Surgery for High Risk Prostate Cancer

Dr Jeremy Grummet
Clinical Uro-Oncology Fellow
Vancouver General Hospital

Where I'm From

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What the…?

Outline

- What exactly is high risk clinically localised CaP?
- How is it currently managed?
- What is the literature on surgery for high risk CaP?
- What have we found here at VGH?
- Why should we re-think our treatment options for these patients?
- What do we need to improve our management and what might the future hold?

Definition

- Biopsy proven CaP
- No evidence of metastases
- High probability of recurrence despite definitive local monotherapy
- But how is this determined?

Definition

- Baseline PSA, clinical stage, biopsy GS chiefly used to determine relapse risk
- Also PSA velocity, percentage of positive biopsy cores
- Multiple stratification methods used – problem 1
- D'Amico definition (PSA >=20, or >=cT2c, or biopsy GS >=8) probably most recognised, used in current AUA CaP guidelines, several others used
- Each parameter predicts poorly - problem 2
  - PSA varies with BPH, inflammation, differentiation of CaP
  - Clinical stage highly subjective, notoriously inaccurate
  - Biopsy GS often downgraded in RP specimen

Definition

Radical Prostatectomy for Clinically Localized, High Risk Prostate Cancer: Critical Analysis of Risk Assessment Methods

Ofer Yossepowitch, Scott E. Eggener, Fernando J. Bianco, Jr., Brett S. Carver, Angel Serio, Peter T. Scardino and James A. Eastham*

From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

- To address problem, MSKCC group analysed rates of PSA recurrence by 8 definitions (J Urol Aug 2007)
- Examined data from 4708 patients undergoing RP alone
- Concluded PSA recurrence significantly greater than non-high risk patients by all definitions
- But, risk varies greatly depending on definition used
- 5 year PSA relapse-free probability 50-80%
- Also found D'Amico definition associated with low PSA recurrence - appropriate?

Definition

- Definitions with highest PSA recurrence rates after surgery alone
  - Nat Comprehensive Ca Network (NCCN)
    - PSA >20, or cT3, or biopsy GS >=8
    - Used in our analysis at VGH
  - Kattan nomogram 5 year PFP 50% or less
    - Using PSA, clinical stage, biopsy GS
- Authors argue for use of continuous multivariable models (nomograms) as best risk stratification tool, but where to set threshold?
  - If too stringent, may miss some patients with occult mets, precluding from multimodal therapy trials
  - If too loose, patients who actually have organ confined disease may forego curative therapy, or undergo multimodal therapy unnecessarily

Definition

- Study weaknesses
  - Selection bias: RP cohort, likely selected smaller cT3, smaller volume disease -> may not represent all high risk patients
  - Only assessed PSA recurrence, not more clinically relevant met-free and cancer-specific survival

Definition - Summary

- Standard criteria for definition of high risk localised CaP yet to be determined
  - Multiple definitions -> heterogeneous groups of patients in literature with highly variable PSA recurrence rate
  - Nomograms may offer most accurate risk stratification
    - May need to incorporate more variables
    - Cut point undecided
- Even if single definition accepted, using current parameters, high risk patients will remain heterogeneous group
- Implication: whilst most high risk patients will fail monotherapy, many won't fail

Population

- CaPSURE data, using D'Amico definition, 15% of CaP pts are high risk (from 41% in 1990)
- Of these, majority are GS >=8 (62%)
- 22% >=cT2c
- 16% PSA >20

Current Management

- SEER cancer registry 1995-2001 (Denberg et al, BJU Aug 2006)
  - 3382 men with cT3
  - 12.3% underwent RP, 53.2% received XRT, 34.5% had ADT or WW but no local therapy
  - Even age <55, only 30% had RP
- Over study period
  - Local therapy increased by 11% (58% to 69%) i.e. in 2001, 31% had no local therapy, 23% were age <70
  - EBRT up 20% (40% to 60%)
  - RP halved (18% to 9%)

