PROspective multicenter observational study on Elective Pelvic nodes (PRO-EPI) Irradiation in Patients with intermediate/high/very high risk prostate cancer submitted to adjuvant or radical Radiotherapy with or without concomitant Androgen Deprivation

"PRO-EPI"

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Study	Multicenter Observational Prospective study
Title	**PRO**spective multicenter observational study on **E**lective **P**elvic nodes (**PRO-EPI**) **I**rradiation in Patients with intermediate/high/very high risk prostate cancer submitted to adjuvant or radical Radiotherapy with or without concomitant Androgen Deprivation.
Background	Prostate cancer (PCa) is the most common male malignancy all over the word causing some concerns for public health. In Italy prostate cancer is in the third place of the cancer mortality scale (8% of all cancer related deaths) even if a constant, though moderate, annual decrease (-1.8%) has been observed for over twenty years as well as a consequent increase in overall survival. Despite these data, still now, in the post PSA era, current estimates indicate that high-risk disease accounts for 15% of all PCa diagnoses in the United States and even more in the low-PSA screening regions. *Radiotherapy for prostate cancer: some open questions* Several modalities, alone and/or in combination, have been advocated to treat patients with intermediate/high/very high risk PCa, but universally accepted consensus guidelines are still lacking. Mounting evidence supports the use of a multimodality approach to treat locally advanced prostate cancer and in particular the combination of Radiation Therapy (RT) with Total Androgenic Deprivation (ADT); adjuvant post-surgical RT is also needed in many cases submitted to radical prostatectomy (RP) because of unexpected extra-capsular invasion or microscopically involved margins. In both cases, some issues are still present regarding RT: volumes of interest, total dose, radiation techniques and fractionation. *Elective nodal irradiation and its association with hormonal manipulation in the context of radical exclusive radiotherapy.* Whether or not elective irradiation of pelvic nodes (ENI) provides any benefit over exclusive RT to prostate only, has been a longstanding therapeutic dilemma being still now increasingly discussed in the modern radiotherapy scenario. Data obtained from international literature are still controversial and ENI is not clearly linked to relevant advantages in terms of overall survival (OS) according to the few randomized clinical trials available and to recent reviews particularly if Whole Pelvic Radiation Therapy (WPRT) is associated with ADT. Neoadjuvant (NHT), concomitant, or adjuvant (AHT) androgen deprivation therapy (ADT) is recommended for selected men with unfavourable intermediate-risk or high risk disease. Long-term ADT is indicated in patients with a high/very high risk of disease recurrence and typically consists of NHT plus RT followed by AHT (for 2-3 years) Conversely, the addition of RT to ADT is related to a significant reduction of cause-specific and all-cause mortality (OS) in comparison with exclusive systemic treatments. *Elective nodal irradiation (ENI) and evolving treatment techniques* Modern technologies contributed to a larger diffusion of ENI after a period during which this practice was almost abandoned due to its worse toxicity

	profile. Intensity Modulated Radiation Therapy (IMRT) may allow to treat larger volumes with better sparing of organs at risk (OARs). Other different techniques can also been used to obtain these results, however, there is no consensus in the literature on the superiority of any of these techniques in terms of tumor control and toxicity reduction. Radiation-induced toxicity is most often associated with high total and daily dose, short recovery time, and a larger amount of normal tissues included in the high dose regions. Data suggest that even in prostate-only RT, toxicity to OARs is more prevalent in the "high-dose" group. Acute gastrointestinal (GI) and genitourinary (GU) complications were however more frequently reported in patients treated with WPRT than in those receiving PORT, possibly due to "old" radiation techniques and less sophisticated dosimetric elaboration. *Elective nodal irradiation in the context of postoperative treatments* Adjuvant RT after RP reduces the risk of PSA failure of about 50% (thus ameliorating biochemical relapse free survival- bRFS) in pN0 patients with pT3-T4 disease, positive surgical margins (R+), also without any association with ADT, and seems to increase survival, particularly metastasis free survival. Patients with negative lymph nodes, but unfavorable prognostic factors such as positive surgical margins, extracapsular involvement (pT3a) and/or seminal vesicles infiltration (pT3b) are therefore recommended to undergo adjuvant RT. In patients with severe post- surgical side effects (urinary incontinence, persistent bleeding) intensive follow up followed by salvage RT at the time of biochemical relapse represents an alternative choice for patients with severe post-surgical side effects (such as urinary incontinence, persistent bleeding). In the adjuvant setting, sterilizing microscopic disease potentially persistent after radical surgery, particularly in high-risk patients, represents the rationale of adding WPRT to prostatic bed radiotherapy in pN0 patients. Goldner et al. evaluated the clinical impact of prostate only adjuvant RT in pN0 patients showing a 5-year biochemical relapse free survival of 100% and 58% in patients with a risk of nodal involvement <15% and >15%, respectively. These findings may be explained by a microscopic involvement of pelvic structures (lymph nodes, bone) other than prostate bed. However, the role of adjuvant post-surgical WPRT need to be validated by large prospective studies, not actually ongoing to our knowledge. Moreover, no clear-cut guidelines are available about the usefulness of adding ADT to adjuvant RT in the different subsets of pN0 patients. On the other hand, nodal involvement (pN1) is a strong negative prognostic factor and adjuvant RT in these patients may be useful to optimize loco-regional control deferring first or second line systemic therapies**.** The standard adjuvant treatment for pN1 PCa patients is represented by long term ADT, but the association with WPRT might significantly increase survival outcomes**.**
Rationale	Open questions are still needed to be answered: - In the exclusive radiotherapy scenario, does ENI produce an overall or biochemical relapse free survival advantage over prostate only radiotherapy for intermediate/high/very high-risk cases? - If ADT is added to prostate only radiotherapy, in intermediate/high/very high-risk cases, ENI is any longer needed?

	- Is ENI, associated or not to ADT, linked with an OS or bRFS survival advantage in patients submitted to adjuvant postsurgical prostate radiotherapy? - Additional toxicity due to the larger volumes treated might be reduced by more sophisticated radiotherapy techniques when ENI is added to prostate? - How many Radiation Oncology centers use ENI to treat patients with intermediate/high/very high-risk prostate cancer, with or without ADT? - The data obtained from the present observational study will be helpful for designing a subsequent randomized controlled trial.
End-points	**Primary**: - Overall survival; **Secondary**: - Cause-specific (CSS) and Biochemical Relapse Free survival (bRFS); - acute and late toxicity evaluation (rectal, bladder, bowel toxicity, according to CTCAE v.4 scale): - Quality of Life deterioration (according to the UCLA-PCI scale).
Study design	This is a prospective, multicenter, observational cohort study aimed to describe the advantage/disadvantage of different treatments of patients with intermediate/high/very high risk prostate cancer, through a web-based database. The study will include **all consecutive patients affected by intermediate, high or very high-risk prostate cancer that fit to the inclusion criteria and who are evaluated at each Centre involved in the study**. Patients may have already undergone or not to radical prostatectomy and/or pelvic lymphadenectomy. ***Phase 1: Establishment of the network of Centers involved in the study*** ***Phase 2: Activation and recruitment of eligible cases*** ***Phase 3: Follow-up (1,3,6,12/18,24/30/36 months)***
Statistical considerations	*Sample size* From previous experiences of the AIRO Prostate Cancer Study Group (AIRO PCSG), at least 15-20 Radiotherapy Centers from different regions of the country will be able to participate to the study. It is conceivable an accrual of at least 400-500 patients within 2 years and a further follow up of at least 3 years for each patient. For intermediate and high risk patients, an overall survival at 5 years of 0.8 has been previously reported (RTOG 94-13). According to the primary end-pint of the study, a sample size of 400 patients will allow to estimate a 5-year survival of 0.8 with 95% confidence interval of 0.76-0.84. *Statistical Analyses* In order to describe the data, mean and standard deviation will be used for normally distributed continuous variables, median and ranges for non-normally distributed continuous variables, proportions and percentages for

