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# Toxicity and feasibility of total neoadjuvant therapy using short course radiation followed by chemotherapy

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***Abstract*---**Introduction:Upfront neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy remained a standard of care for locally advanced rectal cancers. However this strategy is associated with high rates of distant failure. Total neoadjuvant therapy with short course radiation therapy (SCRT) followed by full course of chemotherapy is investigated to assess toxicity&feasibility. Patients and methods: Fifty-one patients with locally advanced rectal cancer

who presented to the National Cancer Institute (NCI), Cairo University, in the period from March 2018 to December 2020 were enrolled. Patients were assigned to neoadjuvant short course radiation therapy (25 Gy/ 5 fractions/1 week), then 2 weeks from the end of radiation they were commenced to full course chemotherapy CAPOX (capecitabine1000 mg/m2 BID, D1-14 and oxaliplatin 130 mg/m2 D1) for 6 cycles, followed by surgery within 4-6 weeks from the last chemotherapy cycle. Type of surgery was decided upon surgeon's discretion. Results: All patients completed their planned radiation therapy. Only 1 patient had grade III radiation related diarrhea. Forty three patients completed their planned chemotherapy course, 8 patients had grade III diarrhea. As regard hematological toxicity, 6 patients developed grade 3 toxicity and only one patient developed grade 4 toxicity. Conclusion:Neoadjuvant short course radiation therapy followed by full course of chemotherapy is safe, feasible and associated with high compliance rate.

***Keywords*---**total neoadjuvant, short course radiation, rectal cancer.

## Introduction

The optimal treatment for locally advanced rectal cancer remains a topic of debate. Neoadjuvant long course chemoradiation followed by surgery remains a standard of care according to the results of the German trial [(1)]. A frequently used sequence for locally advanced rectal cancer is 45 to 50 Gy in 25 to 28 fractions (with concurrent flouropyrimidine chemotherapy) followed after 4 to 8 weeks by surgery then adjuvant chemotherapy. Postoperative chemotherapy could be delayed up to 3 months in this sequence [(2)]**.**The risk of developing metachronous metastases in intermediate and locally advanced rectal cancer is 25–65%[(3,4)] and systemic chemotherapy aims to treat occult or micrometastatic disease. Short course radiation therapy followed by surgery is an alternative option in properly selected patients with more convenience and lower costs. Five-fraction radiation therapy has a long track record as a preoperative regimen, but usually with surgery immediately after radiation therapy [(5, 6)]. However if surgery is delayed, tumors will respond about as much as they would to conventionally fractionated radiation therapy as reported by several both randomized and observational studies with no impact on perioperative morbidity [(7, 8)]. We aimed to investigate safety and feasibility of this approach and further survival & local control data will follow.

## Patients and Methods

This is a prospective, single arm, phase II study which included 51 patients with locally advanced rectal cancer who presented to the National Cancer Institute (NCI), Cairo University, in the period from March 2018 to December 2020 and were meeting our selection criteria. Patients were assigned to neoadjuvant short course radiation therapy (25 Gy/ 5 fractions/1 week), then 2 weeks from the end of radiation they were commenced to full course chemotherapy CAPOX (capecitabine1000 mg/m2 BID, D1-14 and oxaliplatin 130 mg/m2 D1) for 6

cycles, followed by surgery within 4-6 weeks from the last chemotherapy cycle. Type of surgery was decided upon surgeon's discretion. Primary end points included toxicity and feasibility. Toxicity was assessed according to Radiotherapy Oncology group (RTOG) toxicity scoring criteria (appendix 1).

Patients were eligible for inclusion if they were aged 18 years or older with a biopsy proven, locally advanced (cT3, T4 or N+) rectal adenocarcinoma located not more than 15 cm from anal verge and ECOG PS < 2. Exclusion criteria included patients with unresectable tumors in which surgery would never be possible even if substantial tumor downsizing was seen, pregnancy or breast feeding and patients with history of previous pelvic irradiation. All patients were subjected to full history taking and general examination including digital rectal examination (DRE). Complete blood count, liver and kidney functions tests. Staging was performed according to the 2017 AJCC staging system [9]**.** Tumor markers in the form of baseline CEA. Radiological examinations including CT chest and abdomen, MRI of the pelvis & PET-CT if indicated (equivocal findings on routine cross-sectional imaging).

