“Innovazioni tecnologiche in Radioterapia"

Sergio Fersino

Radioterapia Oncologica

Sacro Cuore Don Calabria
CCC
Cancer Care Center
Negrar - Verona

HYPOFRACTIONATION & PROSTATE CANCER

2014

EXPERT REVIEWS

From radiobiology to technology: what is changing in radiotherapy for prostate cancer

Expert Rev. Anticancer Ther. Early online, 1–12 (2014)

Berardino De Bari[1], Alba Fiorentino*[2], Stefano Arcangeli[3], Pierfrancesco Franco[4], Rolando Maria D'Angelillo[5] and Filippo Alongi[2]

[1]*Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois – CHUV, Lausanne, Switzerland*
[2]*Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, Via Sempreboni 5, 37024 Negrar-Verona,*

In the last decades, new technologies have been introduced in the daily clinical practice of the radiation oncologist: 3D-Conformal radiotherapy (RT) became almost universally available, thereafter, intensity modulated RT (IMRT) gained large diffusion, due to its potential impact in improving the clinical outcomes, and more recently, helical and volumetric arc IMRT with image-guided RT are becoming more and more diffused and used for prostate cancer patients. The conventional dose-fractionation results to be the best compromise between the efficacy and the safety of the treatment, but combining new techniques, modern RT allows to overcame one of the major limits of the 'older' RT: the impossibility of delivering higher total doses and/or high dose/fraction. The evidences regarding radiobiology, clinical and technological evolution of RT in prostate cancer have been reported and discussed.

KEYWORDS: outcome • prostate cancer • radiobiology • radiotherapy • technique • technology

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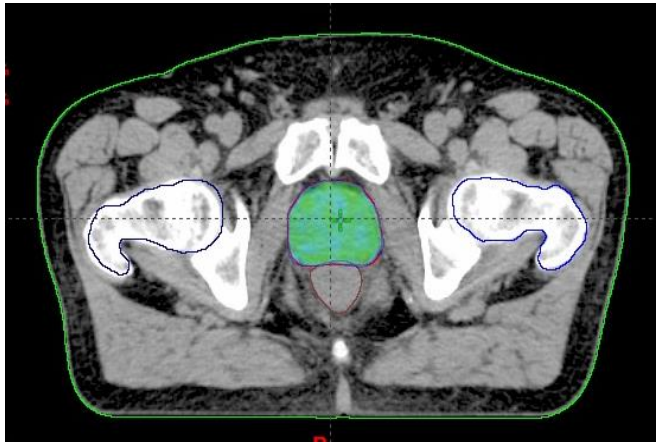
HYPOFRACTIONATION & PROSTATE CANCER:

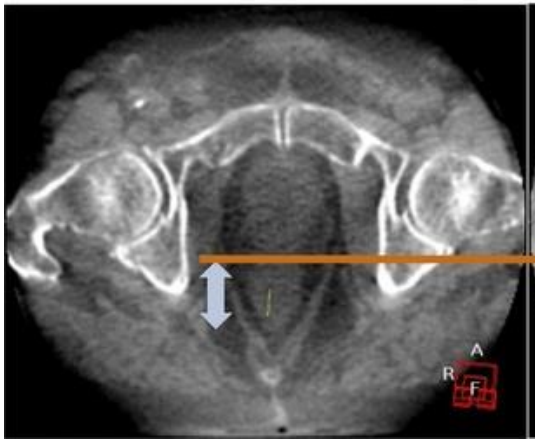
TECHNOLOGY:

HIGH CONFORMAL DOSE & IMAGING ON BOARD

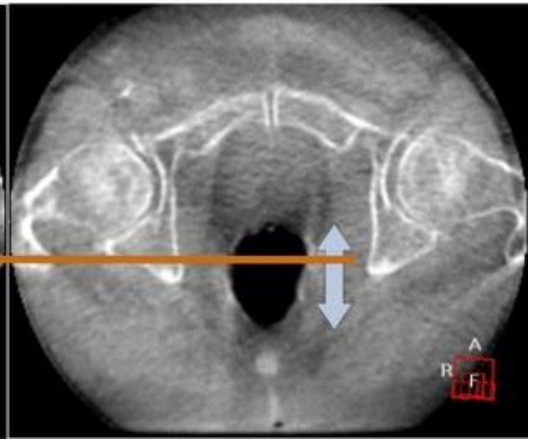
Planning



Treatment day one



Treatment day two



IMRT and similar

> TARGET DOSE
< OARs TOXICITY
DURING ***PRESCRIPTION***

DAILY IGRT

> TARGET DOSE
< OARs TOXICITY
DURING ***DELIVERY***

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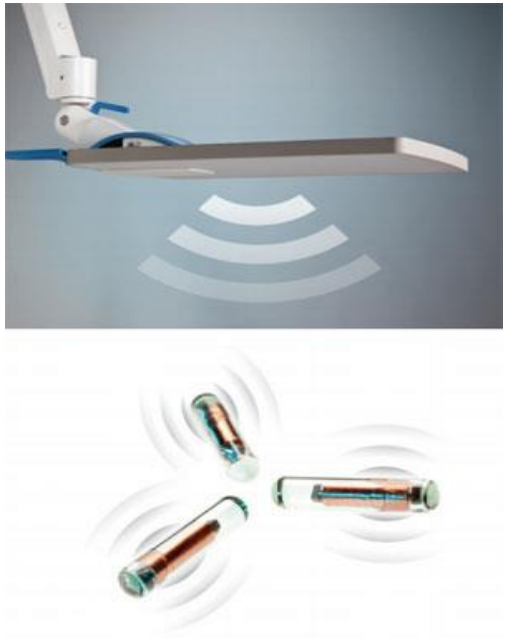
HYPOFRACTIONATION & PROSTATE CANCER:

TECHNOLOGY:

