An update on LDR Brachytherapy

- Alastair Law
- Consultant Clinical oncologist
- Edinburgh Cancer Centre

Introduction

Plan-talk through new papers/abstracts

1)LDR brachy as sole treatment.

2)LDR brachy in combination with EBRT.

3)LDR brachy as salvage treatment.

Comparing Treatment Results Of PROSTATE CANCER

Prostate Cancer Results Study Group 2015

Peter Grimm, DO

Prostate Cancer Center of Seattle

ABOUT THIS REVIEW STUDY

- 31,000+ prostate studies were published between 2000 and Dec. 2013
- 1,188 of those studies featured treatment results
- 252 of those met the criteria to be included in this review study. (*1st & 2nd group)
- Some treatment methods are under-represented due to failure to meet criteria

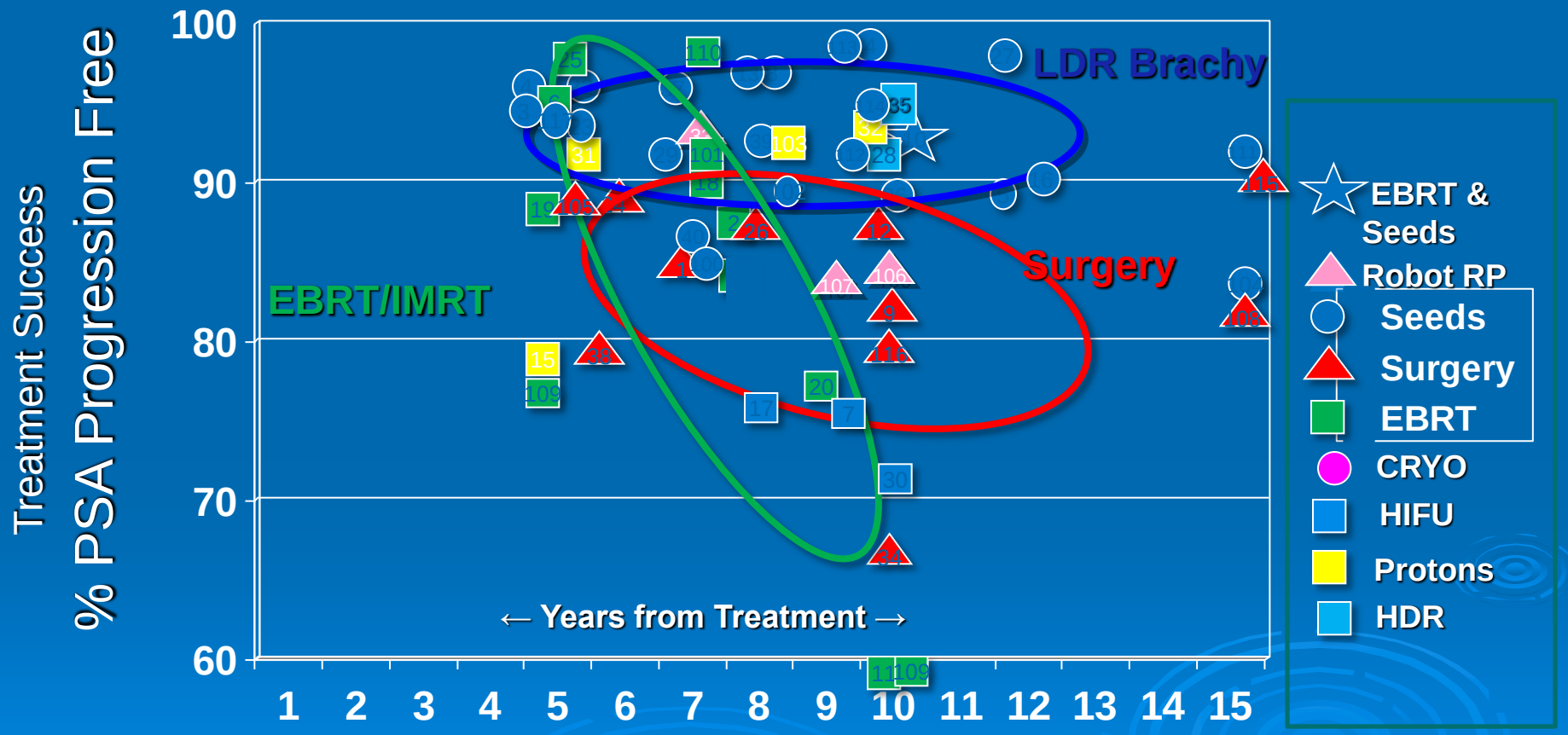
Comment about ellipses

- Treatment results for a treatment are grouped mathematically analyzed to see if the data clusters
- These "ellipses" outline the treatment results allowing you to see the average result and trend of the treatment over time
- Ellipses can only be done if there are 4 or more reported studies, so some treatments may not appear on the slides as ellipses

