Società Italiana di Radiobiologia

XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

"IPOFRAZIONAMENTO NEL TUMORE PROSTATICO: dove stiamo andando e quanto siamo competitivi "

Filippo Alongi MD
Chief/Director Radiation Oncology

Sacro Cuore Don Calabria
CCC
Cancer Care Center
Negrar - Verona

Società Italiana di Radiobiologia

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DICHIARAZIONE

Relatore: FILIPPO ALONGI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(AUGMENIX, ASTELLAS)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(JANSEEN,)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

“IPOFRAZIONAMENTO NEL TUMORE PROSTATICO: dove stiamo andando e quanto siamo competitivi "

- ✓**PROSTATE RADIOTHERAPY TODAY:**
  AVAILABLE TECHNOLOGY AND BIOLOGY KNOWLEDGE

- ✓**MODERATE HYPOFRACTIONATION:**
  THE OPTION OF THE PRESENT

- ✓**EXTREME HYPOFRACTIONATION:**
  THE OPTION OF THE NEXT FUTURE
  (YET PRESENT FOR SELECTED CASES??)

- ✓ **THE SINGLE FRACTION:**
  THE REAL FUTURE OR AN IMPOSSIBLE MITH??

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RADIOTHERAPY & PROSTATE CANCER:

WHAT IS CHANGED IN CLINICAL PRACTICE?

EXPERT REVIEWS

2014

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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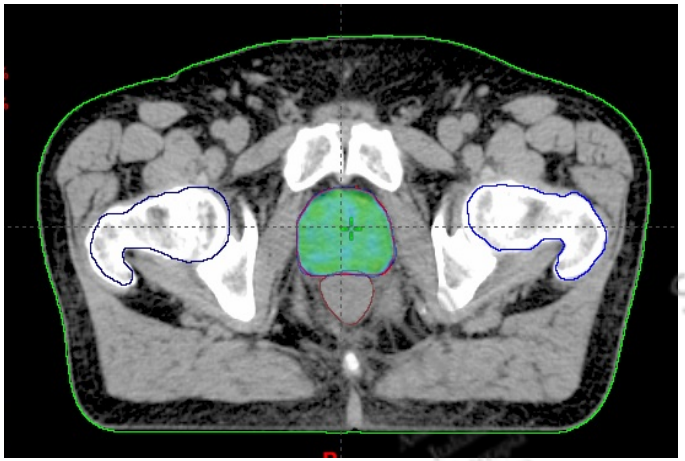
HYPOFRACTIONATION & PROSTATE CANCER:

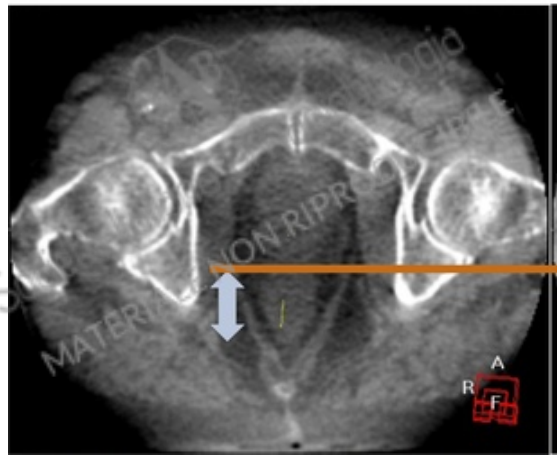
TECHNOLOGY:

HIGH CONFORMAL DOSE & IMAGING ON BOARD

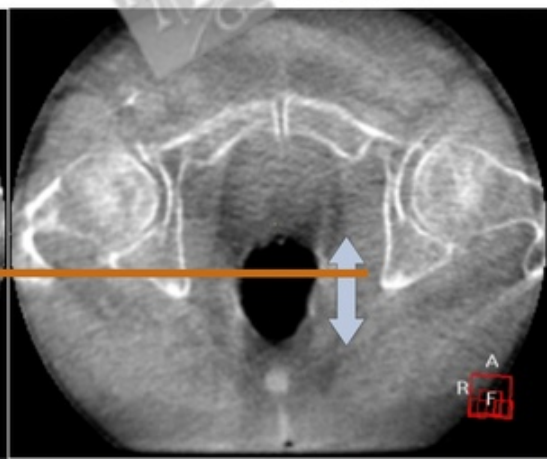
Planning



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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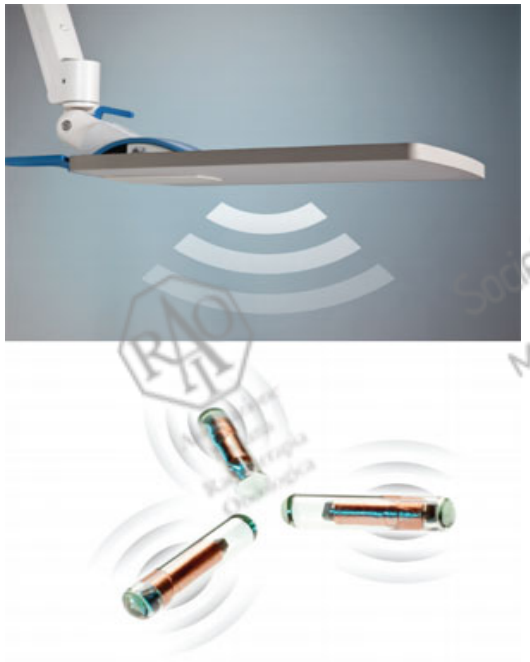
HYPOFRACTIONATION & PROSTATE CANCER:

TECHNOLOGY:

PROSTATE MOTION MANAGEMENT BY REAL TIME TUMOR TRACKING



LINAC INTEGRATED DEVICES

DEDICATED ROBOTIC LINAC WITH INTEGRATED TRECKING SYSTEMS

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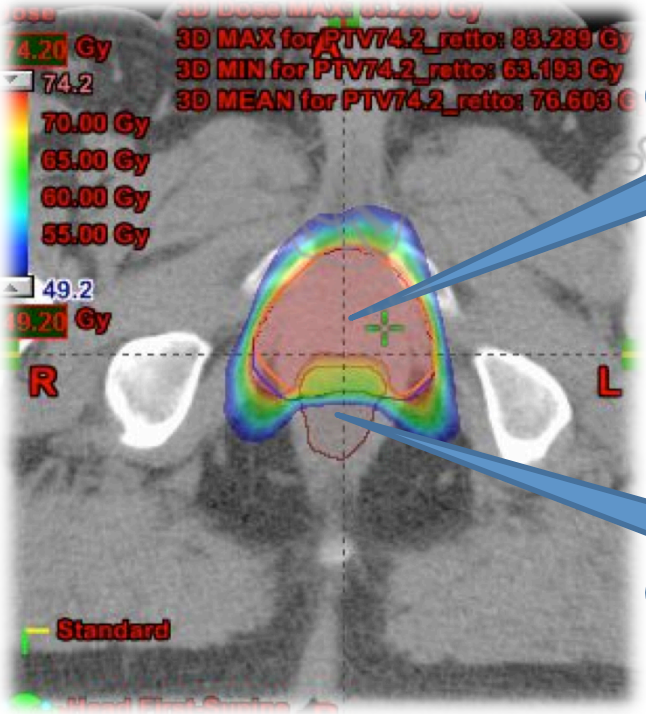
HYPOFRACTIONATION & PROSTATE CANCER:

RADIOBIOLOGICAL CONSIDERATION

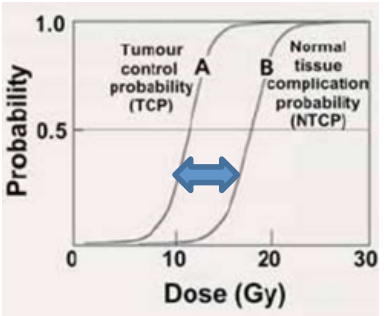
✓Prostate cancer seems particularly suitable for hypofractionated RT having unique sensitivity to increased radiation dose fractions compared to surrounding healthy tissues



Prostate, α/β RATIO= 1.5(?)

Rectum, α/β RATIO= 3

HYPOFRACTIONATION
=
ENLARGING THERAPEUTIC WINDOW



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HYPOFRACTIONATION & PROSTATE CANCER

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

Table 1 | **Superiority randomized controlled trials of moderately hypofractionated radiotherapy for organ-confined prostate cancer**

Study	Patients (*n*) and disease characteristics	Schedule (total dose, *n* of fractions)	Technique	NTD2/1.5*	NTD2/3*	Median follow-up period (months)	Biochemical-recurrence-free survival	Late gastrointestinal toxicity	Late genitourinary toxicity
Lukka *et al.* (2005)[16]	• 470 T1–2 • 466 T1–2	• 66 Gy, 33 • 52.5 Gy, 20	2D	• 66 Gy • 62 Gy	• 66 Gy • 59 Gy	68.5	• 47% • 40%	≥G3: 1.9% (both schedules)	≥G3: 1.3% (both schedules)
Yeoh *et al.* (2011)[17]	• 109 T1–2 • 108 T1–2	• 64 Gy, 32 • 55 Gy, 20	2D and 3D	• 64 Gy • 66.8 Gy	• 64 Gy • 63.3 Gy	90	• 34% • 53%	NR	NR‡
Kuban *et al.* (2010)[18]	• 102 L–I • 102 L–I	• 75.6 Gy, 42 • 72 Gy, 30	IMRT	• 71.3 Gy • 80.2 Gy	• 72.6 Gy • 77.8 Gy	40	• 92% • 96%	• ≥G2: 5.1% • ≥G2: 10%	• ≥G2: 16.5% • ≥G2: 15.8%
Pollack *et al.* (2013)[19]	• 153 L–I–H • 154 L–I–H	• 76 Gy, 38 • 70.2 Gy, 26	IMRT	• 76 Gy • 84.2 Gy	• 76 Gy • 80 Gy	68.4	• 79% • 77%	• ≥G2: 22.5% • ≥G2: 18.1%	• ≥G2: 13.4% • ≥G2: 21.5%
Arcangeli *et al.* (2012)[20]	• 85 H • 83 H	• 80 Gy, 40 • 62 Gy, 20	3D	• 80 Gy • 81.5 Gy	• 80 Gy • 74 Gy	70	• 74% • 85%	• ≥G2: 17% • ≥G2: 16%	• ≥G2: 14% • ≥G2: 11%

Hypofractionated radiotherapy for organ-confined prostate cancer: is less more?

Stefano Arcangeli and Carlo Greco

Arcangeli et al, Nature Review Urology 2016

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

Table 2 | **Noninferiority randomized controlled trials of moderately hypofractionated radiotherapy for organ-confined prostate cancer**

Study (completion date)	Patients (n) and disease characteristics	Schedule (total dose, n of fractions)	Technique	NTD2/1.5*	NTD2/3*	Median follow-up period (months)	Biochemical-recurrence-free survival	Late gastrointestinal toxicity	Late genitourinary toxicity
CHHiP (2015)[31]	3,216 L-I-H	• 74 Gy, 37 • 60 Gy, 20 • 57 Gy, 19	IMRT	• 74 Gy • 77.1 Gy • 73.3 Gy	• 74 Gy • 72 Gy • 68.4 Gy	62.4	• 88% • 91%‡ • 86%	• ≥G2 1.3% • ≥G2 2.3% • ≥G2 2%	• ≥G2 13.5% • ≥G2 13.2% • ≥G2 11.2%
HYPRO (2016)[30]	820 I-H	• 78 Gy, 39 • 64.6 Gy, 19	3D and IMRT	• 78 Gy • 90.4 Gy	• 78 Gy • 82.7 Gy	60	• 77% • 80%§	• ≥G2 18% • ≥G2 22%	• ≥G2 39% • ≥G2 41%
RTOG 0415 (2016)[29]	1,097 L	• 73.8 Gy, 41 • 70 Gy, 28	3D and IMRT	• 69.6 Gy • 80 Gy	• 70.8 Gy • 77 Gy	69.6	• 85.3% • 86.3%‖	• ≥G3 2.6% • ≥G3 4.1%	• ≥G3 2.3% • ≥G3 3.5%
PROFIT (ongoing)[24]	1,204 I	• 78 Gy, 39 • 60 Gy, 20	3D and IMRT	• 78 Gy • 77.1 Gy	• 78 Gy • 72 Gy	NA	NA	NA	NA

Hypofractionated radiotherapy for organ-confined prostate cancer: is less more?

Stefano Arcangeli and Carlo Greco

Arcangeli et al, Nature Review Urology 2016

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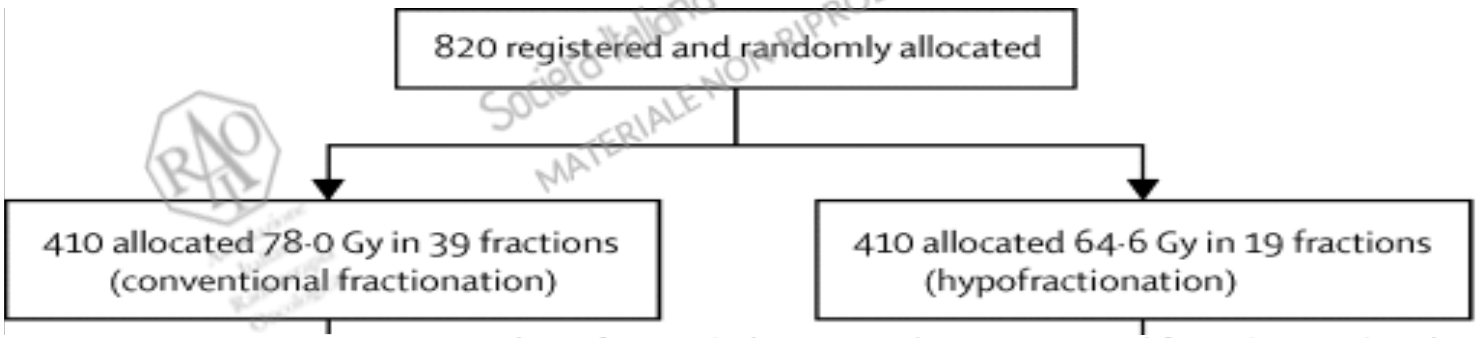
MODERATE HYPOFRACTIONATION & PROSTATE CANCER

NEW!!!!