PROSTATE MOTION MANAGEMENT BY REAL TIME TUMOR TRACKING



LINAC INTEGRATED DEVICES

DEDICATED ROBOTIC LINAC WITH INTEGRATED TRECKING SYSTEMS

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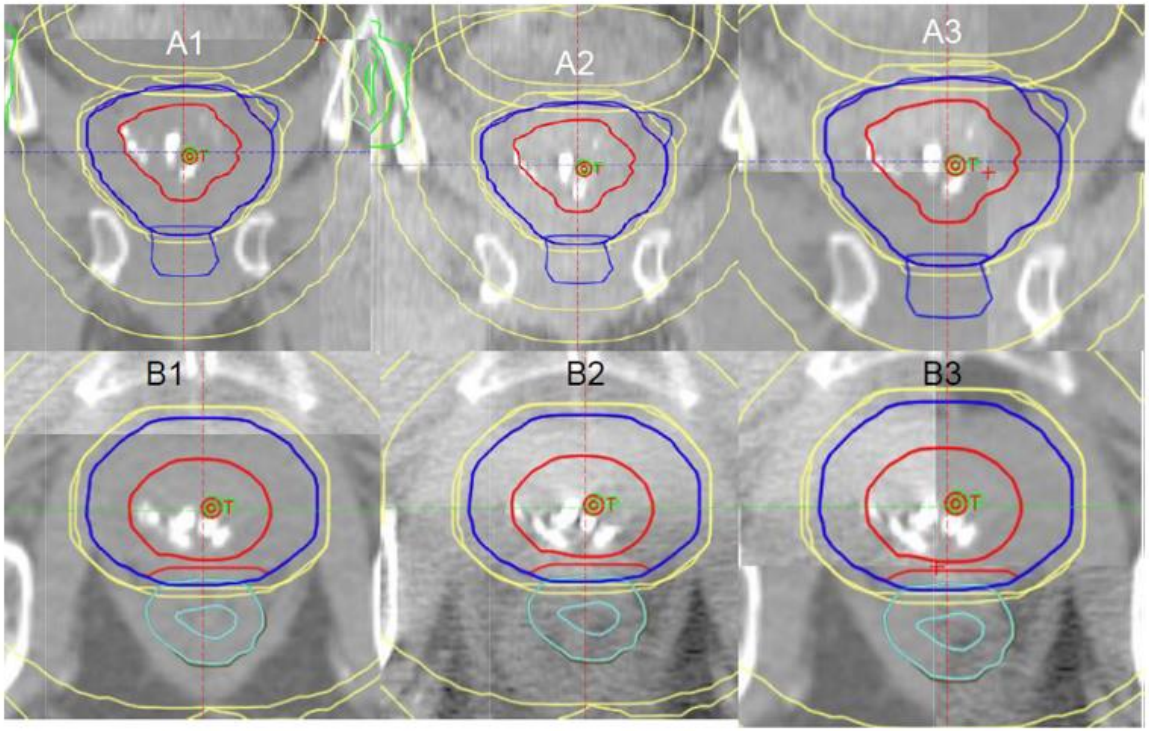
HYPOFRACTIONATION & PROSTATE CANCER:

TECHNOLOGY:

PROSTATE MOTION MANAGEMENT

Intraprostatic calcifications as natural fiducial markers in image-guided radiotherapy for prostate cancer

A. Sbai [a,*], J. Thariat [b,c], N. Tachfouti [d], Q. Pan [e], J.-L. Lagrange [e,f]



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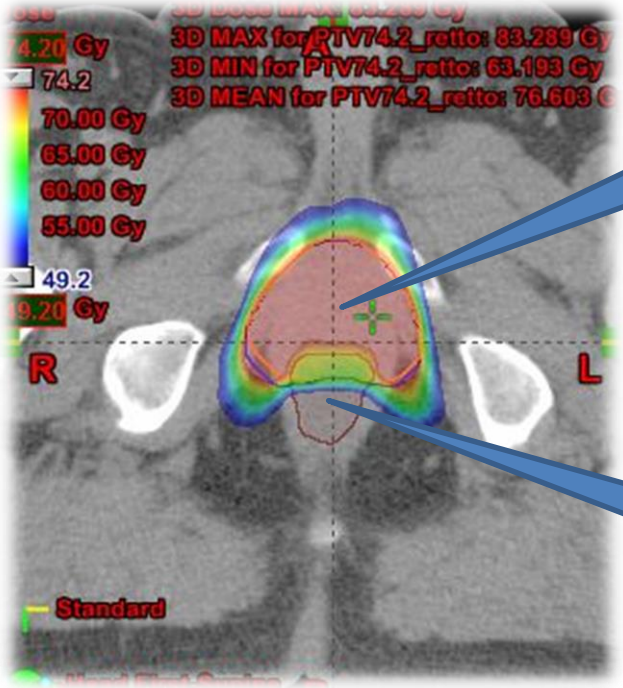
HYPOFRACTIONATION & PROSTATE CANCER:

RADIOBIOLOGICAL CONSIDERATION

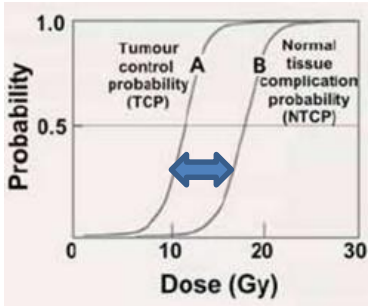
✓Prostate cancer seems particularly suitable for hypofractionated RT having unique sensitivity to increased radiation dose fractions compared to surrounding healthy tissues



Prostate, α/β
RATIO= 1.5(?)

Rectum, α/β
RATIO= 3

HYPOFRACTIONATION
=
ENLARGING
THERAPEUTIC WINDOW



HOW WE TREAT PROSTATE CANCER?