*Next Slide

LOW RISK RESULTS

Weighted

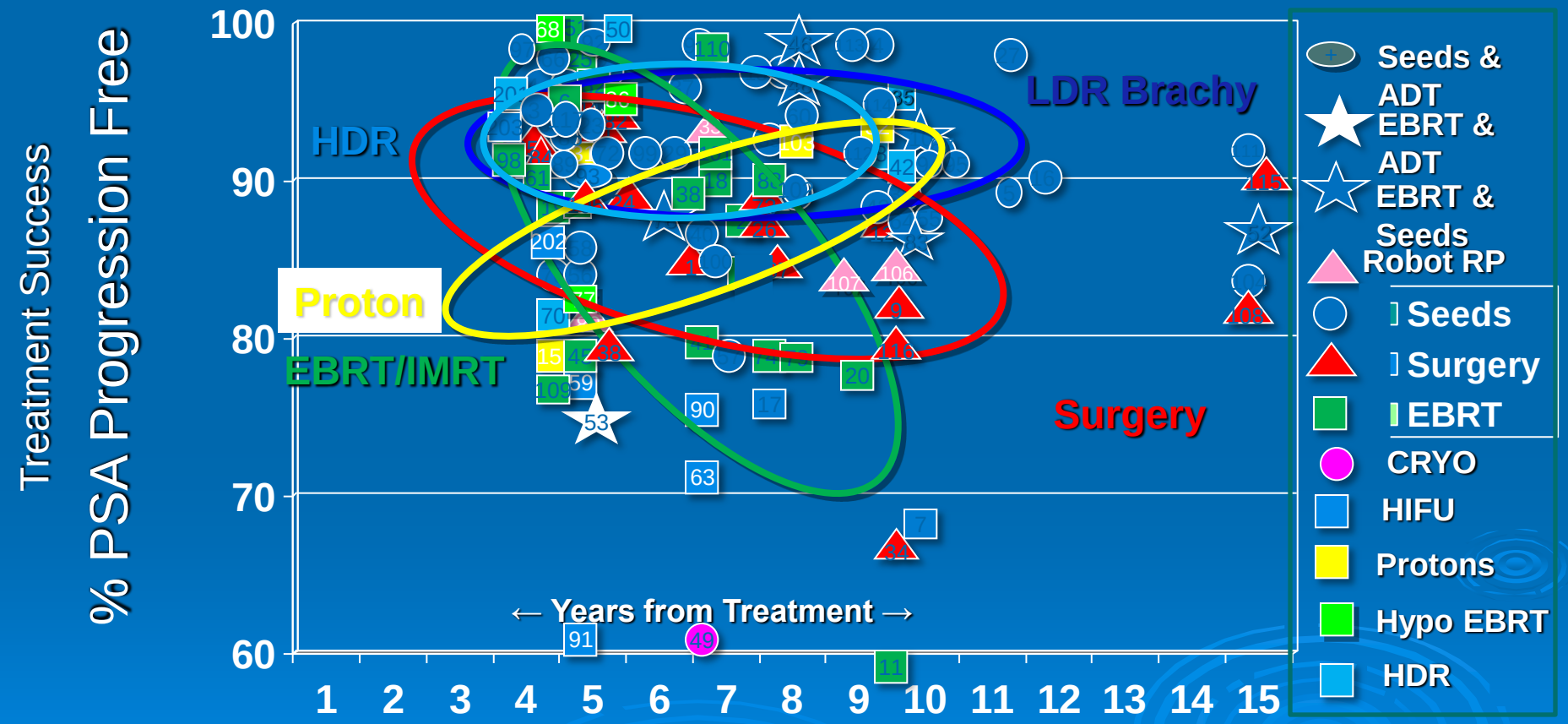


- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

LOW RISK RESULTS

Weighted

>40 months follow-up or less than 100 patients



