SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)

Trial name: **SACRO**

Study code: **ISG -2016-SACRO**

Sponsor's Name and Address: Italian Sarcoma Group
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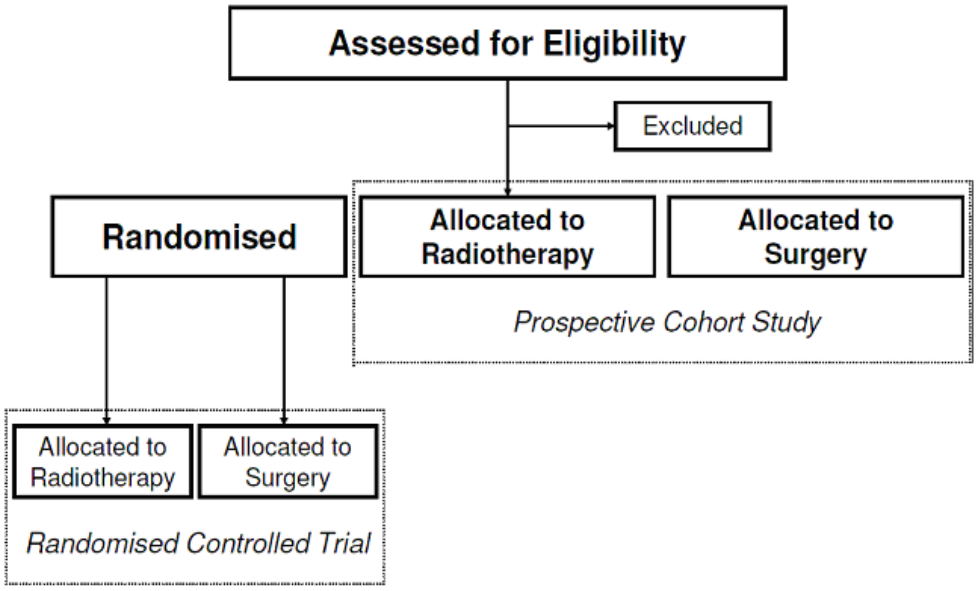
Study Number/Version/Date: Amendament Vers 1.1. 16 November 2020

Type: No Profit

Founding: **Chordoma Foundation**

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol

SYNOPSIS

Type of Study	International, multicentre, non-pharmacological, comparative, open-label, parallel-group, mixed Observational/Randomized Controlled Trial.
Protocol Code	ISG SACRO
Study Design	International, multicentre, non-pharmacological, comparative, open-label, parallel-group, mixed Observational-Randomized Controlled Trial. All the patients, who are candidate for the study will receive full information on the characteristics, potential effectiveness and side effects of the two alternatives treatments (radiotherapy and standard surgical treatment ± RT); Eligible and well-informed patients who give their consent to participate will be asked to choose among 3 alternative treatment options: A. to undergo surgery (± RT) B. to undergo definitive radiotherapy C. to be randomized to either definitive radiotherapy or surgery (± RT). As reported in the subsequent flow-chart patients who refuse randomization (treatment option c.) will be included in the Prospective Cohort Study (PCS) and will be treated accordingly to their choice (treatment option a. or treatment option b.). The same radiotherapy and surgical regimen will be administered in the PCS and in the Randomized Clinical Trial (RCT).  *If for country specific regulation or, institutional reasons a site could not participate to both cohorts (Prospective and Randomized), it is allowed to participate only to the Prospective, non-randomized cohort.* *In this case the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) could approve only the Prospective Cohort Study."*
Sponsor	Italian Sarcoma Group (ISG) Via Ca Ricci 33 40068 San Lazzaro di Savena, Bologna, Italy www.italiansarcomagroup.org

