Practice Changing Innovations in Last 2 Years
Genitourinary Malignancies

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Prostate Cancer

- Grade Group System
- Mp-MRI
- To Treat Pelvic nodes or NOT?
- Hypofractionated RT
- Upfront Chemotherapy in Metastatic disease

Bladder Cancer

- Neoadjuvant Chemotherapy
- Post Cystectomy RT?

Prostate Cancer

New grade group system

Gleason's Score

- Gleason pattern 1 - 5
- Most common pattern (primary) + less common pattern (secondary) = Gleason score
- GS 3+3 = 6 GS - 7 GS - 8 GS -9 GS -10

Risk stratification – D Amico

- Low risk - GS 6
- Intermediate risk - GS 7 (3+4 , 4+3)
- High risk - GS 8 - 10

This is being questioned
Reproducibility of Gleason score ?

ISUP/WHO 2005, 2014 modifications

New grade groups have been proposed

Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein*†‡

*Departments of *Urology, †Pathology and ‡Oncology, The Johns Hopkins Medical Institutions and The James Brady Buchannan Urological Institute, Baltimore, MD, USA*

What's known on the subject? and What does the study add?

- The Gleason scoring system is a well-established predictor of pathological stage and oncological outcomes for men with prostate cancer. Modifications throughout the last few decades – most recently by the International Society of Urological Pathology (ISUP) in 2005 – have attempted to improve the correlation between biopsy and radical prostatectomy Gleason sum and better stratify patients to predict clinical outcomes.
- Based on these clinical outcomes and the excellent prognosis for patients with low Gleason scores, we recommend Gleason grades incorporating a prognostic grade grouping which accurately reflect prognosis and are clearly understood by physicians and patients alike.

ORIGINAL ARTICLE

The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD, Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD, PhD,¶ and the Grading Committee*

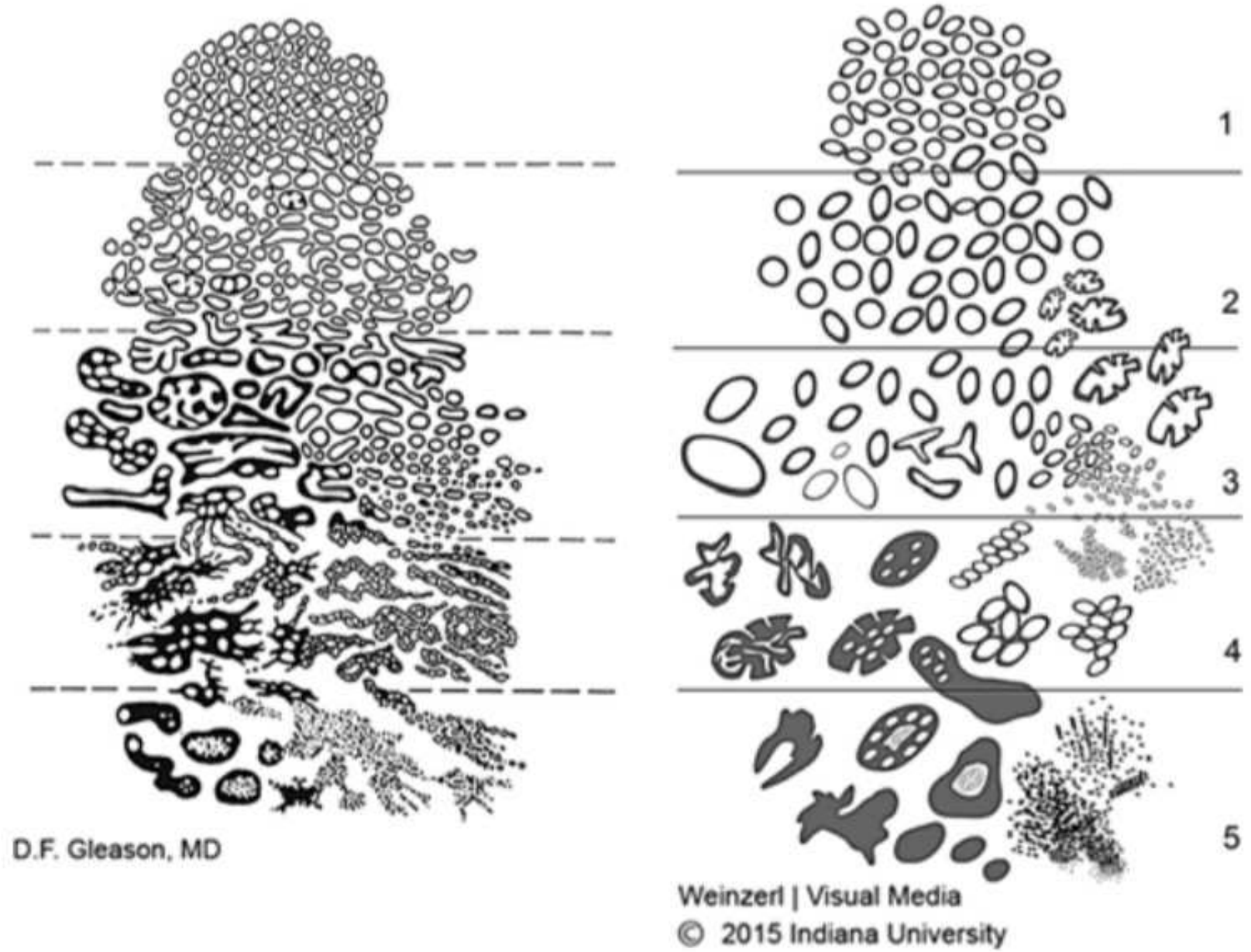

FIGURE 2. Prostatic adenocarcinoma (histologic patterns): original (left) and 2015 Modified ISUP Gleason schematic diagrams.

- **Gleason 7:** 3+ 4 Vs 4 +3

  (But we grouped them together)

- **Gleason 8:** better than 9 ,10

  (But we grouped them 8 – 10)

- **Gleason 6 (3+3)** – when you counsel the patient , he feels that he has cancer which is significant

New grading system Ca P

Grade Group	Gleason Score
Grade Group 1	Gleason score < 6
Grade Group 2	Gleason score 3 + 4 = 7
Grade Group 3	Gleason score 4 + 3 = 7
Grade Group 4	Gleason score 4 + 4 = 8 Gleason score 3 + 5 = 8 Gleason score 5 + 3 = 8

Mp – MRI for prostate cancer

Mp-MRI

- **Images acquired with at least one more sequence – DWI or DCE**
- **Better risk stratification for men on Active Surveillance**
- **May detect poorly differentiated tumors, Extracapsular extension**
- **Equivalent to CT for nodal evaluation**

Prostate Cancer

Pelvic Node RT vs NOT

Elective Pelvic Nodal Irradiation

- **Role controversial**
- **Interest dwindling –**
  1989 – 92% received WPRT, 1994 – 52%, '99 – 23%

  Zelefsky MJ, IJROBP 2004
- **Imaging unreliable for pretreatment nodal staging**
- **Partin Tables, Roach equation to predict pathological stage**

Phase III Trial Comparing Whole-Pelvic Versus Prostate-Only Radiotherapy and Neoadjuvant Versus Adjuvant Combined Androgen Suppression: Radiation Therapy Oncology Group 9413

By M. Roach III, M. DeSilvio, C. Lawton, V. Uhl, M. Machtay, M.J. Seider, M. Rotman, C. Jones, S.O. Asbell, R.K. Valicenti, S. Han, C.R. Thomas Jr, and W.S. Shipley

Purpose: **This trial tested the hypothesis that combined androgen suppression (CAS) and whole-pelvic (WP) radiotherapy (RT) followed by a boost to the prostate improves progression-free survival (PFS) by 10% compared with CAS and prostate-only (PO) RT. This trial also tested the hypothesis that neoadjuvant and concurrent hormonal therapy (NCHT) improves PFS compared with adjuvant hormonal therapy (AHT) by 10%.**

Materials and Methods: **Eligibility included localized prostate cancer with an elevated prostate-specific antigen (PSA) ≤ 100 ng/mL and an estimated risk of lymph node (LN) involvement of 15%. Between April 1, 1995, and June 1, 1999, 1,323 patients were accrued. Patients were randomly assigned to WP + NCHT, PO + NCHT, WP + AHT, or PO + AHT. Failure for PFS was defined as the first occurrence of local, regional, or distant disease; PSA failure; or death for any cause.**

Results: **With a median follow-up of 59.5 months, WP RT was associated with a 4-year PFS of 54% compared with 47% in patients treated with PO RT ($P = .022$). Patients treated with NCHT experienced a 4-year PFS of 52% versus 49% for AHT ($P = .56$). When comparing all four arms, there was a progression-free difference among WP RT + NCHT, PO RT + NCHT, WP RT + AHT, and PO RT + AHT (60% *v* 44% *v* 49% *v* 50%, respectively; $P = .008$). No survival advantage has yet been seen.**

Conclusion: **WP RT + NCHT improves PFS compared with PO RT and NCHT or PO RT and AHT, and compared with WP RT + AHT in patients with a risk of LN involvement of 15%.**

J Clin Oncol 21:1904-1911.

