Specialised Course on Heavy Ion Therapy Research with a Focus on Clinical Aspects

Carbon Ion Radiotherapy for Prostate Cancer – State of the Art

HITRI plus
Heavy Ion Therapy Research Integration

Date: 4th July 2023

Venue: Online via Zoom

Scientific Committee:
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E. Orlandi (CNAO)
S. Harrabi (HIT)
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Disclosures

None

Representing scientifically

1/ MedAustron Ion Therapy Center in Austria
Leading European Institution in CIRT

2/ Christian Albrechts University Kiel in Germany
Leading European Institution in Brachytherapy / Interventional Radiotherapy

WHY CARBON ION RADIOTHERAPY (CIRT) FOR PROSTATE CANCER?

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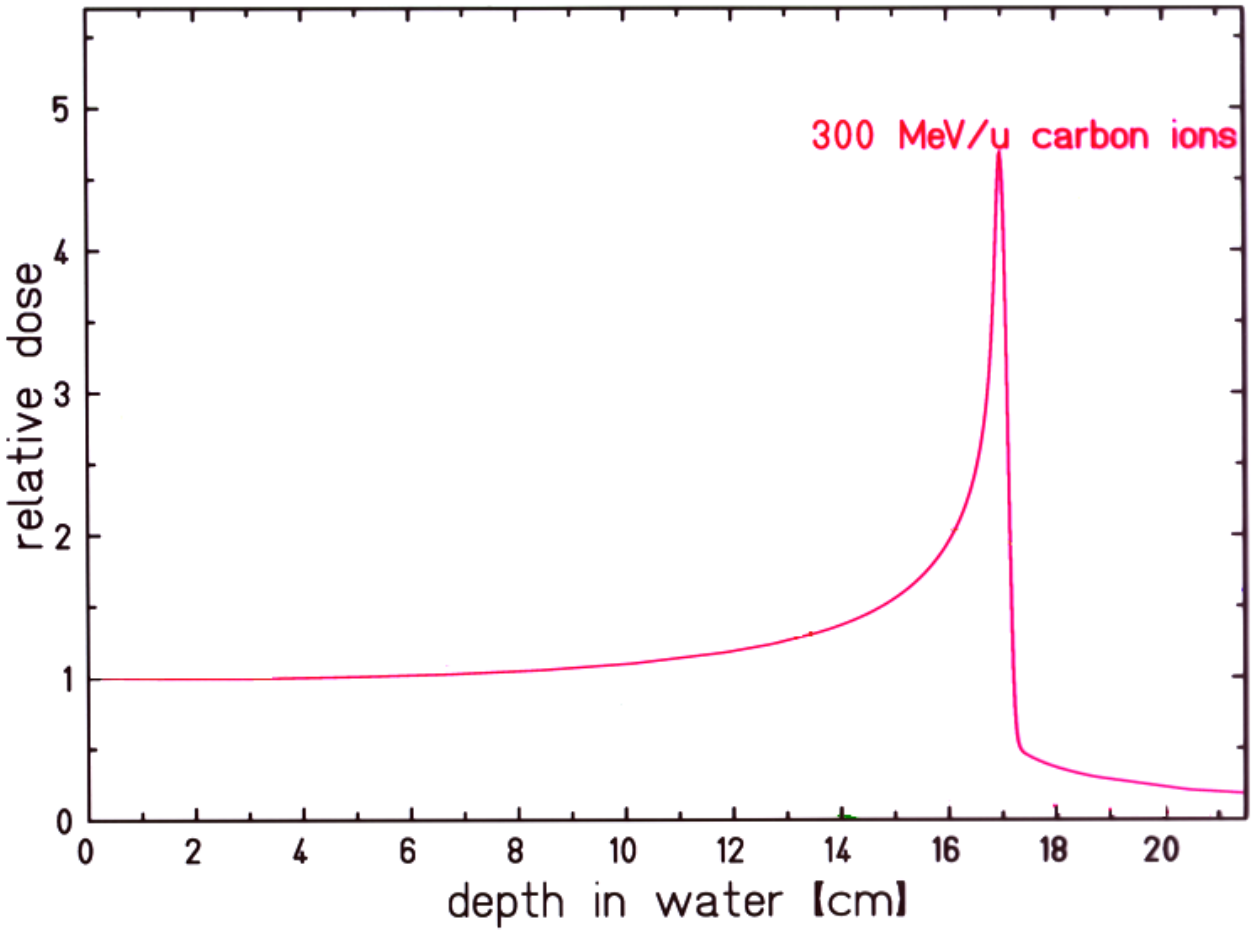
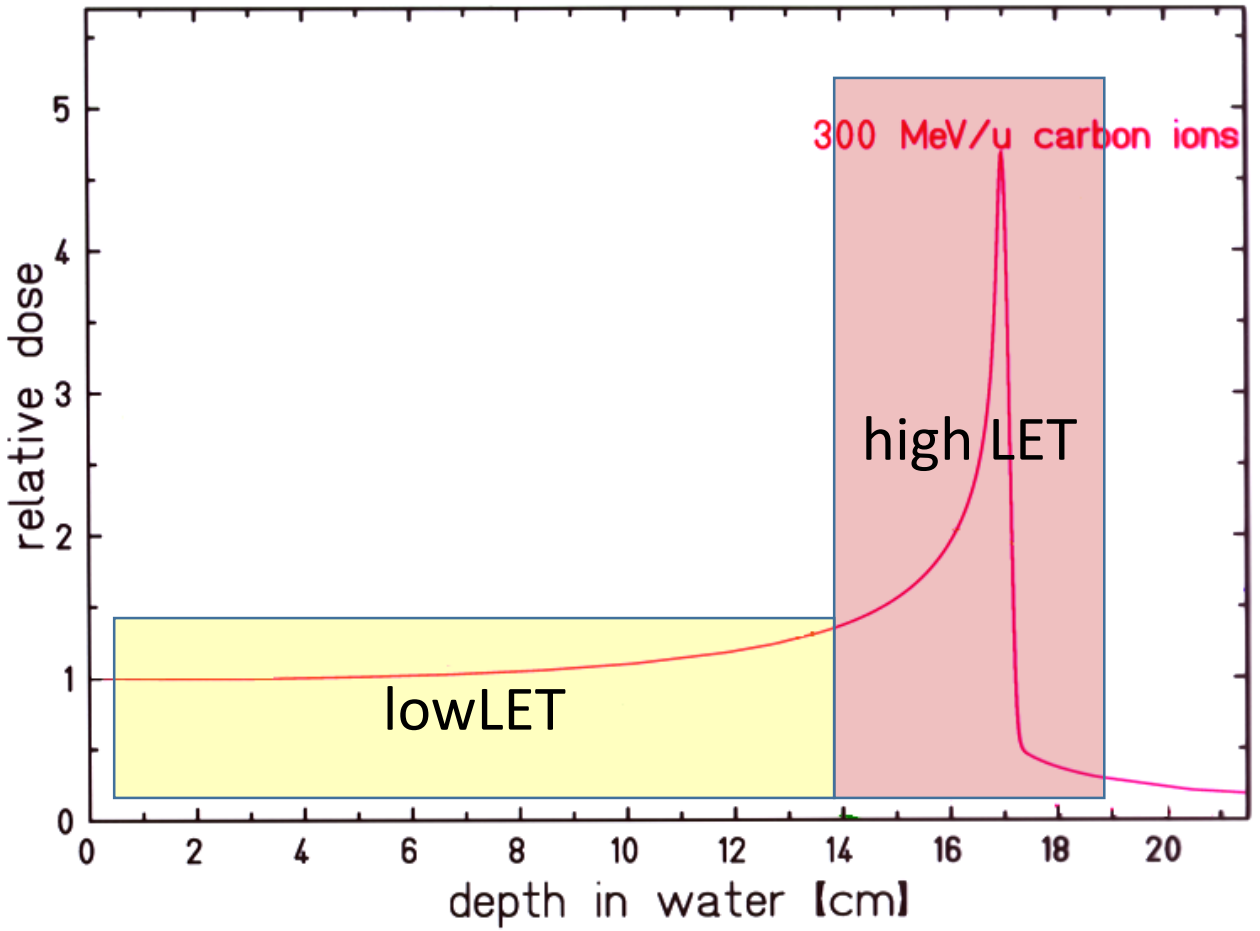
LESSONS LEARNED AND FUTURE DEVELOPMENTS

Carbon ions
Ability to «stop» the beam in a specific depth!



WHY CARBON ION RADIOTHERAPY (CIRT) FOR PROSTATE CANCER?

Carbon ions
High LET RT
(only where you need it)



WHY CARBON ION RADIOTHERAPY (CIRT) FOR PROSTATE CANCER?

