High-risk prostate cancer: multimodality treatment approaches

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High-risk prostate cancer: an heterogeneous disease

EAU

D’Amico CAPRA score

AUA

NCCN

High-risk prostate cancer: an heterogeneous disease


Primary tumor treatment improves patients survival

12,194 patients

cT3-4 PSA 20-99 ng/ml

Non curative intent (WW, ADT, orchidectomy, conservative treatments)

6 yr mortality 23.64%

Primary curative treatment is recommended for HRPCa

30,159 pts Cumulative Pca mortality 15yr 95% CI

CURATIVE 21.7% 18.3–25.3

NOT CURATIVE 35.5% 34.2–36.8


Does local treatment matter?


938 patients N+

Overall survival

5 yr 83.7% 60.1% 80.1% 63.8% 0.03

10 yr 63.8% 28.2% 63.8% 28.2% 0.03

Cox multivariate analysis (RP as reference)

HR 95%CI p

2.042 1.59–2.63 <0.0001
PRIMARY TREATMENT

RADIOTHERAPY
RADICAL PROSTATECTOMY + extended LYMPH NODE DISSECTION

MULTIMODALITY TREATMENT

DEFINITION
Association of different therapeutic strategies to maximize local control and minimize systemic spreading by neoadjuvant or adjuvant treatments next to primary approach

LACK OF CURATIVE EFFECT

RADICAL PROSTATECTOMY
MICROMETASTATIC SPREAD
RESIDUAL DISEASE (PSM, N+)

MICROMETASTATIC SPREAD

Redefining micrometastasis in prostate cancer: a comparison of circulating prostate cells, bone marrow disseminated tumor cells and micrometastasis: Implications to determining local or systemic treatment for biochemical failure after radical prostatectomy

PROSPECTIVE STUDY
185 patients
2008–2011
Negative Bone scan
RADICAL PROSTATECTOMY + HT
Postoperative sampling (66 months)

 Prospective study
92 patients
RADICAL PROSTATECTOMY
CTC after 3 months

CTC
DTC
Micro

Prospective study
52 patients
RADICAL PROSTATECTOMY
CTC after 6 months

CTC
DTC
Micro

Secondary Circulating Prostate Cells Predict Biochemical Failure in Prostate Cancer Patients after Radical Prostatectomy and without Evidence of Disease


<table>
<thead>
<tr>
<th>Prospective study</th>
<th>CTC</th>
<th>Positive surgical margins</th>
</tr>
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<tbody>
<tr>
<td>52 patients</td>
<td></td>
<td>Extra-capsular lympho-vascular infiltration</td>
</tr>
<tr>
<td>RADICAL PROSTATECTOMY</td>
<td>CT after 3 months</td>
<td>pGleason score</td>
</tr>
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**LOCAL RELAPSE**

- Positive biopsy after treatment (6–12 cores)
- Digital rectal examination
- Symptomatic progression of local disease
- Median follow up: 8yr

**References**


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**PSM and ONCOLOGICAL OUTCOMES**

**WHAT?**

- **RADICAL PROSTATECTOMY**
- Radiotherapy
- Hormonal therapy
- Combined therapy

- **NEOADJUVANT**
- **CONCOMITANT**
- **ADJUVANT**
- **SALVAGE**

**NEOADJUVANT**

A systematic review and meta-analysis of randomised trials of neoadjuvant hormone therapy for locally advanced prostate cancer.

**RADICAL PROSTATECTOMY**

10 randomized clinical trials (RCT) 1988-2000:
- cT1-2 (3)
- N0 (9)
- MRI

**Radiotherapy**

- Triptoreline, Goserelin, Cyproterone acetate, Fluoxime, Leuprolide 3-9 months

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**OVERAL SURVIVAL**

FOLLOW UP
- Schulman: 4yr
- Klotz: 6yr
- Aus: 7yr

**DISEASE FREE SURVIVAL**

FOLLOW UP
- 6 months-7yr

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**OS and DSS**

**Cancer Treat Rev. 2009;35(1):9-17.**
NEOADJUVANT

**NEOADJUVANT**

**POSITIVE SURGICAL MARGINS**

**NEOADJUVANT**

**PATHOLOGICAL FEATURES**

**POSITIVE LYMPH NODE INVOLVEMENT**
(relative risk 0.66, 95% CI 0.47–0.94, p = 0.02)

**LONG TERM NEOADJUVANT TREATMENT**
**BETTER RESULTS IN TERMS OF PSM AND DISEASE CONFINEMENT**

**STILL A ROLE BEFORE RADICAL PROSTATECTOMY?**
- CONTEMPORARY SERIES...CHANGE IN DISEASE CHARACTERISTICS
- STUDIES POWERED TO DETECT IMPORTANT OUTCOMES (OS, CSS, MFS)
- LONGER FOLLOW UP
- NEW DRUGS ARE AVAILABLE WITH INTERESTING POTENTIAL