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 3, pp. 646–655, 2007

0360-3016/07/$–see front matter

doi:10.1016/j.ijrobp.2007.04.003

CLINICAL INVESTIGATION **Prostate**

AN UPDATE OF THE PHASE III TRIAL COMPARING WHOLE PELVIC TO PROSTATE ONLY RADIOTHERAPY AND NEOADJUVANT TO ADJUVANT TOTAL ANDROGEN SUPPRESSION: UPDATED ANALYSIS OF RTOG 94-13, WITH EMPHASIS

Results: The difference in overall survival for the four arms was statistically significant ($p = 0.027$). However, no statistically significant differences were found in PFS or overall survival between NHT vs. AHT and WPRT compared with PORT. A trend towards a difference was found in PFS ($p = 0.065$) in favor of the WPRT + NHT arm compared with the PORT + NHT and WPRT + AHT arms.

Conclusions: Unexpected interactions appear to exist between the timing of hormonal therapy and radiation field size for this patient population. Four Phase III trials have demonstrated better outcomes when NHT was combined with RT compared with RT alone. The Radiation Therapy Oncology Group 9413 trial results have demonstrated that when NHT is used in conjunction with RT, WPRT yields a better PFS than does PORT. It also showed that when NHT + WPRT results in better overall survival than does WPRT + short-term AHT. Additional studies are warranted to determine whether the failure to demonstrate an advantage for NHT + WPRT compared with PORT + AHT is chance or, more likely, reflects a previously unrecognized biologic phenomenon.

VOLUME 25 · NUMBER 34 · DECEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG-01

Pascal Pommier, Sylvie Chabaud, Jean Leon Lagrange, Pierre Richaud, François Lesaunier, Elisabeth Le Prise, Jean Philippe Wagner, Meng Huor Hay, Veronique Beckendorf, Jean Philippe Suchaud, Pierre Marie Pabot du Chatelard, Valerie Bernier, Nicolas Voirin, David Perol, and Christian Carrie

From the Centre Léon Bérard, Lyon; Hopital Henri Mondor, Creteil; Insitute Bergonie, Bordeaux; Centre Francois Baclesse, Caen; Centre Eugene Marquis, Rennes; Clinique de L'Orangerie, Strasbourg; Centre Val d'Aurelle, Montpellier; Centre Alexis Vautrin, Nancy; Hopital de Roanne, Roanne; and Centre Paul Papin, Angers, France.

Submitted January 25, 2007; accepted September 6, 2007.

Supported by the Groupe d'Etude des Tumeurs Uro-Genitales (French Genito-urinary Group) of the Fédération Nationale des Centres de Lutte Contre le Cancer, with a grant from the Ligue Nationale Contre le Cancer.

Presented in part at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, October 16-20, 2005, Denver, CO (Pommier P, Perol D, Lagrange J, et al: Does pelvis and prostate radiation therapy compared to prostate radiation therapy alone improve survival in patients with non metastatic prostate carcinoma? Preliminary results of the prospective randomized GETUG01 trial. Int J Radiat Oncol Biol Phys 63:S19-S20, 2005).

Authors' disclosures of potential con-

ABSTRACT

Purpose
To assess the benefit and toxicity and quality-of-life (QOL) outcomes of pelvic nodes irradiation in nonmetastatic prostate carcinoma patients.

Patients and Methods
Between December 1998 and June 2004, 444 patients with T1b-T3, N0 pNx, M0 prostate carcinoma were randomly assigned to either pelvic and prostate radiotherapy or prostate radiotherapy only. Patients were stratified according to the prognostic factor of lymph node involvement (LNI). Short-term 6-month neoadjuvant and concomitant hormonal therapy was allowed only for patients in the high-risk group. The pelvic dose was 46 Gy. The total dose recommended to the prostate was changed during the course of the study from 66 Gy to 70 Gy. Criteria for progression-free survival (PFS) included biologic prostate-specific antigen recurrences or a local or metastatic evolution. Acute and late toxicities were recorded according to the Radiation Therapy Oncology Group and Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scales, respectively. The QOL outcome was recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, the International Prostatic Symptom Score, and the Sexual Function Index scales.

Results
With a 42.1-month median follow-up time, the 5-year PFS and overall survival were similar in the two treatment arms for the whole series and for each stratified group. On multivariate analysis, low LNI risk and hormonal therapy were statistically associated with increased PFS. However, subgroup analyses based on these factors did not show any benefit for pelvic irradiation. There were no significant differences in acute and late digestive toxicities and in QOL outcomes.

Conclusion
Pelvic node irradiation was well tolerated but did not improve PFS.

J Clin Oncol 25:5366-5373. © 2007 by American Society of Clinical Oncology

Radiotherapy and Oncology 110 (2014) 45–54

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journal homepage: www.thegreenjournal.com

Systematic review

The role of elective pelvic radiotherapy in clinically node-negative prostate cancer: A systematic review

Piet Dirix [a,f,*], Steven Joniau [b,g], Laura Van den Bergh [a,f], Sofie Isebaert [a,f], Raymond Oyen [c,h], Christophe M. Deroose [d,h], Evelyne Lerut [e,h], Karin Haustermans [a,f]

Conclusion

Currently, there is insufficient evidence to advocate WPRT in intermediate- or even high-risk localized PCa patients. All three randomized-controlled trials were negative with respect to (biochemical) disease-free survival as well as overall survival. Still, recent surgical series with eLND show a considerable incidence of

the benefit from WRT. Based on current evidence, WPRT should always be combined with at least neo-adjuvant and concomitant ADT. In conclusion, elective pelvic radiotherapy is certainly not standard of care for intermediate- or high-risk prostate cancer, but could be considered in patients at very high risk of LNI either based on validated and contemporary nomograms or on positive SN.

Trial in Progress

NRG ONCOLOGY

RTOG 0924

ANDROGEN DEPRIVATION THERAPY AND HIGH DOSE RADIOTHERAPY WITH OR WITHOUT WHOLE-PELVIC RADIOTHERAPY IN UNFAVORABLE INTERMEDIATE OR FAVORABLE HIGH RISK PROSTATE CANCER: A PHASE III RANDOMIZED TRIAL

SCHEMA (2/26/14)

STRATIFY		RANDOMIZE	
	Risk Group 1. GS 7-10 + T1c-T2b + PSA < 50 ng/ml 2. GS 6 + T2c-T4 or ≥ 50% biopsies + PSA < 50 ng/ml 3. GS 6 + T1c-T2b + PSA > 20 ng/ml		**Arm 1:** Neoadjuvant androgen deprivation therapy + prostate & seminal vesicle RT + boost to prostate & proximal seminal vesicles
	Type of RT Boost 1. IMRT 2. Brachytherapy (LDR using PPI or HDR)		**Arm 2:** Neoadjuvant Androgen Deprivation Therapy + whole-pelvic RT + boost to prostate & proximal seminal vesicles
	Duration of Androgen Deprivation Therapy 1. Short Term (6 months) 2. Long Term (32 months)*		

* 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = avg 32 months

Conclusion

Insufficient evidence for WPRT in IR & HR Ca Prostate

Confounding factors –
ADT (timing/duration), limited lymphadenectomies, outdated nomograms