MODERATE HYPOFRATIONATION: OWN BACKGROUND

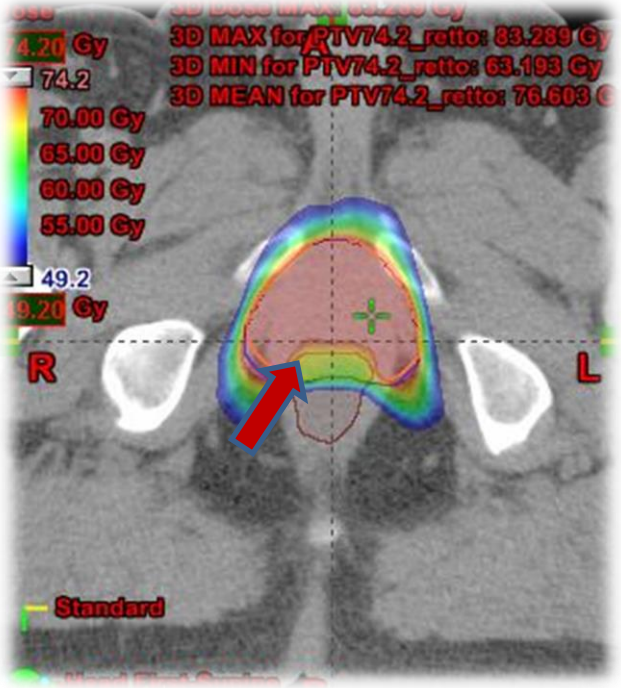
Prostate, seminal vesicles, pelvic lymph node in 28 fractions with VMAT(RAPIDARC)/IGRT on TRILOGY™

Strahlenther Onkol 2012
DOI 10.1007/s00066-012-0171-7
Received: 05 April 2012
Accepted: 13 June 2012

F. Alongi[1] · A. Fogliata[2] · P. Navarria[1] · A. Tozzi[1] · P. Mancosu[1] · F. Lobefalo[1] · G. Reggiori[1] · A. Clivio[2] · L. Cozzi[2] · M. Scorsetti[1]
[1] Department of Radiotherapy, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Milan
[2] Medical Physics Unit, Oncology Institute of Southern Switzerland, Bellinzona

Moderate hypofractionation and simultaneous integrated boost with volumetric modulated arc therapy (RapidArc) for prostate cancer

Report of feasibility and acute toxicity



The margin between CTV and PTV were 8 mm in all direction (including posterioly) but….
In several cases constraining the rectal region overlapping the PTV to receive no more than 65.5 Gy.

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

✓Trials investigating clinical and toxicity outcomes of moderate hypofractionation schedules **have sufficient follow-up** data to show that efficacy and toxicity of these schedules are similar to those of conventionally fractionated regimens
(**non inferiority of Hypo arms**)

✓More specifically, based on **evidence level 1B**, dose-escalated conventionally fractionated RT with IMRT appears to have similar outcomes and toxicities to hypofractionated RT with IMRT.

Arcangeli et al, Nature Review Urology 2016
Zaorsky et al, Cancer Treatment Review 2016

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Prostate Cancer Table of Contents

NCCN Guidelines Index
Prostate Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy (EBRT)

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Moderately hypofractionated image-guided IMRT regimens (2.4 to 4 Gy per fraction over 4-6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.

Moderate Hypofractionation (from 35-42 fractions to 20-28)?
YES!!

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EXSTREME HYPOFRACTIONATION & PROSTATE CANCER

What about Extreme hypofractionation, especially ….the most common 5 session SBRT approach also called…

EXTREME HYPOFRACTIONATION & PROSTATE CANCER

2012

ELSEVIER

Critical Reviews in Oncology/Hematology xxx (2012) xxx–xxx

CRITICAL REVIEWS IN *Oncology Hematology* Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review

Stefano Arcangeli*, Marta Scorsetti, Filippo Alongi

Radiotherapy and Radiosurgery department, Istituto Clinico Humanitas, Humanitas Cancer Center, Rozzano, Milano, Italy

Accepted 23 November 2011

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY XXX (2014) XXX–XXX

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

2014

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

SBRT and extreme hypofractionation: A new era in prostate cancer treatments?

Filippo Alongi[a,*], *Alba Fiorentino*[a], *Berardino De Bari*[b]

[a] *Radiation Oncology Department, Sacro Cuore Hospital, Negrar-Verona, Italy*

[b] *Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanna, Switzerland*

- Low a/B ratio could justify the significant reduction of fractions to increase the therapeutic window
- A Potential technology gain derives from the use of upgraded IGRT, IMRT or integration of both.
- Modern SBRT adopts static, dynamic or volumetric IMRT techniques to provide sharper dose fall-offs and better dose conformity

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EXTREME HYPOFRACTIONATION & PROSTATE CANCER

National Comprehensive Cancer Network®

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PRINCIPLES OF RADIATION THERAPY

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Extreme Hypofractionation (from 35-42 fractions to 3-5)?
YES, but in selected cases and inside protocols!!

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RADIATION ONCOLOGY DEPARTMENT

VARIAN TRILOGY

VARIAN TRILOGY

(BrainLab Equipped)

TRUEBEAM 2.0

(Brain Lab & Calypso Equipped)

HOW WE TREAT PROSTATE CANCER?

MODERATE HYPOFRACTIONATION

Volumes:
Prostate, seminal vesicles, pelvic lymph nodes

Fractions:
20 or 28 fractions

Technique:
VMAT(RAPIDARC)/IGRT
on TRILOGY™

Inclusion Criteria:
- low, intermediate, high risk
- prostate gland >80cc
- IPSS: from 0-20

EXTREME HYPOFRACTIONATION

Volumes:
Prostate only or prostate plus vesicles

Fractions:
5 fractions

Technique:
SBRT by VMAT(RAPIDARC)/IGRT and FFF delivery on TRUE BEAM with or without Calypso System™

Inclusion Criteria:
- low, intermediate risk
- Prostate gland <80 cc
- IPSS:0-7

2 Protocols:
- *37.5Gy in 5 fractions intermediate risk, urethral sparing (Phase II Trial ethical commitee approval)*
- *35 Gy in 5 fractions (out of trial)*

SPACE OAR IN SELECTED CASES

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HOW WE TREAT PROSTATE CANCER?