	categorical variables. Associations between two categorical variables will be assessed through the Pearson's chi-squared test or Fisher test, when appropriate. Differences between two-sample central tendencies will be assessed with a two independent sample t-test or Mann-Whitney U test or Wilcoxon, depending on distribution of the continuous variable. Analysis of variance and covariance and regression models will be used for evaluating the associations of some variables with survival taking account of possible confounders. In order to compare groups in terms of survival end-points, Kaplan-Meier curves will be estimated and log-rank tests will be performed. Periodical analyses are planned in order to check the quality of entered data. The analyses will be performed by using STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) or SPSS Statistical Software.
Inclusion/exclusion criteria	Every prostate cancer patient consecutively evaluated at the recruiting Centers and planned to receive radical exclusive or post-operative radiotherapy will be registered; this registration includes demographic and staging results data. Only intermediate, high, very high patients will have, however, treatment and follow up CRF compiled, based on the inclusion criteria *Inclusion criteria* Men older than or aged 18 years; Histologically confirmed intermediate, high or very high risk prostate cancer patients (NCCN classification: Intermediate Risk T2b and T2c or Gleason Score 7 or PSA value between 10 and 20 ng/mL; High risk: T3a or Gleason score 8-10 or PSA > 20 ng/ml; Very high risk: T3b-T4 or patients with multiple adverse risk factors reported in the high risk category that may be shifted in the very high risk group Patients eligible for -and actually submitted to radical radiotherapy treatment (+/- androgen deprivation) or adjuvant radiotherapy treatment after surgery (radical prostatectomy +/- pelvic lymphadenectomy); No other synchronous or previous malignant tumor other than skin basal cell carcinoma; Patients able to understand and sign the appropriate informed consent; Patients able to fill the Quality of Life (QoL) questionnaire; *Exclusion criteria* Patients aged less than 18; Patients *not* eligible for -and actually *not* submitted to- radical radiotherapy treatment (+/- androgen deprivation) or adjuvant radiotherapy treatment after surgery (radical prostatectomy +/- pelvic lymphadenectomy); Low risk prostate cancer (<T2b and T2c or < Gleason Score 7 or PSA value < 10 ng/mL); Patients with synchronous or previous malignancy other than skin basal cell carcinoma; Patients able to understand and sign the appropriate informed consent (IC) who decide not to subscribe IC; Patients not able to understand and sign the appropriate informed consent (IC) Patients unable to fill the QoL questionnaire.

Study duration	Estimated total time of recruitment is 2 years. It will be followed by a 3 years period of follow up for each patient.
Visits and exams	Every prostate cancer patient consecutively evaluated at the recruiting Centers and planned to receive radical exclusive or post-operative radiotherapy will be registered; this registration includes demographic and staging results data. Only intermediate, high, very high patients will have, however, treatment and follow up CRF compiled, based on the inclusion criteria Eligible patients will then receive all the information necessary to formulate their adhesion to the study and finally the physician will fill in the "Pretreatment" CRF that will include: Demographic Information; Anamnestic data; Initial diagnosis (date; PSA at diagnosis); Risk factors; Staging; Quality of life and symptoms caused by prostate cancer; General quality of life; The choice of the treatment will be done based on commonly used international guidelines and on the specific internal protocol of each participating Center. Since this study is observational, involved patients will be treated following *good clinical practice* and institutional policies procedures. Clinical outcomes and variables, demographic features, dosimetric analysis and acute/late toxicities of both RT (with and without ENI) and ADT will be reported. **Follow-up visits on 1,3,6,12/18,24/30 and 36 months** Every patient will be contacted by the physicians to fill a CRF that will include: Vital state (mortality, date and causes of death) or loss to follow up; Last PSA value; Other treatments (drugs); type of RT and ADT treatment Acute and late toxicities; Biochemical Relapse with PSA value and date of last PSA; Quality of life and symptoms due to prostate cancer; General quality of life. Survival status (mortality, date and cause of death) or exit from the study; If macroscopical recurrence or disease progression will occur, the radiological exams (if performed) will be reported; Further treatments received/planned after radiotherapy; The last available PSA; **Acute/Late toxicity** Genitourinary and gastrointestinal toxicity due to radiation therapy. A CRF will be completed regarding: Technical characteristics of the radiation treatment; Quality of life and complications due to prostate cancer; General quality of life
Toxicity	NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event (AE) reporting. The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Quality of Life	Quality of life and complications due to prostate cancer (Italian UCLA-PCI) General quality of life (SF-12 Standard V1)

Background

The extent of the problem

Prostate cancer (PCa) is the most common male malignancy in the United States and the rest of the Western world and its incidence is rising also in Asia, causing some concerns for public health **[1, 2]**. In Italy prostate cancer is in the third place of the cancer mortality scale (8% of all cancer related deaths) even if a constant, though moderate, annual decrease (-1.8%) has been observed for over twenty years **[3]** as well as a consequent increase in overall survival **[4]**. Despite these data, still now, in the post PSA era, current estimates indicate that high-risk disease accounts for 15% of all PCa diagnoses in the United States **[5]** and even more in the low-PSA screening regions.

Radiotherapy for prostate cancer: some open questions

Several modalities, alone and/or in combination, have been advocated to treat patients with intermediate/high/very high risk PCa **[6]**, but universally accepted consensus guidelines are still lacking. Mounting evidence supports the use of a multimodality approach to treat locally advanced prostate cancer and in particular the combination of Radiation Therapy (RT) with Total Androgenic Deprivation (ADT); adjuvant post-surgical RT is also needed in many cases submitted to radical prostatectomy (RP) because of unexpected extracapsular invasion or microscopically involved margins. In both cases, some issues are still present regarding RT: volumes of interest, total dose, radiation techniques and fractionation.

The efficacy of elective nodal irradiation and the issue of its association with hormonal manipulation in the context of radical exclusive radiotherapy for prostate cancer

Whether or not elective irradiation of pelvic nodes (ENI) provides any benefit over exclusive RT to prostate only, has been a longstanding therapeutic dilemma **[7]** being still now increasingly discussed in the modern radiotherapy scenario **[8, 9]**. Data obtained from international literature are still controversial and ENI is not clearly linked to relevant advantages in terms of overall survival (OS) according to the few randomized clinical trials available **[10]** and to recent reviews **[7, 11, 12, 13, 14, 15],** particularly if Whole Pelvic Radiation Therapy (WPRT) is associated with ADT.

In fact, in the radical setting, the addition of ADT to RT (but not to RP) is linked to a survival benefit in men with intermediate- or high risk disease according to Level I evidence; to date, however, it remains unclear whether this benefit is driven by an effect on micro metastatic disease in the pelvic lymph nodes and/or bones, by hormonal radio sensitization of the primary tumour, or by some combination thereof **[16, 17, 18, 19]**. Consequently, neoadjuvant (NHT), concomitant, or adjuvant

(AHT) androgen deprivation therapy (ADT) is recommended for selected men with unfavourable intermediate-risk or high risk disease. Long-term ADT is indicated in patients with a high/very high risk of disease recurrence and typically consists of NHT plus RT followed by AHT (for 2-3 years) **[20, 21, 22, 23]**. Conversely, the addition of RT to ADT is related to a significant reduction of cause-specific and all-cause mortality (OS) in comparison with exclusive systemic treatments **[24, 25]**.

Elective nodal irradiation and evolving treatment techniques

Modern technologies contributed to a larger diffusion of ENI after a period during which this practice was almost abandoned due to its worse toxicity profile. The larger diffusion of Intensity Modulated Radiation Therapy (IMRT) may allow to treat larger volumes with better sparing of organs at risk (OARs). Modern techniques can also obtain better conformal dose distributions and include static fields ("step-and-shoot") intensity modulated radiotherapy (IMRT), dynamic fields ("sliding-window") IMRT, and, more recently, volumetric modulated arc therapy (VMAT) and helical tomotherapy (Tomotherapy ®). However, there is no consensus in the literature on the superiority of any of these techniques in terms of tumor control and toxicity reduction. Radiation-induced toxicity is most often associated with high total and daily dose, short recovery time, and a larger amount of normal tissues included in the high dose regions. Data suggest that even in prostate-only RT, toxicity to OARs is more prevalent in the "high-dose" group **[26, 27]**. Acute gastrointestinal (GI) and genitourinary (GU) complications were however more frequently reported in patients treated with WPRT than in those receiving PORT, possibly due to "old" radiation techniques and less sophisticated dosimetric elaboration **[28, 29]**. Due to its improved ability in bowel sparing, IMRT may be an effective tool to reduce the risk of toxicities during WPRT **[30, 31, 32, 33]**. Kaidar-Person and colleagues' review **[34]**, summarizes the main international studies on WPRT.

Elective nodal irradiation in the context of postoperative treatments

Adjuvant RT after RP reduces the risk of PSA failure of about 50% (thus ameliorating biochemical relapse free survival- bRFS) in pN0 patients with pT3-T4 disease, positive surgical margins (R+), also without any association with ADT, and seems to increase survival, particularly metastasis free survival **[35]**. Patients with negative lymph nodes, but unfavorable prognostic factors such as positive surgical margins, extracapsular involvement (pT3a) and/or seminal vesicles infiltration (pT3b) are therefore recommended to undergo adjuvant RT. In patients with severe post- surgical side effects (urinary incontinence, persistent bleeding) intensive follow up followed by salvage RT

at the time of biochemical relapse represents an alternative choice for patients with severe post-surgical side effects (such as urinary incontinence, persistent bleeding). **[36].**

In the adjuvant setting, sterilizing microscopic disease potentially persistent after radical surgery, particularly in high-risk patients, represents the rationale of adding WPRT to prostatic bed radiotherapy in pN0 patients. Goldner et al. evaluated the clinical impact of prostate only adjuvant RT in pN0 patients showing a 5-year biochemical relapse free survival of 100% and 58% in patients with a risk of nodal involvement <15% and >15%, respectively. These findings may be explained by a microscopic involvement of pelvic structures (lymph nodes, bone) other than prostate bed. However, the role of adjuvant post-surgical WPRT need to be validated by large prospective studies, not actually ongoing to our knowledge. **[37, 38, 39, 40].** Moreover, no clear-cut guidelines are available about the usefulness of adding ADT to adjuvant RT in the different subsets of pN0 patients.