Global Study Coordinators	Surgery Global Coordinator: Dott. Alessandro Gronchi - Fondazione IRCCS Istituto Nazionale dei Tumori, Milano Radiotherapy Global Coordinator: Dott. Piero Fossati– CNAO di Pavia
Study Objective	**Primary objective:** This study is aimed at estimating the effectiveness of definitive radiotherapy as compared to standard surgical treatment for patients with primary sacral chordoma who are candidates to a complete en-bloc resection, in term of relapse-free-survival (RFS) **Secondary objectives:** To estimate the efficacy, activity, safety, QoL of definitive radiotherapy as compared to standard surgical treatment for patients with primary sacral chordoma who are candidates to a complete en-bloc resection. To identify patients, radiological and pathological characteristics that might be used as predictors of relapse-free survival (RFS)/ progression free survival (PFS), overall survival (OS) To identify patients, radiological and pathological characteristics that might be used as predictors of treatment effects **Primary endpoint** - The RFS, defined for each patient as the time from randomization (RCT) or treatment start date (PCS) to the date of local disease relapse, distant disease relapse, second primary malignancy or death from any cause, whichever occurred first. For patients treated with definitive radiotherapy not achieving CR as well as patients in R1/R2 after surgery not achieving a CR after post-operative radiotherapy the event for the RFS is the disease progression instead of the disease relapse. . Subjects not relapsed or died at the time of the analysis will be censored at the last disease assessment date. Disease relapse/progression will be determined radiologically for any appearance of new malignant lesion/s or dimensional increase of any size of malignant lesion/s already present at the baseline assessment. **Secondary endpoints** **- Efficacy endpoints** - Overall Survival (OS), defined for each patient as the time from randomization (RCT) or treatment start date (PCS) to the date of death from any cause. Subjects alive at the time of the analysis will be censored at the date of last contact. - Survival Post Progression (SPP), defined for each patient as the time from local disease relapse, distant disease relapse or second primary malignancy, whichever occurred first, to the date of death from any cause. SPP is equal to 0 in case of death before disease relapse. For patients treated with Radiotherapy not achieving CR as well as patients in R1/R2 after surgery not achieving a CR after Radiotherapy the starting point for the SPP is the local disease progression instead of the local disease relapse. **- Activity endpoints** - The Local Relapse Failure (LRF), defined for each patient as the time from randomization (RCT) or treatment start date (PCS) to the date of local disease relapse. Distant relapse, second primary malignancy or death before local disease relapse will be considered competing events; subjects alive and not relapsed at the time of the analysis will be censored at the last disease assessment date. Disease relapse will be determined radiologically for any appearance of new malignant lesion/s or dimensional increase of malignant lesion/s already present at the baseline assessment. For patients treated with Radiotherapy not achieving CR as well as patients in R1/R2 after surgery not achieving a CR after Radiotherapy the event for the LRF is the local disease progression instead of the local disease relapse.

	- The Distant Relapse Failure (DRF), defined for each patient as the time from randomization (RCT) or treatment start date (PCS) to the date of distant disease relapse. Local relapse, second primary malignancy or death before any distant disease relapse will be considered competing events; subjects alive and not relapsed at the time of the analysis will be censored at the last disease assessment date. Disease relapse will be determined radiologically for any appearance of new malignant lesion/s or dimensional increase of malignant lesion/s already present at the baseline assessment. - Best Response rate to definitive radiotherapy will be evaluated radiologically at end of RT, 3 months, 6 months and 12 months after radiotherapy - Time to best response rate to definitive radiotherapy will be evaluated radiologically at end of RT, 3 months, 6 months and 12 months after radiotherapy. **- Safety endpoints** - Incidence, nature, severity and seriousness of AEs, according to NCI-CTCAE, version 4.0 (see Appendix 2) - Maximum toxicity grade experienced by each patient for each specific toxicity - Percentage of patients experiencing grade 3-4 toxicity for each specific toxicity - Patients with at least a SAE - Patients with at least a suspect unexpected serious adverse reaction (SUSAR) - Adverse events will be evaluated using the NCI-CTCAE scale, version 4.0 - Post-operative morbidity evaluated according to Clavien-Dindo scale - Neurological impairment evaluated according to CTC-AE scale (version 4.0) - **- Quality of life (QoL) endpoints** - Maximum grade experienced by each patient for each specific item - Maximum grade experienced by each patient for each specific dimension associated with QoL (e.g. functional ability, emotional well-being, sexuality/intimacy, family well-being, treatment satisfaction, and social functioning) - Average grade experienced by each patient for each specific item - Average grade experienced by each patient for each specific dimension associated with QoL (e.g. functional ability, emotional well-being, sexuality/intimacy, family well-being, treatment satisfaction, and social functioning) Quality of Life will be assessed through validated evaluation scale
Disease Study	Localized sacral chordoma
Target Population	Patients with a primary and localized sacral chordoma amenable to complete surgical resection and definitive radiotherapy.
Sample Size	All patients who met the enrollment criteria will constitute the study population that will be splitted in two cohorts according to the choice of each patient. The PCS population will include all patients, who refused randomization and started A. or B. treatment options. The RCT population will include all the enrolled patients who agreed to randomization and were randomized in the RCT study. The safety-QoL population will include all the enrolled patients in both cohort who received option A or B. Recruitment into the RCT will continue until the estimates have become sufficiently stable or extreme to allow a clinical decision in most patients, as indicated by the increasing rate of refusals to accept randomization; recruitment into the PCS will continue until new, more promising or less devastating therapies become available.