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High LET RT
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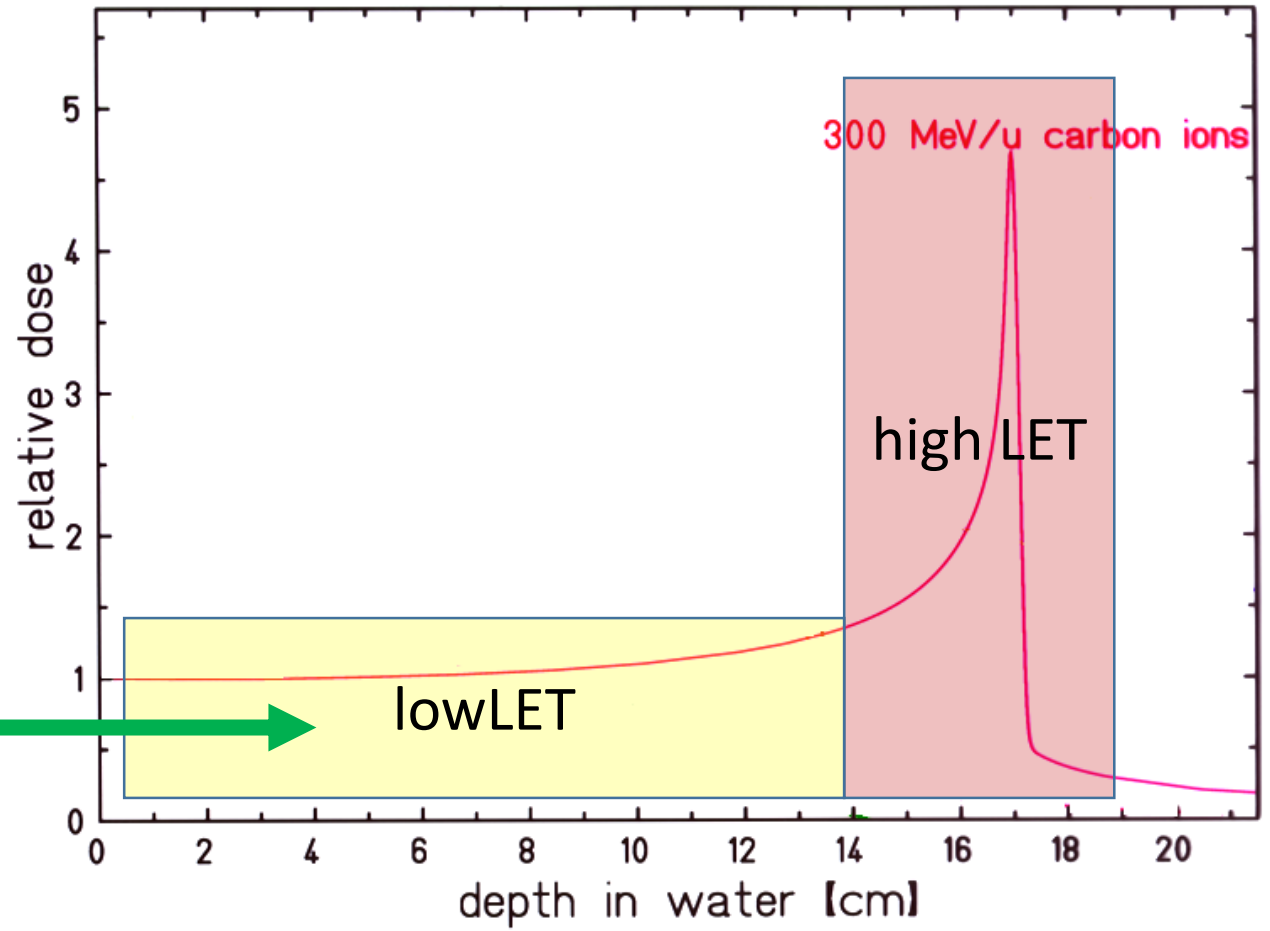
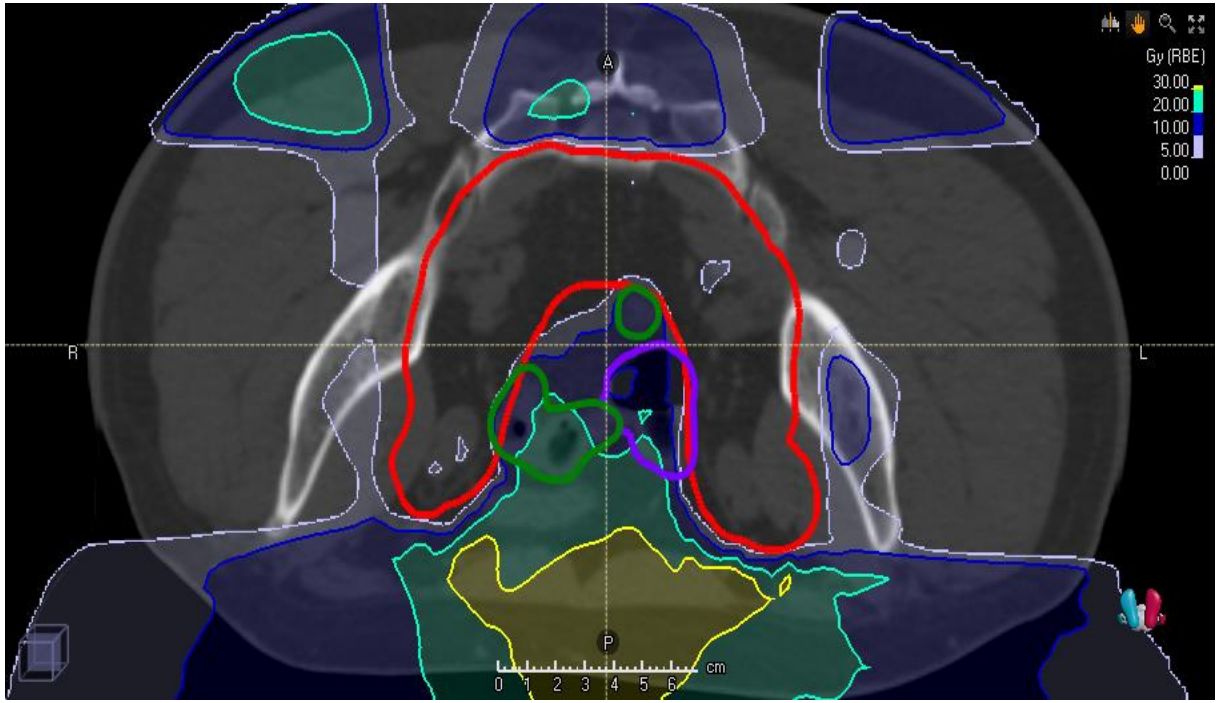
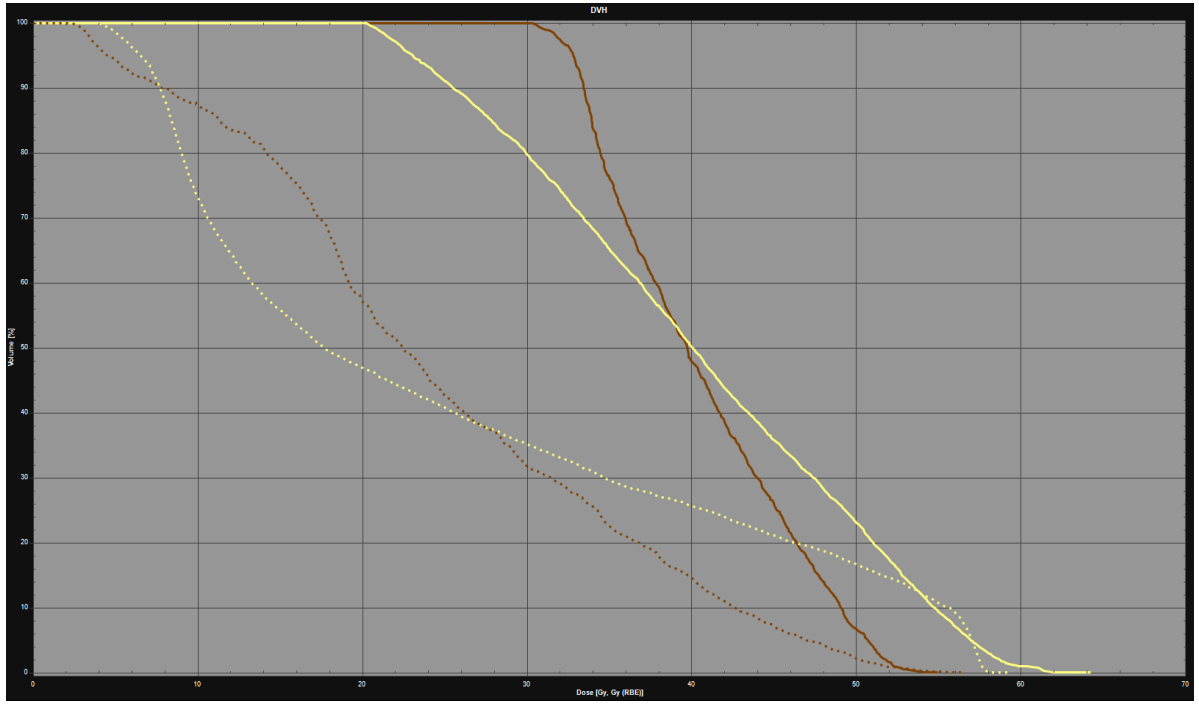
Advantage over high-dose photon RT







Large volumes outside of the targets with additional dose up to 30 Gy in Photon-VMAT technique vs CIRT!

Representative dose comparisson: VMAT Photons vs CIRT

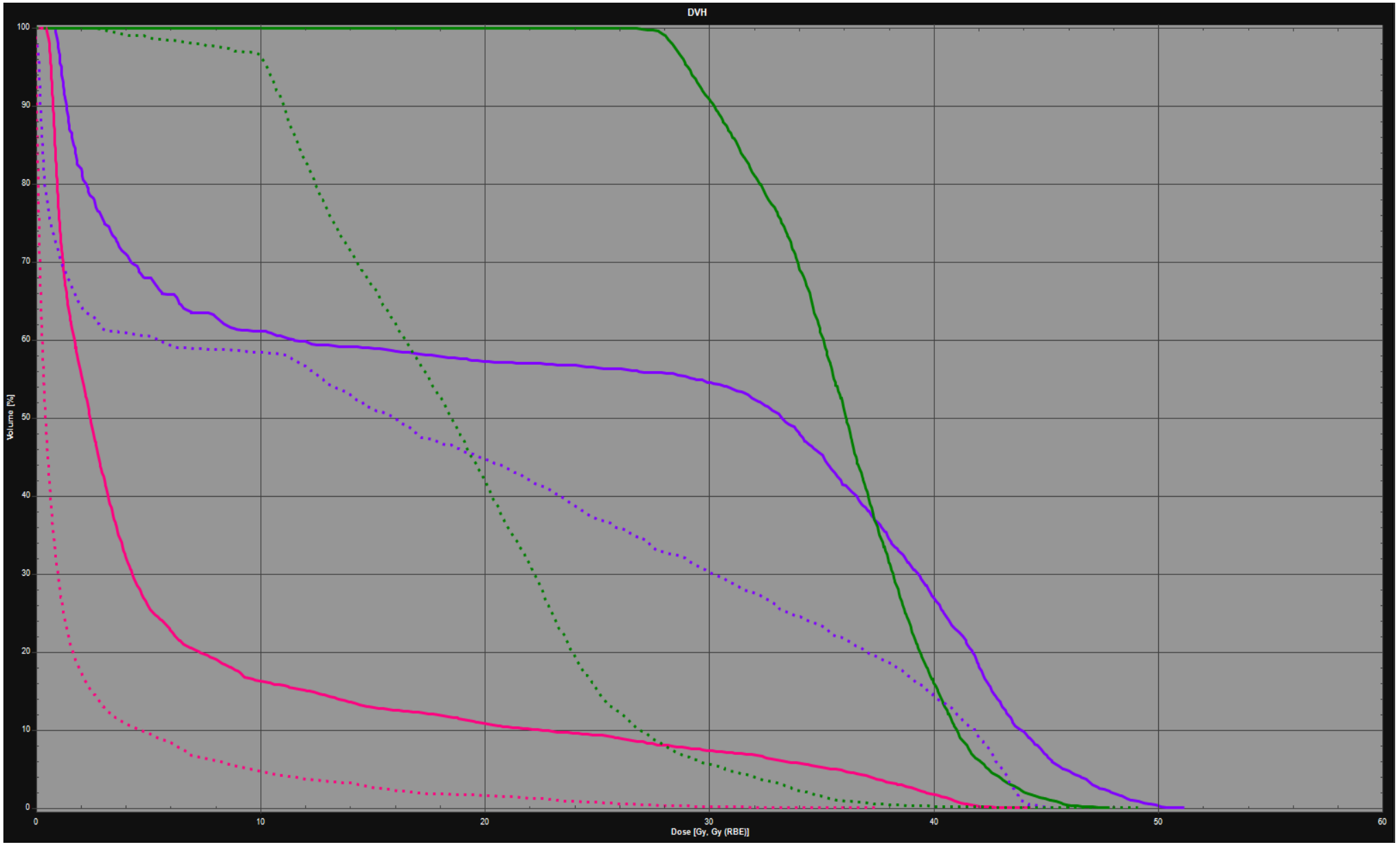
Additional dose bladder in Photon-VMAT of + 59.28%

Additional dose rectum in Photon-VMAT of + 64.83%

Dose	ROI	ROI vol. [cm³]	Dose [Gy, Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
Summed dose: VMAT Sum (CT 1 planning)	bladder	98.34	20.95	21.50	23.07	40.27	40.04	58.71	59.82
Summed dose (RBE): 9xBS1+3xBS2 (CT 1...	bladder	98.34	4.75	5.27	6.53	25.25	17.68	57.48	57.64
Summed dose: VMAT Sum (CT 1 planning)	rectum	21.96	31.07	31.77	32.83	40.45	39.73	51.81	52.29
Summed dose (RBE): 9xBS1+3xBS2 (CT 1...	rectum	21.96	3.11	3.43	4.51	24.54	22.50	50.20	51.79

60 y pt. HR PCA

GS 4+3=7/GG3
cT2c in mpMRT/PSMA-PET
cN0 cM0 in PSMA-PET



DVH comparisson: small bowel (Red), colon (violett) and sigma (green) – continous lines VMAT-Photonen und dasched lines CIRT

