The preliminary findings of this ongoing prospective clinical trial did not show statistically significant difference in 2 year DFS between neoadjuvant intensified chemotherapy and neoadjuvant concomitant chemoradiation arms **but numerically chemoradiation arm was more benefitial.**

Neoadjuvant intensified chemotherapy vs Standard Therapy in Locally Advanced Rectal Cancer

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Background

Standard therapy for locally advanced rectal cancer includes concurrent chemoradiotherapy (CRT) followed by surgery and adjuvant chemotherapy. An alternative strategy - neoadjuvant intensified chemotherapy (NIC) involves administration of neoadjuvant chemotherapy (FOLFOX4) before surgery plus concomitant chemoradiation (in those only who did not achieve MRF (neg.)) with the goal of delivering optimized systemic therapy to eradicate micrometastases. A comparison of these 2 approaches was the aim of study.

Objective

To determine the differences in rates of pathologic complete response (pCR), mesorectal fascia (MRF) involvement, disease-free survival (2 year DFS) between patients receiving NIC vs standard CR.

Methods

This is a prospective single institution clinical trial (ClinicalTrials.gov Identifier: **NCT05378919**). The study included patients with locally advanced stage II-III rectal cancer. Patients were randomized 1:1 for neoadjuvant concomitant chemoradiation or neoadjuvant intensified chemotherapy (FOLFOX4 regimen, a total of 8 cycles). 4-6 weeks after completion of treatment radiological examination was performed and the patients underwent surgery. For those from NIC arm who did not achieve MRF (neg.) additional concomitant chemoradiation was given before surgery. Investigation study design displayed in figure 1.

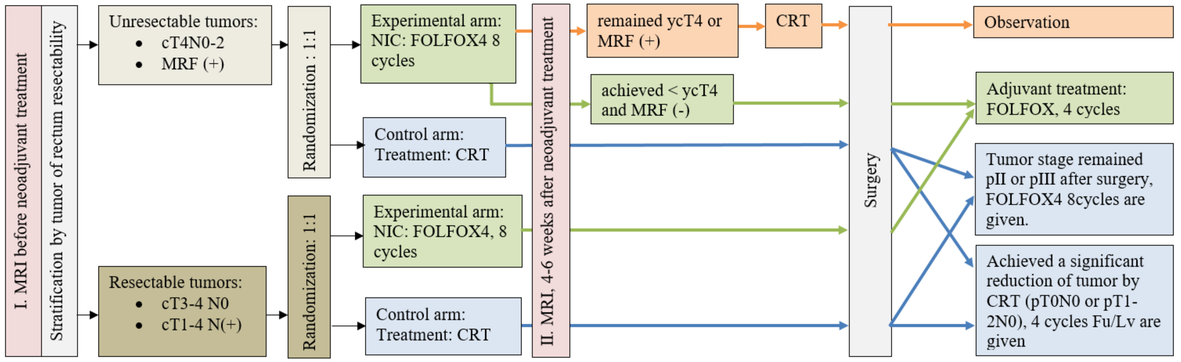

Figure 1. Investigation study design.
***MRI** – magnetic resonance imaging; **MRF** – mesorectum fascia; **CRT** – concomitant chemoradiation; **NIC** – neoadjuvant intensified chemotherapy; **FOLFOX4:** Day 1: Oxaliplatin 85mg/m2 IV over 2 hours, with: Day 1 and 2: Leucovorin 100mg/m2 IV over 2 hours, followed by: Days 1-2: Fluorouracil 400mg/m2 IV bolus on day 1 and 2, then 600mg/m2/day × 2 days (total 1200mg/m2 over 46-48 hours) IV continuous infusion. Repeat cycle every 2 weeks for 8 cycles. **Concomitant chemoradiation**: Radiotheray: Total dose 50 Gy administered during 25 days (2 Gy/day in 5 weeks); chemotherapy: days 1-4 and 29-32: Leucovorin (Lv) 20mg/m2 IV bolus; days 1-4 and 29-32: Fluorouracil (Fu) 400mg/m2 IV bolus. .*