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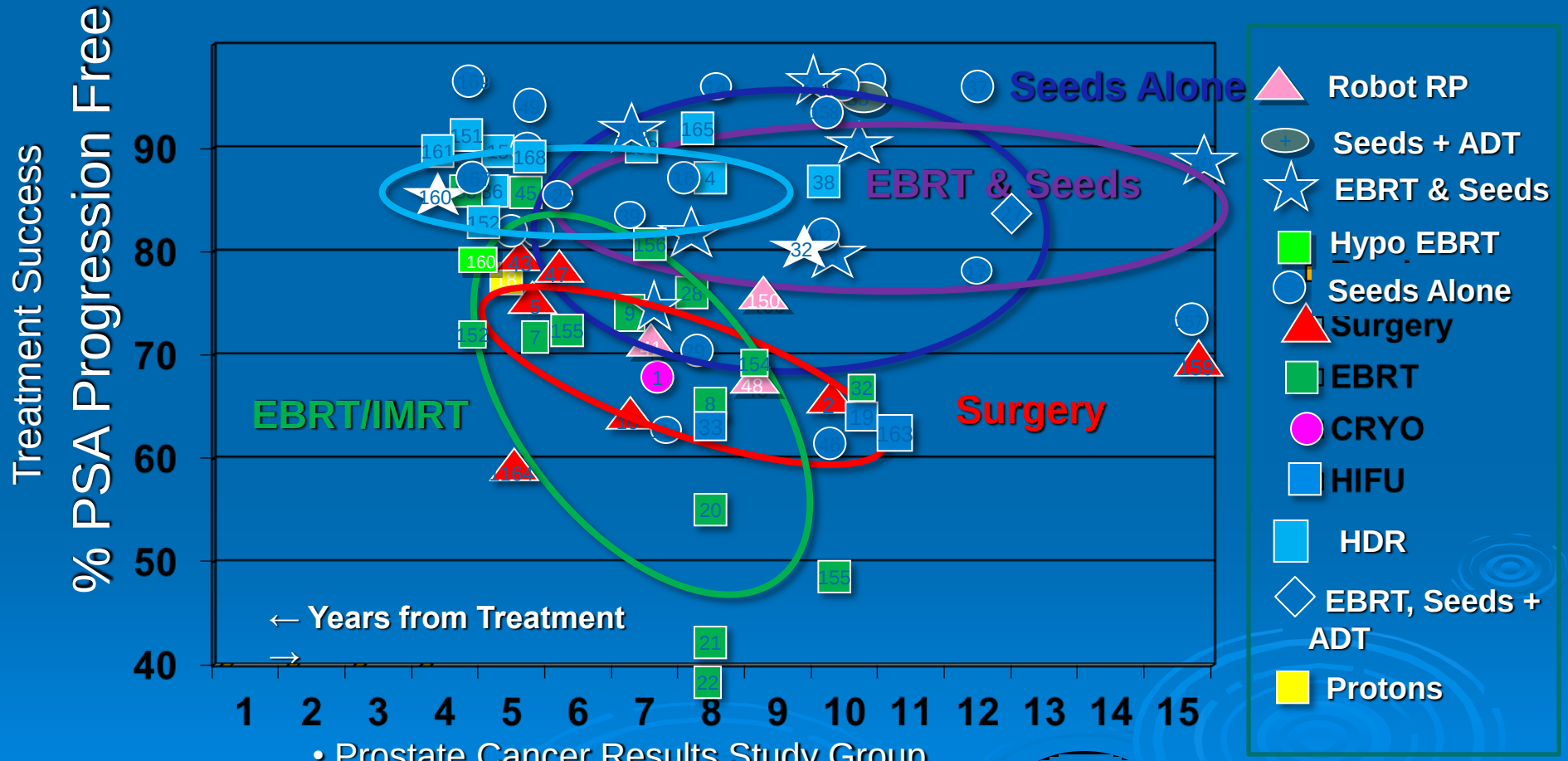
INTERMEDIATE RISK RESULTS

Weighted



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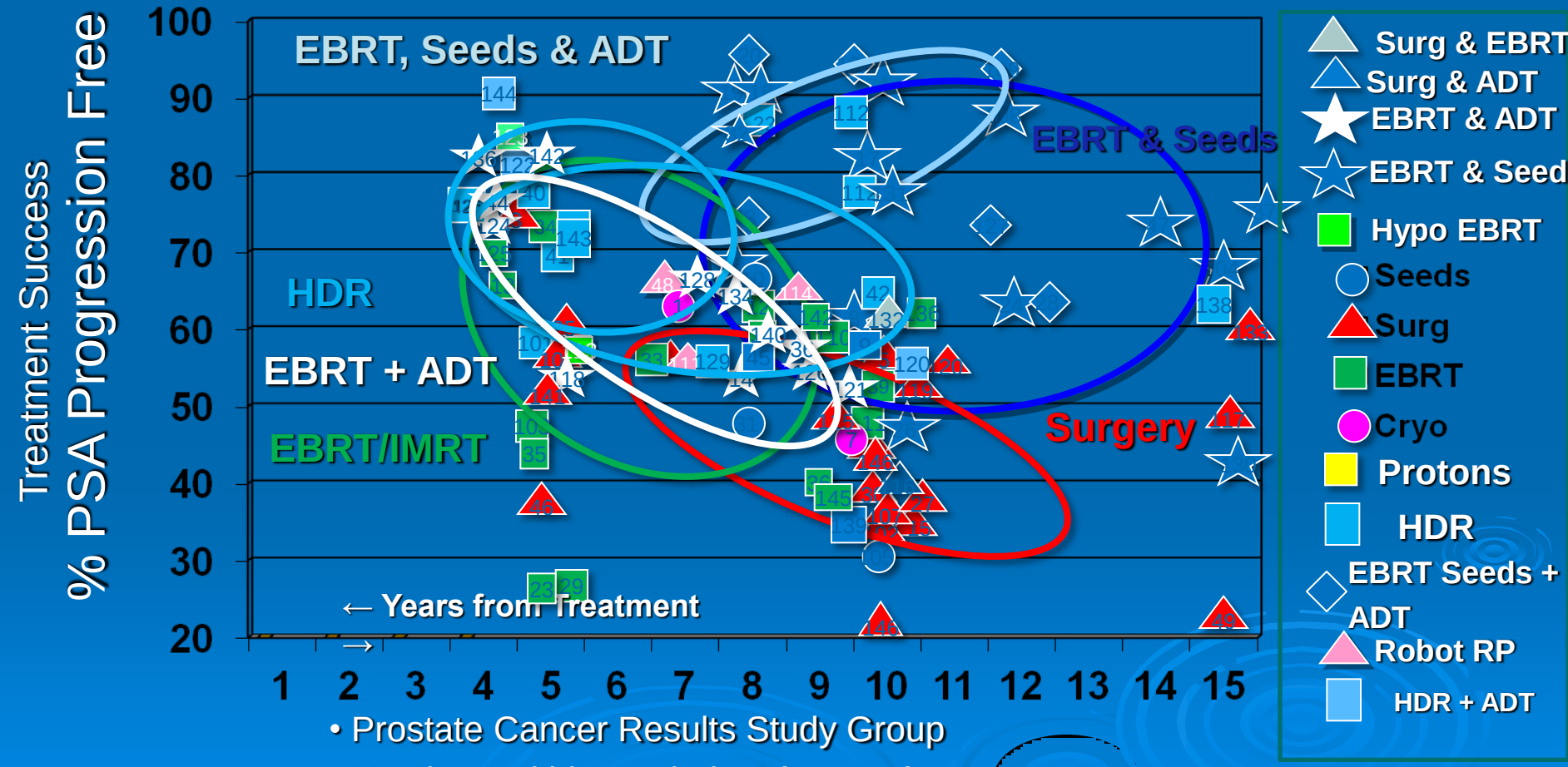
5/18/2016 Update of

