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Intensified neoadjuvant radio-chemotherapy for locally advanced rectal cancer: mono-istitutional experience and long-term results

C. Spatola[1*], L. Raffaele[1], A. Tocco[1], G. Acquaviva[2], R. Milazzotto[1], R. Bevilacqua[1], V. Salamone[1], P.V. Foti[1], P. Milone[1], A. Basile[1], A. Di Cataldo[3], G. Privitera[1]

[1]UOC Radiodiagnostica e Radioterapia oncologica, AOU Policlinico-VE, via S.Sofia 78, 95125 Catania, Italy
[2]UOC Radioterapia, AOE Cannizzaro, via Messina 829, 95125 Catania
[3]UOC Chirurgia Digerente Colorettale, AOU Policlinico-VE di Catania

► ***Original article***

Corresponding authors:
Corrado Spatola, Ph.D.,
Fax: *+390 9537 81315*
E-mail:
cor_spatola@hotmail.com

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ABSTRACT

Background*:** Purpose: The purpose of our study is to demonstrate that intensified neoadjuvant chemo-radiotherapy (CRT) treatment in locally advanced rectal cancer (LARC), aimed at further enhancing the complete pathological response and local disease control, is feasible and well tolerated. ***Materials and Methods*:** From January 2011 to December 2015, 62 patients (women 21, men 41, mean age 61,5, range 36-84) with LARC (cT2-3 cN0-2) were enrolled in our institution. All patients performed an intensified neo-adjuvant CRT treatment according to the following scheme: FOLFOX4 induction chemotherapy for 3 cycles, followed by a concomitant radio-chemotherapy, with concomitant boost pelvic radiotherapy to a total dose to the primary of 54 Gy and daily continuous infusion of 5-Fluorouracil. After 6-8 weeks pts were re-evaluated by means of colonoscopy, body TC and pelvic MRI. ***Results: Intensified CRT compliance was 90%. Grade I-II proctitis according to CTCAE v4.0 was 43%, grade III diarrhea was 10%, grade I-II genito-urinary toxicity was 29%. Eleven patients (19%) had a complete pathological response (pCR), 37 patients had a partial response. Sixty patients received surgery, two refused it: sphincter-saving procedure was performed in 85% of patients, Miles' surgery in 15% of them. Fifty-nine patients are alive, after a median follow-up time of 43 months. Six patients experienced a distant metastatic disease, and two patients a local relapse. ***Conclusion:*** This study has shown that the intensification of preoperative systemic therapy, together with intensification of radiotherapy, was feasible, well tolerated and has obtained high rates of local disease control (96,5%), with 19% of pCR rate.

Keywords: *Intensified radio-chemotherapy, locally advanced rectal cancer, concomitant boost radiotherapy.*

INTRODUCTION

Colorectal cancer is the third most common tumor in both sexes, and, although the distinction between the two sites, colon and rectum, is difficult from an epidemiological point of view, there are considerable differences between them in terms of treatment and natural history.

Over the last 20 years we have seen remarkable changes in the management of locally advanced rectal cancer (LARC). The introduction of total mesorectal excision surgery has dramatically reduced local recurrences and improved survival [1]. Randomised clinical trials have shown that radiotherapy [2,3] and the addition of fluorouracil to radiotherapy [4,5] before surgery further improves local control.

Although the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy of colon cancer has been shown to improve disease-free survival and overall survival [6], no clear evidence exists for the efficacy of adding oxaliplatin to the multimodal treatment of patients with locally advanced rectal cancer.

Treatment intensification is an area of continuous investigation also in the field of radiotherapy. Pelvic irradiation is considered a mainstay of neoadjuvant treatment, with standard dose ranged between 45 and 50 Gy. It is believed that an increased dose to the site of primitive tumor may allow to improve the rate of tumor regression and of pathologic complete response [7]. Moreover, the use of image-guided radiotherapy and, in some circumstances, of intensity-modulated irradiation, can contribute to minimize acute and chronic radiation-induced toxicities.

