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Developments in Neoadjuvant Chemotherapy and Radiotherapy in Rectal Cancer

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1. Introduction

The treatment of rectal cancer has evolved dramatically through the last three decades. Until the 1970's and 1980's, surgery was often the only therapeutic modality employed in the treatment of rectal cancer patients. However, local recurrence with surgery alone was significant resulting in patient morbidity and death (Gunderson & Sosin, 1974; Rich et al., 1983). Some studies have demonstrated that adjuvant chemotherapy and radiotherapy (RT) improved local relapse and survival in patients with tumors extending into the perirectal fat (T3) or with involvement of mesorectal or pelvic lymph nodes (N1-3) (Gastrointestinal Tumor Study Group, 1985; National Institutes of Health Consensus Conference, 1990; Wolmark et al, 2000).

Neoadjuvant chemoradiotherapy has become the standard of care for stages II and III rectal cancer since the CAO/ARO/AIO trial (Sauer et al, 2004). Ever since, efforts have been made in order to discover which drug or combination of drugs have better results in terms of local recurrence and survival.

In this chapter we will give an overview of the history of neoadjuvant chemotherapy and radiotherapy in rectal cancer, the current standards of care as well as ongoing trials in the neoadjuvant setting for locally advanced rectal cancer.

2. Neoadjuvant radiotherapy for rectal cancer

Before the advent of total mesorectal excision surgery, only the Swedish rectal cancer trial and two meta-analyses showed a survival advantage with neoadjuvant radiation therapy (Cammá et al, 2007; Colorectal Cancer Collaborative Group, 2001). The Swedish trial randomly assigned 1168 patients to undergo preoperative RT (25 Gy delivered in 5 fraction in 1 week) followed by surgery within one week or to have surgery alone. The preoperative arm had reduced rates of local recurrence and improved survival among patients with resectable rectal cancer (Swedish Rectal Cancer Trial, 1997). These results were confirmed in a recent update of this trial, with a median follow-up time of 13 years (Folkesson et al, 2005).

Total mesorectal excision (TME) is now the standard of care for rectal cancer surgery, permitting en bloc removal of intact tumor with its lymphatic and vascular supply resulting in a negative circumferential margin and lower local relapse rates. In this setting, two large studies have explored the role of preoperative RT and demonstrated their superiority.

The Dutch Colorectal Cancer Group randomly assigned 1861 patients with rectal cancer either to preoperative RT (5 Gy x 5) followed by TME or to TME alone. They concluded that short-term preoperative radiotherapy reduces the risk of local recurrence at 2 years (2.4% *vs* 8.2%, $p<0.001$) in patients with rectal cancer who undergo a TME. However, neoadjuvant RT did not have any impact on distant relapse or overall survival (Kapiteijn et al, 2001). These results were confirmed on a long-term follow-up study of 6 years (Peeters et al, 2007).
The Medical Research Council (MRC) CR07 and National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) C016 trial was a multicentre (1350 patients from 80 centers in 4 countries) randomized controlled trial comparing short-course preoperative radiotherapy (25 Gy in 5 fractions) with selective postoperative chemoradiotherapy (45 Gy in 25 fractions with concurrent 5-Fluorouracil) for patients with involvement of the circumferential resection margin after TME (Sebag-Montefiore et al, 2009). They reported a reduction of 61% in the relative risk of local recurrence for patients receiving preoperative radiotherapy ($p<0.0001$), an absolute difference at 3-years local recurrence rate of 6.2% (4.4% *vs* 10.6%), a relative improvement in disease-free survival of 24% for patients receiving preoperative radiotherapy ($p = 0.013$) and an absolute difference at 3 years of 6% (77.5% *vs* 71.5%). Overall survival (OS) did not differ between the groups ($p = 0.40$).
Therefore, neoadjuvant radiotherapy has proved to result in better local control than surgery ± adjuvant therapy in locally advanced rectal cancer. The impact on survival has not been clear.

3. Neoadjuvant chemoradiation for rectal cancer

The administration of chemotherapy in combination with radiotherapy can have an additive effect, in which there is no interaction between the treatment modalities and each strategy is separately effective. More promising is a combination in which a synergistic effect is achieved. The main chemotherapeutic agents used in chemoradiotherapeutic combinations for rectal cancer are 5-fluorouracil (5-FU) and oral fluoropyrimidines. The main goals of chemoradiation are the reduction of local and distant recurrences in order to improve survival. It was in this context that in the last decades there have been many studies which have associated diverse chemotherapeutic agents to radiotherapy.

3.1 5-FU plus radiotherapy

Currently, chemoradiation using 5-fluorouracil (5-FU) as a radiosensitizer is considered the common approach for rectal cancer in the neoadjuvant setting. There are a number of mechanisms by which 5-FU could increase radiation sensitivity at the cellular level. First is through the killing of S-phase cells which are relatively radioresistant. 5-FU has also a sensitizing effect related to enzyme thymidylate synthase inhibition and the ability to damage DNA. The primary toxicities of 5-FU include gastrointestinal symptoms including diarrhea, myelosupression, inflammation of mucosae, including the eyes, nose and urinary tract, neurotoxicity at high-dose levels, and rare cardiac toxicity (Zhu & Willett, 2003).
The CAO/ARO/AIO trial (Sauer et al, 2004) compared preoperative with postoperative chemoradiotherapy for locally advanced rectal cancer. In this randomized clinical trial preoperative treatment consisted of 50.4 Gy delivered in fractions of 1.80 Gy/day, 5 days per week, and 5-FU given in a 120 hour continuous intravenous infusion at a dose of 1000 mg/m^2 of body surface area per day during the first and fifth weeks of radiotherapy. Surgery was performed 6 weeks after completion of chemoradiotherapy. One month after

surgery, 4 cycles of 5-FU (500 mg/m²/d) were given. Chemoradiotherapy was identical in the postoperative treatment group except for the delivery of a boost of 5.4 Gy. They concluded that preoperative chemoradiotherapy improved local control (5-year cumulative incidence of local relapse: 6% *vs* 13%, $p = 0.006$) and was associated with reduced toxicity (27% *vs* 40%, $p = 0.001$) but did not improve overall survival (76% *vs* 74%, $p = 0.80$). Significant tumor downstaging was seen after preoperative combined-modality treatment with an 8% pathologic complete response (pCR) rate. Posttrial review showed that sphincter-saving surgeries were more likely to occur in the neoadjuvant chemoradiation group than in the adjuvant group (39% *vs* 19%, $p = 0.004$).

Despite the lack of survival advantage, these findings have set neoadjuvant chemoradiation as the new standard of care in the United States and in Europe in the treatment of rectal cancer.

Recently, European trials have further evaluated the role of concurrent 5-FU-based chemotherapy with radiation therapy in the neoadjuvant treatment of rectal cancer.

A large phase III French study, Fédération Francophone de Cancérologie Digestive (FFCD) 9203, randomized patients with stage II/III rectal cancer to receive RT alone (45 Gy in 25 fractions) or 5-FU/leucovorin (LV) with RT (FU/LV 350/20 mg/m²/d on days 1 to 5 and 29 to 33 of RT). Patients in both arms subsequently underwent surgery and four cycles of 5-FU/LV. The preoperative chemoradiation arm showed a significant improvement in pathologic complete response (pCR) rate (11.4% *vs* 3.6%, $p < 0.05$) and local relapse rate (8.1 *vs* 16.5%, $p < 0.05$). The 5-year survival in both arms was 67% (Gerard et al, 2006).

Another large phase III study, European Organisation for Research and Treatment of Cancer (EORTC) 22921, randomized patients with stage II/III rectal cancer to receive neoadjuvant RT alone (45 Gy in 25 fractions) *vs* RT with bolus 5-FU/LV (350/20 mg/m²/d during the first and fifth weeks of preoperative RT), with a subsequent randomization to postsurgical (3 to 10 weeks after chemoradiation) 5-FU/LV chemotherapy or no postsurgical chemotherapy. The study demonstrated no significant difference in overall survival between the groups that received chemotherapy preoperatively and those who received it postoperatively. The 5-year cumulative incidence rates for local relapse were 8.7%, 9.6%, and 7.6% in the groups receiving chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy ($p = 0.002$). The authors concluded that in patients with rectal cancer who receive preoperative radiotherapy, adding 5-FU–based chemotherapy either preoperatively or postoperatively conferred a significant advantage in terms of local control (Bosset et al, 2005).

3.2 Oral fluoropyrimidines plus radiotherapy

Preoperative RT with continuous i.v. 5-FU infusion has the biologic advantage of prolonging exposure of tumor cells to 5-FU and improving antitumor activity. However, its disadvantages include the requirement of central venous access with potential complications, such as bleeding, thrombosis, infection and pneumothorax (Grem, 1997). Most patients receiving chemotherapy prefer oral therapies to intravenous regimens because of their possibility to receive treatment without attending clinics, to continue daily activities and to maintain a relatively normal lifestyle. There is evidence that, with regular patient education and monitoring, adequate patient compliance to oral medications can be achieved, although issues of compliance and safety remain a concern (Lee et al, 1992).

Oral chemotherapy mimics the pharmacokinetics of continuous 5-FU infusion and avoids technical barriers of i.v. infusion with the advantage of convenience. Oral fluoropyrimidines such as UFT or capecitabine, constitute an attractive alternative.