Patients were simulated in supine position with external skin localizing markers with permanent tattoos were used for daily localization and set-up accuracy. The clinical target volume (CTV) included the primary tumor with 2 cm distal margin, the mesorectal and pre-sacral lymph nodes, the lymph nodes along the internal iliac vessels, up to the level of the of the fifth lumbar vertebra, and the lymph nodes at the obturator foramina, whole rectum and mesorectum. CTV was expanded by 1 cm in all directions to create the planning target volume (PTV). Organs at risk (OARs) were delineated including bladder, bowel and both femoral heads

The plan was made to deliver treatment with multiple beams with three or four-beams "box" technique with high energy photons 6Mv or 15 Mv, using 3D conformal technique, with maximum dose (Dmax) to bladder and bowel kept below 25 Gy and at least 95% of the PTV covered with 95% isodose line. The dose given to all patients was 25 Gy/5 fractions/ 1 week. Six cycles of CAPOX were given to all patients, starting 2 weeks from the end of radiation therapy with the following doses (capecitabine 1000 mg/m$^2$ BID d1-14, oxaliplatin 130 mg/m$^2$ d1).This regimen was recycled every 21 days provided satisfactory labs were obtained.

Surgery was performed 4-6 weeks after last chemotherapy cycle. Type of surgery was decided upon surgeon's discretion after clinical evaluation of the patient at end of treatment course. All patients were subjected to MRI pelvis, CT chest & abdomen post 2 cycles of chemotherapy & each 2 cycles thereafter to ensure treatment response and rule out any progression. PET-CT was reserved if there are any equivocal findings on ordinary imaging.

**Statistical methods**

Data was analyzed using the SPSS version 20 (SPSS Inc., Chicago, IL). Numerical data was expressed as mean and standard deviation or median and range as appropriate. Frequency and percentage of the available data was demonstrated.

## Results

During the period from March 2018 to December 2020, fifty-one patients with locally advanced rectal cancer were enrolled in this single arm, prospective study. The median age of the whole group was 50 years (range, 25-70 years). The median distance from the anal verge for the whole study group was 5 cm (range, 3-15 cm). Thirty-five patients (69%) had lower rectal disease i.e.: < 6 cm from the anal verge and 16 patients (31%) had disease situated > 6 cm from the anal verge. CEA was assessed in all patients as a part of the baseline evaluation. The median CEA level for all patients was 2.65 ng/ml (range, 0.2-32 ng/ml). Thirty seven patients (73%) had CEA levels < 5 ng/ml and fourteen patients (27%) had elevated CEA levels > 5 ng/ ml.

Summary of baseline demographic and clinico-pathological data is shown in table (1). All patients completed their planned radiation therapy. Median overall period of treatment was 5 days (range, 5-15 days). Treatment related toxicities were evaluated during the radiation course and till start of chemotherapy using RTOG/EORTC acute toxicity criteria. Treatment was generally well tolerated. Only 1 patient had grade 3 diarrhea which developed during the week after end of radiation. No grade 3 hematological or skin toxicities were observed. Chemotherapy was generally well tolerated. Forty-three patients completed their planned course. As regard GIT toxicity, Out of those 43 patients ten patients had to reduce capecitabine dose due to grade 3 diarrhea. One patient had grade 4 vomiting.

As regard hematological toxicity, six patients developed grade 3 toxicity and only one patient developed grade 4 toxicity. Four patients stopped due to toxicity (fatigue, diarrhea and gastric upset) and two patients received only 5 cycles and this was considered enough by the medical oncologist given their good response. As regard neuropathy, fifteen patients developed Grade 3 neuropathies. No grade 4 neuropathy were encountered during treatment. Thirty-four patients (67%) underwent curative surgery. Ten patients were in clinical complete response and refused surgery (7 patients were APR candidates based on their original tumor location (2-3 cm) and 3 patients chose wait and see policy despite they were low anterior resection candidates) and one patient had frozen pelvis at the time of exploration.

