HUMANITAS
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IPOGONADISMO,
PATOLOGIA PROSTATICA E
DISFUNZIONI SESSUALI
Endocrinologo e Urologo a confronto

MILANO 28.09.2018

PROTOCOLLI DI RADIOTERAPIA NEL CARCINOMA PROSTATICO E DISFUNZIONE ERETTILE: DIFFERENTI OUTCOMES?

Giuseppe R. D'Agostino
Radiotherapy & Radiosurgery,
Istituto Clinico Humanitas – Rozzano (MI)

Is Radical Prostatectomy the "Gold Standard" for Localized Prostate Cancer?

William M. Mendenhall, MD,† R. Charles Nichols, MD,*† Randal Henderson, MD, MBA,*† and Nancy P. Mendenhall, MD*†*

TABLE 4. Relative Risk (RR) of Biochemical (PSA) Failure Compared With Radical Prostatectomy[3]

	D'Amico Risk Group		
Treatment	**Low**	**Intermediate**	**High**
EBRT	1.1 ($P = 0.79$) (225 pts)	0.8 ($P = 0.26$) (232 pts)	0.9 ($P = 0.26$) (309 pts)
Brachytherapy	1.1 ($P = 0.91$) (32 pts)	3.1 ($P = 0.006$) (15 pts)	3.0 ($P = 0.0002$) (19 pts)
ADT plus brachytherapy	0.5 ($P = 0.21$) (91 pts)	1.6 ($P = 0.22$) (38 pts)	2.2 ($P = 0.02$) (23 pts)
RP	(402 pts)	(247 pts)	(239 pts)

EBRT indicates external-beam radiotherapy; ADT, androgen deprivation therapy; RP, radical prostatectomy.

American Journal of Clinical Oncology • Volume 33, Number 5, October 2010

OUTCOME

TABLE 2. Outcomes After Radiotherapy for Localized Prostate Cancer[4]

Series	No. Pts	Follow-Up	Treatment	Risk Group	bPFS	CSS
MSKCC[8]	561	Median, 7 y Range, 5–9 y	IMRT 81 Gy/1.8 Gy per Fx; 3 mo; ADT in 53%	Low (203 pts)	85% (8 y)	100% (8 y)
				Intermediate (255 pts)	76% (8 y)	96% (8 y)
				High (103 pts)	72% (8 y)	84% (8 y)
Multi-institutional[10]	611	Mean, 5 y Range, 0.2–15.3 y	EBRT + HDR-BT; short course ADT in 29%	Low (46 pts)	96% (5 y)	100% (5 y)
				Intermediate (188 pts)	88% (5 y)	99% (5 y)
				High (359 pts)	69% (5 y)	95% (5 y)
				Overall (611 pts)	73% (10 y)	92% (10 y)
Seattle Prostate Institute[11]	223	Median, 9.4 y Range, 0.6–17.1 y	EBRT + LDR-BT; no ADT	Low (59 pts)	88% (15 y)	—
				Intermediate (50 pts)	80% (15 y)	—
				High (114 pts)	53% (15 y)	—
				Overall (223 pts)	74% (15 y)	—
Cleveland Clinic[12]	770	Median, 45 mo	IMRT 70 Gy at 2.5 Gy/Fx over 5 wk; ADT in 60%	Low (34%)	95% (5 y)	—
				Intermediate (28%)	85% (5 y)	—
				High (38%)	68% (5 y)	—
				Overall (770 pts)	82% (5 y)	—
Schiffler Cancer Center[13]	668	Median, 59 mo	LDR-BT; EBRT–55%; ADT 41%	Low (34%)	98% (8 y)	—
				Intermediate (38%)	98% (8 y)	—
				High (28%)	88% (8 y)	—
Seattle Prostate Institute[14]	230	Median, 42 mo	LDR-BT; no EBRT; no ADT	Low (103 pts)	94% (5 y)	—
				Intermediate (107 pts)	82% (5 y)	—
				High (20 pts)	65% (5 y)	—
				Overall (230 pts)	84% (9 y)	—

Pts indicates patients; MSKCC, Memorial Sloan Kettering Cancer Center; bPFS, biochemical progression free survival; CSS, cause-specific survival; y, years; IMRT, intensity modulated radiotherapy; ADT, androgen deprivation therapy; HDR-BT, high-dose rate brachytherapy; LDR-BT, low-dose rate brachytherapy; Fx, fraction; mo, months; wk, weeks.

American Journal of Clinical Oncology • Volume 33, Number 5, October 2010

ERECTILE FUNCTION

TABLE 3. Meta-Analysis of the Probability of Maintaining Erectile Function After Treatment for Localized Prostate[5,20]

Treatment	No. Pts	~1 yr Post-Rx	No. Pts	~2 yr Post-Rx	Age Adjusted
BT alone	172	76%	No data	No data	80%
BT + EBRT	58	60%	58	60%	69%
EBRT	1343	55%	731	52%	68%
RP					
Nerve sparing	485	34%	128	25%	22%
Standard	3019	25%	2673	25%	16%
Cryotherapy	264	13%	198	15%	13%

BT indicates brachytherapy; EBRT, external beam radiotherapy; RP, radical prostatectomy; yr, years; Rx, treatment.

REVIEW ARTICLE

Is Radical Prostatectomy the "Gold Standard" for Localized Prostate Cancer?

William M. Mendenhall, MD,† R. Charles Nichols, MD,*† Randal Henderson, MD, MBA,*† and Nancy P. Mendenhall, MD*†*

CONCLUSION

The probability of cure is similar after either RP or RT. The likelihood of significant complications is probably higher after RP compared with RT. Preservation of erectile function is at least as good or better after RT compared with RP. Urinary continence is more likely to be preserved after RT compared with RP. Each treatment results in distinct patterns of adverse changes in QOL that are worsened by patient- and tumor-related parameters.

Semin Radiat Oncol. 1993 Jul;3(3):210-220.

Randomized Trials in Loco-Regionally Confined Prostate Cancer: Past, Present, and Future.

Zietman AL[1], Shipley WU.

Author information

[1]Genitourinary Oncology Unit, Massachusetts General Hospital, Boston, MA, USA

Abstract

Over the last 30 years, a vast literature has been published on the available therapeutic approaches for loco-regionally confined prostate cancer. However, it is remarkable how few well designed and well conducted randomized trials have set out to compare them. As a result there is no consensus on the appropriate management of either early stage or locally advanced disease and treatment is still given on the basis of physician preconception, training, and instinct. Published trials have been weakened by the long natural history of prostate cancer and its unpredictable pace. Ten to 15 years are required to fully assess the clinical impact of therapy. By the time of publication, the original therapies frequently have become outmoded or the staging procedures shown to be inadequate by current standards. Prostate-specific antigen is a tumor marker that has powerful prognostic value and detects recurrence long before it becomes clinically apparent. Its use will allow for improved stratification in future studies and shorten the time of follow-up required to assess disease-free survival. Randomized trials will yield results in 5 years rather than the decades previously judged necessary. A renewed emphasis on the randomized trial in prostate cancer is now possible allowing for the rapid and scientific testing of both standard and novel treatment strategies.

The technological evolution

1953

2012

Five-Year Outcomes After Prostatectomy or Radiotherapy for Prostate Cancer: The Prostate Cancer Outcomes Study

Arnold L. Potosky, William W. Davis, Richard M. Hoffman, Janet L. Stanford, Robert A. Stephenson, David F. Penson, Linda C. Harlan

J Natl Cancer Inst 2004;96:1358-67

Table 1. Comparison of 5-year PCOS survey responders on individual urinary, bowel, and sexual domain items*

Domain	RP† (n = 901)	EBRT† (n = 286)	OR (95% CI)
Urinary			
No control or frequent leaks vs. total control or occasional leaks	14.4 (15.3)	4.9 (4.1)	4.4 (2.2 to 8.6)
Leaks ≥2 times per day‡	15.6 (16.1)	4.1 (3.6)	5.3 (2.6 to 10.8)
Wears any pads to stay dry‡	28.6 (28.6)	4.2 (4.2)	9.4 (4.7 to 18.9)
Frequent urination more than half the time‡	10.6 (10.1)	8.9 (9.3)	1.1 (0.6 to 1.9)
Bothered by dripping or leaking urine§	13.9 (14.3)	3.0 (2.6)	6.5 (2.7 to 15.6)
Bowel‖			
Diarrhea‡	23.3 (23.9)	28.8 (26.7)	0.84 (0.55 to 1.26)
Painful bowel movements‡	10.4 (11.5)	12.2 (9.4)	1.31 (0.73 to 2.35)
Bowel urgency‡	17.7 (19.3)	33.4 (28.5)	0.56 (0.36 to 0.87)
Wetness in rectal area‡	13.8 (14.8)	20.6 (18.3)	0.75 (0.47 to 1.20)
Painful hemorrhoids‡	11.0 (10.2)	15.7 (19.6)	0.43 (0.25 to 0.74)
Bothered by frequent bowel movement to pain, or urgency§	4.3 (4.8)	5.0 (4.0)	1.23 (0.52 to 2.89)
Sexual			
No/little vs. some/a lot of interest in sexual activity	46.5 (48.9)	55.2 (47.4)	1.1 (0.73 to 1.6)
No sexual activity vs. any sexual activity	48.9 (50.7)	51.3 (43.9)	1.4 (0.93 to 2.0)
Erection insufficient for intercourse†	76.9 (79.3)	73.1 (63.5)	2.5 (1.6 to 3.8)
Bothered by sexual dysfunction§	47.4 (46.7)	42.0 (44.6)	1.1 (0.75 to 1.6)

*Model-based odds ratios (with external beam radiotherapy patients as referent group) and adjusted percentages are from separate logistic regression models (for each row) each adjusting for treatment propensity score, age at diagnosis, baseline function, race/ethnicity, comorbidity, and educational level. All estimates were weighted to total eligible cases. PCOS = Prostate Cancer Outcomes Study; RP = radical prostatectomy; EBRT = external beam radiotherapy; OR = odds ratio; CI = confidence interval.

†Values in columns are unadjusted percentages (adjusted percentages).

‡Percentages and odds ratio for yes versus no/none.

§For bother items, percentages refer to patients reporting a large or moderate problem versus a small or no problem.

‖For the five bowel function items, percentages refer to patients reporting having the problem every day or some days versus rarely or never.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer

Matthew J. Resnick, M.D., Tatsuki Koyama, Ph.D., Kang-Hsien Fan, M.S., Peter C. Albertsen, M.D., Michael Goodman, M.D., M.P.H., Ann S. Hamilton, Ph.D., Richard M. Hoffman, M.D., M.P.H., Arnold L. Potosky, Ph.D., Janet L. Stanford, Ph.D., Antoinette M. Stroup, Ph.D., R. Lawrence Van Horn, Ph.D., and David F. Penson, M.D., M.P.H.

Men in the prostatectomy group were significantly more likely than those in the radiotherapy group to report having erections insufficient for intercourse at 2 years (odds ratio, 3.46; 95% CI,1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63) (Table 2).

Erectile dysfunction was nearly universal at 15 years, with 87.0% of those in the prostatectomy group and 93.9% of those in the radiotherapy group reporting an inability to achieve an erection sufficient for intercourse.

There was no significant between-group difference in the adjusted odds for erectile dysfunction at 15 years (odds ratio, 0.38; 95% CI, 0.12 to 1.22).

N ENGL J MED 368;5 NEJM.ORG JANUARY 31, 2013

Long-Term Effects of Prostate-Cancer Treatment

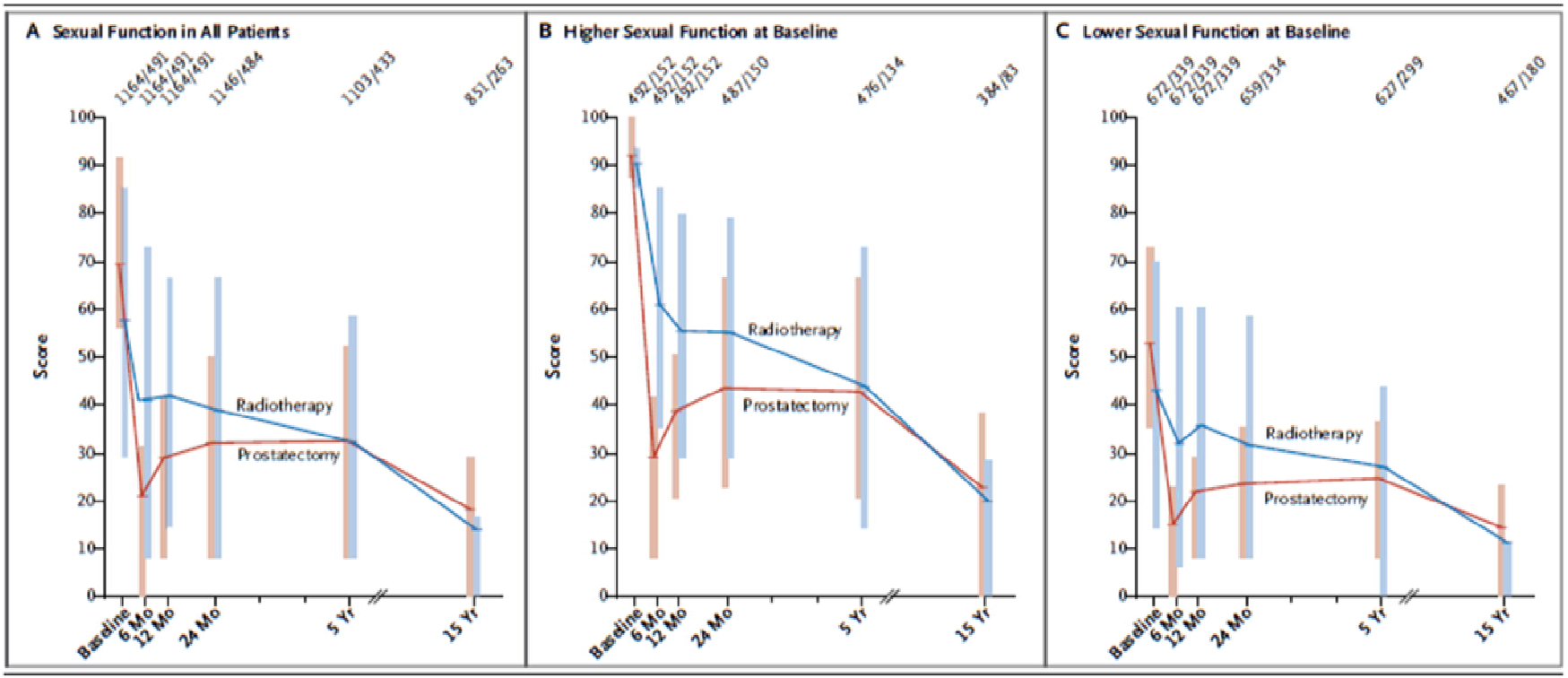


Figure 2. Sexual Function over 15 Years.

Shown is a longitudinal evaluation of mean unadjusted summary scores for sexual function in the overall cohort (Panel A), in a subgroup of men with higher sexual function at baseline (summary score, ≥80) (Panel B), and in a subgroup of men with lower sexual function at baseline (summary score, <80) (Panel C). The range of possible scores is from 0 to 100, with higher scores indicating better function. Bars represent interquartile ranges. The numbers of patients who were evaluated in the prostatectomy group and the radiotherapy group, respectively, are listed for each time point.

N ENGL J MED 368;5 NEJM.ORG JANUARY 31, 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

N Engl J Med 2016;375:1415-24.

Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

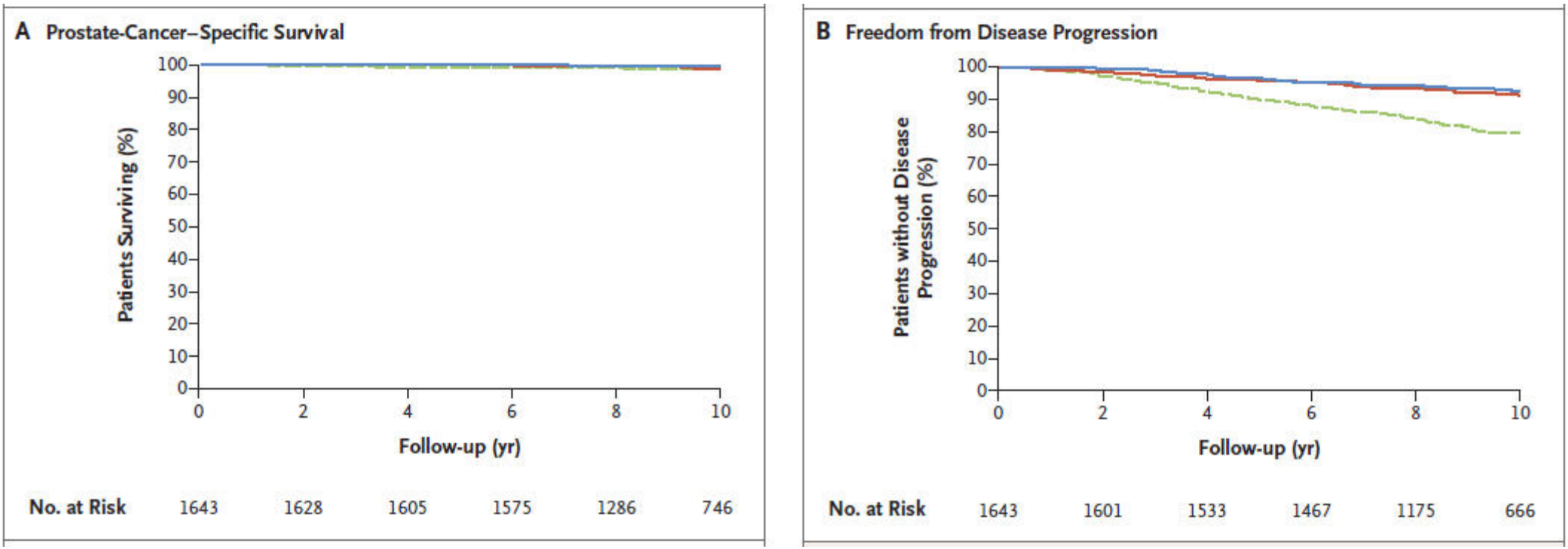
Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

* P values were calculated with the use of a log-rank test of the null hypothesis of no difference in effectiveness across the three treatments. The planned adjusted analysis was not possible owing to the low number of events.

† Deaths due to prostate cancer were defined as deaths that were definitely or probably due to prostate cancer or its treatment, as determined by the independent cause-of-death evaluation committee.

‡ Disease progression was defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

ProtecT: Survival



N Engl J Med 2016;375:1415-24.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

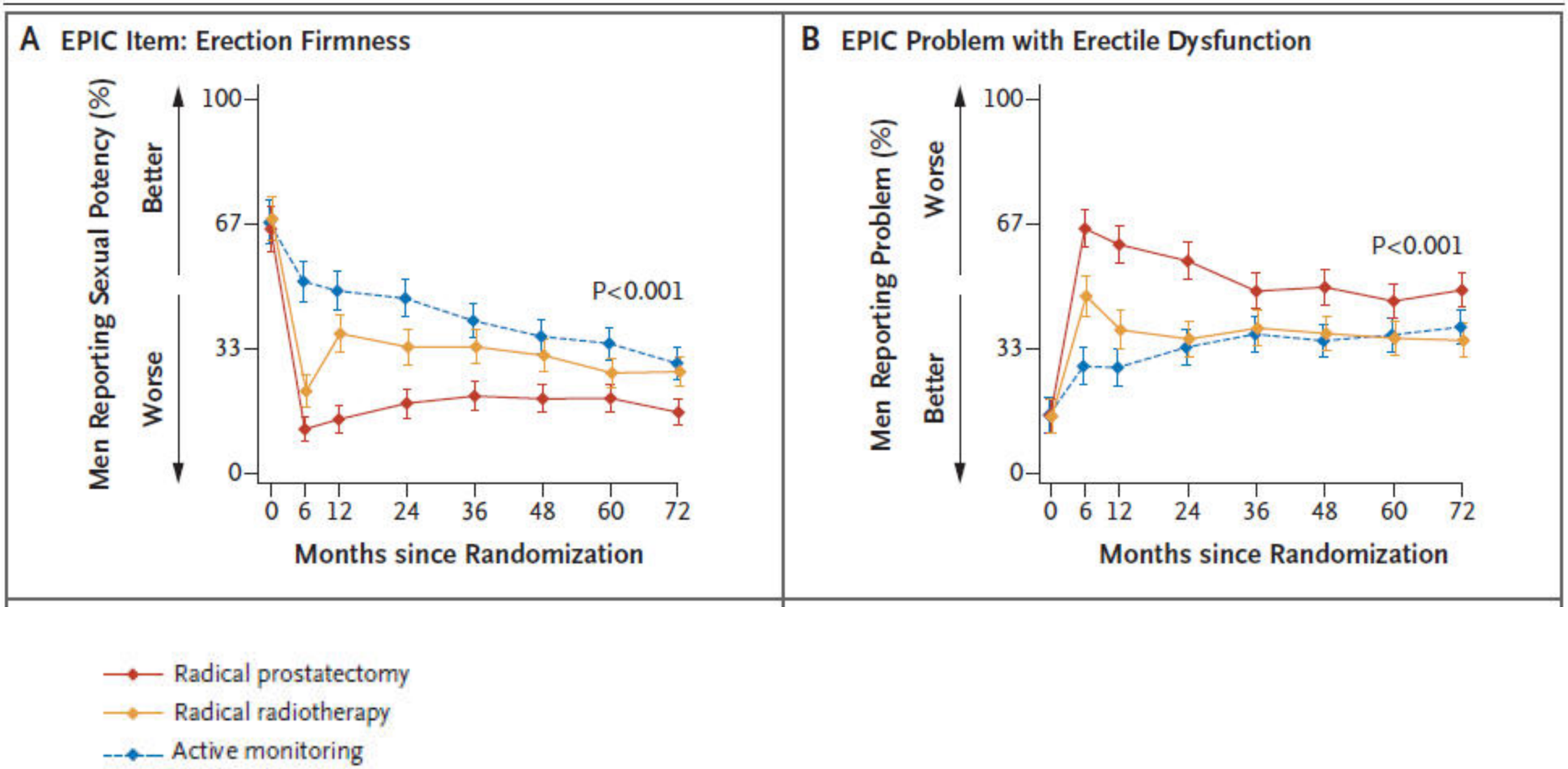
J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh, J.M. Blazeby, T.J. Peters, P. Holding, S. Bonnington, T. Lennon, L. Bradshaw, D. Cooper, P. Herbert, J. Howson, A. Jones, N. Lyons, E. Salter, P. Thompson, S. Tidball, J. Blaikie, C. Gray, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, M. Davis, E.L. Turner, R.M. Martin, and D.E. Neal, for the ProtecT Study Group*

"Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial.

The negative effect of radiotherapy on sexual function was greatest at 6 months, but sexual function then recovered somewhat and was stable thereafter; radiotherapy had little effect on urinary continence. Sexual and urinary function declined gradually in the active-monitoring group".

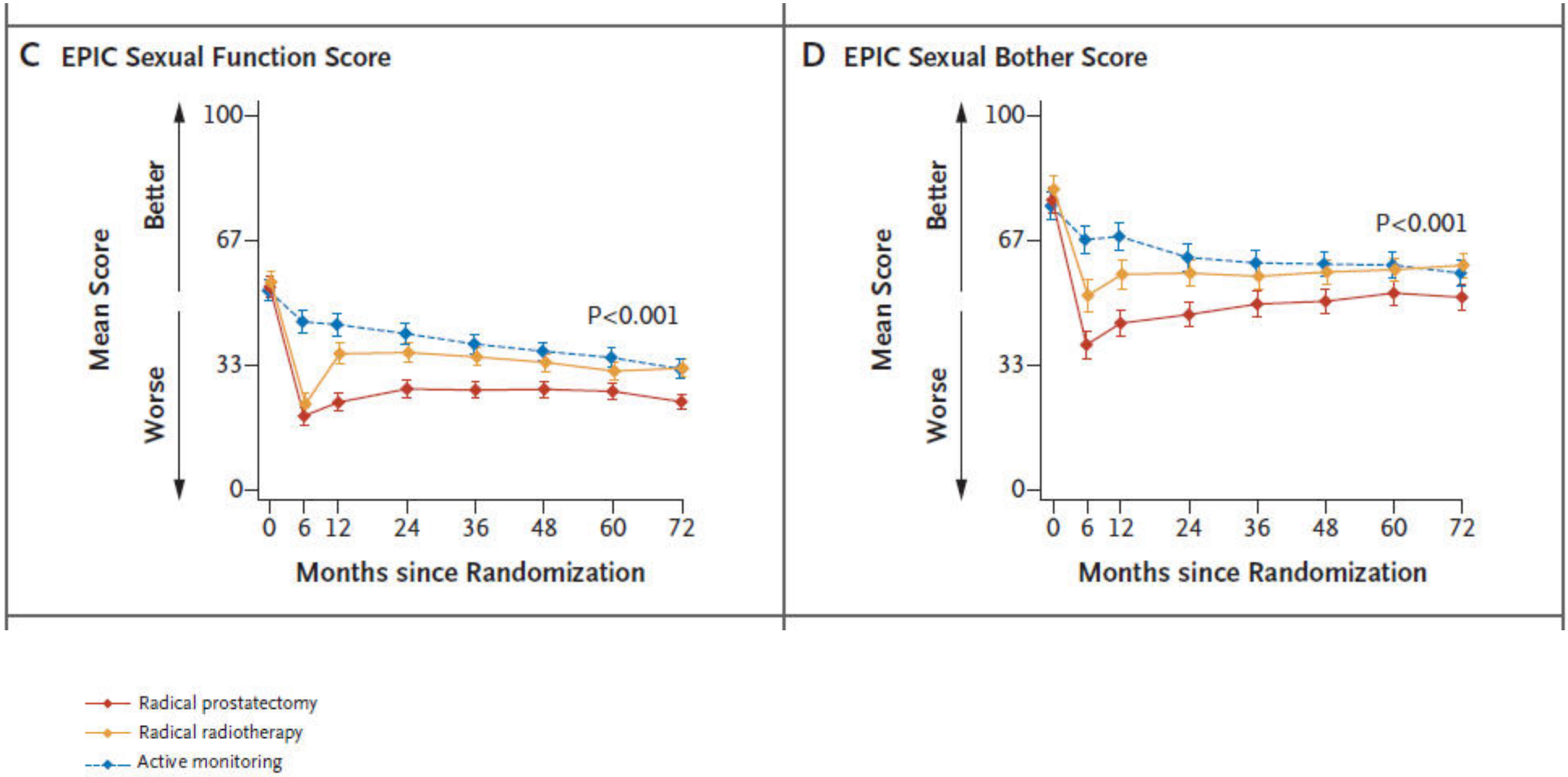
N ENGL J MED 375;15 NEJM.ORG OCTOBER 13, 2016

ProtecT: Outcomes for Sexual Function



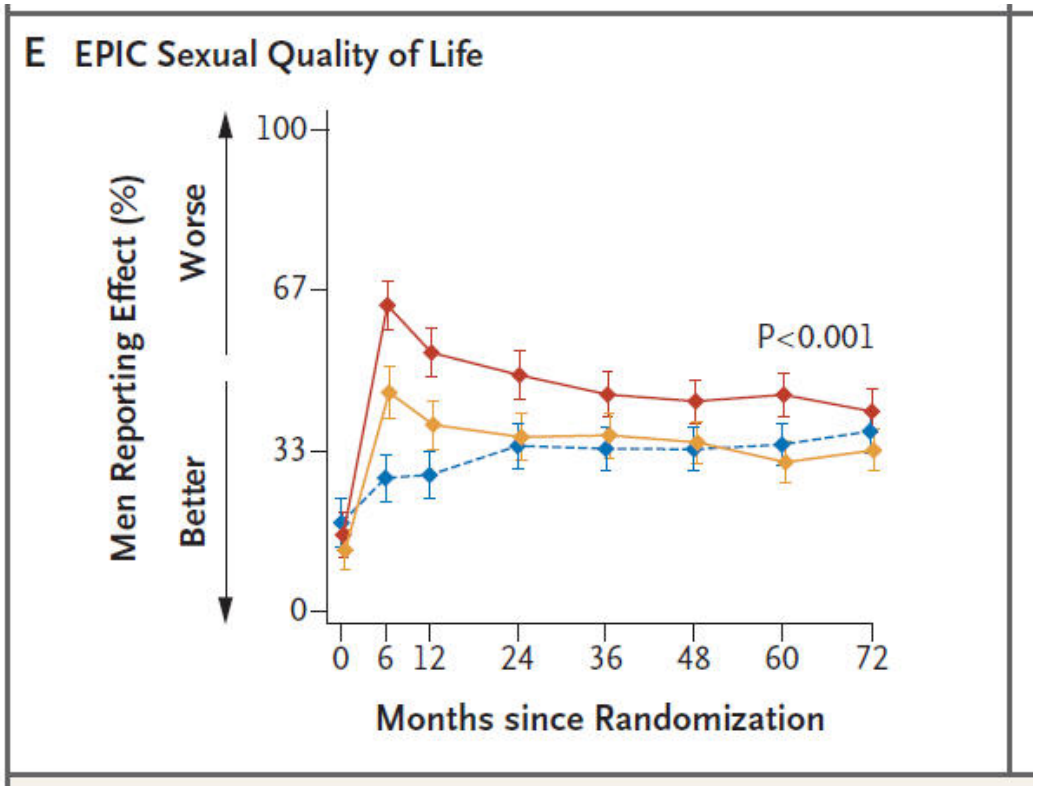
JL Donovan et al. 2016; 375:1425-37

ProtecT: Outcomes for Sexual Function



JL Donovan et al. 2016; 375:1425-37

ProtecT: QoL



JL Donovan et al. 2016; 375:1425-37

ELSEVIER

Critical Reviews in Oncology/Hematology 95 (2015) 144–153

CRITICAL REVIEWS IN
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Advances in the treatment of prostate cancer with radiotherapy

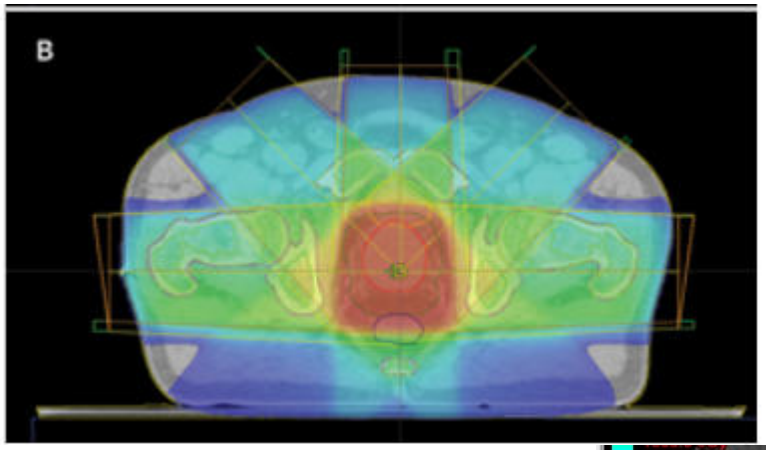
J. Gomez-Millan [a,*], M. Fernanda Lara [b], R. Correa [a], A. Perez-Rozos [a], Y. Lupiañez-Perez [a], J.A. Medina [a]

[a] *Department of Radiation Oncology, University Hospital Virgen de la Victoria, Malaga, Spain*
[b] *Department of Urology, University Hospital Virgen de la Victoria, Malaga, Spain*

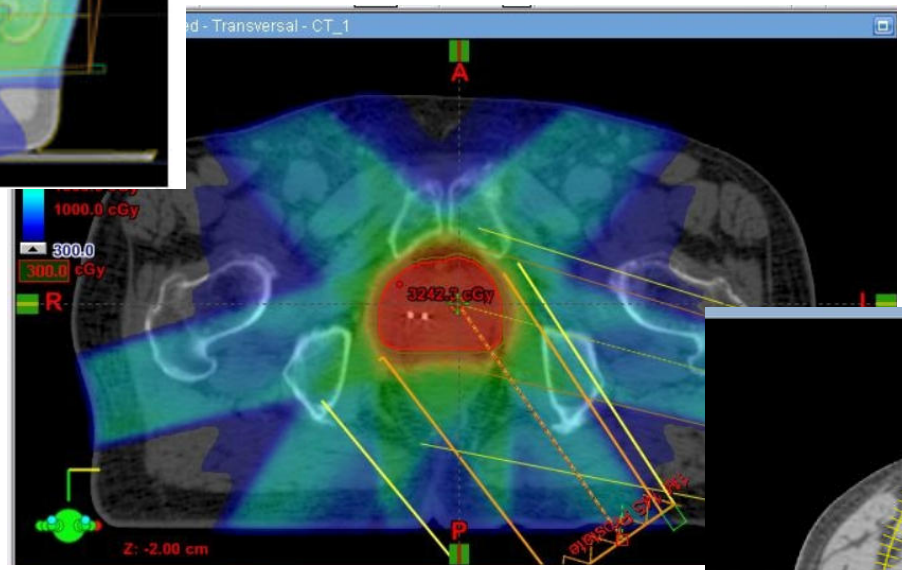
The delivery of curative radiotherapy is always associated with a certain risk of serious side effects. Thus, to raise the therapeutic ratio, new treatments should improve tumour control without adding new side effects to the treatment.