Although there are some studies comparing infusional preoperative chemoradiotherapy (5-FU) with oral neoadjuvant chemoradiotherapy either with capecitabine or UFT (De la Torre et al, 2008; Kim et al, 2007), there is not yet a single randomized study comparing the results of both of these modalities of oral neoadjuvant chemotherapy along with radiotherapy.

3.2.1 Capecitabine plus radiotherapy

Capecitabine is an oral fluoropyrimidine carbamate prodrug of 5-FU designed to generate 5-flurouracil (5-FU) preferentially in tumor cells (Pentheroudakis & Twelves, 2002), as concentration of the key enzyme thymidine phosphorylase is higher in tumor cells compared with normal tissue. In preclinical studies, irradiation with thymidine phosphorylase was found to be upregulated in tumor tissue resulting in a selective synergistic effect of capecitabine on radiotherapy (Schuller et al, 2000; Sawada et al, 1999; Miwa et al, 1998). Capecitabine is administered daily to mimic a continuous infusion of 5-FU (De Bruin et al, 2008). This continuous regimen is likely to have a more constant cytotoxic action, thereby limiting tumor regrowth. The side-effect profile of capecitabine is similar to that observed when 5-FU is given as a protracted infusion and consists mainly in diarrhea. The dose-limiting toxicity is the hand–foot syndrome, occurring as the capecitabine dose reaches 1000 mg/m^2 twice daily. Other toxicities were generally mild to moderate (Van Cutsem et al, 2001; Hoff et al, 2001).

A phase I study on rectal cancer defined the recommended dose of capecitabine to be 825 mg/m^2 twice daily, administered 7 days/week during a conventional RT period of about 6 weeks for preoperative therapy in locally advanced rectal cancer (Dunst et al, 2002).

Some phase II studies confirmed that capecitabine is an adequate substitute for continuous infusional 5-FU in preoperative chemoradiation regimens with regard to the favorable toxicity profile, considerable downstaging effect and pathologic complete response on the tumor, and could increase the possibility of sphincter preservation in distal rectal cancer (Dunst et al, 2004; Kim et al, 2005; De Paoli et al, 2006; Krishnan et al, 2006).

The randomized phase III NSABP-R04 study is currently comparing capecitabine/RT to 5-FU/RT (with and without concurrent oxaliplatin). This will help determine if capecitabine can substitute for 5-FU in the neoadjuvant treatment of rectal cancer. The primary aim of the study is to compare the rate of local-regional relapse in the two groups. Co-primary end points are pCR and progression-free survival (PFS).

In conclusion, neoadjuvant radiotherapy concomitant to capecitabine has proved so far to be well tolerated and is an adequate substitute for continuous infusion of 5-FU.A smaller phase III trial is underway in Germany to compare adjuvant capecitabine chemoradiation versus 5-FU chemoradiation in patients with rectal cancer. PETACC is conducting a neoadjuvant/adjuvant rectal cancer study comparing capecitabine single agent *versus* capecitabine–oxaliplatin combination.

3.2.2 UFT plus radiotherapy

UFT is an oral combination of uracil and tegafur in a fixed 1:4 molar ratio (Hoff et al, 1998). Tegafur is a prodrug converted to 5-FU by the hepatic microsomal system following intestinal absorption. Uracil competitively inhibits dihydropyrimidine dehydrogenase, the chief catabolic enzyme of 5-FU, which results in elevated and maintained concentrations of 5-FU for a prolonged period and thus simulates a continuous infusion of 5-FU to improve the absorption and bioavailability of tegafur (Ho et al, 1998; Sulkes et al, 1998; Hirata et al, 1993).

In preclinical experiments, leucovorin (LV) has been combined with UFT in an attempt to enhance antitumor activity (Okabe et al, 1997). In patients with advanced colorectal cancer, the combination of UFT and oral LV produced objective response rates ranging from 25% to 42% (Pazdur et al, 1999). Preliminary results from two large randomized studies in patients with metastatic colorectal cancer suggested that patients treated with UFT/LV and those receiving bolus intravenous 5-FU/LV may have an equivalent response and survival rate (Pazdur et al, 1999; Carmichael et al, 1999). In the adjuvant setting Japanese investigators compared postoperative UFT to surgery alone; UFT led to a significantly improved 4-year disease-free survival, particularly in patients with rectal cancer (Nakazato et al, 1997). Like infusional 5-FU, UFT is generally well tolerated, with diarrhea, nausea, and anorexia being the most frequent adverse effects. In reported trials, grade 3 or 4 diarrhea occurred in 4% to 21% of patients (Ho et al, 1998; Pazdur et al, 1999; Carmichael et al, 1999). UFT is not associated with significant myelosuppression, mucositis, hand-foot syndrome, or alopecia.

Pharmacokinetic studies have shown that 5-FU plasma levels in patients receiving protracted infusions of 5-FU are similar to those found in patients receiving oral UFT, although peak levels of 5-FU are higher with UFT (Ho et al, 1998). There are a large number of patients who have received UFT plus oral LV as adjuvant chemotherapy or to treat metastatic disease, however, there is less data on the use of UFT/LV with radiation therapy in patients with rectal cancer.

In the phase I study by Hoff et al. (Hoff et al, 2000), 15 patients with resectable stage II/III rectal cancer were treated with escalating doses of UFT (250 – 400 mg/m^2/day) together with a fixed dose of LV (90 mg/day). UFT was taken in three equal doses per day, 5 days/week for the duration of a 5-week course of preoperative RT (1.8 Gy/day administered to the pelvis; total dose of 45 Gy). The maximum tolerated dose (MTD) was UFT 350 mg/m^2/day.

A lower MTD for UFT of 240 mg/m2/day was defined in the phase I study by Pfeffer et al. (Pfeffer et al, 2004). UFT was taken with LV 30 mg/day for 4 weeks and RT (1.8 Gy/day, 5 days/week for 5 weeks; total dose of 45 Gy) was delivered using a three-field technique.

The phase II studies have attempted to improve on the regimens used in the dose-finding studies. Wang et al. combined a dose-intense RT schedule (45 Gy in 4 weeks) with two courses of UFT at lower doses 200 mg/m^2/day on days 1–28 in cycle 1 and 250 mg/m^2/day in cycle 2 (postradiotherapy) with LV in an attempt to minimize side-effects and maintain systemic treatment during the postradiation period. This approach was effective, with high rates of downstaging (75%), pCR (25%) and sphincter preservation (55%); OS and PFS rates at 3 years (92% and 76%, respectively) were excellent. Transient grade 3/4 adverse events were rare (Wang et al, 2005).

In a large phase II study by Fernández-Martos et al, 94 patients with T3–4 tumors received a higher dose of UFT (400 mg/m^2/day) without LV, together with RT 5 days/week for 5 weeks (total dose 45 Gy; 1.8 Gy/day). After surgery, four cycles of adjuvant 5-FU (Mayo regimen) were administered to most patients (76%). Treatment was well tolerated and pCR occurred in 15% of patients (Fernández-Martos et al, 2004).

Different dose regimens were also evaluated. Feliu et al evaluated a regimen with higher doses of UFT but they had a higher toxicity profile (Feliu et al, 2002). Kundel et al studied a combination of lower doses of UFT + LV with a similar tolerability profile but slightly reduced efficacy (Kundel et al, 2007).

In a phase III study UFT/LV has been compared with bolus 5-FU/LV in preoperative chemoradiotherapy for locally advanced rectal cancer. Of 155 patients, pCR rate was 13%

in both arms, although more patients in the UFT group had tumor downstaging (59% *vs* 43%; p = 0.04). Although the study was not powered to exclude clinically significant differences between the groups, outcomes in the UFT group did not differ from those in the 5-FU group. Most notable, however, was the difference in the tolerability profiles, with 5-FU/LV group showing more severe leucopenia compared with the UFT group (De la Torre et al, 2008).

The National Cancer Center of Korea has implemented a pilot study to evaluate a higher dose of enteric-coated tegafur/uracil (400 mg/m²/d) plus LV (90 mg/d) for 7 days a week during 50.4 Gy pelvic RT and concluded that this scheme has showed favorable efficacy (pCR rate 22.2%) and toxicity profiles. A phase II trial is ongoing to test this treatment (Kim et al, 2009).

In conclusion, UFT/LV neoadjuvant treatment concomitant to radiotherapy has proved to be well tolerated with good results in terms of treatment response compared to 5-FU based preoperative schedules. However, there is a lack of randomized trials comparing these both oral fluoropyrimidines in the neoadjuvant setting concomitant to radiotherapy in rectal cancer as well as randomized trials comparing them to 5-FU regimens.

3.3 Oxaliplatin-based combination regimens

Significant interest has arisen in the past several years in developing combinations of 5-FU, oxaliplatin, and RT in the neoadjuvant treatment of rectal cancer. This interest has been supported by the systemic synergistic activity between oxaliplatin and fluoropyrimidines and the added radiation-sensitizing activity of oxaliplatin (de Gramont et al, 2000; Goldberg et al, 2004). The mechanism of radiation sensitization appeared to be through cell-cycle perturbations. It remains controversial whether oxaliplatin should be delivered before or after radiation to maximize its radiosensitizing activity. The main toxicities described are hematologic toxicity (neutropenia, trombocitopenia), nausea and/or vomiting, diarrhea, mucositis and neurologic toxicity which is dose limiting.