Lancet Oncol 2016;

Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial

Prof Luca Incrocci, MD, Ruud C Wortel, MD, Wendimagegn Ghidey Alemayehu, PhD, Shafak Aluwini, MD, Erik Schimmel, MD, Stijn Krol, MD, Peter-Paul van der Toorn, MD, Hanja de Jager, MD, Wilma Heemsbergen, PhD, Prof Ben Heijmen, PhD, Floris Pos, MD



5-year relapse-free survival was 80·5% (95% CI 75·7–84·4) for patients assigned hypofractionation and 77·1% (71·9–81·5) for those allocated conventional fractionation (adjusted hazard radio 0·86, 95% CI 0·63–1·16; log-rank p=0·36). There were no treatment-related deaths.

Interpretation

Hypofractionated radiotherapy was not superior to conventional radiotherapy with respect to 5-year relapse-free survival. Our hypofractionated radiotherapy regimen cannot be regarded as the new standard of care for patients with intermediate-risk or high-risk prostate cancer.

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

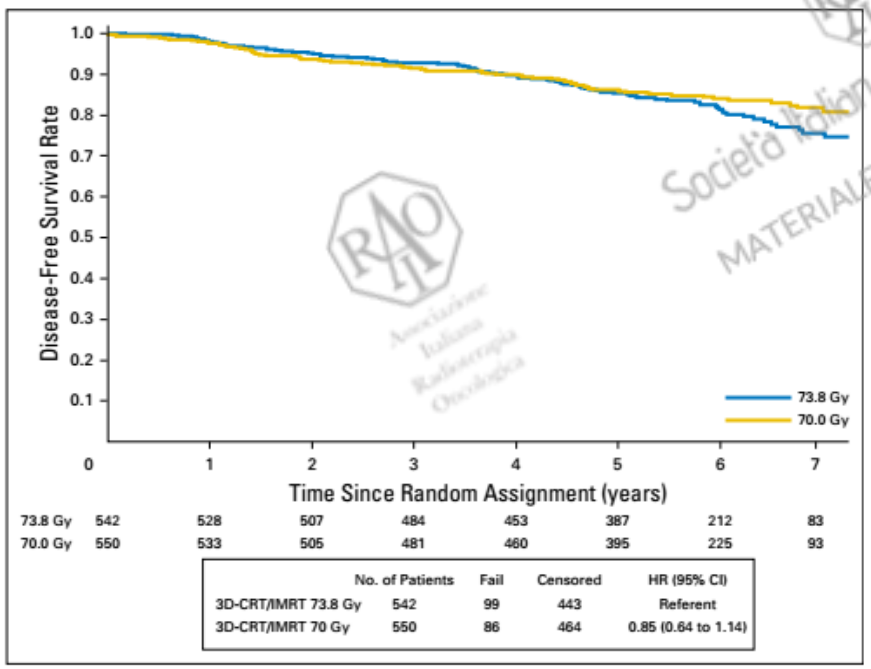
NEW!!!!

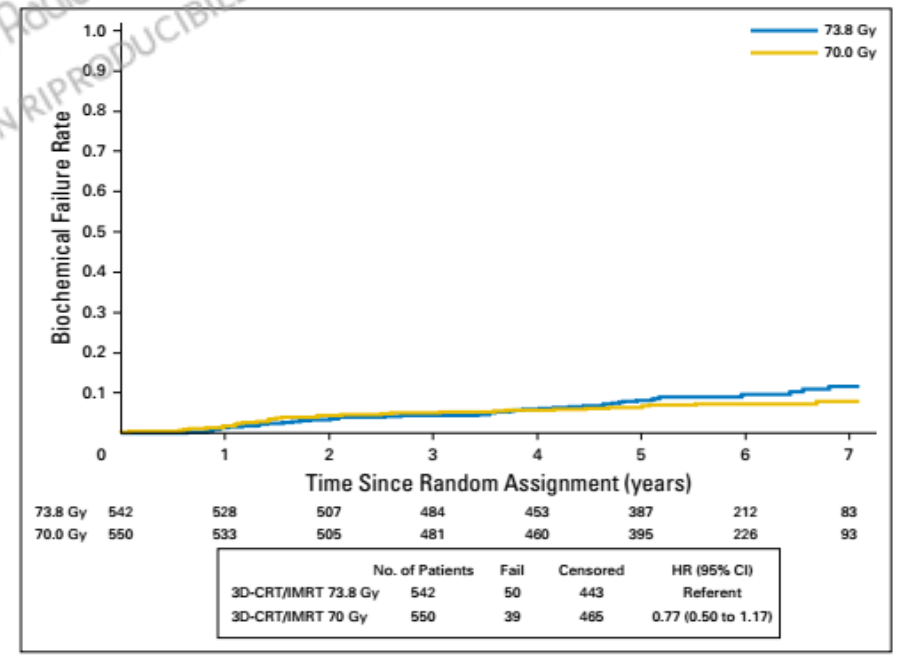
JOURNAL OF CLINICAL ONCOLOGY 2016

Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer

W. Robert Lee, James J. Dignam, Mahul B. Amin, Deborah W. Bruner, Daniel Low, Gregory P. Swanson, Amit B. Shah, David P. D'Souza, Jeff M. Michalski, Ian S. Dayes, Samantha A. Seaward, William A. Hall, Paul L. Nguyen, Thomas M. Pisansky, Sergio L. Faria, Yuhchyau Chen, Bridget F. Koontz, Rebecca Paulus, and Howard M. Sandler

1,115 low risk PC cases randomized to receive: ***73,8 in 41 vs 70 in 28***





Conclusion

In men with low-risk prostate cancer, the efficacy of 70 Gy in 28 fractions over 5.6 weeks is not inferior to 73.8 Gy in 41 fractions over 8.2 weeks, although an increase in late GI/genitourinary adverse events was observed in patients treated with H-RT.

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MODERATE HYPOFRACTIONATION & PROSTATE CANCER

Lancet Oncol 2015

Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

Anna Wilkins, Helen Mossop, Isabel Syndikus, Vincent Khoo, David Bloomfield, Chris Parker, John Logue, Christopher Scrase, Helen Patterson†, Alison Birtle, John Staffurth, Zafar Malik, Miguel Panades, Chinnamani Eswar, John Graham, Martin Russell, Peter Kirkbride, Joe M O'Sullivan, Annie Gao, Clare Cruickshank, Clare Griffin, David Dearnaley*, Emma Hall*

Findings 2100 participants in the CHHiP trial consented to be included in the QoL substudy:

Interpretation The incidence of patient-reported bowel symptoms was low and similar between patients in the 74 Gy control group and the hypofractionated groups up to 24 months after radiotherapy.

