THUNDER 2

THeragnostic Utilities for Neoplastic DisEases of the Rectum by MRI guided radiotherapy

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The study will be financed by ViewRay. the sponsor has positively evaluated the design of the study and will finance it with 36 months funding. The center will inform the sponsor of the forward results with a total report

Abstract

Neoadjuvant chemoradiation therapy (nCRT) is the standard treatment modality in locally advanced rectal cancer (LARC) and patients achieving complete response to treatment (CR) usually have a better prognosis in terms of local control (LC), metastases-free survival (MFS) and overall survival (OS).

Since response to radiotherapy is dose dependent in rectal cancer, dose escalation may lead to higher complete response rates. The possibility to predict patients who will achieve CR before surgery or during nCRT is of crucial importance. Recently, an early tumour regression index (ERI_{TCP}) was introduced, to predict pathological CR (pCR) after nCRT in LARC patients. In particular, the authors found that the patients with ERI_{TCP} <13.1 show a strong response during therapy and have a lower probability to experience distant relapses.

Aim of this clinical trial is to investigate the impact of dose escalation in rectal cancer, identifying the poor responder cases using the ERI index during the course of radiotherapy and increasing the prescribed dose in these patients. Adopting this boosting protocol, an increase of 10% of CR (clinical and pathological) rate is expected.

For patients enrolled in the trial, chemoradiotherapy (CRT) will be administered using the MRI guided Radiotherapy (MRgRT) machine available in our institution.

The initial radiotherapy treatment will consist in delivering 55 Gy in 25 fractions on Gross Tumor Volume (GTV) plus the corresponding mesorectum of 45Gy in 25 fractions on the whole pelvis. Chemotherapy with 5-fluoracil (5-FU) or oral capecitabine will be administered continuously.

A 0.35 Tesla Magnetic Resonance image will be acquired at simulation and every day during MRgRT. At fraction 10, ERI will be calculated.

If ERI will be inferior than 13.1 the patient will continue the original treatment. Patients with complete clinical response will go through wait and see approach.

If ERI will be higher than 13.1 the treatment plan will be reoptimized considering the residual tumor at fraction 10 as new therapy volume, where the dose will be intensified to reach 60.1 Gy.

After the end of CRT, the clinical response will be evaluated 8-10 weeks using high tesla MR and CT images or FDG-PET-CT image 8-10 weeks after the end of nCRT. Surgery will be performed 12-16 weeks after the end of the CRT in case of partial or stable or progression disease, while in case of major or complete clinical response at restaging imaging, a Watch and Wait (W&W) or local excision (LE) approach should be followed. Late toxicity and quality of life (QoL) will be scored at first follow-up (FUP) and at 1 and 2 years of FUP according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 scale, functional scales and QoL questionnaires (LARS and SEXUAL questionnaires, at the start of treatment, after surgery and at 1 and 2 years of FUP), respectively.

The number of cases to be enrolled will be 63: all the patients will be treated at Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome. All the cases will be discussed in weekly multidisciplinary tumor board to share the best therapeutic options, both at the diagnosis and at presurgical restaging.

The statistical analysis will be carried out at KBO Labs in Gemelli.

The primary endpoints will be

- Complete response considered as: ypT0N0 in case of TME, ypT0ycN0 in case of LE, ycT0N0 in case of WW
- Prospective validation of delta radiomics MR-guide Radiotherapy model
- The secondary endpoints will be:
- 3 years LC, MFS, Disease Free Survival (DFS), OS
- R0 resection rate
- TRG1, TRG 2, NAR score
- Sphincter preservation rate
- Organ preservation rate
- Rectal and sexual functions

Introduction

Background / Rationale

Nowadays neoadjuvant chemoradiation therapy (nCRT) is the standard treatment modality in locally advanced rectal cancer (LARC). Regardless of the initial disease stage, approximately 11–42% of these patients achieve a pathological complete response (pCR) after long-course radiochemotherapy (RCT)[1, 2].

Different studies have shown that patients achieving pCR usually have a better prognosis in terms of local control (LC), metastases-free survival (MFS) and overall survival (OS). Conservative surgical approaches have recently been investigated in patients showing clinical complete response (cCR) after nCRT: both local excision (LE) and "Watch and Wait" (W&W) approaches represent to date feasible options in order to reduce morbidities and toxicities related to unnecessary Total Mesorectal Excision (TME) procedures [3, 4].