The aim of the study was to analyze the role of chemo-radiotherapy (CRT) intensification in the preoperative treatment of LARC in terms of feasibility, efficacy and toxicity.

Statistical cumulative probability of overall survival and disease-free relapse were evaluated for all patients.

MATERIALS AND METHODS

We conducted a phase II study at University of Catania in patients with histologically proven locally advanced rectal cancer. Inclusion criteria were the following: 1) tumour location within 12 cm from the anal verge, 2) adenocarcinoma histology, 3) locally advanced stage, confirmed by means a pelvic MRI, 4) written informed consent, 5) absence of metastatic spread, confirmed by staging CT scan, 6) Performance Status of 0-1, according to Eastern Cooperative Oncology Group (ECOG) Scale.

Patient exclusion criteria consisted of the presence of synchronous tumors, cardiovascular disease, history of neurological or psychiatric disorders, and previous pelvic radiotherapy.

Patients were staged according to the American Joint Committee on Cancer (AJCC) TNM Classification (7th edition, 2010) [8].

Before starting CRT and, subsequently, 6-7 weeks after the completion of neoadjuvant treatment, patients underwent pelvic MRI with gadolinium, in order to evaluate the response rate, brain-chest-abdomen CT scan and tumor markers (CEA, Ca 19.9) dosage.

Pelvic staging MRI was conducted by means of a qualitative and quantitative evaluation of diffusion-weighted imaging (DWI), according to our institutional protocol [9]. The imaging was then compared with post-operative staging, to evaluate the correspondence between clinical and pathological assessment.

Clinical outcomes and toxicity data were collected according to Common Terminology Criteria for Adverse Events (CTCAE v4.0).

The protocol in use at our center is performed by means of integration between an initial induction chemotherapy (ICT) and a subsequent concurrent radio-chemotherapy (CRCT), over a period of 11weeks.

Surgery was planned seven to nine weeks after the end of radio-chemotherapy treatment. Patients were treated by the same surgical team at our Institution. The surgeon chose the type of surgery to perform.

Patients' data

Between January 2011 and December 2015, a total of 62 patients were enrolled in this prospective study: 21 were females (34%) and 41 males (66%). The patients' ages ranged between 36-84 years (average = 61.55 years). Patients presented clinically with rectal bleeding (38/62, 61%) that may have been accompanied by a change in bowel habits, such as unexplained constipation and diarrhea, until sub-obstructive symptoms (21/62, 34%). At a pre-treatment evaluation, 69% of patients showed pathological tumor-positive lymph nodes (stage III), 31% of patients were clinically staged as II. The distance of the inferior margin of the tumor lesion was located in the lower rectum at ≤ 5 cm from the anal verge in 49% of patients. The characteristics of patients are listed in table 1.

Induction chemotherapy (ICT) and Radiotherapy Simulation Process (RSP)

After written informed consent had been obtained, eligible patients received, during the ICT phase, a FOLFOX4 chemotherapy schedule for three cycles, with Oxaliplatin 85 mg/mq in 3 hours i.v. infusion (on day 1), 5-Fluoruracil 400 mg/mqi.v. bolus, Folinic acid 200 mg/mq, 5-Fluoruracil 600 mg/mq continuous intravenous infusion over 22 hours (on day 1 and 2), through a peripherally inserted central catheter (PICC). Dexamethasone (8 mg) and ondansetron (8 mg) were administered before the chemotherapy infusion. The cycle was repeated after 14 days, by previous clinical and haematological examination. Toxicity was evaluated using CTCAE v4.0 [10]. Oxaliplatin and 5-FU dose reductions were not planned. For occurrence of hematological toxicity grade 3 or neurological toxicity grade 2, the oxaliplatin administration was interrupted; both chemotherapeutic agents were stopped if grade 3 toxicity was reached. If severe toxicity persisted, did not return to grade 1, or was classified as grade 4, chemotherapy was cancelled. No re-evaluation imaging was programmed at the end of ICT phase.