On the other hand, nodal involvement (pN1) is a strong negative prognostic factor and adjuvant RT in these patients may be useful to optimize loco-regional control deferring first or second line systemic therapies **[41]**. Actually, the standard adjuvant treatment for pN1 PCa patients is represented by long term ADT, but the association with WPRT might significantly increase survival outcomes **[42].** A recent analysis conducted by SEER on "pN1 M0" PCa patients treated with adjuvant WPRT seems to confirm the benefit obtained by the association of WPRT with ADT, demonstrating a survival advantage for intermediate risk patients **[43]**.

Conclusions, rationale and summary of the study

In conclusion, open questions about ENI for prostate cancer still remain:

1. In the exclusive radiotherapy scenario, does ENI produce an overall or biochemical relapse free survival advantage over prostate only radiotherapy for intermediate/high/very high risk cases?

2. If ADT is added to prostate only radiotherapy, in intermediate/high/very high risk cases, ENI is any longer needed?

3. Is ENI, associated or not to ADT, linked with an OS or bRFS survival advantage in patients submitted to adjuvant postsurgical prostate radiotherapy?

4. Additional toxicity due to the larger volumes treated might be reduced by more sophisticated radiotherapy techniques when ENI is added to prostate?

5. How many Radiation Oncology centers use ENI to treat patients with intermediate/high/very high-risk prostate cancer, with or without ADT?

We propose a no-profit, multicenter observational study to collect data of consecutive patients treated with ENI both in the exclusive radical radiotherapy scenario and in the adjuvant postsurgical setting. Cases treated both with and without associated ADT will be recruited to evaluate Overall survival (OS) (that will be the main endpoint), Cause-specific (CSS) and Biochemical Relapse Free survival (bRFS), toxicity and Quality of Life (QoL) (the secondary endpoints).

Aims of the study

Clinical features and outcomes will be assessed as better detailed in the following lines:

1. To define the diffusion of the practice of treating pelvic lymph-nodes in patients affected by intermediate/high/very high risk non-metastatic prostate cancer (PCa) among Italian Radiation Oncology Centres, submitted to radical or post-operative radiotherapy;

2. To define the diffusion of the different radiotherapy techniques used to treat pelvic nodes and the other features of the radiation treatment;

3. To register prospectively biochemical and clinical failure, prostate cancer deaths and deaths for any cause in the population studied;

4. To register prospectively the toxicity due to radiotherapy and androgen deprivation therapy in patients treated with pelvic nodes radiotherapy;

5. To compare clinical outcomes and toxicities observed in the different clinical and therapeutic subgroups with the corresponding historical data relative to PCa patients treated with radiotherapy with or without elective pelvic nodal irradiation, already available in the existing AIRO (Italian Society of Radiation Oncology) databases;

6. To exploit the collected data to define the need and the features of a prospective randomized trial evaluating the efficacy of elective pelvic nodal irradiation in patientsts with intermediate/high/very high risk non-metastatic prostate cancer.

7. The data obtained from the present observational study will be helpful for designing a subsequent randomized controlled trial.

In summary, the study aims at the definition of survival, toxicity and QoL data in a representative sample of intermediate, high and very high risk prostate cancer patients consecutively recruited in Italian Radiation Oncology Centres over two years. Parameters considered will be OS, CSS and bRFS, toxicity (rectal, bladder, bowel toxicity, according to CTCAE v.4 scale) and QoL (according to the SF-12 scale and UCLA-PCI scale). Primary end point will be OS. Secondary endpoints will be CSS, bRFS, gastrointestinal and genitourinary toxicity, QoL deterioration.

Study Design

This is a prospective, multicenter, observational cohort study aimed to describe the advantage/disadvantage of different treatments of patients with intermediate/high/very high risk prostate cancer, through a web-based database.

Study Duration

The recruitment period, taking into account the needed sample size (*v.infra*) will be of two years, followed by three-year follow up period for each patient, with an accrual of at least 400-500 patients.

Population, Procedures

The study will include all consecutive patients affected by intermediate, high or very high-risk prostate cancer that fit the inclusion criteria and who are evaluated at each Centre involved in the study. Patients may have already undergone or not to radical prostatectomy and/or pelvic lymphadenectomy.

Inclusion criteria

- Men older than or aged 18 years;
- Histologically confirmed intermediate, high or very high risk prostate cancer patients (NCCN classification: Intermediate Risk T2b and T2c or Gleason Score 7 or PSA value between 10 and 20 ng/mL; High risk: T3a or Gleason score 8-10 or PSA > 20 ng/ml; Very high risk: T3b-T4 or patients with multiple adverse risk factors reported in the high risk category that may be shifted in the very high risk group
- Patients eligible for -and actually submitted to- radical radiotherapy treatment (+/- androgen deprivation) or adjuvant radiotherapy treatment after surgery (radical prostatectomy +/- pelvic lymphadenectomy);
- No other synchronous or previous malignant tumor other than skin basal cell carcinoma;
- Patients able to understand and sign the appropriate informed consent;
- Patients able to fill the QoL questionnaire;

Exclusion criteria

- Patients aged less than 18;
- Patients *not* eligible for -and actually *not* submitted to- radical radiotherapy treatment (+/- androgen deprivation) or adjuvant radiotherapy treatment after surgery (radical prostatectomy +/- pelvic lymphadenectomy);
- Low risk prostate cancer (<T2b and T2c or < Gleason Score 7 or PSA value < 10 ng/mL);
- Patients with synchronous or previous malignancy other than skin basal cell carcinoma;
- Patients able to understand and sign the appropriate informed consent (IC) who decide not to subscribe IC;
- Patients not able to understand and sign the appropriate informed consent (IC)

- Patients unable to fill the QoL questionnaire.

Involved Centers

The Radiation Oncology Unit of the University and Spedali Civili of Brescia will be the promoter and coordinator Center. From previous studies of the AIRO Prostate Study Group it can be inferred that at least 15-20 Radiation Oncology Centers from different areas of Italy will be involved; this will assure the widest and homogenous participation throughout the country.

Accrual and timeline

The study will start when a sufficient number of Centres will have obtained EC approval.

Estimated total time of recruitment is 2 years. It will be followed by a three years period of follow up for each patient.

Phase 1: Establishment of the network of Centers involved in the study

During this phase the study protocol has to be shared as much as possible within the Italian radiation oncology community in order to identify and involve as many as possible interested Centres throughout the country.

This will be done in official sessions of the Prostate Cancer Study Group (PCSG) of AIRO meetings.

Each center that will become a part of the study will identify a referring physician who must accomplish the systematic recruitment of eligible patients and provide the collection of data on the appropriate *web portal* established in Brescia.

Phase 2: Activation and recruitment of eligible cases

Centers involved will identify all the eligible cases with biopsy proven prostate adenocarcinoma. Patients who are candidate to get involved in the study will be contacted by the physician in charge of the study for each Center. **Every** prostate cancer patient consecutively evaluated at the recruiting Centers and planned to receive radical exclusive or post-operative radiotherapy will be registered; this registration includes demographic and staging results data; only intermediate, high, very high patients will have, however, treatment and follow up CRF compiled (both treated with or without ENI; +/- ADT).

Eligible patients will then receive all the information necessary to formulate their adhesion to the study and finally the physician will fill in the "Pretreatment" Case Report Form (CRF) that will include:

- Demographic Information (date of birth, study title, civil state, working information);
- Another person (relatives, friends,…) as a contact to minimize follow up loss;
- Anamnestic data (height, weight, smoking habit, comorbidities, Cumulative Illness Rating Scale **[44],** Attachment 1);
- Initial diagnosis (date; PSA at diagnosis);
- Risk factors;
- Staging (clinical TNM, date of biopsy, Gleason score, total number of samples, number of positive samples);
- Quality of life and symptoms caused by prostate cancer (using Italian UCLA Prostate Cancer Index) **[45, 46]**;
- General quality of life (SF-12 Standard V1) **[47]**.