WPRT can be considered in very high risk of LNI or positive SNs

Hypofractionation in Prostate Cancer

α/β

Dose at which linear and quadratic components of cell kill are equal

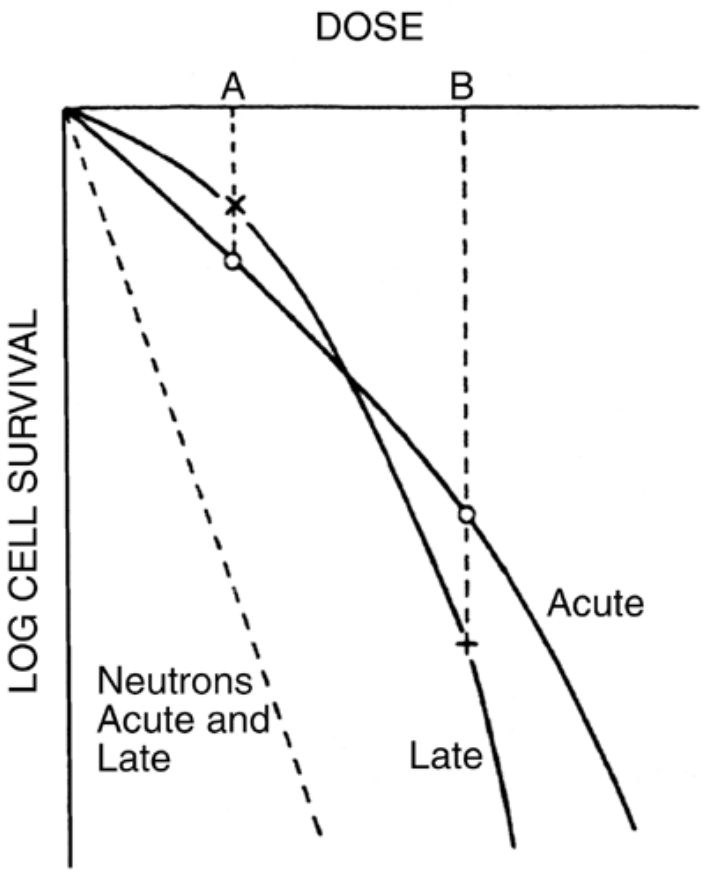
↑ α/β: Cell damage is function of total dose

(Rapidly dividng cells)

↓ α/β: Cell damage is function of dose / fraction

(Slow dividing cells)

Linear-quadratic formula



α (alpha) = initial slope; intrinsic Radiosensitivity, linearly dependent

β (beta) = "curviness" ?repairable injury, proportional to the square of dose

Overall shape depends on both factors.

The α/β ratio thus determines sensitivity of a cell to alterations in fraction size.

In general:

Rapidly proliferating cells are not very sensitive to fraction size (high α/β).

Slowly proliferating cells are very sensitive to fraction size (low α/β)

Hypofractionation

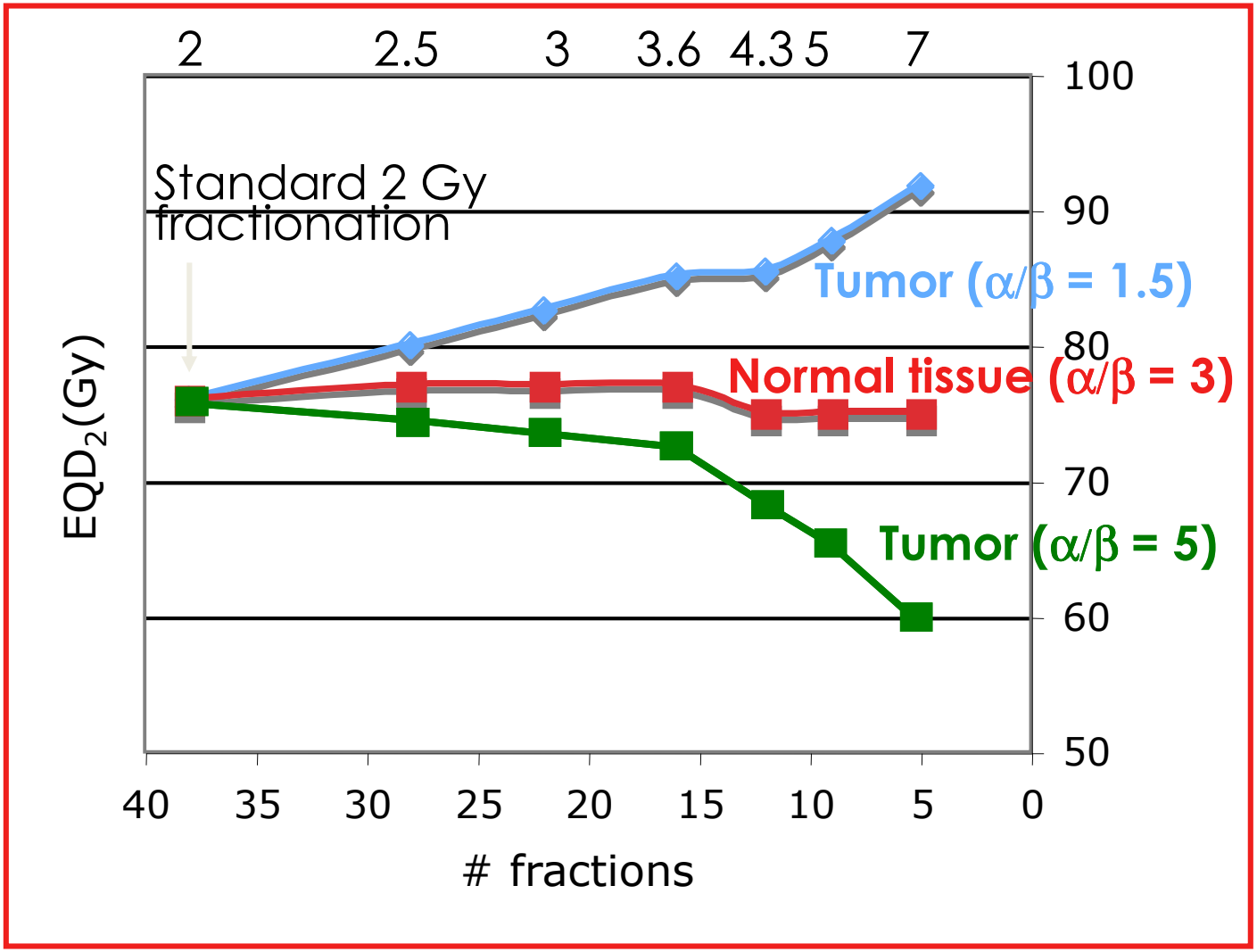
- If α/β < normal tissue
  - Hypofraction has an advantage

- If α/β > normal tissue
  - Hypofraction has a disadvantage

- Moderate Hypofractionation— <35 fractions
- Extreme Hypofractionation — <5 fractions

Tumor EQD_2 versus Hypofractionation

What would happen if α/β were higher than thought?



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Int. J. Radiation Oncology Biol. Phys., Vol. 43, No. 5, pp. 1095–1101, 1999

0360-3016/99/$–see front matter

ELSEVIER

PII S0360-3016(98)00438-6

BIOLOGY CONTRIBUTION

FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

DAVID J. BRENNER, D.SC.,* AND ERIC J. HALL, D.SC.*

Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY

Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 4, pp. 747–748, 1999

0360-3016/99/$–see front matter

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PII S0360-3016(99)00024-3

EDITORIAL

WHAT IS THE α/β RATIO FOR PROSTATE CANCER? RATIONALE FOR HYPOFRACTIONATED HIGH-DOSE-RATE BRACHYTHERAPY

GILLIAN M. DUCHESNE, M.D., F.R.C.R., F.R.A.C.R., AND
LESTER J. PETERS, M.D., F.A.C.R., F.R.A.C.R.

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0360-3016/01/$–see front matter

ELSEVIER

PII S0360-3016(01)01607-8

BIOLOGY CONTRIBUTION

IS α/β FOR PROSTATE TUMORS REALLY LOW?