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

Prostate Cancer Center of Seattle

HIGH RISK RESULTS

Weighted



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OBSERVATIONS

- For most low risk patients, most therapies will be successful.
- There appears to be a higher cancer control success rate for Brachy over EBRT and Surgery for all groups. Serious side effect rates must be considered for any treatment
- Relaxing the report selection criteria doesn't seem to impact the results substantially

What about young men?

- ASCO GU J Clin Oncol 34, 2016 (suppl 2S; abstr 121)
- Daniel Shasha et alDepartment of Radiation Oncology, Beth Israel Medical Center of Mount Sinai, New York, NY;
- **Young patients are most often recommended prostatectomy because few radiation series have reported long-term outcomes specifically for this age group.**
- **Single-institution 13-year oncologic outcomes and morbidity after I-125 prostate brachytherapy (BRT).**
- **Methods: Between 1998-2014, 227 patients < 55 years were prospectively followed after PCa treatment with BRT +/- external-beam irradiation +/- androgen deprivation.**

Brachy in under 55 (cont)

- **Results: With a minimum and median follow-up of 26 and 72.3 months, respectively the 13-year actuarial rate of BC, PCSS, and OS for low-risk disease: 97.8%, 100%, 100%, respectively;**
- **for intermediate-risk disease: 94.0%, 100%, 88.1%, respectively and**
- **for high + very-high-risk disease 83.6%, 89.9%, 77.6%, respectively. Only 3 patients died of prostate cancer.**
- **Permanent incontinence occurred only in the one patient who underwent TURP, 4 transient urethral strictures were all successfully dilated, and no other grade 3 intestinal or urinary complications were reported.**

Brachy in under 55 (cont)

- **In the 77.5 % potent at baseline, preservation was reported at 5 and 10-years overall in 75.8 % and 54.6 %, and with PDE5-I, 83.3% preserved potency at 10-years.**
- **Conclusions: Patients < 55 years achieve excellent and durable prostate cancer control at 13 years after I125 BRT, most notably in high-risk, with prostate cancer specific mortality uncommon in all but very-high-risk group.**
- **Concluded age < 55 years should not be used to discriminate against LDRBT.**

What about second cancers?

- BMJ article-compared second cancers after different treatments for prostate cancer
- Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis
- *BMJ* 2016; 352 (Published 02 March 2016

- Radiotherapy for prostate cancer was associated with higher risks of developing second malignancies of the bladder, colon, and rectum compared with patients unexposed to radiotherapy, but the reported absolute rates were low.
- Likely some bias as higher percentage of smokers, less fit people in EBRT group compared to surgery.
- However not associated with brachytherapy or from the limited data (single study) from IMRT.

Combining Brachy with EBRT- ASCENDE-RT

- **This trial compared the efficacy of EBRT and LDR-B for National Comprehensive Cancer Network (NCCN) high and intermediate-risk disease. Patients assigned to DE-EBRT (46 Gy to pelvis and prostate) then received a conformal EBRT boost (32Gy/16#) (standard arm) or LDR boost 115gy.**
- **By intent-to-treat analysis, the 3-, 5-, 7-, and 9-year Kaplan-Meier RFS estimates are 94% vs 94%, 77% vs 89%, 71% vs 86%, and 63% vs 83% for DE-EBRT and LDR-B respectively (hazard ratio = 0.473; 95% CI 0.292 – 0.765; P = 0.0022).**

