

# Neoadjuvant treatment in locally advanced rectal cancer

Zuleyha AKGUN, Esra KAYTAN SAGLAM

## ABSTRACT

The optimal treatment for locally advanced rectal cancer remains an issue of debate. The surgery with total mesorectal excision (TME) still is the standard of care. In contrast to TME, the addition of adjuvant or neoadjuvant therapy is necessary in terms of local disease control and to increase of survival time. Here, we will review neoadjuvant treatment approach in rectal carcinoma.

**Keywords:** Rectal neoplasms, Neoadjuvant therapy, Radiotherapy, Chemotherapy

## Introduction

The neoadjuvant treatment has high importance; issue that remains controversial is if the radiotherapy should be alone or with chemotherapy. Current guidelines recommend neoadjuvant treatment included radiotherapy with fluorouracil or capecitabine chemotherapy as long-course to a total dose 45-50.4 Gy in 1.8-2 Gy fractions or short-course to a total dose of 25 Gy in five fractions alone for locally advanced rectal cancer. The guidelines also recommend the waiting time between neoadjuvant therapy and surgery 6-8 weeks for long-course and 1-2 weeks for short-course [1, 2].

There are two randomized trials of preoperative versus postoperative therapy for rectal cancer with conflicting results. The German CAO/ARO/AIO 94 trial compared preoperative and postoperative chemoradiotherapy and resulted with statistical significance for reduced local relapse (15%-6%, p: 0.006) in preoperative arm and acute toxicity (40%-27%, p:0.001), chronic toxicity (24%-14%, p:0.01). There was no significance for overall survival [3]. However NSABP R-03 trial did not show any significance for local relapse in preoperative arm. The preoperative arm had high grade 4 acute toxicity and low grade 3 acute toxicity (33%-23%, 41%-50%, respectively). The accrued patients number in NSABP trial was lower and statistical results were affected negatively [4].

By the most tailored neoadjuvant therapy must be aimed that excellent local control, longer survival time and increase the sphincter preservation surgery.

## Short-course neoadjuvant radiotherapy

Short-course renders an immediate and intensive therapy with hypofractionated radiotherapy schedule. There are a lot of trials showed a significant reduction in local relapse with short-course and lead to the acceptance this course [5]. Swedish Rectal Cancer Trial showed that the rate of local relapse reduced from 27% to 11% (p 0.001) and the survival rate in 5-year increased from 48% to 58% with neoadjuvant short-course radiotherapy and surgery arm compared surgery alone [5]. After 13 years of follow up experienced to continue the benefit for local relapse, overall survival and event free survival for short-course radiotherapy and surgery arm (26% to 9%; p:0.001, 38% to 30%; p:0.008, 72% to 62%; p:0.03 respectively) [6]. The Dutch trial compared short-course radiotherapy and surgery as total mesorectal

Zuleyha Akgun, M.D. (✉),  
Department of Radiation Oncology, Memorial Sisli Hospital, Istanbul,  
Turkey  
e-mail: zuleyh@hotmail.com

Esra Kaytan Sağlam, M.D.  
Department of Radiation Oncology, Institute of Oncology, University of  
Istanbul, Istanbul, Turkey.

excision alone [7]. This trial showed significant reduction in local relapse in short-course radiotherapy arm. Twelve years of follow up report confirms that the benefits for local relapse (11% to 5%,  $p < 0.0001$ ) incidence and overall survival with stage 3 cancer with a negative circumferential resection margin (50% to 40%,  $p: 0.032$ ) in short-course preoperative radiotherapy group [8].

The short-course radiotherapy is with acute toxicity included gastrointestinal symptoms or sacral pain occurred after 3-7 days after the completion of radiotherapy in about 10% of patients [9].

Irradiated patients had with more bowel movements and fecal incontinence compared to nonirradiated patients in Swedish rectal cancer trial. Six months after treatment the short-course radiation arm patients had higher diagnosed with bowel obstruction. This late side effect can be associated with large radiotherapy portals (the upper border top of L2 vertebrae) in this trial [10]. Increased incidence of small bowel obstruction was not confirmed by the Dutch TME trial.