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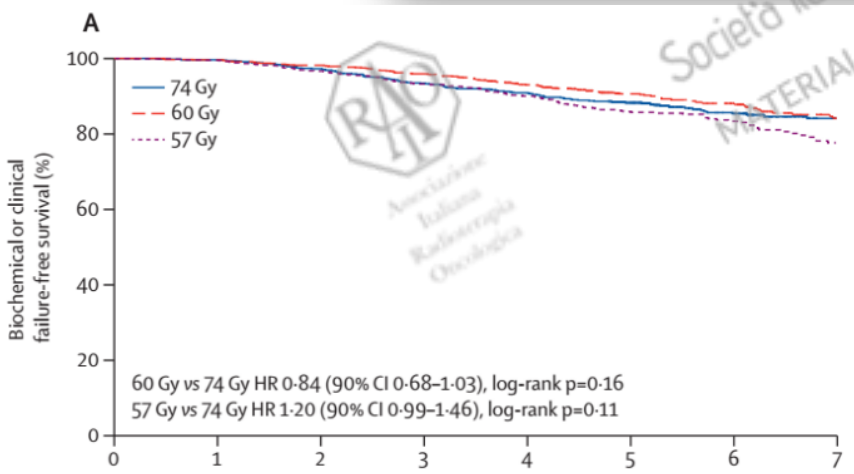
MODERATE HYPOFRACTIONATION & PROSTATE CANCER

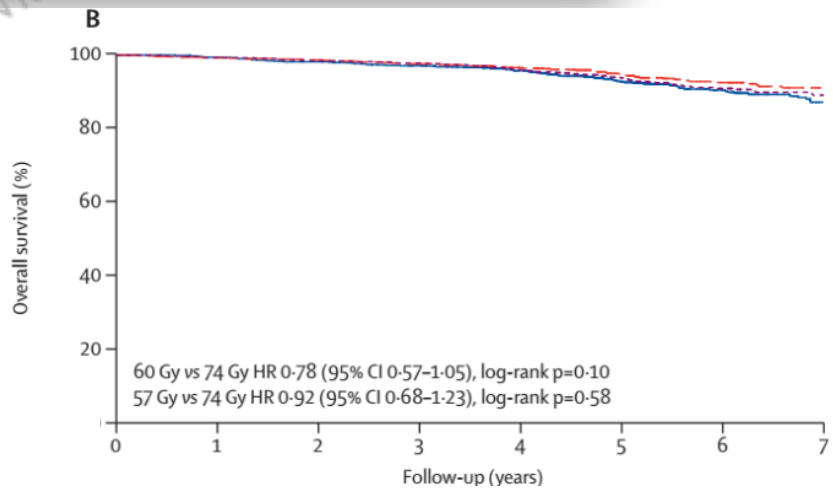
NEW!!!!

Lancet Oncol 2016; 17: 1047–60

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson, Christopher Scrase, John Staffurth, Andrew Stockdale, Jean Tremlett, Margaret Bidmead, Helen Mayles, Olivia Naismith, Chris South, Annie Gao, Clare Cruickshank, Shama Hassan, Julia Pugh, Clare Griffin, Emma Hall, on behalf of the CHHiP Investigators*





Interpretation Hypofractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localised prostate cancer.

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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

STUDY	Longer Arm	Shorter Arm	5-y-Efficacy	Late Toxicity	PROs
CHHIP	37 Fx/2 Gy	20 Fx/3 Gy	Similar	Similar	Similar
PROFIT	39 Fx/2 Gy	20 Fx/3 Gy	Similar	Similar	Similar
NRG 0415	41 Fx/ 1.8 Gy	28Fx/2.5 Gy	Similar	Small ↑ GU/GI	Reporting -
HYPRO	39 Fx/2 Gy	19 Fx/3.4 Gy	Similar	↑ GU	Not reported

HOFFMAN et al.

8-y Update of MDACC RCT
206 Men
75.6 Gy/ 1.8 versus 72 Gy/2.4 Gy

BETTER CANCER CONTROL – A DIFFERENCE EMERGING AFTER 5-YEARS

SIMILAR TOXICITY

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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:

RATIONALE

ELSEVIER

2012

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

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

2014

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

ONCOLOGY AND RADIOTHERAPY

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 α/β*** 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 and ***modern SBRT*** providing sharper dose fall-offs and better dose conformity.

✓***Convenience*** for patients and departments, and for Health system (<costs)

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EXTREME HYPOFRACTIONATION & PROSTATE CANCER: RADIOBIOLOGICAL CONSIDERATIONS

Isoeffective prescription for the late complication at α/β = 3 Gy				
No of fractions	Dose per fraction (Gy)	Total dose (Gy)	Normal tissue (α/β = 3 Gy) normalized total dose (Gy)	Tumor (α/β = 1.5 Gy) normalized total dose (Gy)
35	2	70	70	70
30	2.23	66.92	70	71.32
25	2.53	63.28	70	72.88
20	2.94	58.88	70	74.77
15	3.56	53.37	70	77.13
10	4.6	46.03	70	80.27
5	7	35	70	85

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EXTREME HYPOFRACTIONATION & PROSTATE CANCER: DATA

- ✓Phase I-II trials only
- ✓Minimum F-UP of 24 months

Table 3 | **Phase I–II trials of extremely hypofractionated radiotherapy* for organ-confined prostate cancer**

Study	Patients (*n*) and disease characteristics	Schedule (total dose, n of fractions)	Technique	Median follow-up period (months)	Biochemical-recurrence-free survival	Acute toxicity ≥G3		Late toxicity ≥G3	
						Genitourinary	Gastrointestinal	Genitourinary	Gastrointestinal
Linac-based									
Madsen *et al.* (2007)[36]	40 L–I–H	33.5 Gy, 5	IMRT	41	90%	0%	0%	0%	0%
Aluwini *et al.* (2013)[37]	50 L–I	38 Gy, 4	IMRT and IGRT	23	100%	2%	8%	0%	6%
Loblaw *et al.* (2013)[38]	84 L	35 Gy, 5	IMRT and IGRT	55	98%	0%	1%	1%	1%
Kim *et al.* (2014)[39]	91 L–I	• 45 Gy, 5 • 47.5 Gy, 5 • 50 Gy, 5	IMRT (tomotherapy)	24.5	NR	1.6%	0%	4.9%	4%
Robotic-based									
Fuller *et al.* (2014)[35]	79 L–I	38 Gy, 4	CK	42	• L: 100% • I: 92%	0%	0%	0%	6%
King *et al.* (2012)[40]	67 L	36.25 Gy, 5	CK	32.4	94%	0%	0%	0%	3.5%
Bolzicco *et al.* (2013)[41]	100 L–I–H	35 Gy, 5	CK	36	95%	0%	0%	0%	0%
Chen *et al.* (2013)[42]	100 L–I–H	36.25 Gy, 5	CK	27.6	99%	0%	0%	0%	1%
Oliai *et al.* (2013)[43]	70 L–I–H	• 35 Gy, 5 • 36.25 Gy, 5 • 37.5 Gy, 5	CK	31	• L: 100% • I: 95% • H: 77.1%	0%	4%	0%	3%
Meier *et al.* (2015)[44]	137 I	40 Gy, 5	CK	56	95%	0%	0%	0%	1.5%
Katz *et al.* (2014)[45]	515 L–I–H	35–36.25 Gy, 5	CK	72	• L: 95.8% • I: 89.3% • H: 68.5%	0%	0%	0%	1.7%