CAN **SPACEOAR™** IMPROVE RECTAL SPARING WHEN USED IN **MODERATE** HYPOFRACTIONATION REGIMEN?

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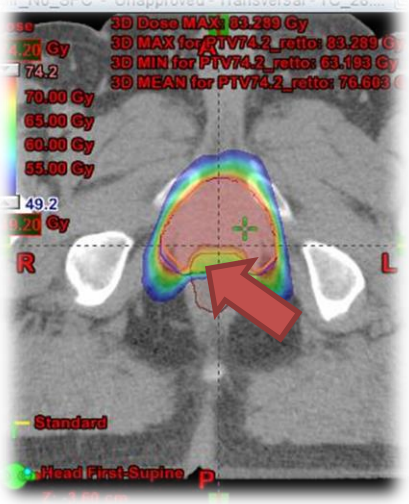
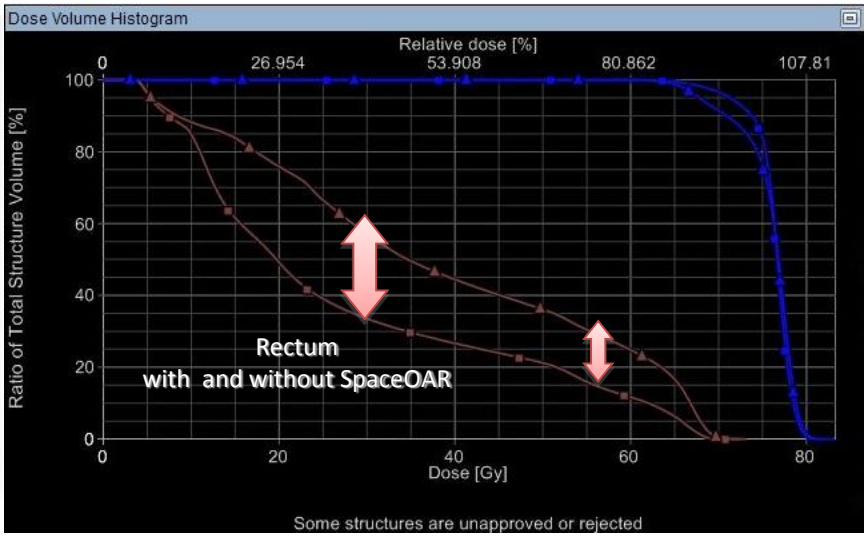
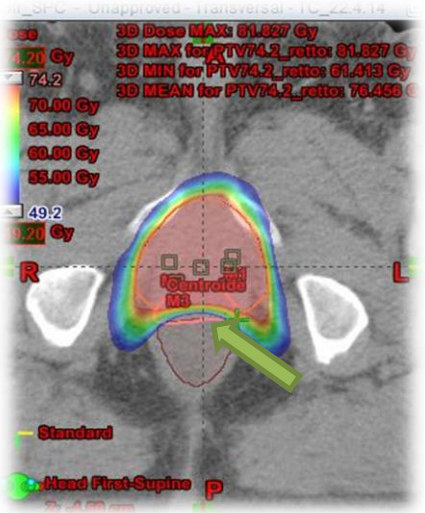
USEFUL OF SPACEOAR™ IN MODERATE HYPOFRACTIONATION:

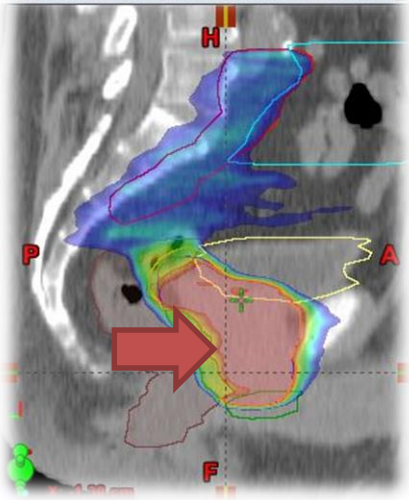
NO SPACER





SPACER

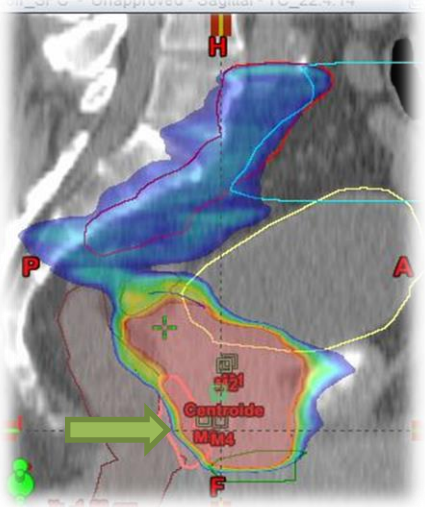




MODERATE HYPOFRATIONATION PLAN COMPARISON WITHOUT AND WITH SPACEOAR

NO HIGH DOSE IN ANTERIOR RECTAL WALL

NO NEED OF REDUCTION OF DOSE IN THE OVERLAP BETWEEN RECTUM AND PROSTATE PTV



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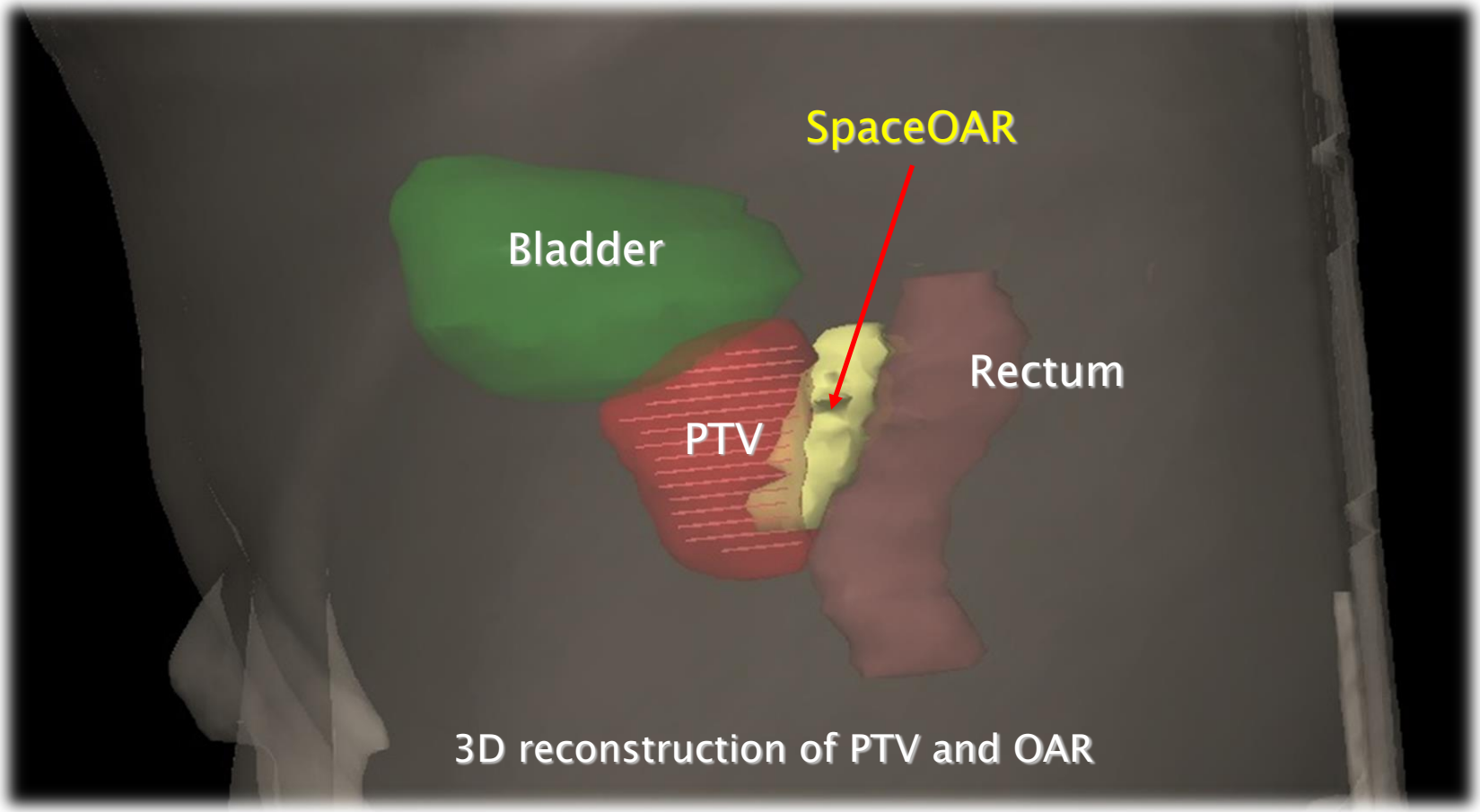
SPACEOAR IN PROSTATE PLANNING



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HOW WE TREAT PROSTATE CANCER?

CAN **SPACEOAR™** IMPROVE RECTAL SPARING WHEN USED IN **EXTREME** HYPOFRACTIONATION REGIMEN?

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HOW WE TREAT PROSTATE CANCER?

EXTREME HYPOFRATIONATION: OWN BACKGROUND

Prostate plus or minus seminal vesicles, 5 fractions with VMAT(RAPIDARC FFF DELIVERY)/IGRT on TRUEBEAM ™

Alongi *et al. Radiation Oncology* 2013, **8**:171
http://www.ro-journal.com/content/8/1/171

2011

RADIATION ONCOLOGY

RESEARCH Open Access

Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study

Filippo Alongi[1,4*], Luca Cozzi[2], Stefano Arcangeli[1], Cristina Iftode[1], Tiziana Comito[1], Elisa Villa[1], Francesca Lobefalo[1], Pierina Navarria[1], Giacomo Reggiori[1], Pietro Mancosu[1], Elena Clerici[1], Antonella Fogliata[2], Stefano Tomatis[1], Gianluigi Taverna[3], Pierpaolo Graziotti[3] and Marta Scorsetti[1]

J Cancer Res Clin Oncol
DOI 10.1007/s00432-014-1732-1

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

2014

Stereotactic body radiotherapy with flattening filter-free beams for prostate cancer: assessment of patient-reported quality of life

Marta Scorsetti · Filippo Alongi · Elena Clerici · Tiziana Comito · Antonella Fogliata · Cristina Iftode · Pietro Mancosu · Piera Navarria · Giacomo Reggiori · Stefano Tomatis · Elisa Villa · Luca Cozzi

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HOW TO TREAT PROSTATE CANCER?

EXTREME HYPOFRATIONATION: Rectal Damage??