During the ICT phase, patients underwent to radiotherapy simulation process (RSP), in order to prepare the radiotherapy treatment plan. A planning computerized tomography (CT) scan was performed in the treatment position that is the same for both initial simulation and subsequent treatment. Patients were placed in the prone position using a belly-board device to displace the small bowels out of the treatment fields. CT images were acquired from the level of L1 to 3 cm below the anal marker with 5 mm slice spacing. CT data were analyzed using Treatment Planning Software (XIO®) for target volume definition and dose solutions, according to our institutional protocol [11-12].

The planning target volume 1 (PTV1) encompassed the primary tumor, the mesorectal and posterior pelvic sub-regions, and the regional node. The presacral, obturator and internal iliac lymph nodes were included in treatment volumes in all patients. The external iliac lymph nodes were included if clinically positive or in the case of T4 tumor. The PTV2 included the tumor mass with a 2 cm 3-D margin. The organs at risk (OARs) were bowel (Dmax< 55 Gy), bladder (V50 60%; V60 50%), femoral heads (V50 60%), and anal canal (Dmax< 55 Gy).

Radiotherapy was planned using a 3D-Conformal technique or a static step-and-shoot Intensity-modulated technique (figure 1). Radiotherapy treatment plan details will be specified in the next paragraph.

Concurrent radio-chemotherapy (CRCT)

During the CRCT phase, patients received a five daily continuous i.v. infusion of 5-Fluoruracil at 200 mg/mq per die during all radiotherapy treatment period.

Radiation therapy was delivered to PTV1 to a dose of 45 Gy, with a conventional fractionation of 1.8 Gy/day, by means of 6-15 MV energy photons of linear accelerator Siemens ONCOR. The volume of the primary tumor in the rectum, called concomitant boost or PTV2, was irradiated during the last six fractions, after an interval of 6 hours from the first fraction. This volume received a dose of 9 Gy, with a fractionation of 1.5 Gy/day.

Using the above described concomitant-boost technique, a total dose of 54 Gy is given to the primary tumor. This dose is at least 10% higher than that conventionally used in the currently accepted protocols for neoadjuvant and adjuvant irradiation of rectal cancer.

Radiation therapy was delivered with a 3-D conformal three-field technique (two lateral fields and one postero-anterior field) or a static step-and-shoot Intensity-modulated radiotherapy (IMRT), when clinically or technically required. The indication to IMRT were as follows: any previous abdominal surgery, due to the high risk of intestinal adhesions, and high dose to small bowel with 3D treatment plan (V15>120 cc or V45>195 cc of small bowel).

Patients were set up daily, using sagittal and lateral tattoos and a laser to prevent lateral rotation. Megavoltage cone-beam computer tomography Image-guided radiotherapy (MV-CBCT IGRT) system was used to check treatment organization twice a week from the

start to the end of treatment; CBCT images were compared with planning CT scan.

Patients' evaluation

All patients were examined by chest and abdomen CT, colonoscopy and pelvic MRI at two time points: about one week (1-3 days) prior neoadjuvant treatment and 6-7 weeks after the end of CRCT phase, to evaluate clinical response. Patients underwent conventional high resolution T2-weighted MRI sequences and diffusion weighted imaging (DWI), with qualitative and quantitative evaluation, through measurements of tumor's apparent diffusion coefficient (ADC). Our previous study has demonstrated that qualitative and quantitative DWI findings improve the diagnostic performance of MRI in the evaluation of tumor response to neoadjuvant CRT in patients with LARC, especially in the detection of post-treatment pathologic complete response (ypCR), with a sensitivity of 80% and specificity of 100% [8].

Table 1. Patients characteristics, with definition of cTNM stage, localization of the tumor from anal verge and ECOG performance status. Each characteristic is defined by absolute number and percentage. Legend: cTNM: clinical Tumor Node Metastases staging. ECOG: Easter Cooperative Oncology Group performance status.