3.3.1 Oxaliplatin/5-FU plus radiotherapy

The Cancer and Leukemia Group B (CALGB) investigated a combination of escalating weekly doses of oxaliplatin in combination with continuous-infusion 5-FU at 200 mg/m²/d and RT at 1.8 Gy/fraction for a total of 50.4 Gy in a phase I/II study. The recommended phase II dose of oxaliplatin in this combination was identified as 60 mg/m²/wk (in 6 doses). Although 25% of patients had a pCR, this treatment was associated with an excessive rate (38%) of grade 3/4 diarrhea (Ryan et al, 2006).

The Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial investigated the effect of adding oxaliplatin to preoperative FU-based pelvic chemoradiation in patients with locally advanced rectal cancer. Randomization was between infused 5-FU (225 mg/m²/day) concomitant to external-beam pelvic RT (50.4 Gy in 28 daily fractions) or the same regimen plus weekly oxaliplatin (60 mg/m² x 6). They concluded that the addition of weekly oxaliplatin to standard FU-based preoperative chemoradiation significantly increased toxicity without affecting local tumor response. The reduced pathologic M+ rate suggested a potential effect on distant micrometastases. However, longer follow-up is needed to assess the impact on efficacy endpoints (Aschele et al, 2009).

The randomized NSABP-R04 trial is currently addressing the value of adding oxaliplatin to 5-FU radiation therapy.

3.3.2 Oxaliplatin/capecitabine plus radiotherapy

Capecitabine/oxaliplatin combinations have demonstrated efficacy and tolerability comparable to that of 5-FU/oxaliplatin in the first-line treatment of metastatic colorectal cancer. Several studies have investigated the combination of capecitabine, oxaliplatin, and radiation in the neoadjuvant treatment of rectal cancer in hopes of improving both local and systemic disease control.

In a phase I/II study, daily capecitabine (including weekends) was combined with a fixed dose of oxaliplatin at 130 mg/m² on days 1 and 29 concurrently with RT 45 Gy (25 fractions) in patients with borderline or unresectable rectal cancer. The MTD of capecitabine in this combination was 650 mg/m² twice daily. A total of 96 patients were enrolled and there was a pCR in 19% of patients and only 22% experienced grade 3/4 adverse events, the most common being gastrointestinal (Glynne-Jones et al, 2006).

Roedel et al conducted a phase II neoadjuvant study of capecitabine and oxaliplatin (XELOX) plus radiation in 110 patients with locally advanced rectal cancer. The regimen consisted of capecitabine at 825 mg/m² twice daily on days 1 to 14 and 22 to 35 along with oxaliplatin 50 mg/m² on days 1, 8, 22, and 29, plus RT (50.4 Gy in 28 fractions). Grade 3 toxicity, mainly diarrhea, occurred in 14% of patients. Of the resected specimens 15% showed a pCR (Roedel et al, 2006).

The Capecitabine Oxaliplatin Radiotherapy and Excision (CORE) study investigated a variant regimen of capecitabine twice daily on Mondays through Fridays and weekly oxaliplatin at 50 mg/m² concurrently with radiation at 45 Gy in patients with threatened or positive circumferential margins by magnetic resonance imaging. Initial results from this multicenter phase II study showed an R0 resection rate of 67% and a pCR rate of 13% (Rutten et al, 2006).

Other researchers have investigated a capecitabine/oxaliplatin regimen similar to the one used in the CORE study (Machiels et al, 2005; Alonso et al, 2007; Ofner et al, 2007; Carlomagno et al, 2007; Salimichokami et al, 2006). These studies were associated with pCR rates of 14% to 24%, tumor-downstaging rates of 52% to 78%, and grade 3/4 diarrhea rates of 8% to 30%.

The current recommended dose for capecitabine given twice daily on radiation days with weekly oxaliplatin and RT (1.8 Gy × 25–28 fractions) is 825 mg/m² twice daily and 50 mg/m² weekly for capecitabine and oxaliplatin, respectively.

The recommended doses of capecitabine, oxaliplatin, and radiation therapy may tend to be lower in the United States than in Europe, because higher rates of toxicity have been reported in the US for capecitabine monotherapy or capecitabine/oxaliplatin combinations (Haller et al, 2006). The exact etiology for the discrepancy in toxicity at equal capecitabine dosing may be related to increased folic acid supplementation in the American diet. It is prudent at this time to consider 725 mg/m² twice daily dosing for capecitabine in combination with weekly oxaliplatin (50 mg/m²) and RT (50.4 Gy) in the US until further safety data become available from NSABP-R04. The 825 mg/m² dose level of capecitabine combined with a similar oxaliplatin/RT regimen is clearly tolerable and feasible in Europe.

The phase III trial ACCORD 12/0405 – Prodige 2 randomly assigned patients to receive 5 weeks of RT 45Gy/25 fractions with concurrent capecitabine 800 mg/m² twice daily 5 days/week (CAP45) or RT 50Gy/25 fractions with same dose of capecitabine plus oxaliplatin 50 mg/m² once weekly (CAPOX50). More preoperative grade 3 to 4 toxicity occurred in the CAPOX50 group (25% *vs* 1%, $p<0.001$). The ypCR rate was 13.9% with CAP45 and 19.2% with CAPOX50 ($p = 0.09$). In this trial, a benefit of Oxaliplatin was not

demonstrated and they concluded that this drug should not be used with concurrent irradiation (Gerard et al, 2010).
A large phase III pan-European trial (PETACC-6) comparing capecitabine and oxaliplatin chemoradiation with capecitabine chemoradiation alone as neoadjuvant treatment in T3/4 N1/2 patients is in development.

3.3.3 Oxaliplatin/UFT plus radiotherapy

Patients in a phase I/II study by Aschele et al. received weekly oxaliplatin (60 mg/m^2/day), escalating doses of UFT (200 – 350 mg/m^2/day, 5 days/week) and LV (90 mg/day, fixed dose) during RT (total dose 50.4 Gy). Nine patients had a major down-staging (ypT0-2 pN0) with 4 pCRs (2 of them among the 6 patients treated at the highest dose level). The authors concluded that oral UFT may replace infusional 5-FU in combination with weekly oxaliplatin and standard pelvic radiotherapy with low toxicity and promising activity. The recommended dose for further studies is 350 mg/m^2/day (Aschele et al, 2009).
Preliminary results from a phase II study by Fernández-Martos et al. demonstrated that UFT 400 mg/m^2/day, taken 5 days/week for 5 weeks and oxaliplatin 85 mg/m^2 on days 1, 15 and 29 can be administered safely with radiotherapy (50 Gy total) to patients with locally advanced rectal cancer. A pCR rate of 15% was observed (Fernández-Martos et al, 2005).

3.4 Irinotecan-based combination regimens

The addition of the topoisomerase-I inhibitor irinotecan to 5-FU significantly improves response rates, median time to progression and overall survival compared with 5-FU/LV alone in patients with metastatic colorectal cancer. Preclinical studies have demonstrated irinotecan to be a potent radiosensitising agent in human lung tumour xenografts and colorectal cancer. Irinotecan may potentiate radiation by attaching to the DNA-topoisomerase I adducts in sites of DNA single strand breaks. Alternatively, fractionated radiotherapy could synchronise the tumor cell population in the S phase of the cell cycle, where cells are more sensitive to irinotecan chemotherapy. The major dose limiting toxicity of combining irinotecan with 5-FU and radiation was diarrhea. The rate of severe neutropenia did not appear to be increased.
Given its systemic and radiosensitizing activities, irinotecan has been incorporated in the neoadjuvant treatment of rectal cancer.

3.4.1 Irinotecan/5-FU plus radiotherapy

In a phase I/II study, Mitchell et al evaluated a weekly irinotecan regimen in combination with 5-FU and concurrent pelvic radiation. Patients with primary or recurrent clinical stage T3/4 adenocarcinoma of the rectum received escalating doses of weekly irinotecan (30 to 50 mg/m^2) in combination with continuous-infusion 5-FU and concurrent RT (50.4 Gy). The MTD in this study was identified as irinotecan at 50 mg/m^2 in combination with 5-FU at 225 mg/m^2/d on radiation days. pCR rate was 24% (Mitchell, 2000).
In another irinotecan-based neoadjuvant trial, 37 patients were treated with irinotecan at 50 mg/m2/wk and continuous-infusion 5-FU (250 mg/m^2/d, days 1–43) concurrently with RT (50.4 Gy in 28 fractions). The pCR rate was 22%, tumor-downstaging rate was 75%, and PFS at 40 months was 73% (Klautke et al, 2005).