Arcangeli et al, Nature Review Urology 2016

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EXTREME HYPOFRACTIONATION & PROSTATE CANCER:

OWN EXPERIENCE DATA

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]

35 Gy in 5 fractions

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

Table 1 Patient characteristics

N. of patients	40
Median Age [year]	70 [56, 80]
Median Initial PSA [ng/mL]	6.25 [0.50, 13.43]
Median Gleason Score	6 [6,7]
NCCN Low Risk Class	26
NCCN Intermediate Risk Class	14
Median F-UP [months]	10 [3-14]
N. of patients with SpaceOAR™	8

Clinical ONCOLOGY

2016

High-quality Linac-based Stereotactic Body Radiation Therapy with Flattening Filter Free Beams and Volumetric Modulated Arc Therapy for Low–Intermediate Risk Prostate Cancer. A Mono-institutional Experience with 90 Patients

G. D'Agostino *, C. Franzese *, F. De Rose *, D. Franceschini *, T. Comito *, E. Villa *, F. Alongi †, R. Liardo *, S. Tomatis *, P. Navarria *, P. Mancosu *, G. Reggiori *, L. Cozzi *, M. Scorsetti *

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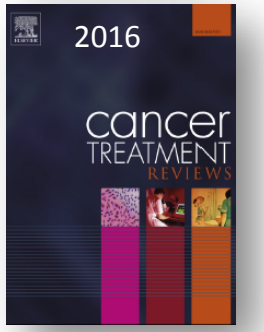
Cancer Care Center
Negrar - Verona

EXTREME HYPOFRACTIONATION & PROSTATE CANCER



Comparison of outcomes and toxicities among radiation therapy treatment options for prostate cancer

Nicholas G Zaorsky, Talha Shaikh, Colin T Murphy, Mark A Hallman, Shelly B Hayes, Mark L Sobczak, Eric M Horwitz

➢SBRT had promising rates of BF, ***with shorter follow-up*** (5-year FFBF of >90% for low-risk patients).

Zaorsky et al, Cancer Treatment Review 2016

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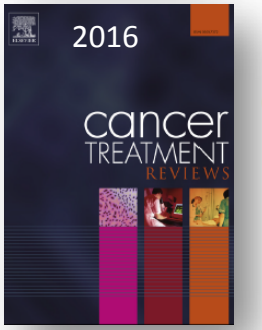
EXTREME HYPOFRACTIONATION & PROSTATE CANCER



Comparison of outcomes and toxicities among radiation therapy treatment options for prostate cancer

Nicholas G Zaorsky, Talha Shaikh, Colin T Murphy, Mark A Hallman, Shelly B Hayes, Mark L Sobczak, Eric M Horwitz

Moreover, SBRT also has more contraindications than conventional RT, and patients with ***certain contraindication*** (e.g. inflammatory bowel disease, large transurethral removal of prostate defect) ***are excluded*** on clinical trials

Zaorsky et al, Cancer Treatment Review 2016

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EXTREME 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.

Extreme Hypofractionation (from 35-42 fractions to 4-5)?
YES, but in selected cases and inside protocols!!

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SBRT : WHO CAN WE TREAT? HOW WE CAN TREAT?

WARNING FOR RECTALTOXICITY MOVING FROM 7 Gy 10 Gy /session.

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*

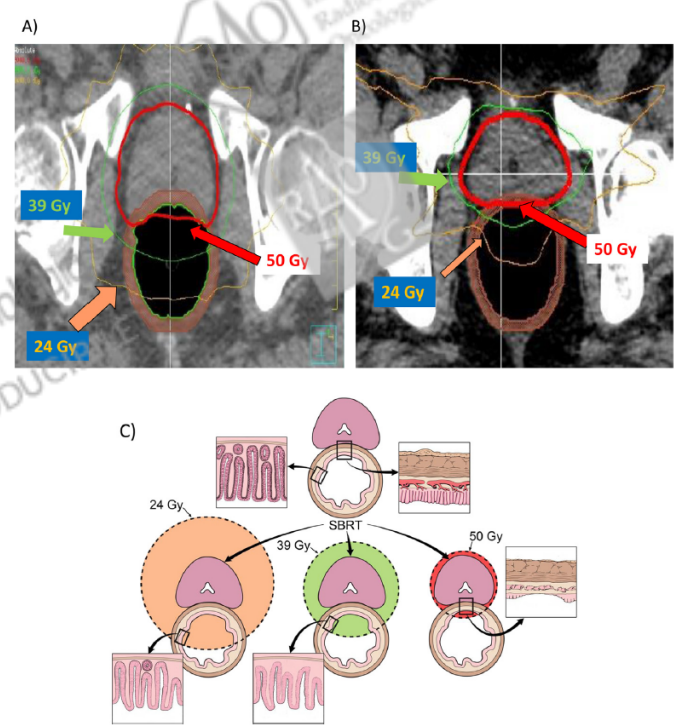

Fig. 2. Representative treatment plans of patients treated to 50 Gy in 5 fractions, with (A) grade 2 acute and grade 3 delayed rectal toxicity, and (B) grade 1 acute/delayed rectal toxicity only. (C) Representation of biologic consequence of rectal wall irradiated to 24 Gy, 39 Gy, and 50 Gy.

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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SBRT : WHO CAN WE TREAT? HOW WE CAN TREAT?

