



## Dosimetric comparison and time consuming evaluations for neoadjuvant 5-fields versus 7-fields Intensity-Modulated Radiation Therapy for locally advanced rectal cancer.

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### ABSTRACT

Preoperative – multidrug - chemoradiotherapy schedule (PCR) is proven to be the standard approach in patients with locally advanced rectal cancer (LARC). The main limiting factor of PCR delivery is severe acute gastrointestinal (GI) toxicity due to the small bowel irradiated volume. Compared to 3-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiotherapy (IMRT) plans, with 7 or more fields, by highly conformal dose distributions, will minimize the dose received by small bowel, but required an increase in overall treatment time. The purpose of this study was to investigate if simple IMRT plans were comparable to conventional 7-fields IMRT in terms of dose distribution, with the advantage of reducing time delivery.

### Indexing terms/Keywords

Rectal cancer; intensity-modulated radiotherapy; Bowel sparing; Planning and treatment times.

### Academic Discipline And Sub-Disciplines

Radiation oncology.

### SUBJECT CLASSIFICATION

Rectal cancer radiotherapy treatment.

### TYPE (METHOD/APPROACH)

Retrospective analysis.

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## INTRODUCTION

### Methods.

Twelve patients with histologically proved LARC underwent PCR with concurrent chemotherapy with Oxaliplatin 50 mg/m<sup>2</sup> intravenously weekly x 6 weeks + Capecitabine 1500 mg/m<sup>2</sup> day (on days 1,14 every 21 days) and 7-field IMRT step-and-shoot technique at the cumulative dose of 50.4 Gy to the target volume, with conventional fractionation schedule of 1.8 Gy each day. Dose calculation for selected Organ at Risks (OARs) such as femoral heads, bladder and small bowel, were performed. Without exceeding OARs dose constraints or compromising target coverage, for each treated patients, a "simple" IMRT plan with 5 fields was computed and retrospectively compared with 7-field IMRT. Dosimetric parameters and treatment time data were analyzed.

### Results.

As expected, homogeneity of dose distribution was significantly better for 7F-IMRT than 5F-IMRT; while in terms of Conformation Number, as proposed by van't Riet et. Al, we registered no statistically significant differences between the two IMRT techniques resulting in equal sparing of healthy tissues. We recorded a median delivering treatment time of 7.9 minutes for 5F-IMRT and of 12.3 minutes for 7F-IMRT, with a difference statistically significant.

### Conclusions.

This preliminary study demonstrated that the reduction in the number of fields obtained with the 5F-IMRT is a strategy to improve treatment time delivery without a detriment in target coverage and normal tissue sparing in PCR for LARC patients.

### Introduction

Preoperative – multidrug - chemoradiotherapy schedule (PCR) is proven to be the standard approach in patients with locally advanced rectal cancer (LARC) because it has been shown to improve local control, to reduce toxicity and to increase sphincter preservation rate for patients with low-lying tumors. (1, 2) The NSABP R-03 trial is the first study that demonstrated a significant improvement in 5-year disease-free survival with PCR and a trend toward improved overall survival at 5-years. (3, 4, 5, 6).

In recent years, multidrug chemotherapy regimen was related to an increased of pathological response rate and local control. (7, 8, 9)

The main limiting factor of PCR delivery is severe acute gastrointestinal (GI) toxicity due to the small bowel irradiated volume. Higher rates of acute severe toxicity may lead to breaks during treatment course, potentially reducing local control and survival rate. (10)

Compared to 3-dimensional conformal radiation therapy (3DCRT), 5-, 7- and 9- field intensity-modulated radiotherapy (IMRT) plans, by highly conformal dose distributions, will minimize the dose received by small bowel and colon reducing the incidence of high grade acute GI toxicity. (11, 12, 13, 14) In addition, IMRT leads significant dose reduction to the bladder and femoral heads. (15)

On the basis of this clinical advantages, we implemented at our academic Department of Radiation Oncology the use of IMRT for LARC patients. Being a more complex treatment than 3DCRT, IMRT often leads to an increased use of resources, such as time and staff. (16)

Previous studies have suggested that a larger number of beams was necessary to provide the optimal IMRT dose distribution but with an increase of daily treatment session time, potentially detrimental in a Department equipped with a single linear accelerator unit (LINAC). Successful attempts have been made at reducing the number of beams, with the added advantage of shorter delivery times. (17, 18)

This comparative dosimetric study aimed to investigate if, in patients who underwent PCR for LARC, a "simple" 5-fields IMRT was comparable to conventional 7-fields IMRT in terms of target dose distribution, conformity index and normal tissue sparing, with the advantage of reducing time delivery, important end-point in our academic Department equipped with a single LINAC.