To increase the therapeutic index of radiation, two different strategies have been studied: the first one based on physics and technology, and the second one based on biology.

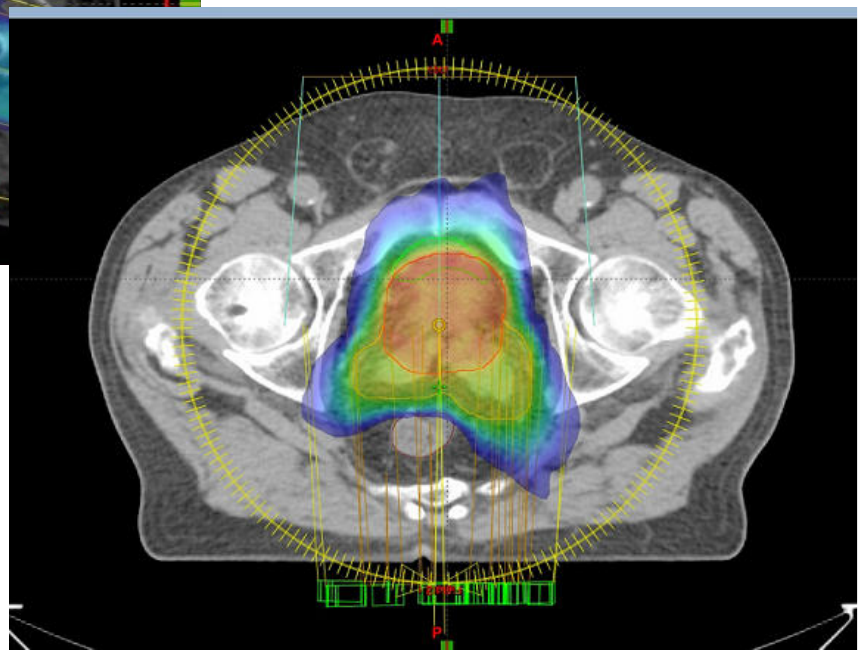
From 3D-RT to VMAT



3D-RT

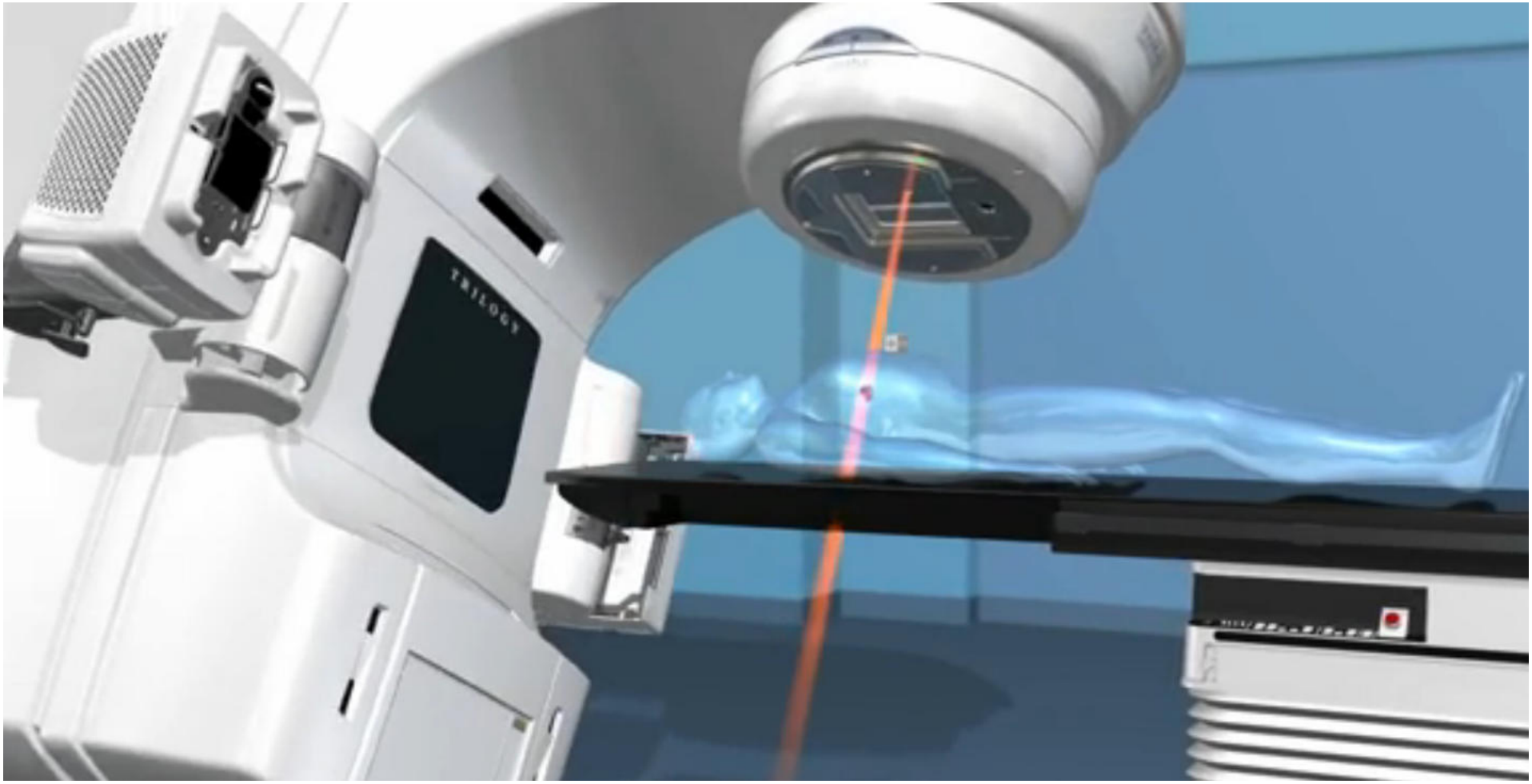


IMRT

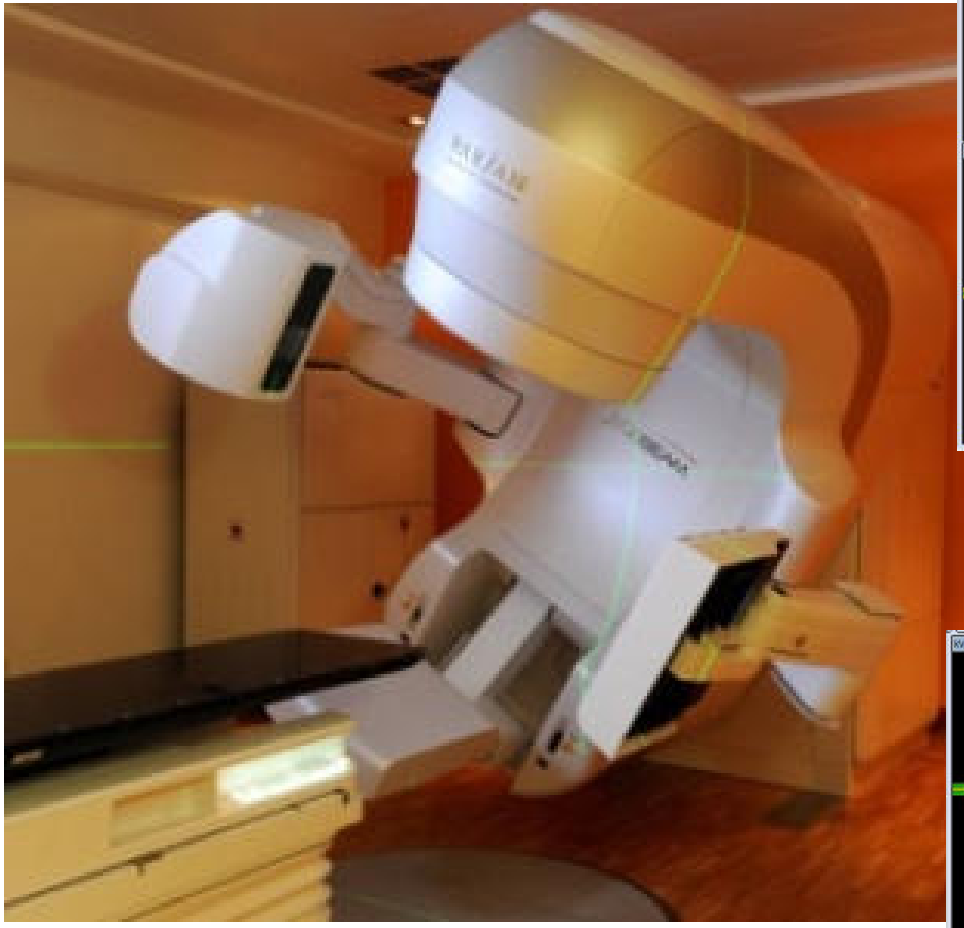


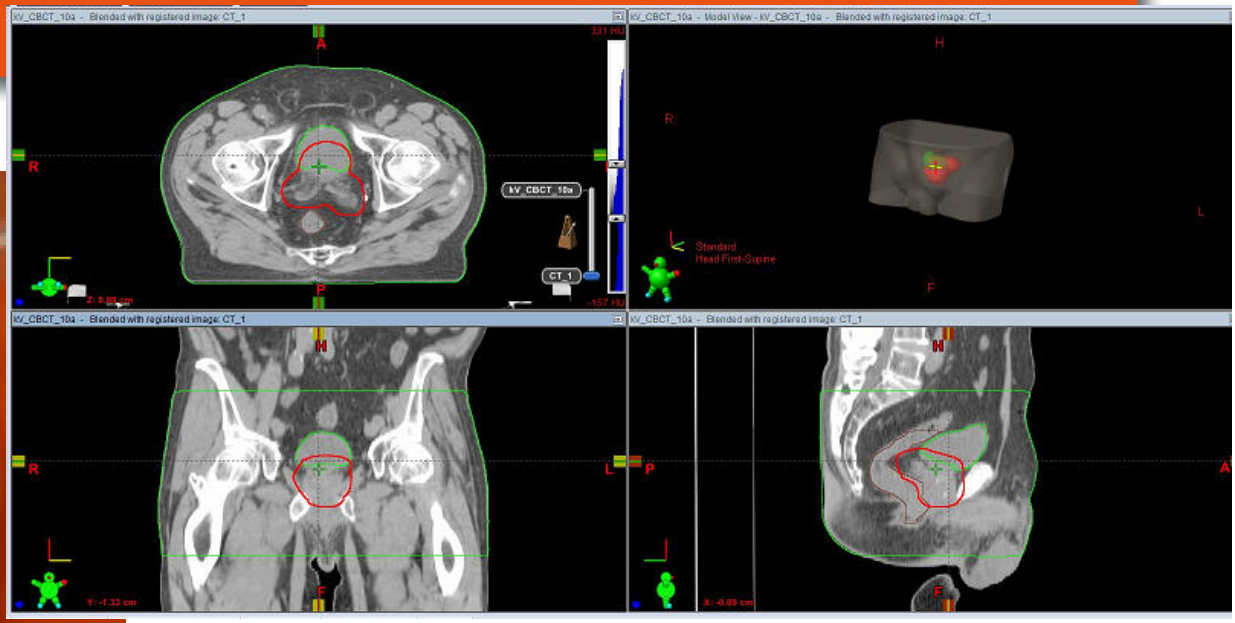
VMAT

Volumetric Modulated Arc Therapy (VMAT)



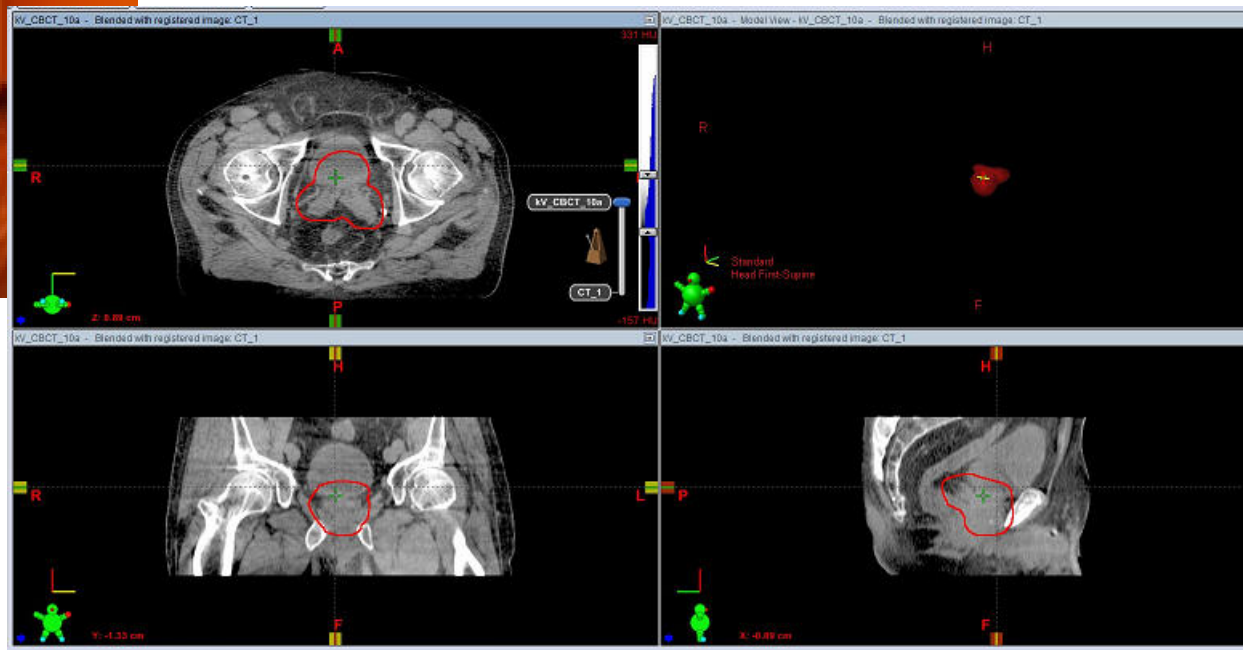
Cone Beam CT





Simulation CT

kV CB-CT



IGRT advantages

- PTV margins substantially decreased
- Substantial reduction in irradiated volume
- Better sparing of organ at risk