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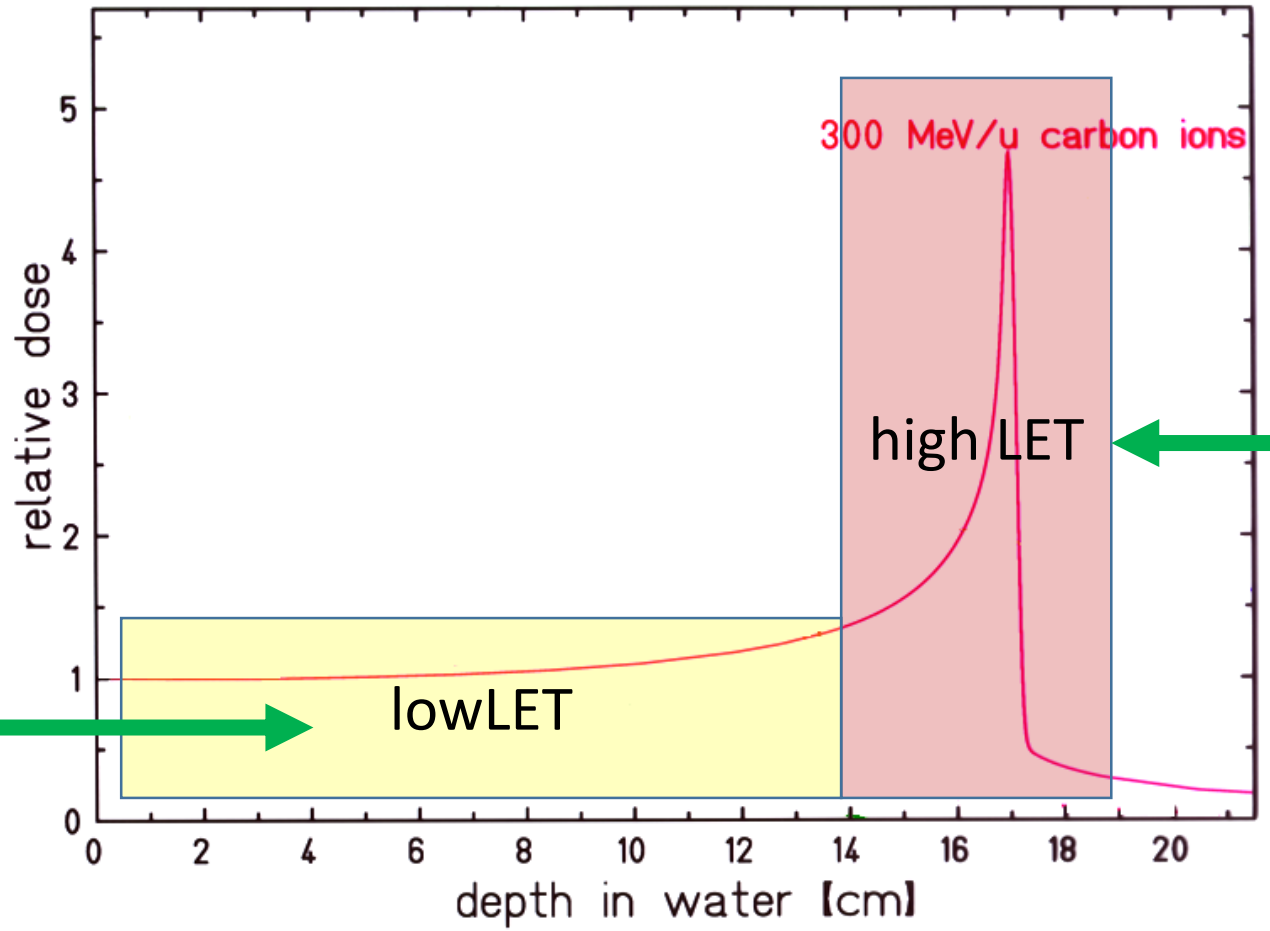
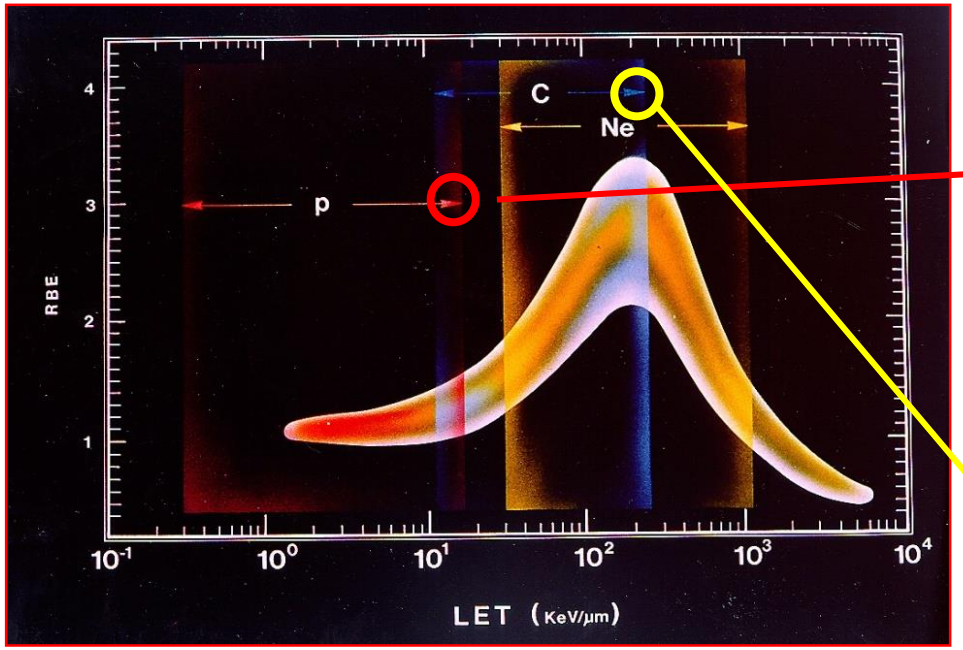
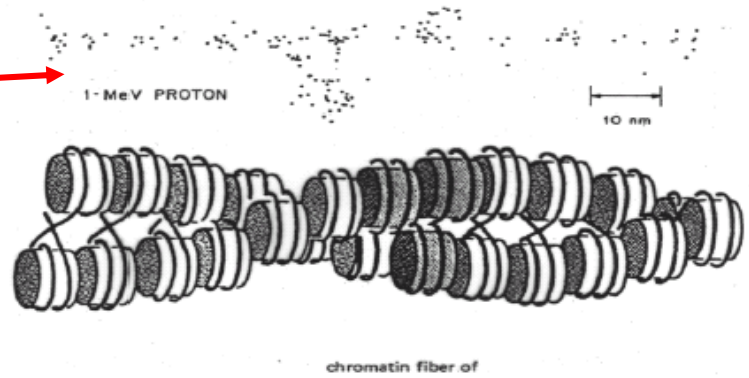


Advantage over high-dose photon RT

Advantage over proton RT

LET





low LET

l----------l----------l---------l-----

(<20 Ke V/micron)

high LET

l---l---l---l---l---l---l---l--- l--- l---

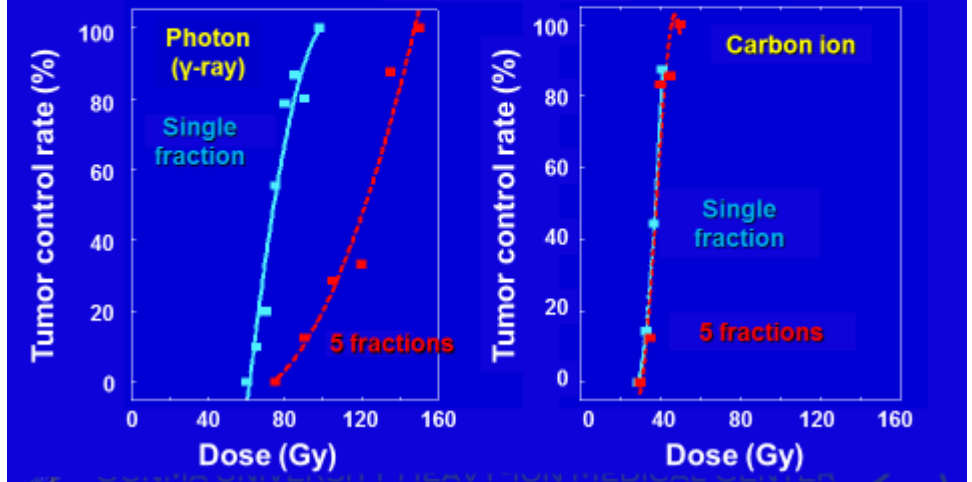
(> 20 – 1000 KeV/micron)

Courtesy Piero Fossati

Fractionation effects

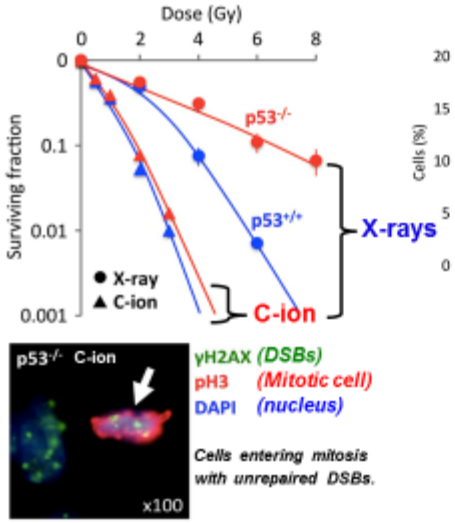
Carbon ion beam has minimal fractionation because of less repair capability

HSG tumor cells — K. Ando et al.

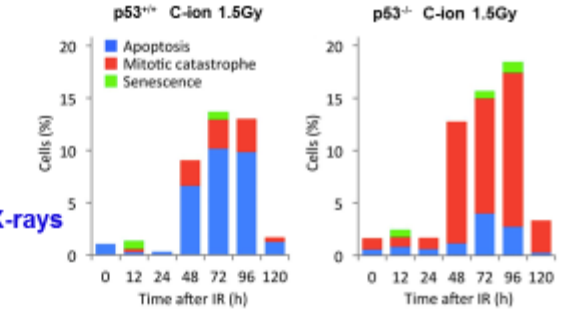


C-ion efficiently induce mitotic catastrophe in apoptosis-resistant p53 mutant cancer cells

Colony formation assay

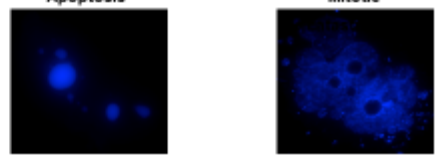


Cell death evaluation by DAPI staining



γH2AX *(DSBs)*
pH3 *(Mitotic cell)*
DAPI *(nucleus)*

Cells entering mitosis with unrepaired DSBs.

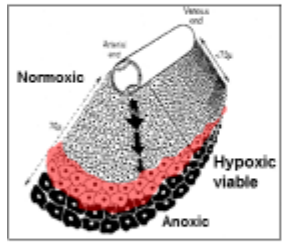


Courtesy of dr. Sato

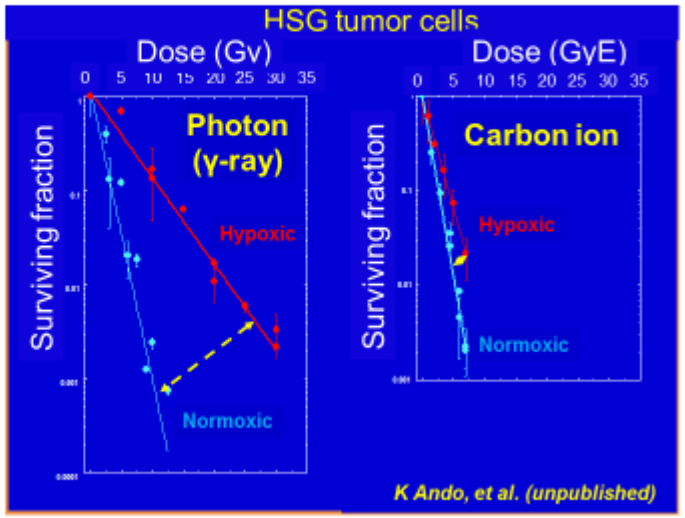
Amornwichet, Oike, Shibata, Nakano, 2014 Plos One

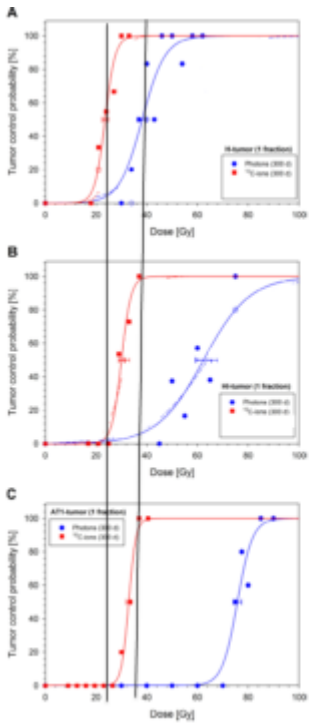
Radiation Sensitivity by Hypoxia

Carbon ion beam have significantly smaller OER than photons



Courtesy of dr. Sato





Well diferentiated prostate cancer

Moderately diferentiated prostate cancer

poorly diferentiated prostate cancer

Modified from C. Glowa et al. / Cancer Letters 378 (2016) 97–108

Courtesy Piero Fossati

CIRT Prostate | Radiobiological and Physical Advantages

- Radiobiological properties of carbon ions which make this modality theoretically well suited to treat hypoxic tumours characterized by a **low alfa/beta ratio** in their photons dose response curve.