- **Data awaited on metastases-free survival, time to next treatment (ie hormone treatment) survival in these groups.**
- **Would data be same if just treated prostate with EBRT rather than whole pelvis?**

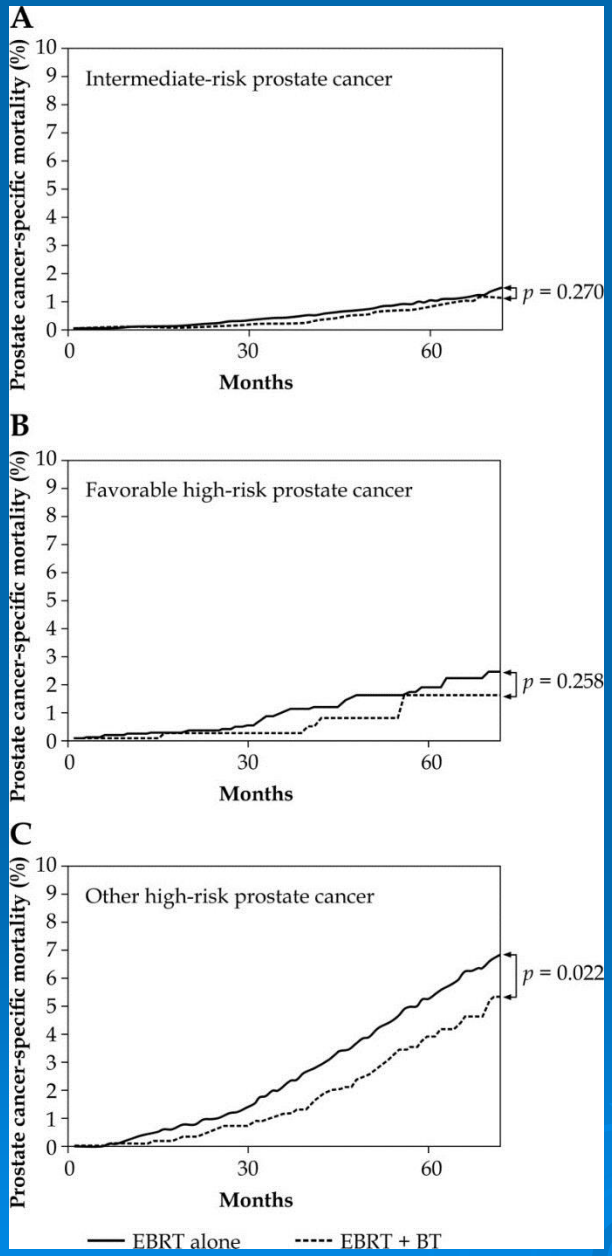
Combining Brachy with EBRT-Is there a group that benefits most?

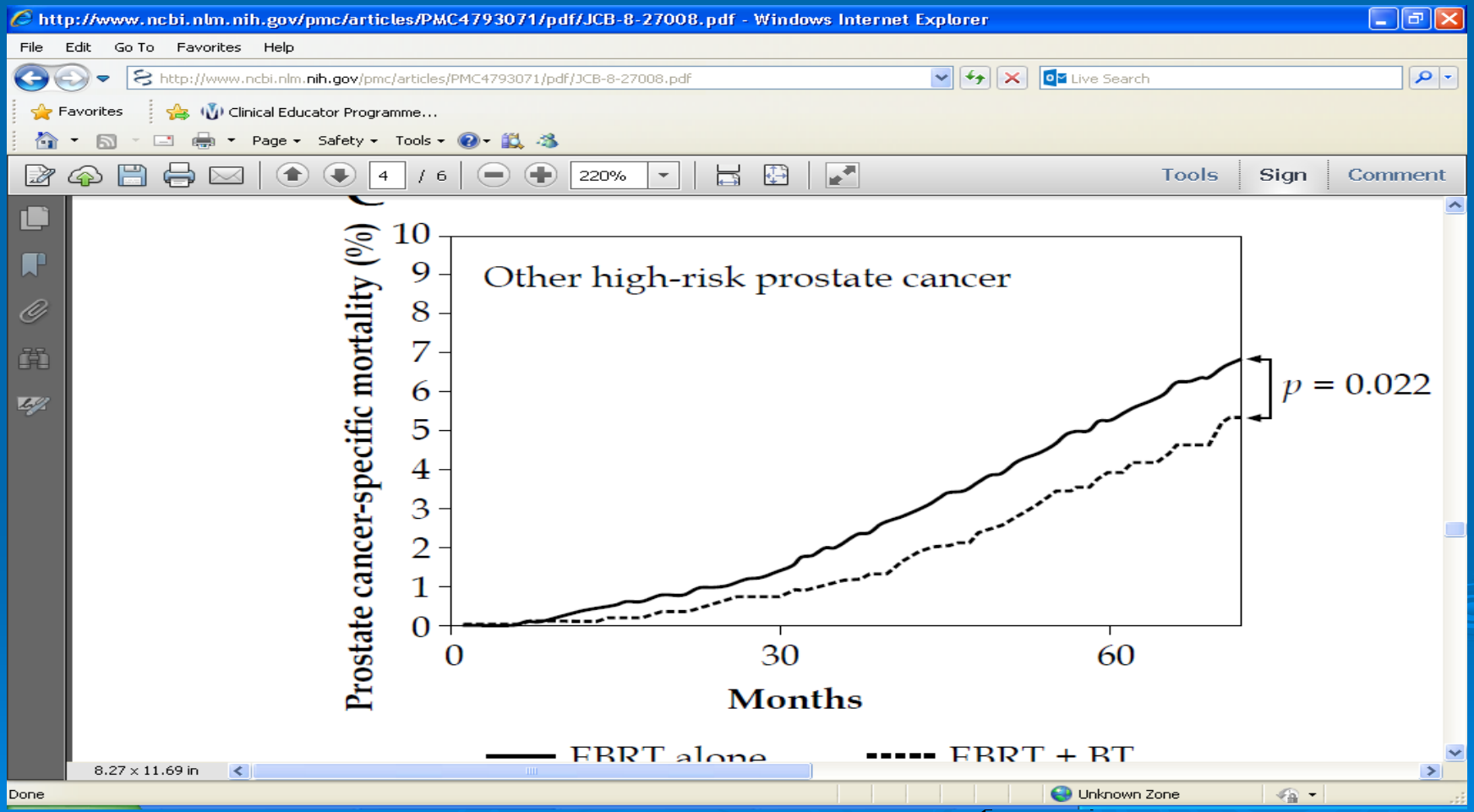
- Contemp Brachytherapy. 2016 Feb; 8(1): 1–6.
- **Brachytherapy boost and cancer-specific mortality in favorable high-risk versus other high-risk prostate cancer**
- Vinayak Muralidhar et al. Colaboration between Harvard, Annarbor and MD Anderson3