The Dutch TME trial showed that irradiated males had more ejaculation problems can be associated by irradiation seminal vesicles, erectile dysfunction can be related with damage of the small vessels [11].

### Long-course neoadjuvant chemoradiotherapy

Short-course is commented in terms of does not give permission chemotherapy as concurrently. The Polish trial compared preoperative short-course radiotherapy and preoperative long-course chemoradiotherapy with randomized 316 patients. There were no significant differences in local relapse, sphincter preservation or survival rate. The rate of circumferential resection margin was higher in short-course radiation arm (4% to 13%,  $p: 0.01$ ) [12]. Another important trial TROG-0104 compared short-course radiotherapy and long-course preoperative chemoradiotherapy, after surgery the patients received adjuvant chemotherapy. There was no significance in local relapse, overall survival between two groups. But there was significance for increased T down staging in the long-course arm ( $p: 0.003$ ).

There are a lot of randomized trials compared preoperative and postoperative chemoradiotherapy have shown significance for local control rates [13]. Long-course preoperative chemoradiotherapy has some advantage as allow systemic therapy concurrently, possibility of achieving down staging of the tumor, less acute toxicity, improved radio-sensitivity due to better oxygenated cells in contrast to postoperative era and higher sphincter preservation rates [14]. Recent literature has been reported that the rate

complete response in patients 15-30% with long-course chemoradiotherapy. Complete response lead to better prognosis [15]. Rate of local relapse is effected by totally excision with negative circumferential resection margin and complete or good response may allow it.

Preoperative chemoradiotherapy can downstage and improve resectability in unresectable tumors also with acceptable acute toxicity and event free survival. On the other hand distant metastases still observed 30% of patients. Braendengen M et al. compared preoperative chemoradiation as long-course plus 5FU/LV and long-course radiotherapy alone in unresectable or recurrent rectal cancer patients and described significance in local relapse reduction and event free survival in chemoradiotherapy arm [16]. Long-course radiotherapy is given usually with 5FU, either as a continuous infusion in combination with leucovorin, or capecitabine, UFT. It is criticized that the chemotherapy used less than fully doses as concurrent chemoradiotherapy era, has no effect on survival.

Oral capecitabine produced good clinical outcome in conjunction with neoadjuvant radiotherapy for locally advanced rectal cancer patients. Hofheinz et al showed the rate of ypCR (14%) was significantly more in capecitabine group ( $p=0.09$ ) compared with fluorouracil [17].

There is a phase II trial showed that neoadjuvant chronomodulated capecitabine and concurrent radiation therapy is effective and well tolerated with low toxicity profile [18]. This study reported excellent ypCR rate (20%), low rates of grade III diarrhea (10.5%), grade 3 thrombocytopenia (only one patient), grade II or III proctitis (10.5%), hand and foot syndrome (3.3%). There were no grade IV toxicities.

### Comparison of the regimens

The Polish trial, one of the studies that compared between short-course radiotherapy and long-course chemoradiotherapy, reported no significance in survival, sphincter preserving and local relapse for 5 years follow-up. The Trans-Tasman Radiation Oncology Group (TROG 01.04) study also compared between short-course radiotherapy and long-course chemoradiotherapy, included adjuvant chemotherapy with 5FU and folinic acid for 6 months in both arms. Median follow-up was 5.6 years. The results of this trial were similar for short-course and long-course in terms of local relapse (7.5% versus 5.7%), event free survival (67% versus 71%), overall survival (74% versus 70%) and late effects (7.6% versus 8.8%). The authors found both trials underpowered in terms of number of randomized patients to detect the significance between two regimens. Another conclusion that

quality of life documentation was poor in Polish study and this lead no significant difference between two arms.

Stockholm trials reported significant higher in postoperative mortality, bone fractures, small bowel obstruction, fistulae and thromboembolism in short-course regimen. The Dutch TME study demonstrated that the higher rate of postoperative complications and secondary malignancy in short-course arm. Another important point from Dutch TME study that the rate of non-cancer related causes was higher in elderly patients (Table 1).