Since response to radiotherapy is dose dependent in rectal cancer, dose escalation may lead to higher complete response rates. Burbach et al. meta-analyses showed that dose escalation above 60 Gy for LARC results in high pCR-rates and acceptable toxicity.

In the framework of a fully personalized medicine, the possibility to predict the patients who will achieve complete response (CR) before surgery or even during nCRT is of crucial importance.

Several prediction models have been developed to predict CR in LARC, providing clinicians with valuable decisional support systems (DSS) for multidisciplinary oncological care tailoring, so that patients "predicted as not responding" will take advantage of intensified treatments, while those "predicted as responding" will undergo a therapeutic approach more oriented to organ preservation [5].

The Van Stiphout et al. model predicted pCR in LARC based on clinical features (cT-stage, cN-stage) and early sequential (18)F-FDG PETCT imaging (response index of SUVmean and maximal tumour diameter during treatment) [6].

An increasing number of studies focused on the possibility to predict pCR analysing Magnetic Resonance Imaging (MRI), as this modality is generally the gold standard diagnostic imaging technique for rectal cancer

Some MR based models revealed predictive value of the images acquired before or during CRT, so offering the clinical opportunity of modulating the CRT treatment.

In particular, Boldrini et al. demonstrated the variation of radiomic features during therapy (known as delta radiomic approach)correlated delta radiomics data of low-tesla hybrid MR images with cCR in LARC patients and undergoing nCRT: the most predictive feature ratios in cCR prediction were the L_least and glnu ones, calculated at the second week of treatment (22 Gy) with a p value=0.001 [7].

In our centre the standard treatment schedule for LARC consists of nCRT, with a total radiotherapy dose of 55 Gy in fractions of 2.2 Gy on Gross Tumor Volume (GTV) plus the corresponding mesorectum and 45 Gy in 25 fractions of 1.8 Gy with a Simultaneous Integrated Boost (SIB), in combination with capecitabine +/- oxaliplatin in relation to clinical stage. [8]

Moreover, a work recently published by Fiorino et al. introduced an early tumor regression index (ERI_{TCP}) to predict pCR after nCRT in LARC patients. [9] This parameter was defined as follows:

$$ERI = -ln\left[\left(1-\left(\frac{V_{mid}}{V_{pre}}\right)\right)^{V_{pre}}\right]$$

Where V_{pre} is the GTV volume measured at the time of simulation and V_{mid} is the volume at the second week of treatment. This parameter was considered a potential biomarker in predicting long-term disease-free survival. The first experience was performed on 1.5 Tesla MRI images and our internal experience showed the validity of this parameter also on 0.35 T MRI images, reporting an area under curve of 0.93 on a total of 52 cases.

In particular, the authors found that patients with an ERI_{TCP} lower than 13.1 show a strong response during therapy and have a lower probability to experience distant relapses, because responding tumours could result more sensitive to therapy and/or less aggressive and, consequently, less subject to metastatic spread.

On the other hand, patients with ERI_{TCP} >13.1 values could benefit from more aggressive loco-regional treatment, for instance through dose escalation to the residual tumour, by inducing a strong local immune reaction helping in reducing the risk of (or postponing) any metastatic spread

Applying the ERI_{TCP} index we want to increase dose at 60 Gy in a SIB3 schedule on the primary tumor (GTV) contoured at the second week of treatment + 3 mm of expansion by MRI guided radiation therapy (MRgRT) in patients with a low prediction of pCR, treated with an MRI-LINAC hybrid machine.

The current predictive model based on ERI_{TCP} will be improved with the integration of radiomics feature extracted from MRI images acquired in simulation and during the different treatment fractions. The feasibility of a delta radiomics approach will be also evaluated and the features proposed by Boldrini et al [7] will be used in case where ERI_{TCP} show limited accuracy in prediction ($12.8 \leq ERI_{TCP} \leq 13.2$)[7].

Aims

- Increasing of 10% of CR response rate in not responder rectal cancer patients treated with MRI-LINAC hybrid machine
- Evaluating the feasibility of delta radiomic-based predictive models in MR-guided Radiotherapy

Experimental Design

This trial will enroll patients with locally advanced rectal cancer with the aim to evaluate the importance of increasing the dose to increase the CR rate in rectal cancer.