The choice of the treatment will be done based on commonly used international guidelines and on the specific internal protocol of each participating Center.

Since this study is observational, involved patients will be treated following *good clinical practice* and institutional policies procedures.

Clinical outcomes, (such as overall survival and biochemical relapse free survival) and variables, demographic features, dosimetric analysis and acute/late toxicities of both RT and ADT will be reported.

Phase 3: Follow-up (1, 3, 6, 12, 18, 24, 30, 36 months)

After the end of the radiotherapy treatment patients will be evaluated 1, 3, 6, 12, 18, 24, 30 and 36 months since the last session.

Every patient will be contacted by the physicians to fill a CRF that will include:

- Vital state (mortality, date and causes of death) or loss to follow up;
- Last PSA value;

- Other treatments (drugs);
- Treatment : type of treatment, start date, PSA value before treatment; if surgery type of surgery and pathological TNM, margins, Gleason Score, number of positive lymph nodes; if external RT (intent, modality, technique, dose/fraction, volumes, concomitant hormonal therapies); if brachytherapy (type, intent, dose); if hormone therapy (type of drugs, start and end date, total duration);
- Acute and late toxicities;
- Biochemical Relapse with PSA value and date of last PSA;
- Quality of life and symptoms due to prostate cancer (Italian UCLA-PCI);
- General quality of life SF-12.

Toxicity and response evaluation

The enrolled patients will undergo the first follow up visit one month after the end of radiotherapy. On that occasion, clinical examination will be performed and previously prescribed blood tests, if required, will be evaluated. Genitourinary and gastrointestinal toxicity due to radiation therapy for prostate cancer will be reported according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event (AE) reporting. The CTCAE version 4 is identified and located on the CTEP web site at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm **[48]**

In addition, a Case Report Form (CRF) will be completed (see Attachment 2), regarding:

- Technical characteristics of the radiation treatment (dose, volume, technique, association or not with hormonal therapy);
- Quality of life and complications due to prostate cancer (according to Italian UCLA-PCI) **[45, 46];**
- General quality of life (SF-12 Standard V1) **[47].**

Thereafter patients will be evaluated at 3-months, 6-months and 12-months after the end of radiotherapy, and then every 6 months for at least 24 months. During all those scheduled follow up visits, PSA level (jointly with testosterone, in case of association with hormonal therapy) and

previously prescribed blood texts if required, will be evaluated. Patients will undergo clinical examination, and genitourinary and gastrointestinal toxicity will be assessed according to the CTCAE v4.0 classification scale). In addition, a CRF (see Attachment 3) will be completed at each visit, regarding:

- Survival status (mortality, date and cause of death) or exit from the study;
- If macroscopical recurrence or disease progression occurred, the radiological exams (if performed);
- Further treatments received/planned after radiotherapy;
- The last available PSA;
- Quality of life and complications due to prostate cancer (Italian UCLA-PCI) **[45, 46];**
- General quality of life (SF-12 Standard V1) **[47].**

The Italian UCLA-PCI and SF-12 Standard V1 questionnaires reported in Attachment 2 and Attachment 3 **[45, 46, 47]** will be given by the referring physician and self-compiled by patients in physician's absence, eventually with the help of a nurse if necessary; thereafter, the referring physician will insert the data to the database.

Data Collection, Confidentiality

Data will be collected through an *ad hoc* web based software, built to guarantee:

1. Respect of the Italian laws and of the international rules about GMP and privacy, according also to the general principles fixed by the Helsinki declaration and its subsequent updates;

2. The anonymization of the patient records;

3. The possibility for each participating Center to have unrestricted access to its own data;

4. The restriction of the access to the full dataset composed by the sum of the records provided by the single Centers; this will be allowed only after the authorization of the PI and the Study Coordinator. Once the study will be completed, access to the whole database will be possible only after having obtained the authorization of the AIRO President in charge and of the AIRO Board;

5. The safe storage of the data, along with that of the previous AIRO-PCSG studies, along with.

The use of the software will be elucidated to the single participating Centers in *ad hoc* start up

meetings, to guarantee an appropriate and homogeneous data collection; a tool bar will however be devised, to automatically verify inconsistencies in the data collected.

Statistical Considerations

Sample size

From previous experiences of the AIRO PCSG **[49, 50]**, at least 15-20 Radiotherapy Centers from different regions of the country will be able to participate to the study. It is conceivable an accrual of at least 400-500 patients within 2 years and a further follow up of at least 3 years for each patient. For intermediate and high risk patients, an overall survival at 5 years of 0.8 has been previously reported (RTOG 94-13) **[51]**. According to the primary end-point of the study, a sample size of 400 patients will allow to estimate a 5-year survival of 0.8 with 95% confidence interval of 0.76-0.84 [**52].**

Statistical Analyses

In order to describe the data, mean and standard deviation will be used for normally distributed continuous variables, median and ranges for non-normally distributed continuous variables, proportions and percentages for categorical variables. Associations between two categorical variables will be assessed through the Pearson's chi-squared test or Fisher test, when appropriate. Differences between two-sample central tendencies will be assessed with a two independent sample t-test or Mann-Whitney U test or Wilcoxon, depending on distribution of the continuous variable.

Analysis of variance and covariance and regression models will be used for evaluating the associations of some variables with survival taking account of possible confounders.

In order to compare groups in terms of survival end-points, Kaplan-Meier curves will be estimated and log-rank tests will be performed.

Periodical analyses are planned in order to check the quality of entered data.

The analyses will be performed by using STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) or SPSS Statistical Software.

Ethical committee

After the final approval by the AIRO-PCSG, the Protocol will be submitted to the Ethical Committee (EC) of the Study Coordinating Centre; when it will be approved, the single participating Centres will consequently apply for approval of their EC. According to the judgment of the PI and of the Study Coordinator, the first patient will be enrolled when a sufficient number of Centres will have obtained EC approval. This will be the starting date for the study.

The present study will be performed in accordance with the present protocol, with the principles of Good Clinical Practice in the respect of the ICH GCP guidelines and the ethical principles contained in the Helsinki declaration.

Publication rules

Interim and final results of the study will be published under the final responsibility of the PI and of the Study Coordinator.

The following publication rules will be enforced:

1. The participating Centers should approve the paper;

2. Only Centers contributing to more than 5% of the cases collected will have a person quoted as Author of the paper; however, every Center contributing to the common database, as well as the people working to realize the Study, will be publicly quoted and their contribution acknowledged in the paper;

3. Authorship is granted in proportion to:

    a. the cases contributed to the database;

    b. the contribution to:

        - study concept ;

        - study organization;

        - study conduction;

        - article conception;

- article drafting and writing;

- article reviewing;

- article approval.

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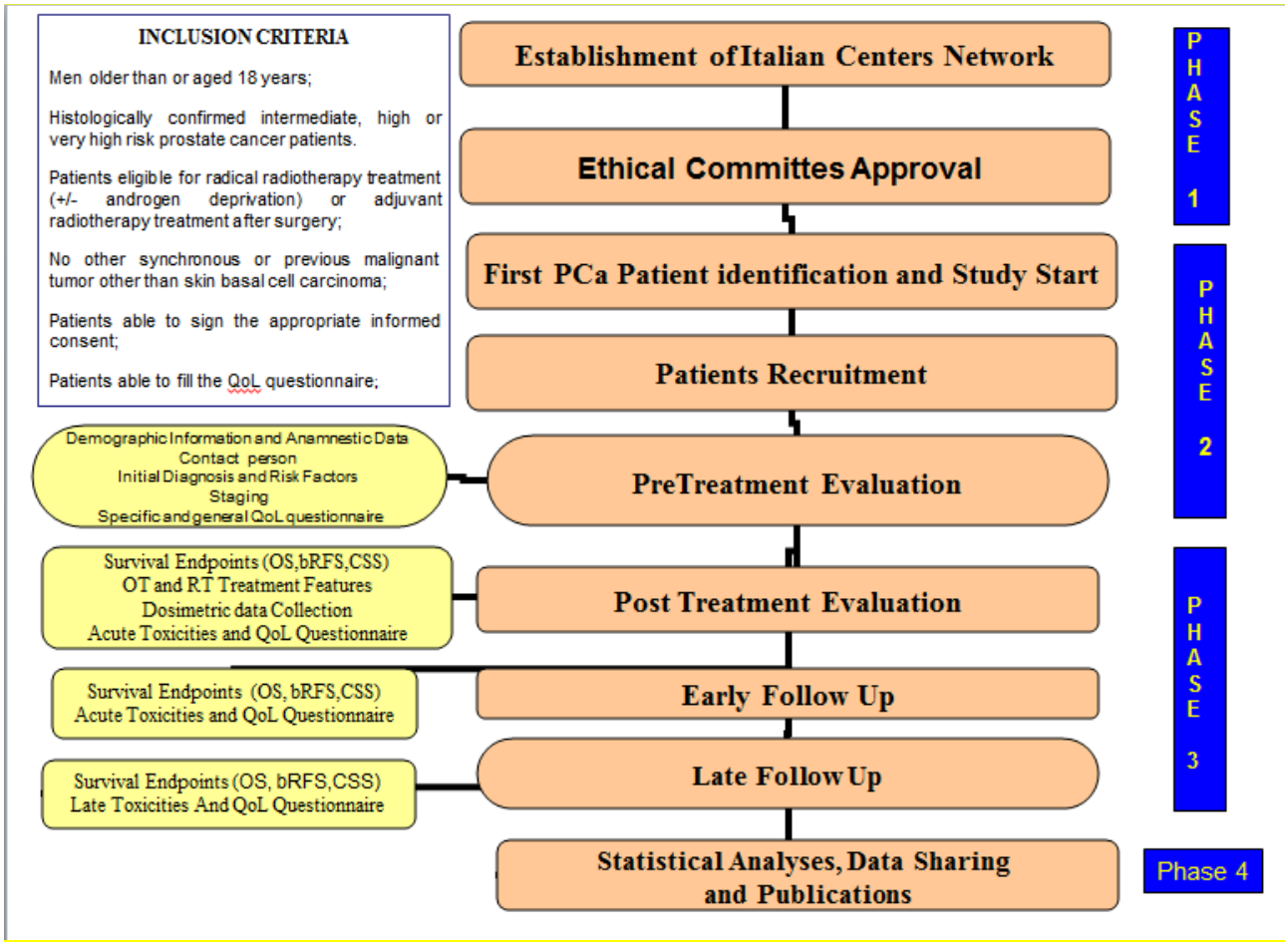
Summary of the study