	The study will be closed when all the enrolled patients will have completed the study treatment; the database lock and the last and definitive statistical analysis will be done approximately one year after the last patient has been enrolled.
Treatments	Definitive radiotherapy (adron therapy, carbon ion radiotherapy or proton therapy) as compared to standard surgical treatment.
Inclusion Criteria	1. Histologically confirmed diagnosis (brachyury expression) of primary sacral chordoma,of any diameter and arising at any site from S1 to coccyx. 2. Age≥18years 3. ECOG-performance status (PS) 0-2 (Appendix 5) 4. No previous antineoplastic therapy 5. Macroscopic tumor detectable at MRI/CT scan 6. Patient amenable for surgery 7. Patient amenable for RT
Exclusion Criteria	1. Distant metastasis (M+) 2. Inability to maintain treatment position 3. Prior radiotherapy to the pelvic region 4. Prior therapy for sacral chordoma (including surgery, cryoablation, hyperthermia, etc) 5. Local conditions that increase the risk of RT toxicity (tumor ulcerated skin infiltration, non-healing soft tissue infection, fistula in treatment field) 6. Rectal wall infiltration 7. General conditions that increase the risk of RT toxicity (active sclerodermia, xeroderma pigmentosum, cutaneous porphyria) 8. Presence of a second active cancer (with the exception of non-melanoma skin cancer in-situ cervix neoplasia and other in-situ neoplasia) 9. Severe comorbidities resulting in a prognosis of less than 6 months 10. Inability to give informed consent 11. Other malignancy within the last 5 years 12. Performance status ≥ 2 (ECOG). 13. Significant cardiovascular disease (for example, dyspnea > 2 NYHA) 14. Significant systemic diseases grade ≥3 on the NCI-CTCAE v4.03 scale, that limit patient availability, or according to investigator judgment may contribute significantly to treatment toxicity 15. Women who are pregnant or breast-feeding - Women of childbearing potential must have a negative pregnancy test performed within 7 days before the start of treatment. Postmenopausal is defined as: - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments - LH and FSH levels in the post menopausal range for women under 50 - Radiation-induced oophorectomy with last menses >1 year ago - Chemotherapy-induced menopause with >1 year interval since last menses - Surgical sterilisation (bilateral oophorectomy or hysterectomy) 16. Psychological, familial, social or geographic circumstances that limit the patient's ability to comply with the protocol or informed consent

Statistical methods	This study is designed following a Bayesian statistical approach; the final objective of the bayesian statistical analysis will be to estimate a posterior probability distribution of the relative efficacy of the 2 treatment strategies being compared. To this aim, two independent, but sequential analyses are planned; the 1st one will be carried out on the PCS population (Learning data analysis) and the 2nd on the RCT population (Primary data analysis).