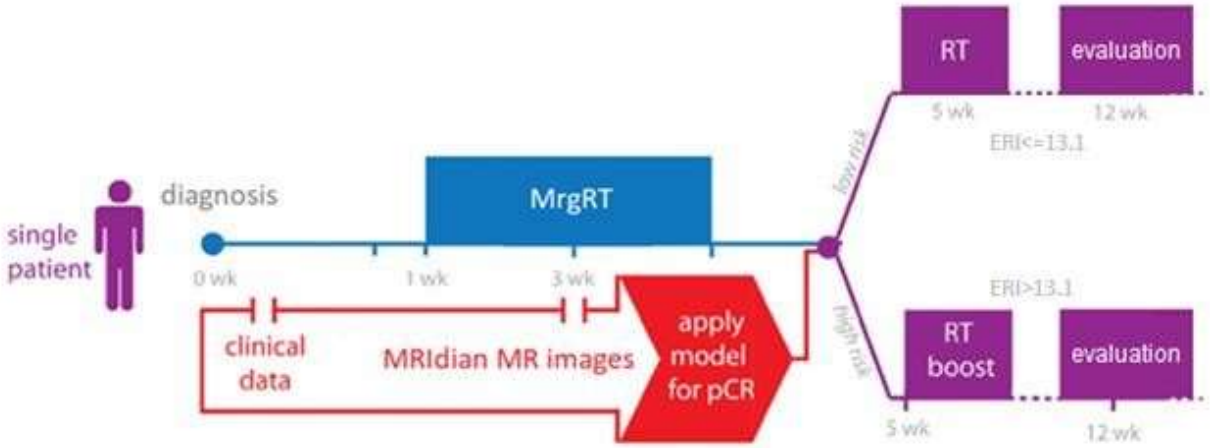
The initial radiotherapy treatment will consist in delivering 55 Gy in 25 fractions on GTV plus the corresponding mesorectum of 45Gy in 25 fractions on the whole pelvis. Chemotherapy with 5-fluoracil (5-FU) or oral capecitabine will be administered continuously.

A 0.35 Tesla Magnetic resonance image will be acquired at simulation and every day during MRgRT. At fraction 10, ERI will be calculated.

If ERI will be inferior than 13.1 the patient will continue the original treatment. Patients with complete clinical response could undergo TME, LE or WW according to Multidisciplinary Team (MDT) decision.

If ERI will be higher than 13.1 the treatment plan will be reoptimized considering the residual tumor at fraction 10 as new therapy volume, where the dose will be intensified to reach 60.1 Gy.

The scheme of the clinical protocol is depicted in figure below:



The clinical response will be evaluated with MRI pelvis repeated 8-10 weeks after the end of CRT. Surgery, which will consist of total (or partial) mesorectal excision, will be performed 10-12 weeks after the end of the CRT.
In case of cCR a W&W or LE approach could be followed, according to MDT decision. Postoperative complications, late toxicity, rectal and sexual functions will be reported.Postoperative chemotherapy will be defined on to clinical and pathologic risk factors, according to MDT decision.

Methods

Inclusion criteria

The study will be carried out only at the University Hospital Fondazione Policlinico Universitario A. Gemelli IRCCS. All patients will be treated in Gemelli from the date of approval of the protocol by the ethics committee. The recruitment period will be one year.
All the cases will be discussed in weekly multidisciplinary tumor board, consisted of core group of surgeons, radiation oncologists, medical oncologists, radiologists, pathologists to share the best therapeutic options, both at the diagnosis and at presurgical restaging. TNM 7th edition will be used for staging.
Before start of the treatment all the enrolled patients have to achieve a MRI pelvis and a CT, PET-CT should be considered discretionary (= baseline imaging examinations).
Patients enrolled have to satisfy the following criteria:

- Histological proven adenocarcinoma of the rectum cT2-3, N0-2 or cT4 for anal sphincter involvement N0-2a, M0
- No prior radiotherapy in pelvic region;
- Tumour located between 0 and 15 cm above the anal verge;
- Not mesorectal fascia involvement for tumor
- No extramesorectal nodes involvement
- No extramural venous invasion (EMVI)
- No rectal mucinous adenocarcinoma histology
- No contra-indications for MRI
- ECOG 0-1
- Age over 18 years

