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PENCIL BEAM SCANNING PROTON THERAPY REIRRADIATION FOR LOCALLY RECURRENT RECTAL CANCER: CLINICAL OUTCOME, TOXICITY AND DOSIMETRIC COMPARISON FROM A SINGLE CENTER EXPERIENCE

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ABSTRACT

Purpose: treatment for locally recurrence rectal cancer is challenging. Reirradiation can be a curative or palliative treatment, and part of multi modality treatment. However, it presents risk of late complications given the radiation sensitivity of nearby organs and tissues of the abdomen and pelvis. The aim of the present study is to report the outcome and toxicity of reirradiation with Pencil Beam Scanning Proton Therapy (PBS-PT) for patients with locally recurrent rectal cancer.

Methods and materials: a single-institution, retrospective analysis of 15 patients with history of pelvic radiotherapy for rectal cancer receiving PBS-PT for local recurrence was performed. Data on patient, treatment characteristics, outcomes and acute and late toxicity were collected. Dosimetrical comparison between Photon and Proton for challenging plans was done. Univariate analyses (UVA) of several factors for outcomes including FDG-PET/CT median maximum standardized uptake value (SUVmax), changes in Neutrophil/Lymphocytes ratio after PT was performed.

Results: the median reirradiation dose was: 50 GyRBE (range 50,4-39,6 GyRBE). Two patients received concurrent chemotherapy. The 1-year local control, progression-free survival, and overall survival rates were 66.7%, 33,3%, 93,3% respectively. Acute grade >3 toxicity rate was 6,6%, while late grade >3 toxicity was 13,3%. At UVA Cox proportional hazards model analyses no one of the variables showed a significant difference in all outcomes. Dosimetrical comparison showed a substantial advantage in favor of PT for pre-sacral and sacral region of relapse.

Conclusions: in our study PBS-PT for locally recurrent rectal cancer demonstrated low acute toxicity rates and acceptable late toxicity supporting the use of PBS-PT as an option for this patient population.

INTRODUCTION

Epidemiology and standard treatment of rectal cancer

The ACS (American Cancer Society) estimates 152,810 new cases of colorectal cancer in 2024. Men will account for 81,540 cases and women will account for 71,270, according to estimates. Of these, 106,590 cases will be colon cancer, and 46,220 cases will be rectal cancer. CRC (colon-rectal cancer) is the second leading cause of all cancer-related deaths in the U.S., with an estimated 53,010 deaths in 2024, a slight increase over last year's estimated. [1]

Surgery

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions. These methods include local procedures, such as polypectomy, transanal local excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with TME and coloanal anastomosis, abdominoperineal resection [APR]). [2, 3]

Transanal local excision is only appropriate for selected T1, N0 earlystage cancers. TEM can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more proximal lesions.

A meta-analysis reported a substantial risk of local recurrence in patients with high-risk pT1 and pT2 rectal cancer who receive no additional therapy following local excision. [4]

Completion TME or adjuvant chemoRT (for pT1) were found to mitigate that risk. Results of a multiinstitutional, single-arm, open-label, non-randomized, phase II trial suggest that chemoradiotherapy with CAPEOX followed by local excision may be a safe alternative to transabdominal resection in patients with T2N0 distal rectal cancer. [5]

A meta-analysis also suggests that this approach of neoadjuvant chemoRT followed by local excision may be a safe and effective alternative for patients with any T and any N stage of rectal cancer who refuse or are unfit for transabdominal resection. [6]

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a "tumor package" through sharp dissection and is designed to spare the autonomic nerves. [3,7,8]

Organ-preserving procedures that maintain sphincter function are preferable, but not possible in all cases. Preoperative chemoRT or TNT (Total Neoadjuvant Therapy) may result in tumor downsizing and a decrease in tumor bulk.

In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis.

For lesions in the mid to upper rectum, an LAR extended 4 to 5 cm below the distal edge of the tumor using TME, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required.

An APR with TME should be performed when the tumor directly involves the anal sphincter or the levator muscles. An APR is also necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy. [9]

Neoadjuvant/adjuvant Radiotherapy (RT) for stage II (T3–4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer is usually included in the treatment due to the relative high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection.

Combined-modality therapy

Combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), and chemotherapy is recommended for the majority of patients with stage II or stage III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. The current guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy.

The Total Neoadjuvant Therapy Approach (TNT), a treatment approach for stage II or III rectal cancer, including courses of both chemoRT and chemotherapy given as neoadjuvant therapy before transabdominal resection, has been gaining prominence. This approach was first tested in several small, phase II trials, but more recently has been supported by phase III trial data. [10]

A large, prospective, randomized trial from the German Rectal Cancer Study Group (CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer. [11]

Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs. 13%; P = .006) and treatment-associated toxicity (27% vs. 40%; P = .001), although OS was similar in the two groups. [12]

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue. First, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in patients with rectal cancer. [11]

Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected).

When not using a TNT approach, preoperative chemoRT is recommended for patients with stage II/III rectal cancer. Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen. [13,14,15,16]

These results have also been supported by systemic review and meta-analyses showing a higher pathologic complete response rate with TNT. [17, 18]

It is not established whether it is better to start with chemotherapy, then follow with chemoRT, or vice versa when following a TNT approach.

Results from the phase II Organ Preservation in Rectal Adenocarcinoma (OPRA) trial suggest that initiating treatment with chemoRT may improve TME-free survival. [19,20]
Moreover, neoadjuvant chemo-radiotherapy (nCRT) followed by watch-and-wait also achieved organ preservation in half of the patients. [20]
Overall, it appears that short-course RT gives effective local control and the same OS comparing with conventional RT schedules, and therefore is considered as an appropriate option for patients with locally advanced rectal cancer. A multidisciplinary evaluation, including a discussion of the need for downstaging and the possibility of long-term toxicity, is recommended when considering short-course RT. [21,22,23]

Treatment of locally recurrent disease locally recurrent rectal cancer

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. Despite optimal outcome with nCRT followed by total mesorectal excision, local recurrence rates remain between 5% and 18%. [20,24]
In recent, single-institution, retrospective analysis of 735 patients with stage II/III rectal cancer treated with preoperative chemoRT followed by TME, locoregional recurrence rate at 5 years was 4.6%, occurring at a median of 24.7 months. [25]
In a single-center study, Yu et al reported low rates of 5-year local recurrence (5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemo-RT, and 49% of recurrences occurred in the low pelvic and presacral regions with an additional 14% occurring in the mid and high pelvis. [26]
For patients with locally recurrent rectal cancer treated with salvage surgery, complete surgical resection (R0 resection) has a survival advantage over R1 and R2 resection. [27,28,29]
On the contrary, a retrospective study found that re-resection was not associated with improved survival in patients with isolated locoregional recurrence (3.6 years with surgery vs. 3.2 years without surgery; P = .353). [30]
However, curative surgery for locally recurrent rectal cancer, such as total pelvic exenteration, is not always possible, moreover it significantly impairs the patient's quality of life, and some patients prefer nonsurgical treatment for locally recurrent rectal cancer.
Patients with unresectable lesions should be treated with systemic therapy, chemoRT, or short-course RT according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended. Potentially resectable isolated pelvic/anastomotic recurrence may be managed with neoadjuvant therapy, including chemotherapy before or after chemoRT or short-course RT, followed by resection. When following this approach, starting neoadjuvant therapy with chemotherapy is preferred. IORT or brachytherapy should be considered with resection if it can be safely delivered. [31, 32]
In a study of 43 consecutive patients with advanced pelvic recurrence of CRC who had not undergone prior RT, treatment with 5 weeks of 5-FU by infusion concurrent with RT enabled the majority of patients (77%) to undergo re-resection with curative intent. [33]
In one study of 48 patients with recurrent rectal cancer and a history of pelvic radiation, the 3-year rate of grade 3–4 late toxicity was 35%, and 36% of patients treated were able to undergo surgery following radiation. [34]

Re-irradiation: challenges and current consensus

Re-irradiation refers to a new course of radiotherapy either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises toxicity concerns. [35]
Re-irradiation is a general term for two scenarios that we will distinguish in this consensus by referring to type 1 or type 2 re-irradiation: re-irradiation type 1 is a new course of radiotherapy that has geometrical overlap with the irradiated volume of previous courses; re-irradiation type 2 is a new course with concerns of toxicity from the cumulative doses but in which there is no overlap with the irradiated volume of previous courses. [36]
Re-irradiation may be offered to patients with recurrent, metastatic, or new malignancies following initial radiotherapy in different anatomical regions The need to balance tumor control with the risk of severe toxicity from cumulative radiation doses to previously irradiated organs is the crucial challenge in re-irradiation.