A phase II trial (Mohiuddin et al, 2006) evaluated 5-FU plus hyperfractionated RT in comparison with standard RT combined with infusional 5-FU and weekly irinotecan. The Irinotecan arm consisted of 5-FU (225 mg/m^2/d Mondays through Fridays) plus irinotecan (50 mg/m^2/wk) and conventional RT (50.4 Gy for T3 and 54 Gy for T4). The tumor-downstaging rate was 78% and pCR rate was 28%.
A modest pCR rate (14%) was described in another study (Navarro et al, 2006) of continuous-infusion 5-FU (225 mg/m^2/d), irinotecan (50 mg/m^2/wk), and concurrent RT (45 Gy).
Irinotecan was also investigated on a daily × 5 schedule in combination with a standard-bolus 5-FU/LV-plus-RT regimen. A total of 59 patients were treated with RT (45 Gy), 5-FU/LV (350/20 mg/m^2/d) on days 1 to 5 and 29 to 33, and escalating doses of irinotecan (6, 8, 10, 12, 14, 16, 18, and 20 mg/m^2/d) on days 1 to 5 and 29 to 33. Irinotecan at 18 mg/m^2 was selected as the recommended dose for future studies. A pCR was observed in 24% patients and tumor downstaging in 41% of patients (Glynne-Jones et al, 2007).
The above studies incorporating irinotecan with 5-FU and radiation appear to show promising results, as seen in the pCR rate and the number of patients who eventually had successful surgery. Nonetheless, toxicity (mainly diarrhea) is of concern.

3.4.2 Irinotecan/capecitabine plus radiotherapy

The combination of irinotecan, capecitabine and radiation therapy has been investigated in the neoadjuvant treatment of rectal cancer.
In a phase I study, Hofheinz et al evaluated a weekly regimen of Irinotecan in combination with twice-daily capecitabine and radiation therapy. The recommended regimen from this study consisted of capecitabine at 500 mg/m^2 twice daily in combination with weekly Irinotecan at 50 mg/m^2/wk plus RT (50.4 Gy in 28 fractions). An interesting pCR rate of 21% was seen (Hofheinz et al, 2005).
A phase II study further evaluated the safety and efficacy of these dose levels in 36 patients. A pCR was seen in 15% of patients, tumor downstaging in 55% and grade 3/4 diarrhea in 11% of patients (Willeke, 2007).
In another phase I/II study, Klautke et al investigated a regimen of weekly Irinotecan at 40 mg/m^2 in combination with escalating doses of capecitabine twice daily and concurrent RT (50.4 Gy). The maximum tolerated dose was confirmed at the 750 mg/m^2 capecitabine dose level. Pathologic complete response was achieved in15%, while pathologic downstaging was seen in 62% of patients (Klautke et al, 2006).
No adequately powered head-to-head studies have compared irinotecan- or oxaliplatin-based neoadjuvant chemoradiation studies. In a small neoadjuvant randomized phase II study, similar downstaging was seen for both capecitabine/oxaliplatin– and capecitabine/irinotecan–based neoadjuvant radiation. The irinotecan-based combination was associated with increased diarrhea and chemoradiation-induced fibrosis (Privitera et al, 2006).
Although preliminary, the current findings indicate that combinations of capecitabine and weekly irinotecan are feasible in this setting.

3.4.3 Irinotecan/UFT plus radiotherapy

Preliminary results from a Japanese phase I trial in which UFT (300 mg/m^2/day, 5 days/week) was combined with concurrent weekly irinotecan (starting at 30 mg/m^2) and RT (2 Gy/day, 40–50 Gy total) resulted in an excess of grade 3 diarrhea (Yasui et al, 2006).

3.5 Bevacizumab-based chemoradiation

Vascular endothelial growth factor (VEGF) mRNA and protein expression is markedly upregulated in metastatic colon and rectal cancer and is associated with disease progression and inferior survival. VEGF blockade serves as a potent and nontoxic enhancer of radiation therapy. It can reduce tumor vascular permeability and tumor interstitial pressure, thus enhancing delivery of large molecules to tumors. Life-threatening toxicities seen to date have included hemorrhage and thrombosis. Less severe toxicities include proteinuria, hypertension, fever, chills, rash, headache, infection, epistaxis and mouth ulceration.

Based on the improved outcome of the addition of bevacizumab with 5-FU/LV–based regimens in the metastatic setting and the synergy with radiation therapy in preclinical models, there is a strong rationale for combining antiangiogenic therapy with neoadjuvant chemoradiation therapy in patients with rectal cancer.

3.5.1 Bevacizumab/5-fu plus radiotherapy

The safety of bevacizumab in the neoadjuvant chemoradiation setting was established in a phase I/II study. A total of 22 patients received bevacizumab (5 or 10 mg/kg) every 2 weeks, continuous-infusion 5-FU (225 mg/m^2/24 h), and RT (50.4 Gy), followed by surgery in 7 to 9 weeks. Two of the five patients in the cohort receiving bevacizumab at 10 mg/Kg with 5-FU plus RT experienced grade 3/4 dose-limiting diarrhea and colitis during treatment. This regimen showed significant downstaging (55%) with a 22% pCR rate. Bevacizumab at 5 mg/kg every 2 weeks in combination with RT plus 5-FU yielded promising results and did not show any dose-limiting toxicity or perioperative morbidity/mortality (Willett et al, 2007).

3.5.2 Bevacizumab/capecitabine plus radiotherpy

Crane et al reported the preliminary results of a phase II trial in patients with T3/T4 or node-positive rectal cancer receiving preoperative RT (50.4 Gy), every-other-week bevacizumab (5 mg/kg for three doses starting concurrently with RT), and capecitabine (900 mg/m^2 orally twice a day on RT days only), followed by surgery. No grade 3 toxicity was observed. Five patients (29%) achieved a pCR (Crane et al, 2007).

Torino et al presented the results of a phase II study of neoadjuvant antiangiogenic therapy (intravenous infusion of bevacizumab 5 mg/Kg each two weeks for 4 courses, the first administration 2 weeks before chemoradiotherapy) combined with capecitabine (825 mg/m^2 twice daily) and RT (50.4 Gy / 28 fractions) in patients with locally advanced rectal cancer. The authors concluded this is a feasible and safe regimen with a tumor downstaging rate of 6.9%, a pCR rate of 9.3% and conservative surgery in 72.5% patients (Torino et al, 2008).

3.5.3 Bevacizumab plus xeliri/-xelox plus radiotherapy

Bevacizumab was also evaluated with capecitabine and either oxaliplatin or irinotecan in a pilot feasibility study. A total of 11 patients with advanced rectal cancer received bevacizumab (5 mg/Kg) every 2 weeks with capecitabine (1000 mg/m^2 twice daily on days 1 to 14 before the chemoradiation phase and then 825 mg/m^2 twice daily during RT on days 22 to 55) plus irinotecan at 180 mg/m^2 (XELIRI) or oxaliplatin at 130 mg/m^2 (XELOX) on days 1, 22, 43, and concurrent radiotherapy (54 Gy). Surgery was carried out 8 weeks after the completion of chemoradiation. Only one patient had grade 3 diarrhea and was unable to complete the planned chemotherapy. In combination with XELIRI/-XELOX plus RT,

bevacizumab neither increased the treatment toxicity profile nor provoked any surgical delay or modifications (Privitera et al, 2007).
Another phase I trial from the Duke University evaluated the combination of concurrent capecitabine, oxaliplatin, and bevacizumab in patients with stage II–IV rectal cancer. A total of 11 patients were treated with escalating doses of capecitabine, oxaliplatin, and a fixed dose of bevacizumab (15 mg/Kg on day 1 and 10 mg/Kg on days 8 and 22). At dose level 1, patients were treated with oxaliplatin at 50 mg/m^2 weekly, capecitabine at 625 mg/m^2 twice daily, and concurrent RT (50.4 Gy) without dose-limiting toxicity. At dose level 2 (capecitabine, 825 mg/m^2 twice a day), two patients had dose-limiting toxicities of diarrhea and tenesmus-type symptoms. The recommended phase II dose was bevacizumab at 15 mg/Kg on day 1 and 10 mg/Kg on days 8 and 22, oxaliplatin at 50 mg/m^2 weekly, and capecitabine at 625 mg/m^2 twice a day on radiation days (Czito et al, 2007).
These studies suggest that the addition of bevacizumab to chemoradiation is safe and feasible in the neoadjuvant treatment of rectal cancer. Larger studies are needed to investigate whether the addition of this agent results in additional benefits in terms of tumor downstaging or disease-free survival.

3.6 Cetuximab plus chemoradiation

Cetuximab is a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR). EGFR is expressed in 25% to 75% of colorectal cancer and its overexpression has been associated with poor prognosis and increased risk for metastasis. This agent has significant clinical activity in metastatic colorectal cancer, both as monotherapy or in combination with irinotecan.
Cetuximab has a long-life and a convenient weekly dosing schedule. It is generally well tolerated with acne-like rash and nail changes being the most common side effects.

3.6.1 Cetuximab/5-FU plus radiotherapy

A pilot study conducted at Memorial Sloan-Kettering Cancer Center investigated the safety of cetuximab in combination with standard neoadjuvant 5-FU and RT in patients with locally advanced or locally recurrent rectal cancer. A total of 20 patients received cetuximab at 400 mg/m^2 on day 1 followed by 250 mg/m^2/wk × 4, continuous-infusion 5-FU at 225 mg/m^2/d over 5.5 weeks, and concurrent pelvic RT (50.4 Gy). Of the 20 patients enrolled, 12% of patients had a pCR. Grade 3 diarrhea was seen in 10% of patients (Chung, 2006).