EXTREME HYPOFRATIONATION: BACKGROUND FOR RECTAL PROTECTION

Review Paper

SBRT for prostate cancer: Challenges and features from a physicist prospective

Pietro Mancosu [a,*], Stefania Clemente [b], Valeria Landoni [c], Ruggero Ruggieri [d], Filippo Alongi [d], Marta Scorsetti [a,f], Michele Stasi [e]

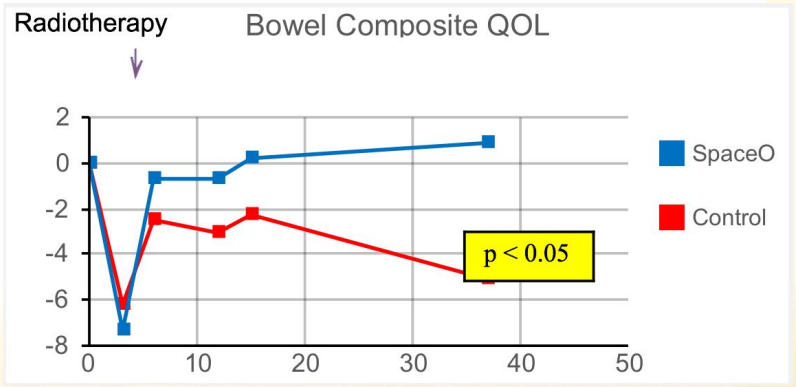
Technical solutions: anatomy modifiers for minimizing rectum dose

Spacer

Only few studies conceived the trans-perineal insertion, under trans-rectal ultrasound guidance, of a self-absorbable hydrogel [42]. This device works temporary as prostate–rectum interface spacer: when correctly placed in the Denonville's fascia, it is able to enlarge the usual distance between posterior part of the prostate and anterior rectal wall from few millimeters to more than one centimeter. Such synthetic polyethylene–glycol based hydrogels were first proposed by Susil and colleagues [43]. Authors quanti-

ASTRO DAILY NEWS

58th Annual Meeting September 25 - 26, 2016



Continued Benefit to Rectal Separation for Prostate RT: Final Results of a Phase III Trial

Phase III Trial SpaceOAR versus NOT with IMRT_IGRT: 222 pts

Significant Advantage mintained in time in reducing rectal roxicity and QoL

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SBRT : WHO CAN WE TREAT? HOW WE CAN TREAT?

GU LATE TOXICITY: More late urinary flare????

Clinical Oncology 27 (2015) 270–279

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Stereotactic Body Radiotherapy for Prostate Cancer

D.R. Henderson, A.C. Tree, N.J. van As

Academic Uro-oncology Department, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

Received 3 November 2014; received in revised form 2 December 2014; accepted 15 January 2015

✓QOL in SBRT patients is important.

✓Urinary late flare are not so uncommon, as well as brachytherapy.

✓EPIC & IPSS Questionnaires are strongly suggested to select properly the patient.

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SBRT : WHO CAN WE TREAT? HOW WE CAN TREAT?

Int J Radiat Oncol Biol Phys. 1999 Jul 1;44(4):789-99.

American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer.

Nag S[1], Beyer D, Friedland J. Grimm P. Nath R.

Usually, patients with a prostate volume > 60 cc are excluded from SBRT studies, following the example of HDR brachytherapy [27].

UROLOGIC ONCOLOGY Seminars and Original Investigations 2011 Volume 29, Issue 1, Pages 52–57

Neoadjuvant androgen deprivation for prostate volume reduction: The optimal duration in prostate cancer radiotherapy

Johan F. Langenhuijsen, M.D., Emile N. van Lin, M.D., Ph.D., Aswin L. Hoffmann, M.Sc., Ilse Spitters-Post, B.Sc., J. Alfred Witjes, M.D., Ph.D., Johannes H. Kaanders, M.D., Ph.D., Peter F. Mulders, M.D., Ph.D.

Conclusions

In this study, we have shown that the most significant prostate volume reduction is achieved after 3 months of MAB with a maximum reduction after 6 months. Therefore, the optimal duration of neoadjuvant androgen deprivation to reduce prostate volume before prostate cancer radiotherapy is 6 months. In small prostates 3 months of hormonal treatment may be enough for maximal volume reduction.

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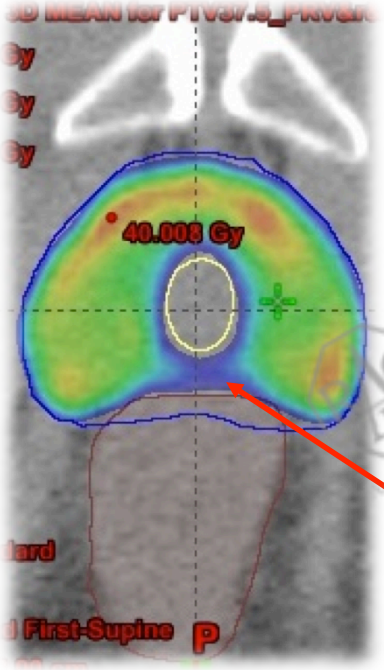
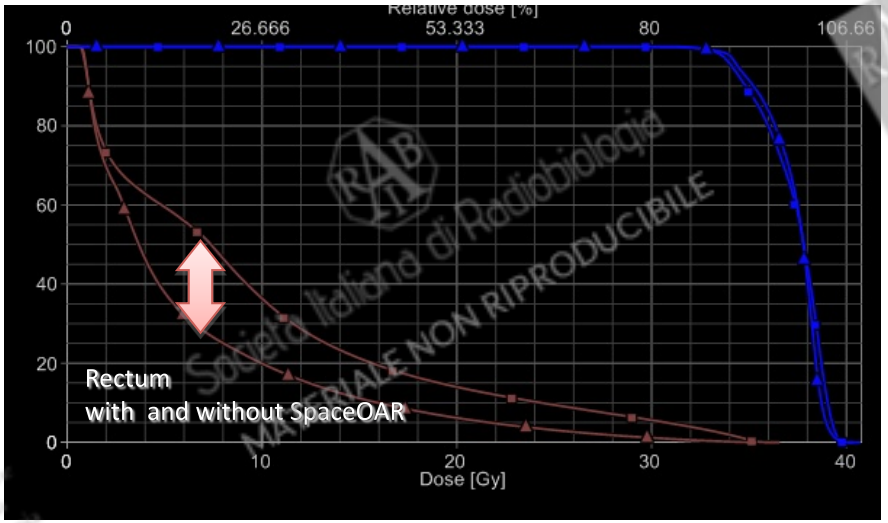
SBRT : HOW WE TREAT PROSTATE CANCER?

