

Protocol

Effects of irradiation doses <10 Gy and irradiated bone volume on the change in blood counts during and after pelvic irradiation

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ABSTRACT

Background: Bone marrow is one of the organs at risk of complications during irradiation due to its radiosensitivity. Hematopoietic toxicity remains one of the main toxicities during irradiation of pelvis. Modern radiotherapy techniques, such as intensity modulation and three-dimensional conformal radiotherapy, allow for better dose compliance in target volumes while optimally sparing organs at risk. There is a lack of prospective studies and comparative trials specifying the dose constraints according to the presence or absence of chemotherapy and correlating with the patient's bone marrow potential.

Methods: This monocentric and prospective study conducted by the Strasbourg Europe Cancerology Institute aims to evaluate the hematological toxicity in patients treated with pelvic irradiation for prostate, rectum, anal canal, endometrium, or cervix cancer. One hundred patients will be included. The primary objective is to quantify the relationship between acute hematological toxicity and delivered doses and irradiated volumes in pelvic bone marrow for pelvic cancers. The prescribed dose to the pelvis depends on the tumor location, from 25 Gy in 5 fractions for rectal cancer to 78 Gy in 39 fractions for low-risk prostate cancer. Hematological toxicity will be measured by weekly blood count during radiotherapy and at one month and three months after the end of radiotherapy.

Conclusions: The aim of this study is to improve and optimize radiotherapy if a dose limit or volume constraint is imposed by the results of the study. To our knowledge, this is the first study including several types of pelvic cancers and involving patients treated exclusively with radiotherapy, chemoradiotherapy or radiohormonotherapy.

Trial Registration: Trial registration number is NCT04626466.

Keywords: Bone marrow, Hematologic toxicity, Pelvic irradiation, Radiotherapy, IMRT

INTRODUCTION

Irradiation of the pelvic lymph node areas is required for the management of many cancers, including prostate, rectum, anal, endometrium and cervix cancer. Bone marrow is one of the organs at risk of complications during irradiation with external radiotherapy, regardless of the technique used, especially when combined with concomitant or sequential chemotherapy. The addition of intensity modulation (IMRT) to 3D conformal radiation

therapy (3D-RT) has resulted in better dose conformality in target volumes while optimally sparing organs at risk, including bone marrow.¹

Despite these technical and dosimetric advances, hematopoietic toxicity remains one of the main toxicities during irradiation of pelvic lymph node areas, especially when concomitant chemotherapy is used, the volume of bone marrow irradiated is large, and the dose delivered to the bone marrow is high.²⁻⁸

Thirty to eighty percent of patients who have received chemoradiotherapy develop one or more acute hematological toxicities during pelvic irradiation. These toxicities may compromise patient prognosis if chemotherapy must be reduced, interrupted or stopped. These complications may also result in subsequent hospitalizations due to the infectious complications to which patients are exposed. Many improvements in bone marrow protection have been achieved since the advent of IMRT. Functional or metabolic imaging has made it possible to more precisely define the areas of active bone marrow to be preferentially protected. To date, the French standard RECORAD agrees that bone marrow contouring is performed on bone structures during dosimetric scanning, while the dosimetric constraints only concern the femoral heads and iliac bone.⁹ There is a lack of prospective studies and comparative trials to customize the constraints according to the presence or absence of chemotherapy and to correlate this to the patient's bone marrow potential. Kuntz et al tend to show the need to use other bone structures, such as the lumbosacral spine, ischia, pubis or active bone marrow; however, the lack of prospective studies on this topic has limited these practices in routine clinical practice.¹⁰

The aim of our study is to quantify the relationship between hematological toxicity and the radiation dose received by bone marrow.

METHODS

Recruitment and study design

This interventional, nonrandomized, monocentric, descriptive, and prospective pilot study was conducted by the University Radiotherapy Department of the Strasbourg-Europe Cancerology Institute (ICANS). All eligible patients were prescreened and consulted in the radiotherapy department. During this consultation, explanations were given about the treatment purpose, goals of the study, implications, design, aims, requirements, and timeline. According to the department protocols, the treated volumes, the delivered dose, and the constraints on organs at risk were the same regardless of whether the patients participated in the study.⁹

Figure 1 shows the different stages of the clinical trial. Participants underwent weekly blood check-ups throughout the duration of radiotherapy (4 to 8 weeks), as well as at 1 month and 3 months after the end of radiotherapy, to measure hematological toxicity according to CTCAEv5.0. These tests include a blood count and an assessment of kidney function.