- **Purpose**
- Used a large, national cancer database to investigate whether patients with favorable high-risk prostate cancer benefit from EBRT + BT compared to EBRT alone. Recent retrospective data suggest that brachytherapy (BT) boost may confer a cancer-specific survival benefit in radiation-managed high-risk prostate cancer.
- Sought to determine whether this survival benefit would extend to the recently defined favorable high-risk subgroup of prostate cancer patients (T1c, Gleason 4 + 4 = 8, PSA < 10 ng/ml or T1c, Gleason 6, PSA > 20 ng/ml).

Brachytherapy boost and cancer-specific mortality in favorable high-risk versus other high-risk prostate cancer et al

- **Material and methods**
- Identified 45,078 patients in the Surveillance, Epidemiology, and End Results database with cT1c-T3aN0M0 intermediate- to high-risk prostate cancer diagnosed 2004-2011 treated with external beam radiation therapy (EBRT) only or EBRT plus BT.
- Multivariable competing risks regression to determine differences in the rate of prostate cancer-specific mortality (PCSM) after EBRT + BT or EBRT alone in patients with intermediate-risk, favorable high-risk, or other high-risk disease after adjusting for demographic and clinical factors.


A
Prostate cancer-specific mortality (%)
Intermediate-risk prostate cancer
p = 0.270
Months
B
Prostate cancer-specific mortality (%)
Favorable high-risk prostate cancer
p = 0.258
Months
C
Prostate cancer-specific mortality (%)
Other high-risk prostate cancer
p = 0.022
Months
EBRT alone
EBRT + BT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Live Search
Favorites
Clinical Educator Programme...
Page Safety Tools
4 / 6
220%
Tools Sign Comment
Other high-risk prostate cancer
Prostate cancer-specific mortality (%)
10
9
8
7
6
5
4
3
2
1
0
0
30
60
Months
p = 0.022
EBRT alone
EBRT + BT
8.27 x 11.69 in
Done
Unknown Zone

Combining Brachy with EBRT-Is there a group that benefits most?(cont)

- **Results**
- EBRT + BT was not associated with an improvement in 5-year PCSM compared to EBRT alone among patients with favorable high-risk disease (1.6% vs. 1.8%;, and intermediate-risk disease (0.8% vs. 1.0%, AHR: 0.83, 95% CI: 0.59-1.16, *p* = 0.270).
- Others with high-risk disease had significantly lower 5-year PCSM when treated with EBRT + BT compared with EBRT alone (3.9% vs. 5.3%; AHR: 0.73; 95% CI: 0.55-0.95; *p* = 0.022).
- **Conclusions**
- Brachytherapy boost is associated with a decreased rate of PCSM in some men with high-risk prostate cancer but not among patients with favorable high-risk disease.
- Results suggest that the recently-defined “favorable high-risk” category may be used to personalize therapy for men with high-risk disease.

- Interesting as might expect the highest risk men to gain less from addition of EBRT due to the higher prevalence of micro mets at presentation.

- Factors such as the use of high-dose-rate (HDR) versus low-dose-rate (LDR) BT,seed type, dose of radiotherapy, quality of radiation therapy,he specifics regarding EBRT or BT technique, receipt of hormone therapy, or bulk of disease (e.g. number of cores positive and percentage of core involvement), are not available in the SEER database.