Characteristics		Patients number (percentage)
Stage cTNM	II	43 (69%)
	III	19 (31%)
Localization	≤ 5 cm from the anal verge	30 (49%)
	> 5 cm to < 8 cm from the anal verge	19 (30%)
	> 8 cm to < 12 cm from the anal verge	13 (21%)
ECOG Performance Status	0	39 (63%)
	1	20 (32%)
	2	3 (5%)

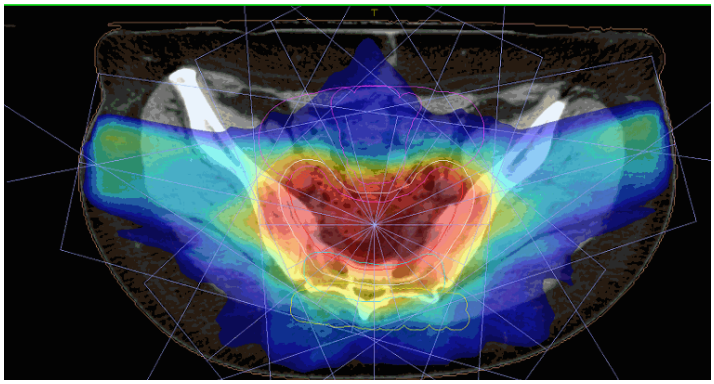

Figure 1. Radiotherapy treatment plan, with dose distribution and dose-volume histograms (DVHs), for a static step-and-shoot IMRT technique.

RESULTS

Out of sixty-two patients recruited, fifty-six completed treatment as scheduled. Induction chemotherapy was well tolerated by 96% of patients, with only two patients reported gastro-intestinal grade III toxicity after the second cycle of FOLFOX and, for this reason, they did not perform the third cycle.

The majority of patients, 51/62 (82%), report a rapid symptomatic relief during or after the ICT phase, as regards tenesmus, sub-obstructive symptoms, rectal bleeding and pelvic pain.

The concurrent radio-chemotherapy phase was completed as scheduled in fifty-eight patients (94%). Four patients stopped the planned neoadjuvant treatment during CRCT phase due to the development of Grade III diarrhea: one patient interrupted both radio and

chemotherapy during concomitant boost phase at a total dose of 4410 cGy, after 24 fractions. Three patients suspended concomitant 5-fluoruracil, radiotherapy was stopped for an average period of 9 days, but it was completed later.

Re-staging after neoadjuvant treatment and surgery

As previously specified, all patients were re-evaluated at the end of CRT, about one week before the planned surgery, by means of chest and abdomen CT, colonoscopy and pelvic MRI with DWI study.

A clinical (both with endoscopy and MRI) partial response (cPR) was detected in 55% of patients (n=34), a clinical complete response (cCR) in 18% of patients (n=11), while a clinical stable disease (cSD) was seen in 27% of patients (n=17).

Sixty patients were eligible for surgery, while two patients were excluded because they refused surgical procedure. The response assessment after neoadjuvant therapy has indicated a complete clinical regression of the tumor for one patient and a partial response for the other non-surgical patient: for both a close follow-up approach was activated.

Surgery was planned at least 8 weeks after the end of CRT, the average interval was 10 weeks (range 8-13 weeks). All patients were evaluated and subjected to surgery by the same surgical team. A low anterior resection with sphincter preservation was performed in 51 patients (85%), with a temporary diverting loop ileostomy for 22 of them, while a Miles abdomino-perineal resection was requested in 9 patients (15%).Three patients had a post-surgical complications, as perianastomotic fistula (two patients) and intestinal obstruction (1 patient). No positive surgical margins were detected at definitive histopathology.

The response obtained after neoadjuvant intensified radio-chemotherapy allowed surgeons to perform sphincter saving surgery in 33 patients initially selected for abdomino-perineal resection. Among them, 21 patients had a distal tumor location ≤ 5 cm from the anal verge and 12 patients just over 5 cm. Patients underwent to Miles' surgery (n=9) had a distal tumor location between 1 to 3 cm from the anal verge and, regardless of the response to neoadjuvant treatment, they had to undergo this type of surgery.