Decreases Toxicity

- Higher doses to the tumor
- Increases the possibility to use non conventional fractionation (SBRT)

Improves local control rates

EAU – ESTRO – SIOG Guidelines on Prostate Cancer 2017

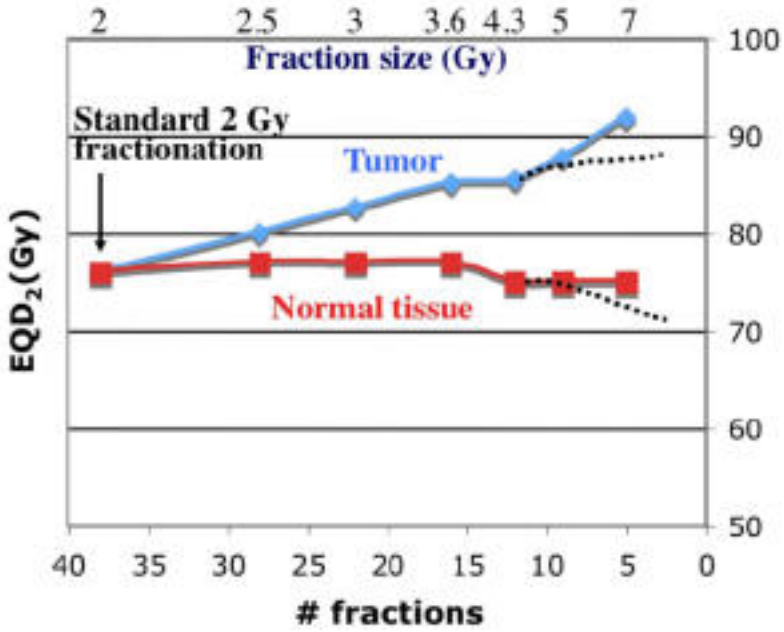
Table 8 – Summary of the main findings regarding treatment of nonmetastatic prostate cancer

Recommendation	LE	GR
Management decisions should be made after all treatments have been discussed in a multidisciplinary team	4	A*
Offer RP to patients with low- and intermediate-risk PCa and a life expectancy >10 yr	1b	A
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, GS <7, and PSA <10 ng/ml, or refer to Partin tables/nomograms)	2b	B
In intermediate- and high-risk disease, use mpMRI as a decision tool to select patients for nerve-sparing procedures	2b	B
Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy >10 yr	2a	A
Offer RP in a multimodality setting to selected patients with locally advanced (cT3a) PCa and a life expectancy >10 yr	2b	B
Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b–4 N0 or any T N1)	3	C
Do not offer NHT before RP	1a	A
Do not offer adjuvant HT for pN0	1a	A
Offer adjuvant ADT for node-positive (pN+)	1b	A
Offer EBRT using IMRT to all risk groups	2a	A
In patients with low-risk PCa, without a previous TURP, with a good IPSS and a prostate volume <50 ml, offer LDR brachytherapy	2a	A
In low risk PCa, use a total dose of 74–78 Gy	1a	A
In intermediate- risk PCa use a total dose of 76–78 Gy, in combination with short-term ADT (4–6 mo)	1b	A
In patients with high-risk localised PCa, use a total dose of 76–78 Gy in combination with long-term ADT (2–3 yr)	1b	A
In patients with locally advanced cN0 PCa, offer radiation therapy in combination with long-term ADT (2–3 yr)	1a	A
In patients with cN1 PCa, offer pelvic external irradiation in combination with immediate long-term ADT	2b	B
Offer adjuvant ADT for pN1 after ePLND	1b	A
Discuss adjuvant ADT with additional radiation therapy for pN1 after ePLND	2b	A
Offer observation (expectant management) for pN1 after ePLND when two or fewer nodes show microscopic involvement with a PSA <0.1 ng/ml and absence of extranodal extension	2b	B
In patients with pT3N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival	1a	A
Inform patients with pT3N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases	2b	A
Only offer cryotherapy and HIFU within a clinical trial	3	B
Do not offer focal therapy of the prostate outside a clinical trial	3	A

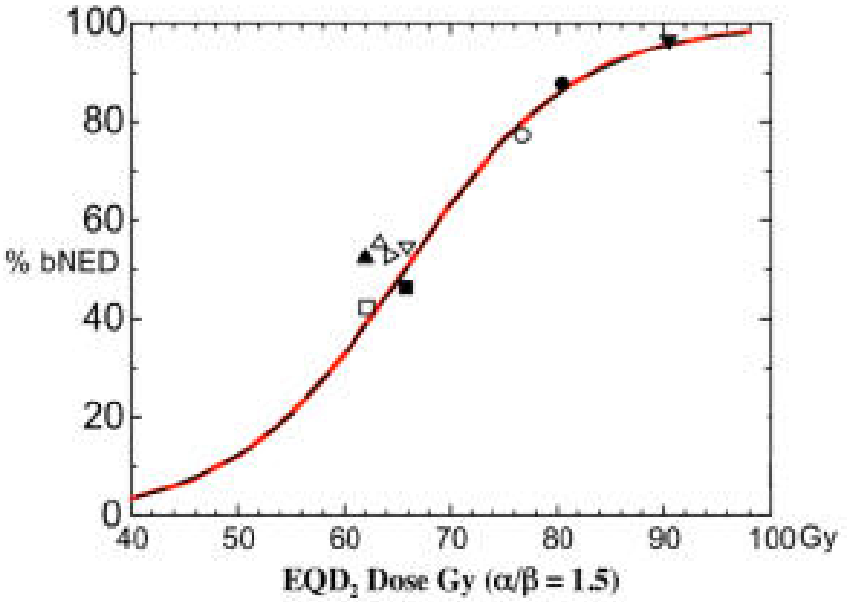
ADT = androgen-deprivation therapy; EBRT = external beam radiation therapy; ePLND = extended pelvic lymph node dissection; GR = grade of recommendation; GS = Gleason score; HIFU = high-intensity focussed ultrasound; HT = hormone therapy; IMRT = intensity-modulated radiation therapy; IPSS = International Prostate Symptom Score; LDR = low-dose rate; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; NHT = neoadjuvant hormone therapy; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

* Upgraded following Panel consensus.

HYPOFRACTIONATION FOR PROSTATE CANCER



Increasing therapeutic advantage with increasing hypofractionation



bDFS rates versus equivalent doses from six hypofractionation studies

Ritter et al., Cancer J 2009:15, 1-6

Contemporary RCTs of moderate hypofractionation

Author	No.	Total dose (Gy)	Fractions	Dose/fraction (Gy)	Acute reactions RTOG ≥2 (%)		Late reactions (5 yr F.U) RTOG ≥2 (%)		RT technique	ADT (%)	5 yr biochemical/ clinical recurrence free (%)
					GI	GU	GI	GU			
CHHiP (1-3)	1,065	74	37	2.0	25	46	13.7	9.2	IMRT/IGRT[a]	97	88.3
	1,074	60	20	3.0	38**	49	11.9	11.7	IMRT/IGRT[a]	97	90.6
	1,077	57	19	3.0	38**	46	11.3	6.6	IMRT/IGRT[a]	97	85.9
PROFIT (4)	608	78	39	2.0	11[d]	30[d]	14[d]	23[d]	IMRT/IGRT	5[c]	79.0
	598	60	20	3.0	17[d]	30[d]	9[d]	23[d]	IMRT/IGRT	5[c]	79.0
HYPRO (5-7)	410	78	39	2.0	31.2	57.8	39.0	17.7****	CFRT	67	77.1
	410	64.6[++]	19[++]	3.4[++]	42.0*	60.5	41.3	21.9****	CFRT	67	80.5
RTOG 0415 (8)	542	73.8	41	1.8	10.3	27.1	14.0***	22.8	CFRT/IMRT[b]	0	91.9
	550	70	28	2.5	10.7	27.0	22.4***	29.7	–	0	93.7
Fox Chase (9)	151	76	38	2.0	–	–	22.5	13.4	IMRT	47	78.6
	152	70.2	26	2.7	–	–	18.1	21.5	IMRT	45	76.7

*, P=0.0015; **, P<0.001; ***, P=0.02 for comparison of HFRT with SFRT groups; ****, higher cumulative grade ≥3 late GU toxicity with hypofractionation, HFRT 19%, CFRT 13% (P=0·02); [+], trials include those recruiting more than 300 patients with hypofractionation schedule using ≥2.5 Gy/fraction treatment given with five fraction/week schedules except; [++], hypofractionated group treated with 3 fractions/week; [a], IGRT used in 30% of patients; [b], IMRT used in 79% of patients; [c], personal communication from Dr. C. Catton; [d], estimated from presented data. CFRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy, IGRT, image guided radiotherapy; ADT, androgen deprivation therapy.

D. Dearnaley, E Hall. Transl Androl Urol 2017; 6:134-136

Clinical Oncology 29 (2017) 3–5

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Editorial

Hypofractionation for Prostate Cancer: Time to Change

D. Dearnaley *†, I. Syndikus ‡, S. Gulliford *, E. Hall *

* The Institute of Cancer Research, London, UK
† Royal Marsden NHS Foundation Trust, London, UK
‡ Clatterbridge Centre for Oncology, Bebington, UK

The evidence base for hypofractionation in prostate cancer has been strengthened by publications from four randomised controlled trials within the last 12 months.

In total, 6357 patients have been randomised to receive treatment with either conventional fractionation or modestly hypofractionated schedules.

Across the studies, patients with low-, intermediate and high-risk prostate cancers have been included, treating with or without additional androgen deprivation therapy (ADT). The four trial designs are complementary and have addressed different hypotheses. All have reported 5 year efficacy outcomes (time to biochemical or clinical failure) as well as early and late toxicity profiles.

Definitive Radiation Therapy

Biological modelling suggests that PCa may be sensitive to an increased dose per fraction resulting in the investigation in RCTs of hypofractionation (HFX) in localised disease. The largest reported randomised trial, using IMRT in predominantly intermediate-risk localised PCa, (CHHiP trial) demonstrates 60 Gy in 20 fractions (3 Gy/fraction) is non-inferior to 74 Gy in 37 fractions with 5-yr recurrence free rates of 90%. A third arm using 57 Gy in 19 fractions (3 Gy/fraction) was not demonstrated to be non-inferior in terms of biochemical control. No significant differences in the proportion or cumulative incidence of 5-yr toxicity were found when using the 3 Gy per fraction schedules

THE JOURNAL OF
SEXUAL MEDICINE

Sexual Function After Hypofractionated Versus Conventionally Fractionated Radiotherapy for Prostate Cancer: Results From the Randomized Phase III HYPRO Trial

Ruud C. Wortel, MD,[1] Floris J. Pos, MD, PhD,[2] Wilma D. Heemsbergen, PhD,[2] and Luca Incrocci, MD, PhD[1]

Aim: To compare sexual function in patients with prostate cancer treated with 78 Gy in 39 fractions of 2 Gy or 64.6 Gy in 19 fractions of 3.4 Gy.

Methods: In total, 820 men with intermediate- to high-risk T1b-T4NX-0MX-0 prostate cancer were enrolled in the phase III HYPRO trial (2007−2010) and randomized to conventional fractionation (39 × 2 Gy) or hypofractionation (19 × 3.4 Gy). Sexual function was assessed at baseline and at 6, 12, 24, and 36 months after treatment using the International Index of Erectile Function (IIEF). For this analysis, patients (n = 322) with a baseline assessment, at least one follow-up assessment, and no or short-term (6-month) androgen-deprivation therapy were included.

Main Outcome Measures: Mean IIEF domain scores were compared between treatments in the total population and the hormone-naïve population (n = 197) using the independent t-test. Incidences of severe erectile dysfunction (domain score < 11) at last follow-up were calculated in patients with partial or full baseline function. Binary logistic regression analyses were applied to calculate the odds ratio of hypofractionation vs conventional fractionation and to adjust for clinical factors.

Results: Median age was 71 years (interquartile range = 67−71) and median follow-up was 37 months (interquartile range = 25−38). Androgen-deprivation therapy was prescribed in 125 (39%). IIEF domain scores decreased after treatment but were comparable between treatment arms at baseline and during follow-up. Orgasmic function scores in hormone-naïve patients were significantly higher at 3 years after hypofractionation (4.08 vs 2.65, $P = .031$). In patients (n = 120) with partial or full baseline erectile function, the incidence of erectile dysfunction at last follow-up was 34.4% for hypofractionated treatment vs 39.3% for conventional treatment (adjusted odds ratio = 0.84, 95% CI = 0.37−1.90, $P = .67$).

Conclusion: No significant differences in erectile functioning between conventional and hypofractionated radiotherapy were found. Hormone-naïve patients reported significantly higher orgasmic function scores at 3 years after hypofractionation.

J Sex Med 2016;13:1695−1703.

HYPRO Study

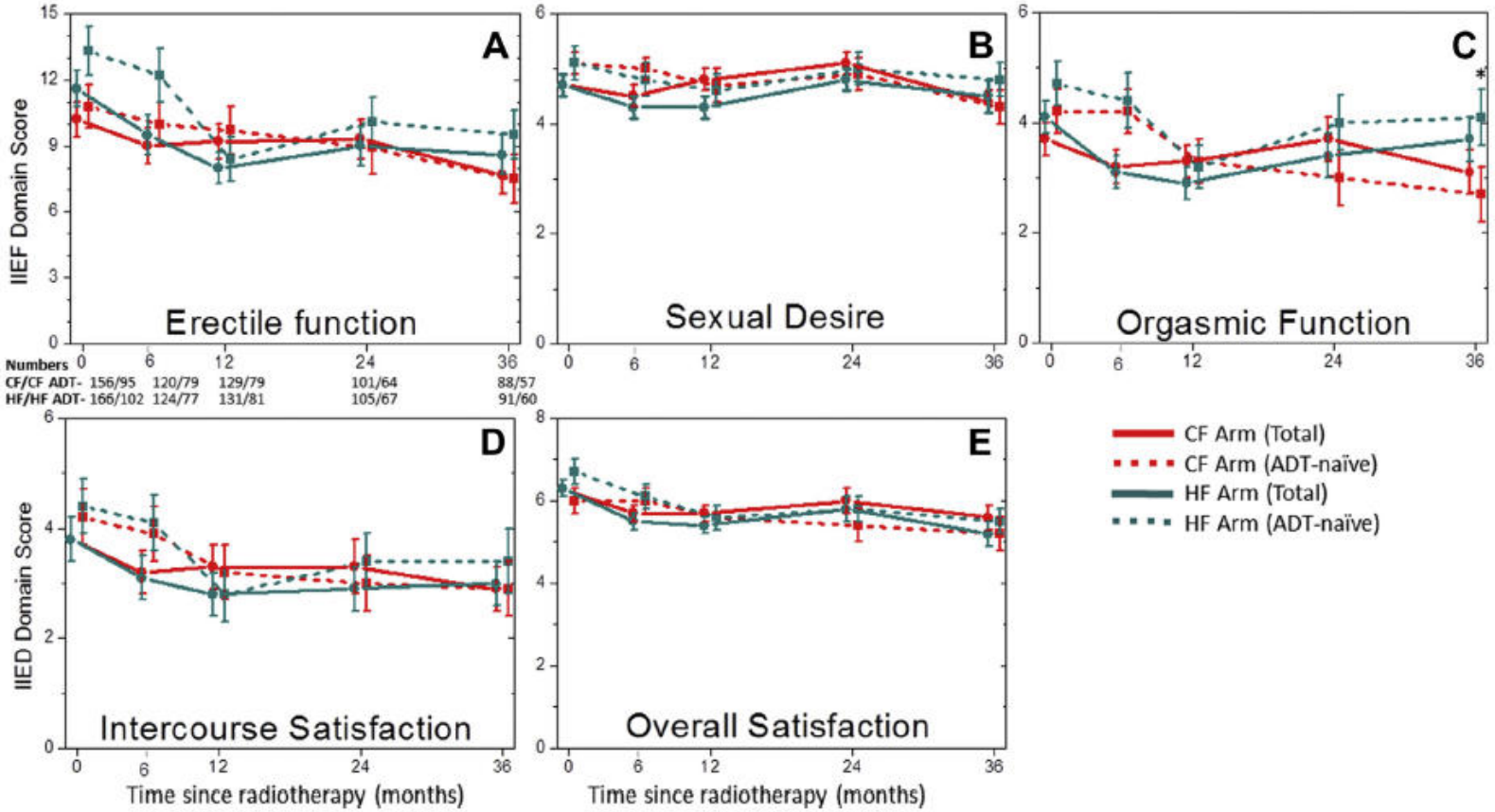


Figure 2. Panels A to E present mean IIEF domain scores ± standard error by assigned treatment arm. *$P < .05$ for ADT$^-$ population (by independent t-test). ADT$^-$ = naïve to androgen-deprivation therapy; CF = conventional fractionation; HF = hypofractionation; IIEF = International Index of Erectile Function. Figure 2 is available in color at www.jsm.jsexmed.org.