JACK FOWLER, D.SC., PH.D.,* RICK CHAPPELL, PH.D.,† AND MARK RITTER, M.D., PH.D.*

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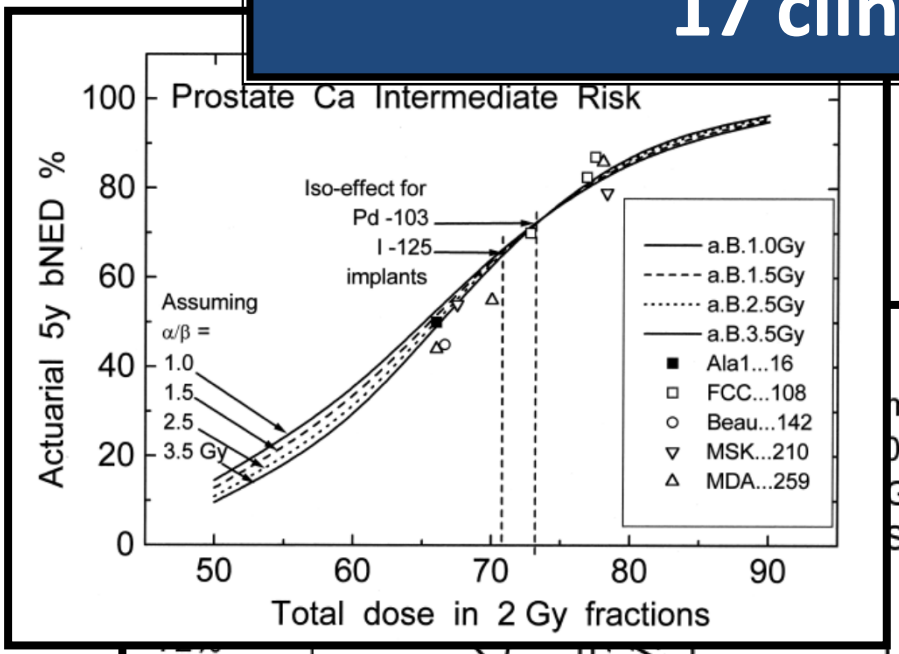
17 clinical trials



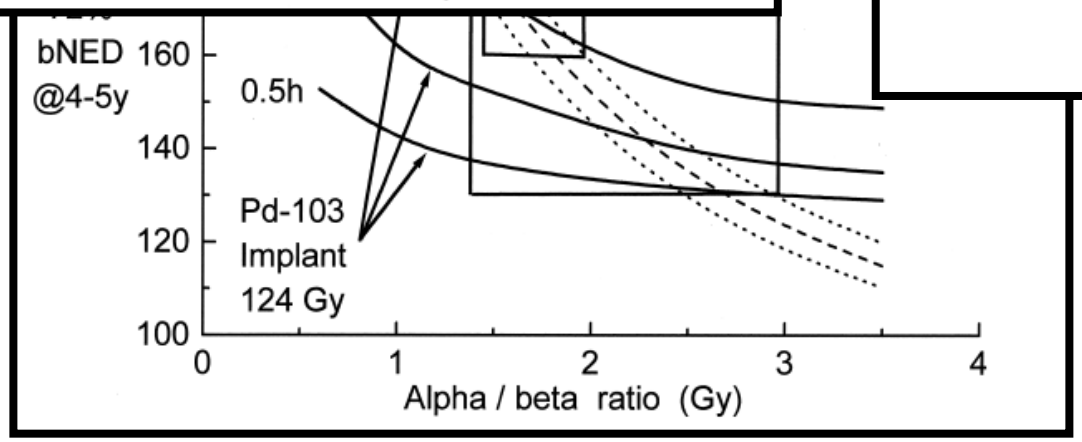
$$E = \alpha \times N \times d \times RE,$$

$$RE = 1 + \frac{R_0}{\mu + \lambda} \times \frac{\beta}{\alpha} = 1 + \frac{d}{\left(1 + \frac{\mu}{\lambda}\right) \times \frac{\alpha}{\beta}}.$$

This implies

$$E = \alpha \times N \times d \left\{ 1 + \frac{d}{\left[\left(1 + \frac{\mu}{\lambda}\right) \times \frac{\alpha}{\beta}\right]} \right\}$$

$$= (\alpha \times N \times d) + \frac{\beta \times N \times d^2}{\left(1 + \frac{\mu}{\lambda}\right)}.$$



α/β Prostate $\leq$ 1.5

Acta Oncologica, 2005; 44: 265–276

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

The radiobiology of prostate cancer including new aspects of fractionated radiotherapy

JACK F. FOWLER

Emeritus of Medical School of Wisconsin University, Department of Human Oncology, University of Wisconsin-Madison, USA

Table V. Hypofractionated schedules calculated for external beam radiotherapy for constant late rectal complications assuming $\alpha/\beta = 3$ Gy.

		Rectal		Tumor	
Hypofractionated Schedule	Total Dose (Gy)	BED Gy3 for $\alpha/\beta = 3$Gy	Late rectal Complications NTD $_{2Gy}$ ($\alpha/\beta = 3$Gy)	Calculated NTD$_{2Gy}$ ($\alpha/\beta = 1.5$Gy)	Estimated bNED (from Figure 1)
37F × 2.00	74.0	123.3	74.0 Gy	74.0 Gy	75.5%
25F × 2.69	65.73	123.3	74.0	78.7	82.8
20F × 3.06	61.11	123.3	74.0	79.6	84.0
15F × 3.69	55.33	123.3	74.0	82.0	87.3
10F × 4.77	47.65	123.3	74.0	85.4	90.0
5F × 7.73	36.16	123.3	74.0	90.2	94.0
3F × 9.70	29.10	123.3	74.0	93.1	95.8

HYPOFRACTIONATED VERSUS CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOR PROSTATE CARCINOMA: FINAL RESULTS OF PHASE III RANDOMIZED TRIAL

ERIC E. YEOH, M.D., F.R.C.P. (EDIN.), F.R.C.R., F.R.A.N.Z.C.R.,* ROCHELLE J. BOTTEN, B.SC. (HONS.),* JULIE BUTTERS, B.H.SC.,* ADDOLORATA C. DI MATTEO, B.SC. (HONS.),* RICHARD H. HOLLOWAY, M.D., F.R.A.C.P.,† AND JACK FOWLER, D.SC., PH.D., F.INST.P.‡

Departments of *Radiation Oncology and †Gastroenterology, Royal Adelaide Hospital, Adelaide, Australia; ‡Department of Human Oncology, University of Wisconsin Medical School, Madison, WI (Emeritus)

- Therapeutic advantage without additional toxicity

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial

David Dearnaley, Isabel Syndikus, Georges Sumo, Margaret Bidmead, David Bloomfield, Catharine Clark, Annie Gao, Shama Hassan, Alan Horwich, Robert Huddart, Vincent Khoo, Peter Kirkbride, Helen Mayles, Philip Mayles, Olivia Naismith, Chris Parker, Helen Patterson, Martin Russell, Christopher Scrase, Chris South, John Staffurth, Emma Hall

ACUTE AND LATE TOXICITY IN A RANDOMIZED TRIAL OF CONVENTIONAL VERSUS HYPOFRACTIONATED THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER

GIORGIO ARCANGELI, M.D.,* JACK FOWLER, PH.D.,† SARA GOMELLINI, M.D.,* STEFANO ARCANGELI, M.D.,* BIANCAMARIA SARACINO, M.D.,* MARIA GRAZIA PETRONGARI, M.D.,* MARCELLO BENASSI, PH.D.,‡ AND LIDIA STRIGARI, PH.D.‡

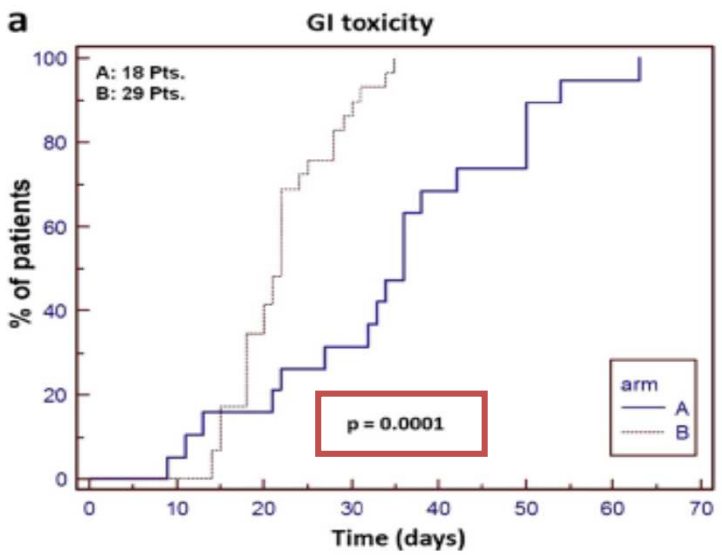
*Department of Radiation Oncology and ‡Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, Rome, Italy; †Emeritus, Departments of Human Oncology and Medical Physics, University of Wisconsin Medical School, Madison, WI