- Favourable physical properties (specifically the **sharp lateral penumbra, small spot size**) which can optimally spare organs : rectal sparing and even selective urethral sparing.

- Preclinical data in animal models have confirmed that the efficacy of carbon ions in the treatment of **prostate tumour is only minimally dependant on tumour differentiation and hypoxia**

- **carbon ion could induce faster and better re-oxygenation** (in comparison to photons) specifically in poorly differentiated prostate tumours

- Two publications focused on the risk of second cancer and on the risk of mortality form any cancer **after CIRT suggesting that the risk of second cancer might be substantially lower** in comparison with modern photons radiotherapy

Glowa C, Radiother Oncol ,2021
Bendinger AL, Radiat Res , 2020
Glowa C, Radiother Oncol , 2019
Glowa C, Radiat Oncol , 2017

Glowa C, Cancer Lett , 2016
Bendinger AL Radiat Res, 2020
Mohamad O, Lancet Oncol , 2019
Kasuya G, Cancer Sci, 2017

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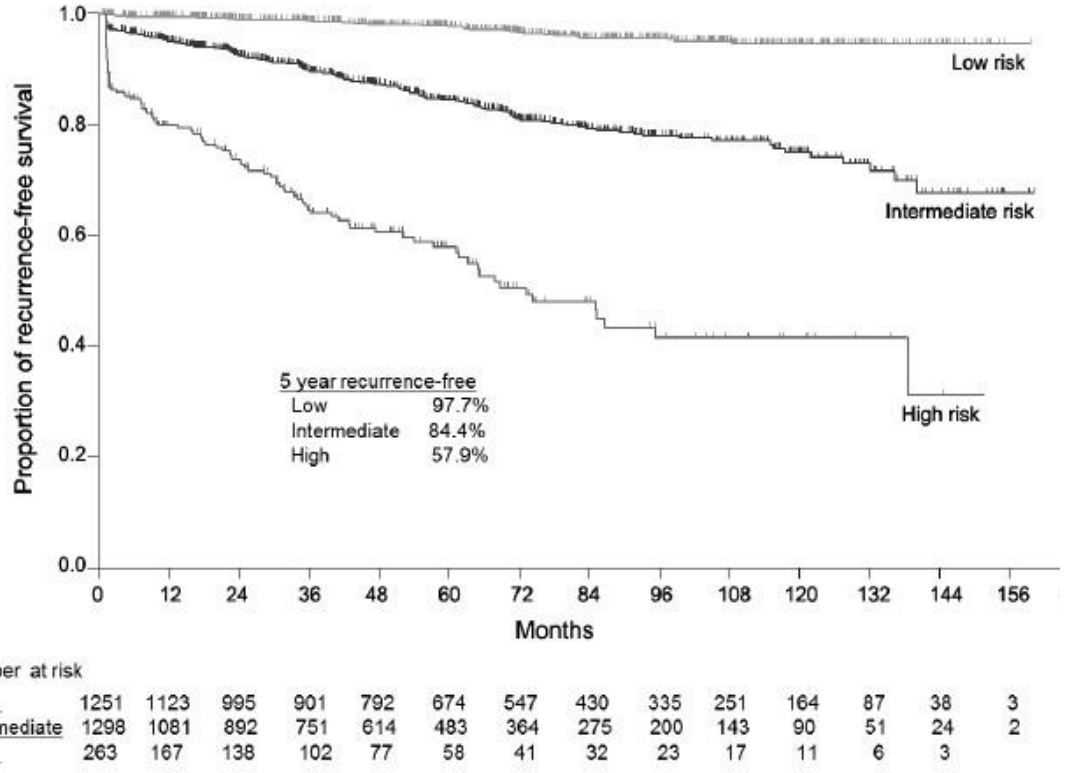
Eur Urol. 2017 Apr;71(4):618-629.

EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent.

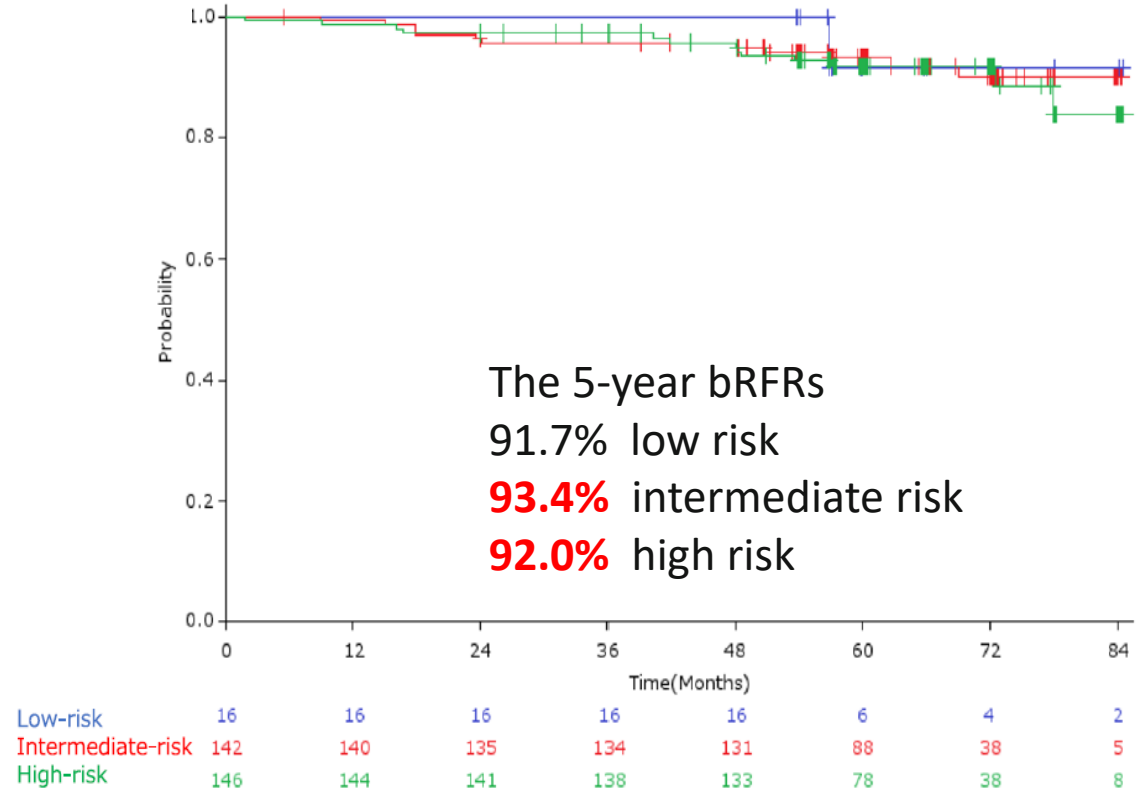
Mottet N[1], Bellmunt J[2], Bolla M[3] et al .

Table 1 EAU risk groups for biochemical recurrence of localised and locally advanced prostate Cancer			
Low-risk	Intermediate-risk	High-risk	Very high-risk
PSA < 10 ng/mL	PSA 10–20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7	or GS 7	or GS >7	any GS
and cT1-2a	or cT2b	or cT2c	cT3 – cT4 or cN+
Localised	Localised	Localised	Locally advanced

5-year survival by risk classes – conventional RT vs CIRT



(Nelson J, 2014)