The pathological examination after surgery showed a substantial correlation with pre-operative clinical data, previously reported. A pathological complete response (ypCR), defined as the absence of tumor cells in the operative specimen, was observed in 11 patients (19%). Among them, four patients were staged initially as stage II, while seven patients presented a clinical positive lymphnodes at diagnosis. A pathological partial response (ypPR) was observed in the majority of patients, 36/60 (60%), with 23 of them harbored tumors that were classified as stage I. Among them, 12 patients had clinical positive nodes at diagnosis. Patients with pathological stable disease (ypSD) were 13/60 (22%), with 10 patients harboring nodal metastases. See Table 2 for post-operative pathological staging.

Toxicity

Fifty-one patients (82%) presented an acute toxicity of any grade, taking into account both induction and concurrent phases. The main represented toxicity was gastro-intestinal one, evident in 56% of patients. Diarrhea of grade I-II was noted in 19 patients (30%), grade III in 6 patients (10%): two patients suspended chemotherapy after 2 cycles of induction FOLFOX, one patient interrupted both radio and chemotherapy during concomitant boost phase, while three patients suspended only concomitant 5-fluoruracil and continued radiotherapy. Proctitis and tenesmus were the most common symptoms, evident in 52% of patients, even though most patients had these symptoms already at the time of recruitment, before starting treatment. Proctitis was related to radiotherapy and it appeared or increased during the last 2 weeks of CRCT phase. Other gastro-intestinal acute toxicities, included constipation, chemotherapy-induced nausea and vomiting (CINV) o radiotherapy-induced nausea and vomiting (RINV) of grade I-II, were detected in 26% of patients.

Genitourinary (GU) toxicity was observed in 29% of patients. An increased urinary frequency

was reported by 14% of patients during the CRCT phase, main during the last two weeks of treatment. Disuric symptoms of grade I-II, both with or without a bacterial cystitis, was reported in 18% of patients. No grade III-IV GU toxicity was reported.

Hematological toxicity as thrombocytopenia of grade I-II was observed during the induction phase in four patients (7%), mainly related to oxaliplatin chemotherapy. Six patients presented oxaliplatin-induced sensory peripheral neuropathy of grade I-II.

Skin toxicity as radiation-induced dermatitis of grade I-II was reported in 29 patients (47%), and of grade III in 2 patients (3%). Skin reactions were more frequent in patients with distal tumor location ≤ 5 cm from the anal verge. No cardiovascular treatment-related events were observed.

Table 3 summarizes the incidence of acute toxicity.

Late toxicity was collected for all patients at least 6 months after the end of treatment. Main represented symptoms were gastro-intestinal, with fecal incontinence reported by 18% of patients and increased defecation frequency reported by 25% of patients. Chronic cystitis was observed only in 4 patients. Peripheral neuropathy did not interfere with daily activities and it resolved spontaneously in all patients after about 8-10 months after the treatment.

Survival and local control data

Recruitment of patients ended in December 2015. To date, all patients underwent a close follow-up that ranged between 23-82 months, with an average and median follow-up time respectively of 41 and 43 months.

Among 62 patients recruited 59 are still alive. Two patients experienced distant metastases after 17 and 22 months from surgery and died respectively after 25 and 33 months of systemic disease, while one died for a local recurrence. Overall, two local recurrences were detected with no evidence of metastatic spread, at 21 and 26 months from surgery: for one patient re-operation was not applicable because of the infiltration of the sacrum, so a palliative radio-chemotherapy was applied and patient died after 8 months. Second patient was re-operated, underwent to radio-chemotherapy again and to date is free from recurrence. Distant metastases were recorded in other 6 patients, of which 4 presented liver metastases only, two patients liver and lung metastases. The average time of systemic spread was 25 months from surgery. Patients with advanced disease are still alive and under treatment.

In summary, results showed a recurrence rate (RR) of 3,5% and, then, a local control rate (LCR) of 96,5% with our intensive protocol of induction chemotherapy and concurrent radio-chemotherapy followed by surgery. Overall survival (OS) rate was 95,2%, as well as for cause-specific survival (CSS) rate, since 3 patients died for local recurrence or metastatic disease. Relapse-free survival (RFS) rate was 84% (figures 2-3).