PROTOCOL: *37.5 Gy in 5 fractions, urethral & rectal sparing*

NO SPACER





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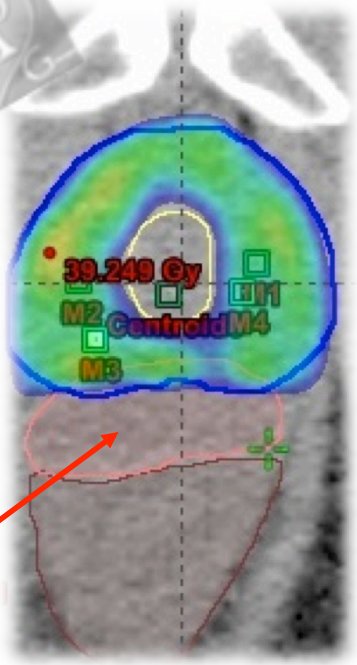


Anterior Rectal wall

NO SPACEOAR
Dose Distribution
Isodose 95%

SPACEOAR
Dose distribution
Isodose 95%

MEIER et al.
Multicenter study with 5-y median follow up
309 Men given 40 Gy/5 Fr with tight constraints
1.6% grade ≥ 3

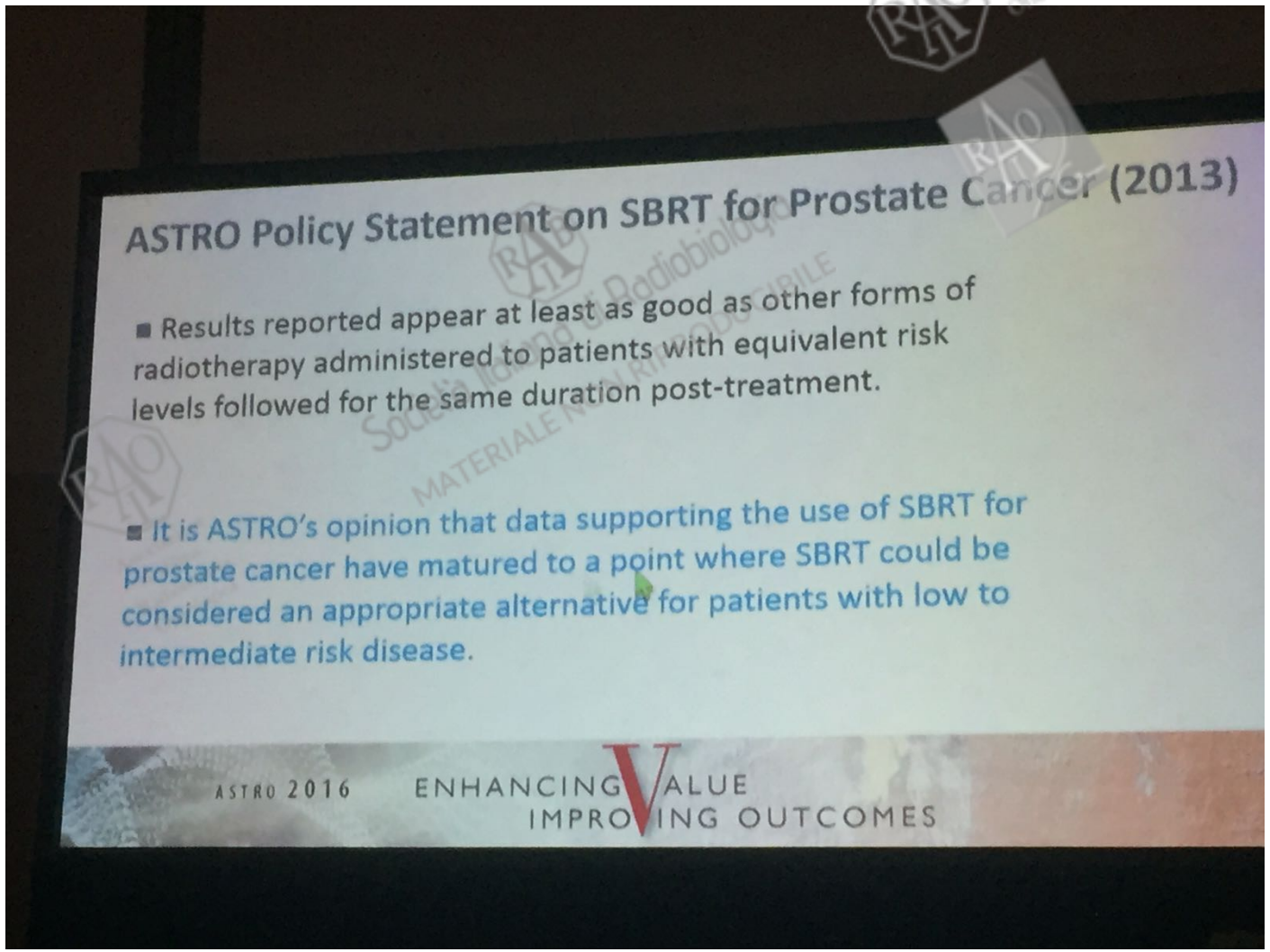
GRECO et al.
45Gy/5Fr with urethral sparing technique
Feasible

DESS et al.
University of Michigan
830 SBRT patients with excellent QoL data

HYPO-RT-PC
Non-Inferiority Trial
Conventional RT vs 6.1 Gy x 7 Fr
866 pts: similar toxicity results at 2-years

ASTRO DAILY NEWS

58th Annual Meeting September 25 – 26, 2016



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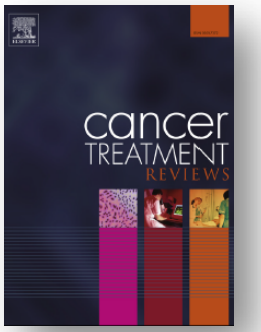
SBRT : HOW WE TREAT PROSTATE CANCER?



2016, accepted!

Extreme hypofractionation for early prostate cancer: biology meets technology

Berardino De Bari, M.D.; Stefano Arcangeli, M.D.; Delia Ciardo, M.Sc.; Rosario Mazzola, M.D.; Filippo Alongi, M.D.; Elvio G Russi, M.D.; Riccardo Santoni, M.D.; Stefano M Magrini, M.D.; Barbara A Jereczek-Fossa, M.D. Ph.D

On the Behalf of Italian Association of Radiation Oncology (AIRO)

•While awaiting long-term data on efficacy and toxicity, the analysed studies suggest that the **outcome profile** of this approach, alongside the patient convenience and reduced costs, **is promising.**

•Forty-eight ongoing clinical trials are also presented as a preview of the expectation from the near future.

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SBRT : HOW WE TREAT PROSTATE CANCER?

Table 5 – Ongoing Clinical trials. Ongoing trials on ultra-hypofractionation in prostate radiotherapy identified in the Clinicaltrials.gov registry, updated to the 1st February 2016.