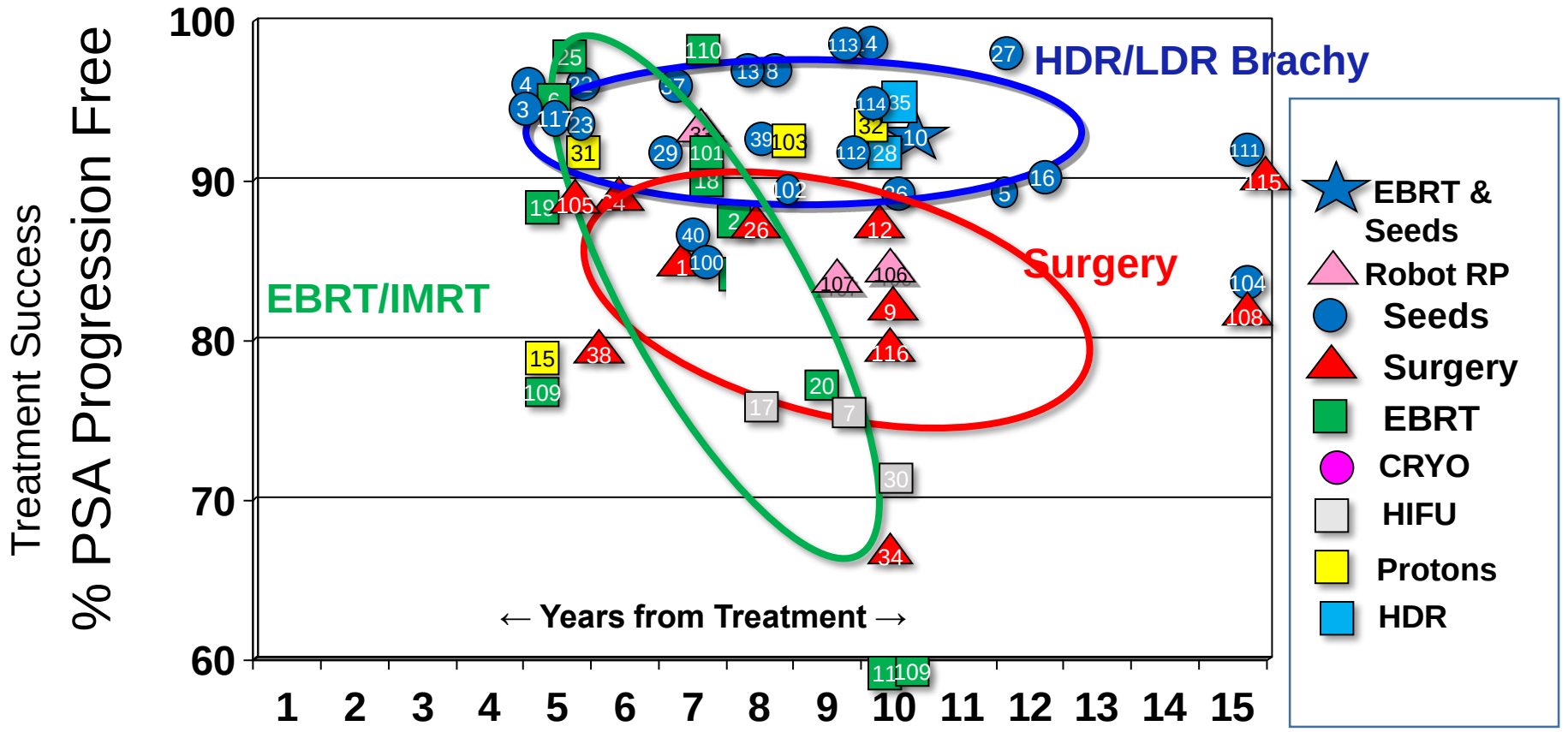


The 5-year bRFRs
91.7% low risk
93.4% intermediate risk
92.0% high risk

Kawamura et al 2020

LOW RISK RESULTS

Weighted

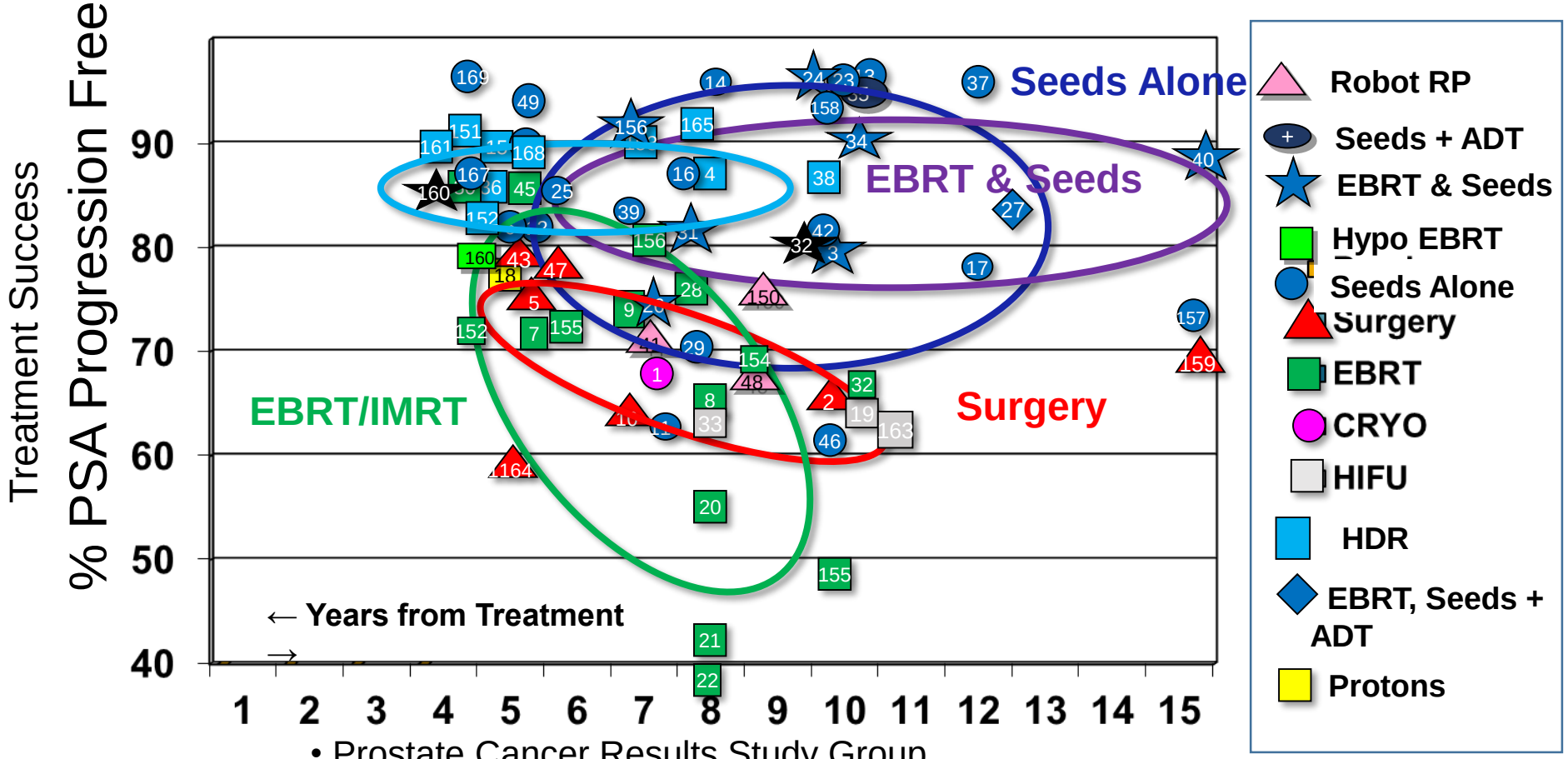


- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

BJU Int, 2012, Vol. 109(Supp. 1)

INTERMEDIATE RISK RESULTS

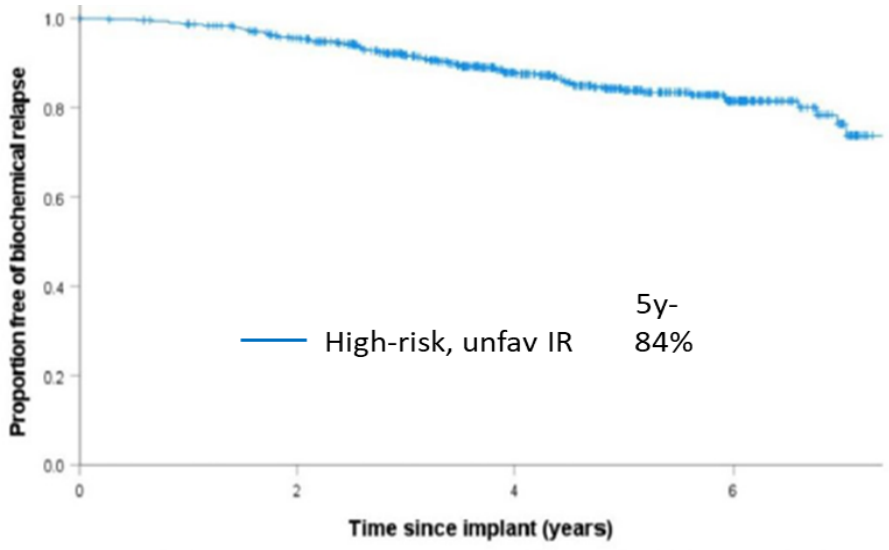
Weighted



- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

best level 1 evidence

ASCENDE TRIAL ph-EBRT/BT



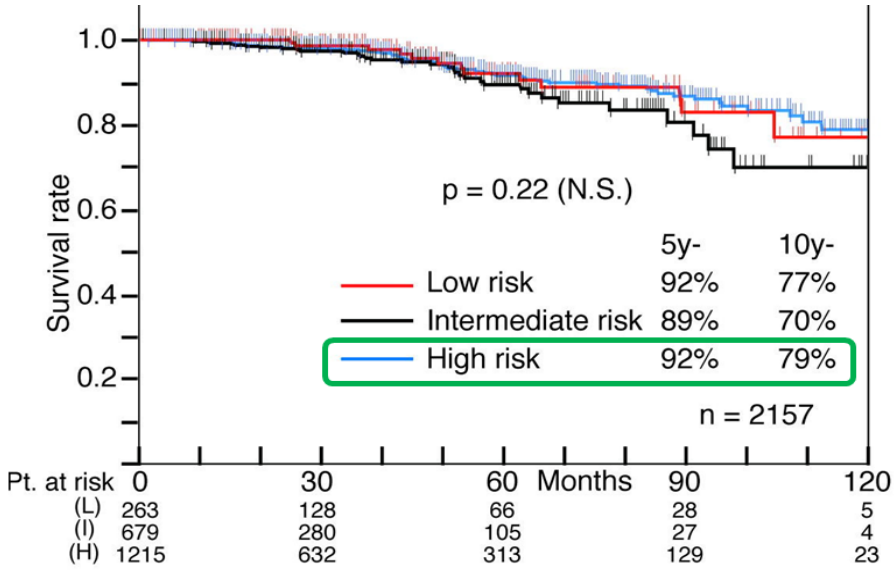
5-year grade 3 toxicities:

- **GI: 3.2%**
- **GU: 5.2%**
- **clinically significant decline in mean scores of physical role and sexual function**

Morris WJ, the ASCENDE-RT Trial, Int J Radiat Oncol Biol Phys, 2017

best long-term CIRT

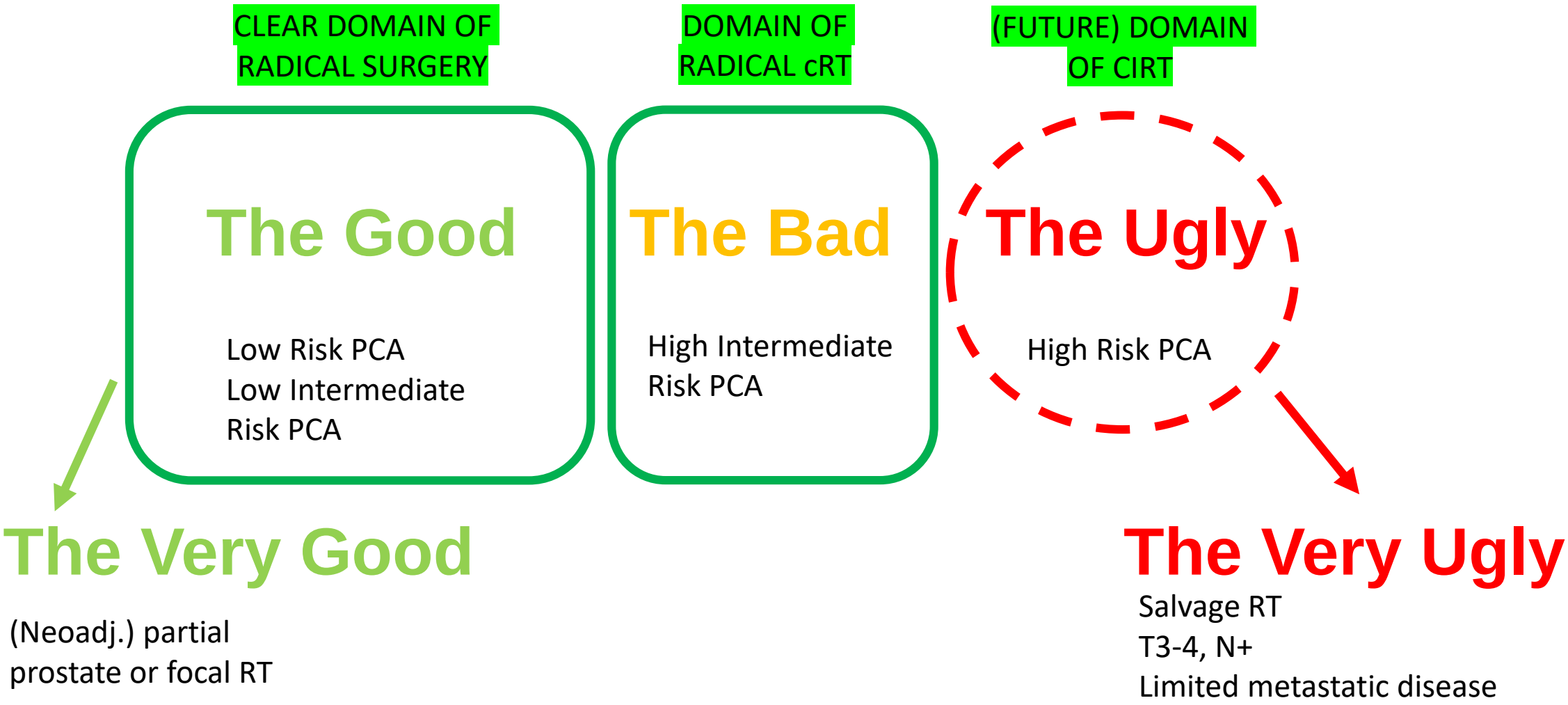
JCROS hypofractionation



5-year grade 3 toxicities:
GI: 0%
GU: 0%

Nomiya T, JCROS Br J Cancer, 2014

Differential Interdisciplinary Therapeutic Options



Differential Interdisciplinary Therapeutic Options

CLEAR DOMAIN OF RADICAL SURGERY

The Good	The Bad	The Ugly
Low Risk PCA Low Intermediate Risk PCA	High Intermediate Risk PCA	High Risk PCA

ALTERNATIVES: BRACHY-MONO, IMRT/VMAT, SBRT

LAST TERRITORY: PROTONS (e.g. small bowel in contact to prostate, pelvic pre-irradiation, genetic syndromes with increased radiation sensitivity etc.)

Genetic syndromes with increased radiation sensitivity

1. Ataxia teleangiectasia (ATM), Louis-Bar-Syndrome

   - Multisystem disease with progressive cerebellar ataxia (begin 1-4y), cutaneus teleangiectasia and immunologic symptoms (disposition to infection/tumor and radiosensitivity immune defect)

2. Cockayne-Syndrome
3. Werner Syndrome
4. Rett Syndrome
5. Bloom Syndrome
6. Nijmegen Breakage Syndrome
7. Rothmund-Thomson Syndrome
8. Xeroderma pigmentosum

…Etc.