Current Management

- Rate of local therapy increasing, but all XRT
- RP decreasing
- Nearly ¼ pts who may be eligible for local therapy were not receiving it
- Why?
  - Optimal management is unknown
  - High risk of recurrence with monotherapy + concern re morbidity of local therapy leads clinicians to be nihilistic -> ADT, WW
  - Clinicians feel need to do something in face of aggressive cancer, but want to avoid surgery (high positive margin rate, ?morbidity) -> XRT

Current Management

- WW
  - Natural history of high risk CaP is very high chance of disease progression and/or death (Connecticut tumour registry)
  - Not appropriate unless pt has short life expectancy due to competing co-morbidities or refuses to accept risks of treatment morbidity
- ADT
  - May defer disease progression and prolong survival but must balance against complications of long-term therapy
  - Not curative

XRT + ADT

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial

Michel Bolla, Laurence Collette, Léo Blank, Padraig Warde, Jean Bernard Dubois, René-Olivier Mirimanoff, Guy Storme, Jacques Bernier, Abraham Kuten, Cora Sternberg, Johan Mattelaer, José Lopez Torecilla, J Rafael Pfeffer, Carmel Lino Cutajar, Alfredo Zurlo, Marianne Pierart

- Lancet July 2002
- RCT comparing XRT alone vs XRT + 3 yrs ADT in high risk pts
  - >=cT3 or GS 7-10 (91% >=cT3)
  - 412 pts, 1987-95, median age 71, median follow-up 5.5 yrs
  - PSA recurrence defined as >1.5 and increasing on 2 consecutive measures
  - Found XRT + ADT significantly better clinical disease-free and overall survival

XRT + ADT

- Combined arm bNED survival 76% at 5 yrs
  - Of 203 receiving XRT + ADT, only 1/2 had T assessed
  - Only 80% of those had T above castrate levels
- Clinical disease-free survival 74%
- Overall survival 78%
- Cancer-specific survival 95%

Surgery

Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome

JOHN F. WARD, JEFFREY M. SLEZAK*, MICHAEL L. BLUTE†, ERIK J. BERGSTRALH* and HORST ZINCKE†
*Division of Urology, Naval Medical Center, Portsmouth, VA, *Division of Biostatistics, and †Department of Urology, Mayo Clinic, Rochester, MN, USA*

- Largest cohort from Mayo Clinic, BJU 2005
- Retrospective study of pts undergoing RP for cT3 CaP
  - 842 pts, 1987-97, median age 66, median follow-up 10.3 yrs
  - PSA recurrence defined as PSA >=0.4

Surgery

- 23% received NHT; of 661 men without NHT, 27% had pT2 CaP
- Adjuvant therapy defined as commencing <90 days after RP
  - XRT 16%
  - ADT 51%
- Complication rates similar to cT2 pts assessed over same period
- bNED survival 58% at 5 yrs (cf 76% Bolla), no mention of T levels

Surgery

- Clinical disease-free survival 85% (cf 74% Bolla)
- Overall survival 90% (cf 78% Bolla)
- Cancer-specific survival 95% at 5 yrs
- CDF survival most meaningful for comparison at 5 yrs
  - Expect CSS to remain high after short time
  - bNED survival hampered by ADT

Surgery

- At 15 yrs
  - bNED survival 38%
  - Overall survival 53%
  - Cancer-specific survival 79%
- Study weaknesses
  - Retrospective analysis and tertiary referral -> not representative of all cT3 cancers
  - Uncontrolled for neoadjuvant and adjuvant therapies

Surgery

Intermediate-Term Potency, Continence, and Survival Outcomes of Radical Prostatectomy for Clinically High-Risk or Locally Advanced Prostate Cancer