The decision for reirradiation has to be guided by important rules:

1. Interdisciplinary management and shared decision making Treatment alternatives treatment alternatives to radiotherapy and salvage options after radiotherapy should be discussed in an interdisciplinary team, including surgeons and medical oncologists, together with the patient for shared decision making

2. Accurate selection of the patient:

ECOG Performance Status < 2
Less than 6 months since previous Radiotherapy
Progressive disease as best response to previous radiotherapy, relapsing tumor could have selected RT resistant clones
Estimated survival < 6 months
ReRT should be excludedif residual toxicity from prior RT, persistent Grade 3 or grater radiation induced toxicity

3. The response to and benefit from initial radiotherapy should guide the decision for or against re-irradiation and might help to estimate the most appropriate dose in case of recurrence within the previously irradiated volume

4. Evaluation of the prevuious Radiotheraoy Treatment/s:

Assessment of cumulative doses
Date/Year of start/end of treatment
Number of previous courses
Dose Prescription and fractionation
PDF Plan Report
DICOM Plan Report

3D DICOM Plan Report is usually preferable to the plan in PDF format if available

If the previous dose distribution is available electronically, at least an overlay of dose distributions in 3D is mandatory, rather than a numerical summation of the prescribed physical dose and of the doses received by Organs at Risks (OARs).
Generally, dose per fraction to normal tissue will never be the same across treatments, even when prescription dose per fraction is the same, and this effect will be even more pronounced when different prescription doses are used per fraction.
A physical dose summation across multiple treatment courses will almost never make radiobiological sense, except for the few random voxels in which the dose per fraction happens to be the same for the different treatments.
Biologically equieffective doses should be calculated when performing dose summations of treatment plans, especially when different doses are used per fraction; optimally, the full 3D dose distributions should be converted to equieffective doses before dose summation to allow any volume effects to be considered. [36]
The linear-quadratic model is the most widely used and validated radiobiological model for explaining both the effect of fractionation and the specific differences in response to irradiation between different primary tumours or normal tissues:
The linear-quadratic model describes the response of neoplastic cells to a certain dose of radiotherapy and it allowed to calculate the equivalent dose delivered in 2 Gy per fraction (EQD2), that is the biologically equivalent dose to a total dose D administered in fractions d:

$$EQD2 = D\ ((d + \alpha/\beta)/(2 + \alpha/\beta)$$

or it can be used to assess the effective biological dose of a course of radiotherapy (biologically effective dose, BED), that is, the true biologically delivered dose:

$$BED = nd\ (1 + (d / \alpha/\beta)$$

Bentzen and colleagues have reviewed the usage, interpretation, and challenges of the linear-quadratic model. In the setting of re-irradiation, the linear-quadratic model might be applied for calculating radiobiological equieffective doses (eg, EQD2) for different dose and fractionation schemes, which is crucial for assessing cumulative doses. In the absence of clinical radiobiological data specific for re-irradiation, published established α/β values for primary irradiation of tumour and organs at risk should be used acknowledging the uncertainties about estimated α/β for primary irradiation. [36,37]

5. Tissue recovery: Tissue-dependent recovery or dose discount consist in the amount of the previously given dose that is assumed to be recovered and can be substracted for further cumulative dose calculations.

Tissue-dependent recovery after radiotherapy or dose discount is still subject to ongoing research and, therefore, a reliable recommendation on their use is not possible, except for the evidence for

the recovery specifically of the brain and the spinal cord based on preclinical animal models, but also on retrospective series in humans. [38,39]
However, some articles has set recovery as 25% more of the normal constraint if the elapsed time interval was 6- 12 months; 50% more than the normal constraint, if the elapsed time interval was > 12 months after the last radiation (recover from occult damage). [40]

6. Dose constraints:
In general, if established dose constraints of an organ at risk are not exceeded in the dose summation, re-irradiation can be deemed safely.
Prioritisation of target volumes and the dose to organs at risk should be guided by the patient's life expectancy, risk acceptance, and the general treatment goal
When analysing the doses to organs at risk, potentially shorter latencies of irreversible toxicities after previous irradiation should be considered.
Cumulative doses allowed for some OARs are under investigation, no consensus is available

7. Considering concomitant radiosensitising systemic therapy with re-irradiation, the potential of excess radiatiotherapy-induced toxicities should be discussed critically. [36]

Why Proton Therapy

Reirradiation for locally recurrent RC and de novo RC with prior radiation for other pelvic malignancy can administered either as part of a curative or palliative regimen, and can be part of multi modality treatment for patients eligible to concomitant chemotherapy and/or curative resection, having the most favorable survival outcomes.
However, it presents risk of late complications given the radiation sensitivity of nearby organs and tissues of the abdomen and pelvis in particular, the bladder, bowel, bone marrow, and lumbosacral plexus. This affects the approach of reirradiation in multiple ways, including treatment volumes, prescribed dose, fractionation scheme, and technique of delivery.
Numerous experiences have described disease and toxicity outcomes of reirradiation for RC, using modifications in treatment delivery to achieve safe and effective therapy. [41]
A prospective study by Valentini et al reported disease outcomes and treatment toxicities demonstrating the safety and efficacy of hyperfractionated reirradiation with concurrent chemotherapy. [42]
These findings have been corroborated by multiple retrospective studies. [43]
However, to our knowledge, nearly all published studies have evaluated reirradiation using either 3-dimensional conformal radiation therapy (RT) or intensity modulated RT techniques. [44,45,46]
Proton beam therapy (PBT) has unique physical characteristics and protons display a specific, highly concentrated dose distribution in depth known as the Bragg peak which allows for radiation to be precisely delivered to the tumor. In addition, rather low levels of energy are deposited in tissues proximal and distal to the tumor, thus minimizing the damage to the adjacent, healthy tissue. [47]
Therefore, PBT enables a higher dose for locally recurrent rectal cancer without severe toxic effects compared with conventional photon radiation therapy.
In the past decades, proton beam therapy has been implemented clinically, taking advantage of its unique physical characteristics of dose deposition from the 'Bragg peak'. The development of the

Pencil Beam Scanning (PBS) technique allows the proton system to optimize the energies and numerous spots to deliver the radiation dose layer by layer and spot by spot in 3-dimensional, just like a 3D-printer.
Literature evaluating rectal reirradiation with proton therapy (PT) is emerging and has demonstrated a significantly reduced low dose to the bowel and bone marrow, as well as clinical feasibility, safety, and efficacy thus far with passive-scatter techniques. [48,49]
Pencil Beam Scanning-ProtonTherapy (PBS-PT) provides true intensity modulated PT; thus, it can be hypothesized that its use may result in improved short- and long term toxicity profiles in the setting of reirradiation for recurrent rectal cancer.

Aim of the Study

The aim of the study was to collect and report the disease and toxicity outcomes from a retrospective, single-institution experience using PBS-PT for reirradiation for RC.
Moreover we performed a dosimetric comparison between Photons and Protons plan to identify a possible target of patients to be selected for PT reirradiation.

MATERIALS AND METHODS

Patient Selection and Treatment

An institutional retrospective chart review was completed of all patients with prior pelvic RT, treated with reirradiation using PBS-PT for rectal cancer relapse at the Trento Proton Therapy Center between 2014 and 2022.
Twenty-one patients were identified but those with pelvic prior RT for malignancy different from rectal cancer or without confirmed histology of rectal adenocarcinoma relapse were excluded, so finally 15 patients were selected to be included in the study.
All patients had ECOG Performance Status < 2 and no residual toxicity Grade 3 or grater from prior radiation. No one patient had progressive disease as best response to previous radiotherapy. All patients had an estimated survival > than 6 months.
First radiation had been performed not less than 6 months before PT. Median time from the initial radiation to reirradiation was 50,8 months (Range 15-166 months).
Every patients was presented at a multidisciplinary tumor board. Concurrent chemotherapy and curative-intent surgical resection were planned whenever feasible and appropriate.
Patient demographic information and disease characteristics, were collected and they are summed in Table 1.
Median age at the time of reirradiation was 65 years (range: 50- 84). Recurrence site was mostly localized in the presacral region (67%).
Eleven patients performed 18-fluorodeoxyglucose-positron emission computed tomography (18 FDG-PET-CT) before and after PT, the median maximum standardized uptake value (SUV (max))-lesion before PT was 13,34 (range 7,3-18,1).
Patients had complete blood count with differential before and after PT.
All patients had received multiple treatments before PT: all, except one, had performed surgery at diagnosis, and in three cases patients had surgery also at the first recurrence disease; 8 patients had permanent colostomy and all patients had multiple cycles of systemic therapy before PT.
PT was performed in most cases at the first relapse (8 patients), in 5 cases at the second relapse and in 2 cases at the third relapse.
For 14 patients PT rapresented the second course of RT, only in one case the patient had already received two corses of RT (3DCRT and SBRT) and PT was the third irradiation course.