- Adequate hematological function:
    - granulocyte count > 1500/microl
    - Hemoglobin level > 10 g/dl
    - Platelet count > 100000/microl
    - ALT/AST: 7-45 UI/L
- No other malignancies in the previous history (except skin and initial cervical cancer);
- Absence of important comorbidities: severe cardiac or coagulative disease, moderate or severe restrictive/obstructive lung deficit, severe cognitive impairment, moderate and severe renal and hepatic impairment.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial;
- Absence of pregnancy or lactating female patients;
- Written informed consent

Clinical workflow

Patients who meet the enrollment criteria will perform pre-operative CRT treatment that will take 5 weeks.

The total RT dose on the pelvis (CTV elective = CTV1) will be 45 Gy in 25 fractions of 1.8 Gy. The total RT dose on GTV plus the corresponding mesorectum (CTV primary = CTV2) will be 55 Gy in 25 fractions of 2.2 Gy, with a simultaneous integrated boost (SIB). [8]

The primary tumour (boost volume) (10^{th} fraction recountoured GTV primary + 3 mm margin = CTV3) will be 60.1 Gy in 15 fractions of 2.54 Gy, with SIB, starting from the 2nd week according to ERI_{TCP} model. RT will only be administered 5 days per week. Chemotherapy with 5-FU or oral capecitabine is administered continuously (no interruption during the weekend). The dose of 5-FU is 225 mg/mq/day in continuous infusion. The dose of capecitabine is 1650 mg/m2/day chronomodulated.

The CTV2 will be contoured on the MRI acquired at the beginning of treatment and on MRI at fraction 10 and the ERI_{TCP} will be calculated.

If ERI_{TCP} will be inferior than 13.1 the patient will continue the original treatment with a total dose of 55 Gy on CTV2.

If ERI_{TCP} will be higher than 13.1 the treatment plan will be reoptimized considering a further therapy volume. The volume boost will be delineated on the MRI acquired at the fraction 10 and the dose will be intensified to obtain a total dose of 60.1 Gy.

The clinical response will be evaluated with MRI pelvis and CT or FDG-PET-CT repeated 8-10 weeks after the end of nCRT. Surgery, which will consist of total (or partial) mesorectal excision, will be performed 10-12 weeks after the end of the CRT in case of partial or stable or progression disease. In case of major or complete clinical response at restaging imaging, endoscopic examination should be performed. In case of cCR a W&W or LE approach could be followed, according to MDT decision.

Radiotherapy setting

Patients will be treated with an MRI-LINAC hybrid machine. Patients will be immobilized in the supine position, using the Fluxboard device (FluxboardTM, MacroMedics, The Netherlands) in an appropriate, fully personalized and comfortable configuration.

A first acquisition of a 25-seconds (sec.) sequence will be performed as alignment image and used for the definition of the irradiation field. A second 175 sec. sequence with higher morphological definition will be then acquired for planning purposes and fused with a standard simulation CT, since the MRI does not have relative electron density information needed for plan calculation.

The delineation of the clinical target volume of the pelvis (CTV1) will be performed on the 0.35T MRI. The CTV1, which includes the primary rectal tumour, the mesorectal subsite, the posterior pelvic subsite and the lateral lymph nodes, will be delineated manually according to the guidelines proposed by Valentini et al. Planning target volume (PTV) 1 is the CTV1 + 0.5 cm in all directions. [10]

The CTV2 includes the primary rectal tumour plus corresponding mesorectum. PTV2 is the CTV2 + 0.5cm in all directions. In case of boost intensification, the boost volume (CTV3) will be defined as the GTV delineated on MRI of week 2 (22 Gy) and a margin of 0.3 cm will be added. No margin to PTV will be added (PTV3 = CTV3).

The normal tissue volumes (Organs at Risk – OaRs) to be contoured are bladder, small bowel, anal canal, uterus, vagina, penile bulb, prostate and seminal vescicles, femoral heads and iliac bones. The treatment plan used for each patient will be based on analysis of the volumetric dose. An "inverse planning" using computerized optimization will be used (Intensity Modulated Radiation Therapy – IMRT). The treatment aim will be the delivery of radiation to the PTV and the exclusion of non-involved tissue as much as feasible.