- It is possible that did not find a benefit to BT boost among favorable high-risk patients due to a lack of power or due to the relatively short median follow-up of 3.6 years. However, subgroup had a large number (*n* = 2,785) of patients.

- Where does the role of docetaxol chemo fit in for locally advanced high risk disease? No survival benefit shown at present in Stampede but will report longer-term follow-up in due course, but note that estimates of the treatment effect in failure-free survival and prostate-cancer-specific survival are extremely similar for patients with and without metastases at presentation.

Comparing Side Effects between treatment with after low dose rate BT (LDR) and high dose rate BT (HDR) as well as LDR+EBRT and HDR+EBRT

- 2016 ASCO Genitourinary Cancers Symposium
- Jonathan D. Tward, Stephanie Jarosek,et al;
- Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

- Background: objective was to compare the incidence of late UAEs after low dose rate BT (LDR) and high dose rate BT (HDR) as well as LDR+EBRT and HDR+EBRT.

- Methods: Identified men treated with LDR (n=12,801), HDR (n=685), LDR+EBRT (8,518) and HDR+EBRT (n=2,392) from the SEER-Medicare Database. The populations were balanced by propensity weighting and the Kaplan-Meier incidence of severe UAEs was compared.
- Propensity-weighted Cox proportional hazards models were used to compare the adjusted hazard of UAEs. These UAEs were compared to a cohort of men not treated for prostate cancer.

- **Results:** Median follow-up was 4.3 years. At 8 years, the propensity weighted cumulative UAE incidence was highest after HDR+EBRT (28%) and lowest after LDR (17%; see Figure).
- The absolute excess risk over non-treated controls of a UAE at 8 years was 1.9%, 3.8%, 8.4% and 12.9% for the LDR, HDR, LDR + EBRT, and HDR + EBRT respectively. This translates into a number needed to harm of 53, 26, 12, and 8 persons.

Conclusions: LDR and HDR brachytherapy are statistically indistinguishable for late severe urinary adverse events.

However, combination radiotherapy (either HDR+EBRT or LDR+EBRT) increases the risk of severe UAEs compared to HDR alone or LDR alone.
In the 8 years following brachytherapy treatment, the increased risk of urinary toxicity occurs almost exclusively within the 2 years following therapy, and then declines to a baseline hazard.

The hypothesis that late urinary radiation toxicity accelerates over time is not supported by this study

LDR alone vs LDR and EBRT

- *Journal of Clinical Oncology*, 2016 Genitourinary Cancers Symposium (January 7-9, 2016). **Comparative study of late rectal toxicity in veterans undergoing low-dose rate prostate brachytherapy treated with or without supplemental external beam radiotherapy.**
- **Nicholas A Serrano et al** Department of Radiation Oncology, Virginia Commonwealth University Richmond, VA
- **Background:** Supplemental external beam radiation therapy (sEBRT) is often prescribed in men undergoing low dose rate (LDR) brachytherapy for prostate cancer. A population of patients was analyzed to assess the effect of sEBRT on late rectal toxicity.

LDr alone vs LDr and EBRT (cont)

- **Methods:** This retrospective cohort study examined LDR brachytherapy patients, treated with or without sEBRT, with a minimum of 5 years follow-up. Longitudinal assessments were evaluated using the Computerized Patient Record System, and toxicities were coded using the CTCAE v4.0.
  Results: Median follow-up was 7.5 years for 245 consecutive patients from 2004 and 2007. sEBRT was administered to 33.5%. Follow-up beyond 5 years was available for 89%.
- Overall rates of grade 2 and 3 rectal toxicities were 6.9% and 2.9%, respectively. The risk of grade 2 rectal toxicity was 2.8-fold higher for patients receiving sEBRT (1.1 - 7.2, 95% CI, p = 0.02).

LDr alone vs LDr and EBRT(cont)

- The risk of grade 3 rectal toxicity was 11.9-fold higher for patients who received sEBRT (1.5 - 97.4, 95% CI, p = 0.003).
- Six out of 7 patients with a grade 3 rectal toxicity received sEBRT, including one who required an abdomino perineal resection due to radiation proctopathy.
- **Conclusions:** In a cohort of LDR brachytherapy patients with high rates of follow-up, sEBRT+LDR was associated with significantly higher risk of grade 2 and 3 late rectal toxicity. This analysis supports previous findings and maintains concern about the supplemental use of EBRT with LDR brachytherapy while its benefit for tumor control has yet to be prospectively validated.