Stacy Loeb, Norm D. Smith, Kimberly A. Roehl, and William J. Catalona

- Loeb et al reported on Catalona series of high risk pts undergoing RP (Urology 2007)
- Much smaller (288), different group (cT2b with GS 8-10 or PSA >15 [88%]; or cT3)
- Median follow-up of 7.3 yrs
- 54% received adjuvant XRT +/- ADT
- PSA recurrence defined as >0.2 confirmed by 2nd measurement
- bNED 39% at 7 yrs (less adjuvant therapy, stricter recurrence definition, higher risk pts?)
- Cancer-specific survival 92% at 7 yrs

Surgery

RADICAL PROSTATECTOMY AS PRIMARY TREATMENT MODALITY FOR LOCALLY ADVANCED PROSTATE CANCER: A PROSPECTIVE ANALYSIS

RYAN K. BERGLUND, J. STEPHEN JONES, JAMES C. ULCHAKER, AMR FERGANY, INDERBIR GILL, JIHAD KAOUK, AND ERIC A. KLEIN

- Cleveland Clinic series of high risk pts undergoing RP (Urology 2006)
- Similar group (281) but more even spread of high risk parameters, mean follow-up of <3 yrs only
- 30% received NHT/neoadjuvant chemo
- bNED 70% at 34 months (no adjuvant therapy)
- More meaningful for assessing complication rate of 10% (vs 7% for contemporaneous RP for less advanced CaP)

VGH Experience

- Definition: 1 or more of –
  - *PSA >20ng/ml*
  - *Gleason Score ≥8*
  - *Clinical Stage =T3*

VGH Experience

- Prospectively updated database
- RP for high risk CaP
- 2 surgeons
- Single institution
- NHT patients included
- Neoadjuvant chemotherapy patients as part of trial protocols excluded
- 211 men for analysis

VGH Experience

- Baseline:
  - PSA
  - Gleason score
  - % cores positive
  - Clinical stage
  - No. high risk factors
  - NHT
- Treatment outcome:
  - Pathologic stage
  - PSA recurrence (PSA ≥ 0.2 ng/ml)

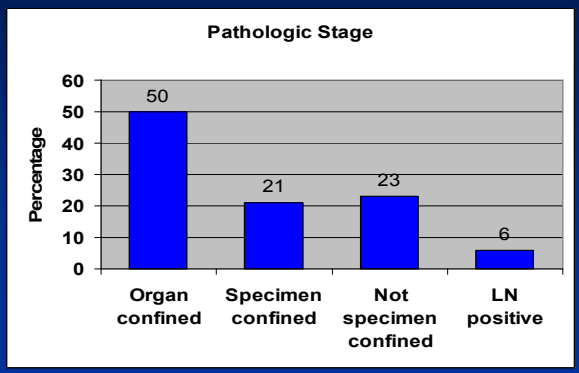
VGH Experience

- Median age: 63.2 years
  - Range 46.5 – 77.3
- Median follow-up: 4.34 years
  - Range 2 months – 10 years

VGH Experience

Risk factor	Low	Intermediate	High
PSA	<10 45%	10-20 17%	≥20 38%
Gleason sc.	<7 14%	7 26%	>7 60%
Cores pos.		<50% 43%	≥50% 57%
Clin. T stage	1 29%	2 46%	3 25%
No. RFs	1 79%	2 18%	3 3%

VGH Experience



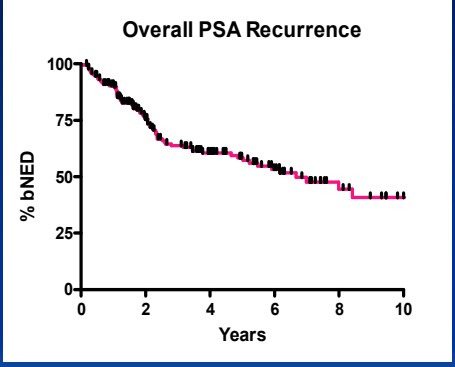
- NHT in 72%

VGH Experience

- Patients without NHT, change of Gleason score from biopsy to pathological specimen
  - 7% upgraded
  - 54% equal
  - 37% downgraded

