SCENARIO

- A 66 year old man underwent Robotic – Radical Prostatectomy for a T1c Gleason 4+4 , PSA 15 ng/ml prostate cancer. His follow up PSA has been <0.03 ng/ml and 9 months after surgery , his PSA was noted to be 0.4 ng/ml . 3 months later , his PSA was 0.8ng/ml.
QUESTIONS

1. What do you understand by term of BCR

2. How does it differ between patient treated with RP and RT

3. How can differentiate between Local and Systemic Failures

4. What are Treatment options and evidence of each treatment
• Most common primary treatment for localized disease is radical prostatectomy (RP)

• About 2/3 patients, prostatectomy constitutes a cure, but within 10 years up to 1/3 patients will present with recurrent disease

• Recurrence is thought to result from **residual subclinical disease** in the operative site that later manifests as **a rising PSA level, a local tumor recurrence, metastatic disease or occult metastatic disease** that was present at the time of the prostatectomy

• Risk of recurrence is greater in patients with adverse pathology

  positive surgical margins (PSM)

  seminal vesicle invasion (SVI)

  extraprostatic extension (EPE)

  higher Gleason scores
1. BIOCHEMICAL RECURRENCE (BCR)

- PSA expected undetectable within 6/52 post successful RP
- Term BCR = PSA recurrence / ? Treatment failure
- Previously – recurrence on DRE / development of metastatic disease
- Current definition (International consensus) – a detectable or rising PSA value after surgery that is $\geq 0.2$ ng/ml with a second confirmatory level $\geq 0.2$ ng/ml *(Recommendation; Evidence Strength: Grade C) – Polascik et al (J.Urol 1999) . Moul et al (J. Urol 2000) . Pound et al (JAMA 1999)*
- Most appropriate definition for BCR post RP still uncertain
ULTRASENSITIVE PSA

- Introduction of ultrasensitive PSA test - possible to screen patients after RP and predict risk of BCR after surgery at early stage

- More precise measurement of PSA nadir after radical surgery:
  
  patients with a PSA nadir < 0.01 ng/mL developed an early relapse in 4% of cases

  by contrast, patients with PSA nadir of 0.04 ng/mL or higher developed an early relapse in 89% of cases

- EAU 2013
## 2.BCR POST RP vs RT

<table>
<thead>
<tr>
<th>BCR</th>
<th>Post RP</th>
<th>Post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA value</td>
<td>( \geq 0.2 \text{ ng/ml} ) with a second confirmatory level ( \geq 0.2 \text{ ng/ml} )</td>
<td>i. ASTRO Consensus panel – 3 consecutive increases following RT</td>
</tr>
</tbody>
</table>
|           |kipine 2013                                                             | i. New definition - \( \geq 2 \text{ ng/ml} \) above nadir
|           |                                                                         | ~EAU Guideline 2013                                                    |

* ~EAU Guideline 2013
### 3. LOCAL vs SYSTEMIC FAILURE (POST RP) – EAU GUIDELINE 2013

<table>
<thead>
<tr>
<th>Post RP</th>
<th>Local</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation of PSA level</td>
<td>&gt; 3 years post RP</td>
<td>&lt; 1 year post RP</td>
</tr>
<tr>
<td>PSA Velocity</td>
<td>&lt; 0.75ng/ml/year</td>
<td>&gt; 0.75ng/ml/year</td>
</tr>
<tr>
<td>PSA DT</td>
<td>&gt; 11 months post RP</td>
<td>4 – 6 months post RP</td>
</tr>
<tr>
<td>Gleason score of Prostatectomy specimen</td>
<td>Less than 6</td>
<td>8 - 10</td>
</tr>
<tr>
<td>Pathological stage</td>
<td>Less than pT3a No, pTxD, pTxR1</td>
<td>pT3b, pTxpN1</td>
</tr>
</tbody>
</table>
ROLE OF POST RP RADIOTHERAPY

<table>
<thead>
<tr>
<th>ADJUVANT (IMMEDIATE)</th>
<th>SALVAGE (DELAYED )</th>
</tr>
</thead>
<tbody>
<tr>
<td>administration of RT to post-prostatectomy patients at a higher risk of recurrence because of adverse pathological features prior to evidence of disease recurrence (i.e., with an undetectable PSA)</td>
<td>administration of RT to prostatic bed and possibly to the surrounding tissues, including lymph nodes, in PSA recurrence after surgery but no evidence of distant metastatic disease</td>
</tr>
<tr>
<td>usually administered within four to six months following RP ( Generally, RT is initiated after the return of acceptable urinary control)</td>
<td></td>
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</tbody>
</table>
TREATMENT OPTIONS FOR THIS 66 YO POST RRP FOR T1c GLEASON 4+4 , PSA 15 NG/ML WITH POST RRP PSA OF < 0.03ng/ml → 0.4 ng/ml (9/12) → 0.8 ng/ml (12/12)

- Pt has BCR – Local or Systemic ?
- Most likely to be Systemic failure due to :
  1. increase PSA value < 1 year post RP
  2. early PSA DT
  3. Gleason score of 8

Stephenson et al identified a PSA value of > 0.4 ng/mL, followed by another increase, as the best cut-off level for indicating the development of distant metastases.