Signature page

Coordinating Investigator: Prof. Stefano Maria Magrini

Place and date, ___Brescia li 18/01/2016_____

Signature, _____

Principal Investigator: Michela Buglione di Monale e Bastia, MD

Place and date, ___Brescia li 18/01/2016_____

Signature, _____

ATTACHMENT 1 – CRF PRE TREATMENT

GENERAL HISTORY

Date of Birth	|__|__| / |__|__| / |__|__|__|__| day month year		
Educational qualification	1 .	Academic degree or Bachelor's degree	
	2..	High school diploma or high school degree (4-5 years)	
	3..	High school diploma or high school degree (2-3 years)	
	4..	Secondary school diploma/Professional training diploma	
	5..	Elementary school diploma (3-5 years)	
	6 .	No degree	
Marital status	1 .	Married/Cohabitant	
	2 .	Widower	
	3 .	Separated/divorced	
	4 .	Unmarried	
Job status	1 .	Employed	
	2 .	Unemployed or job quest	
	3 .	Retiree	
	4 .	Never worked	
Contact people	1 .	Wife, cohabitant	Phone number
	2..	Daughter/son	Phone number
	3..	Daughter-in-law /son-in-law	Phone number
	4..	Other, specify_____	Phone number

Weight	|__|__|__|.|__| kg	
Smoke	1 .No	
	2.. Yes, in the past, no more now	
	3.. Yes	
Hemoglobin (from bood tests reported in the last 6 months)	|__|__|__|.|__| g/dl	**Blood tests date** |__|__| / |__|__| / |__|__|__|__| day month year

CUMULATIVE ILLNESS RATING SCALE (CIRS)

(Conwell Y et al, 1993)

Indicate for each apparatus the score that best expresses the degree of injury. For diseases that produce lesions in more than one apparatus all present lesions must be reported. For example, an acute cerebrovascular accident (stroke) can damage neurological, vascular, musculoskeletal apparatus and skin at the same time. A metastasized tumor has to be reported either at the apparatus site of the primary tumor or at the vascular system, indicating the extent of the lymph node involvement. If an apparatus is affected by more diseases, the total damage resulted from various diseases must be reported.

For each apparatus the score is so allocated:

1 = ABSENT: "no injuries of an organ / apparatus".

2 = MILD: "the damage does not interfere with the normal activities; therapy is not necessarily required; the prognosis is favorable (eg. hernias, hemorrhoids). "

3 = MODERATE: "the lesion interferes with normal life activities; therapy is required; the prognosis is good (eg. stones, diabetes, fractures). "

4 = SERIOUS: "The injury is debilitating; urgent treatment is required; the prognosis is doubtful (eg. inoperable cancer, emphysema, heart failure)."

5 = VERY SERIOUS: "the injury can be fatal; emergency treatment is required or it is no longer indicated any treatment; the prognosis is severe (eg. myocardial infarction, stroke, intestinal bleeding, embolism). "

		None	Mild	Moderate	Serious	Very serious
1.	Cardiac	1	2	3	4	5
2.	Hypertension (rating is based on severity)	1	2	3	4	5
3.	Vascular, lymphatics, haematopoietic	1	2	3	4	5
4.	Respiratory (under the larynx)	1	2	3	4	5
5.	Eye, ear, nose, throat, larynx	1	2	3	4	5
6.	Upper gastro-intestinal	1	2	3	4	5
7.	Lower GI (intestines, hernias)	1	2	3	4	5
8.	Hepatic (liver only)	1	2	3	4	5
9.	Renal (kidneys only)	1	2	3	4	5
10.	Genito-urinary (ureter,-genitals)	1	2	3	4	5
11.	Musculoskeletal and - integumentary	1	2	3	4	5
12.	Neurological (except dementia)	1	2	3	4	5
13.	Endocrine- metabolic, infections, toxicity	1	2	3	4	5
14.	Cognitive-psychiatric behaviour	1	2	3	4	5

DIAGNOSIS AT PRESENTATION

First diagnosis date	|__|__| / |__|__| / |__|__|__|__| day month year		
PSA at diagnosis	|__|__|__|__|.|__|__|__| ng/mL		
Risk factors	Family history for prostate cancer If yes, specify the degree of kinship 1.. first degree (father, son) 2.. second degree (brother , grandfather , nephew, paternal or maternal uncle)	**Yes** 0	**No** 1
	Diabetes	**Yes** **0**	**No** **1**
Clinical TNM Staging	T |__|__|	N |__|__|	M |__|__|
Biopsy date	|__|__| / |__|__| / |__|__|__|__| day month year		
Gleason Score	|__| + |__| = |__|__| ISUP[1]: 1.. before 2005 2.. after 2005		
Number of blood tests	|__|__|		
Number of positive blood tests	|__|__|		

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DRUG THERAPY

Does the patient take any sexual rehabilitation drugs? 0 No 1 Yes

If yes, specify:

Commercial name	Formulation	Dosage	Unit of measurement	Frequence	Continuity of therapy	Since number	Since period
_____		|__|__|__|		|__|__|/qd |__|__|/weekly |__|__|/monthly other |__|__|/_____	. continuous . discontinuous . when required	|__|__|	. days . weeks . months . years
_____		|__|__|__|		|__|__|/qd |__|__|/weekly |__|__|/monthly other|__|__|/____	. continuous . discontinuous . when required	|__|__|	. days . weeks . months . years
_____		|__|__|__|		|__|__|/qd |__|__|/weekly |__|__|/monthly other|__|__|/____	. continuous . discontinuous . when required	|__|__|	. days . weeks . months . years
_____		|__|__|__|		|__|__|/qd |__|__|/weekly |__|__|/monthly other|__|__|/____	. continuous . discontinuous . when required	|__|__|	. days . weeks . months . years

Does the patient take any other medications? 0 . No 1 Yes

If yes, specify:

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

Commercial name _____

TREATMENT CHARACTERISTICS

Aim of Radiation Therapy 1 Definitive

2 Adjuvant

If adjuvant RT, specify:

Surgery

Surgical approach
1 . Open
2 . Laparoscopy
3 . Robot assisted
4 . Conversion to open
5 . TURP
6 . Other, specify_____

Lymphadenectomy
1 . No
2 . Yes
If yes, number of removed nodes |__|__|
Number of positive nodes |__|__|

Nerve Sparing
1 . No
2 . Yes, monolateral
3 . Yes, bilateral

Pathological TNM after surgery T |__|__| N |__|__| M |__|__|

Margins
1 R0
2 R1
3 R2

Gleason Score after surgery |__| + |__| = |__|__|

Pre-treatment PSA |__|__|__|__|.|__|__|__| ng/mL

PSA date |__|__| / |__|__| / |__|__|__|__|
day month year

SF-12 STANDARD ITALIAN VERSION

(Apolone G et al. 2001)

		Eccellent	Very good	Good	Fair	Poor
1	In general, you would say that your health condition is:	1	2	3	4	5

The following questions regard some activities you might do during a typical day. Does <u>your health condition actually</u> limit you in doing these activities?