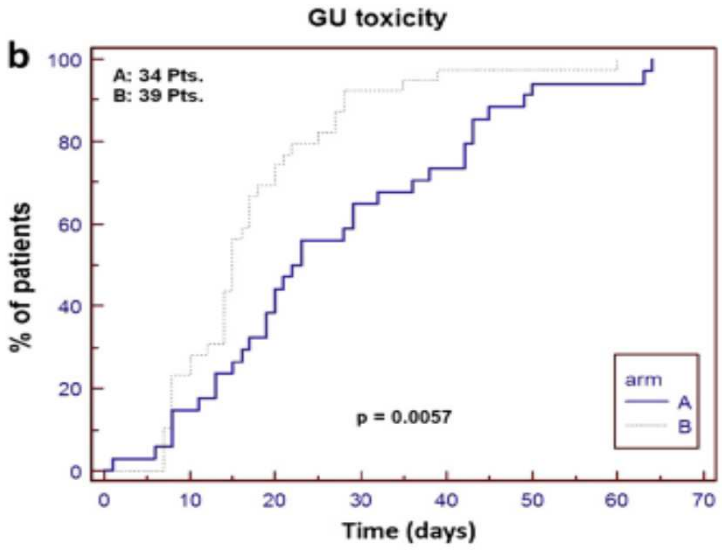
n = 168

80Gy / 40 Fr/ 8wks

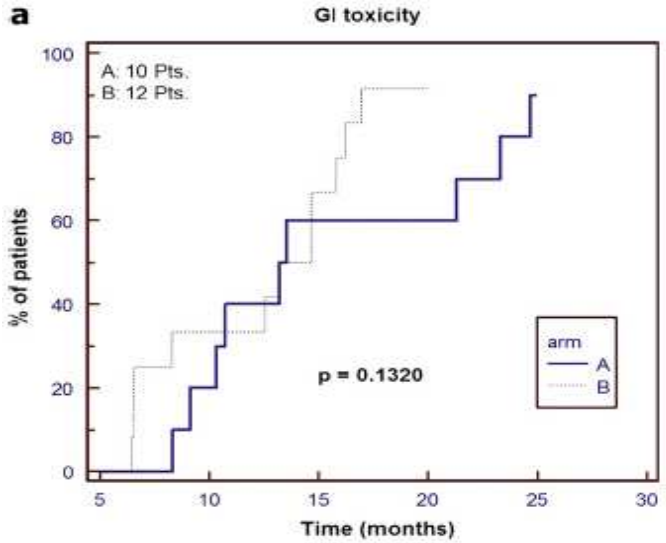
62Gy / 20 Fr/ 5wks

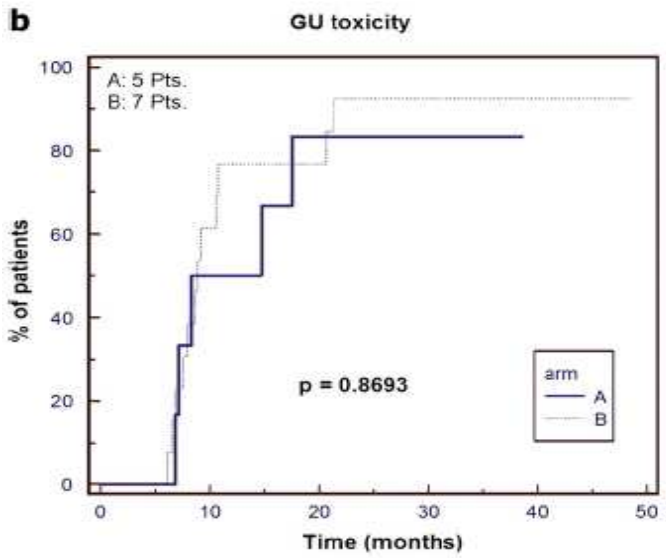
9 months total androgen blockade





Acute Toxicity





Late Toxicity

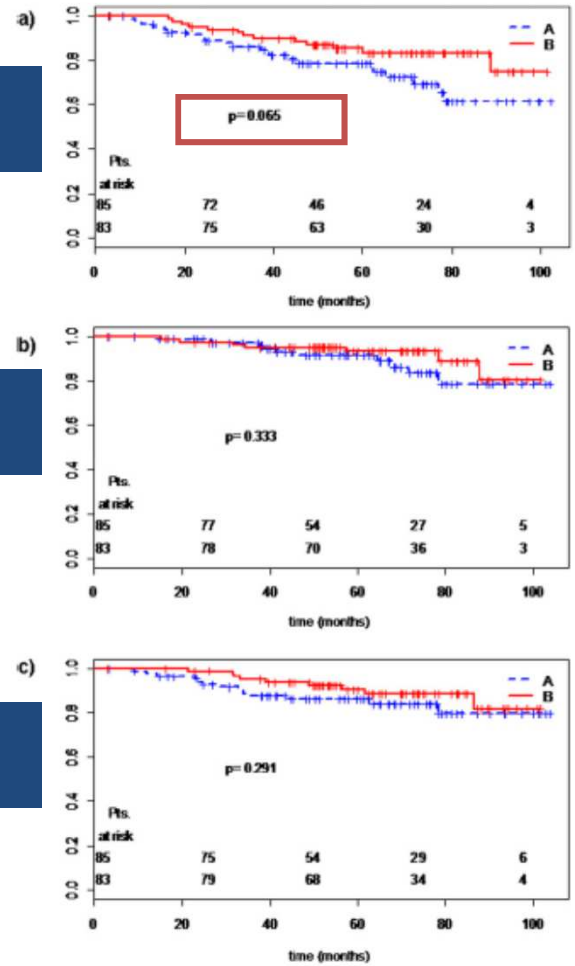
Updated Results and Patterns of Failure in a Randomized Hypofractionation Trial for High-risk Prostate Cancer

Stefano Arcangeli, MD,* Lidia Strigari, PhD,† Sara Gomellini, MD,* Biancamaria Saracino, MD,* Maria Grazia Petrongari, MD,* Paola Pinnarò, MD,* Valentina Pinzi, MD,* and Giorgio Arcangeli, MD*

Biochemical failure

Local failure

Distant failure



- Isoeffctiveness with 2Gy schedules
- Trend towards significance in FFBF
- Better FFBF in pt with iPSA < 20ng/mL

HYPOFRACTIONATION

PMH / PROFIT	**60.0 at 3.0 Gy**	**vs**	**78.0 at 2.0 Gy**
RTOG 0415	**70.0 at 2.5 Gy**	**vs**	**73.8 at 1.8 Gy**
CHHiP(UK)	**60.0 at 3.0 Gy**	**vs**	**74.0 at 2.0 Gy**

MODERATE HYPOFRACTIONATION
SAFE AND EFFECTIVE

Moderate Hypofractionation
RTOG 0415, ASTRO 2016

Quality of Life Assessments

Hypofractionated RT can reduce treatment time by one-third with comparable QOL for prostate cancer patients

NRG Oncology/RTOG 0415 trial shows similar side effects following conventional and accelerated RT for early stage, low-risk disease

HYPO-RT-PC trial

Randomized multi-institutional phase III trial in Scandinavia

42.7 at 6.1 Gy	vs	78 at 2 Gy
7 fractions		39 fractions

N=866, Minimum FU: 2y, Median FU: 4.2y

Eligible patients: INTERMEDIATE RISK

T1c to T3a, PSA $\leq$20 and one or two of three risk factors:

- Stage T3a
- Gleason $\geq$7
- PSA >10

TECHNIQUE:	3DCRT	80%
	VMAT	20%

HYPO-RT-PC trial - ASTRO 2016

Extremely hypofractionated radiation therapy shows promising toxicity results for intermediate risk prostate cancer patients

Large Scandinavian trial finds comparable side effects at two years following 42.7 Gy delivered in seven fractions compared to 78 Gy delivered in 39 treatments

N=866, Minimum FU: 2y. Median FU: 4.2y

Grade 2+ toxicities at 2 yrs	Urinary	Bowel
42.7 at 6.1 Gy :	5.4%	2.2%
	$p = 0.59$	$p = 0.20$
78 at 2Gy:	4.6%	3.7%

Impotence	Baseline	At 2 years
Extreme Hypofractionation:	16%	34%
Conventional fractionation:	16%	34%

Quality of life at 2 years: NO DIFFERENCE

Urinary (p=0.17), Bowel (p=0.12), Sexual Function (p=0.71).