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Genitourinary Cancer

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

*Departments of *Radiation Oncology and §Urology, ‡Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas; †Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota; ‖Department of Radiation Oncology, University of Colorado, Denver, Colorado; ¶Department of Radiation Oncology, University of Florida Health Cancer Center at Orlando Health, Orlando, Florida; #Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, California; and **Prairie Lakes Hospital, Watertown, South Dakota*

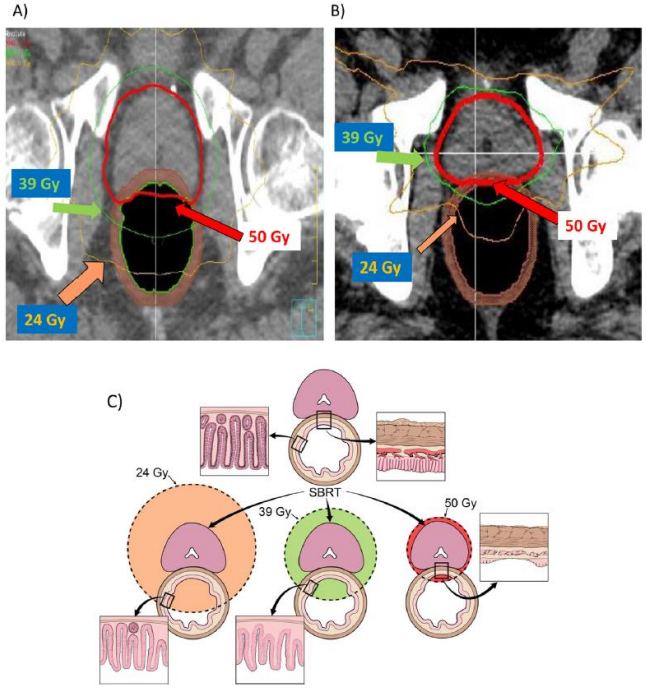

Fig. 2. Representative treatment plans of patients treated to 50 Gy in 5 fractions, with (A) grade 2 acute and grade 3 delayed rectal toxicity, and (B) grade 1 acute/delayed rectal toxicity only. (C) Representation of biologic consequence of rectal wall irradiated to 24 Gy, 39 Gy, and 50 Gy.

One potential strategy is to distance the anterior rectum from the prostate, to reduce dose to the rectum, such as that afforded by injectable rectal spacers (26-29). These spacers would likely be particularly effective at reducing the high dose associated with vascular/stromal injury and will likely lead to significant reduction of HGDRT.

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IMPACT OF SPACER IN SBRT: PUBLISHED REPORT

BJR
AN INTERNATIONAL JOURNAL OF RADIOLOGY, RADIATION ONCOLOGY AND ALL RELATED SCIENCES

2015

Volumetric-modulated arc stereotactic body radiotherapy for prostate cancer: dosimetric impact of an increased near-maximum target dose and of a rectal spacer

[1]RUGGERO RUGGIERI, PhD, [1]STEFANIA NACCARATO, PhD, [1]PAVEL STAVREV, PhD, [1]NADEJDA STAVREVA, PhD, [1]SERGIO FERSINO, MD, [1]NICCOLÒ GIAJ LEVRA, MD, [1]ROSARIO MAZZOLA, MD, [2]PIETRO MANCOSU, PhD, [2]MARTA SCORSETTI, MD and [1]FILIPPO ALONGI, MD

[1]Radiation Oncology, Ospedale Sacro Cuore Don Calabria, Verona, Italy
[2]Radiotherapy and Radiosurgery Department, IRCCS Istituto Clinico Humanitas, Milan, Italy

Study analysis of the first 11 patient

Clinical Results

All patients finished the treatment with a minimum FUP of 60 days after the end of the treatment.

Acute rectal toxicity was recorded as follow:

-2 patients experienced rectal G1 toxicity (tenesmus),

-1 patient complain G2 rectal pain needing drugs.

In 8 cases no rectal toxicity was documented within 6 months

IMPACT OF SPACER IN SBRT: PLANNING COMPARISON

BJR
AN INTERNATIONAL JOURNAL OF RADIOLOGY, RADIATION ONCOLOGY AND ALL RELATED SCIENCES

2015

(d_{pr})= at midgland slice, the distance in mm from the posterior edge of the prostate to the inner rectal wall

Study analysis of the first 11 patient

No spacer	*Spacer*
7.00	11.00
7.00	11.00
8.00	18.00
4.00	17.00
3.00	19.00
6.00	19.00
4.00	16.00
7.00	15.00
5.00	15.00
4.00	8.00
3.00	10.00

"Further, as a result of spacer insertion, mean (sd) d_{pr} values were increased from 5.3 (1.8) mm to 14.5 (3.9) mm (p=.000005)"

Ruggieri R et al. BJR 2015

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USEFUL OF SPACEOAR™ IN EXTREME HYPOFRACTIONATION:

SPACEOAR: pt. #1 in Negrar Cancer Care Center

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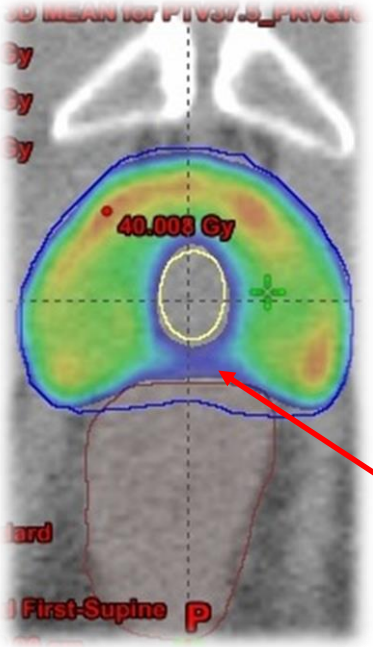
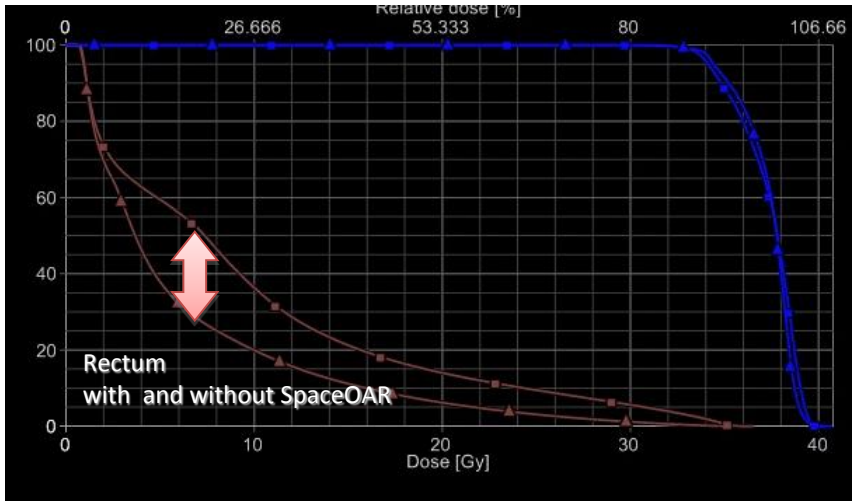
USEFUL OF SPACEOAR™ IN EXTREME HYPOFRACTIONATION:

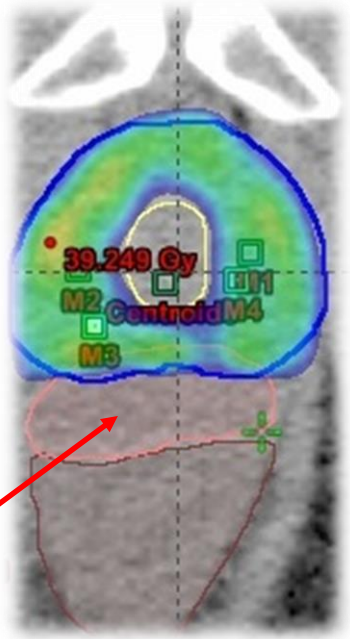
SPACEOAR™ PROTOCOL: *37.5 Gy in 5 fractions, urethral sparing*

NO SPACER





NO SPACER



Anterior Rectal wall

NO SPACEOAR
Dose Distribution
Isodose 95%

SPACEOAR
Dose distribution
Isodose 95%

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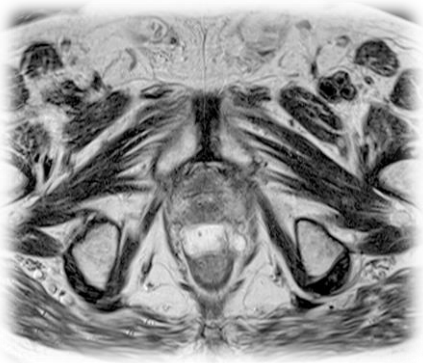
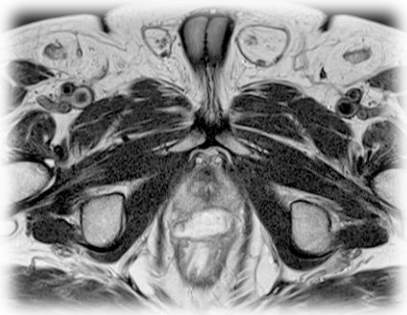
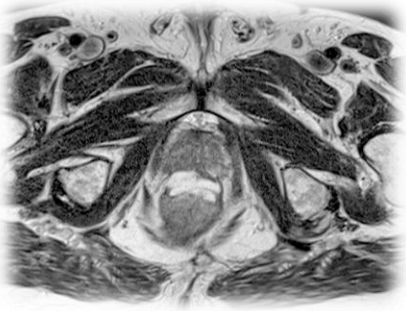
USEFUL OF SPACEOAR™ IN EXTREME HYPOFRACTIONATION:

SPACEOAR: other cases in Negrar Cancer Care Center







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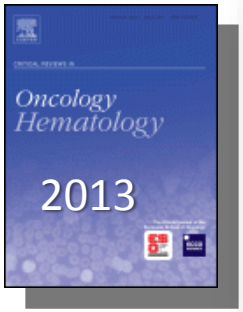
SBRT REIRRADATION: A NEW FRONTIER?



Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review

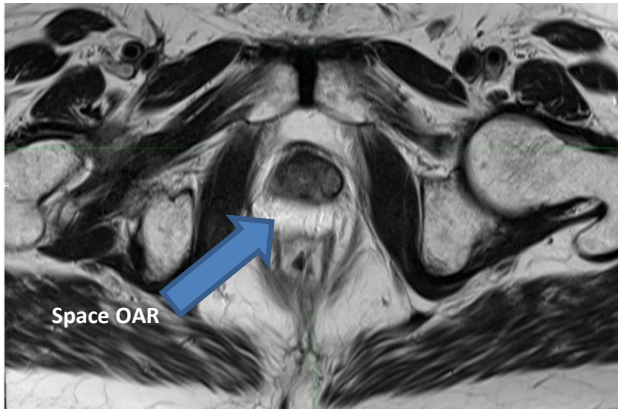
Filippo Alongi [a], Berardino De Bari [b,*], Franco Campostrini [c], Stefano Arcangeli [d], Deliu Victor Matei [e], Egesta Lopci [f], Giuseppe Petralia [g], Massimo Bellomi [g], Arturo Chiti [f], Stefano Maria Magrini [b], Marta Scorsetti [a], Roberto Orecchia [h], Barbara Alicja Jereczek-Fossa [h]

SBRT and hydrogel temporary spacer between prostate and rectum: a salvage re-irradiation strategy for prostate cancer recurrence

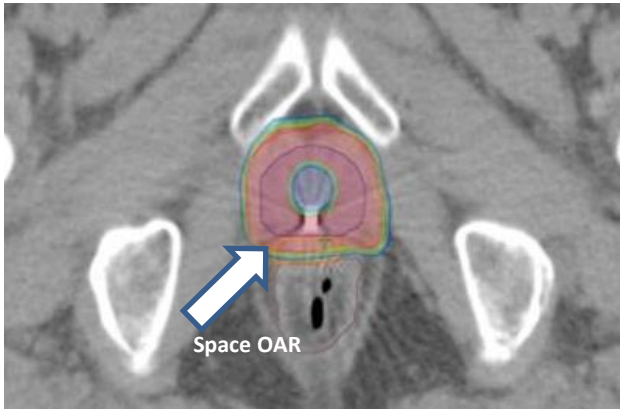
Alongi et al.Minerva Urologica e Nefrologica 2016