Inclusion criteria

For inclusion in the study, patients must be affiliated with national or local social security and must meet all the following criteria: age: ≥ 18 years old and < 80 years old; World Health Organization (WHO) scale 0 to 2;

histological confirmation- prostate cancer, cervical cancer, endometrial cancer, cancer of the middle or lower rectum, and cancer of the anal canal; biological constants at the inclusion should be: hemoglobin > 10 g/dl, leukocytes $4.0-11.0 \times 10^9/l$, neutrophils $1.5-7.7 \times 10^9/l$, and platelets $150-400 \times 10^9/l$; and the subject must give free and informed consent and signed the consent form.

Exclusion criteria

Patients with the following criteria cannot be included in the trial: history of hemopathy, leukopathy, or disease of the immune system; biological constants at inclusion- hemoglobin < 10 g/dl or > 18 g/dl (males) and > 16 g/dl (females), leukocytes < 4.0 or $> 11.0 \times 10^9/l$, neutrophils < 1.5 or $> 7.7 \times 10^9/l$, platelets < 150 or $> 400 \times 10^9/l$; history of radiotherapy or chemotherapy; patients with metastatic cancer; sarcomatous histology; patients under legal protection, guardianship, or curatorship; and pregnant or breastfeeding women.

Objective of the study and evaluation criteria

Table 1 shows the objectives of the study and how they will be evaluated. The primary endpoint is acute hematological toxicity. This objective will be addressed by quantifying the relationship between hematological toxicity, delivered dose and irradiated volume, which are exposure factors. This relationship will be quantified by an odds ratio (OR) in an ordinal logistic regression. The odds ratio will be the measured parameter quantifying the relationship between exposure and the main criterion of judgment, which is toxicity.

Practical conduct of the study

Biological check-up

When the patient agrees to participate in the study, a first preinclusion blood test is performed. This blood sample is taken on the day of the dosimetric scan to avoid imposing an additional trip in ICANS. It is analyzed by the laboratory of the University Hospital of Strasbourg for all patients participating in the study to minimize interlaboratory variability.

This first biological check-up will serve as a reference for the whole study. Weekly check-ups are carried out seven days after the start of radiotherapy treatment. Every week, patients are seen in consultations, and clinical and biological tolerance is evaluated. At 1 month and 3 months postradiotherapy, a consultation with the radiotherapy oncologist to evaluate clinical and biological tolerance is planned, followed by a blood test. As with the preinclusion blood tests, follow-up blood tests are also carried out at ICANS and analyzed by the laboratory of the University Hospital of Strasbourg to minimize the rates of interlaboratory variability. Table 2 shows the different symptoms collected during the follow-up consultations.

Radiotherapeutic planning and bone delineation

All patients will receive a planning computed tomography (CT) scan with a slice thickness of 5 mm. Afterwards, these CT scans are used to outline pelvic organs at risk (OARs), to contour the clinical target volume (CTV) and to define the planning target volume (PTV). The CTV and PTV and prescribed dose are dependent on cancer location and may include pelvic lymph node areas depending on the stage of the disease.¹¹⁻¹⁶

Usual practices validated in terms of radiation doses depend on the tumor site. Normofractionated irradiation delivers 1.8 to 2 Gy per fraction, 1 fraction per day, 5 fractions per week. Hypofractionated irradiation (more than 2 Gy per fraction, 1 fraction per day, 5 fractions per week) and fractionated stereotactic radiotherapy (from 4 to

25 Gy in a limited number of fractions) are permitted.¹⁷ The standard prescribed doses in normofractionated treatment for prostate cancer are 66 Gy after radical prostatectomy, 74 to 78 Gy for an in-position prostate, 46 to 54 Gy for rectal cancers^{18,19}, 50 to 65 Gy for anal cancers^{12,20}, and 45 to 50 Gy for cervical and endometrial cancers.^{11,12,14-16,18-20}

Irradiation of pelvic lymph node areas is allowed when necessary, classically at a dose of 46 to 50.4 Gy in normofractionation treatment. An integrated simultaneous boost or sequential boost on clinically invaded lymph nodes is also authorized in classical fractionation or hypofractionation under stereotactic conditions.²¹⁻²³

In addition to the usual risk organs, bone structures are delineated on bone CT scans (Figure 2).²⁴

