features that may predict the activity and toxicity of specific drugs [67]. This is particularly important as new drugs and classes of drugs are becoming available for the treatment of locally advanced rectal cancer. Similarly, efforts are being made to develop imaging tools that allow the identification of responding and non-responding patients early during pre-operative chemoradiation.
Although the search for newer agents remains important, optimizing the use of available drugs and active treatment regimens is in fact a high priority in the medical treatment of rectal cancer.

conclusions

Concurrent, radiosensitizing and sequential, adjuvant, FU-based chemotherapy is currently used in addition to radiation and optimized surgery in order to minimize the risk of local and systemic failure in locally advanced rectal cancer. Additional drugs are being incorporated in the treatment programs mainly aiming to reduce metastases at distant sites. Efforts are also being made to increase treatment convenience replacing intravenous administration with oral derivatives of the fluoropyrimidine. The need of tailored treatment programs based on patient and/or tumour characteristics is then becoming more and more compelling. This involves an improved selection based on clinical factors to discriminate between patients who require an intensified pre-operative treatment, either to make a radical resection feasible or to allow a more conservative surgical approach, from patients that are fully operable without major functional losses but have a high risk of recurrence justifying pre-operative treatment from a last category of patients with a lower risk of recurrence due to more favourable location (proximal) and clinical stage (minimal extramural penetration) that may benefit from initial surgery with selective adjuvant treatment based on pathological findings.

Micro-array DNA technologies and pharmacogenomics may provide further help in modulating treatment intensity, based on the risk of recurrence, and also in the choice between different drugs, based on prediction of response and toxicity. Patients' preferences and expectations should also be understood and taken into account in the decision making process. In particular, a conscious willingness is required in accepting aggressive treatment programs that may have important functional implications. A further expansion of the multidisciplinary team for rectal cancer that includes not only a surgeon, a radiotherapist and a medical oncologist but also dedicated radiologists, pathologists, molecular biologists, stoma therapy nurses and psychologists may thus be expected in the near future.

references