Upfront chemotherapy for the metastatic prostate cancer

- Taxane based chemotherapy found be effective in CRPC
- Its use ‘upfront’ at the time of first diagnosis has been proposed
- Improved overall survival with upfront chemotherapy in some trials

Trial	Arms	Result
GETUG-AFU -15	ADT + Docetaxel Vs ADT alone	58.9 vs 54.2 months
CHARRTED	ADT + Docetaxel vs	Median OS 57.6 vs 44 months (13.6 months)
High volume disease	ADT alone	Greater benefit with high volume disease
Low volume disease		Median OS 49 .2 vs 32.2 months (17 months)
STAMPEDE (ASCO -2015)	ADT + Docetaxel vs	Median OS 77 vs 67 months (10 months)
Metastatic Node positive High risk - Locally advanced	ADT alone	Metastatic disease – 65 months vs 43 months (22 months benefit)

New data on …

- Improved survival of 56 months with use of Docetaxel + ADT at first diagnosis !

- Meta-analysis of CHARTTED trial , GETYUG trial , STAMPEDE trial – Dec 2015

  2992 men

  4 yr DFS - 49 % for ADT + D 40 % for ADT alone

  4 yr treatment failure - 64% for ADT+D ,80% for ADT alone

  (Vale CL ,et al . Lancet Oncol 2015)

BJUI
BJU International

Comments

Will chemotherapy change the management of prostate cancer?

Clare Gilson*,†, Matthew R. Sydes* and Simon Chowdhury†

*Medical Research Council Clinical Trials Unit, Guy's Hospital, and †Department of Medical Oncology, Guy's Hospital, London, UKprostate cancerchemotherapydocetaxel

BJUI , August 2016 : 118 (2)

There is also the issue of whether men with high-risk locally advanced prostate cancer should be offered docetaxel. Importantly, no evidence of heterogeneity is seen in the STAMPEDE data in a cohort where 40% of men had non-metastatic disease. Both STAMPEDE and GETUG-12 trials show that docetaxel can safely delay disease progression but mature survival data is needed to address whether the initial findings of the Radiation Therapy Oncology Group (RTOG) 0512 trial presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2015 can be supported [8,9]. Long-term follow-up and updated meta-analyses will help provide the necessary evidence in this disease setting, but there is a clear need for predictive biomarkers in this heterogeneous patient group, to guide patients and their clinicians' in their decision making.

The investigators must use this opportunity to work with their colleagues to interrogate the tumour samples from men in these trials, to see if they can identify biomarkers that predict docetaxel activity. We will not get this opportunity again, as docetaxel and ADT will become the standard of care for future studies. Indeed, the STAMPEDE trial protocol has been amended to permit upfront docetaxel as part of the standard-of-care for all suitable new patients joining the trial.

The clinical benefit from the addition of docetaxel to ADT is one of the largest seen in any oncology study. We think all suitable men presenting with newly diagnosed metastatic prostate cancer should be considered for six cycles of docetaxel in addition to ADT. We also think it should be considered for some men with high-risk locally advanced disease on the basis of a significant improvement in PFS.

As the standard of care changes, further questions arise as to the optimum sequencing of treatment, together with the safety and efficacy of strategies that combine treatments. The stratification of this heterogeneous patient group is key in enabling the management of prostate cancer to catch up with the molecularly driven approaches possible in other cancers such as lung and colorectal. Upfront chemotherapy will change the way we manage metastatic prostate cancer, but we still need to be able to know who is likely to benefit most and in whom alternative strategies are still needed.

Conflicts of interest

Simon Chowdhury reports grants and personal fees from Sanofi-Aventis outside the published work. Matthew R. Sydes reports grants and non-financial support from Sanofi-Aventis.

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Radical prostatectomy for high risk and oligo-metastatic CaP

Multimodal approach

- Multimodality treatment in prostate cancer management is now well established
- Good loco regional control + care of metastatic disease (like in other malignancies)
- RP not a big deal today

- Would it improve survival ?

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Comments

Is there a place for cytoreduction in metastatic prostate cancer?

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Introduction

Cytoreductive treatment in metastatic prostate cancer (mPCa) primarily refers to local control of the primary tumour by radical prostatectomy (RP) or radiotherapy; however, extirpative treatment of limited metastatic disease by stereotactic body radiotherapy or surgical resection may further reduce or even possibly eliminate disease burden. This comment piece explores the theory and evidence for RP in the setting of mPCa.

What is the Rationale for Radical Prosatectomy in Metastatic Prostate Cancer?

In recent years we have seen a shift in the role of RP. There has been a reduction in radical surgery for candidates with low-risk disease. We now believe that men with high-risk disease are most likely to benefit. Where once lymph node-positive disease was an indication to abandon RP, there is findings are important for hypothesis generation, and indicate that, even in advanced disease, surgical removal of the primary cancer may have the potential to alter the disease trajectory by limiting metastatic spread. Similarly, targeted treatment of oligometastases may also reduce further spread. By limiting disease burden, cytoreduction may also delay or obviate the need for systemic therapies and their associated side effects.

Cytoreductive surgery in other malignancies (such as colon, breast, ovarian and kidney) has been associated with clear survival benefits and improved response to systemic therapy [6]. Based on present insights into the biology of metastasis in PCa, similar benefits may be seen with cytoreduction in this setting. In addition, in well selected men, RP has been shown to reduce the need for palliative surgery to control local disease progression [7].

What is the Evidence in Metastatic Prostate Cancer?

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Which Patients?

In identifying the ideal candidates for cytoreductive RP, studies will need to establish the limits of burden of disease at which the benefits of cytoreductive surgery outweigh any harms. How much is too much disease? Is benefit seen only in limited mPCa? If so, what constitutes limited metastases? Consideration will also need to be given to the imaging method used to detect metastases. With the development of new imaging techniques that have a high sensitivity [9], such as PSMA positron emission tomography, previously occult metastatic disease is now being recognized.

Which Treatment and Does Treatment Sequencing Matter?

Systemic treatment constitutes the current standard practice in mPCa. Investigating the role of cytoreductive RP should primarily focus on its use in conjunction with systemic therapy (neoadjuvant and/or adjuvant ADT). The MD Anderson Cancer Center is currently recruiting for one such randomized trial: 'Randomized, phase II trial of best systemic therapy or best systemic therapy plus definitive treatment (radiation or surgery) of the primary tumour in metastatic (M1) prostate cancer' [10]. Similarly, radiotherapy in the setting of newly diagnosed mPCA is currently being investigated in the multistage multi-arm randomized controlled trial STAMPEDE (www.stampedetrial.org). This trial, investigating standard of care (ADT with or without radiotherapy) with or without systemic therapy, shows the importance of a multimodal approach for advanced disease.

Cytoreductive treatment may now be an option when considered in the context of multimodal therapy. Large, multicentre randomized controlled trials are needed to establish its safety and efficacy. Until further evidence is available, cytoreductive RP should be undertaken in a clinical trial setting only.

Carcinoma Urinary Bladder

NACT for the MIBC

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European Association of Urology

Review – Bladder Cancer

A Systematic Review of Neoadjuvant and Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer

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from nonresponders among patients with invasive UCB receiving neoadjuvant MVAC [57,58]. Provocatively, topoisomerase IIa, a target of doxorubicin, was downregulated in the nonresponder group. In another study, an association of low/intermediate tumor *BRCA1* mRNA levels (which mediates DNA repair) and long-term outcomes was identified in patients receiving NC [59]. Serial cystoscopic biopsies may provide access to tumor and stroma for profiling. A SWOG-coordinated US National Cancer Institute (NCI) supported trial will randomize patients to GC or DD-MVAC and is designed to validate tumor tissue–based molecular profiles as predictive biomarkers. In this trial, the molecular profile is based on in vitro drug sensitivities and microarray analyses of the NCI-60 cancer cell line panel (COXEN), which appears to provide a robust approach to personalized therapy [60]. In addition, the residual tumor tissue following NC may be enriched for cells with resistance mechanisms and stem cell properties and may provide an excellent resource to inform the development of non–cross-resistant systemic therapy [61].