The prescription dose is normalized to target mean according to ICRU 83 [11].

The reported doses for each PTV shall include the prescription dose as well as the maximum point dose, % target volume receiving >105% and >110% of its prescribed dose and the % target volume receiving $\geq$ 95 % of the prescribed dose, and the mean dose to the PTV's. Doses to the organs at risk will also be recorded.

Daily the patient will be positioned on the isocenter, visualized by the skin marks.

To improve the reproducibility, an internal protocol will be used to achieve stable conditions of bladder filling: patients are instructed to drink 500 cc of water 30 min before simulation and before each treatment session.

A cine-MRI gating protocol will be performed on PTV2 or PTV3, setting a 5% region of interest (ROI) value in a 3 mm boundary from the CTV2 or CTV3, ensuring therefore that the target volume is always in the proper position. Delay time value is set at 0 sec, so that the movement of the ROI outside the boundary would immediately trigger the beam off.

Patients with low prediction of cCR ($ERI_{TCP} > 13.1$) will receive an intensification dose of RT starting at week 3, with a simultaneous integrated boost (SIB):

- CTV1 = pelvic nodes, receives 45 Gy in 25 fractions of 1.8 Gy;
- CTV2 = GTV + corresponding mesorectum, receives 55 Gy in 25 fractions of 2.2Gy;
- CTV3= GTV + 3mm margin, receives 60.1 Gy in 15 fractions of 2.54 Gy.

In case of high prediction of cCR ($ERI_{TCP} < 13.1$) patients receive the standard dose:

- CTV1 = pelvic nodes, receives 45 Gy in 25 fractions of 1.8 Gy;

CTV2 = GTV + corresponding mesorectum, receives 55 Gy in 25 fractions of 2.2Gy.

Evaluation procedures

The following evaluation procedures will be adopted at the different phases of the trial:

Before start of CRT

a) Complete detailed medical history & physical examination including digital rectal examination

b) Blood sample to check platelets, neutrophils and hemoglobin + CEA
c) Colonoscopy
d) Tumour biopsy proving adenocarcinoma of the rectum
e) MRI pelvis, total colonoscopy, total body CT or PET-CT
f) Filling in the QoL questionnaires

During CRT

The patients should attend a weekly visit to the treating physician who will perform:

a) An interval history and physical examination with digital rectal examination (DRE)
b) Blood sample to check platelets, neutrophils and hemoglobin
c) Evaluation of the acute toxicities: diarrhea, proctitis, pelvic pain, cystitis, skin toxicity. Scoring will be performed according to the CTCAE (Common Terminology Criteria for Adverse Events) vs. 4.0

Between end of CRT and surgery

The patients should attend a 6-weekly visit to the treating physician who will perform:

a) An interval history and physical examination with digital rectal examination
b) Evaluation of the following acute toxicities: diarrhea, proctitis, pelvic pain, cystitis, skin toxicity. Scoring will be performed according to the CTCAE vs. 4.0
c) MRI pelvis will be performed at 8-10 weeks from the end of CRT
d) In case of clinical complete or near-complete response a rectoscopy must be performed

Complete clinical response will be defined by the presence of all these criteria, independently reviewed by the multidisciplinary tumor board members:

A. Complete absence of palpable masses at DRE
B. Restaging MRI findings:
- ✓ No lymph nodes detected or lymph nodes with short axis <5 mm;
- ✓ No primary tumor residual at morphological and diffusion weighted imaging (DWI) series with complete integrity of rectal wall layers.
- ✓ Hypointense parietal thickening in T2 sequences without evidence of hyperintense residual lesions in DWI sequences or hypointense lesions in apparent diffusion coefficient (ADC) map.