3.6.2 Cetuximab/capecitabine plus radiotherapy

A Belgian phase I/II trial evaluated a regimen of cetuximab, capecitabine, and RT in 40 patients with endoscopically staged locally advanced rectal cancer. Patients were treated with a loading dose of cetuximab at 400 mg/m^2 the first week followed by 250 mg/m^2/wk × 5, escalating doses of capecitabine twice daily, and concurrent RT (45 Gy in 25 fractions). The recommended regimen consisted of capecitabine, 825 mg/m^2 twice daily, in combination with cetuximab and RT. This dose level was investigated in 30 patients. Only 2 patients (5%) experienced a pCR. Grade 3 diarrhea occurred in 15% of patients (Machiels, 2007).

3.6.3 Cetuximab/capecitabine/oxaliplatin plus radiotherapy

Cetuximab was also investigated in combination with oxaliplatin, capecitabine, and concurrent RT. Rodel et al conducted a phase I/II trial of cetuximab (400 mg/m^2 loading

dose followed by 250 mg/m²/wk × 5), oxaliplatin 50 mg/m² weekly, escalating doses of capecitabine (days 1 to 14 and days 22 to 35), and RT (50.4 Gy). The phase II dose was identified at a capecitabine dose level of 1650 mg/m²/d on days 1 to 14 and 22 to 35. A total of 48 patients were enrolled on the phase II trial. Tumor downstaging was observed in 47% patients with pCR in 9% patients. Grade 3-4 diarrhea was seen in 19% patients. This combination is feasible and safe and the addition of cetuximab did not compromise chemotherapy doses and did not lead to higher toxicity. However, the addition of cetuximab produced a relatively low rate of pathologic responses and underachieved the assumptions. Further preclinical and clinical research is necessary to clarify the mechanism and define the reason of this phenomenon (Rödel, 2007).

3.6.4 Cetuximab/irinotecan/capecitabine plus radiotherapy

Cetuximab has been similarly investigated in Irinotecan-based neoadjuvant rectal cancer trials. A German phase I trial investigated a combination of cetuximab, irinotecan, and capecitabine in 20 patients with rectal cancer. Cetuximab was given weekly (400 mg/m² loading dose followed by 250 mg/m² on days 8, 15, 22, and 29) and escalating doses of irinotecan and capecitabine with pelvic RT (50.4 Gy). Irinotecan at 40 mg/m² and capecitabine at 500 mg/m² twice daily were determined as the recommended doses for future studies. About 7% of patients with T3 disease and 80% with T2 disease achieved a pCR (Hofheinz, 2006).

Larger phase II trials are ongoing.

4. Short course *vs* long course radiotherapy

As mentioned above, randomized trials have demonstrated superior local control, lower toxicity and better compliance of radiotherapy or radiochemotherapy administered before rather than after surgery. Similar long-term survival, local control and late morbidity have been reported for both these methods in non-comparative studies.

The benefit of the short-course schedule is a lower rate of early toxicity than with chemoradiation. It is less expensive and more convenient, especially in centers with a long waiting list. On the other hand, the use of high doses per fraction raises concern about late toxicity.

Conventionally fractionated chemoradiation might be better than the short course radiation schedule at reducing local recurrences as well as permitting better sphincter preservation because tumor bulk is reduced before surgery. However, there is no firm evidence to support this. In Europe, there is still much debate about the two different approaches to preoperative therapy.

Bujko et al have randomly assigned 312 patients to receive either preoperative irradiation (25 Gy / 5 fractions) and surgery within 7 days or chemoradiation (50.4 Gy / 28 fraction with bolus 5-FU and LV) and surgery 4-6 weeks later. Early toxicity was higher in the chemoradiation group (18.2% *vs* 3.2%, $p<0.001$). After a median follow-up of 48 months, there were no differences on 4-year OS (67.2% *vs* 66.2%, $p = 0.960$), disease free survival (58.4% *vs* 55.6, $p = 0{,}820$), local recurrence (9% *vs* 14.2%, $p = 0.170$) or severe late toxicity (10.1% *vs* 7.1%, $p = 0.360$) (Bujko, 2006).

The intergroup trial (TROG, AGITG, CSSANZ, RACS) also randomized patients either to short course radiotherapy (25 Gy in 5 fractions in 1 week, followed by surgery the following week, and 6 courses of postoperative chemotherapy) or long course chemoradiotherapy

(pelvic RT 50.4 Gy, 1.8 Gy/fraction, in 5.5 weeks, continuous infusion 5-FU 225 mg/m²/day during RT, followed by surgery in 4 to 6 weeks, and 4 courses of postoperative chemotherapy). Each course of postoperative chemotherapy was to be 5-FU 425 mg/m² and folinic acid 20 mg/m² for 5 days. There was no clear evidence for a difference between short course radiotherapy and long course chemoradiotherapy in terms of 3-year local recurrence rates (7.5% vs 4.4%, p = 0.24). Distant recurrence (5-year distant recurrence-free rates were 72% *vs* 69%, $p = 0.85$) and OS rates (5-years OS were 74% *vs* 70%, $p = 0.56$) were similar. Both provided good local control. Late toxicity rates were not substantially different between arms (RTOG grade 3-4: 7.6% *vs* 8.8%; $p = 0.84$) (Ngan, 2010).

The Stockholm III trial addressed issues regarding the fractionation of radiotherapy and timing of surgery for rectal cancer. They randomized patients into 3 groups: Group 1 - short-course RT (5 x 5Gy) and surgery within 1 week; Group 2 - short-course RT (5 x 5Gy) and surgery after 4-8 weeks; Group 3 – long-course RT (25 x 2Gy) and surgery after 4-8 weeks. Severe acute toxicity was low, irrespective of fractionation. Short-course radiotherapy with immediate surgery had a tendency towards more postoperative complications, but only if surgery was delayed beyond 10 days after the start of radiotherapy (Pettersson, 2010).

The Berlin Cancer Society is recruiting patients for a multi-centre randomized study either to short-course radiotherapy (25 Gy / 5 fractions) + TME surgery within 5 days or radiochemotherapy (50.4 Gy / 28 fractions with continuous infusion 5-FU) + TME surgery 4-6 weeks later. All patients received adjuvant chemotherapy (12 weeks continuous infusion 5-FU) (Siegel, 2010).

5. Prognostic factors for responders to chemoradiation

The predictive factors for response to neoadjuvant chemoradiotherapy in rectal cancer have not been well characterized. A better understanding of predictive factors eventually may lead to the development of risk-adapted treatment strategies, such as more aggressive preoperative regimens, in patients who are less likely to respond to standard preoperative therapy.

The role of tumor markers, CEA and CA19.9, in rectal cancer is still in debate. In 2006 Yoon-ah Park et al showed that elevated pretreatment CEA levels (>5ng/ml) were associated with poor tumor response to preoperative chemoradiation (Park, 2006). Das et al (Das, 2007) concluded that CEA level (>2.5 ng/ml) resulted in significantly lower pCR rates ($p = 0.015$).

The most commonly reported early endpoint is the rate of pCR. It appears to be associated in some non randomized studies with improvement in PFS (Janjan, 2001; Valentini; 2002). It has been shown in one randomized trial that time interval between RT and surgery influences the degree of downstaging, with 10% of patients operated within 2 weeks of RT experiencing pathological downstaging compared to 26% of patients operated 6-8 weeks after RT ($p = 0.005$) (Francois, 1999). Many studies have shown that neoadjuvant chemoradiotherapy significantly increases the rate of pCR, as well as nodal and tumor downstaging.

The most recent published article (Maas, 2010) evaluating the long-term outcome in patients with a pCR after chemoradiotherapy for rectal cancer concluded that patients with pCR have better long-term outcome than those who did not. They stated that pCR might be indicative of a prognostically favourable biological tumor profile with lower propensity for local or distant recurrence and improved survival.

The Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology analyzed retrospectively 566 patients with LARC achieving pCR after neoadjuvant therapy and they verified that this favorable group of patients had a very low rate of local recurrence (1.2%) and a favorable clinical outcome independent of the neoadjuvant chemotherapy schedule used, achieving a 5-year PFS of 84.7% and 5-year OS of 91.6%. In such a group of patients, the use of postoperative chemotherapy could be very debatable. Conversely, the subset of patients older than 60 years, with cStage III and treated with a radiation dose of 45 Gy or less experienced a relatively worse prognosis, even after achieving ypCR. The prognosis of the high-risk group of patients compares with the outcome of a non-selected population (Capirci, 2008).

Some other studies (Kim, 2006; Fernandez-Martos, 2004; Rodel, 2005; García-Aguilar, 2003). also showed excellent oncologic outcomes in patients with pCR. Valentini et al (Valentini, 2002) have demonstrated that, after preoperative chemoradiotherapy, clinical response and tumor and nodal pathologic downstaging have a close correlation with improved outcome. Indeed, patients with tumor downstaging had a 5-year local control of 87.8%, a PFS of 73.1% and an OS of 82.9%, while those who had not tumor downstaging had a local control of 70.5%, a PFS of 47.2% and an OS of 60.9%. Those patients with nodal downstaging also had better 5-year local control (84.3%), PFS (67.1%) and OS (74.3%) than those who did not have nodal downstaging (72%, 42.2% and 56.1%, respectively).