(pers. comm., M. Stockle). Additionally, patients with residual disease after NC should be offered trials evaluating potentially non–cross-resistant new agents in an effort to improve the otherwise dismal long-term outcomes demonstrated by these patients (Table 3). Such efforts are already underway, with separate phase 2 trials evaluating sunitinib (NCT01042795) or a Her2 targeting autologous antigen presenting cell-based vaccine (NCT01353222) in those with Her2-expressing disease (by fluorescent in situ hybridization) at RC (with or without prior NC).

4. Conclusions

Data support the use of cisplatin-based combinations as NC preceding RC for patients with muscle-invasive resectable UCB. Despite the lack of robust data, high-risk patients who qualify for cisplatin may be offered AC in the absence of a trial. Future studies using the neoadjuvant paradigm and integrating biologic agents may improve the efficacy of systemic therapy and improve outcomes.

Table 1 Key randomized prospective trials of surgery alone or with neoadjuvant chemotherapy

Trial	Patients, *n*	Regimen	Survival benefit
Nordic Cystectomy I [22]	325	Cisplatin plus doxorubicin	No
Nordic Cystectomy II [23]	317	CM	No
International Collaboration of Trialists [26]	976	CMV×3	Yes
SWOG/US Intergroup [27]	317	MVAC×3	Yes

CM=cisplatin, methotrexate; CMV=cisplatin, methotrexate, vinblastine; SWOG=Southwest Oncology Group; MVAC=methotrexate, vinblastine, doxorubicin, cisplatin.

Table 4 Reported or completed randomized trials of radical cystectomy alone or followed by adjuvant chemotherapy

Institution	Patients, *n*	Regimen	Survival benefit	Completed accrual
University of Southern California [43]	91	CISCA	Yes	Yes
University of Mainz, Germany [44]	49	MVAC/MVEC	Yes	Yes
Swiss Group for Clinical Cancer Research, Switzerland [47]	77	Cisplatin	No	Yes
Stanford University [46]	55	CMV	No	Yes
US Intergroup [52]	114*	MVAC	No	No
Italian multicenter [50]	194	GC	No	No
SOGUG [51]	142	PCG	Yes	No
EORTC (NCT00028756)	242	MVAC, GC, DD-MVAC	Not reported	No

* Of 521 registered patients, 499 underwent p53 assessment, 272 (55%) were positive, and 114 (42%) were randomly assigned to MVAC versus no adjuvant therapy.

Post Cystectomy Radiotherapy

Adjuvant RT

pT3pN2M0
pT3pN0M0, R1

- Whether to treat??
- How much to treat??

No standard guidelines yet to define role of adjuvant RT

Data??

YES

LEVEL III Evidence

The Problem..

- Predominant site of failure is distant
- 20%-45% locoregional failures post cystectomy
- No well-defined role of adjuvant RT

- MRC phase III Trial (2011) reported 48% pelvic recurrence rate with or without NACT
- Canadian multicentre survey (2011) showed 48-50% rate of pelvic failure
- SWOG/U Penn (2013) 41% and 20% pelvic failure rates in high and intermediate risk groups

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Clinical Investigation

Patterns of Failure After Radical Cystectomy for pT3-4 Bladder Cancer: Implications for Adjuvant Radiation Therapy

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Methods & Materials:

Study Period – 2007-2014

334 patients, pT3-4 N0-1

Radical Cystectomy + BPLND (@ tertiary care centre)

Path: Genitourinary pathologists, as per AJCC Staging & WHO grading system

Follow-up –

- Chest & A+P Imaging – CT/MRI/PET q 3 to 6 mths for 2 years

- LF –

  Soft tissue abnormality within the pelvic soft tissue or within the pelvic nodes

  Recurrences superior to aortic bifurcation or in inguinal nodes, considered as distant metastases

Locoregional Failures (LF):

Common Iliac Nodes	Int/Ext Iliac Nodes
Obturator Nodes	Presacral Nodes
Cystectomy Bed	Pelvic Sidewall

Other – recurrences within iliac muscle and rectosigmoid nodes

Cont..

	1yr	2yr	3yr
OS	63%	43%	39%
LF	16%	28%	31%

LF – 58pts (17%)

Locoregional only – 20

Concurrent with DM - 38

Table 2 Univariate and multivariate analysis of overall survival

Variable	2-year survival rate	P*	Hazard ratio	95% CI	P†
Preoperative variables					
Sex		.872			
Male	41%				
Female	49%				
Age		.029	1.16	(0.8-1.6)	.379
<71	46%				
≥71	40%				
BMI		.564			
≤27	46%				
>27	42%				
Race		.191			
Caucasian	45%				
African American	33%				
Smoking status		<.001	3.90	(1.9-10.0)	<.001
Nonsmoker	78%				
Smoker	60%				
Unknown status	21%				
Perioperative chemotherapy		.056	1.85	(1.3-2.7)	<.001
No	39%				
Yes	47%				
BCG		.709			
No	42%				
Yes	47%				
Clinical stage		.471			
T1	51%				
T2	39%				
T3	55%				
T4	35%				
Pathologic variables					
Pathologic stage		<.001	1.79	(1.3-2.5)	.001
pT3	53%				
pT4	24%				
LN Involvement		<.001	1.84	(1.3-2.7)	.001
Negative	53%				
Positive	32%				
Histology		.517			
Urothelial carcinoma	41%				
Non-urothelial carcinoma	48%				
Carcinoma in situ		.668			
No	43%				
Yes	41%				
Multifocal		.532			
No	42%				
Yes	43%				
Surgical variables					
Margin status		.002	1.41	(1.0-2.1)	.071
Negative	48%				
Positive	33%				
Lymph nodes removed		.008	1.78	(1.1-2.8)	.022
≤12	23%				
>12	45%				

Table 3 Univariate and multivariate analyses of local-regional failure

Variable	2-year freedom from LF rate	P*	Hazard ratio	95% CI	P†
Preoperative variables					
Sex		.061	1.66	(0.9-3.5)	.131
Male	68%				
Female	82%				
Age		.164			
<71	68%				
≥71	76%				
BMI		.174			
≤27	76%				
>27	68%				
Race		.212			
Caucasian	73%				
African American	62%				
Smoking status		.279			
Nonsmoker	76%				
Smoker	75%				
Unknown	66%				
Neoadjuvant chemotherapy		.759			
No	73%				
Yes	62%				
Adjuvant chemotherapy		.552			
No	75%				
Yes	69%				
Perioperative chemotherapy		.648			
No	77%				
Yes	69%				
BCG		.278			
No	69%				
Yes	85%				
Clinical stage		.928			
T1	79%				
T2	71%				
T3	58%				
T4	72%				
Pathologic variables					
Pathologic stage		<.001	1.92	(1.1-3.4)	.033
pT3	80%				
pT4	49%				
LN involvement		<.001	2.57	(1.5-4.7)	.001
Negative	81%				
Positive	60%				
Histology		0.783			
Urothelial carcinoma	70%				
Non-urothelial carcinoma	75%				
Carcinoma in situ		0.178			
No	78%				
Yes	61%				
Multifocal		0.978			
No	74%				
Yes	69%				
Surgical Variables					
Margin Status		.017	1.36	(0.5-4.0)	.547
Negative	78%				
Positive	51%				
Serosal margins		<.001	1.67	(0.7-4.5)	.283
Negative	77%				
Positive	38%				

Results cont..