Proton Therapy intent*:* in all cases but one PT was performed only in case of exclusion of surgery, that means that PT was performed with curative intent, only in one case it was performed as neoadiuvant treatment

Table 1 (Patient and disease characteristics)

Characteristics	**No.**	**%**
Age		
Median (y)	65	-
Range (y)	50-84	-
Recurrence Sites		
Single	11	73
Multiple	4	26
Recurrence Location		
Perirectal region	7	46
Presacral Region	10	67
Sacral Bone	6	40
Frequency of recurrence		
First Recurrence	7	46
Second or more Recurrence	8	53,33
Sex		
Female	4	27
Male	11	73
ECOG		
0	10	67
1	5	33,33
Histology		
Adenocarcinoma	15	100
Primary Tumor Stage		
I	2	13,33
II	3	20
III	7	46
IVA	1	6,66
Unknown	1	6,66
Recurrent Tumor irradiated (cc), median (range)	331 (129-593)	-
Type of Surgery performed at diagnosis		
AbdominoPerineal Resection (APR)	8	53,33
Low Anterior Resection (LAR)	6	40
No Surgery	1	6,66
Intent PT		
NeoAdjuvant Therapy	9	60
Adjuvant Therapy	8	53,33
Radiotherapy Setting		
Neoadjuvant	8	53,33
Adjuvant	2	13,33
At relapse	5	33,33
Treatment		
PBT alone	13	86,66
Concurrent Chemotherapy	2	13,33

Proton Therapy

Positioning, Immobilization and Simulation CT scan

Patients underwent computed tomography (CT) simulation in the supine or prone (1 case) position with a comfortably full bladder and combifix-kneefix-lokbar immobilization.

Definition of Proton Therapy Volumes

Gross tumor volume (GTV) was delineated using physical examination, CT simulation, and diagnostic imaging data (positron emission tomography and/ or magnetic resonance imaging).
A clinical target volume (CTV) was generated by expanding the GTV by 1.5 to 3.0 cm craniocaudally, extending to the pelvic sidewall laterally, including the presacral space posteriorly and the mesorectum were still present.
When a boost was planned, a second smaller isotropic expansion of 0.5 to 1.0 cm was used, or simply the gross tumor without expansion.
The choice of CTV expansion is based on the method outlined by Valentini et al. [42] with smaller expansions on the GTV used in cases of inoperable recurrences involving the bone. Planning target volumes were generated by dosimetry, accounting for setup and proton beam range uncertainty. Earlier cases used a uniform 5 mm expansion, later transitioning to nonuniform expansions (3.5-5 mm) based on translational uncertainty, and eventually generation of a planning target volume using robust optimization algorithms.

Dose Prescription and Plan Optimization

Access to full information on previous treatments, including imaging, treatment plans, and dose distributions was requested for all patients to assess cumulative dose summation, electronic format of the plan was preferred when available, however it was not possible to obtain that for all patients, in 11 cases Electronic Plan Report was at our disposal and in 4 cases we had only the Dose Plan Report accessible.
If the previous dose distribution was available in electronic format, a 3D overlay of the dose was done, in the other cases a numerical summation of the prescribed physical dose was performed.
In cases of electronic format available, the dose distribution of the first irradiation was transferred or mapped on the new CT scan and that was done alligning the images of the two CT scan (of the first RT and of PT) using image registration. Rigid registration was done, than Deformable Registration (DIR) was performed, in this way we could map and visualize the dose of the first RT on the Proton Therapy Target and OARs. The deformed dose obtained was than used to prescribe the *summed dose constraint*s for reirradiation only if the anatomy of the patient has not substantially changed from the first to the second irradiation, it was possible in 10 patients, in one case in which

patient received colostomy between the two irradiation, only the the dose on the statistical dose report were taken into account.
To calculate the radiobiological equieffective doses (eg, EQD2) for different dose and fractionation schemes, which is crucial for assessing cumulative doses, the linear-quadratic model was applied.

That was useful to create the new prescription, taking into account the doses already received by the OARs nearby the target, refferring to the consensus approved OARs constraints or to prescribe *summed doses* suggested by papers that have a somewhat agreement made by the experience of the Physicians.
In our cases we usually applied the *summed doses constraints* suggestested by Abusaris et al. [40] taking into account the time between the two radiation courses: *Rectum* Dmax $\leq$ 100 Gy3 RBE; *Bowel* Dmax 90 $\leq$ Gy3 RBE; *Bladder* Dmax $\leq$ 110 Gy3 RBE; *Sacral Nerves* (Cauda Equina and Lumbo Sacral Plexus) Dmax $\leq$ 105 Gy3 RBE.However uncertentais in the registration due to multiple factors (i.e. large anatomical variations, image acquisition artefact, lack of coontrast, choice of parameters) can introduce dose mapping uncertaintes so we used the summed dose process only in these cases were the uncertentais in registration were not significant.
All PBS-PT plans underwent peer review per departmental protocol.
Median Total Dose delivered was: 50 GyRBE (range 50,4-39,6 GyRBE) in all cases with standard fractionation 1.8-2.0 GyRBE/Fraction.
Plan optimization was performed using Raystation (RaySearch Laboratories, Stockholm, Sweden). All patients were treated with PBS-PT, typically with 2 posterior oblique fields with single-field optimization (SFO) technique, in some cases using a third field and/or multiple-field optimization (MFO).
Using PBS-PT, the anterior edge of the field can be shaped and modulated off of bladder and bowel. When using a multiple field optimization technique, air in the bowel was accounted for using a density override algorithm
To account for the setup and range uncertainties the selective robustness optimization was applied (using assigned perturbations including range uncertainties of ±3.5% while isocenter shifts of ±3 mm were already included in the PTV).

Set-up check and Quality Assurance during treatment

CT-on-rail images were acquired prior to daily treatment to check postioning.
Quality assurance CT images to evaluate the effect of setup and inter-fraction anatomical changes on the accumulated dose were obtained during the course of therapy, with frequency depending on the particular case and clinical discretion, if the dose distribution resulted altereted both for the Target or for the OAR constraints, an Adaptive Replan was performed.

Concomitant Therapy

For two patients chemotherapy was associated to PT: Capecitabine 825 mg/m2 Per Os BID, Monday–Friday, on days of radiation treatment only, throughout the duration of RT.

Dosimetric comparison of Plans

Dosimetric comparisons were performed for target coverage and high-priority organs at risk (OARs) between IMRT plans and replanned with IMPT.
For comparative purpose, IMPT proton plans were created for the same prescription doses as for the photon treatments on RayStation treatment planning system using multifield optimization (MFO) with PBS. The number of fields was different for each patient, according to the plan's complexity. Additionally, a 3.5 cm water equivalent thickness range shifter was introduced as appropriate for superficial tumors to cover the target volume proximally. The optimization assumed a CTV-based robust optimization, with a set-up uncertainty of 5 mm and a 3.5% calibration curve uncertainty. Beside the target coverage and dose to OARs, the robustness of each proton plan was followed using 5 mm setup and 3.5% calibration uncertainty. The optimization criteria were the same as for the photon plans, except the target coverage, which required for 98% volume of the CTV to receive at least 95% of the prescribed dose (V95% >98%). None of the plans were normalized, since the mean dose to target was close to 100%. For both photon (X) and proton (P) plans V98%, homogeneity index and Dmax for CTV were extracted for dosimetric comparison.

Follow-up and endpoints

Toxicity was assessed using provider documentation from weekly on-treatment visits, clinical evaluation one month after treatment and every three months for the first year, every six months thereafter. Toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v. 5.0). Adverse Events collected in the three months after PT were classified as acute, while those persisting or occurring later were classified as late.
Treatment response was stratified using an initial imaging test after PBT. Imaging modality used depended on the one used before treatment, usually MRI or 18F-FDG-PET/CT. The response criteria in MRI used response evaluation criteria in solid tumors (RECIST). The response criteria in 18F-FDG-PET/CT used the European Organisation for Research and Treatment of Cancer criteria. [50] Complete resolution of FDG uptake in all lesions was determined as a complete metabolic response (CMR). A reduction of greater than 25% in the sum of the maximum standardized uptake value (SUVmax) after PBT was determined as partial metabolic response (PMR). An increase of more than 25% in the sum of the SUVmax or the appearance of new FDG-avid lesions were defined as progressive metabolic disease (PMD). Not qualifying as CMR, PMR, or PMD was defined as stable metabolic disease.

Statistical Analysis

We estimated overall survival (OS), progression-free survival (PFS), and local control (LC) using the KaplanMeier method. The follow-up period started on the date of PBT completion.
LC was calculated from completion of reirradiation to time of local failure by pathologic or radiologic confirmation. Patients who did not experience Local Progression were censored at the time of the last follow-up visit.
PFS was calculated from completion of reirradiation to the date of any progression (local or at distance) or death, irrespective of the cause.

OS was calculated from completion of reirradiation to the date of death, irrespective of the cause.
A univariable Cox proportional hazards model was used to model the relationship between several parameters and outcome.
A P value of <.05 was considered statistically significant.