Table 2. Pathological staging of patients, both in absolute number and percentage. Legend: Stage yp: post neoadjuvant and post-surgical T and N stage.

Characteristics	Patients number (percentage)
Stage ypT0 ypN0	11 (19%)
Stage ypT1 ypN0	16 (27%)
Stage ypT2 ypN0	7 (12%)
Stage ypT3 ypN0	12 (19%)
Stage ypT4 ypN0	2 (3%)
Stage yp anyT ypN1	12 (20%)
Stage yp anyT ypN2	0 (0%)

Table 3. Report of acute toxicity, according to Common Terminology Criteria for Adverse Events (CTCAE v4.0). Legend: CINV: chemotherapy-induced nausea and vomiting. RINV: radiation-induced nausea and vomiting.

Toxicity	Grade I-II n (%)	Grade III n (%)
Diarrhea	19 (30)	6 (10)
CINV, RINV	14 (22)	0 (0)
Proctitis	27 (43)	6 (9)
Constipation	2 (4)	0 (0)
Dysuria	11 (18)	0 (0)
Increased urinary frequency	9 (14)	0 (0)
Skin toxicity	29 (47)	2 (3)
Hematological toxicity	4 (7)	0 (0)
Sensorial peripheral neuropathy	6 (10)	0 (0)

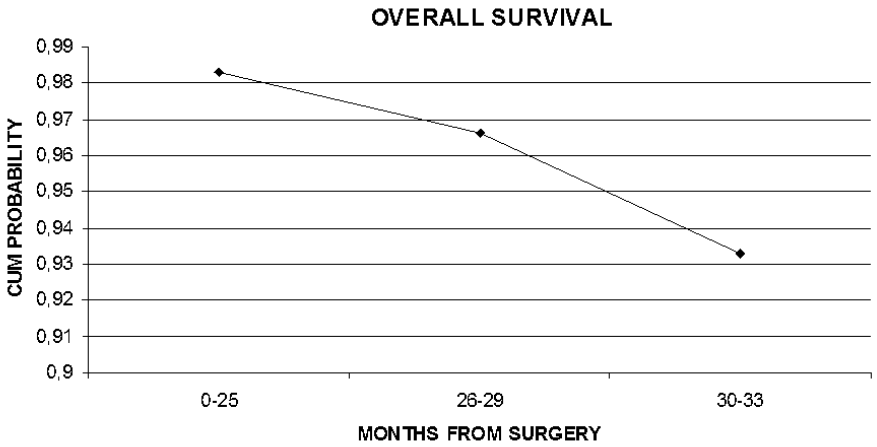

Figure 2. Cumulative probability of overall survival from time of surgery.

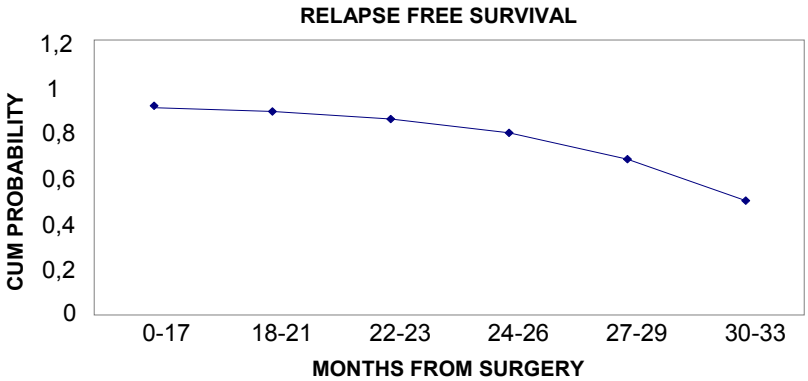

Figure 3. Cumulative probability of relapse-free survival from time of surgery.

DISCUSSION

In recent years, improvement in surgical procedures, with the implementation of total mesorectal excision [13], and the development of recent radiotherapy techniques, as intensity-modulated radiotherapy, have improved the rate of local control and survival in patients affected by locally advanced rectal cancer. The role of the addition of 5-FU to radiotherapy is also clearly defined [4].