C. No detection of residual lesions or the presence of a fat scar at endoscopic examination.

Follow-up after treatment

In case of WW or LE, the patients should attend a 3-monthly visit (until 2 years) to the treating physician who will perform:

a) History and physical examination including DRE
b) Blood sample to control platelets, neutrophils and hemoglobin + CEA
c) Rectoscopy
d) Colonoscopy until 1 year, if negative after 3 years
e) MRI every 6 months
f) Total body CT every year

g) Evaluation of the following late toxicities: incontinence, diarrhea, pelvic pain, sexual dysfunction. Scoring will be performed according to the CTCAE vs. 4.0

h) Filling in the QoL questionnaires one year after the end of the treatments

Month	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood test + CEA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Rectoscopy	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pelvis MRI		**X**		**X**		**X**		**X**		**X**		**X**		**X**
Thorax-abdomen CT-scan				**X**				**X**		**X**		**X**		**X**
Colonoscopy				**X**								**(X)**		

In case of TME surgery, the patients should attend a 3-monthly visit (until 1 years), then a 6-monthly visit to the treating physician who will perform:

a) History and physical examination including DRE

b) Blood sample to control platelets, neutrophils and hemoglobin + CEA

c) Colonoscopy until 1 year, if negative after 3 years

d) Total body CT every year

e) Evaluation of the following late toxicities: incontinence, diarrhea, pelvic pain, sexual dysfunction. Scoring will be performed according to the CTCAE vs. 4.0

f) Filling in the QoL questionnaires after surgery and one year after the end of the treatments

Month	1.5	3	6	9	12	18	24	30	36	42	48	54	60
Physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood test + CEA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Colonoscopy					**X**				**X**				**X**
Thorax- abdomen CT-scan		**X**		**X**		**X**		**X**		**X**		**X**	
Full abdomen US			**X**		**X**		**X**		**X**		**X**		**X**
Surgical piece histology	**X**												

End-points

For the clinical trial the following primary and secondary and points will be considered

Primary

- Complete response considered as: ypT0N0 in case of TME, ypT0ycN0 in case of LE, ycT0N0 in case of WW
- Prospective validation of delta radiomics MR-guide Radiotherapy model

Secondary

- 3 years LC, MFS, DFS, OS
- R0 resection rate
- TRG1, TRG 2, NAR score
- Sphincter preservation rate
- Organ preservation rate
- Rectal and sexual functions

Sample size determination

According to our internal validation of ERI_{TCP} on MRIdian images based on 43 patients, for patients where ERI is higher than 13,1 the probability to obtain pCR is 3%, having the validation of the test a specificity equal to 97%. Based on the results of our study, out of 36 patients who had an ERI greater than 13, only 1 went to pCR (1/36 = 3%)

The objective of the trial is to ensure that with dose intensification, the percentage of pCR among patients with ERI greater than 13 passes from 3% to 13%.

Using a 95% confidence level (i.e. the possibility that the trial goes on and we get this improvement in patients not because we have increased the dose but for pure ass is 5% (alpha = 0.05) and wanting to set up a trial that has a test power of 80% (that is, having the ability to detect an 80% difference when this difference really exists) the number of patients to enrol who will have an ERI greater than 13 is 42 [12].

Considering that about usually the 84% of patients investigated does not show pCR, the total number of patients to be enrolled for the clinical protocol is 42: 0.84 = 50.

With p0 = 3%, p1 = 13%, using a confidence level of 95% and a power of 80% gives a trial size of 42 with a cut-off of at least 4 patients recovered to accept that a phase III trial should be undertaken [13].

Considering a drop-out rate of 20%, the total number of patients to be enrolled is equal to 63.

Data Analysis

Image and data analysis will be carried out at KBO Labs in Rome. MR images and contours will then be exported to MODDICOM and radiomic features will be analyzed in terms of absolute values and of delta ones (calculated as the ratio between the simulation value and the single fractions ones). First order histogram, morphological, textural and fractal features will be firstly analyzed. The methodology proposed in Boldrini et al. will be applied [7].

The total number of features will be analyzed respect to the outcomes in order to detect the most significant ones using AUC and Mann-Whitney test.

Tumour clinical (cT, cN) and geometrical features (volume, surface, volume/surface ratio) will be finally added to setup a multivariate logistic model (based on a generalized linear model) and predict clinical and pCR.
Model performance will be evaluated by ROC analysis and internal bootstrapping for detecting calibration errors (TRIPOD classification 1b) [14].
Clinical patients data will be prospectively collected using BOA. All patient's data will be redirected and integrated in large data warehouse of property of Fondazione Policlinico Universitario Agostino Gemelli.

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