RESULTS

Follow-up and outcome

The initial imaging test was performed at a median of 2 or 3 months after PT.
Eleven patients (73%) received 18F-FDG-PET/CT as the initial imaging modality. Median SUVmax of 18F-FDG-PET/CT after PBT was 8,063 (range 0-14,2). Four patients underwent MRI, 9 patients performed both the imaging.
Three patients had Neutrophil/Lymphocytes ratio post PT increase after PT while it was almost stable in 3 cases, reduced at least of 1 unit in the other cases (60%).
As the first response to PT: one patient (6,6%) had complete response (CR), 8 (53,3%) had partial response, 4 (26,6%) stable disease and 2 (13,3%) patients progression disease.
Two patients underwent surgery after irradiation with R0 resection, surgery was proposed also to another patient but he refused.
At a median Follow Up of 30 months (range: 4-108): 11 (73,3%) patients had developed distant metastases (Lung, Bone, Lymphnodes), 5 (33,3%) patients had local progression, 10 (66,6%) patients had no local relapse, 9 (60%) patients were alive, 6 (40%) patients had died for progression at distance.

The 1-year LC, PFS, and OS rates were 66.7%, 33.3%, and 93.3%, respectively. At a median Follow Up of 30 months (range: 4-108) LC was 66%, PFS 26,7% and OS 60% (fig. 1).

Fig.1: Local Control

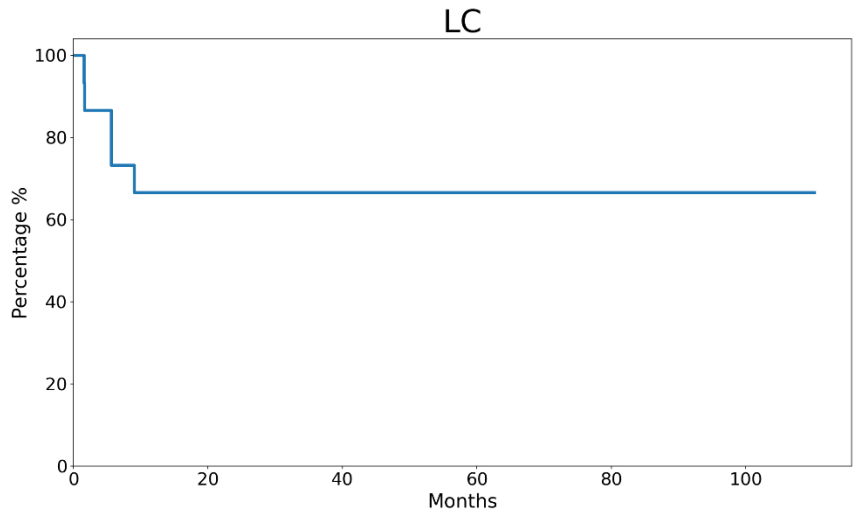


Fig.2: Progression Free Survival

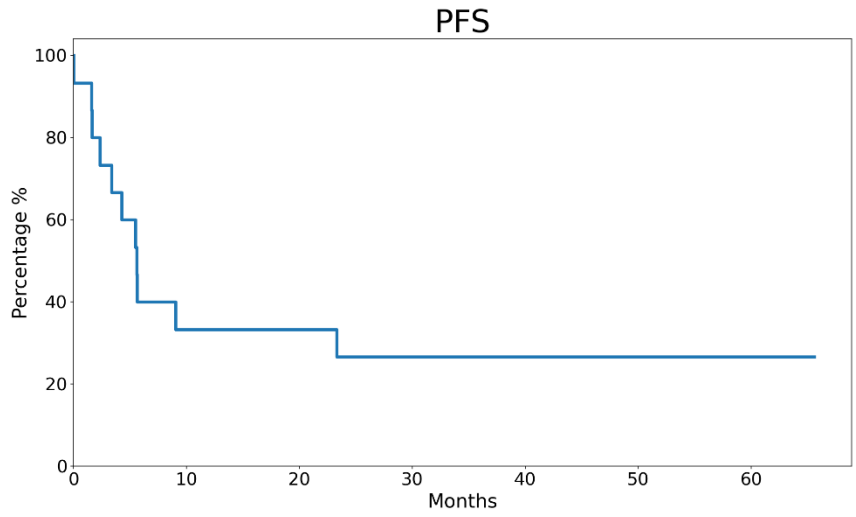
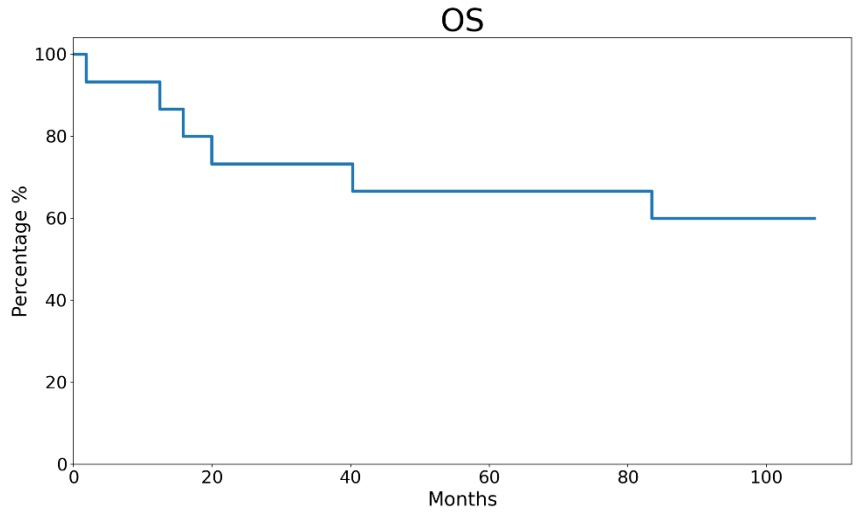


Fig.3: Overall Survival



Univariate analyses (UVA) using the Cox proportional hazards model for outcomes are summarized in Table 2.
No one of the analyzed variables show a significant difference in all outcomes.
Multivariate analyses were not performed owing to the small sample size

Table 2 (UVA)

Variable	***Local Control (P-Value)***	***Progression Free Survival (P-Value)***	***Overall Survival (P-Value)***
Age at Protontherapy	0,207	0,926	0,077
Time between RT-PT	0,234	0,152	0,323
Total Dose (Gy)	0,419	0,176	0,621
Irradiated Volume (cc)	0,487	0,582	0,300
Neutrophil/Lymphocytes ratio pre PT	0,220	0,441	0,362
Neutrophil/Lymphocytes ratio post PT	0,367	0,286	0,626
Neutrophil/Lymphocytes ratio post PT increase	0,488	0,411	0,772
FDG-PET/CT SUVmax pre PT	0,400	0,876	0,464
FDG-PET/CT SUVmax post PT	0,893	0,898	0,586
Sex	0,654	0,187	0,204
Site of Disease	0,415	0,542	0,415
Chemotherapy association	0,218	0,159	0,756
Proton Result (RC/PR/SD)	1,00	0,594	0,512

Toxicity

Only one patient experience acute toxicity ≥ G3 (6,6 %), after eleven fractions of treatment, this patient didn't complete PT. Treatment of complication was entirely in a medical ward without stay in either intermediate or intensive care.
All the other patients completede the planned Treatment
Acute toxicities are listed in Table 3.

Table 3 (acute toxicities)

Toxicity	**Tot (%)**	**G1**	**G2**	**G3**	**G4**
Fatigue	3 (20)	3	--	--	--
Paresthesia	2(13)	1	1	--	--
Pain	2(13)	2	--	--	--
Proctitis	1(7)	1	--	--	--
Radiation Dermatitis	2(13)	1	1	--	--
Abdominal Stomia Subocclusion	1(7)	--	--	1	--

Late Toxicity were developed in 7 (46,6%) patients. Three patients developed late Lumbo-Sacral toxicity conditioning pain G2, that requested the use of painkillers, all of these three patients had received total summed dose D1 > 100 GyRBE. For no one of them a recover of the dose received by the lumbo-sacral plexus in the first irradiation was considered. All patients who did not developed lumbo-sacral plexopaty received Doses < 100 GyRBE.

One patient reported sintomatic late ureteral stenosis three months after the end of PBT, determining hydronephrosis and renal dysfunction that required elective operative intervention; to note that the stenosis was already present at the beginning of treatment due to the ab extrinseco compression by the mass of disease, after treatment it worsened and nephrostomy was necessary.
One patient suffered of sacral bone fracture five months after PBT conditioning pain G3, requiring the use of Morphine to reduce the pain.
8 patients didn't reported late side Eefects and 3 patients reported symptoms improvement (reduction of pain).
Late Toxicities are listed in Table 4.