Trial Number	Phase	Objectives/Description	Schedule	Status
NCT00911118	I	To test the safety of SBRT in low- and intermediate-risk Pca	32.5-35 Gy / 5 fx / 5 d	Not recruiting
NCT00969202	I	To evaluate the tolerance and side effects of SBRT in early stage PCa	N.P.	Recruiting
NCT01976962	I	To evaluate safety and efficacy of Functional MR-guided SBRT of PCa	Prostate: 36.25 Gy / 5 fx DIL: 40 Gy / 5 fx	Not yet open
NCT02653248	I	To investigate safety of the dose of SBRT in organ confined prostate cancer	40 Gy or 45 Gy or 50 Gy / 5 fx / 12 d	Recruiting
NCT01146340	I-II	To evaluate the safety and efficacy of a short course of step and shoot IGRT in low- and intermediate-risk PCa	40 Gy / 5 fx / 29 d	Completed
NCT01517451	I-II	To evaluate the effectiveness and toxicity of a combined regimen of SBRT with ADT for 4 months total	36.25 Gy / 5 fx / 10 d	Recruiting
NCT01540994	I-II	To evaluate a short course of SBRT in low-risk early stage PCa treatment	5 fx	Recruiting
NCT01578902	I-II	To determine the safety and efficacy of a short course of SBRT for the treatment of low-risk PCa	35 Gy / 5 fx / 29 d	Completed
NCT02031328	I-II	To determine the side effects, quality of life and efficacy of adaptive SBRT in low- and intermediate-risk PCa	26 Gy / 2 fx / 7 d	Not recruiting
NCT02254746	I-II	To test the safety and efficacy of SBRT with concomitant boost on DIL in patients with organ confined T2-T3 N0 PCa.	Prostate: 36.25 Gy / 5 fx; DIL: 45-50 Gy / 5 fx	Recruiting
NCT02470897	I/II	To evaluate the side effects and best dose of SBRT following urethral-sparing IMRT to help avoid radiation to normal tissue in patients with prostate cancer.	36.25 Gy / 5 fx / 10 d	Recruiting
NCT02623647	I-II			Recruiting
NCT00643617	II			Not recruiting
NCT00941915	II	anatomy of the day (SMART study)	d	Not recruiting
NCT00977860	II	To determine the rates of acute and late grade 3 or higher GI and GU toxicity observed during a 24 month follow-up and to estimate the rate of BDFS at 2 years following hypofractionated SBRT for low and intermediate risk PCa	36.25 Gy / 5 fx / 10 d	Recruiting
NCT01045148	II	To evaluate the effects of CK prostate radiosurgery in terms of morbidity and efficacy	38 Gy / 4 fx *or* 34 Gy / 5 fx	Recruiting
NCT01409473	II	To determine the safety and effectivenss of SBRT with simultaneous boost to DIL with IMRT in low- and intermediate-risk localized PCa	Prostate: 40 Gy / 5 fx (Low risk), 45 Gy / 5 fx (Intermediate risk); DIL: 50 Gy / 5 fx / every other day (10-14 d)	Withdrawn
NCT01423474	II	To compare the toxicity of two radiation schedules for low- and intermediate-risk PCa	40 Gy / 5 fx / 11 d *vs.* 40 Gy / 5 fx / 29 d	Not recruiting
NCT01434290	II	To compare the safety of SBRT and moderately fractionated treatments	36.25 Gy / twice a week / 2½ w *vs.* 51.6 Gy / 5 d a week / 2½ w	Not recruiting
NCT01505075	II	To determine the safety and efficacy of an SBRT for the treatment of high-risk PCa	Prostate: 40 Gy / 5 fx / 29 d; Seminal vesicles: 30 Gy / 5 fx / 29 d	Not recruiting

....MORE THAN 48 REGISTERED SBRT STUDY ON GOING..

“IPOFRAZIONAMENTO NEL TUMORE PROSTATICO: dove stiamo andando e quanto siamo competitivi "

- ✓PROSTATE RADIOTHERAPY TODAY: AVAILABLE TECHNOLOGY AND BIOLOGY KNOWLEDGE
- ✓MODERATE HYPOFRACTIONATION: THE OPTION OF THE PRESENT
- ✓EXTREME HYPOFRACTIONATION: THE OPTION OF THE NEXT FUTURE (YET PRESENT FOR SELECTED CASES??)
- ✓ **THE SINGLE FRACTION: THE REAL FUTURE OR AN IMPOSSIBLE MITH??**

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SBRT : WHAT IS THE LANDSCAPE FOR THE FUTURE?

SINGLE DOSE THE LAST FRONTIER?

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SBRT : WHAT IS THE LANDSCAPE FOR HTE FUTURE?

SINGLE DOSE THE LAST FRONTIER?

Tumori, 100: e87-e86, 2014

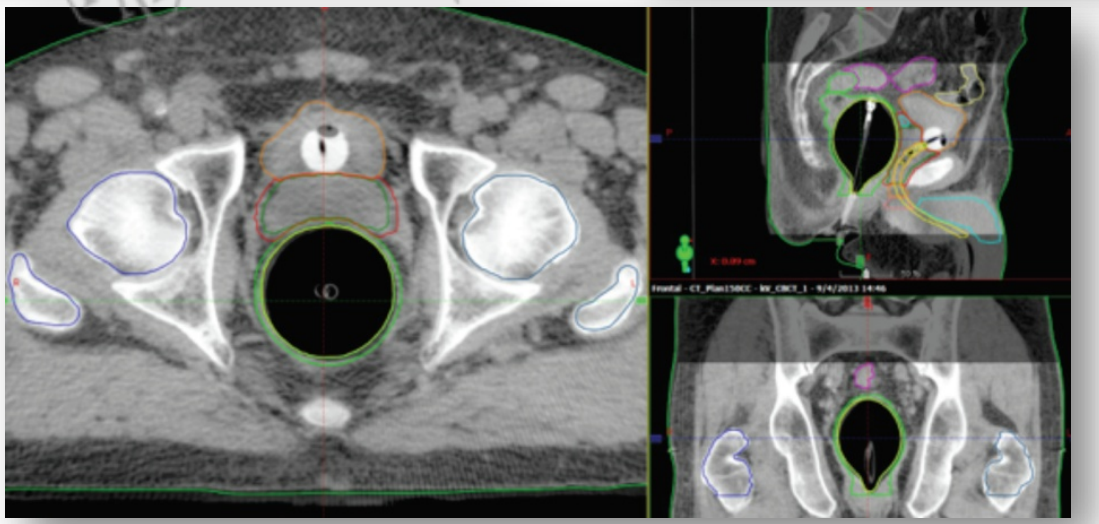
LETTER TO THE EDITOR

Could single-high-dose radiotherapy be considered the new frontier of stereotactic ablative radiation therapy?

Filippo Alongi[1], Berardino De Bari[2], and Marta Scorsetti[3]

[1]Radiation Oncology Department, Sacro Cuore Hospital, Negrar-Verona, Italy; [2]Service de Radio-Oncologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [3]Radiotherapy and Radiosurgery Department, Humanitas Cancer Center, Rozzano, Milan, Italy

In summary, an increasing amount of preliminary data seems to confirm the potential feasibility and efficacy of SABR. Nevertheless, this therapeutic approach should still be considered investigational, as no long-term data exist about clinical outcomes and acute and late toxicity rates. Patient selection is a crucial issue and prospective trials are needed to accumulate evidence and standardize treatments and dose-volume constraints. Future improvements and further data will confirm or refute the effectiveness and good tolerability of the single-dose approach.



Greco C, EMJ 2013

HYPOFRACTIONATION SUMMARY

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 and data reprted are confirming 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.

SINGLE FRACTION?

✓Few ongoing study, No available data….expertise, patient selection and technology will be crucial.

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THANK YOU….

SEE YOU SOON IN NEGRAR???