Bone scintigraphy and abdominal CT scan are of no additional diagnostic value unless PSA serum levels are > 20 ng/mL or PSAV is > 20 ng/mL/year.
TREATMENT OPTION FOR HIM

- Timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial.
- Systemic failure post RP is predicted with > 80% accuracy by:
  - PSA relapse < 1 year
  - PSADT of 4-6 months
  - Gleason score 8-10
  - Stage pT3b, pTx pN1
- Treatment depend on presumed site of failure, the patient’s general condition and personal preferences.
ADJUVANT HT POST RP

- Survival advantage for adjuvant ADT after RP has only been confirmed in patients with positive lymph node PCa in a single randomised study - Messing et al

- Several retrospective analyses from the Mayo Clinic have shown that adjuvant HT after RP had a positive effect on the time to progression and cancer death in pT3b and N+ patients

- Large series from the Mayo Clinic with a median follow-up of 10.3 years show that adjuvant HT in surgically managed N+ patients decreased the risk of BCF and local recurrence, but did not have a significant impact on systemic progression or CSS
ANDROGEN DEPRIVATION THERAPY (ADT)

- A retrospective study including 1,352 patients with postop PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) vs. delayed ADT (at the time of clinical metastases)

- Early ADT was able to delay the time to clinical metastases in high-risk patients (Gleason score > 7 and/or a PSADT < 12 months) – recent retrospective study from Mayo Clinic

- ADT had no overall impact on the PCa-specific mortality
ANTIANDROGENS

- In a prospective placebo-controlled, randomised trial of adjuvant bicalutamide (150 mg) was able to decrease progression in men with locally advanced PCa, but did not result in an OS benefit - Mcleod et al

- Gynecomastia and breast tenderness – most predominant side effects of treatment for organ-confined and locally advanced PCa, the incidence of hot flushes, loss of libido, and impotence was significantly lower than expected for LHRH agonists and complete androgen deprivation (CAD)
INTERMITTENT ANDROGEN DEPRIVATION (IAD)

- a potential alternative to CAD in order to:
  1. Delay time to androgen independence + hormone-refractory dis
  2. Minimise side effects
  3. Reduce the costs of prolonged therapies

- No long-term data from large-scale RCTs to confirm superiority of IAD over CAD for survival

- In the setting of PSA-only recurrences, there are no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy to justify the routine clinical application of IAD, despite its potential benefits
MINIMAL ANDROGEN BLOCKADE

- In some studies, **finasteride and flutamide** have been combined for the management of PSA-only recurrences, since the two agents work additively by blocking the intraprostatic conversion of testosterone to dihydrotestosterone (DHT) and blocking the intracytoplasmic DHT receptor - *Harding P et al*

- In the latest report (87), including 73 patients, administration of finasteride (10 mg/day) and low-dose flutamide (250 mg/day) resulted in a mean PSA nadir of 1.35 ng/mL within 6 months

- Longer follow-up of a larger patient cohort is needed, and randomised phase III trials using modern antiandrogens with fewer gastrointestinal and hepatic side effects are mandatory
HT POST RP COMBINED WITH RT AND/OR CHEMOTHERAPY

- Addition of HT to SRT (n = 78) was not associated with any additional increase in the CSS – Trock et al

- A phase II trial including 74 patients with postoperative PSA recurrences showed that combined treatment with SRT plus 2 years of CAD (castration + oral antiandrogen) had relatively minor long-term effects on quality of life – Pearce et al

- Currently- no indication for chemotherapy in patients with PSA-recurrence only
ONGOING TRIAL

More efficacy data are needed and the potential increase in side effects should be considered when combining therapies.

- Results are eagerly awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting.

- Radiotherapy and ADT in combination after local surgery are being investigated in a recently started, large, randomised, controlled study sponsored by the Medical Research Council.

- The study is addressing the timing of RT (adjuvant vs early salvage) and the duration of HT (none vs. short-term vs. long-term) used together with postoperative RT.
  - Primary outcome measure will be CSS (cancer specific survival).
  - Secondary outcome measures will include OS, ADT administered outside the protocol, and reported treatment toxicity.
  - Study is also aiming to assess the long-term effect of RT after RP on sexual, urinary, and bowel function, and the long-term effect of ADT on sexual function and the overall quality of life.
**MANAGEMENT OF PSA RELAPSE POST RP (EAU GUIDELINE 2013)**

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>GR</th>
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<tbody>
<tr>
<td>Local recurrences are best treated by salvage RT with 64-66 Gy at a PSA serum level &lt; 0.5 ng/mL</td>
<td>B</td>
</tr>
<tr>
<td>For patients with presumed local recurrence who are too unfit or who are unwilling to undergo RT, expectant management can be offered.</td>
<td>B</td>
</tr>
<tr>
<td>PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in a reduced frequency of clinical metastases</td>
<td>B</td>
</tr>
<tr>
<td>LHRH analogues/antagonists/orchiectomy or bicalutamide (150 mg/day) can be used when there is an indication for HT.</td>
<td>A</td>
</tr>
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</table>
## Presumed Local failure post RP

Patients with presumed local failure only may be candidates for salvage RT. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL. Other patients are best offered a period of watchful waiting (active monitoring), with possible HT later on.

## Presumed Systemic failure

There is some evidence that early HT may be of benefit with or without local failure, delaying progression and possibly achieving a survival benefit in comparison with delayed therapy. The results are not uncontroversial. Local therapy is not recommended except for palliative reasons.
THANK YOU

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