The last 20 years have seen the development of studies concerning the role of radio-chemotherapy treatment in neoadjuvant phase. Today, pre-operative concurrent radio-chemotherapy with 5-FU has

demonstrated to improve local control as compared with the same protocol delivered after surgery [14].

Recently, attention has shifted towards the goal of increasing survival, often dependent on the systemic control of the disease, and increase the rate of sphincter saving surgery. For this reason, several studies have been conducted to evaluate the role of polichemotherapy and/or to intensify radiotherapy dose, comparing results with 5-FU infusion, to date considered the standard of care.

In this setting, the addition of oxaliplatin to fluoropyrimidine-based chemotherapy has been shown to improve disease-free survival and overall survival in colon cancer[6], but still there is no clear evidence for the efficacy of adding oxaliplatin to the multimodal treatment of patients with locally advanced rectal cancer. Moreover, concerns have arisen regarding the compliance of radio-chemotherapy regimens adopted. In both STAR-01 and ACCORD trials, addition of oxaliplatin to 5-FU based radio-chemotherapy increased toxicity rates. In those studies, grade 3-4 diarrhea was recorded in 15% and 13% of patients given oxaliplatin*vs*4% and 3% of those in the control group, respectively [15-16].

As regards to radiotherapy, pelvic irradiation is conventionally due to a dose of 45-50 Gy, because of the increased risk of acute and chronic gastro-intestinal and uro-genital toxicities with higher doses. Conversely, it is believed that an increased dose to the site of primitive tumor may allow to improve the rate of tumor regression and of pathologic complete response[7], and the latter is now considered of meaningful prognostic significance in terms of overall survival. Previous study has demonstrated a positive role of concomitant boost radiotherapy both in terms of local outcomes and OS in patients with rectal cancer [17].

In present study, we evaluate the feasibility, tolerability and results of an intensified chemo-radiotherapy in patients affected by LARC. In our treatment protocol, we intensified both chemotherapy, through the addition of oxaliplatin to 5-FU infusion, and radiotherapy, by means of a concomitant boost technique, with the implementation of IMRT and IGRT.

Results of our study are encouraging in terms of effectiveness. The induction FOLFOX chemotherapy gave a rapid clinical benefit and symptomatic relief in more than 80%. Together with the subsequent concurrent chemo-radiotherapy and concomitant boost technique, our protocol has reached a local control rate of 96,5% at a median follow-up time of 43 months, with only two recurrences detected during follow-up.

The choice of performing neoadjuvant treatment in two subsequent phases has been made in order to maximize the response rate, while maintaining a high tolerability. As results, both acute and chronic toxic effects were reduced compared with those registered in studies where intensification of radio-chemotherapy for LARC was tested[15-16]. We report a cumulative gastrointestinal acute toxicity in 56% of patients, but most of it was related to grade I-II toxic side effects; grade III diarrhea, that is the limiting toxicity, was reported in 6 patients (10%). In addition, protocol compliance was high, with 56 patients (90%) received the treatment as programmed, while 5 had a interruption of chemotherapy, maintaining the prescribed radiotherapy dosage, and only one interrupted both chemo and radiotherapy.

Survival rates, both overall and cause-specific, were high: 95% of patients are alive after a median follow-up time of 43 months (range 23-82 months). RFS was 87%, with two cases of local relapse and 6 cases of distant metastases.

CONCLUSION

Our treatment protocol with intensification of both neoadjuvant induction chemotherapy, through the addition of oxaliplatin to 5-Fluoruracil, and of radiotherapy, by means of a concomitant boost pelvic radiotherapy, with implementation of modern techniques, such as IMRT and IGRT, was feasible and well tolerated. The high rates of local disease control, sphincter

-saving surgery, pCR and overall survival obtained were encouraging in order to continue the evaluations at a longer follow-up. Tolerability was slightly better than that registered in literature, because of the use of sequential FOLFOX4 ICT and CRCT. Further studies are needed to allow implementation of intensified neoadjuvant treatment for LARC in the routinary clinical practice.

***Conflicts of interest*:** *Declared none.*

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