		Yes, it limits a lot	Yes, it limits a little	No, it does not limit at all
2	**Activities of moderate physical effort** , such as moving a table , using the vacuum cleaner , playing bowls or a riding a bicycle	1	2	3
3	Climbing **several** flights of stairs	1	2	3

During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your physical health condition</u>?

		Yes	No
4	**Accomplished less** than you would like	1	2
5	You had to limit certain **kinds** of occupation or other activities	1	2

During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your emotional state (such as feeling depressed or anxious)</u>?

		Yes	No
6	**Accomplished less** than you would like	1	2
7	You did not do work or other activities as **carefully** as usual	1	2

		Not at all	A little bit	Moderately	Quite a bit	Not at all
8	<u>During the last 4 weeks</u>, How much has pain hindered your usual work (at home and outside)?	1	2	3	4	5

How long <u>during the last 4 weeks</u> have you felt

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	All of the time
9	calm and serene?	1	2	3	4	5	6
10	full of energy?	1	2	3	4	5	6
11	discouraged and sad	1	2	3	4	5	6

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time
12	<u>During the last 4 weeks,</u> how long have your <u>physical health condition or your emotional state</u> interfered with your social activities, with family, with friends?	1	2	3	4	5

COMPLICATIONS DUE TO PROSTATE CANCER

ITALIAN UCLA PROSTATE CANCER INDEX

(Gacci M et al, 2005)

URINARY FUNCTION

This session regards the urinary routine. Please consider only the last 4 weeks.

1. Over the LAST 4 WEEKS, how often have you leaked urine?
   1 Every day.
   2 About once a week
   3 Less than once a week
   4 Not at all.

2. Which of the following best describes your urinary control during the LAST 4 WEEKS?
   1 No control whatsoever
   2 Frequent dribbling
   3 Occasional dribbling
   4 Total control

3. How many pads or adult diapers per day have you usually used to control leakage during the LAST 4 WEEKS?
   1 3 or more pads per day
   2 1-2 pads per day
   3 No pads

4. How big a problem, if any, has each of the following been for you?
   Dripping urine or wetting your pants?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

   Urine leakage interfering with your sexual activity?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

5. Overall, how big a problem has your urinary function been for you during the LAST 4 WEEKS?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

BOWEL FUNCTION

The following section talks about all the bowel function and abdominal pain. Please consider only the last 4 weeks.

6. How often have you had rectal urgency (felt like you had to pass stool, but did not) during the LAST 4 WEEKS?
   1 More than once a day
   2 About once a day
   3 More than once a week
   4 About once a week
   5 Rarely or never

7. How much distress have your bowel movements caused you during the LAST 4 WEEKS?
   1 Severe distress

2 Moderate distress
3 A little distress
4 No distress

8. How often have you had crampy pain in your abdomen or pelvis during the LAST 4 WEEKS?
1 Several times a day
2 About once a day
3 Several times a week
4 About once this month
5 Rarely or never

9. In particular, how big was the problem of bowel habits during the LAST 4 WEEKS?
1 Big problem
2 Moderate problem
3 Little problem
4 Very small problem
5 No problem

SEXUAL FUNCTION

THE NEXT SECTION IS ABOUT YOUR SEXUAL FUNCTION AND SEXUAL SATISFACTION. MANY OF THE QUESTIONS ARE VERY PERSONAL, BUT THEY WILL HELP US UNDERSTAND THE IMPORTANT ISSUES THAT YOU FACE EVERY DAY. REMEMBER THAT YOUR ANSWERS TO THIS QUESTIONNAIRE WILL BE KEPT CONFIDENTIAL AND WILL BE USED ONLY FOR RESEARCH PURPOSES. PLEASE ANSWER HONESTLY ABOUT THE LAST 4 WEEKS ONLY.

10. HOW WOULD YOU RATE EACH OF THE FOLLOWING DURING THE LAST 4 WEEKS?

	Very poor	Poor	Fair	Good	Very good
A. Your ability to have an erection?.	1	2	3	4	5
B. Your ability to reach orgasm (clima	1	2	3	4	5

11. How would you describe the usual QUALITY of your erections?
1 None at all
2 Not firm enough for any sexual activity
3 Firm enough for masturbation and foreplay only
4 Firm enough for intercourse

12. How would you describe the FREQUENCY of your erections?
1 I NEVER had an erection when I wanted one
2 I had an erection LESS THAN HALF the time I wanted one
3 I had an erection ABOUT HALF the time I wanted one
4 I had an erection MORE THAN HALF the time I wanted one
5 I had an erection WHENEVER I wanted one

13. Overall, how would you rate your sexual function during the LAST 4 WEEKS?
1 Very poor
2 Poor
3 Fair
4 Good
5 Very good

14. Overall, how big a problem has your sexual function been for you during the LAST 4 WEEKS?
1 No problem
2 Very small problem
3 Small problem
4 Moderate problem
5 Big problem

ATTACHMENT 2 – 1 MONTH FOLLOW UP

Date of starting treatment	|__|__| / |__|__| / |__|__|__|__| day month year
Date of ending treatment	|__|__| / |__|__| / |__|__|__|__| day month year
Pre-treatment PSA	|__|__|__|__|.|__|__|__| ng/mL

External Beam Radiation Therapy	
Aim of Radiation Therapy	1 Radical exclusive 2 Adjuvant 3 Salvage post-operative 4 Other, specify_____
Modality	1 IGRT 2 Non IGRT
Technique Technique-2	1 3D-CRT 2 IMRT (step and shoot) 3 IMRT (volumetric) 4 SBRT (stereotactic body radiotherapy)

	1 Sequential RT 2 SIB IMRT
Dose/fraction V1	|__|__|,|__|__| Gy
Total dose V1	|__|__|,|__|__| Gy
Dose/fraction V2	|__|__|,|__|__| Gy
Total dose V2	|__|__|,|__|__| Gy
Dose/fraction V3	|__|__|,|__|__| Gy
Total dose V3	|__|__|,|__|__| Gy
Rectum V25	Value
Rectum V50	Value
Rectum V60	Value
Rectum D50	Value
Rectum Dmax	Value
Bladder Dmax	Value
Bladder D50	Value
Bladder V50	Value
Bladder V70	Value
Penile Bulb Dmax	Value
Penile Bulb D90	Value
Small bowel V15 (contouring individual bowel loops)*	Value
Small bowel V45 (contour peritoneal space)*	Value
*contouring of the peritoneal space is required for all patients, optional contouring individual bowel loops	
Target volume V1	1 Prostate only 2 Prostate and basis of seminal vescicles 3 Prostate and seminal vescicles 4 Prostate plus pelvis (nodal volume) 5 Prostate and seminal vescicles and pelvis (nodal volume)

Target volume V2	1 Prostate plus pelvis 2 Nodal volume only 3 Prostate and seminal vescicles 4 Prostate and basis of seminal vescicles 5 Prostate only
Target volume V3	1 Nodal volume only 2 Prostate and seminal vescicles 3 Prostate and basis of seminal vescicles 4 Prostate only
Association with hormonal therapy	1 Radiotherapy alone 2 Radiotherapy and neoadjuvant hormonal therapy (before radiation therapy) 3 Radiotherapy and adjuvant hormonal therapy (after radiation therapy) 4 Radiotherapy and neoadjuvant + adjuvant hormonal therapy

Hormonal therapy		
Type of hormonal therapy	1	ADT
	2	Periferic Antiandrogen If antiandrogen, specify the type: 1 Acetate ciproterone 2 Bicalutamide 3 Flutamide 4 Other, specify_____ If antiandrogen, specify the dose: _____
	3	LHRH Agonist (or GnRH)
	4	LHRH Antagonist (or GnRH)
	5	Other, specify _____
Date of starting hormonal therapy	|__|__| / |__|__| / |__|__|__|__| day month year

Acute Toxicities

Rectal Acute Toxicity (Grade)		Date Tox.	
Urinary Acute Toxicity (Grade)		Date Tox.	
Small Intestine Acute Toxicity (Grade)		Date Tox.	

