

Treatment Of High Risk Prostate Cancer The Role of Surgery

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Financial Disclosure

- I have no significant relationships to disclose

High-Risk Prostate Cancer The Case for a Radiation-Based Approach

- Mature prospectively gathered data
- RCT proof that lives are saved by EBRT
- RCT proof that higher radiation dose superior
- RCT evidence that addition of ADT improves outcomes for higher risk patients

Adjuvant ADT improves disease control and survival for high risk cancer compared to conventional dose (70Gy) XRT alone (Bolla et al, Lancet 2002)

Randomized trial of men with T1-2 G3 or T3-4 showed

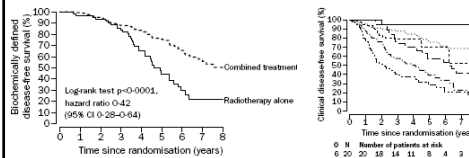


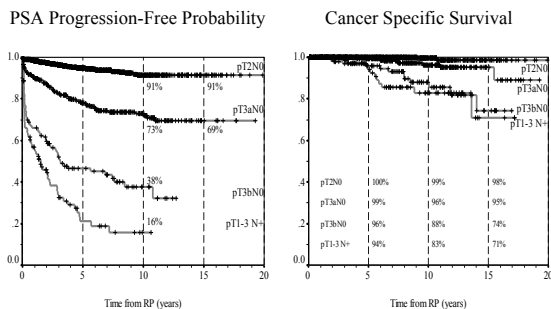
Figure 3: Kaplan-Meier estimates of the biochemically defined disease-free survival

Number of failures: N=number of patients.

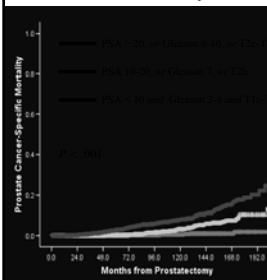
Figure 5: Clinical disease-free survival by risk category and treatment group

Number of failures: N=number of patients.

Long Term Results of RP by Pathological Stage (MSK series)



Risk of death from prostate cancer by AUA Risk Group*



Risk Group	Pts	PCa Death	15-yr PCSM
High	1816 (19%)	108 (79%)	19%
Intermediate	3327 (35%)	10 (7%)	10%
Low	4338 (46%)	19 (14%)	2%

Majority of deaths were among high risk group, but the risk of death from PCa (19%) was still less than from other causes (31%).

Stephenson A et al. JCO 2009; 27:4300.
*AUA Prostate Cancer Guidelines, 2008

Distant Metastases and Death from Prostate Cancer after Radical Prostatectomy or Radiotherapy:

A Comparison of Clinical Cohorts Adjusted for Case Mix
(J Clin Oncol 2010; 28(9):1508-13)

Michael J. Zelefsky, James A. Eastham, Angel M. Cronin,
Zvi Fuks, Zhigang Zhang, Yoshiya Yamada,
Andrew Vickers and Peter T. Scardino

Methods

- 2380 consecutive patients, 1993-2002, cT1c – T3b.
- Treated by 2 experienced surgeons or 3 radiation oncologists (“best practice”);
- Matched for stage, grade, PSA, age, year of treatment
- Open RP (n=1318)
 - Complete PLND, no frozen sections; no neoadjuvant ADT
- XRT (≥ 81 Gy) to prostate only (n=1062)
 - 56% treated with 3-6 months of neoadjuvant ADT
- Median follow up for those alive without metastases was 5.1 years after RP and 5.0 years after XRT
- Endpoints: development of metastases, death from prostate cancer at 8 years

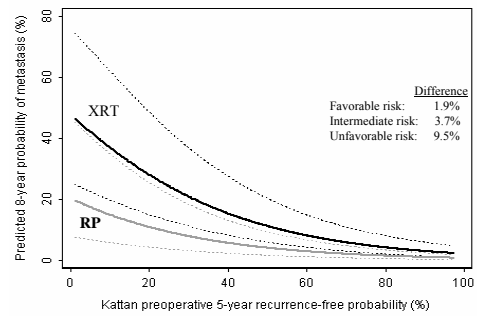
Zelefsky M et al, JCO 2010; 28(9):1508-13

Metastasis after RP or EBRT

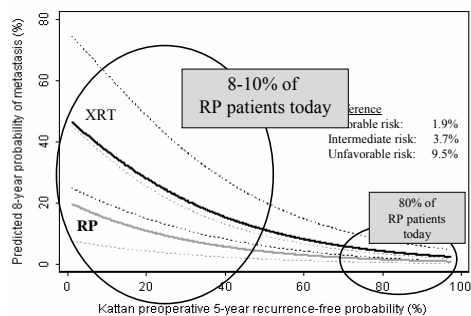
- The 8-year probability of freedom from mets:
 - 97% (95% CI: 95%, 98%) for RP
 - 93% (95% CI: 90%, 95%) for EBRT.
- After adjustment for case mix, surgery was associated with a reduced risk of metastasis (HR: 0.35; 95% CI: 0.19, 0.64; $p < 0.001$)
- Results were similar for prostate cancer-specific mortality (HR: 0.32; CI: 0.13, 0.80; $p = 0.01$).