On the other hand, Salvatore Pucciarelli et al have not found statistically significant differences for PFS and OS on comparing the actuarial survival curves of patients with different tumor responses to preoperative treatment, whether evaluated as tumor regression grade or as pTNM stage (Pucciarelli, 2004).

It was in this context that we developed a single-institute study to evaluate the therapeutic response and impact on survival of preoperative RT, alone or combined with chemotherapy, in patients with locally advanced rectal cancer. We studied 132 patients treated preoperatively either with RT alone, RT and concomitant oral chemotherapy (capecitabine or UFT+LV) or RT and concomitant chemotherapy with 5-FU in continuous infusion. Patients were then submitted to adjuvant chemotherapy. In our study we verified that the combination of chemotherapy to RT significantly increased the tumor response, especially the nodal downstaging, at the expense of a higher but manageable toxicity (majority grade 1-2 toxicities). It also allowed a higher complete surgical resection without increasing postoperative complications rate. Tumor downstaging was superior (p = 0.224) in patients treated with chemoradiotherapy (CAP/UFT-LV + RT: 47.7%; 5-FU + RT: 52.4%) than in patients of the RT arm (26.7%). Nodal downstaging was significantly better (p = 0.008) in CAP/UFT-LV + RT group comparing to RT group and 5-FU+RT group (82.1% *vs* 54.5% and 54.8%, respectively). The neoadjuvant chemoradiotherapy groups had better pCR (CAP/UFT-LV + RT GROUP: 16.9%; 5-FU + RT GROUP: 11.9%) compared to the RT arm (0%) (p = 0.207). We registered a locoregional control of 95%, the global 3- and 5-year PFS was 75% and 68%, respectively, the global 3- and 5-year OS was 88% and 80%, respectively. Both 5-year OS (84% *vs* 59%, p = 0.038) and PFS (69% *vs* 55%, p = 0.05) were significantly higher in patients treated with neoadjuvant chemoradiation than in the RT group. We have also found a better PFS in those patients who had pCR (100% *vs* 62%, p = 0.023). When considering only those patients cT3-4 who had downstaging to ypT0-2, we found a significantly better locoregional control (100% *vs* 89, p = 0.027), PFS (88% *vs* 43%, p = 0.003) and OS (89% *vs* 77%, p = 0.048). Adjuvant chemotherapy had no impact on locoregional control, PFS or on OS (Conde, 2010).

6. Conclusions

Neoadjuvant therapy is widely accepted as the current standard of care for locally advanced rectal cancer and has evolved from the use of preoperative radiation alone to wider use of preoperative combined chemoradiation. Downstaging of disease has been significantly improved and pCR which was historically below 10% with preoperative radiation alone, now range from 15-30% with preoperative chemoradiation. In a number of studies pCR following neoadjuvant therapy appears to be a strong surrogate for effectiveness of treatment with lower local recurrence of disease and improved sphincter preservation and survival of patients. While the availability of new chemotherapeutic drugs (oxaliplatin, irinotecan) and molecular targeted agents (bevacizumab, cetuximab) holds a great deal of promise, we have seen that in many cancers, more drugs or more intensive regimens are not always as successful as we would have hoped. Early results in phase II trials appear to have a pCR plateaued at 20-30%. The use of multi-drug combinations increased toxicity of treatment hence resulting in a suboptimal therapeutic ratio.

The historical problem of high local pelvic recurrence following surgery (20-30%) no longer is a cause of poor survival in patients (<10%). The problem remains the persistent high rate of distant metastasis (30-35%) in this disease. New paradigms in neoadjuvant therapy are therefore needed to further improve results of treatment. Although we have not been successful in developing new agents that are effective radiation sensitizers in rectal cancer, this is still a very worthwhile goal, and innovations in biologics and nanoparticles could be of major importance (Mohiuddin M., et al, 2009).

7. References

Alonso V., Lambea J., Salud A., et al. (2007). Preoperative chemoradiotherapy with Capecitabine and Oxaliplatin in locally advanced rectal carcinoma: A phase II trial (abstract 4044). *J Clin Oncol*, Vol. 25, No. 18S, (2007), pp. 174-179.

Aschele C., Pinto C., Cordio S., et al. (2009). Preoperative fluorouracil (FU)-based chemoradiation with and without weekly Oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial. *J Clin Oncol*, Vol. 27 No.18S, (2009) (suppl; abstr CRA4008).

Aschele C., Vitali M., Caroti C., et al. (2009). A phase I study of Uracil/Tegafur (UFT) and oral Leucovorin (LV) + weekly Oxaliplatin (OXA) and preoperative radiotherapy (RT) in locally advanced rectal cancer (LARC). ASCO 2009 (Abstr 409).

Bosset J., Calais G., Mineur L., et al. (2005). Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results EORTC 22921. *J Clin Oncol*, Vol. 23, (2005), pp. 5620-5627.

Bujko K., Nowacki M.P., Nasierowska-Guttmejer A., et al. (2006). Long-term results of a randomized trial comparing preoperative short course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer; *Br J Surg*, Vol. 93, (2006), pp. 1215-1223.

Cammá C., Giunta M., Fiorica F., et al. (2000). Preoperative Radiotherapy for resectable rectal cancer. A meta-analysis. *JAMA*, Vol. 284, (2000), pp. 1008-1015.

Capirci C., Valentini V., Cionini L., et al. (2008). Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term

analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys*, Vol.72, No. 1, (2008), pp. 99-107.

Carlomagno C., Ferrante A., Solla R., et al. (2007). Preoperative chemoradiation therapy with Capecitabine (CAP) and Oxaliplatin (OX) in locally advanced rectal cancer (LARC): A phase II study (abstract 301). *Gastrointestinal Cancers Symposium*, (Jan 2007), pp. 19-21.

Carmichael J., Popiela T., Radstone D., et al. (1999). Randomized comparative study of ORZELt (oral Uracil/Tegafur (UFT™) plus Leucovorin (LV)) versus parenteral 5-fluorouracil (5-FU) in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol*, Vol. 18, No. 264a, (1999), (abstr 1015)

Chung K.Y., Minsky B., Schrag D., et al. Phase I trial of preoperative Cetuximab with concurrent continuous infusion 5-fluorouracil and pelvic radiation in patients with local-regionally advanced rectal cancer (abstract 3560). *J Clin Oncol*, Vol. 24, No. 18S, (2006), pp. 161-169.

Colorectal Cancer Collaborative Group. (2001). Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet*, Vol. 358, (2001), pp. 1291-1304.

Conde S., Borrego M., Teixeira T., et al. (2010). Impact of neoadjuvant chemoradiation on pathologic response and survival of patients with locally advanced rectal cancer. *Rep Pract Oncol Radiother*, Vol. 15, (2010), pp. 51-59.

Crane C., Eng C., Chang G., et al. (2007). Preliminary results of a phase II trial concurrent Bevacizumab with neoadjuvant Capecitabine based chemoradiation for locally advanced rectal cancer (abstract SS-10). *Oncology*, Vol. 5 (suppl 2), No.4, (2007).

Czito B.G., Bendell J.C., Willett C.G., et al. (2007). Bevacizumab, Oxaliplatin, and Capecitabine with radiation therapy in rectal cancer: Phase I trial results. *Int J Radiat Oncol Biol Phys*, Vol. 68, (2007), pp. 472-478.

Das P., Skibber J.M., Rodriguez-Bigas M.A., et al. (2007). Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. *Cancer*, Vol. 109, (2007), pp. 1750-17555.

De Bruin A.F., Nuyttens J.J., Ferenschild F.T., et al. Preoperative chemoradiation with Capecitabine in locally advanced rectal cancer. *Netherl J Medicine*, Vol. 66, (2008), pp. 71-76.

de Gramont A., Figer A., Seymour M., et al. (2000) Leucovorin and fluorouracil with or without Oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*, Vol. 18, (2000), pp. 2938-2947.

De la Torre A., Garcia-Berrocal M.I., Arias F., et al. (2008). Preoperative chemoradiatiotherapy for rectal cancer: randomized trial comparing oral Uracil and Tegafur and oral Leucovorin vs. intravenous 5-fluorouracil and Leucovorin. *Int J Radiat Oncol Phys*, Vol. 70, (2008), pp. 102-110.

De Paoli A., Chiara S., Luppi G., et al. (2006). Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. *Ann Oncol*, Vol. 17, (2006), pp. 246-251.

Dunst J., Reese T., Sutter T. et al. (2002). Phase I trial evaluating the concurrent combination of radiotherapy and Capecitabine in rectal cancer. *J Clin Oncol*, Vol. 20, No. 19, (2002), pp. 3983-3991.

Dunst J., Reese T., Debus J. et al. (2004). Phase-II-study of preoperative chemoradiation with Capecitabine in rectal cancer. *Proc Am Soc Clin Oncol*, Vol. 23, (2004), pp. 260 (Abstr 3559).

Feliu J., Calvilio J., Escribano A. et al. (2002). Neoadjuvant therapy of rectal carcinoma with UFT–Leucovorin plus radiotherapy. *Ann Oncol*, Vol. 13, (2002), pp. 730–736.

Fernandez-Martos C., Aparicio J., Bosch C. et al. (2004). Preoperative Uracil, Tegafur, and concomitant radiotherapy in operable rectal cancer: a phase II multicenter study with 3 years' follow-up. *J Clin Oncol*, Vol. 22, (2004), pp. 3016–3022.