J Sex Med 2016;13:1695–1703.

HYPRO Study

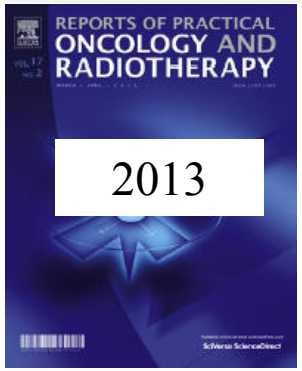
Table 2. Results of binary logistic regression analysis for the incidence of erectile dysfunction at last follow-up

	Erectile dysfunction (IIEF-EF score < 11)			
	Baseline model		Final model	
Factor	OR	*P* value	OR (95% CI)	*P* value
Age (≥ 71 vs <71 y)	2.02	.07	1.59 (0.71–3.59)	.26
Baseline erectile dysfunction (no vs mild to moderate)	0.26	.001	0.26 (0.11–0.62)	.002
Diabetes mellitus (yes vs no)	1.49	.42		
Cardiovascular medication (yes vs no)	2.63	.065	3.13 (1.04–9.45)	.043
Prostate volume (>50 vs ≤50 cm^3)	1.17	.69		
Androgen-deprivation therapy (yes vs no)	0.92	.96		
Seminal vesicle dose group (1 vs 2 vs 3)	1.44	.22		
Transurethral resection of prostate (yes vs no)	0.33	.32		
Treatment arm (hypofractionation vs conventional)	0.80	.71	0.84 (0.37–1.90)	.67

IIEF-EF = International Index of Erectile Function erectile function domain, OR = odds ratio.

J Sex Med 2016;13:1695–1703

Stereotactic Body Radiation Therapy



Extracranial stereotactic body radiotherapy. Review of main SBRT features and indications in primary tumors

Carmen Rubio[a,*], *Rosa Morera*[b,*], *Ovidio Hernando*[a], *Thomas. Leroy*[c], *S. Eric Lartigau*[c,*]

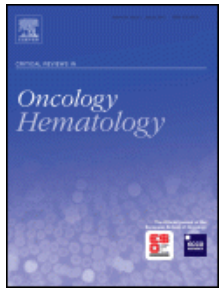
SBRT requires **a high level of accuracy** for all phases of the treatment process:

- effective patient immobilization
- precise target localization
- highly conformed dosimetry
- image guided systems for treatment verification

The implementation of SBRT in routine requires a careful considering of **organ motion.** Gating and tracking are effective ways to do so, and less invasive technologies "fiducials free" have been developed.

Due to the hypofractionated scheme, the physician must pay attention to **new dosimetric constraints in organ at risk and new radiobiological models** are needed to assess the optimal fractionation and dose schemes.

SBRT and extreme Hypofractionation for prostate cancer



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Critical Reviews in Oncology/Hematology 84 (2012) 101–108

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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

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Seminars in
RADIATION
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Stereotactic Body Radiotherapy for Low- and Intermediate-Risk Prostate Cancer

Amar U. Kishan, MD, and Christopher R. King, MD, PhD

With over a decade's worth of clinical experience to guide stereotactic body radiotherapy (SBRT) for the treatment of clinically localized prostate cancer (PCa), sufficient data exist for robust conclusions to be made regarding its efficacy and the toxicities associated with this treatment. We briefly review the fundamental radiobiological basis of SBRT for PCa and provide a comprehensive synthesis of the medical literature to date, focusing on clinical outcomes and toxicities. When possible, we draw comparisons to comparable data for conventionally fractionated radiotherapy. Finally, a brief overview of technical considerations is presented. Although randomized clinical trials comparing SBRT with conventionally fractionated radiotherapy are underway, the current body of evidence supports the efficacy and safety of SBRT for PCa.
Semin Radiat Oncol 27:268-278

SBRT Monotherapy Series

Reference	No. of Patients	Follow-up (Y)	Regimen	Risk Profile	BCRFS	Physician-Reported Toxicity
Harvard trial[78]	45	3.7	35-36.25 (7-7.25 × 5)	Low: 100%	3 y: 97.7%	CTCAE v4.0 Acute GU 2: 19% GI 2: 7% Late GU 2: 17%; 3: 2.2% GI 2: 7%; 3: 4.4%
University of California, San Francisco (UCSF)[69]	20	1.53	38 (9.5 × 4)	Low: 45% Int: 45% High: 10%	Crude: 100%	CTCAE v3.0 Acute GU 2: 45% GI 2: 17%† Late GU 2: 8%; 3: 5% GI 2: 3%
Georgetown[79,80]	100	2.3	35-36.25 (7-7.25 × 5)	Low: 37% Int: 55% High: 8%	2 y Low: 100% Int: 100% High: 87.5%	CTCAE v3.0 Acute GU 2: 35% GI 2: 5% Late GU 2: 17%; 3: 1% GI 2: 1%
Sunnybrook[81]	84	4.58	35 (7 × 5)	Low: 100%	5 y: 98%	CTCAE v3.0 Acute GU 2: 19%; 3: 1% GI 2: 10% Late GU 2: 5% GI 2: 7%; 4: 1%
Humanitas[82,83]	90	2.25	35 (7 × 5)	Low: 58.9% Int: 41.1%	Crude Low: 100% Int: 95%	CTCAE v4.0 Acute GU 2: 32.2% GI 2: 6.6% Late GU 2: 2.2%
21st century oncology[84]	102		40 (8 × 5)	Low: 100%		CTCAE v3.0 Acute GU 3: 0.98%
Genesis health care[85]	79	3.5	38 (9.5*4)	Low: 50.6% Int: 49.4%	5 y Low: 100% Int: 92%	CTCAE v3.0 Acute GU 2: 10% GI 2: 0% Late GU 2: 9%; 3: 6% GI 2: 1%

Semin Radiat Oncol 27:268-278 © 2017

SBRT Monotherapy Series

Reference	No. of Patients	Follow-up (Y)	Regimen	Risk Profile	BCRFS	Physician-Reported Toxicity
Total	1812					Any grade ≥ 3 Acute GU: 0.28% GI: 0.17% Late GU: 1.61% GI: 0.61%
Pooled analyses Consortium[31,37]	1100	3	36.25 (median)	Low: 58% Int: 30% High: 11%	5 y: Low: 95% Int: 84% High: 81%	Reported as EPIC QOL decline, refer text
Radiosurgical Society (RSS) registry[93]	437	1.67	36.25 (most common)	Low: 43.2% Int: 49.25 High: 7.6%	Low: 99% Int: 94.5% High: 89.8%	CTCAE v3.0 Acute GU 2: 4% GI 2: 1% Late GU 2: 8% GI 2: 2%
Registry for Prostate Cancer Radiosurgery (RPCR)[94]	2000*	2	35-40 Gy in 4-5 fractions	Low: 41% Fav-int: 6% Unfav-int: 25% High: 11%	Low: 99% Fav-int: 97% Unfav-int: 85% High: 87%	CTCAE v3.0 Late GI 3: 0.05%

Semin Radiat Oncol 27:268-278 © 2017

Clinical Oncology 28 (2016) e173–e178

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Original Article

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 *

* *Radiosurgery and Radiotherapy Department, Istituto Clinico Humanitas Cancer Center and Research Hospital, Rozzano, Milan, Italy*

† *Radiotherapy Department, Ospedale Sacro Cuore don Calabria, Negrar, Milan, Italy*

Received 23 January 2016; received in revised form 30 May 2016; accepted 1 June 2016

SBRT in prostate cancer: Humanitas Experience

Table 1
Patient characteristics

Parameter	Value
No. patients	90
Recruitment	December 2011 – March 2015
Median age (range)	71 (48–82)
Median Gleason Score (range)	Gleason 6: 58 (64.5%) Gleason 7: 32 (35.6%)
Median initial PSA (range)	6.9 ng/ml (2.7–17)
NCCN low risk class	53
NCCN intermediate risk class	37
Mean CTV (range)	59.0 cm^3 (25.1–110.2)
Mean PTV (range)	111.8 cm^3 (52.7–210.9)

PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network; CTV, clinical target volume; PTV, planning target volume.

G. D'Agostino et al. / Clinical Oncology 28 (2016) e173–e178

Simulation and Target definition

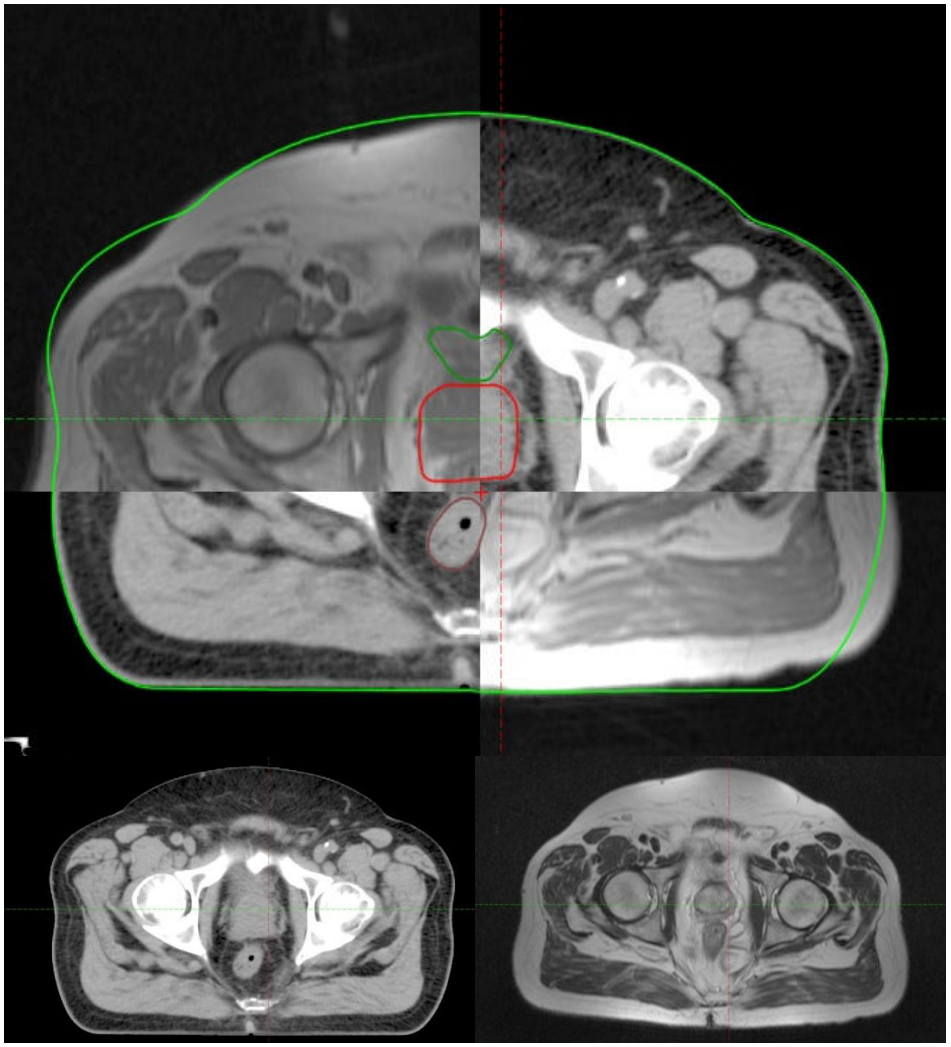
- Simulation CT

- Simulation MRI

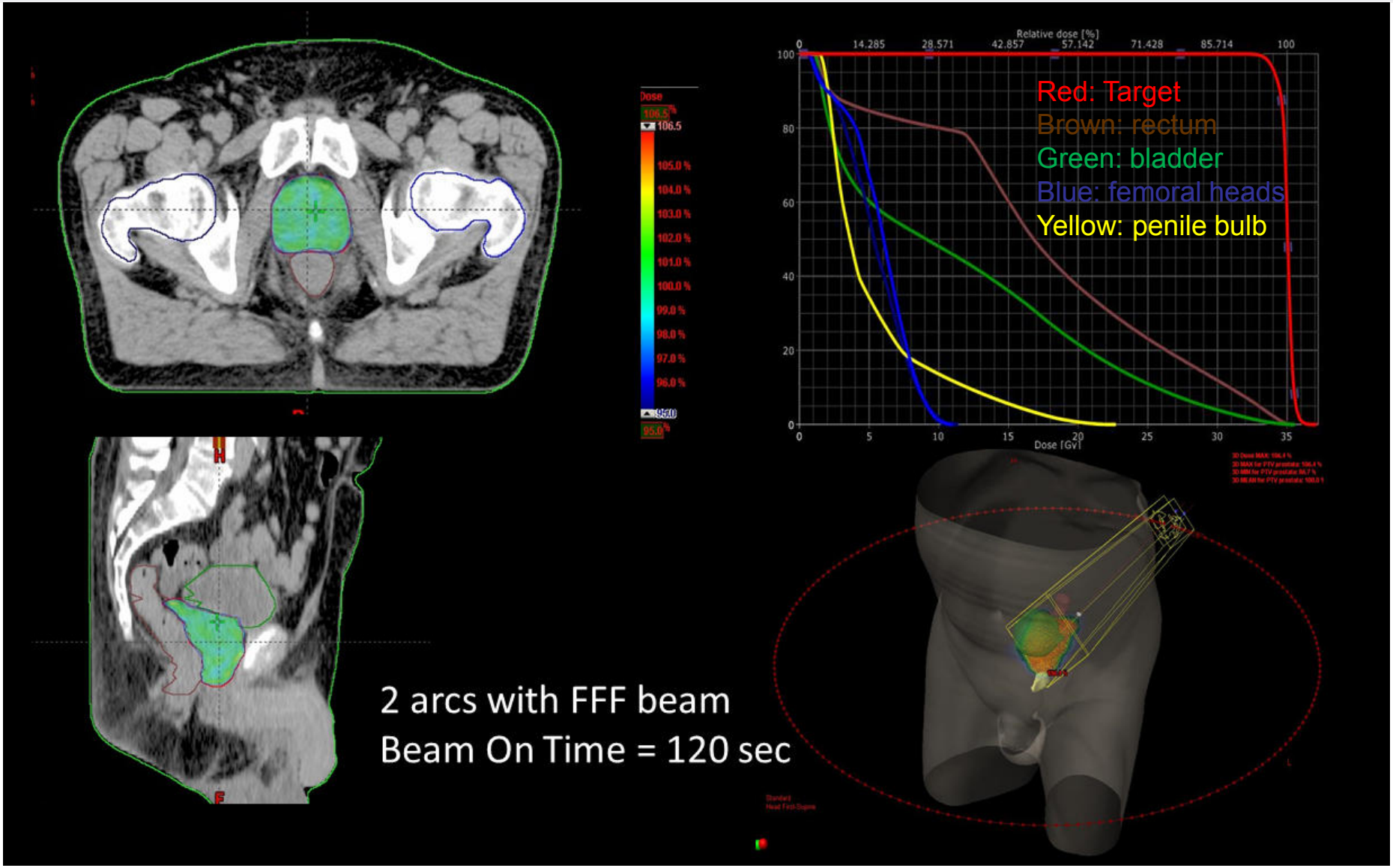
- CT/MRI registration

CTV: prostate (+ SV in the case of intermediate risk disease)