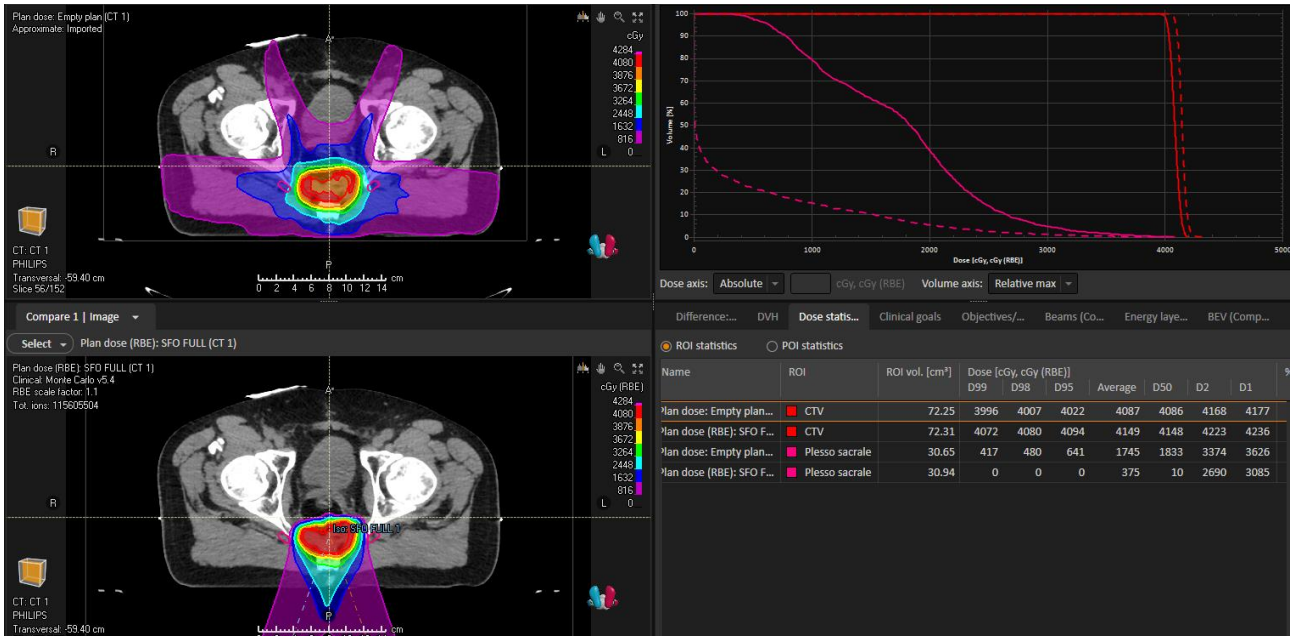
Table 4 (late toxicities)

Toxicity	**Tot (%)**	**G1**	**G2**	**G3**	**G4**
Pain	5(33)	1	3	2	--
Discromia	1(7)	1	--	--	--
Stipsi	1(7)	1	--	--	--
Fatigue	1(7)	--	1	--	--
Bone fracture	1(7)	--	--	1	--
Lumbo-Sacral Plexopathy	3(2)	--	3	--	--
Ureteral Stenosis	1(7)	--	--	1	--

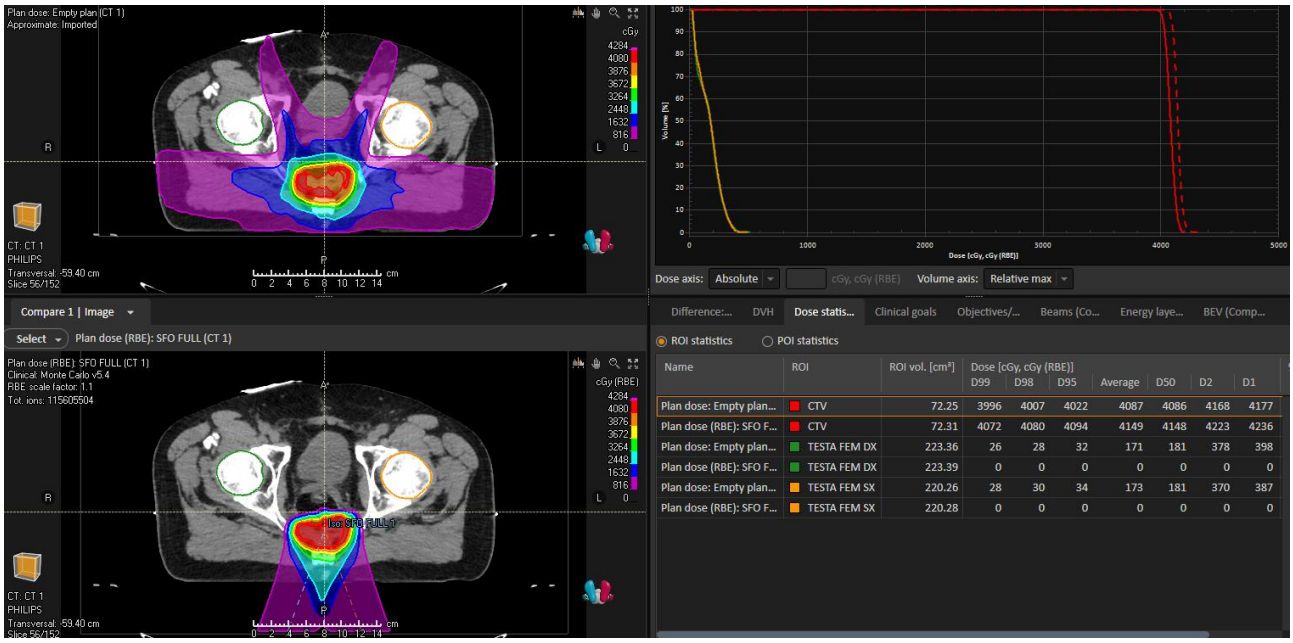
Dosimetrical Comparison Results

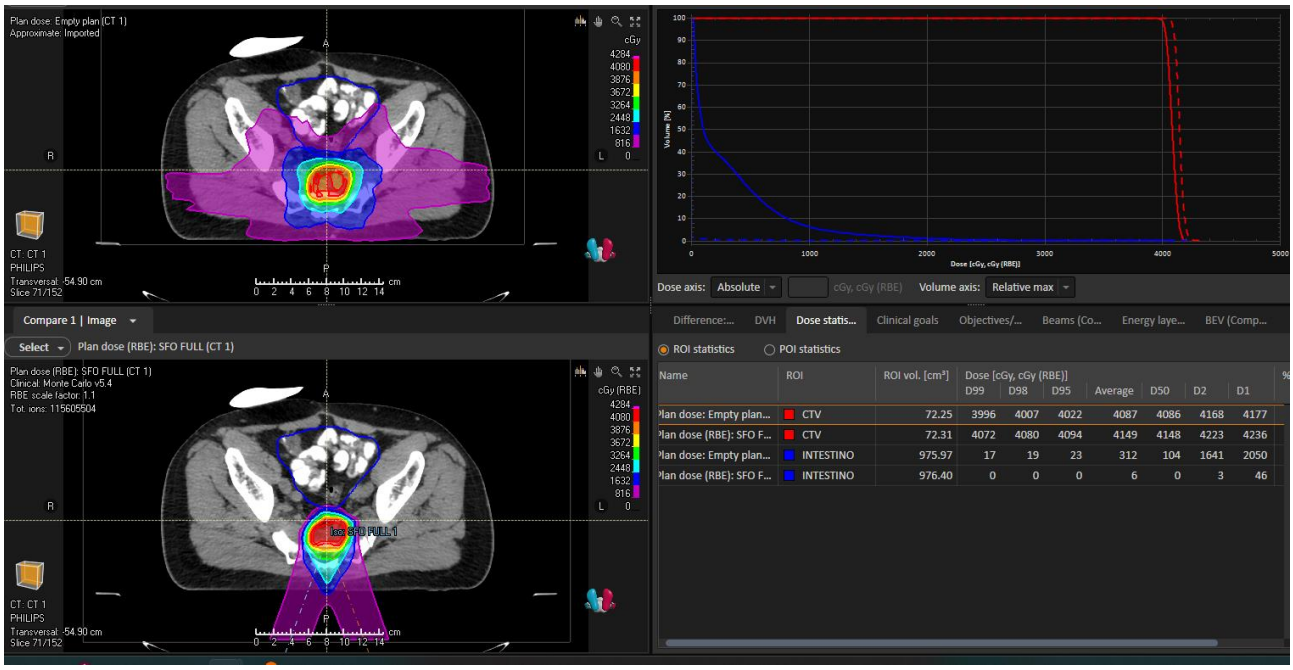
In collaboration with the Radiotherapy Department of Sant'Orsola Malighi Hospital, Bologna, three IMRT anonymized treatment plan of rectal carcinoma reirradiation were replanned with IMPT.
Three cases chosen for the comparison were challenging for IMRT coverage of the target or the respect of OARs constraints.
The same doses prescribed for IMRT treatments were prescribed for IMPT plans.
Clinically relevant dose constraints were selected for comparison between proton and photon plans, in particular: dose received from the 1% of volume (D1) for sacral plexus, bladder, small bowel, femoural head.
First case: presacral lesion nereby intestinal loops and sacral plexus, one level of prescription dose for reirradiation: **40,80 Gy in 34 bday fractions** (**1.2 Gy/fraction)**
In this case reduction of D1 on the sacral plexus and on the small bowel were 6 Gy(%) and 20 Gy (%) respectively (Fig. 4).