Zelefsky M et al, JCO 2010; 28(9):1508-13

Probability of Freedom from Metastasis at 8 years
Adjusted for nomogram predicted 5 year freedom from biochemical recurrence



Probability of Freedom from Metastasis at 8 years
Adjusted for nomogram predicted 5 year freedom from biochemical recurrence



Unadjusted Probability of Prostate Cancer-Specific Death According to NCCN Risk Group

NCCN Risk	No. pts	No. events	8-year XRT		8-year RP	
			%	95% CI	%	95% CI
Low	952	1	0.0	0	0.0	0
Intermediate	1019	10	4.5	1.8-10.8	1.9	0.5-6.5
High	409	19	9.5	4.5-17.9	3.8	1.2-11.5

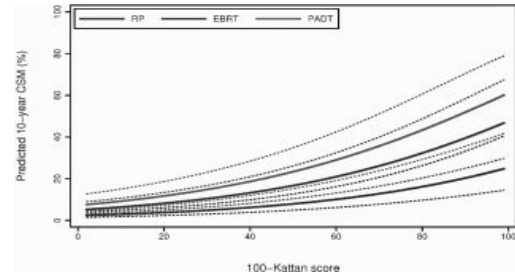
8-years after treatment for NCCN high-risk CaP, the likelihood of dying from prostate cancer was more than double if radiation was used rather than surgery

Metastasis after RP or EBRT Conclusion

- Metastatic progression is infrequent in men with low-risk prostate cancer treated with either RP or EBRT
- Patients with higher risk disease treated with RP have a lower risk of metastatic progression and prostate cancer-specific death than men treated with EBRT

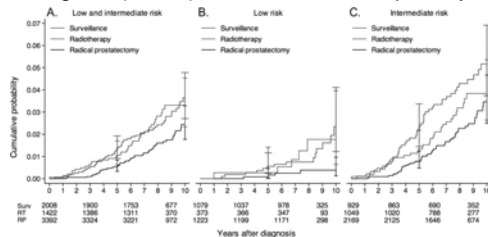
Zelevsky M et al, JCO: 28(9): 1508-13

Predicted 10-year prostate cancer-specific mortality (CSM) after RP, EBRT, and PADT



Cooperberg et al. Cancer 2010; 116:5226

Prostate cancer-specific mortality for patients who were treated with surveillance, radiation therapy, or radical prostatectomy in the National Prostate Cancer Register (NPCR) of Sweden Follow-up Study



Stattin P et al. JNCI 2010;102:950-958

Comparative series evaluating oncologic outcomes following RRP versus RT for prostate cancer

Study	No. Patients RP	XRT	Median FU (yr) RP	XRT	Outcome (RP vs XRT)
Liu [2008] SEER data	2567	2006	11		10-yr cancer-specific survival: 98% vs 94%
Zelevsky [2010] MSKCC data	1318	1062	5.1	5.0	8-year metastasis-free survival: 97% vs 93%
Cooperberg [2010] CaPSURE data	5066	1143	3.9	4.5	HR for prostate cancer death 2.2 after RT vs RP
Boorjian [2011] Mayo Clinic/FCCC	1238	265 (RT) 344(+ADT)	10.2	6.0 7.3	10-yr overall survival: 77% vs 67% (+ADT) vs 52% (RT)
Abdollah [2011] SEER data	160787	149967	5.0	4.9	10-yr cancer-specific mortality: 3.6 vs 6.5%

Clinically Localized High-Risk CaP Conclusion

- RP is at least equivalent to radiation therapy in preventing metastasis and death from prostate cancer in men with high-risk disease
- There is no rationale for excluding such men from surgical consideration

Secondary Treatment

- RP (n=1318)
 - 79 (6%) received postop radiation (20 adjuvant and 59 salvage)
 - 141 (10.8%) developed BCR and 107 of these were treated.
- XRT (n=1062)
 - No post-radiation adjuvant hormone therapy
 - 207 (19.5%) developed BCR and 92 (8.7% of total) received hormones
 - Only 4 (0.4%) had salvage RP.

Salvage therapy was initiated at a median of 13 months after RP and 69 months after XRT.

Zelevsky M et al, JCO 2010; 28(9):1508-13

Radiation Induces Gene Fusions

- *In vitro* studies: LNCaP prostate cancer cell line
 - Androgen sensitive
 - Lack *TMPRSS2-ERG* fusion
- Treatment with DHT induced gene fusions
 - Gene fusion not seen in DU145-lack AR
- LNCaP cells treated with DHT and radiation
 - 1 Gy: 2.3% of clones had the gene fusion
 - 3 Gy: 25% of clones had the gene fusion

Mani R-S et al. Science 326: 1230, 2009

Radiation Induces Gene Fusions

- LNCaP cells treated with either DHT or XRT
 - *TMPRSS2-ERGb* fusions induced
 - All 8 isoforms of the gene fusion were identified
 - In the same proportion seen in human tissues
 - 1 event in 10,000 cells
 - DNA breaks are not random
 - Specific patterns of translocations are selected

Lin C et al. Cell 139: 1069-1083, 2009

Conclusions

- Expanding role of RP in high-risk patients
 - High-risk patients more suitable for surgery than in the past
 - Surgery is feasible/successful in high-risk prostate cancer
 - Surgery provides oncologic outcomes similar to or better than other treatment options
- Adjuvant/salvage RT is a viable option with less impact on QOL than salvage treatments after primary RT
- Local therapy alone is often inadequate for patients with high-risk prostate cancer
 - Role of systemic therapy combined with surgery is under investigation