VGH Experience

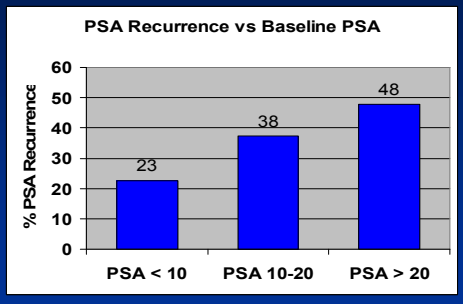
- Overall bNED rate of 68.4% (median f/up 4.34 yrs)
- Adjuvant XRT in 3.3%
- Median time to recurrence: 21.2 mths
- Actuarial bNED of 40.7% at 10 yrs

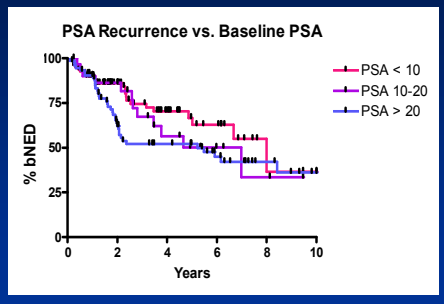


VGH Experience

- 41% of patients with PSA recurrence underwent salvage XRT
- Insufficient data on T levels to exclude potential lasting effect of
  - NHT on PSA recurrence rate
  - ADT on PSA re-recurrence rate after salvage XRT+ADT

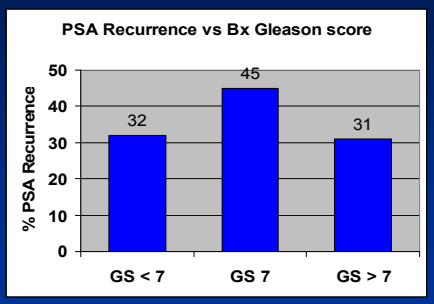
VGH Experience

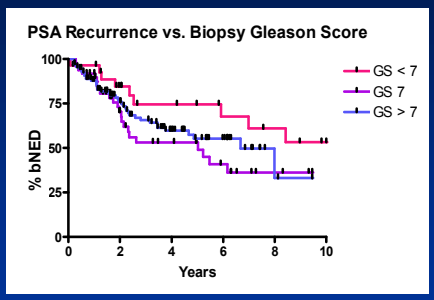




- PSA > 20 was predictive of PSA recurrence
  - Fisher Exact test, p=0.0043
- No significant difference of KM curves
  - Logrank test, p=0.14