Fig. 4 (First case plan comparison)



Name	ROI	ROI vol. [cm³]	Dose [cGy, cGy (RBE)] D99	D98	D95	Average	D50	D2	D1
Plan dose: Empty plan...	CTV	72.25	3996	4007	4022	4087	4086	4168	4177
Plan dose (RBE): SFO F...	CTV	72.31	4072	4080	4094	4149	4148	4223	4236
Plan dose: Empty plan...	Plesso sacrale	30.65	417	480	641	1745	1833	3374	3626
Plan dose (RBE): SFO F...	Plesso sacrale	30.94	0	0	0	375	10	2690	3085

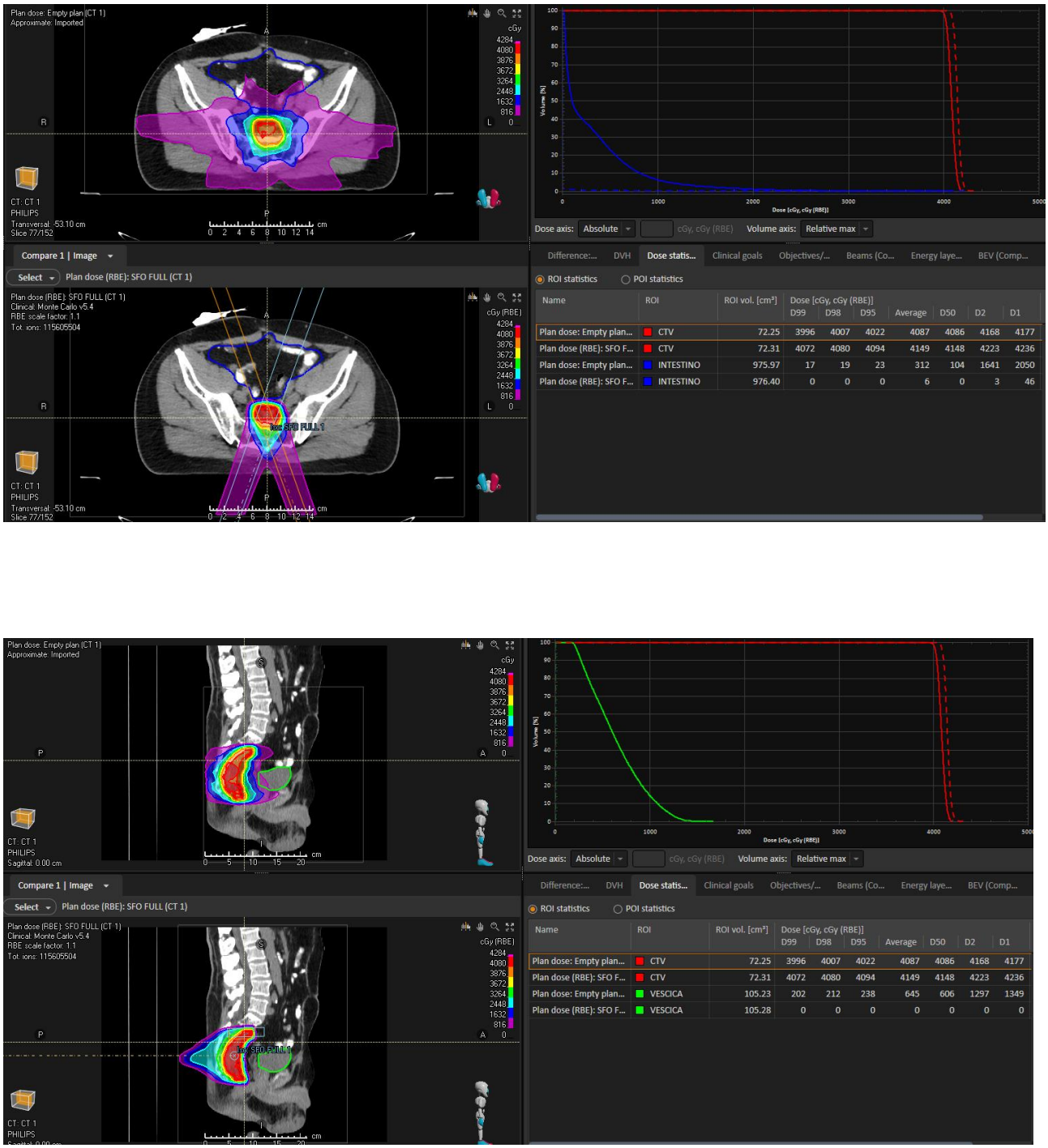




In the ***second case***, presacral lesion, with critical close proximity to small bowell and bladder, two level of prescription dose: **30 Gy in 25 bid fractions (1.2 Gy/fraction) + BOOST 10.8 Gy in 9 bid fractions (1.2 Gy/fraction)**

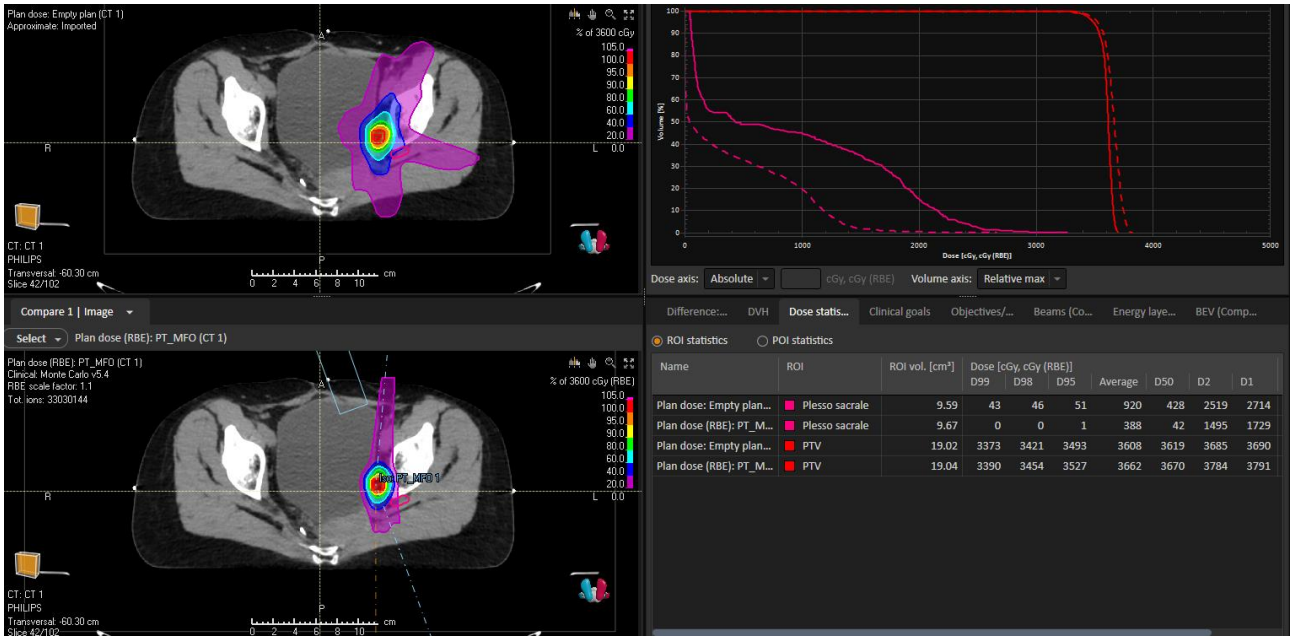
In this case reduction of D1 to the Small Bowel was of 20 Gy (%) and 13 Gy (%) to the bladder (Fig.5).