GI Acute Toxicity (small bowel) (see Table 1)	select (1=G0, 2=G1, 3=G2, 4=G3, 5=G4, 6=Unknown) Date yyyy-mm-dd
Rectal Acute Toxicity	select (1=G0, 2=G1, 3=G2, 4=G3, 5=G4, 6=Unknown) Date yyyy-mm-dd
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Late Toxicity bladder/ rectum	select (1=Yes, 2=No, 3=Unknown) Date yyyy-mm-dd
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Cystitis	select (1=G0, 2=G1, 3=G2, 4=G3, 5=G4, 6= Unknown) Date yyyy-mm-dd
Impotence	select (1=No, 2=Yes pre RT, 3=Yes post RT, 4= Unknown) Date yyyy-mm-dd
Incontinence	select (1=No, 2=Yes pre RT, 3=Yes post RT, 4=Unknown)

TABLE 1 – Toxicity

RECTAL/SMALL BOWEL Acute TOX
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G4: Acute or subacute obstruction, fistula or perforation, haemorrhage requiring blood transfusion. Abdominal pain or tenesmus requiring ileostomy

BLADDER Acute TOX
G0: No Toxicity
G1: Low urinary tract symptoms (LUTS) and dysuria not requiring any treatment
G2: LUTS, dysuria and urgency requiring treatment or anaesthetics
G3: Severe LUTS, urgency, dysuria, pelvic pain or bladder spasms and haematuria
G4: Haematuria requiring blood transfusion, urinary obstruction, ulceration and necrosis

Late TOX PROCTITIS
G0: No Toxicity
G1: Mild rectal pain, Slight diarrhoea (less than 5 discharges). Small bleeding
G2: Diarrhoea (more than 5 discharges). Significant mucosal secretions and intermittent rectal bleeding
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Late TOX CYSTITIS
G0: No Toxicity
G1: Slight epithelial atrophy, small telangiectasia, microscopic haematuria
G2: Moderate LUTS, Intermittent macroscopic haematuria
G3: Severe LUTS and dysuria spread of telangiectasia. Frequent haematuria. Reduction in bladder capacity (less than 150 cc)
G4: Necrosis, bladder capacity reduced (less than 100 cc). Severe haemorrhagic cystitis

SF-12 STANDARD ITALIAN VERSION

(Apolone G et al. 2001)

		Excellent	Very good	Good	Fair	Poor
1	In general, you would say that your health condition is:	1	2	3	4	5

The following questions regard some activities you might do during a typical day. Does <u>your health condition actually</u> limit you in doing these activities?

		Yes, it limits a lot	Yes, it limits a little	No, it does not limit at all
2	**Activities of moderate physical effort** , such as moving a table , using the vacuum cleaner , playing bowls or a riding a bicycle	1	2	3
3	Climbing **several** flights of stairs	1	2	3

During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your physical health condition</u>?

		Yes	No
4	**Accomplished less** than you would like	1	2
5	You had to limit certain **kinds** of occupation or other activities	1	2

During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your emotional state (such as feeling depressed or anxious)</u>?

		Yes	No
6	**Accomplished less** than you would like	1	2
7	You did not do work or other activities as **carefully** as usual	1	2

		Not at all	A little bit	Moderately	Quite a bit	Not at all
8	<u>During the last 4 weeks</u>, How much has pain hindered your usual work (at home and outside)?	1	2	3	4	5

How long <u>during the last 4 weeks</u> have you felt

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	All of the time
9	calm and serene?	1	2	3	4	5	6
10	full of energy?	1	2	3	4	5	6
11	discouraged and sad	1	2	3	4	5	6

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time
12	<u>During the last 4 weeks,</u> how long have your <u>physical health condition or your emotional state</u> interfered with your social activities, with family, with friends?	1	2	3	4	5

COMPLICATIONS DUE TO PROSTATE CANCER

ITALIAN UCLA PROSTATE CANCER INDEX

(Gacci M et al, 2005)

URINARY FUNCTION

This session regards the urinary routine. Please consider only the last 4 weeks.

1. Over the LAST 4 WEEKS, how often have you leaked urine?
   1 Every day.
   2 About once a week
   3 Less than once a week
   4 Not at all.

2. Which of the following best describes your urinary control during the LAST 4 WEEKS?
   1 No control whatsoever
   2 Frequent dribbling
   3 Occasional dribbling
   4 Total control

3. How many pads or adult diapers per day have you usually used to control leakage during the LAST 4 WEEKS?
   1 3 or more pads per day
   2 1-2 pads per day
   3 No pads

4. How big a problem, if any, has each of the following been for you?
   Dripping urine or wetting your pants?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

   Urine leakage interfering with your sexual activity?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

5. Overall, how big a problem has your urinary function been for you during the LAST 4 WEEKS?
   0 No problem
   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

BOWEL FUNCTION

The following section talks about all the bowel function and abdominal pain. Please consider only the last 4 weeks.

6. How often have you had rectal urgency (felt like you had to pass stool, but did not) during the LAST 4 WEEKS?
   1 More than once a day
   2 About once a day
   3 More than once a week
   4 About once a week
   5 Rarely or never

7. How much distress have your bowel movements caused you during the LAST 4 WEEKS?
   1 Severe distress

2 Moderate distress
3 A little distress
4 No distress

8. How often have you had crampy pain in your abdomen or pelvis during the LAST 4 WEEKS?
1 Several times a day
2 About once a day
3 Several times a week
4 About once this month
5 Rarely or never

9. In particular, how big was the problem of bowel habits during the LAST 4 WEEKS?
1 Big problem
2 Moderate problem
3 Little problem
4 Very small problem
5 No problem

SEXUAL FUNCTION

THE NEXT SECTION IS ABOUT YOUR SEXUAL FUNCTION AND SEXUAL SATISFACTION. MANY OF THE QUESTIONS ARE VERY PERSONAL, BUT THEY WILL HELP US UNDERSTAND THE IMPORTANT ISSUES THAT YOU FACE EVERY DAY. REMEMBER THAT YOUR ANSWERS TO THIS QUESTIONNAIRE WILL BE KEPT CONFIDENTIAL AND WILL BE USED ONLY FOR RESEARCH PURPOSES. PLEASE ANSWER HONESTLY ABOUT THE LAST 4 WEEKS ONLY.

10. HOW WOULD YOU RATE EACH OF THE FOLLOWING DURING THE LAST 4 WEEKS?

	Very poor	Poor	Fair	Good	Very good
A. Your ability to have an erection?.	1	2	3	4	5
B. Your ability to reach orgasm (clima	1	2	3	4	5

11. How would you describe the usual QUALITY of your erections?
1 None at all
2 Not firm enough for any sexual activity
3 Firm enough for masturbation and foreplay only
4 Firm enough for intercourse

12. How would you describe the FREQUENCY of your erections?
1 I NEVER had an erection when I wanted one
2 I had an erection LESS THAN HALF the time I wanted one
3 I had an erection ABOUT HALF the time I wanted one
4 I had an erection MORE THAN HALF the time I wanted one
5 I had an erection WHENEVER I wanted one

13. Overall, how would you rate your sexual function during the LAST 4 WEEKS?
1 Very poor
2 Poor
3 Fair
4 Good
5 Very good

14. Overall, how big a problem has your sexual function been for you during the LAST 4 WEEKS?
1 No problem
2 Very small problem
3 Small problem
4 Moderate problem
5 Big problem

ATTACHMENT 3 – 3, 6, 9, 12, 18, 24, 36 MONTHS FOLLOW UP

At ….. months from Radiation Therapy, the patient is:	1 **Alive** 1 NED – *no evidence of disease*
	2 With biochemical recurrence (<u>only</u> defined by PSA level according to Phoenix Criteria[1]) Date of defining <u>biochemical recurrence</u> |__|__| / |__|__| / |__|__|__|__| day month year
	3 With biochemical and clinical recurrence (<u>also</u> defined through methods other than PSA level): o Clinical examination o ultrasonography o MRI o CT scan o Bone scintigraphy o PET-choline Date of defining <u>clinical recurrence</u> |__|__| / |__|__| / |__|__|__|__| day month year
	4 [metastatic]Castration Resistant Prostate Cancer ([<u>m</u>]<u>CRPC</u> according to EAU guidelines[2-3]): o Oligometastases (max 3 lesions in max 2 non-visceral districts) o Extended disease Type of [m]CRPC: o Local and/or nodal (pelvic and lumbar-aortic) o Only bone metastases o local bone and nodal o visceral Date of defining [m]CRPC |__|__| / |__|__| / |__|__|__|__| day month year **Plasmatic Testosterone at [m]CRPC** |__|__|__|__|.|__|__|__|ng/mL
	2 **Died** Date of the death |__|__| / |__|__| / |__|__|__|__| day month year Cause of the death _____
	3 **Lost at follow-up, explain the reason:**

	1He does not adhere anymore for health reasons, specify_____ 2He is not interested anymore to take part in the study 3He is not traceable
Does the patient still undergo Hormonal Therapy?	1. Yes If yes: (FILL IN POINT **4** BELOW) 0 No If no: **Date of ending hormonal therapy** |__|__| / |__|__| / |__|__|__|__| day month year
Has he developed new comorbidities? **(It is possible to fill in more than one option)**	0 . No 1 . Yes If yes: 1 Cardiac (specify _____) 2 Vascular (including hypertension) 3 Pulmonary (specify _____) 4 Eye, ear, nose, throat, larynx 5 Gastro-intestinal (specify _____) 6 Hepatic (liver only) 7 Renal (kidneys only) 8 Musculo-skeletal (specify _____) 9 Intertegumentary (skin) 10 Neurological (specify _____) 11 Endocrine-metabolic (specify _____) 12 Cognitive-psychiatric, behaviour 13 Genito-urinary (ureter-genitals) (specify _____) 14 Other malignancies (including Haematopoietic malignancies)