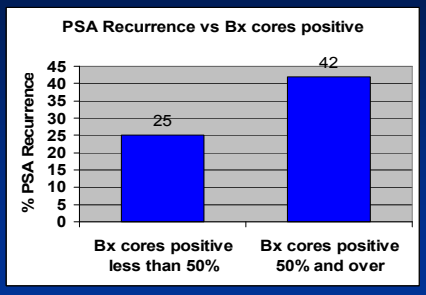
VGH Experience

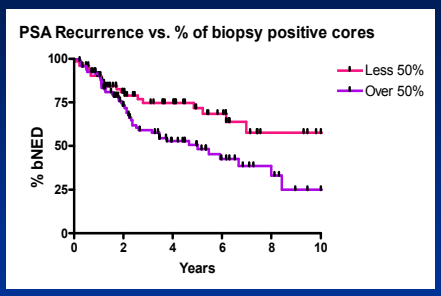




- No significant difference, p=0.18

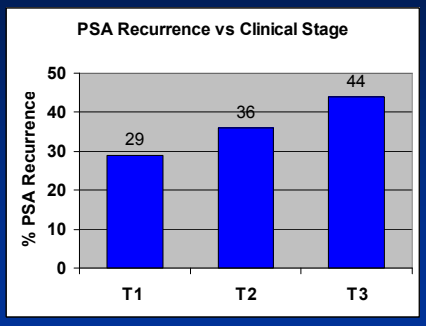
VGH Experience

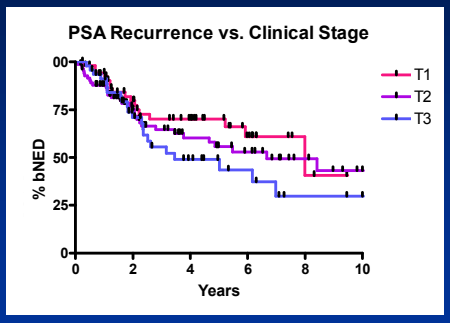




- >50% cores positive on biopsy was predictive of PSA recurrence
  - Logrank test, p=0.0185

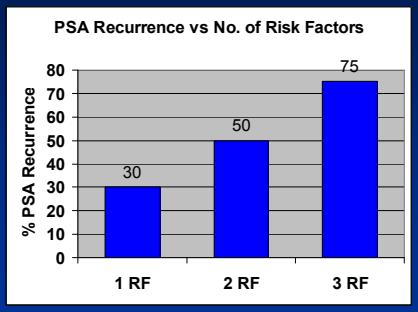
VGH Experience

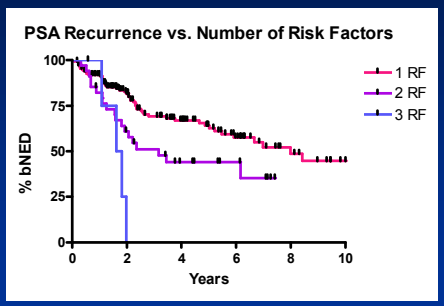




- No significant difference, p=0.32

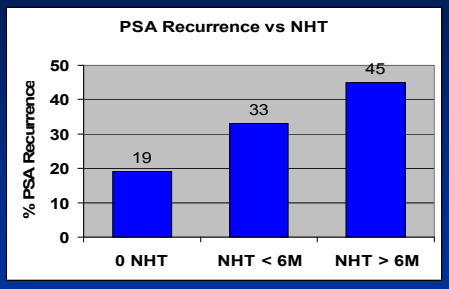
VGH Experience

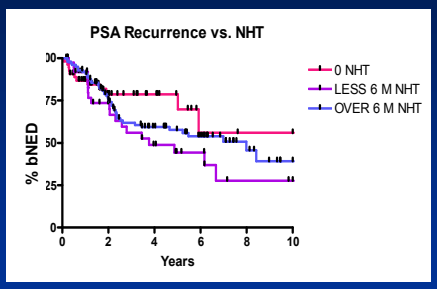




- Number of risk factors was predictive of PSA recurrence
  - Logrank test p=0.0005

VGH Experience





- No significant difference, p=0.34

VGH Experience

- Multivariate analysis: independent predictors of PSA recurrence -
  - PSA (p=0.033)
  - % Biopsy cores positive (p=0.035)
    - More accurate indicator of tumour volume than clinical stage

VGH Experience

- Summary
  - Cohort typical of current high risk pts
  - Good bNED rates with surgery as part of multimodal therapy, comparable to other published series
  - Consistent with other data supporting use of % of positive biopsy cores as parameter for risk stratification

The Case for Surgery

- For surgery to be a standard option, first need to show equivalent or lower clinical progression rates to XRT+ADT, acceptable morbidity
- Literature appears to support this
- What other advantages may surgery offer?