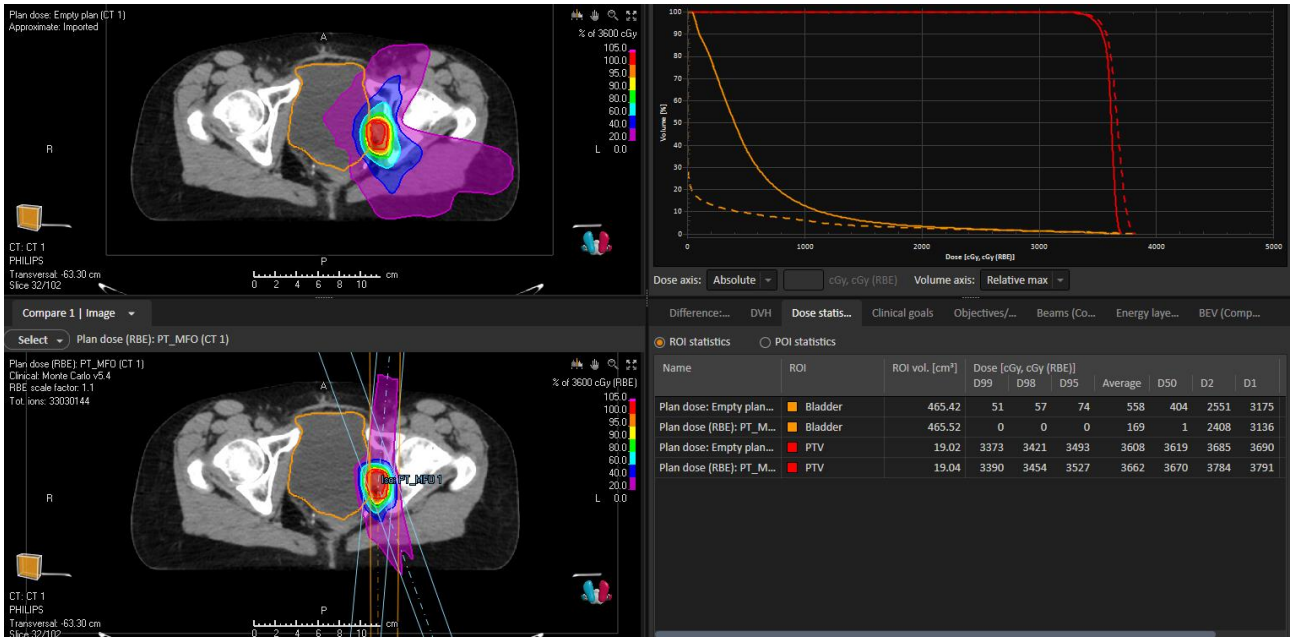
Fig. 5 (Second case plan comparison)

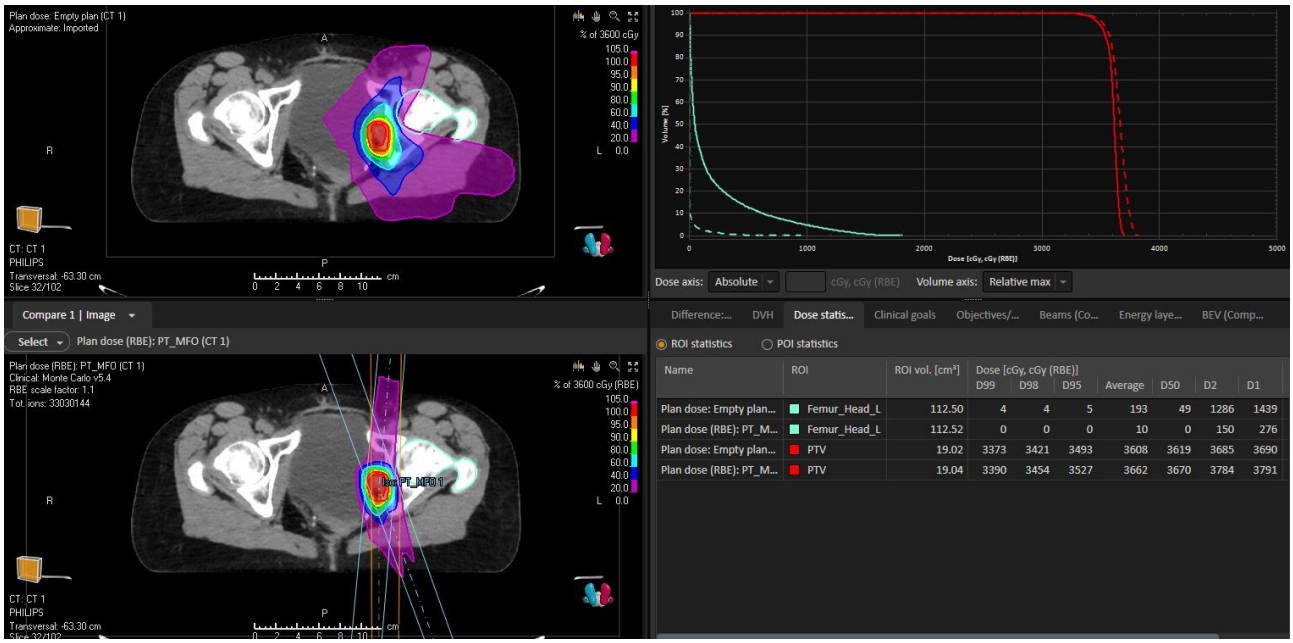


Third case: obturator lymph nodal lesion located close to bladder in the medial edge, to the femoral head and to the sacral plexus posteriorly: **36 Gy in 6 fractions (6 Gy/fractions)**
In this case reduction of D1 obteined with PT were smaller: D1: 10 Gy; 11 Gy and no differences for Sacral Plexus Femural Head and Bladder respectively. (Fig.6).

Fig. 4 (Third case plan comparison)






Plan dose: Empty plan (CT 1)
Approximate: Imported
% of 3600 cGy
105.0
100.0
95.0
90.0
80.0
60.0
40.0
20.0
0.0
R
L
A
P
CT: CT 1
PHILIPS
Transversal: -63.30 cm
Slice 32/102
cm
0 2 4 6 8 10
Volume [%]
Dose [cGy, cGy (RBE)]
Dose axis: Absolute
cGy, cGy (RBE)
Volume axis: Relative max
Compare 1 | Image
Select
Plan dose (RBE): PT_MFO (CT 1)
Plan dose (RBE): PT_MFO (CT 1)
Clinical: Monte Carlo v5.4
RBE scale factor: 1.1
Tot. ions: 33030144
% of 3600 cGy (RBE)
PT_MFO 1
Difference:...
DVH
Dose statis...
Clinical goals
Objectives/...
Beams (Co...
Energy laye...
BEV (Comp...
ROI statistics
POI statistics
Name
ROI
ROI vol. [cm³]
Dose [cGy, cGy (RBE)]
D99
D98
D95
Average
D50
D2
D1
Plan dose: Empty plan... Femur_Head_L 112.50 4 4 5 193 49 1286 1439
Plan dose (RBE): PT_M... Femur_Head_L 112.52 0 0 0 10 0 150 276
Plan dose: Empty plan... PTV 19.02 3373 3421 3493 3608 3619 3685 3690
Plan dose (RBE): PT_M... PTV 19.04 3390 3454 3527 3662 3670 3784 3791

DISCUSSION

Rectal cancer is the eighth worldwide of neoplasia for incidence, with an age standardised rate of 1.73 per 100,000 persons/year.
GLOBOCAN 2020 estimates that there are 0.7 million new cases of rectal cancer, and this number is expected to increase to 1.16 million in 2040. [51]
Neoadjuvant chemoradiation, total mesorectal excision, and adjuvant therapy or TNT have helped to reduce local failure of rectal cancer, but despite this, the incidence of locally recurrent rectal cancer is still 4–8% and usually recurrences occur in the irradiation field field or at its margins, to note that 78% of field recurrences occur in the lower pelvic and presacral regions. [22,52]
The treatment of choice for locally recurrent rectal cancer is surgery with radical margins (R0). In cases where this is not possible, RT with or without chemotherapy is a viable alternative that may lead the patient to radical surgery.
Resection of locally recurrent rectal cancer is difficult due to the altered and diverse anatomy of the organs and critical structures in the pelvis and the presence of fibrosis after the first tretaments: surgery and first course of RT and decreases the chance of an R0 margin. [27,53,54]
Re-irradiation may play a role in increasing the rate of radical (R0) resection or in the definitive treatment of inoperable patients.
The trouble concerning re-irradiation in this group of patients is related both in terms of the received dose of the organs at risk (OARs) and the time elapsed between the two irradiations.
There are not enough studies on dose constraints for OARs, so radiation oncologists do not have clear guidelines on the doses that can be administered to avoid acute and late side effects. [55]
Administering a suboptimal dose to reduce the risk of side effects can result in failure to control the disease or leave patients permanently inoperable. [56,52]
Progress in radiation treatment made in the past years have lead to modern techniques and daily imaging monitoring allow highly conformal treatments to be delivered to the target site while avoiding OARs. Nevertheless, there are few studies on the use of these techniques in rectal cancer recurrence re-irradiation. Previous literature reviews aimed to evaluate the efficacy of re-irradiation and determine the optimal treatment for locally recurrent rectal cancer and concluded that re-irradiation had favorable survival outcomes when combined with surgery and showed good oncologic and palliative efficacy with or without surgery. Unfortunately, most of these studies used 3D techniques. Nowadays, most RT centers have and use advanced technologies, so the literature data based on 3D techniques areno longer reliable for determining the doses that can be used to avoid the side effects of re-reirradiation in this patient population. [41,57]
In addition, radiation therapy is increasingly moving toward the use of new technologies: Carbon ion RT (CIRT), PT, and MR-Linac-guided adaptive RT.
In our serie we demonstrated promising outcomes in PT-treated patients with locally recurrent rectal cancer. The 1-year LC, PFS, and OS rates were 66.7%, 33.3% and 93.3% respectively. At a median Follow Up of 30 months (range: 4-108) local control was 66%; PFS 26,7% and OS 60%