Dose Escalation PCA: Biochemical Control (BC)

Level 1 Evidence – 4 randomized Trials

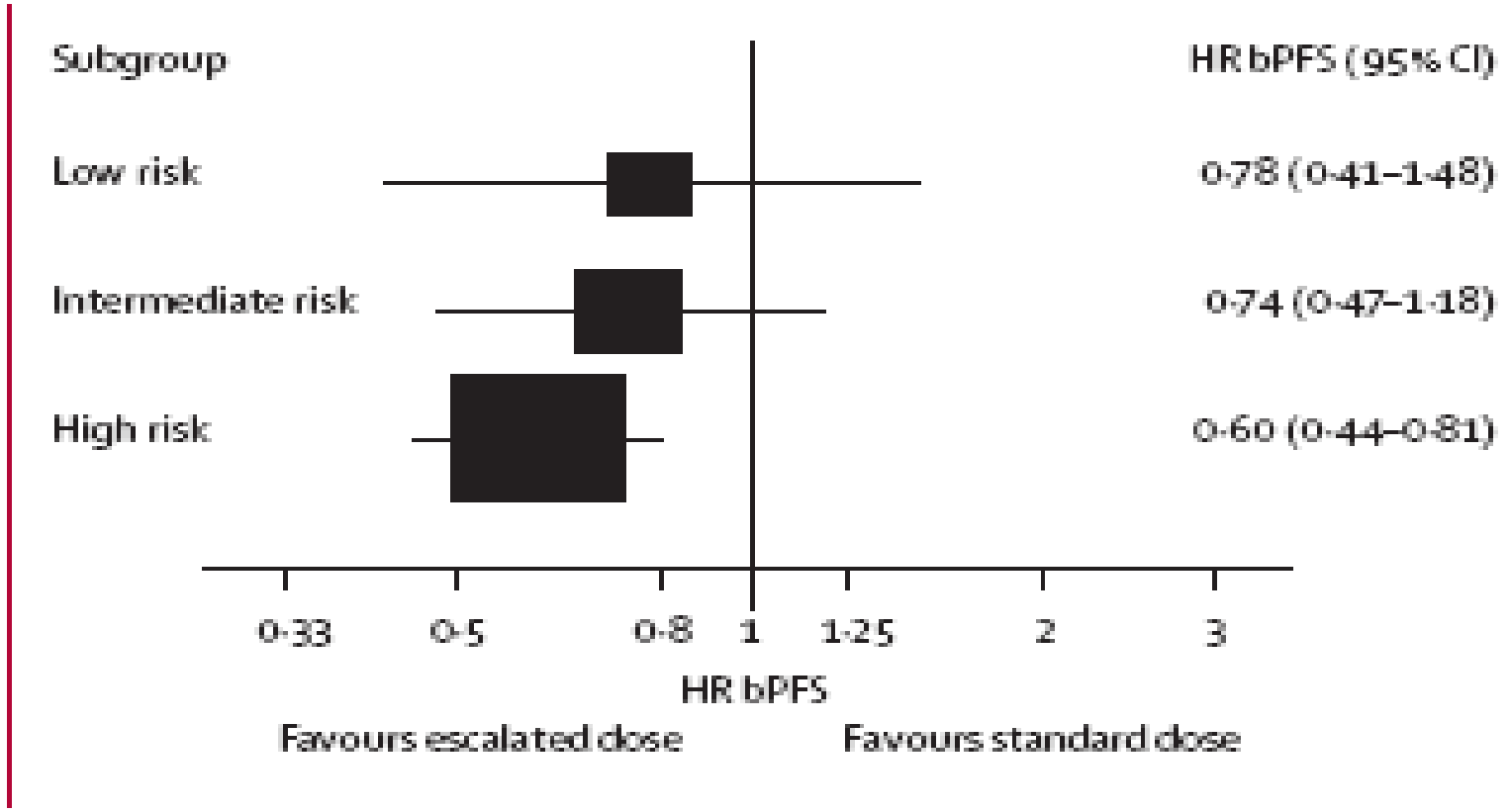
Study	BC better for escalation in % (N)	Standard (70 Gy or < 70 Gy Total Dose TD) BC %	Escalation BC %
MD Anderson	+13% (N=305)	53 % 70 Gy	66 % 78 Gy
Dutch Multicenter	+6% (N=669)	64 % 68 Gy	70 % 78 Gy
MRC RT01	+11% (N=843)	60 % 64 Gy	71 % 74 Gy
Protons	+15-20% (N=389)	60 % 70.2 GyE	80 % 79.2 GyE
Total N=2206	+11.9%	**68 Gy**	**77.3 Gy**

Technical Development

Toxicity Risk with Dose Escalation ▲
RTOG Grad =/> 2 up to 14% more Tox

Benefit in Biochemical Control with Dose Escalation - 12%

Which Risk Groups do benefit from Dose Escalation?



Dearnaley et al. Lancet Oncology, 2007

PAST – Review of Evidence / Lessons learned

- **Dose escalation is required** in **ALL Risk Strata**
  - Level 1 Evidence
- Dose escalation to **EQD2 of about 80 Gy** is required
  - Level 1 Evidence
- Dose escalation **with interstitial brachytherapy boost is superior** versus external beam alone
  - Level 1 Evidence (ASCENDE)

CAVEATS

- Dose escalation is associated with **increased risk of high-graded side effects**
- **Photons are inferior** to protons in terms of TOX

ULTRA-HYPOFRACTIONION / DOSE INTENSIFICATION – Partial Volume Implant

Kiel Concept – extreme dose escalation in peripheral zone, but intended „underdose“ in the urethra/trigonum

Ziel Volumen	Kurze Beschreibung	Gesamtdosis in Gy	Fraktionsdosis in Gy
1	Gesamte Prostata/ Samenblasen + complete pelvic lymphatic region	50	2 (25 Fraktionen, 5 x / Woche)
2	Gesamtprostata	*aprox. 18 **30,9	*9 (2 Fraktionen, 2. Woche und 4. Woche)
3	Periphäre nach Zone Mc Neal	*30 **77,25	*15 (2 Fraktionen, 2. Woche und 4. Woche)

Target CTV1 treated with Photons (Linac 15 MEV)

Targets CTV2 and CTV3 treated with HDR Brachytherapy (Ir-192) - Afterlaoding

*Nominal Dose in Brachytherapy in Gy

**Biological Equivalent Dose 2 Gy per Fraction = EQD2 (α/β estimates 3)

EQD2 (α/β estimates 3) Total = **81 Gy CTV2** / **127.25 Gy CTV3**

ULTRA-HYPOFRACTIONION / EVIDENCE FOR DOSE INTENSIFICATION (> 94 Gy)

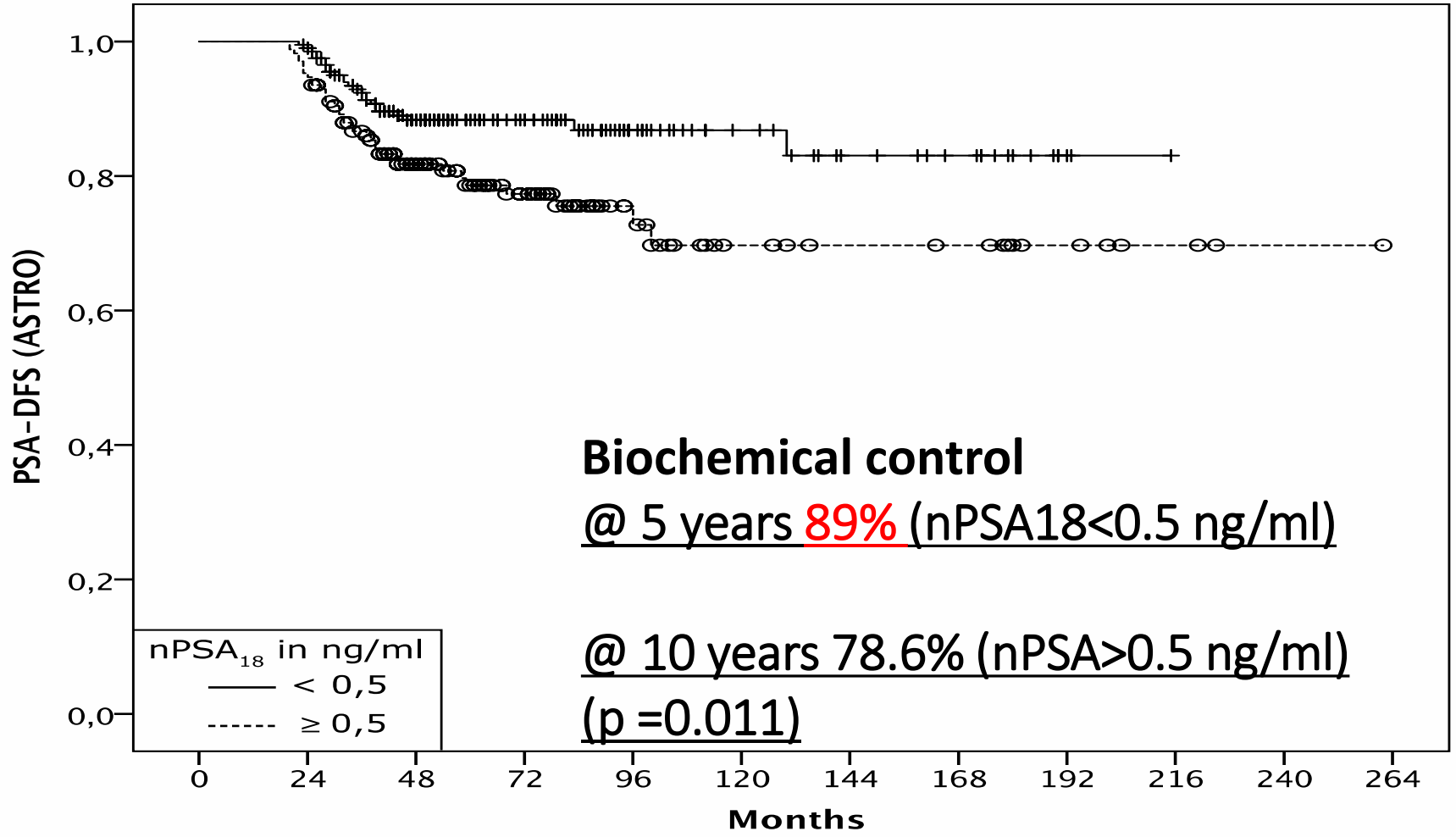
Hypofractionated conformal HDR brachytherapy in hormone naïve men with localized prostate cancer. Is escalation to very high biologically equivalent dose beneficial in all prognostic risk groups?

Galalae RM, Martinez A, Nuernberg N, et al. Strahlenther Onkol. 2006 Mar;182(3):135-41. doi: 10.1007/s00066-006-1448-5.

- 579 men were consecutively treated with pelvic EBRT and dose escalating HDR-BT since 1986; For the **cohort of hormone-naïve men (n=324)**, **dose escalation to > 94 Gy** resulted in a better 5-year BC of 59% versus **85%** ($p < 0.001$). **Striking dose escalation effect** was seen in the groups with two or three poor prognostic factors ($p = 0.022$ and $p < 0.001$).

Early Predictor for biochemical control Nadir PSA 18 Months

Schroeder, Galalae et al. Brachytherapy 2019; 18(1): 8-12. (N=459)



High-dose RT and Level 1-Evidence for SpaceOAR

A prospective, randomized patient-blinded clinical study was performed comparing image-guided intensity modulated prostate radiotherapy (79.2 Gy in 44 fractions) in men with or without prostate-rectum hydrogel spacer. Patients were followed up for 3 years, allowing assessment of long-term safety and efficacy

The mean **additional space** created between the prostate and the rectum was **just over 1** cm, which allowed significant rectum and penile bulb radiation dose reduction, resulting in **less acute pain**, **lower rates of late rectal toxicity**, and **improved bowel and urinary quality of life (QOL)** scores from 6 months onward. **Improvements in sexual QOL** were also observed at 37 months in baseline-potent men, with 37.5% of control and 66.7% of spacer men capable of "erections sufficient for intercourse."

- **Late G1+ rectal toxicity through 37 months favored the spacer arm (2% vs 9%, *P* <.03),** with no spacer men experiencing rectal toxicity greater than G1. There was no difference between groups in regard to late G1+ urinary toxicity, although fewer spacer men experienced G1+ urinary incontinence (4% vs 15%, *P* = .046).

High-dose RT and Level 1-Evidence for SpaceOAR

Hydrogel Spacer Prospective Multicenter **Randomized** Controlled Pivotal **Trial**: Dosimetric and **Clinical** Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, Kurtzman S, Bogart J, Hsi RA, Kos M, Ellis R, Logsdon M, Zimberg S, Forsythe K, Zhang H, Soffen E, Francke P, Mantz C, Rossi P, DeWeese T, Hamstra DA, Bosch W, Gay H, Michalski J.