**NEOADJUVANT**

**CANCER SPECIFIC SURVIVAL**

6 months neoadjuvant at 5 yr (HR 0.56, p = 0.04) → high risk patients

8-15 yr DSM (23% RT + N vs 36% RT, p = 0.01)¹


**NEOADJUVANT**

**RADIOThERAPY**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Follow-up Length</th>
<th>Results</th>
</tr>
</thead>
</table>
Neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TRIG 96.01 randomised trial


1996-2000
818 pts
Neo 6 mm
Neo 3 mm
RT alone
Distant progression

Locally advanced Pca
RT +6mHT vs RT+3yHT
HR 1.71 (95% CI, 1.14 to 2.57)
Log-rank p = 0.002


EBRT + 3yr HT
Locally advanced Pca


Mitchell CR, Boorjian SA, Umbreit EC et al. 20-Year survival after radical prostatectomy as initial treatment for cT3 prostate cancer. BJU Int. 2012;110(11):1709-13


Downgrading
bGS ≥ 8 to pGS ≤ 7
45%

Dowling
238 pts
Prospectively collected
Downgrading GS5 to GS4
49%

238 pts
Downstaging cT3 to cT2
26%
SURGERY AND MULTIModal APPROACHES

Risk factor | CSS %
--- | ---
T3 | 90-99 85-92 62-84
5yr | 10yr | 15yr

Risk factor | CSS %
--- | ---
GS | 96 94-96 95
5yr | 10yr | 15yr

Risk factor | CSS %
--- | ---
PSA >20ng/ml | 93-97 83-91 71-78
5yr | 10yr | 15yr

ORGAN confined: 0.8
ECE+: 7
pT3b: 32
pGS 8-10: 31
N+: 42

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ADJUVANT RADIOTHERAPY

RISK FACTORS

SEMINAL VESICLES INVASION
PSM
EXTRA-CAPSULAR EXTENSION


ADJUVANT HORMONAL THERAPY


log-rank test: p = 0.004
hazard ratio: 2.5

ADJUVANT HORMONAL THERAPY

- INDICATED FOR BULKY N+ AFTER RADICAL PROSTATECTOMY
- IF N+>2 IS PARTICULARLY INDICATED
- RT ASSOCIATION IN N+ PATIENTS HAS TO BE CONFIRMED FROM PROSPECTIVE SERIES BUT IT CAN BE JUSTIFIED IF LOCAL RISK FACTORS ARE PRESENT
- DURATION OF TREATMENT HAS TO BE CLARIFIED FOR SUBGROUPS

SALVAGE RADIOTHERAPY


Pooled data from 886 pts
SALVAGE RT
Pre RT <0.5 ng/ml 6.7% ADT
BIOCHEMICAL RELAPSE FREE SURVIVAL (BRFS)
71% (48-81.8) 5yr
LINEAR TREND BETWEEN PSA & BRFS
LOWERING TO PSA<0.2 ng/ml 2yr BRFS 84%

AND IN THE MEANTIME?
SALVAGE RADIOTHERAPY & SURVIVAL

Retrospective study
519 pts (cT1-T3)
RP → BR
No RT, SRT, SRT + ADT, ADT
Median follow up: 11.3 yr
ALL CAUSE MORTALITY


SALVAGE RADIOTHERAPY

Retrospective study
635 pts RP → BR
No RT, SRT, SRT + ADT
Median follow up: 9 yr
PSA MORTALITY


SALVAGE RADIOTHERAPY

- IMPROVEMENT OF BIOCHEMICAL RELAPSE FREE SURVIVAL
- IT SHOULD BE STARTED WITH A CONFIRMED PSA PROGRESSION WITHIN 0.5 ng/ml
- EARLY SALVAGE RADIOTHERAPY
- DEFINITIVE RESULTS ON HARD END POINTS ARE EXPECTED FROM ONGOING RANDOMIZED CLINICAL TRIALS
- MULTIDISCIPLINARY DECISION MAKING

MULTIMODALITY FOR HIGH RISK PROSTATE CANCER

- MAXIMAL EFFORT TO TREAT PATIENTS AT HIGHER RISK OF DEATH
- HRPCA IS DIFFICULT TO CURE BY PRIMARY TREATMENT ALONE
- MULTIMODALITY TO MAXIMIZE LOCAL CONTROL
- MULTIMODALITY TO MAXIMIZE SYSTEMIC CONTROL
- MULTIMODALITY TO MAXIMIZE LOCAL & SYSTEMIC CONTROL
- UNTIL EVIDENCE BASED RESULTS WILL BE AVAILABLE
- A MULTIDISCIPLINARY DECISION MAKING IS OFTEN REQUIRED