Locally recurrent rectal cancer exhibits very low radio sensitivity. Tanaka et al reported that 3-year OS and LC rates with 3-dimensional conformal radiation therapy were 45.2% and 19.6%. 3. [58]
A phase 2 study of concurrent capecitabine and irinotecan with intensity modulated radiation therapy for recurrent rectal cancer reported 3-year OS and local progression-free survival rates of 36.5% and 33.9%, respectively.14 Based on these reports, chemoradiation therapy (CRT) using the

intensity modulated radiation therapy technique for locally recurrent rectal cancer had insufficient outcomes. [59]
There are a small number of studies on PBT for locally recurrent rectal cancer. In 2012, Hamauchi et al reported PT with 70 Gy (RBE) in 25 fractions for 13 patients with locally recurrent rectal cancer with a median follow-up time of 42 months, showing a 46% LC rate with less severe toxicity. [60]
A recent sistematic review examined studies in which various technique have been used to understand whether they had an impact on oncological outcomes and toxicities in patients treated with re-irradiation for locally recurrent rectal cancer [61]
Six papers reported results in terms of one-year LC. The median value was 89.0% (range 78.0–100.0%). Four papers reported 2-year LC, with a median value of 71.60% (range 52.0–93.7%).
The Median OS was reported in five studies and it ranged between 9.1 and 47.0 months, with a median value of 36.9 months. One-year and two-year OS were reported in six studies with a median value of 90.0 (range 76.8–100%) and 73.0% (range 27.2–93.0%), respectively.
Data regarding PFS were reported in four studies: median 1-year PFS was 65.6% (range 58.0–80.2%), and median 2-year PFS was 39.5% (range 10.7–68.7%). [61]
One year local control and OS were of 76.3% and 87.5% in the historical study by Valentini et al.
The median follow-up was 36 months (range, 9–69 months). Overall 5-year local control, distant metastasis-free survival, and disease-free survival were 38.8%, 42.0%, and 29.2%. [42]
Nowadays only few studies ha reported results about treatment with PT in locally recurrent rectal cancer and only one used PT.
Hiroshima et al reported that 12 patients with locally recurrent rectal cancer were treated with PBT. The 3-year OS, PFS, and LC were 71.3%, 12.1%, and 80.2%, respectively. In their study, 6 of the 12 patients received concurrent S-1 chemotherapy during PT. [62]
While in the Takagawa et al study three and 5-year OS, PFS, and LC were 72.1% and 44.6%, 37.9% and 37.9%, and 55.0% and 47.2%, respectively. The median survival time was 54.4 months. [63]
The 1-year LP, PFS, and OS rates reported by Koroulakis et al in their study of patients treated with PT were 33.7%, 45.0% and 81.8% (95% CI, 67.3%-96.3%), respectively. [64]
Rate of acute grade > 3 toxicity in our study was 6,6%, one patient with GI complication while the most rapresented side effect was G1 fatigue (20%) followed by 2 cases of radiation dermatitis G1 and G2 (13%). All but 1 patient completed the planned course of re-irradiation.
These results are comparable to the rate reported by Valentini et al (5.1%), who accounted for gastrointestinal toxicity too.
The rate of late grade >3 toxicities (G3) was 13.3% and they were related to uretheral stenosis and sacral bone fracture. 53.3% of patients didn't report late side effects and 3 patients had symptoms improvement.
Three patients (20%) developed neuropathy of lumbo-sacral plexopathy determining pain G2.
Comparing these late G3 toxicity with those reported by Valentini et al is difficult because late toxicities were not graded.

Mantello et al in tehir systematic review with evaluating multiple techniques, describe overall G3 acute toxicity rate ranging from 0% to 22.7%. Six papers recorded acute G3 GI toxicity and it ranged from 0% to 13.6%. Acute G3 GU toxicity was reported in six studies ranging from 0% to 5.5%. Five studies registered acute G3 neuropathy and it ranged from 0 to 5.5%. Acute G3 pain and infection were reported in three studies ranging from 0 to 2.6% and 0 to 6.5%, respectively.

Overall, the G3 late toxicity rate ranged from 0% to 37.7%. Late G3 GU toxicity was recorded in five studies, and it ranged from 0% to 13.0%. Three studies registered late G3 neuropathy ranging from 0 to 5.2%, all of this studies utilized Carbon Ion as re-irradiation technique. Late G3 pain and infection were reported in three studies ranging from 0 to 2.6% and 0 to 16.9%, respectively. [61]

Takagawa et al in their study with using PT recorded Grade 4 late gastrointestinal toxic effects in 3 patients: in 2 cases re-irradiation was associated with further local recurrence after initial PT. The remaining patient developed perforation of the ileum 8 months after receiving 72 Gy (RBE) in 30 fractions of PT. Partial resection of the ileum was performed, and the perforated ileum was close to the irradiation field. The patient had a history of bevacizumab use before PT. [63]

In the study of Koroulakis et al, patient treated with PT, grade 3 acute toxicity was experienced in 3 (10.7%) patients, in two cases it was GI toxicity and 1 case patient did not complete RT owing to toxicity.

The 1-year rate of late grade >3 toxicities was 13.3%. Six late G3 toxicity occurred in 4 separate patients, with no evidence of tumor recurrence at toxicity onset, patients developed fistula in multiple site of irradiation (enterocutaneous, rectovaginal, colovaginal) in one case the patient had a history of significant late toxicity from prior irradiation and in another case the patient was receiving bevacizumab systemic therapy at the time of the fistula diagnosis. [64]

Regarding the utility of 18-F-FDG-PET/TC Takagawa et al reported that in the UVA, the SUVmax of 18F-FDG-PET/CT before PT (cutoff value, 10) showed significant difference for OS (hazard ratio [HR], 4.14; 95% confidence interval [CI], 1.12-15.34; P = .03), PFS (HR, 3.37; 95% CI, 1.14-9.94; P = .027), and LC (HR, 4.91; 95% CI, 1.38-17.49; P = .012). [63]

In our study neither SUVmax of 18F-FDG-PET/CT before PT of after PT had significant impact on outcome.

Previous studies demonstrated that increased NLR was associated with decreased overall survival in various cancer types. Furthermore, owing to the exquisite radiosensitivity of circulating lymphocytes, which is required for the anti-tumoral immune response, RT is often accompanied by lymphopenia, which can subsequently infuence not only NLR but also cancer recurrence and survival. [65-67]

RT and chemotherapy are the leading causes of high NLR in patients with cancer. Radiation-induced lymphopenia is a direct consequence of the irradiation of blood passing through the irradiated body area during RT. The frequently increased NLR in patients undergoing helical tomotherapy can be explained by the exposure of the bone marrow to low dose radiation dispersed outside the target area. [68]

In the study of Yang et al, NLR, was signifcantly associated with an increased risk of development of distant metastasis.

In the era of radiation-induced immunomodulation, preserving the immune status of patients is crucial for improving outcomes. [69]

Therefore, the idea of optimization of active bone marrow sparing-IMRT, which was tested and proven in a gynecologic malignancy, is worth considering in PT as well.

In the study of Yang et al the post-RT NLR cut-of value which demonstrated the largest difference of DMFS was 4.0. A total of 555 patients (41.0%) had a post-RT NLR≥4 and were consequently classifed into the high NLR group.

In our study all patients had post-RT NLR < 4, that could confirm that a decrease in the amount of irradiated volumes and consequently in the amount of irradiated bone marrow can be traduced in a better preservation in circulating lymphocytes.
Moreover our results demonstrated that neither Neutrophil/Lymphocytes ratio pre PT, Neutrophil/Lymphocytes ratio post PT or Neutrophil/Lymphocytes ratio post PT increase had a singnificative impact on the outcomes.
Dosimetric comparison between IMRT and PT plans demonstrated evident superiority in anatomical situation in which the target is located in sacral or pre-sacral region, that allow in fact significant better sparing of bowel and bladder, depending on the volume of irradiation sometimes even of lumbo-sacral plexus. While irradiation of target lateral to OARs tring to be spared doesn't add any kind of advantage in terms of OARs sparing.
This study had some limitations. First, the number of patients was very small, and the study design was retrospective.
Second, the assessment of outcome and acute and late toxicities was dependent on assessments that were not standardized, with imaging ranging from pelvic magnetic resonance to positron emission tomography/CT to CT. Maturation and expansion of these data will better establish disease and toxicity outcomes in these patients. Longer follow-up and further accrual may help establish a dose-response relationship with respect to disease outcomes as well as the development of late toxicity

CONCLUSIONS

Re-irradiation using PT for locally recurrent rectal cancer patients with prior pelvic irradiation was safe and feasible

The low acute and acceptable late toxicity rates, only one treatment interruption, reported here thus far support PT as an option for this high-risk patient population in particular for patients with recurrent disease loated in the sacral or presacral region. Moreover it could be interesting to compare dosimetrical bone marrow sparing with PT vs IMRT in prospective setting and if it can be related to lymphocyte count reduction and outcome.

Further follow-up and prospective studies, will help further clarify disease outcomes and toxicity profiles.

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