The Case for Surgery

- Extended PLND
  - May increase CaP-specific survival but conflicting data from small single institution series
    - Joslyn and Konety examined SEER database (Urology 2006)
    - Over 13,000 pts undergoing RP 1988-91
    - Decreased risk of CaP-specific mortality
    - If >4 LNs removed cf. no LND, regardless of LN involvement
    - If >10 LNs removed and LNs negative cf. no LND (HR 0.85, p=0.038)
    - Explanation: micromets missed by standard histologic analysis are removed
  - Finds more positive LNs
    - Early ADT

The Case for Surgery

- Accurate staging
  - Most accurate staging of disease is pathological
    - Clinical staging remains poor
  - Up to ¼ pts thought to be high risk may have organ-confined disease, only require monotherapy for cure
    - Otherwise subject to XRT + 3 yrs ADT
    - Or, no definitive local therapy, denying pt chance for cure
  - LN positive pts can be commenced on ADT

The Case for Surgery

- Multimodal therapy
  - Recent RCTs show biochemical recurrence rate halved with adjuvant XRT post-RP
    - (too small or follow-up too short to show survival difference)
  - Hope for effectiveness of chemohormonal therapy in high risk setting following success of taxanes in HRPC
  - Surgery as primary definitive treatment allows full range of adjuvant therapies p.r.n. (XRT, ADT, ?chemo)
  - Failure of XRT as primary therapy, salvage RP less desirable
  - Especially important given likelihood of progression, i.e. allows matching of treatment intensity to aggressiveness of disease

The Case for Surgery

- Potential improved survival if progress to metastatic CaP
  - Based on evidence in RCC and ovarian Ca, Thompson et al (J Urol, Sept 2002) re-analysed data from SWOG 8894 (orchidectomy vs orchidectomy + flutamide in men with metastatic CaP)
  - Of 1286 men, 148 had undergone previous RP
  - Significant decrease in risk of death if had RP cf. no RP (HR 0.77)
  - Also found increased risk of death if had previous XRT (HR 1.22)
  - ?Prevention of new metastases from primary tumour
  - Major limitation of selection bias: clinical stage at diagnosis not known

The Case for Surgery

- Excellent local control
  - Wide resection reduces positive margins (55% to 16%), may reduce symptoms from local recurrence further (Dussinger et al, Urology, Nov 2005)
- Local recurrence with XRT
  - Bladder outlet obstruction
  - Haematuria
  - Pelvic pain
  - Upper tract obstruction
  - 69% with post-XRT local recurrence required surgical intervention, most commonly TURP (Holzman et al, J Urol, Dec 1991)

The Case for Surgery

- Follow-up
  - PSA monitoring after RP more straightforward
    - If PSA not <0.2 at first post-op reading, indicates residual disease
    - PSA rise after being <0.2 indicates recurrence
    - But need to measure T if had NHT
  - After XRT can be difficult to interpret
    - PSA may take up to 18 months after XRT completed to nadir
    - PSA bounce up to 3 yrs after XRT
    - Unable to differentiate bounce from recurrence (less problematic with Phoenix definition)
    - Increased uncertainty (in addition to lack of pathological staging)

The Case for Surgery

- Until surgery and XRT are compared head-to-head in RCT +/- adjuvant chemohormonal therapy, we won't know which has better cancer control

Summary

- Comparable clinical progression to XRT+ADT
- Comparable morbidity to surgery for intermediate risk CaP (standard)
- Extended PLND may further reduce CaP-specific mortality
- Most accurate staging (esp. with extended PLND)

Summary

- Allows adjuvant or salvage XRT as part of multimodal therapy approach
- Patients who do progress may have improved survival
- Excellent local control
- Improved follow-up

Future

- Current patients categorised as high risk are heterogeneous
  - Some have micrometastatic disease
  - Some have local extraprostatic disease
  - Some have neither
- Need better staging
  - Biomarker not only CaP-specific but metastatic CaP-specific

Future

- Most (but by not all) high risk patients will eventually progress
- Need better treatments
  - Multimodal therapy likely to offer best chance
  - RCTs underway
    - CALGB 90203: RP vs neoadjuvant estramustine + docetaxel + RP
    - SWOG 9921: RP + adjuvant ADT vs + mitoxantrone also
    - DVA: RP vs RP + adjuvant docetaxel
    - RADICALS: RP + adjuvant XRT +/- ADT vs RP + salvage XRT +/- ADT

Thank you / Merci