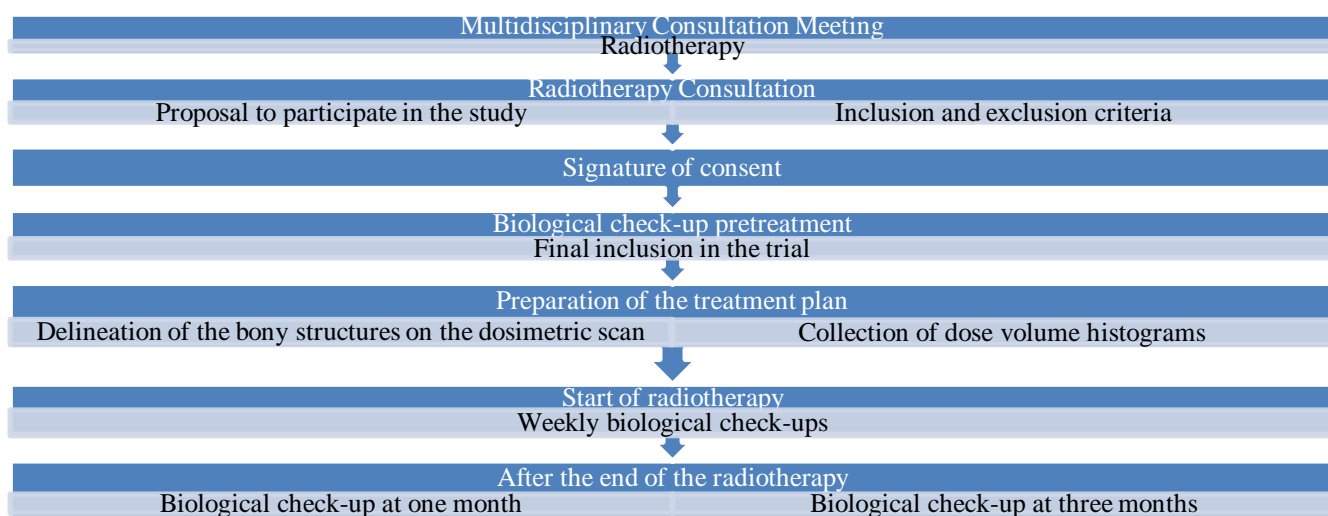


Figure 1: Timeline for MIFADORESOL.

Table 1: Objectives and evaluation criteria.

Objectives	Evaluation criteria
Primary endpoint	
Quantification of the relationship between acute hematological toxicity and delivered doses and irradiated volumes in the pelvic bone marrow for pelvic cancers	Assessment of acute hematological toxicity according to CTCAEv5.0:
	Hemoglobin
	Platelets
	Neutrophils
	Lymphocytes
Secondary endpoints	
Evaluation of viral, bacterial, and fungal infections during and for 3 months after radiotherapy	Collection of clinical signs of viral, bacterial, or fungal infections according to CTCAE v5.0 throughout treatment at 1 and 3 months
	Collection of definitive and transient discontinuations of concomitant chemotherapy
Evaluation of the impact of radiation-induced hematological toxicity on the administration of chemotherapy for the concerned patients.	Collection of the number of patients who required a reduction in chemotherapy dose.
	Collection of cumulative doses and theoretical doses of chemotherapy
	Collection of the definitive or transitory halting of the entire treatment

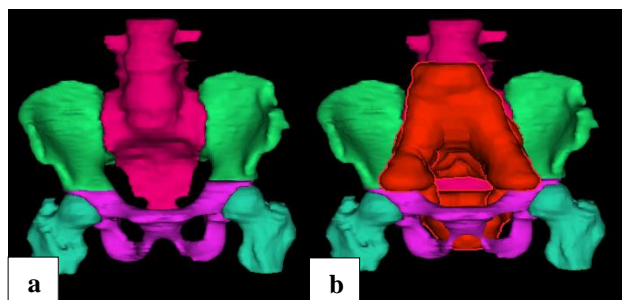


Figure 2: 3D view of the pelvis (a) 3D view of delineated pelvic bone and (b) 3D view of the PTV inside bone structures (case of prostate cancer with lymph node irradiation).

Pink: lumbosacral column; green: iliac crest; blue: femoral heads; purple: lower pelvis; red: PTV

Table 2: Clinical collection of hematological toxicity at 1 and 3 months.

Toxicity	Parameter
Hematologic toxicity	Fever
	Shivers
	Hypothermia
	Necessity of hospitalization for hematological toxicity after RT
Anemia	Transfusion
	EPO
	Per os treatment of iron deficiency
Thrombocytopenia	Spontaneous bleeding
	Anticoagulant treatment
Leukopenia	Infection
	If yes, where?
	Bacterial infection
	Viral infection
	Fungal infection
	Parasitic infection
If yes, which germ?	

Bone structures include right and left femoral heads: lower limit is located below the lesser trochanter; lower pelvis including the pines, pubis, and acetabulum; right and left iliac bones: the iliac crest in its entirety, the lower limits of which correspond to the upper edges of the femoral heads; lumbosacral spine: includes the entire sacrum and whose upper limit is 5 cm above the PTV; and total pelvis: the sum of all the above structures.