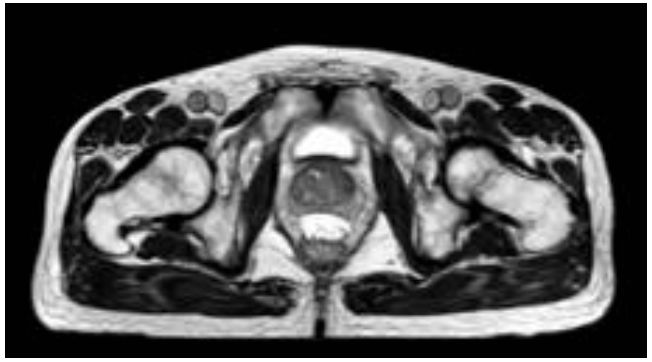
Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III **Trial**. Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, Kurtzman S, Bogart J, Hsi RA, Kos M, Ellis R, Logsdon M, Zimberg S, Forsythe K, Zhang H, Soffen E, Francke P, Mantz C, Rossi P, DeWeese T, Daignault-Newton S, Fischer-Valuck BW, Chundury A, Gay H, Bosch W, Michalski J.Hamstra DA, et al. Int J Radiat Oncol Biol Phys. 2017 Apr 1;97(5):976-985. doi: 10.1016/j.ijrobp.2016.12.024. Epub 2016 Dec 23.

Absorbable Hydrogel Spacer Use in Prostate Radiotherapy: A Comprehensive Review of Phase 3 **Clinical Trial** Published Data. Karsh LI, Gross ET, Pieczonka CM, Aliotta PJ, Skomra CJ, Ponsky LE, Nieh PT, Han M, Hamstra DA, Shore ND.Karsh LI, et al. Urology. 2018 May;115:39-44. doi: 10.1016/j.urology.2017.11.016. Epub 2017 Nov 23.

LESSONS LEARNED AND FUTURE DEVELOPMENTS

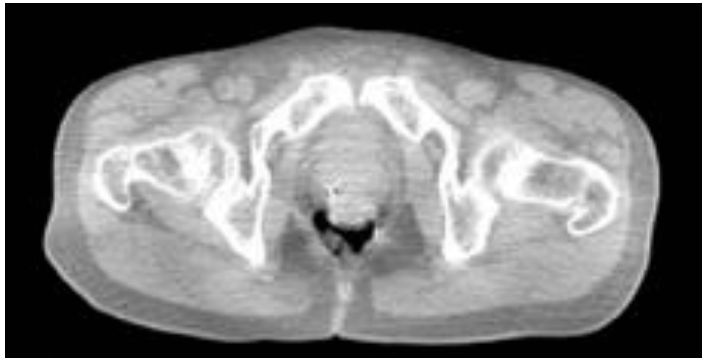
SpaceOAR Vue
Next-generation Hydrogel with CT radiopacity

SpaceOAR Vue Hydrogel in different image modalities



T2-weighted MRI

Computed Tomography



kV Cone-beam CT

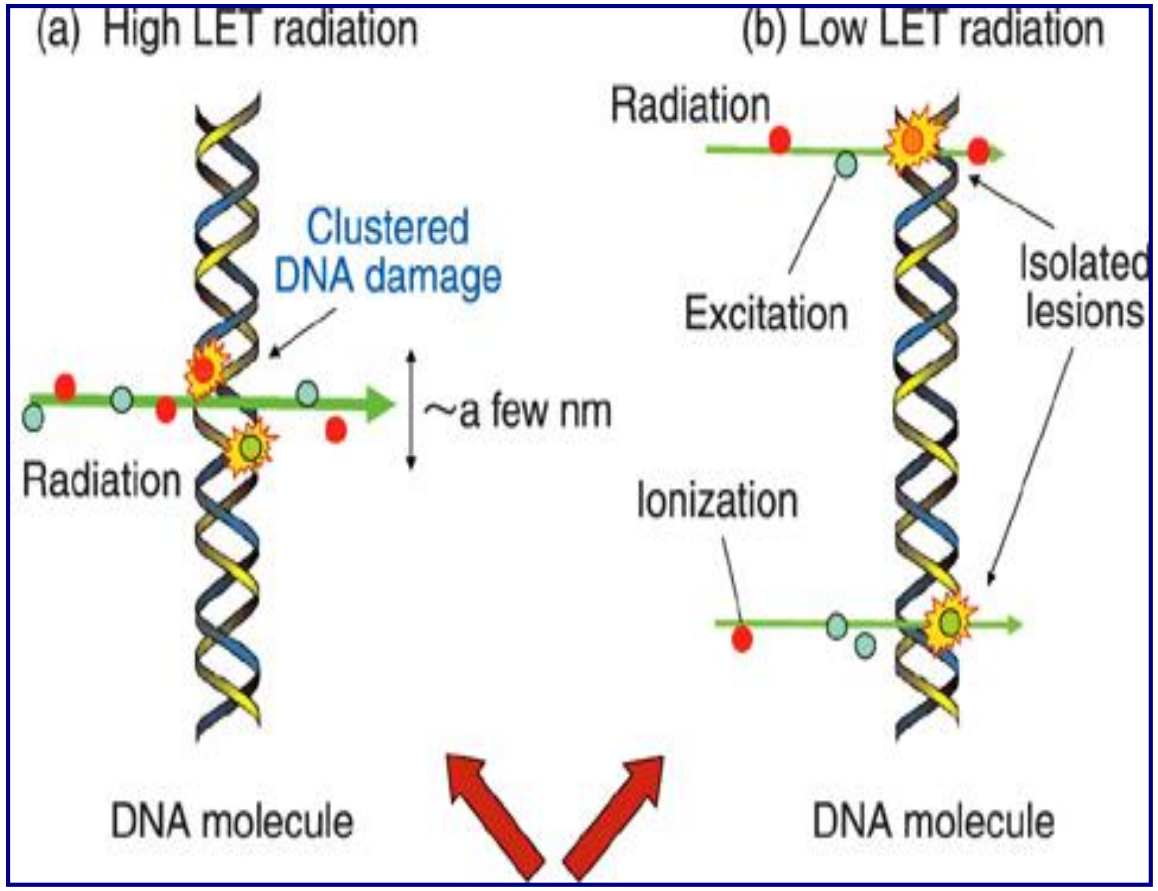
Used technology is meaningful !

CIRT

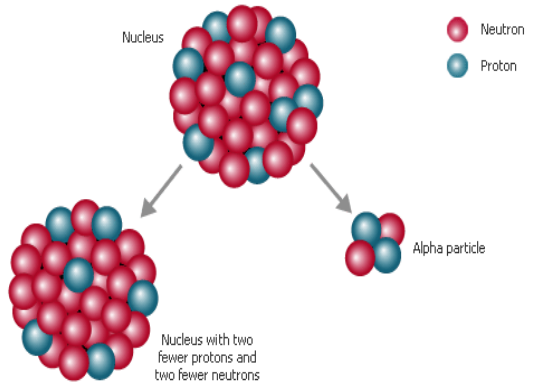
AVOID TOX IN HIGH DOSE RT (Grade III < 1%)

INCREASE EFFECTIVITY BY DOSE INTENSIFICATION
(Local control very high - LR only 1% - 2% // distant control > 90%)

DaRT – **a new brachytherapy source** - alpha radiation causes DNA breaks and cell death



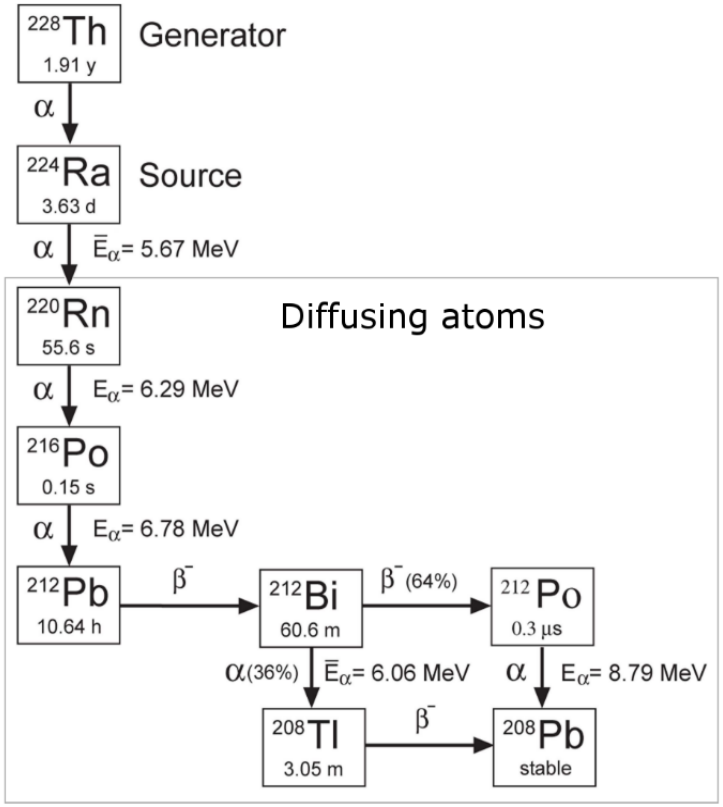
Alpha radiation is the most destructive type of radiation.
It can cause double strand DNA breaks that the cell can't repair.



DaRT Brachytherapy – alpha radiation causes DNA breaks and cell death (pre-clinical data)

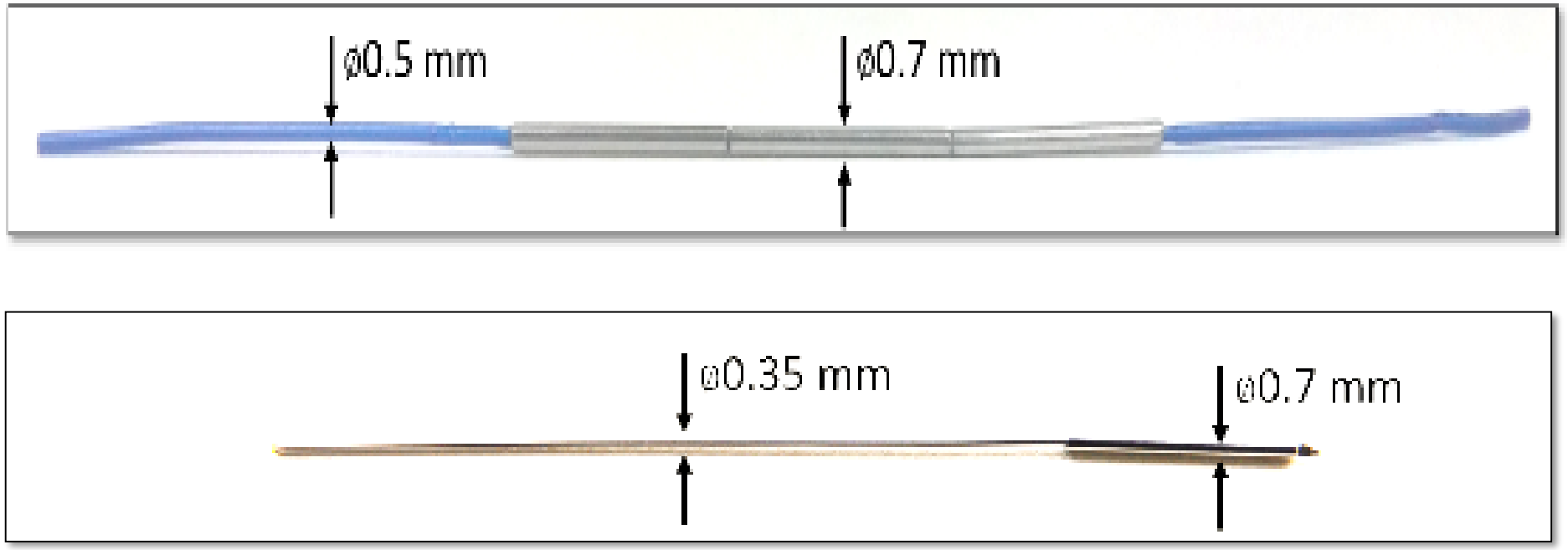
Tumor treated with inert wire (29 days after treatment)

Tumor treated with DART wire (29 days after treatment)