## Discussion

The choice of total neoadjuvant therapy has become very appealing recently due to enhanced pathological response and better treatment compliance. In this single arm, prospective, phase II study, we used total neoadjuvant therapy utilizing short course radiation therapy (5 Gy x5), followed by six cycles of CAPOX then surgery. In our study, the whole course of chemotherapy was administered in the preoperative phase which was similar to what was done in RAPIDO trial [(10)] and unlike STELLAR trial; in which patients were given six cycles of CAPOX divided into four preoperative cycles after short course radiotherapy and two adjuvant cycles[(11)].

In terms of treatment compliance, our treatment was generally well tolerated. All patients were able to complete their planned neoadjuvant radiation therapy. Only one patient had grade 3 radiation related diarrhea. During chemotherapy, forty three patients (84%) were able to complete their planned course. This is consistent with what was observed in other large trials. In RAPIDO trial [10], and in STELLAR trial [11] eighty five and eighty three percent of patients were able to complete their treatment plan. This high completion rate is a potential advantage of total neoadjuvant therapy using this design versus the standard chemoradiation approach followed by surgery and adjuvant chemotherapy. In the later approach, reported rates of completion of adjuvant chemotherapy are lower than pre-operative treatment and variable in large scale trials. In EORTC 22921 trial, among those who were assigned to postoperative chemotherapy, only 43% received their planned treatment and 27% have never started their planned treatment [12].

This high completion rate can be attributed to receiving treatment in the pre-operative phase, while the patient is still more fit and has a good reserve before going to surgery. In addition, patients after their definitive surgery may become more reluctant to receive further treatment. Surgical complications also lead to delay in some patients or failure to receive treatment in others. The most common toxicity during treatment was diarrhea. Ten patients (20%) had grade 3 diarrhea during their treatment which necessitated dose reductions or treatment breaks. This comes in line with rates reported from RAPIDO trial (18%).

**Conclusion**

In summary, our data come in line with other data reported from larger scale trials. Total neoadjuvant treatment is an appealing strategy given its higher rates of treatment completion .Optimal sequencing and radiation fractionation schedules have yet to be defined, however this design looks more convenient compared to protracted radiation protocols with less frequent hospital visits especially in the time of COVID pandemic and in a busy department like ours.

**Appendix (1): RTOG acute toxicity scoring**

**Lower GI/ Pelvis**

GI: Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics.
GII: Diarrhea requiring parasympatholytic drugs (e.g. Lomotil) / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics
GIII: Diarrhea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distention (flat plate radiograph demonstrates distended bowel loops).
GIV: Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

**Hematological**
**WBCs**

GI: 3.000 - < 4.000 cell/mm3
GII: 2.000 - < 3.000 cell/mm3
GIII: 1.000 - < 2.000 cell/mm3
GIV: < 1.000 cell/mm3

**Platelets**

GI: 75,000 - < 100,000 cell/mm3
GII: 50,000 - < 75,000 cell/mm3
GIII: 25,000 - < 50,000 cell/mm3
GIV: < 25,000 cell/mm3 or spontaneous bleeding

**Neutrophils**

GI: 1.500 - < 1.900 cell/mm3
GII: 1.000 - < 1.500 cell/mm3
GIII: 500 - < 1.000 cell/mm3
GIV: < 500 cell/mm3 or sepsis

**Hgb / Hct**

GI: 11 - 9.5 gm/dl (28% - < 32%)
GII: < 9.5 - 7.5 gm/dl (< 28%)
GIII: < 7.5 - 5.0 gm/dl (Packed cell transfusion required)
GIV: none

Table (1): Summary of baseline clinico-epidemioloigcal characteristics

| Total (n=51) | N (%) |
|---|---|
| Age | |
| < 50 | 25(49) |
| >50 | 26(51) |
| Sex | |
| Female | 31(61) |
| Male | 20(39) |
| Distance from AV | |
| < 5cm | 28(55) |
| >5 cm | 23(45) |
| Stage | |
| II | 1(2) |
| III | 50(98) |
| Baseline CEA | |
| < 5 | 37(73) |
| >5 | 14(27) |
| Grade | |
| I | 1(2) |
| II | 49(96) |

| III | 1(2) |
|---|---|

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