Salvage Brachytherapy

- **Background**
- **Increasing number of case series showing encouraging results from use of brachytherapy after local recurrences after prostate radiotherapy.**
- **Questions remain on which patients benefit most and whether whole or focal brachytherpay can be used.**

Salvage brachytherapy for locally recurrent prostate cancer after radiotherapy

- Journal of Clinical Oncology, 2016 Genitourinary Cancers Symposium (January 7-9, 2016).
- **Marisa Kollmeier, Niyati Harneja, Mary Lin, Sean Matthew McBride and Michael J. Zelefsky**
- Memorial Sloan Kettering Cancer Center, New York, NY
- **Background:** To report the toxicity and outcomes of patients undergoing salvage brachytherapy for locally recurrent prostate cancer.
- **Methods:** Between 4/03 and 4/15, 98 patients with biopsy-proven locally recurrent prostate cancer underwent low dose rate (LDR-125Gy) (n=37) or high dose rate (HDR-32Gy in 4 fractions) (n=61) brachytherapy. The median PSA at relapse was 2.57ng/mL (range 0.43-13.5) with median time to relapse was 6 years (range 0.96-14.4y).
- Gleason score at relapse was upgraded from initial Gleason score in 67 patients (70%) with 38 patients graded 8 at relapse. 44 patients also received hormone therapy (median duration of 17.3 months) pre and post-salvage brachytherapy.

Salvage brachytherapy for locally recurrent prostate cancer following definitive radiation therapy (cont).

Marisa Kollmeieret al Memorial Sloan Kettering Cancer Center, New York, NY

- **Results:** Median followup is 31 months (range 1-101 mos). Median peak IPSS score was 19 with a median time to peak IPSS of 4 mos. Overall, mean change in IPSS from baseline was +2.4.
- Acute grade 3 GU and GI toxicity occurred in 6% and 0%, respectively. Late grade 3 GU and GI toxicity occurred in 6% and 4%, respectively.
- Six patients (6%) developed late urethral strictures requiring intervention, 3 of whom developed subsequent urinary incontinence.

Salvage brachytherapy for locally recurrent prostate cancer following definitive radiation therapy (cont).

Marisa Kollmeieret al Memorial Sloan Kettering Cancer Center, New York, NY

- Urinary incontinence requiring pads occurred in 16% (16/98). Rectal bleeding was the most common late GI toxicity (14%); however only 2 patients required intervention.
- PSA relapse occurred in 26/98 (27%) patients and 14/98 (14%) developed distant metastasis during the followup period. The 3 year PSA RFS, DMFS and OS was 70.1%, 92%, and 90.5%, respectively.

- **Conclusions:** Salvage brachytherapy is curative for a significant proportion of patients with locally recurrent prostate cancer following radiation therapy. Urinary symptoms peak at 4 months post-brachytherapy. The rate of moderate to severe GU or GI toxicity is 5-15%. Further efforts to reduce toxicity including focal approaches

Review of Salvage Treatment incl Brachytherapy

- **Review in March 2016 from Holland looked at the evidence from focal salvage treatments including cryotherapy, brachytherapy and hifu.**
- **Authors Da Smit et al World Journal of Urology 2016**

- **Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review**

Review of salvage treatment post Rt failure

- The aim of this review was to evaluate current literature to assess whether focal salvage leads to a comparable or favourable recurrence rate and less toxicity compared to whole-gland salvage.
- A literature search was performed using PubMed, Embase and the Cochrane Library. A total of 3015 articles were screened and assessed for quality.
- Eight papers [on focal cryoablation (*n* = 3), brachytherapy (*n* = 3) and high-intensity focused ultrasound (*n* = 2)] were used to report outcomes.

- **Results**
- One-, 2-, 3- and 5-year biochemical disease-free survival (BDFS) ranges for focal salvage are, respectively, 69–100, 49–100, 50–91 and 46.5–54.5 %.
- Severe genitourinary, gastrointestinal and sexual function toxicity rates are 0–33.3 %.
- **Conclusion**
- Provisional data suggest that BDFS rates of focal salvage are in line with those of whole-gland approaches. There is evidence that focal salvage could decrease severe toxicity and preserve erectile function.

And Finally

- Brachytherapy **March–April, 2016**Volume 15, Issue 2, Pages 156–162
- **Abstract**
- **Purpose**
- To determine the impact of fellow, resident, or medical student (MS) involvement on outcomes in patients undergoing permanent 125I prostate seed implant.
- . Cases were stratified according to resident, fellow, MS, or attending involvement. Outcomes were compared using analysis of variance, logistic regression, and log rank tests.

- **Results**
- A total of 291 patients were evaluated. Fellows, residents, and MS were involved in 47 (16.2%), 231 (79.4%), and 34 (11.7%) cases, respectively.
- Thirteen (4.4%) cases were completed by an attending physician alone. There was no difference in freedom from biochemical failure when comparing the resident, fellow, or attending alone groups (p = 0.10).
- There was no difference in *V*100 and *D*90 (volume of the prostate receiving 100% of the prescription dose) outcomes when comparing resident cases to fellow cases (p = 0.72) or attending alone cases (p = 0.78). T
- When examining treatment toxicity, fellow cases had higher rates of acute Grade 2 + GU toxicity (p = 0.028).
- **Conclusions**
- Interstitial prostate seed implants can be safely performed by trainees with appropriate supervision. Hands-on brachytherapy training is effective and feasible for trainees.

- Would this paper had been published if a difference had been shown?!
- Gives opportunity?