SBRT REIRRADATION: CLINICAL EXPERIENCE WITH SPACEOAR™

First course RT :76Gy in 2010 with 3DCRT
ADT for 3 years and still ongoing



Pre treatment MRI
Pre-RT PSA: 6.2ng/ml



Re-SBRT : 30Gy in 5 fractions
With VMAT FFF
Every other daydays

Post treatment MRI
Post-RT PSA: 2.68ng/ml

Alongi et al.Minerva Urologica e Nefrologica 2016

Sacro Cuore Don Calabria

Cancer Care Center Negrar - Verona

STEREOTACTIC BODY RT(SBRT):
LIMPH NODE OLIGOMTS

Alongi *et al. Radiation Oncology* 2012, **7**:204
http://www.ro-journal.com/content/7/1/204

RADIATION ONCOLOGY

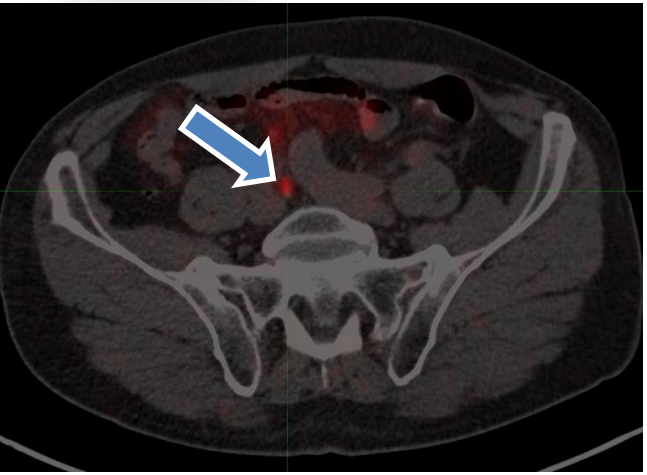
RESEARCH Open Access

Volumetric modulated arc therapy with flattening filter free beams for isolated abdominal/pelvic lymph nodes: report of dosimetric and early clinical results in oligometastatic patients

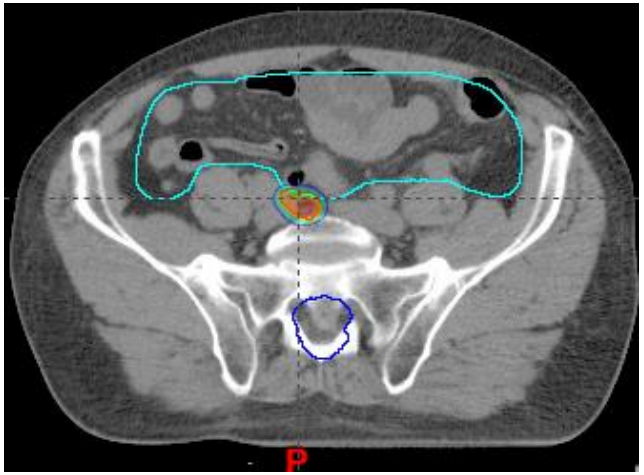
Filippo Alongi[1*], Antonella Fogliata[2], Elena Clerici[1], Pierina Navarria[1], Angelo Tozzi[1], Tiziana Comito[1], Anna Maria Ascolese[1], Alessandro Clivio[2], Francesca Lobefalo[1], Giacomo Reggiori[1], Luca Cozzi[2], Pietro Mancosu[1], Stefano Tomatis[1] and Marta Scorsetti[1]

Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

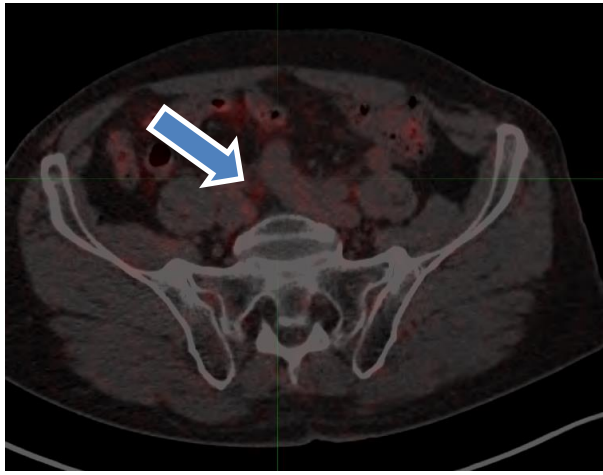
Criteri di Valutazione della risposta in Oncologia:
Monitoring Response after SABR
PSMA



PET/CT PSMA
before SBRT
PSA value: 0.14 ng/mL



SBRT PET/CT PSMA
Guided
30 Gy in 5 Fr



PET/CT PSMA
Post-SBRT
PSA value: 0.04 ng/mL

Conclusions

MODERATE HYPOFRACTIONATION

✓Phase III Trials of moderate hypofractionation **have sufficient follow-up** data to confirm that efficacy and tolerability are similar to those of conventionally fractionated regimens (Level I b).

✓Using **IMRT for Hyfractionation** is possible to reduce potential minimal risks of greater late toxicities.

EXTREME HYPOFRACTIONATION

✓Phase I-II Trials are promising but **have not sufficient follow-up** data to confirm that efficacy and tolerability are similar to those of conventionally fractionated regimens.

✓Appropriate selection is crucial to reduce potential minimal risks of greater late toxicities.

SPACEOAR™ seems is feasible, useful and able to take advantege in: *moderate /extreme hypofractionation (and reirradiation)* prostate cancer RT