### Materials and methods

Twelve patients with LARC underwent PCR from March 2011 to March 2012 at Radiation Oncology Unit of San Luigi Hospital, Orbassano, Turin. All patients had histologically proved rectal adenocarcinoma. Pre-treatment evaluation provided colonoscopy, contrast-enhancement imaging of the chest, abdomen and pelvis by computed tomography (CT) and endo-rectal ultrasound (EUS) in addition to physical and digital rectal examination, complete blood count, urine analysis and liver function tests. Pelvic Magnetic resonance imaging (MRI) was employed in all patients. The 7th edition (2010) of TNM staging standard of American Joint Committee on Cancer (AJCC) was used.

The patient and tumor characteristics are listed in Table 1.



Table 1: selected patient and tumor characteristics.

<b>Sex (M/F)</b>	9 (75%)/ 3 (25%)
<b>Median Age (years)</b>	63 (49-77)
<b>Clinical Tumor stage</b>	
<b>T3</b>	9 (75%)
<b>T4</b>	3 (25%)
<b>Clinical Nodal stage</b>	
<b>N0</b>	4 (34%)
<b>N1</b>	8 (66%)

Abbreviations: M: male; F: female.

All patients received concurrent chemotherapy with Oxaliplatin 50 mg/m<sup>2</sup> intravenously weekly x 6 weeks + Capecitabine 1500 mg/m<sup>2</sup> day (on days 1,14 every 21 days). A non contrast-enhanced planning CT simulation (AcqSim, Philips, the Netherlands) was performed in supine position with immobilization device (ProSTEPTM, Elekta, Atlanta, GA, USA) to minimize set-up variability.

Patients were instructed to have a full bladder, obtained drinking 0.5 l of water, before CT study scan acquisition and before each treatment session, in order to reduce organ motion. Therefore, patients should be simulated with small bowel contrast. Axial images of 5 mm thickness were acquired from the L4-L5 vertebral body to 2 cm below the anal edge and imported to the treatment planning system workstation (Oncentra MasterPlan v3.3, SP 3, Nucletron, B.V., Veenendaal, the Netherlands).

The Gross Tumor Volumes (GTVs) and Clinical Target Volumes (CTVs) were contoured according to the recommendations of ICRU reports N° 50 and 62. (19) The GTV (GTV T) was defined as primary tumor (including the mesorectal space around primary tumor) and involved lymph nodes (GTV T+N). The CTV was defined as primary tumor, mesorectal region, mesorectal, internal iliac and pre-sacral lymph nodes; in cT4 external iliac lymph nodes was included. The Planning Target Volume T+N (PTV T+N) and PTV T were generated by adding 1 cm margin to each CTVs. Selected Organ at risks (OARs) were the femoral heads, bladder and small bowel. Femoral heads were contoured from the cranial extremity to the small trochanter, including the femoral neck; the bladder was outlined entirely and small bowel was defined as the peritoneal cavity inferior to L5/S1.

The prescription doses with conventional fractionation schedule of 1.8 Gy/day for PTV T+N and PTV T were 45 Gy and 50.4 Gy, respectively. Several beam arrangements were tested, with optimal results achieved using a 7-beam arrangement. All patients were treated with a 7-field IMRT step-and-shoot technique with 6-MV photons (7F-IMRT), with the following gantry angles 0°, 40°, 80°, 110°, 250°, 280°, 320°, 70 segments, 10 MV beam energy in direct step-and-shoot modality via LINAC (Sinergy Platform; Elekta Atlanta, GA, USA). Dose calculation was performed with Plan Optimization module (Raysearch Laboratories, Sweden) in Oncentra MasterPlan version 3.3 SP3 (Nucletron BV, the Netherlands). Collapsed-cone convolution methods were employed for final dose calculations. The dose was prescribed at the ICRU point. The optimization setting had the goal of covering greater than 95% of the PTV volume with the 95% of prescription dose limiting hotspots to 107% of the prescription dose, in particular anteriorly, for small bowel sparing. Retrospectively, for each treated patients, a "simple" IMRT plan with 5 beams (5F-IMRT) arrangement (0°, 72°, 144°, 216°, 288°), ≤ 50 segments was computed, without exceeding OAR dose constraints or compromising PTV coverage.

### Dosimetric and time evaluation.

The PTVs dose distribution obtained by the two IMRT techniques were compared using PTV mean dose (dose to 50 % of the PTV), Homogeneity Index (HI) and Conformity Index (CI) .