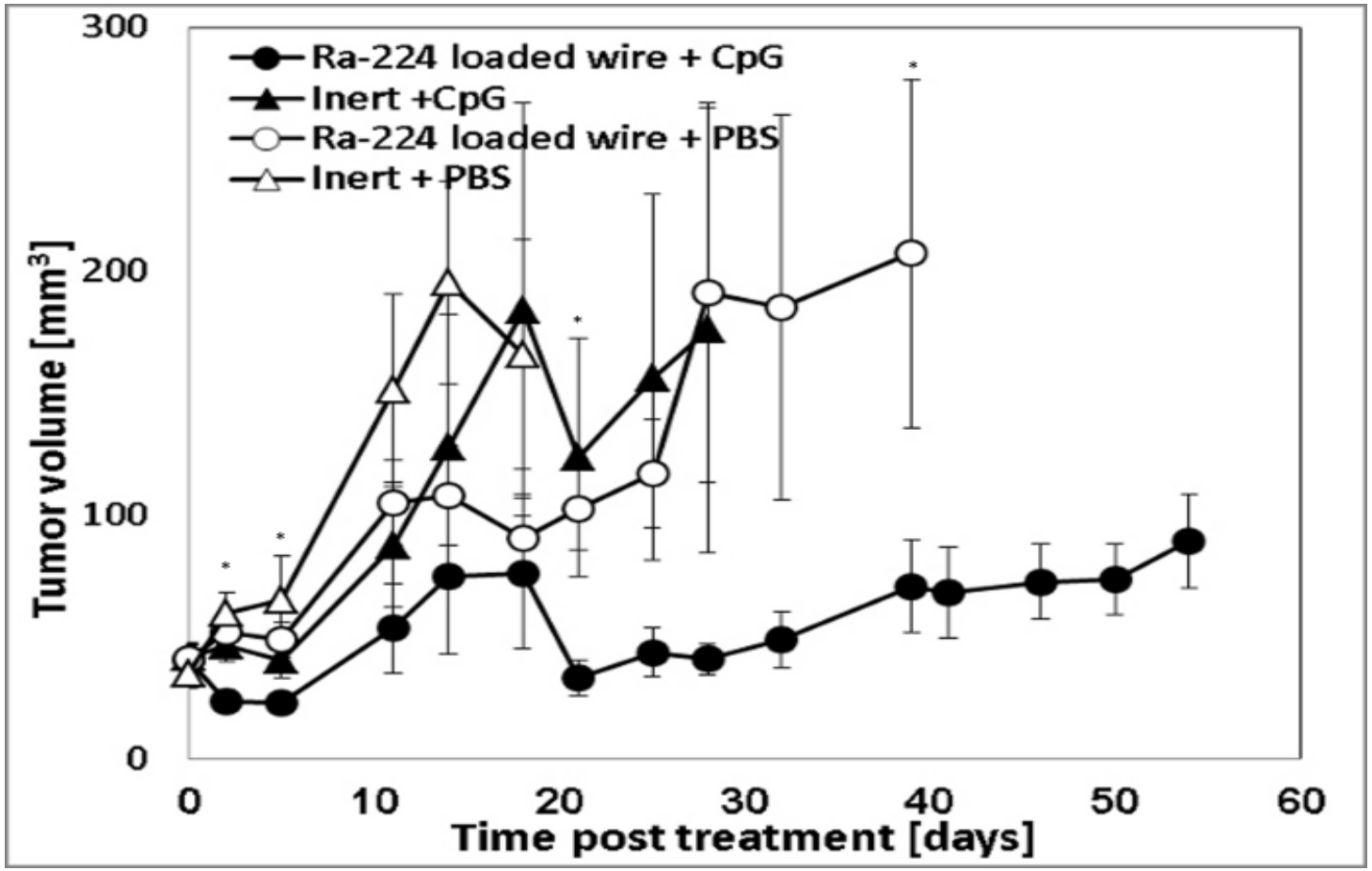
Cooks T, Tal M, Raab S., Efrati M, Reitkopf S, Lazarov E, Etzyoni R, Schmidt M, Arazi L, **Kelson I, Keisari Y**. Intratumoral Ra-224-loaded wires spread alpha emitting atoms inside solid human tumors in athymic mice and can achieve local tumor control. ***Anticancer Res* 2012**; 32(12):5315-21.

DaRT Brachytherapy – application by intratumoral insertion of Ra-224 embedded stainless-steel wires



DaRT was applied by intratumoral insertion of Ra-224 embedded stainless-steel wires.

Confino H, Hochman I, Efrati M, Schmidt M, Umansky V, Kelson I, Keisari Y. Tumor ablation by intratumoral Ra-224 loaded wires induces anti-tumor immunity against experimental metastatic tumors. ***Cancer Immunol Immunother*** **2015**; 64(2):191-9. doi: 10.1007/s00262-014-1626-8.



1. Tumor ablation by DaRT rendered the **animals resistant to a second tumor challenge** in two tumor models, colon carcinoma and **breast carcinoma**.

2. **Improved tumor control** could be achieved by a **combined treatment** with **DaRT and the immunoadjuvant, CpG.**

Future perspectives: Evidence by prospective phase I/II trials for New Brachytherapy Sources - DaRT

RIG-1-Like Receptor Activation Synergizes With **Intratumoral Alpha Radiation to Induce** Pancreatic Tumor Rejection, **Triple-Negative Breast Metastases Clearance, and Antitumor Immune Memory** in Mice.

frontiers in Oncology

Front Oncol. 2020; 10: 990.
Published online 2020 Jul 17. doi: 10.3389/fonc.2020.00990

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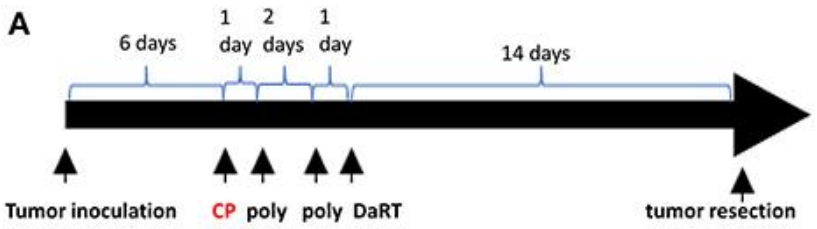

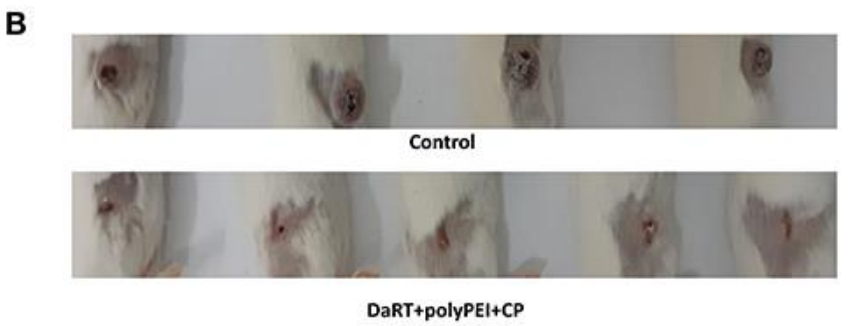

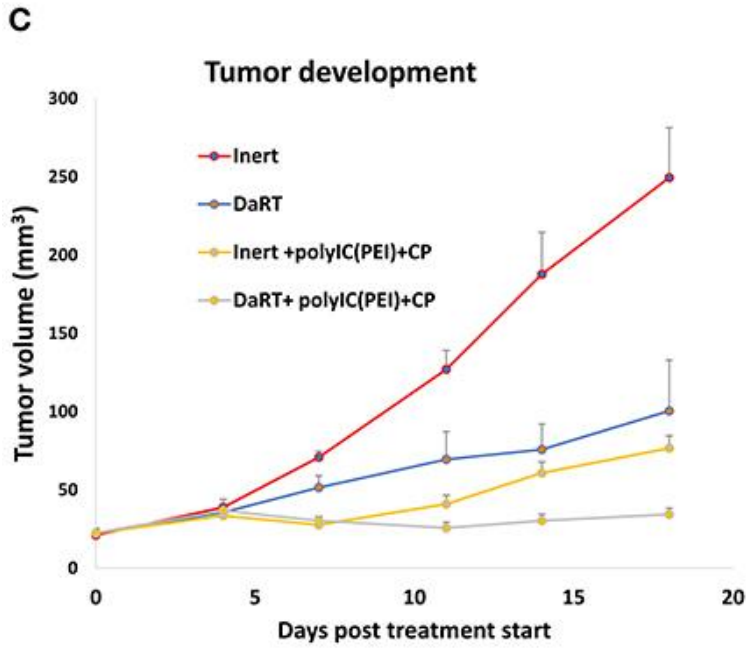

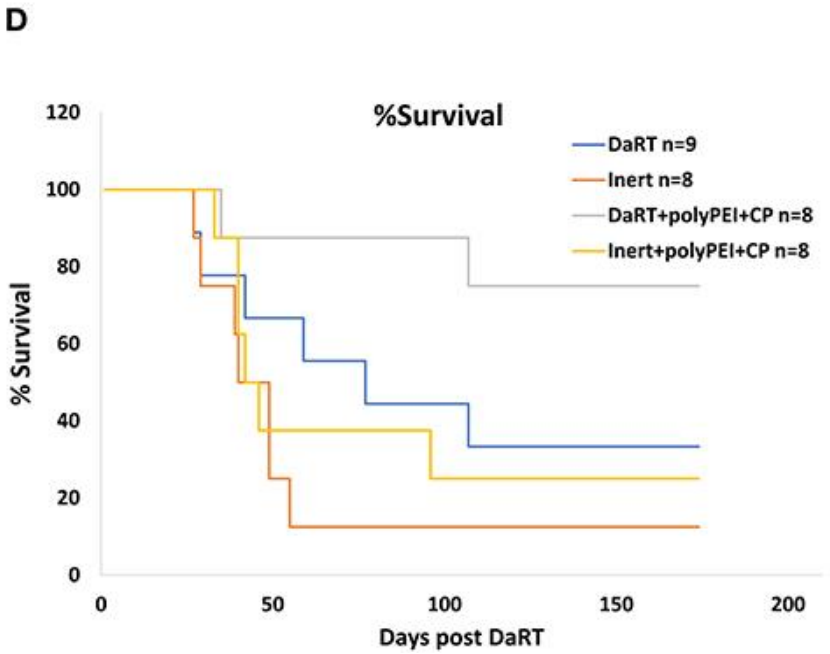

The effect of systemic low-dose CP in combination with local polyIC^{PEI}+DaRT on tumor development and metastasis-related death. **(A)** Schematic representation of the treatments with low-dose cyclophosphamide combined with DaRT+polyIC^{PEI} and tumor resection. **(B)** Representative tumors on the day of tumor resection. **(C)** Mice were treated with CP (100 mg/kg, i.p.) combined with polyIC^{PEI} (30 µg/60 µl i.t.) + DaRT (activity = 85 kBq). Presented are tumor volume ± SEM. $P_{t-test} < 0.05$ for DaRT+polyIC^{PEI}+CP compared all other treatments. **(D)**Kaplan–Meier survival curves of tumor-resected mice following treatment. $P_{log-ranktest} < 0.01$; < 0.05, for DaRT+ polyIC^{PEI}+CP vs. inert+vehicle control or polyIC^{PEI}+CP, respectively.

Potential benefit of Particle Therapy

Increase of radiation dose to target volume → *Improvement of local control/survival in locally advanced cases*

Reduction of dose to healthy tissues → *Reduction of side effects & secondary cancer*

Use of high-LET particles (ions) → *Improvement of local control/survival and replacement (?) of surgery in radio-resistant tumors*

Many Thanks!

Particle radiotherapy competes with photon-based RT & rad. surgery in *classical* PCA indications (Low Risk & Favorable Intermediate Risk), can reduce side effects and has the potential to improve local control. (Level 1 evidence in one phase III trial).

Carbon ion therapy can improve local control & biochemical control with limiting/avoiding toxicity in *specific* PCA indications (Very High Risk & High Risk & Unfavorable Intermediate Risk) /radioresistant tumors / re-irradiation etc.

Comparative studies (possibly phase III) are difficult to conduct, but should be designed in a collaborative setting.