	15 Other, specify _____
Has he undergone further treatments for prostate cancer, subsequent to those reported in Attachment 1 (1-month follow up)?	0 No 1 Yes If yes: 1 Surgery 2 External Beam Radiation Therapy 3 Brachytherapy 4 Radiometabolic Therapy 5 Hormonal Therapy 6 Focal Therapy 7 Chemotherapy 8 Others, specify _____

If he has undergone further treatments, specify:

Date of starting the new treatment |__|__| / |__|__| / |__|__|__|__|

day month year

PSA before starting the new treatment |__|__|__|__|.|__|__|__| ng/mL

1 External Beam Radiotherapy

Aim of Radiotherapy	1	Palliative
	2	Other, specify_____
Modality	1	IGRT
	2	Non IGRT
Technique	1	3D-CRT
	2	IMRT
	3	SBRT (stereotactic body radiotherapy)
If palliative Radiotherapy, site	1	Bone lesions

		2	Nodal lesions
		3	Visceral metastases
		4	Pelvic lesions
		5	Others
	Dose/fraction	|__|__|,|__|__| Gy	
	Total dose	|__|__|,|__|__| Gy	
	Association with Hormonal Therapy	1	Radiotherapy alone
		2	Radiotherapy and neoadjuvant Hormonal Therapy (before RT)
		3	Radiotherapy and adjuvant Hormonal Therapy (after RT)
		4	Radiotherapy and neoadjuvant + adjuvant Hormonal Therapy
2	**Brachytherapy**		
	Type of brachytherapy	1	LDR (internal radiation therapy)
		2	HDR
	Aim of brachytherapy	1	Exclusive
		2	Other, specify_____
3	**Radiometabolic Therapy**		
	If yes	1	With alfa-emittent particles
		2	Other, specify _____
4	**Hormonal Therapy**		
	Type of Hormonal Therapy	1	ADT
		2	Antiandrogen

		If antiandrogen, specify the type: 1 Ciproterone acetate 2 Bicalutamide 3 Flutamide 4 Other, specify_____ If antiandrogen, specify the dose: _____
		3 LHRH-Agonist (or GnRH) 4 LHRH-Antagonist (or GnRH) 5 Other, specify _____
	The used drugs	_____
5	**Focal Therapy**	
	Type of Focal Therapy	1 High Intensity Focused Ultrasound 2 Criotherapy 3 Other, specify _____
	Aim of Focal Therapy	1 Curative 2 Palliative 3 Other, specify_____
6	**Chemotherapy**	
	Type of drug	_____
	Treatment scheme	
7	**Second line Hormonal Therapy**	
	Type of drug	
	Treatment scheme	

<u>Has he planned further treatments</u> related to prostate cancer, subsequent to those reported in Attachment 1 (1-month follow up)?	0 No 1 Yes, specify: If yes: 1 Surgery 2 Esternal Beam Radiation Therapy 3 Brachytherapy 4 Radiometabolic Therapy 5 Hormonal Therapy 6 Focal Therapy 7 Chemotherapy 8 Others, specify _____
If he does not have undergone further treatments, is he able to remember the last PSA value?	1 Yes If yes: PSA |__|__|__|__|.|__|__|__|ng/mL Date of the PSA value test |__|__| / |__|__| / |__|__|__|__| day month year 0 No If no: Does he agree to ask it to his family doctor? 0 No 1 Yes What is his family doctor's name? _____ PSA referred by the family doctor |__|__|__|__|.|__|__|__|ng/mL Date of the PSA value test referred by the family doctor |__|__| / |__|__| / |__|__|__|__| day month year

References

1. Buyyounouski MK, Hanlon AL, Eisenberg DF, Horwitz EM, Feigenberg SJ, Uzzo RG, Pollack A. "Defining biochemical failure after radiotherapy with and without androgen deprivation for prostate cancer", Int J Radiat Oncol Biol Phys. 2005; 63(5):1455-62.
2. Heidenreich A, Bastian PJ, Bellmunt J "EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer", Eur Urol 2014; 65: 467-479.
3. Kirby M, Hirst C, Crawford ED "Characterising the castration-resistant prostate cancer population: a systematic review", Int J Clin Pract 2011; 65(11):1180–1192.

Acute Toxicities

Rectal Acute Toxicity (Grade)		Date Tox.	
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SF-12 STANDARD ITALIAN VERSION

(Apolone G et al. 2001)

		Excellent	Very good	Good	Fair	Poor
1	In general, you would say that your health condition is:	1	2	3	4	5

The following questions regard some activities you might do during a typical day. Does <u>your health condition actually</u> limit you in doing these activities?

		Yes, it limits a lot	Yes, it limits a little	No, it does not limit at all
2	**Activities of moderate physical effort** , such as moving a table , using the vacuum cleaner , playing bowls or a riding a bicycle	1	2	3
3	Climbing **several** flights of stairs	1	2	3

During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your physical health condition</u>?

		Yes	No
4	**Accomplished less** than you would like	1	2
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During the <u>last 4 weeks</u> have you had the following problems at work or during other daily activities, <u>because of your emotional state (such as feeling depressed or anxious)</u>?

		Yes	No
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7	You did not do work or other activities as **carefully** as usual	1	2

		Not at all	A little bit	Moderately	Quite a bit	Not at all
8	<u>During the last 4 weeks</u>, How much has pain hindered your usual work (at home and outside)?	1	2	3	4	5

How long <u>during the last 4 weeks</u> have you felt

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	All of the time
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11	discouraged and sad	1	2	3	4	5	6

		All of the time	Most of the time	A good bit of time	Some of the time	A little of the time
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COMPLICATIONS DUE TO PROSTATE CANCER

ITALIAN UCLA PROSTATE CANCER INDEX

(Gacci M et al, 2005)

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This session regards the urinary routine. Please consider only the last 4 weeks.

1. Over the LAST 4 WEEKS, how often have you leaked urine?
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   2 About once a week
   3 Less than once a week
   4 Not at all.

2. Which of the following best describes your urinary control during the LAST 4 WEEKS?
   1 No control whatsoever
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   3 Occasional dribbling
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3. How many pads or adult diapers per day have you usually used to control leakage during the LAST 4 WEEKS?
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4. How big a problem, if any, has each of the following been for you?
   Dripping urine or wetting your pants?
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   1 Very small problem
   2 Small problem
   3 Moderate problem
   4 Big problem

   Urine leakage interfering with your sexual activity?
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   2 Small problem
   3 Moderate problem
   4 Big problem

5. Overall, how big a problem has your urinary function been for you during the LAST 4 WEEKS?
   0 No problem
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BOWEL FUNCTION

The following section talks about all the bowel function and abdominal pain. Please consider only the last 4 weeks.

6. How often have you had rectal urgency (felt like you had to pass stool, but did not) during the LAST 4 WEEKS?
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   4 About once a week
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7. How much distress have your bowel movements caused you during the LAST 4 WEEKS?
   1 Severe distress

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9. In particular, how big was the problem of bowel habits during the LAST 4 WEEKS?
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SEXUAL FUNCTION

THE NEXT SECTION IS ABOUT YOUR SEXUAL FUNCTION AND SEXUAL SATISFACTION. MANY OF THE QUESTIONS ARE VERY PERSONAL, BUT THEY WILL HELP US UNDERSTAND THE IMPORTANT ISSUES THAT YOU FACE EVERY DAY. REMEMBER THAT YOUR ANSWERS TO THIS QUESTIONNAIRE WILL BE KEPT CONFIDENTIAL AND WILL BE USED ONLY FOR RESEARCH PURPOSES. PLEASE ANSWER HONESTLY ABOUT THE LAST 4 WEEKS ONLY.

10. HOW WOULD YOU RATE EACH OF THE FOLLOWING DURING THE LAST 4 WEEKS?

	Very poor	Poor	Fair	Good	Very good
A. Your ability to have an erection?.	1	2	3	4	5
B. Your ability to reach orgasm (clima	1	2	3	4	5

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5 I had an erection WHENEVER I wanted one

13. Overall, how would you rate your sexual function during the LAST 4 WEEKS?
1 Very poor
2 Poor
3 Fair
4 Good
5 Very good

14. Overall, how big a problem has your sexual function been for you during the LAST 4 WEEKS?
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