The dose distribution homogeneity was evaluated using the HI defined as:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} ,$$

where D2% , D98% and D50% are the dose to 2%, 98% and 50% of the PTV, respectively.

The ICRU 62 definition of CI, as the quotient of the treated volume at 95% of prescription dose and PTV volume, was used (19):

$$CI = \frac{TV_{95\%}}{TV} ,$$

where TV95% is the target volume covered by the 95% isodose and TV is the target volume.

Finally, in order to take into account irradiation of the target volume and irradiation of healthy tissues we used an index called Conformation Number (CN) proposed by van't Riet et al. (20):



$$CN = CI \times \frac{TV_{95\%}}{V_{95\%}}$$

where CI is the Conformity Index as explained before and V95% is the 95% isodose volume calculated within external contour.

Dosimetric parameters were calculated using tabular cumulative dose volume histogram (DVH) data. Normal tissue sparing was evaluated using the following parameters: percentage of volume receiving 40 Gy (V40) < 40% for the bladder, Dmax (2%) ranged from 40-45 Gy for small bowel and for femoral heads. (21, 22, 23) Finally, we evaluated the differences between the two IMRT treatment time, computed as time of delivering for all treatment fields, excluding patient set-up and treatment verification imaging.

### Statistics

Paired two-tailed Student t-test was used to analyze the differences between 5F-IMRT and 7F-IMRT. The threshold for statistical significance was  $p \leq 0.05$ . All data were analyzed using the statistical package R and RCommander plug-in ([www.r-project.org](http://www.r-project.org), [www.rcommander.com](http://www.rcommander.com), R Development Core Team, University of Auckland, New Zealand). (24)

### Results

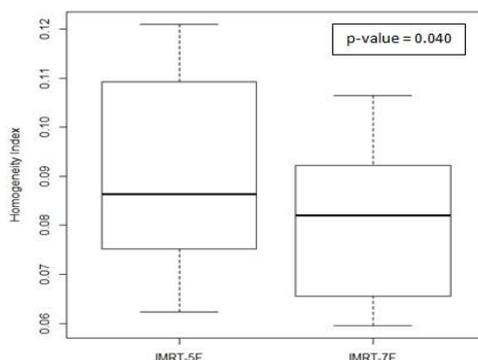
Conventional 7F-IMRT was performed in 5.5 weeks with a total of 28 daily fractions and all patients completed PCR as scheduled. The dosimetric parameters analyzed regarding PTV and OARs are listed in Tab. 2.

**Table 2: dosimetric parameters analysis.**

PTV - OARs		Dosimetric parameters	5F-IMRT	7F-IMRT	p value
BLADDER		D2% 45-50 Gy	49.3	50.0	0.021
SMALL BOWEL		D2% 45-50 Gy	47.4	46.1	0.193
FEMORAL HEADS	right	D2% 40-45 Gy	45.2	44.7	0.879
	left	D2% 40-45 Gy	45.4	44.9	0.903
PTV HOMOGENEITY		D2%	52.3	52	0.012
		D98%	48	48.1	0.082
		D50%	50.3	50.2	0.230
		HI (D2%-D98%)/D50%	0.09	0.1	0.010
PTV CONFORMITY		V95% (cm <sup>3</sup> )	1523	1533.3	0.115
		VPTV (cm <sup>3</sup> )	1553	1553	--
		CI (V95%/VPTV)	0.98	0.99	0.108

Abbreviations: PTV: Planning Target Volume; OARs: organ at risks; 5F-IMRT: five fields intensity modulated radiation therapy; 7F-IMRT: seven fields intensity modulated radiation therapy; HI: homogeneity index; CI: conformity index; VPTV: volume of PTV; D%: dose at % of volume.

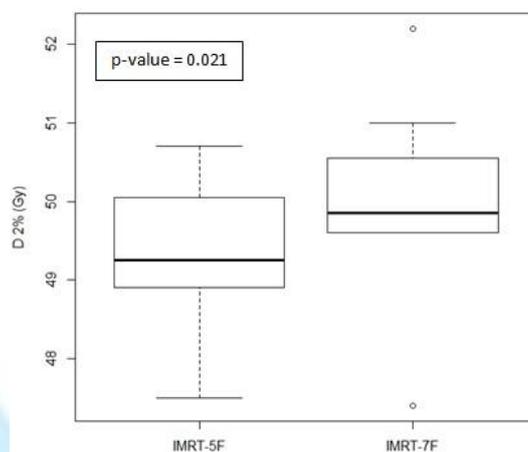
As expected, homogeneity of dose distribution evaluated by HI, was significantly better for 7F-IMRT than 5F-IMRT (p-value=0.040, mean difference=0.099, HI mean: 0.09 vs. 0.08), reflecting a small lack of PTV coverage with the 5F-IMRT; differences in terms of CI were not statistically significant showing only a trend (p-value=0.066, mean difference= -0.012, CI mean: 0.98 vs 0.99). (Fig. 1)



**Fig. 1: box plot of Homogeneity Index (HI) between 5F-IMRT and 7F-IMRT.**

In terms of CN we registered no statistically significant differences between the two IMRT techniques resulting in equal sparing of healthy tissues ( $p$ -value=0.299, mean difference=0.015).