PTV: CTV + 5 mm margin in each direction

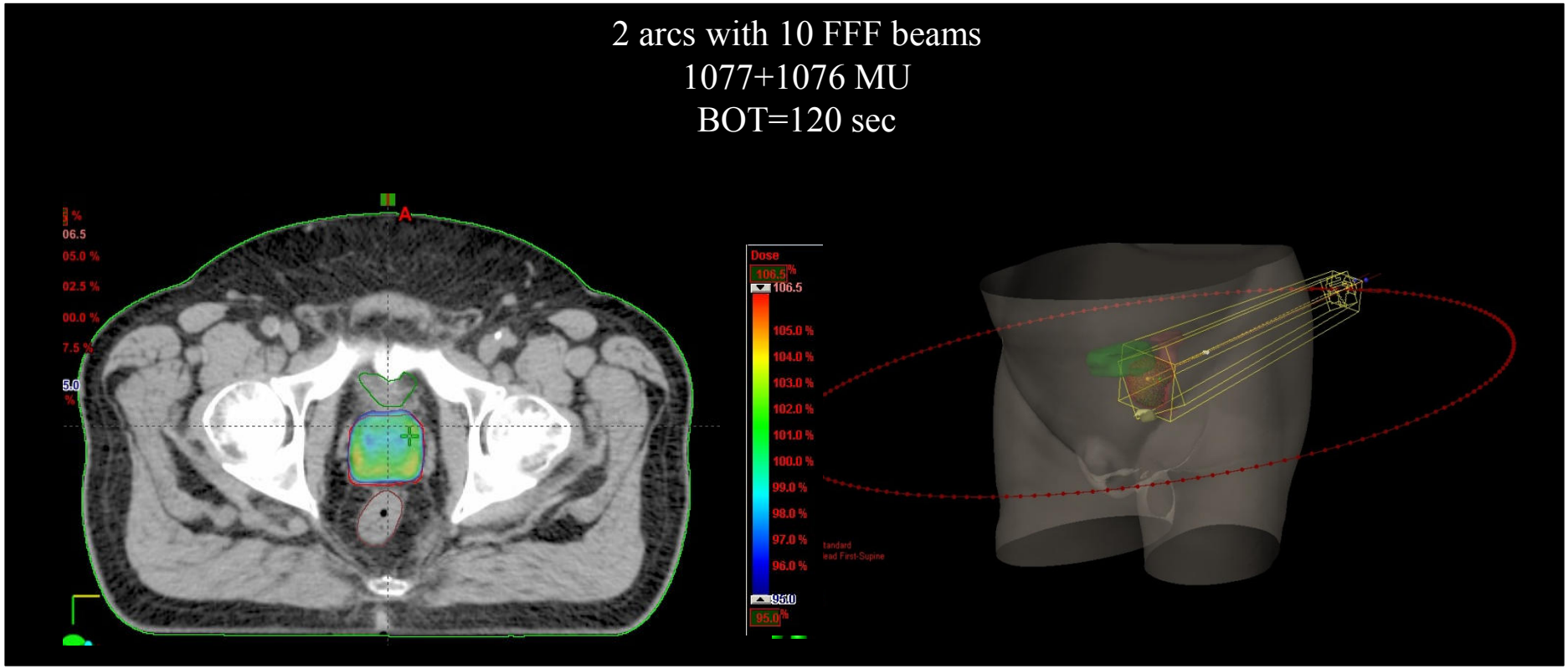


Treatment planning

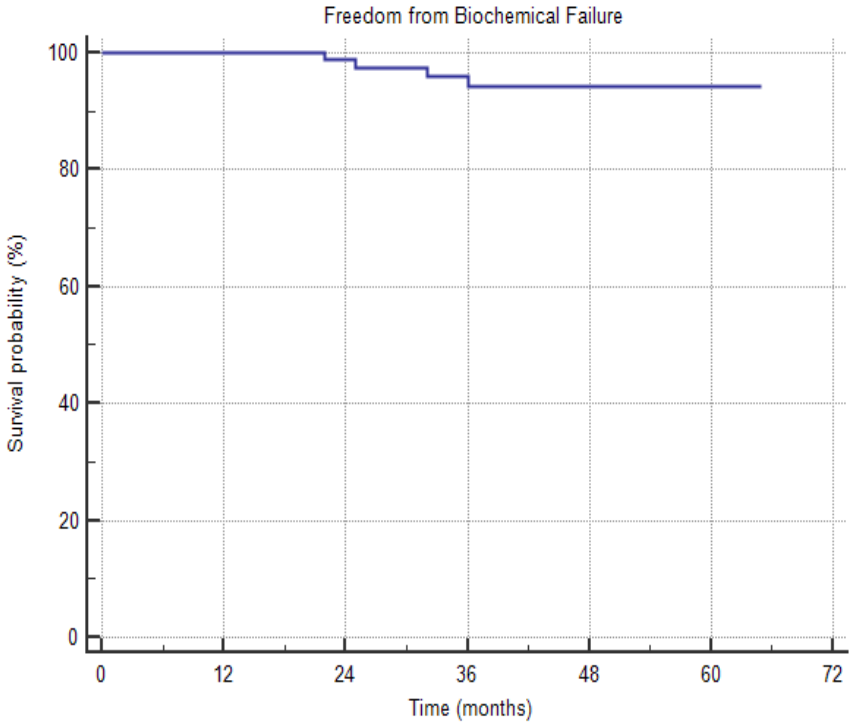


SBRT in prostate cancer: Humanitas Experience

Schedule: [5 x 7 Gy = 35 Gy] delivered in 5 alternative days

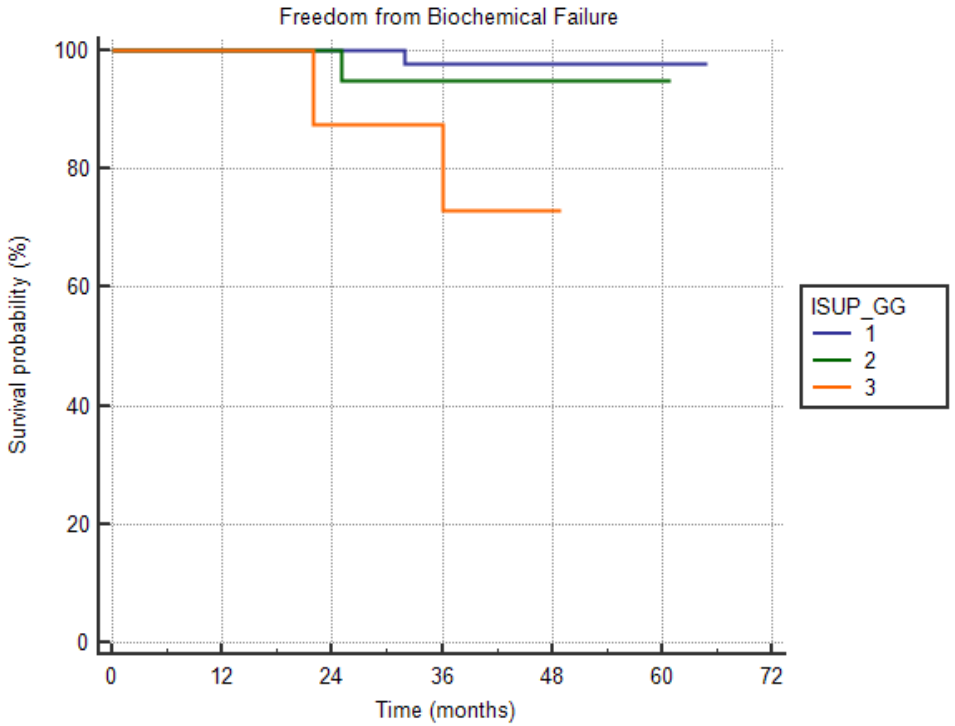


Freedom from Biochemical Failure



Median Follow-up 48 months (range 10-67)

Overall 4y-FFBF: 94.2%



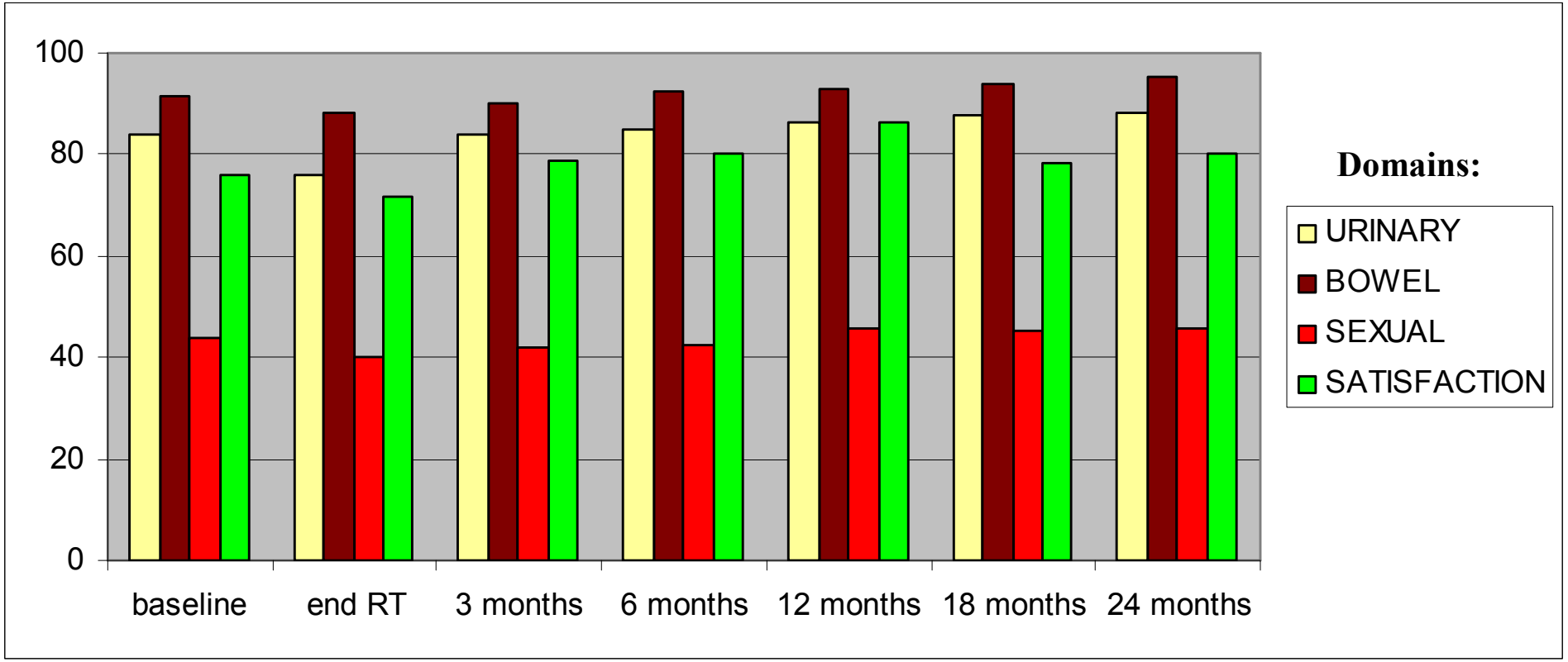
4y-FFBF:

- GG1: 97.7%
- GG2: 95.0%
- GG3: 72.9% (p = 0.028)

HR: 3.67 (95% C.I.: 1.07 – 12.55; p= 0.037)

D'Agostino et al. ESTRO 2018

Patients' Reported QoL in EPIC Questionnaires



Among patients who were sexually potent before starting radiotherapy, only two patients reported the occurrence of erectile dysfunction as a consequence of treatment, after 6 and 12 months, respectively. In the remaining patients, no effect on erectile function was noted.

G. D'Agostino et al. / Clinical Oncology 28 (2016) e173–e178

Erectile function after stereotactic body radiotherapy for localized prostate cancer

Robert T. Dess*, Holly E. Hartman†, Nima Aghdam‡, William C. Jackson*, Payal D. Soni*, Ahmed E. Abugharib*, Simeng Suy‡, Neil B. Desai§, Zachary S. Zumsteg¶, Rohit Mehra**, Todd M. Morgan††, Felix Y. Feng‡‡, Daniel A. Hamstra§§, Matthew J. Schipper†, Sean P. Collins‡ and Daniel E. Spratt*

Table 2 Univariable and multivariable models of functional erections at 24 and 60 months.