OS influenced by –

- ✓ LN involvement
- ✓ No. of nodes dissected
- ✓ Pathologic stage
- ✓ Smoking status
- ✓ Perioperative chemotherapy

LF influenced by –

- ✓ LN involvement
- ✓ Pathologic stage

Multivariate Analysis

Failure Pattern –

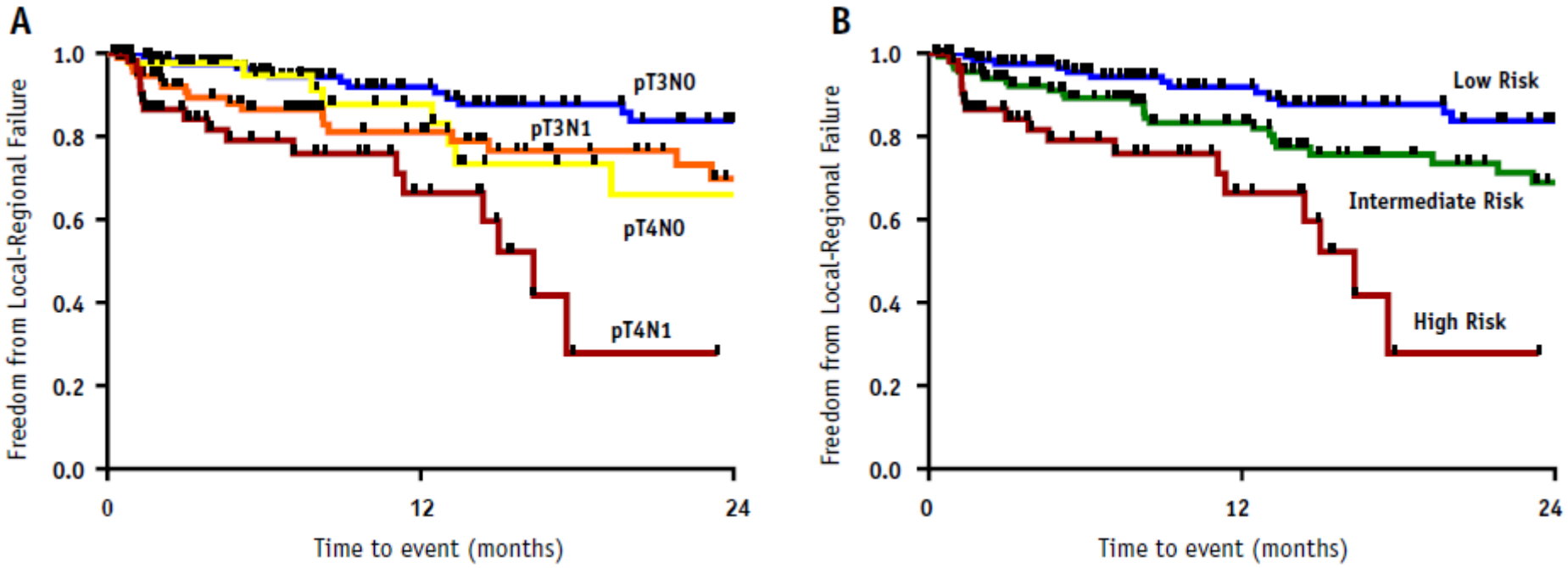
- **+ve serosal margin – high risk of failure in CI, obturator, presacral nodes**
- **LN involvement – increased failure in all nodal regions and pelvic sidewall but NOT cystectomy bed**
- **pT4 disease – high risk of failure in obturator region**

Risk Stratification –

High Risk – pT4N1

Intermediate Risk – pT4N0, pT3N1

Low Risk – pT3N0



Summary

- One-third of locoregional failures are isolated and precedes distant relapse
- Highest risk of locoregional failure in pT4 or node positive patients
- Common sites of pelvic failure are external, internal iliac & obturator nodal regions

Potential value of RT for select high risk pts

Positive node pts to be considered for RT to nodal regions only??

Ongoing trials

NRG-GU001:

Randomised Phase II Trial of postoperative Adjuvant IMRT following Cystectomy for pT3/pT4 N0-2 Urothelial Bladder cancer

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Clinical Investigation

Development and Validation of Consensus Contouring Guidelines for Adjuvant Radiation Therapy for Bladder Cancer After Radical Cystectomy

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Summary

Several organizations are developing clinical trials of adjuvant radiation therapy (RT) for bladder cancer patients at elevated risk of locoregional failure. Clinical target volumes and organs at risk for this treatment have not been defined in detail. We developed a multi-institutional, multidisciplinary, international consensus contouring guide for bladder cancer adjuvant RT. Negative-margin patients should be treated to the pelvic nodes alone, and positive-margin patients should be treated to the pelvic nodes and cystectomy bed.

Purpose: To develop multi-institutional consensus clinical target volumes (CTVs) and organs at risk (OARs) for male and female bladder cancer patients undergoing adjuvant radiation therapy (RT) in clinical trials.

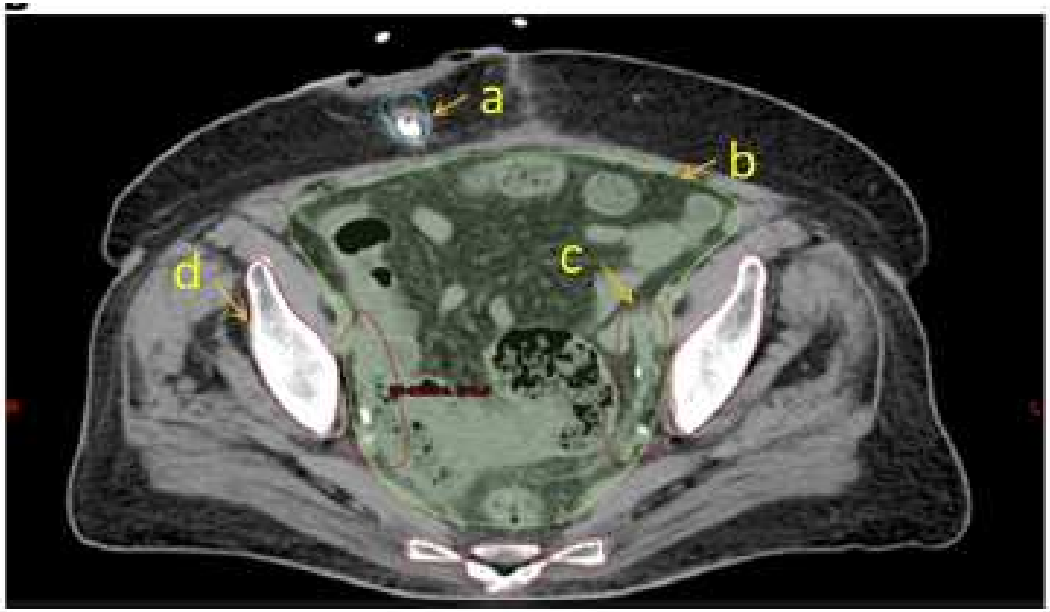
Methods and Materials: We convened a multidisciplinary group of bladder cancer specialists from 15 centers and 5 countries. Six radiation oncologists and 7 urologists participated in the development of the initial contours. The group proposed initial language for the CTVs and OARs, and each radiation oncologist contoured them on computed tomography scans of a male and female cystectomy patient with input from $\geq$1 urologist. On the basis of the initial contouring, the group updated its CTV and OAR descriptions. The cystectomy bed, the area of greatest controversy, was contoured by another 6 radiation oncologists, and the cystectomy bed contouring language was again updated. To determine whether the revised language produced consistent contours, CTVs and OARs were redrawn by 6 additional radiation oncologists. We evaluated their contours for level of agreement using the Landis-Koch interpretation of the κ statistic.

Results: The group proposed that patients at elevated risk for local-regional failure with negative margins should be treated to the pelvic nodes alone (internal/external iliac, distal common iliac, obturator, and presacral), whereas patients with positive margins should be treated to the pelvic nodes and cystectomy bed. Proposed OARs included the rectum, bowel space, bone marrow, and urinary diversion. Consensus language describing the CTVs and OARs was developed and externally validated. The revised instructions were found to produce consistent contours.

Conclusions: Consensus descriptions of CTVs and OARs were successfully developed and can be used in clinical trials of adjuvant radiation therapy for bladder cancer.

Table 2 Anatomic borders of the cystectomy bed clinical target volume to include for patients with positive margins

Superior	The contour will extend 2 cm superior to the superior aspect of the pubic symphysis.
Anterior	The contour will extend to the posterior aspect of the pubic rami/symphysis. Above and below the pubic symphysis, the contour will stop anteriorly at the planes defined by extending lines superiorly (plane 1 in Figs. 2 and 3) and inferiorly (plane 2 in Figs. 3 and 4) from the posterior aspect of the symphysis.
Posterior	The contours will abut the anterior one-third of the external ano-rectal circumference without extending into the ano-rectum. Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superiorly from the anterior border of the rectum (plane 3 in Figs. 2 and 3).
Lateral	The contour will extend to the medial border of the obturator internus muscles bilaterally. Inferior to the obturator internus muscles, the lateral border of the contour will extend to the vaginal wall or the prostate bed.
Inferior	The contour will stop 2-3 mm (1 computed tomography slice on axial images) above the penile bulb for males and 1 cm below the lower pole of the obturator foramen for females.



Thank You