Results

85 patients (pts.) were included into the study and analyzed. The median follow-up of pts. is 36 months (1-77 months). Both groups are well balanced: by age, sex, disease stage, MRF status. At baseline, MRF was involved in 21/42 pts. (50%) in the NIC arm and in 25/43 pts. (58%) in CRT arm. The pelvic MRI was performed after neoadjuvant treatment. Radiologically, MRF remained involved after initial treatment in 13/42 pts. (31%) NIC group and 11/43 pts. (26%) in the CRT group.

Surgery was not performed in 5/42 pts. (12%) from NIC arm due to disease progression (1) or early deaths during neoadjuvant treatment (thromboembolism (2), stroke (1), covid-19 infection (1) and in 6/43 pts. (14%) in the CRT arm (1 pts. remained not resectable, 2 cases of disease progression, 3 refused surgery but one of them achieved a complete response). Additional neoadjuvant CRT was given to 7 / 42 pts. in the NIC arm. After this treatment, surgery was performed 6/7 pts. and R0 surgery was achieved. Surgery was not performed for only one pts due disease progression.

After surgery, circumferential resection margin (CRM) was involved in 2/30 pts. (7%) in NIC and in 3/33 pts. (9%) CRT groups with no statistically significant difference between these groups (p=0.6). pCR was achieved in 9/30 pts (30%) NIC group and in 12/33 pts. (36%) CRT group (not sig. difference between groups). After treatment in NIC arm, a reduction in the tumor stage (evaluated by radiologist) was observed in 5/42 (12%) pts, and in pathologists report – in 20/30 pts (67%). In CRT arm, radiological down staging was achieved in 12/43 pts. (28%) and pathologically in 24/33 (73%), but no statistical difference was observed. Two-year DFS was 66.7% and 80% in NIC and CRT groups, respectively (p = 0.2) (*Figure 2*). Two-year overall survival (OS) did not differ statistically significantly between groups to *(Figure3).* 14 pts. have died during the follow-up period: 10/42 pts. (24%) in the NIC group, of whom 6/42 (14%) due to disease progression, 4/42 have died due to other reasons (thromboembolism (2), stroke (1), covid-19 infection (1)); 4/43 pts. (9%)have died in the CRT group: 2/43 (5%) due to disease progression, 2 have died due to other reasons (thromboembolism (1), pneumonia (1)); respectively (p = 0.071) (*Table1*).

	NIC	CRT
Reduction in the tumor stage (radiologist)	12%	28%
Reduction in the tumor stage (pathologist)	67%	73%
Two-year DFS	66.7%	80% (p 0.204)
Two-year OS	85.7	96.9% (p 0.106)

Table 1. Main results among NIC and CRT arms.

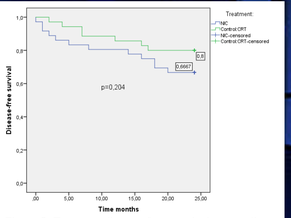

Figure 2. Two-year disease-free survival among the matched cases. Calculated by intention-to-treat group.

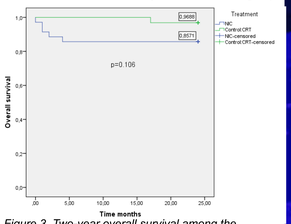

Figure 3. Two-year overall survival among the matched cases. Calculated by intention-to-treat group.

Conclusions

The preliminary findings of this ongoing prospective clinical trial did not show statistically significant difference in 2 year DFS and OS between neoadjuvant intensified chemotherapy and neoadjuvant concomitant chemoradiation arms but numerically chemoradiation arm was more benefitial.

Key words

Rectum, Neoadjuvant treatment, intensified chemotherapy, chemoradiation