Fernandez-Martos C., Bosch C., Aparicio J. et al. Oxaliplatin, Uracil/Tegafur (UFT) and radiotherapy in operable rectal cancer. Preliminary results of a multicenter phase II study. *J Clin Oncol*, Vol 23 (16 Suppl) (Abstr 3648), (2005).

Folkesson J., Birgisson H., Pahlman L., et al. (2005). Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate; *J Clin Oncol*, Vol. 23, (2005), pp. 5644-5650.

Francois Y., Nemoz C., Baulieux J., et al. (1999). Influence of the interval between radiation therapy and surgery on downstaging and rate of sphincter sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol*, Vol. 17, (1999), pp. 2396-2402.

García-Aguilar J., de Anda E.H., Sirivongs P. et al. (2003). A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis *Colon Rectum*, (2003), pp. 298-304.

Gastrointestinal Tumor Study Group. (1985). Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Eng J Med*, Vol. 312, (1985), pp. 1465-1472.

Gérard J.P., Conroy T., Bonnetain F., et al. (2006). Preoperative radiotherapy with or without concurrent fluorouracil and Leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol*, Vol. 24, (2006), pp. 4620-4625.

Gérard J.P., Azria D., Gourgou-Bourgade S., et al. (2010). Comparison of Two Neoadjuvant Chemoraditherapy Regimens for Locally Advanced Rectal Cancer: Results of the Phase III Trial ACCORD 12/0405-Prodige 2. *J Clin Oncol*, Vol. 28, (2010), pp. 1638-44.

Glynne-Jones R., Sebag-Montefiore D., Maughan T.S., et al. (2006). A phase I dose escalation study of continuous oral Capecitabine in combination with Oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer. *Ann Oncol*, Vol. 17, (2006), pp. 50-56.

Glynne-Jones R., Falk S., Maughan T.S., et al. (2007). A phase I/II study of Irinotecan when added to 5-fluorouracil and Leucovorin and pelvic radiation in locally advanced rectal cancer: A Colorectal Clinical Oncology Group Study. *Br J Cancer*, Vol. 96, (2007), p. 551-558.

Goldberg R.M., Sargent D.J., Morton R.F., et al. (2004). A randomized controlled trial of fluorouracil plus Leucovorin, Irinotecan, and Oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*, Vol. 22, (2004), pp. 23-30.

Grem J.L. (1997). Systemic treatment options in advanced colorectal cancer: perspectives on combination 5-fluorouracil plus Leucovorin. *Semin Oncol*, Vol. 24(Suppl. 18), (1997), pp. 8-18.

Gunderson L.L., Sosin H. (1974). Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcninoma of the rectum. Clinicopathologic correlation and implications for adjuvant therapy. *Cancer*, Vol. 34, (1974), pp. 1278-1292.

Haller D.G., Cassidy J., Clarke S., et al. (2006). Tolerability of fluoropyrimidines appears to differ by region (abstract 3514). *J Clin Oncol*, Vol. 24, No. 18S, (2006), pp. 149.

Hirata K., Sasaki K., Yamamitsu S., et al. (1993). A comparison of 5-fluorouracil concentration of 5-fluorouracil drip infusion versus oral UFT in plasma of same patients. *Jpn J Cancer Chemother*, Vol. 20, (1993), pp. 1409-1411.

Ho D.H., Pazdur R., Covington W. et al. (1998). Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral Uracil plus N1-(2′-tetrahydrofuryl)-5-fluorouracil. *Clin Cancer Res*, Vol. 4, (1998), pp. 2085–2088.

Hoff P.M., Pazdur R., Benner S.E., et al. (1998). UFT and Leucovorin: A review of its clinical development and therapeutic potential in the oral treatment of cancer. Anticancer *Drugs*, Vol. 9, (1998), pp. 479-490.

Hoff P.M., Janjan N., Saad E.D. et al. (2000). Phase I study of preoperative oral Uracil and Tegafur plus Leucovorin and radiation therapy in rectal cancer. *J Clin Oncol*, Vol. 18, (2000), pp. 3529–3534.

Hoff P.M., Ansari R., Batist G., et al. (2001). Comparison of oral Capecitabine versus intravenous fluorouracil plus Leucovorin as firstline treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol*, Vol. 19, (2001), pp. 2282–2292.

Hofheinz R.D., von Gerstenberg-Helldorf B., Wenz F., et al. (2005). Phase I trial of Capecitabine and weekly Irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer. *J Clin Oncol*, Vol. 23, (2005), pp. 1350-1357.

Hofheinz R.D., Horisberger K., Woernle C., et al. (2006). Phase I trial of Cetuximab in combination with Capecitabine, weekly Irinotecan, and radiotherapy as neoadjuvant therapy for rectal cancer. *Int J Radiat Oncol Biol Phys*, Vol. 66, (2006), pp. 1384-1390.

Janjan N.A., Crane C., Feig B.W., Cleary K. et al. (2001). Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. *Am J Clin Oncol*, Vol. 24, (2001), pp. 107–112.

Kapiteijn E., Marijnen C.A.M., Nagtegaal I.D., et al. (2001). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer; *N Engl J Med*, Vol. 345, No 9, (2001), pp. 638-646.

Kim J.C., Kim T.W., Kim J.H., et al. (2005). Preoperative concurrent radiotherapy with Capecitabine before total mesorectal excision in locally advanced rectal cancer; *Int J Radiat Oncol Biol Phys*, Vol. 63, No 2, (2005), pp. 346-353.

Kim N.K., Baik S.H., Seong J.S., et al. (2006). Oncologic outcomes after neoadjuvant chemoradiation followed by curative resection with tumor-specific mesorectal excision for fixed locally advanced rectal cancer: Impact of postirradiated pathologic downstaging on local recurrence and survival. *Ann Surg*, Vol. 244, No 6, (2006), pp. 1024-30.

Kim D.Y., Jung K.H., Kim T.H., et al. (2007). Comparison of 5-Fluorouracil/Leucovorin and Capecitabine in preoperative chemoradiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*, Vol. 67, (2007), pp. 378-384.

Kim S.Y., Hong S.Y., Kim D.Y., et al. (2009). A pilot study of neoadjuvant chemoradiation with higher dose enteric-coated Tegafur/Uracil plus Leucovorin for locally advanced rectal cancer. *ECCO/ESMO 2009* (poster).

Klautke G., Feyerherd P., Ludwig K., et al. (2005). Intensified concurrent chemoradiotherapy with 5-fluorouracil and Irinotecan as neoadjuvant treatment in patients with locally advanced rectal cancer. *Br J Cancer*, Vol. 92, (2005), pp. 1215-1220.

Klautke G., Kuchenmeister U., Foitzik T., et al. (2006). Concurrent chemoradiation with Capecitabine and weekly Irinotecan as preoperative treatment for rectal cancer: Results from a phase I/II study. *Br J Cancer*, Vol. 94, (2006), pp. 976-981.

Krishnan S., Janjan N.A., Skibber J.M., et al. (2006). Phase II study of Capecitabine (Xeloda®) and concomitant boost radiotherapy in patients with locally advanced rectal cancer; *Int J Radiat Oncol Biol Phys*, Vol. 66, No. 3, (2006), pp. 762-771.

Kundel Y., Brenner B., Symon Z. et al. (2007). A phase II study of oral UFT and Leucovorin concurrently with pelvic irradiation as neoadjuvant chemoradiation for rectal cancer. *Anticancer Res*, Vol. 27, (2007), pp. 2877–2880.

Lee C.R., Nicholson P.W., Souhami R.L., et al. (1992). Patient compliance with oral chemotherapy as assessed by a novel oral technique; *J Clin Oncol*, Vol. 10, (1992), pp. 1007-1013.

Maas M., Nelemans P.J., Valentini V., et al. (2010). Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*, Vol. 11, No. 9, (2010), pp. 835-44.

Machiels J.P., Duck L., Honhon B., et al. (2005). Phase II study of preoperative Oxaliplatin, Capecitabine and external beam radiotherapy in patients with rectal cancer: The RadiOxCape study. *Ann Oncol*, Vol. 16, (2005), pp. 1898-1905.

Machiels J.P., Sempoux C., Scalliet P., et al. (2007). Phase I/II study of preoperative Cetuximab, Capecitabine, and external beam radiotherapy in patients with rectal cancer. *Ann Oncol*, Vol. 18, (2007), pp. 738-744.

Mitchell E.P. (2000). Irinotecan in preoperative combined-modality therapy for locally advanced rectal cancer. *Oncology*, Vol. 14, (2000), pp. 56-59.

Miwa M., Ura M., Nishida M., et al. (1998). Design of a novel oral fluoropyrimidine carbamate, Capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer*, Vol. 34, (1998), pp. 1274-81.

Mohiuddin M., Winter K., Mitchell E., et al. (2006). Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. *J Clin Oncol*, Vol. 24, (2006), pp. 650-655.

Mohiuddin M., Mohiuddin M., Marks J., et al. (2009). Future directions in neoadjuvant therapy of rectal cancer: Maximizing pathological complete response rates. *Cancer Treatment Reviews*, Vol. 35, (2009), pp. 547-52.