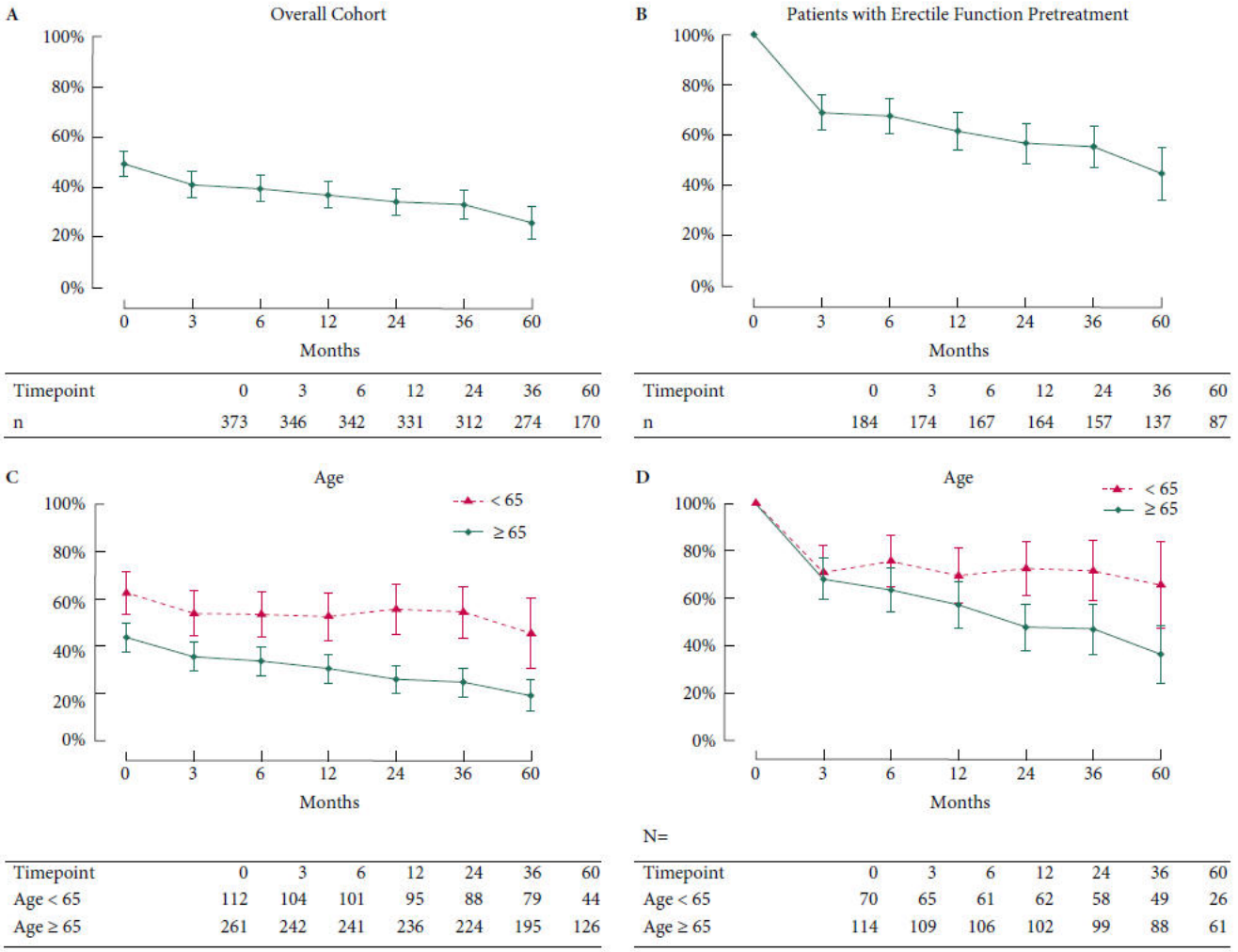
	Univariable analysis								Multivariable analysis							
	24 months (n = 312)				60 months (n = 170)				24 months (n = 312)				60 months (n = 170)			
	OR	95% CI		P	OR	95% CI		P	aOR	95% CI		P	aOR	95% CI		P
Patient factors																
Age (per 10 years)	0.44	0.30	0.64	<0.001	0.32	0.18	0.57	<0.001	0.66	0.43	1.00	0.05	0.34	0.16	0.72	0.005
Pretreat HRQoL (per 10 points)	1.58	1.41	1.79	<0.001	1.63	1.36	1.95	<0.001	1.55	1.37	1.74	<0.001	1.54	1.27	1.87	<0.001
BMI (per 5 points)	0.82	0.63	1.07	0.15	0.50	0.31	0.82	0.005					0.45	0.26	0.78	0.004
Partner status	1.037	0.60	1.80	0.90	0.87	0.40	1.89	0.73								
Diabetes	0.76	0.42	1.39	0.37	0.27	0.08	0.93	0.039								
Hypertension	0.62	0.38	1.02	0.06	0.44	0.22	0.90	0.025								
Coronary artery disease	0.75	0.38	1.47	0.40	0.27	0.06	1.20	0.09								
Major depression	0.43	0.16	1.17	0.10	–	–	–	–								
Baseline sexual medication use	0.78	0.47	1.29	0.33	1.11	0.55	2.23	0.78								
Pretreatment testosterone	1.00	0.998	1.001	0.73	1.00	0.997	1.002	0.68								
Tumour and treatment factors																
T stage group*	0.33	0.14	0.76	0.01	0.72	0.25	2.07	0.54								
Gleason group†	0.84	0.62	1.14	0.25	0.67	0.41	1.09	0.11								
PSA < 4 vs PSA ≥ 4 ng/mL	1.56	0.07	3.63	0.30	1.05	0.36	3.09	0.92								
SBRT dose	1.14	0.69	1.87	0.61	0.88	0.34	2.28	0.79								

*HRQoL, health related quality of life; SBRT, stereotactic body radiotherapy; OR, odds ratio; aOR, adjusted odds ratio. At 60 month time point, no patients had major depression and erectile function, thus estimates using logistic regression are not valid. *T1–T2a, T2b–2c, T3. †(1) Gleason 6, (2) 3 + 4, (3) 4 + 3, (4) 8, (5) 9–10.*

BJU Int 2018; **121**: 61–68

ERECTILE FUNCTION AFTER SBRT

Fig. 1 Unadjusted proportions of patients reporting functional erections at each follow-up for the whole cohort (**A**), those with baseline erectile function (**B**), the whole cohort dichotomized by age 65 years (**C**), and those with baseline erectile function dichotomized by age 65 years (**D**).



Timepoint	0	3	6	12	24	36	60
n	373	346	342	331	312	274	170

Timepoint	0	3	6	12	24	36	60
n	184	174	167	164	157	137	87

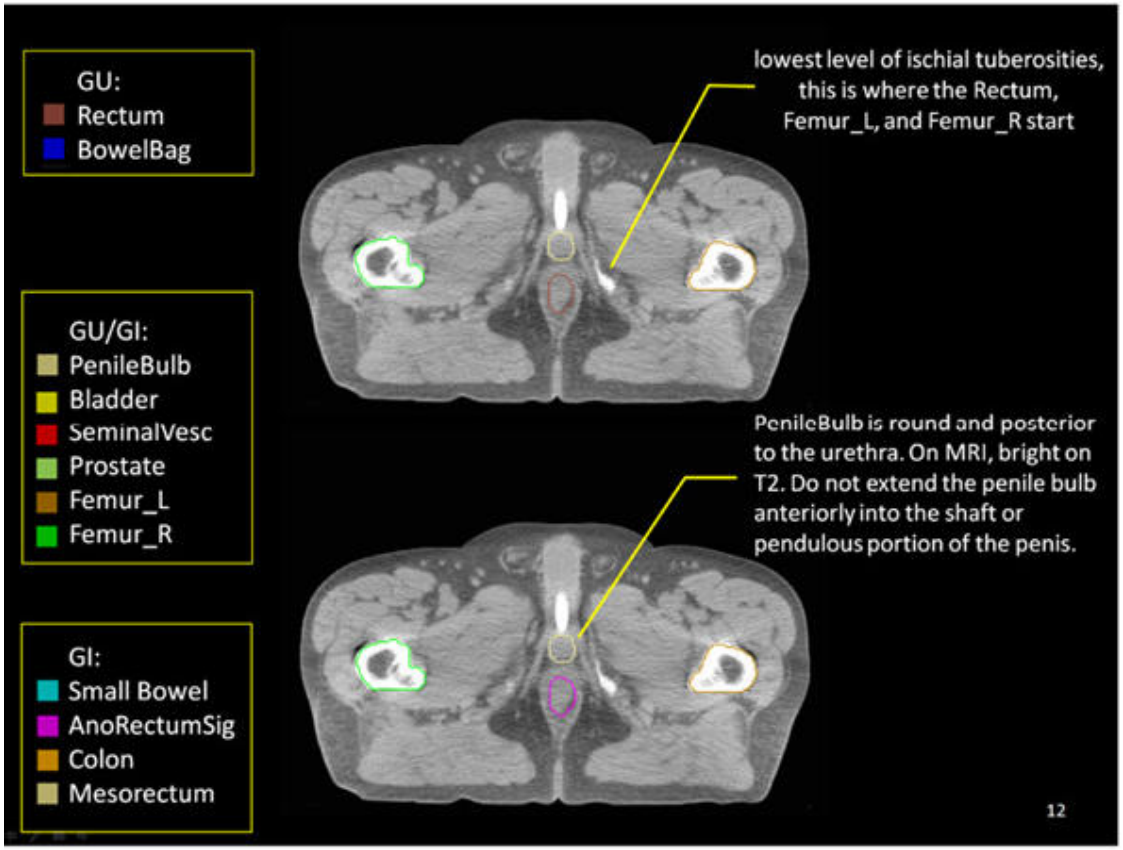
Timepoint	0	3	6	12	24	36	60
Age < 65	112	104	101	95	88	79	44
Age ≥ 65	261	242	241	236	224	195	126

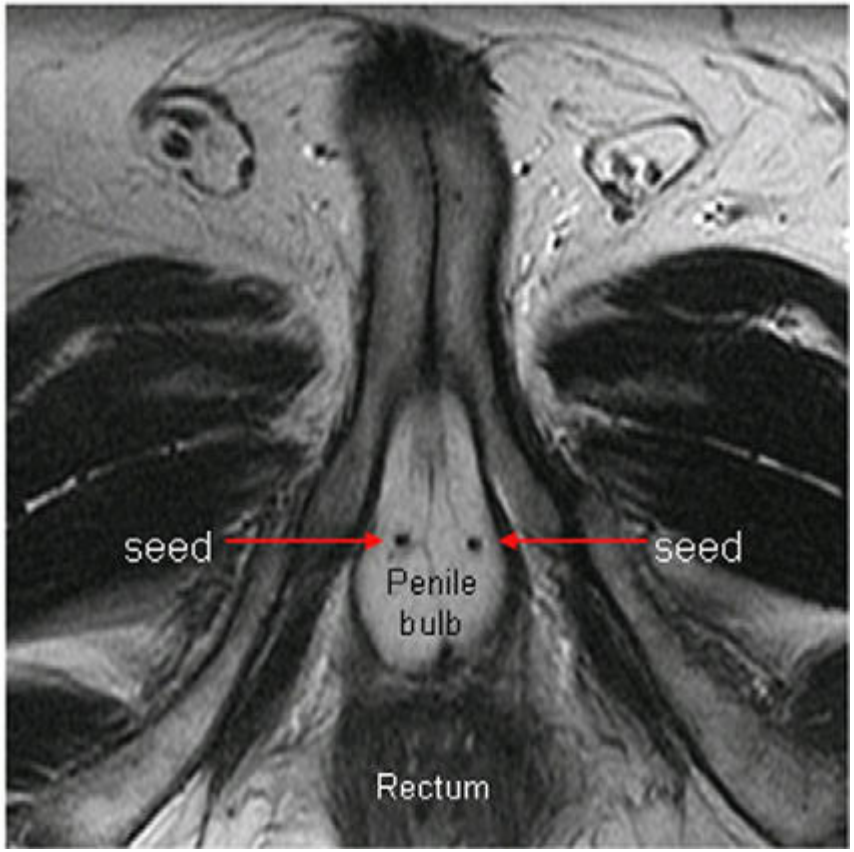
N=

Timepoint	0	3	6	12	24	36	60
Age < 65	70	65	61	62	58	49	26
Age ≥ 65	114	109	106	102	99	88	61

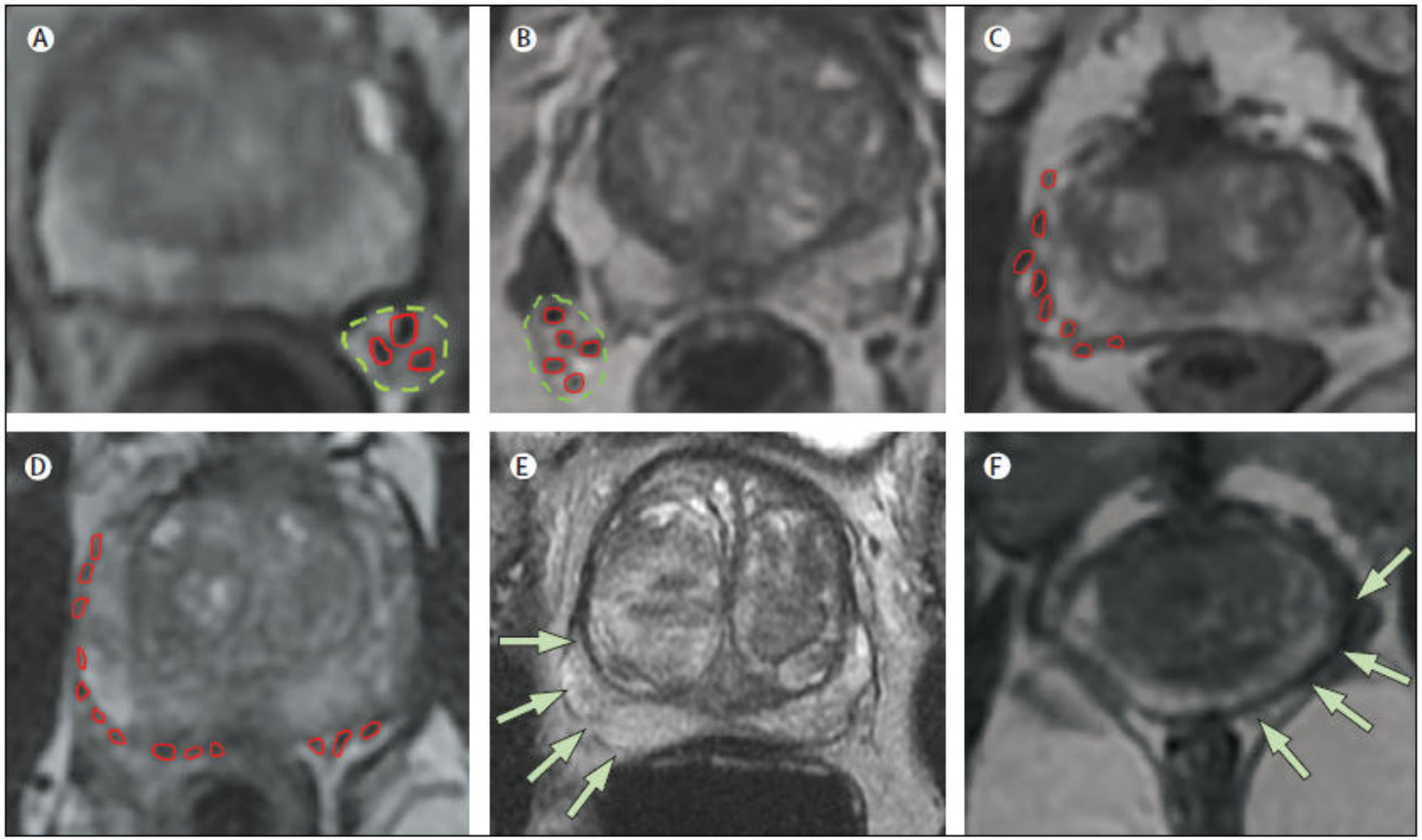
BJU Int 2018; **121**: 61–68

PENILE BULB


GU:
Rectum
BowelBag
GU/GI:
PenileBulb
Bladder
SeminalVesc
Prostate
Femur_L
Femur_R
GI:
Small Bowel
AnoRectumSig
Colon
Mesorectum
lowest level of ischial tuberosities, this is where the Rectum, Femur_L, and Femur_R start
PenileBulb is round and posterior to the urethra. On MRI, bright on T2. Do not extend the penile bulb anteriorly into the shaft or pendulous portion of the penis.
12


seed
seed
Penile bulb
Rectum

NEUROVASCULAR BUNDLE



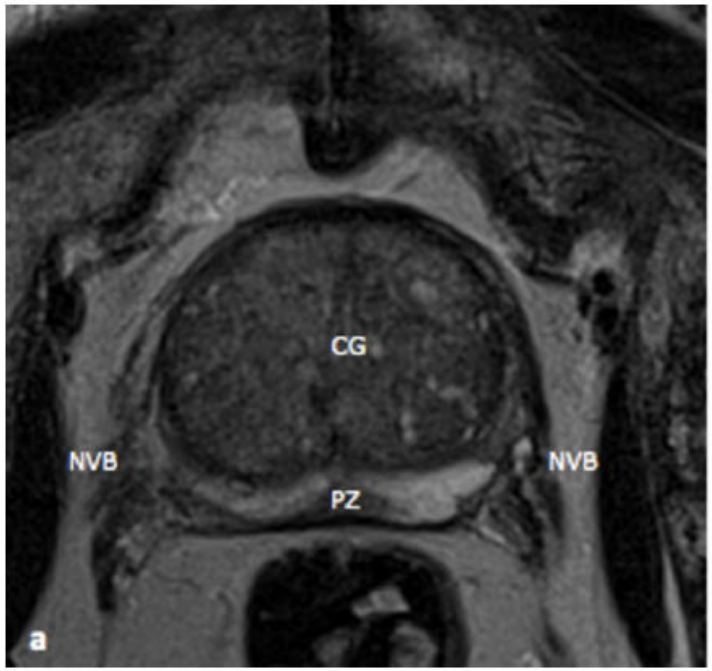


Figure 4: **Nerve bundle variation**
A and B show the classical neurovascular bundle near the posterolateral prostate. Green circles mark classic neurovascular bundles at the posterolateral prostate. Red circles mark individual neurovascular elements sometimes organised into bundles and sometimes distributed broadly around the prostate. C and D show the adherent nerve plexus pattern. E and F show the rare absent variant with no neurovascular elements.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S130–S134, 2010

0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.04.094

QUANTEC: ORGAN-SPECIFIC PAPER **Pelvis: Penile Bulb**

RADIATION DOSE–VOLUME EFFECTS AND THE PENILE BULB

MACK ROACH, III, M.D., FACR,* JIHO NAM, M.D.,† GIOVANNA GAGLIARDI, PH.D.,‡ ISSAM EL NAQA, PH.D.,§ JOSEPH O. DEASY, PH.D.,§ AND LAWRENCE B. MARKS, M.D.†

*Department of Radiation Oncology, University of California-San Francisco, San Francisco, CA; †Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC; ‡Department of Medical Physics, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; and §Department of Radiation Oncology, School of Medicine, Washington University in St. Louis, St. Louis, MO

The dose, volume, and clinical outcome data for penile bulb are reviewed for patients treated with external-beam radiotherapy. Most, but not all, studies find an association between impotence and dosimetric parameters (e.g., threshold doses) and clinical factors (e.g., age, comorbid diseases). According to the data available, it is prudent to keep the mean dose to 95% of the penile bulb volume to <50 Gy. It may also be prudent to limit the D70 and D90 to 70 Gy and 50 Gy, respectively, but coverage of the planning target volume should not be compromised. It is acknowledged that the penile bulb may not be the critical component of the erectile apparatus, but it seems to be a surrogate for yet to be determined structure(s) critical for erectile function for at least some techniques. © 2010 Elsevier Inc.