Statistical analysis

The analysis of the primary endpoint will be carried out by multivariate ordinal logistic regression, allowing the toxicity grade to be related to the volume irradiated and the dose delivered, adjusting for other potential confounding factors. Secondary endpoints are either binary criteria (presence or not of a viral, fungal, or bacterial infection; stopping or not of a treatment; adaptation or not of a

treatment) or quantitative criteria (cumulative and theoretical doses of chemotherapy). Binary criteria will be processed using multivariate binary logistic regressions, and quantitative criteria will be treated using multivariate linear regressions, allowing the effect of dose, volume, and other potential confounding factors on chemotherapy doses to be quantified. When appropriate, the non-Gaussian data (based on the Shapiro-Wilk test) will be transformed with the Box-Cox method to allow the use of linear regression. A sensitivity analysis will be performed using a gamma regression model to account for the probably skewed distribution spread to the right of the chemotherapy dose. In all models, any missing data will be treated by multiple imputation (MICE method, in SAS or R).

Ethics approval and consent to participate

The committee for the protection of persons from the southwest and overseas granted a favorable opinion to the MIAFDORESOL study on 03 July 2020 (CPP2020-05-051a/2020-A01108-31). Patients are being recruited over a period of 1 year starting in August 2020.

Calculation of the number of patients required

The calculation of the number of subjects required was based on the study of the relationship between the decrease in leukocytes and the average dose administered to patients. According to the literature, conventional pelvic radiotherapy delivers an average of 40 Gy \pm 20 Gy, resulting in grade 2 toxicity in 55% of patients and grade 3 toxicity in 35% of patients. A reduction in bone marrow dose would allow a 40% reduction in these toxicities, that is, 33% grade 2 and 21% grade 3.^{7,25-28}

By including 80 patients, the precision of the correlation coefficient is ± 0.17 . To compensate for the possible loss to follow-up, it is necessary to increase the number of patients to be included by 25%, that is, a total of 100 patients.

DISCUSSION

IMRT is an inverse planning technique that allows calculation of the dose deposition, while the constraints to the organs at risk are defined before the calculation of the treatment plan. Therefore, it is essential to know the dose constraints in organs at risk as precisely as possible.

Radiation-induced hematologic toxicity is probably underestimated due to the lack of systematic biological examination in patients treated with exclusive pelvic irradiation and the inability to discriminate radiation-induced hematopoietic toxicity from chemo-induced hematopoietic toxicity in patients receiving concomitant treatment. This is all the more important when the pre-irradiation blood counts are low, the volumes irradiated are large, and the doses delivered are high. Leukocytes and neutrophils are the most radiosensitive elements of the

blood, and their nadir is reached around the third week of treatment. Although IMRT showed a clear improvement in DVH (dose volume histogram) compared to RT3D, few studies have shown a consequent decrease in hematological toxicity and were able to deduce bone marrow constraints.^{2,25-41}

This prospective, single-center pilot trial assesses acute hematological toxicity among all the most common pelvic cancers. The aim is to improve and optimize radiotherapy if a dose limit or volume constraint is imposed by the results of the study. To our knowledge, this is the first study including several types of pelvic cancers and involving patients treated exclusively with radiotherapy, chemoradiotherapy or radiohormonotherapy. This study has several limitations.

Cancers with sarcomatous histology were excluded because they are often associated with hematotoxic chemotherapies, which could introduce a bias related to the already low rates of blood cells before the beginning of radiotherapy, with low pre-irradiation blood counts being a prognostic factor of bone marrow radiation toxicity impact. Another potential selection bias will be the before-after analysis, where patients will be their own controls.⁴² The preinclusion biological check-up is used as a reference. Patients undergo a total of seven to twelve blood tests spread over 4 to 6 months. Due to the heavy demands of the biological and clinical follow-up, follow-up bias is possible as either nonresponse bias or loss to follow-up bias. Confounding factors could be introduced by the presence or absence of chemotherapy, red blood cell transfusion, granulocyte colony-stimulating factor (G-CSF) or erythropoietin (EPO) treatment as well as patient-related factors, such as patient age, renal failure, and anticoagulant therapy; however, the number of patients should reduce the impact of these factors by the possibility of subgroup analyses.

Trial status

Patient recruitment has not yet been completed.

CONCLUSION

Bone marrow is one of the organs at risk of complications during irradiation with external radiotherapy, regardless of the technique used, especially when combined with concomitant or sequential chemotherapy. The addition of intensity modulation (IMRT) to 3D conformal radiation therapy (3D-RT) has resulted in better dose conformity in target volumes while optimally sparing organs at risk, including bone marrow. Despite these technical and dosimetric advances, hematopoietic toxicity remains one of the main toxicities during irradiation of pelvic lymph nodes. This prospective study is to our knowledge, the first study including several types of pelvic cancers and involving patients treated exclusively with radiotherapy, chemoradiotherapy or radio-hormonotherapy. The aim of this study is to quantify the relationship between

haematological toxicity and the radiation dose received by bone marrow. Eventually, if a dose limit or a volume constraint is identified, the radiotherapy can be optimized.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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