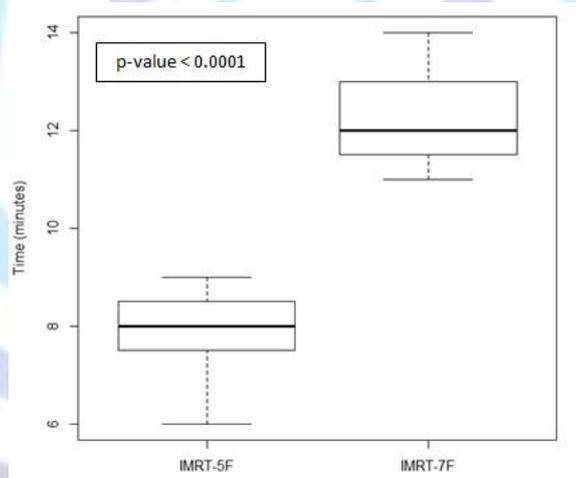
The D2% of the bladder volume is less with 5F-IMRT than with 7F-IMRT technique ( $p$ -value= 0.021, mean difference= - 0.625 Gy, D2% average: 49.3 Gy vs. 50.0 Gy). (Fig. 2).



**Fig. 2: box plot of the D<sub>2%</sub> of the bladder volume with 5F-IMRT and 7F-IMRT, respectively.**

Regarding femoral heads and small bowel no statistic differences between 5F-IMRT and 7F-IMRT in terms of D2% were recorded.

Considering the lower number of plan Monitor Units (MUs) and beam segments for 5F-IMRT, finally, we recorded that the median delivering treatment time was 7.9 minutes and 12.3 minutes for 5F-IMRT and 7F-IMRT, respectively, with a difference statistically significant ( $p < .0001$ ). (Fig. 3).



**Fig. 3: box plot of treatment time delivery between 5F-IMRT and 7F-IMRT, computed in minutes.**

## Discussion

The implementation of IMRT technique in PCR for LARC treatment, that allows to concentrate radiation doses to the target volume minimizing the unnecessary doses to the surrounded normal tissues while reducing acute and late toxicities, can be considered the standard of care in this clinical setting. (25, 26)

Several groups have explored methods to simplify IMRT plans, including use of planning algorithms to control number of segments and beams, in different clinical setting with the aim to reduce the negative impact of dosimetric and geometric uncertainties associated with more complex IMRT. (27)

Regarding rectal cancer, fewer experiences are present in literature. Guerrero Urbano et al. investigate the potential of number of beams in IMRT plan to spare the bowel in rectal tumor. The authors showed that reducing the number of beams did not impact on the target coverage or bowel and bladder sparing; furthermore, a more simple IMRT is associated with shorter delivery times. (18) The Radiation Therapy Oncology Group, in the 0822 RTOG protocol, affirmed that 5-, 7- and 9- IMRT plans were all significantly better in sparing bowel than the 3-field IMRT plan, with clinical promising data for 5F-IMRT. (18, 28)



According to published study, our preliminary data showed that target coverage and dosimetric parameters appears to be comparable between the two different techniques, while treatment time delivery was reduced by using 5F-IMRT.

Other benefits related to simple IMRT include improving patient's set-up and compliance, minimizing intra-fraction errors.

Considering patient set-up, imaging verification and treatment delivery, a 5F-IMRT solution is more advantageous in a Department of Radiation Oncology equipped with a single LINAC for patients waiting list, without compromising treatment quality.

## Conclusion

The implementation of IMRT in the clinical practice as a part of neo-adjuvant concomitant treatment for LARC was associated with a clinically significant decrease in acute GI toxicity compared with 3D-CRT. However, used as routine therapy, IMRT leads to an increase in daily overall treatment time.

The reduction in the number of beam segments obtained with the 5F-IMRT is a strategy to improve treatment time delivery without a detriment in target coverage and normal tissue sparing.

We believe this technique is a sensible compromise suitable for clinical delivery in this setting of patients with efficient use of radiotherapy resources, particularly in an academic Department equipped with a single LINAC.

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