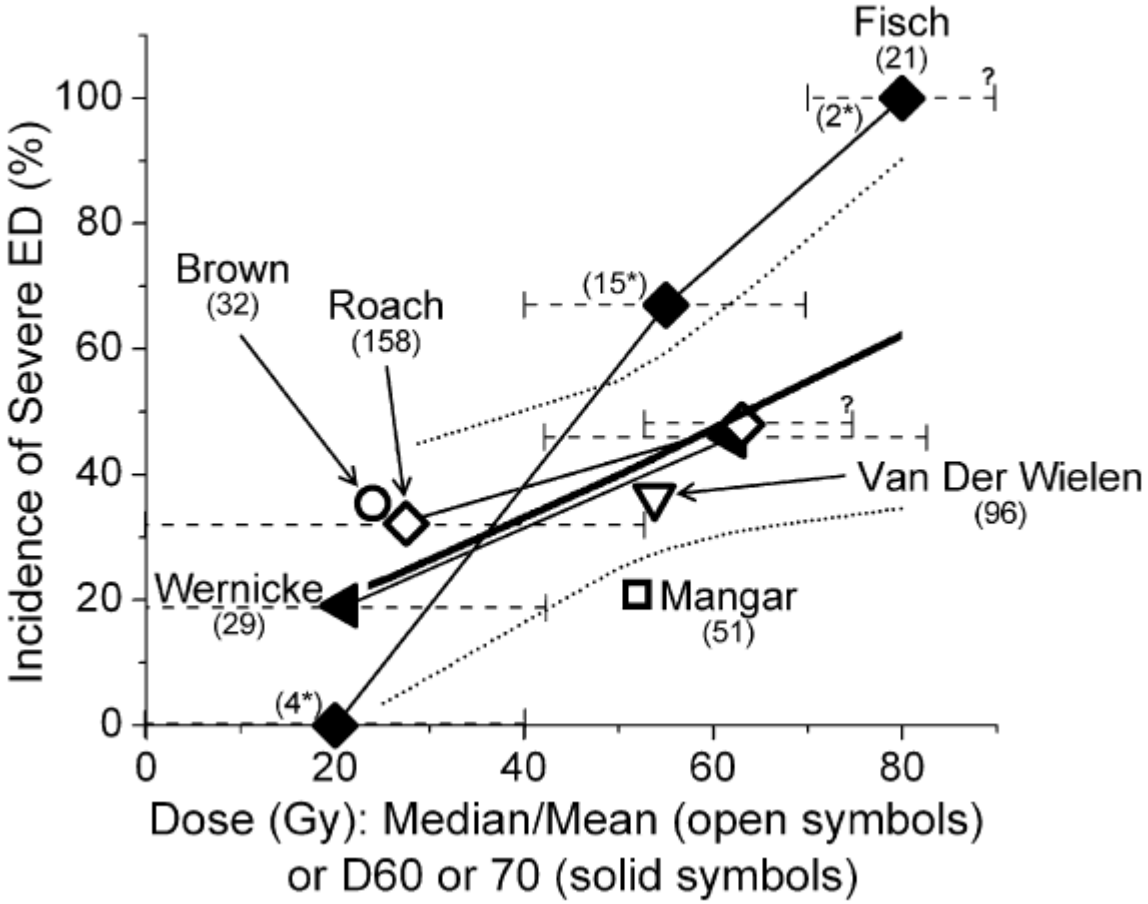

Fig. 2. Incidence of erectile dysfunction according to the radiation dose to the penile bulb. The *x* axis values are estimated according to the range of doses reported. The data for Fisch *et al*. (7) at 20, 55, and 80 Gy represent the reported rates of erectile dysfunction at <40, 40–70, and >70 Gy, respectively. Similarly, for Wernicke *et al*. (14) and Roach *et al*. (10), each symbol represents the rates of erectile dysfunction at ≤42 vs. >42 and <52.5 vs. ≥52.5 Gy, respectively. The dashed horizontal lines reflect the dose ranges ascribed to each data point. The upper *x*-axis range of the highest data point for Fisch *et al*. (7) and Roach *et al*. (10) are unknown. The mean doses of van der Wielen *et al*. (13) and Mangar *et al*. (8) are estimated from the subgroup data. The *x*-axis values for Wernicke *et al*. (14) are D60 and for Fisch *et al*. (7) are D70 (i.e., minimum dose received by 60% or 70% volume of the penile bulb). A thick solid line represents the fitted model with sample size correction, with 95% confidence intervals (dotted curves).

Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy

Joe Y Lee*, Daniel E Spratt*, Adam L Liss, Patrick W McLaughlin

Treatment selection for men undergoing curative treatment for prostate cancer is often a challenging decision in view of the goal of maximising cure while maintaining quality of life. Previous quality-of-life comparisons suggest that specific outcomes are associated with type of treatment (surgery vs radiation); however, the functional anatomy approach, starting with nerve-sparing prostatectomy, assumes that quality-of-life outcomes are established by anatomic preservation. Emerging applications of the functional anatomy approach for prostate radiation will ultimately allow for individualised treatments that address the normal tissue variants visible on MRI. Such approaches will encompass all essential functions affected by treatment including genitourinary, rectal, and sexual functions. In this Review, we outline the current techniques in functional anatomy-based preservation related to sexual outcomes, and outline the capacity of vessel-sparing radiotherapy to preserve sexual function in 90% of patients at the 5 year follow-up while maintaining excellent cure rates.

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*Authors contributed equally

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA (J Y Lee MD, D E Spratt MD, A L Liss MD, Prof P W McLaughlin MD); Agnesian Cancer Center, Fond du Lac, WI, USA (A L Liss); and Assarian Cancer Center, Novi, MI, USA (Prof P W McLaughlin)

BALANCE OF CURE AND QUALITY OF LIFE

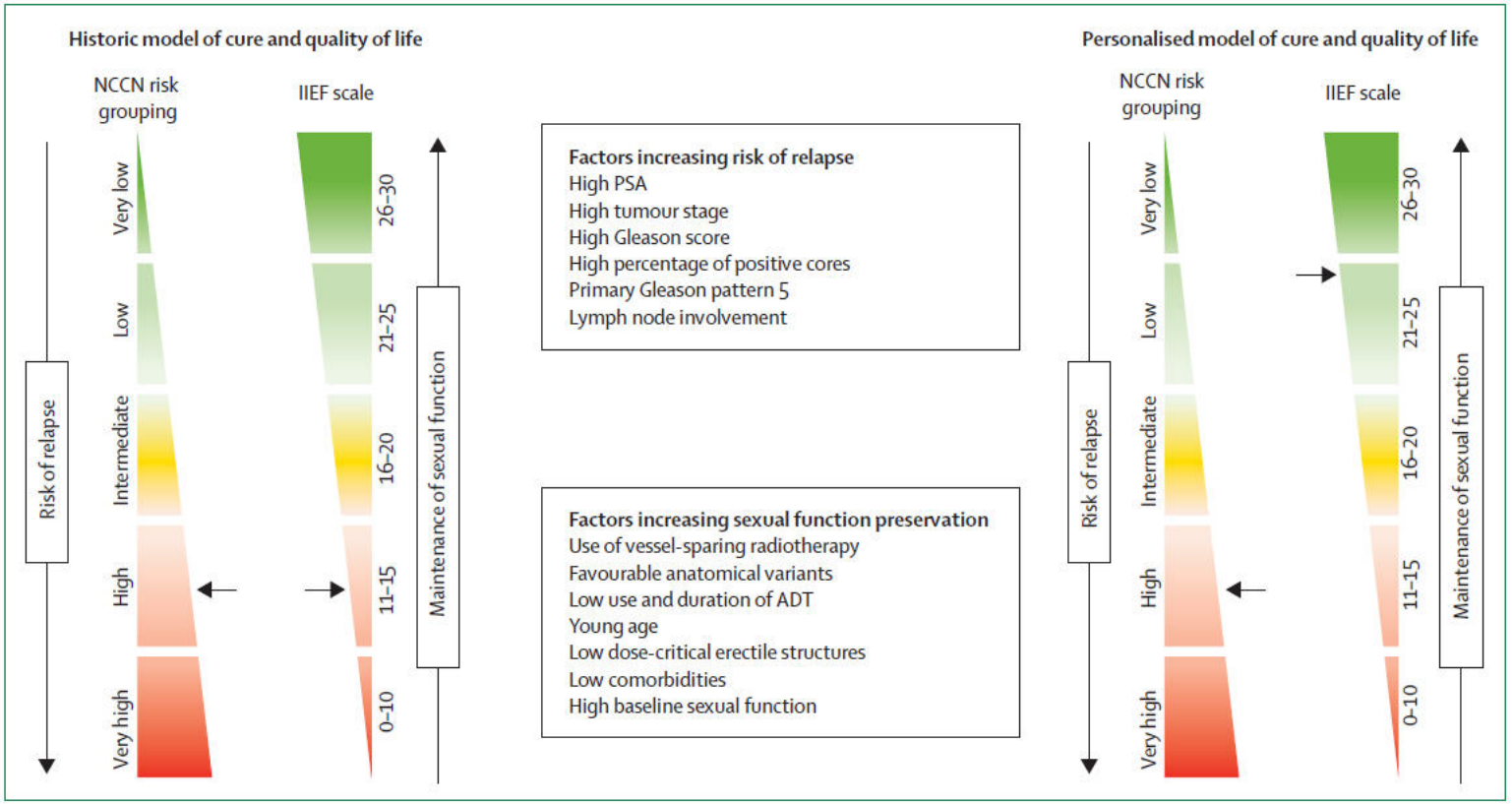

Figure 1: **Balance of cure and quality of life**
Risk of relapse and maintenance of sexual function can be disconnected by personalising treatment in the modern model (right) versus the connected historic model (left). ADT=androgen deprivation treatment. IIEF=International Index of Erectile Function. NCCN=National Comprehensive Cancer Network. PSA=prostate specific antigen.

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VESSEL-SPARING RADIATION

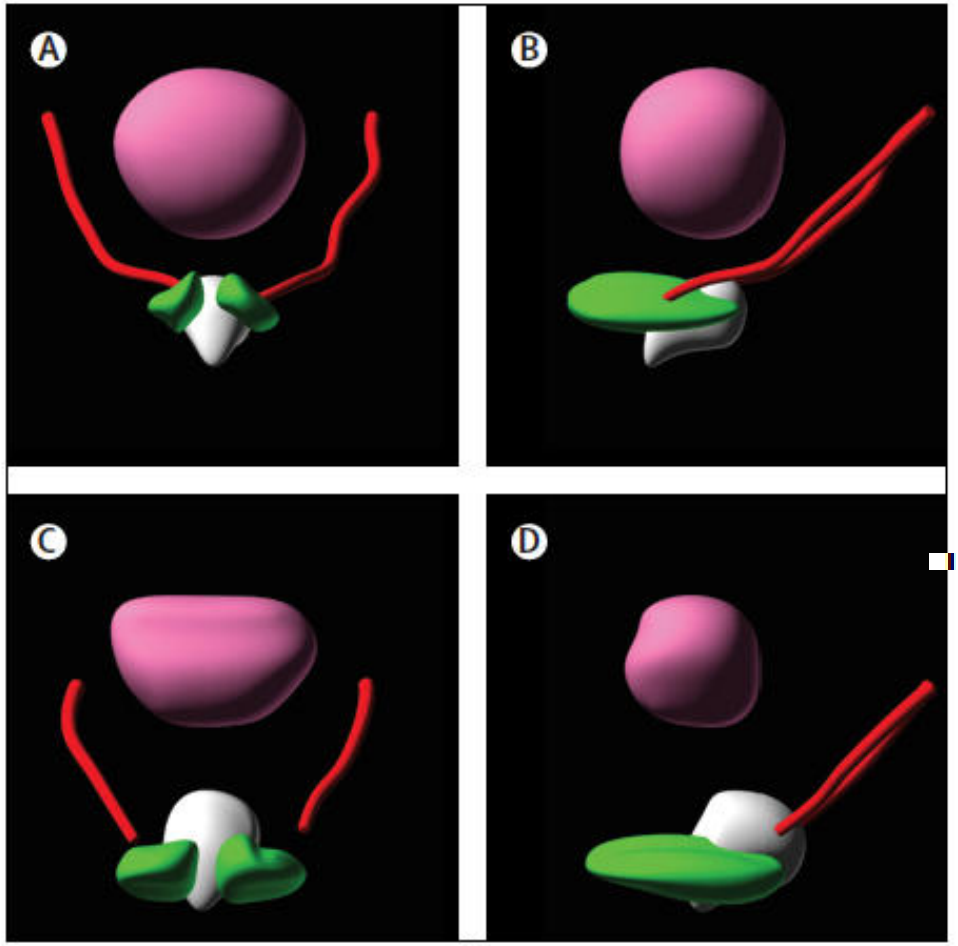

Figure 3: **Representation of coronal and sagittal treatment planning views**
The prostate (pink) lies close to the internal pudendal arteries (red), penile bulb (white), and corpus cavernosa (green) in A and B. Favourable separation of the prostate from the penile bulb and the corpus cavernosa is shown in C and D. A and C are coronal orientation and B and D are sagittal.

There are two key elements in vessel-sparing radiation.

First, accurate definition is needed for the prostate and its inferior extent or apex. Axial, coronal, and sagittal T2-weighted MRI sequences are obtained and registered to the CT simulation to define the prostate.

Second, definition is needed for the internal pudendal artery with non-contrast time-of-flight sequence as well as the erectile tissue of the corpus cavernosa with MRI.

Unquestionably, the accurate definition of the prostate is essential to directly spare erectile tissue by maximising separation, and also to limit external sphincter radiation and its long-term consequences.

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Treating prostate cancer with radiotherapy

Anna Wilkins and Chris Parker

The toxic effect profile of prostate radiotherapy seems comparable or possibly even favorable, with respect to that of other treatment modalities. Data on the adverse effects of prostate radiotherapy relate to treatment as it was delivered in the past. Recent technical advances, such as intensity modulation and image guidance, will hopefully further improve the toxicity profile of prostate radiotherapy. Furthermore, our ability to predict an individual's risk of radiotherapy toxicity will improve, and will aid treatment individualization.

Wilkins, A. & Parker, C. *Nat. Rev. Clin. Oncol.* 7, 583–589 (2010);