**Table I:** Randomized trials of neoadjuvant treatment

| Trial                           | N    | pCR   | Local Recurrence | RFS/ DFS | OS       |
|---------------------------------|------|-------|------------------|----------|----------|
| Swedish Rectal Cancer Trial (6) | 1168 |       |                  |          | 13 years |
| RT + S                          |      |       | 9%               |          | 38%      |
| S                               |      |       | 26%              |          | 30%      |
| Dutch Trial (8)(Stage III)      | 1861 |       |                  |          | 10 years |
| RT + S                          |      |       | 5.8%             |          | 50%      |
| S                               |      |       | 11.3%            |          | 40%      |
| Polish Trial (10)               | 316  |       |                  | 4 years  | 4 years  |
| SCRT + S                        |      | 1%    | 9%               | 58.4%    | 67.2%    |
| CT/RT + S                       |      | 16%   | 14%              | 55.6%    | 66.2%    |
| TROG 01.04 (11)                 | 323  |       |                  | 5 years  | 5 years  |
| SCRT + S                        |      | 1%    | 7.5%             | 67%      | 74%      |
| CT/RT + S                       |      | 15%   | 5.7%             | 71%      | 70%      |
| Istanbul R-01 Trial (20)        | 153  |       |                  | 5 years  | 5 years  |
| CT/RT + S (4w)                  |      | 14.3% | 11.8%            | 73.2%    | 76.5%    |
| CT/RT + S (8w)                  |      | 19.7% | 10.3%            | 74.2%    | 74.2%    |

### Reconstructions in short-course preoperative radiotherapy

Short-course radiotherapy is practical and useful choice but has high rate of postoperative complications and integration of chemotherapy resulted with intolerance. Traditionally after short-course radiotherapy performed surgery immediately. Achieving complete tumor regression with minimally morbidity is not easy in short-course. It seems that tumor regression after neoadjuvant therapy is related with the time elapsed between completion of neoadjuvant

therapy and surgery. A lot of studies support the idea that degree of tumor down staging is probably time-dependent [19]. Retrospective series reported short-course with a delayed surgery was associated with lower rates of acute toxicity [20,21]. Stockholm III study compared short-course radiotherapy followed by surgery within 1 or 4-8 weeks and long-course radiotherapy followed by surgery within 4-8 weeks. Interim analysis was not reported any significance in acute toxicity [22].

Faria et al. found that in phase II study, short-course followed by delayed surgery was feasible and had good tolerance. In this study all patients underwent total mesorectal excision surgery and had negative surgical margins, ypT0 rate was 10% [23]. Saglam et al. compare the efficacy of four-week versus eight-week delay before surgery. In this study 4-week and 8-week groups did not differ with regard to lateral surgical margin positivity (9.2% vs.5.1%, P=0.33, respectively), pathological tumor regression rate (P=0.90), overall survival (5-year, 76.5% vs. 74.2%, P=0.60) and local recurrence rate (11.8% vs. 10.3%, 0.77) [24]. Based on these conclusions the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) randomized trial compared short course followed by 6 courses of capecitabine plus oxaliplatin and fluoropyrimidine-based preoperative long-course chemoradiotherapy before surgery [25]. There is a prospective randomized study continues compare a total dose of 3300 cGy in10 fractions with concurrent chemotherapy as capecitabine 825 mg/m<sup>2</sup>/BID delayed surgery and long-course chemoradiotherapy delayed surgery by Hoon Lee et al [26]. This study reported very low toxicity profiles, very high rate of sphincter preservation (91.2%). In this study reported the rate of grade 3 hematologic toxicity 3.8%, grade 3 postoperative complications such as ileus and wound dehiscence 2.5%. There was no grade 4 toxicity.

Trying to reduce the rate of radiation toxicity accelerated nowadays. Precise radiation techniques as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and proton therapy allow delivering high dose to tumor and low dose to normal tissue (Figure 1).

Reduced treatment-related toxicity and long survival time can be possible with the advent of new treatment techniques and schedules in locally advanced rectal cancer patients. Results from recruiting randomized trials will shed new light on these efforts.



**Figure 1.** IMRT allows to spare anterior pelvis partially and similar with 3 field technique but VMAT plan allows a limit dose to organ at risk

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