Nakazato H., Koike A., Saji S., et al. (1997). Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: A prospective randomized clinical trial. *Proc Am Soc Clin Oncol*, Vol. 16, (1997), pp. 279a (abstr 990).

National Institutes of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *J Am Med Assoc*, Vol. 264, (1990), pp. 1444–1450.

Navarro M., Dotor E., Rivera F., et al. (2006). A Phase II study of preoperative radiotherapy and concomitant weekly Irinotecan in combination with protracted venous infusion 5-fluorouracil, for resectable locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*, Vol. 66, (2006), pp. 201-205.

Ngan S., Fisher R., Goldstein D., et al. (2010). A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: An intergroup trial (TROG, AGITG, CSSANZ, RACS); *J Clin Oncol*, Vol. 28, (2010), pp. 15s (suppl; abstr 3509).

Ofner D., de Vries A., Thaler J., et al. (2007). Preoperative Oxaliplatin (O), Capecitabine (X), and external beam radiotherapy (RT) in patients (pts) with newly diagnosed, primary operable, locally advanced rectal cancer (LARC) (abstract 14527). *J Clin Oncol*, Vol. 25, No. 18S, (2007), pp. 627.

Okabe H., Toko T., Saito H., et al. (1997). Augmentation of the chemotherapeutic effectiveness of UFT, a combination of Tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, by oral 1-Leucovorin. *Anticancer Res*, Vol. 17, (1997), pp. 157-164.

Park Y., Sohn S., Seong J., et al. (2006). Serum CEA as a predictor for the response to preoperative chemoradiation in rectal cancer. J. Surg. *Oncol*, Vol. 93, (2006), pp. 145-150.

Pazdur R., Douillard J.Y., Skillings J.R., et al. (1999). Multicenter phase III study of 5-fluorouracil (5-FU) or UFT™ in combination with Leucovorin (LV) in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol*, Vol. 18, (1999), pp. 263 (abstr 1009).

Peeters K.C.N.J., Marijnen C.A.M., Nagtegaal I.D., et al. (2007). The TME Trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma; *Ann Surgery*, Vol. 246, No. 5, (2007), pp. 693-701.

Pentheroudakis G., Twelves C. (2002). The rational development of Capecitabine from the laboratory to the clinic. *Anticancer Res*, Vol. 22, (2002), pp. 3589–3596.

Pettersson D., Cedermark B., Holm T., et al. (2010). Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer; *Br J Surg*, Vol. 97, No. 4, (2010), pp. 580-587.

Pfeffer M.R., Kundel Y., Zehavi M. et al. (2004). A phase I study of oral UFT given concomitantly with standard preoperative radiotherapy for rectal cancer. *Isr Med Assoc J*, Vol. 6, (2004), pp. 595–598.

Privitera G., Spatola C., Acquaviva G., et al. (2007). Addition of Bevacizumab (Beva) to xeliri/xelox chemoradiotherapy in neoadjuvant setting for patients (pts) with locally advanced rectal cancer (LARC): A feasibility study. *J Clin Oncol*, Vol. 25, No. 18S, (2007), pp. 631 (abstract 14583).

Privitera G., Spatola C., Acquaviva G., et al. (2006). Neoadjuvant XELOX vs XELIRI in combination with concomitant boost 3D-conformal radiotherapy in locally advanced rectal cancer (LARC) (abstract 3570). *J Clin Oncol*, Vol. 24, No. 18S, (2006), pp. 163.

Pucciarelli S., Toppan P., Friso M.L. et al. (2004). Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. *Dis Colon Rectum*, Vol. 47, (2004), pp. 1798-1807.

Rich T., Gunderson L.L., Lew R., et al. (1983). Patterns of recurrence of rectal cancer after potencially curative surgery. *Cancer*, Vol. 52, (1983), pp. 1317-1329.

Rodel C., Martus P., Papadoupolos T., et al. (2005). Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol*, Vol. 23, (2005), pp. 8688-8696.

Rodel C., Arnold D., Hipp M., et al. (2007). Phase I-II Trial of Cetuximab, Capecitabine, Oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. *Int J Radiat Oncol Biol Phys*, Vol. 70, (2007), pp. 1081-1086.

Roedel C., Arnold D., Hipp M., et al. (2006). Multicenter phase II trial of preoperative radiotherapy with concurrent and adjuvant Capecitabine and Oxaliplatin in locally advanced rectal cancer; German Rectal Cancer Study Group. *Gastrointestinal Cancers Symposium*, (2006), (abstract 349).

Rutten H., Sebag-Montefiore D., Glynne-Jones R., et al. (2006). Capecitabine, Oxaliplatin, radiotherapy, and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: Results of an international multicenter phase II study. *J Clin Oncol*, Vol. 24, No. 18S, (2006), pp. 153 (abstract 3528).

Ryan D.P., Niedzwiecki D., Hollis D., et al. (2006). Phase I/II study of preoperative Oxaliplatin, Fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901. *J Clin Oncol*, Vol. 24, (2006), pp. 2557-2562.

Salimichokami M., Vafai M., Derakhshani S., et al. (2006). Phase-2 study of neoadjuvant chemoradiation in locally advanced rectal adenocarcinoma: The Radio-Xelox study. *J Clin Oncol*, Vol. 24, No. 18S, (2006), pp. 620(abstract 13549).

Sauer R., Becker H., Hohenberger W., et al. (2004). Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Eng J Med*, Vol. 351, (2004), pp. 1731–1740.

Sawada N., Ishikawa T., Sekiguchi F., et al. (1999). X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of Capecitabine (Xeloda) in human cancer xenografts. *Clin Cancer Res*, Vol. 5, (1999), pp. 2948-2953.

Schuller J., Cassidy J., Dumont E., et al. (2000). Preferential activation of Capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol*, Vol. 45, (2000), pp. 291-297.

Segab-Montefiore D., Stephens R.J., Steele R., et al. (2009). Preoperative radiotherapy versus selective postoperative Chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomized trial. *Lancet*, Vol. 373, (2009), pp. 811-820.

Siegel R., Burock S., Wernecke K., et al. (2009). Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomized study of the Berlin Cancer Society – Study protocol; *BMC Cancer*, Vol. 9, (2009), pp. 50.

Sulkes A., Benner S.E., Canetta R.M. (1998). Uracil-ftorafur: An oral fluoropyrimidine active in colorectal cancer. *J Clin Oncol*, Vol. 16, (1998), pp. 3461–3475.

Swedish Rectal Cancer Trial. (1997). Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*, Vol. 336, (1997), pp. 980-987.

Torino F., Cascinu S., Ciardiello F. et al. (2008). A Phase II Study of Neoadjuvant Antiangiogenic Therapy Combined With Capecitabine (C) and Radiotherapy (RT) in Patients with Locally Advanced Rectal Cancer (LARC). *ESMO 2008* (abstract 418P)

Valentini V., Coco C., Picciocchi A., et al. (2002). Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. *Int J Radiat Oncol Biol Phys*, Vol. 53, (2002), pp. 664–674.

Van Cutsem E., Twelves C., Cassidy J., et al. (2001). Oral Capecitabine compared with intravenous fluorouracil plus Leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. *J Clin Oncol*, Vol. 19, (2001), pp. 4097–4106.

Wang L.W., Yang S.H., Lin J.K., et al. (2005). Pre-operative chemoradiotherapy with oral Tegafur–Uracil and Leucovorin for rectal cancer. *J Surg Oncol*, Vol. 89, (2005), pp. 256–263.

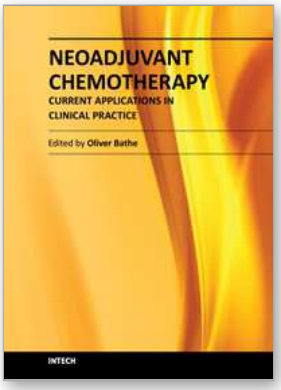
Willeke F., Horisberger K., Kraus-Tiefenbacher U., et al. (2007). A phase II study of Capecitabine and Irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer, Vol. 96, (2007), pp. 912-917.

Willett C., Duda D., Boucher Y., et al. (2007). Phase I/II study of neoadjuvant Bevacizumab with radiation therapy and 5-fluorouracil in patients with rectal cancer: initial results. J Clin Oncol, Vol. 25, No. 18S, (2007), pp. 173(abstract 4041).

Wolmark N., Wieand H.S., Hyams D.M., et al. (2000). Randomizes trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02; J Natl Cancer Inst, Vol. 92, (2000), pp. 388-396.

Yasui M., Ikeda M., Sekimoto M., et al. (2006). Preliminary results of phase I trial of oral Uracil/Tegafur (UFT), Leucovorin plus Irinotecan and radiation therapy for patients with locally recurrent rectal cancer. World J Surg Oncol, Vol. 4, (2006), pp. 83.

Zhu A.X., Willett C.G. (2003). Chemotherapeutic and biologic agents as radiosensitizers in rectal cancer; Semin Rad Oncol, Vol. 13, No. 4, (2003), pp. 454-458.



Neoadjuvant Chemotherapy - Current Applications in Clinical Practice

Edited by Dr. Oliver Bathe

ISBN 978-953-307-994-3
Hard cover, 268 pages
Publisher InTech
Published online 01, February, 2012
Published in print edition February, 2012

The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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