RADIOThERAPY IN PROSTATE CANCER

LAURA REBEGEA
Prostate cancer is the second most frequently cancer diagnosed in men in world and the 6th leading of the cancer deaths in men.

- accounting for around 8% of all new cancer cases and 15% in men.

- Age-adjusted incidence rates of prostate cancer have increased dramatically
  - because of the increased availability of screening for prostate-specific antigen (PSA) in men without symptoms of the disease.

https://www.google.ro/?gws_rd=ssl#q=prostate+cancer+epidemiology+worldwide
Several nomograms, tables and formulae have been proposed to divide patients into prognostic groups and predict the probability of extracapsular tumor extension, seminal vesicles involvement or lymph node metastasis.

Patients are stratified into risk groups based on the T stage, pretreatment PSA and Gleason score.

<table>
<thead>
<tr>
<th>Risk stratification for men with localized prostate cancer</th>
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</thead>
<tbody>
<tr>
<td>Pretreatment PSA</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Low risk</td>
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<tr>
<td>Intermediate risk</td>
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<tr>
<td>High risk</td>
</tr>
</tbody>
</table>
STAGING AND RISK ASSESSMENT

Low-risk
- Imaging tests are not routinely recommended
- Should not routinely have a pelvic lymph node dissection (PLND)

Intermediate risk
- Bone scintigraphy should be considered if bone metastases are suspected, Gleason score >6 or PSA ≥ 15ng/ml

High-risk
- CT/MRI of pelvis should be considered
- Bone scintigraphy should be performed
- Patients who are to be treated with RP should have an extended bilateral PLND
The optimal treatment for clinically localized PC is controversial

- Active surveillance
- RP
- EBRT: TD ≥ 74Gy
- LDR-BT or HDR-BT

- **3DCRT, IMRT, BT and RP** - result are similar in terms of BRFS

- Immediate post-operative RT after RP is not routinely recommended
- Immediate HT alone or as adjuvant therapy after RP is not recommended
- Watchful waiting with delayed HT in the event of symptomatic progression is an option for patients who are not suitable or unwilling to have radical treatment
Radical treatment should be discussed if live expectancy is \( \geq 10 \) years:
- RP
- EBRT: TD \( \geq 74\)Gy
  - If a moderate EBRT dose (< 70Gy) is used, it should be accompanied by 6 months of ADT
- LDR - BT or HDR-BT

Immediate post-operative RT after RP is not routinely recommended

Patients with positive surgical margins or extracapsular extension after RP should be informed about adjuvant RT

Watchful waiting with delayed HT in the event of symptomatic progression is an option for patients who are not suitable or unwilling to have radical treatment.
Radical treatment should be discussed if live expectancy is ≥ 5 years:

Radical treatment options include:

- RP or
- EBRT + neo (adjuvant) treatment

RP - younger patients and/or those in good physical condition

Patients undergoing RP for locally advanced (T3-4) disease should be informed of the post-operative treatment (adjuvant RT and/or ADT)

Patients undergoing RP for N1 disease who are at high risk of disease progression should be receive post-operative ADT

- RT+HT after RP - is not standard but may be considered

For patients receiving RT with disease stage ≥ T2b, adjuvant HT for ≥ 6 months is recommended
GETUG-01 French phase III trial
- 444 patients
- TD=46Gy/23fr, d/fr=2Gy - whole pelvis vs.
- TD=66-70Gy/33-35fr, d/fr=2Gy - prostate only
- Showed no differences between to lots in PFS, in QoL, toxicities

Pelvic radiotherapy may be performed to patients with high risk of lymph node involvement conforming to next equation (Roach):

\[
\text{Lymph node risk (\%)=2/3xPSA+[(Gleason score-6)x10]}
\]

High risk patients (Gleason=8-10, T3-T4 clinical stage or LN risk>30%) should be also considered for 2-3 years of neoadjuvant and adjuvant HT
Treatment position: supine, arms across the chest

Immobilization devices - to ensure patient comfort and to maintain daily positioning reproducibility
Principal causes for prostate displacement:
- Very full bladder
- Distended rectum

**Bladder should be comfortably full** prior to CT scanning; this also serves to reduce the proportion within the PTV; the patient drinks approx. 350ml during the hour prior to scanning

**Rectum should be empty;** patients with distended rectum at planning have been increased biochemical and local failure after EBRT

To reduce the prostate movement:
- Use endorectal balloons or endorectal obturators during the planning and treatment
- Intraprostatic radio-opaque makers placed in the prostate before treatment planning
BEAM ENERGY AND DOSE DISTRIBUTION

- **3DCRT**
  - high-energy photon beams (>10 MV)
  - Simplify techniques
  - Decrease morbidity

- **IMRT**
  - Typically 6-MV photon beam
  - Dose distribution is conforming to dose constraints applicable for targets and normal tissues
  - RTOG Consensus Guidelines

**IMRT provides:**
- Highly conformal dose distribution compared with 3DCRT
- Better sparing of bowel and bladder, treatment-related complication,
- Dose escalation to high-risk lymph node areas

Updated Oncology 2015: State of the Art News & Challenging Topics, 2015 Summer school in Oncology, Bucharest, 15 - 19 June
Radical radiotherapy: prostate ± seminal vesicles

- **GTV** - difficult to define precisely by clinical examination and conventional imaging
- Current practice - define the entire prostate gland and all part of the SV using the diagnostic MRI
  - provides better soft tissue contrast compared to CT,
  - is particularly useful in identifying the prostatic apex and distinguishing between bladder base and anterior rectal wall
- GTV can sometimes be delineated using MRI
Radical radiotherapy: prostate ± seminal vesicles

- **CTV = Prostate +/- SV+/−LN**
- In defined:
  - CT/MRI
  - PET
- **Low-risk prostate cancer CTV = entire prostate only**
- **Intermediate - risk prostate cancer CTV = prostate + proximal 1cm of bilateral SV**
High-risk prostate CTV = prostate + proximal 2 cm of the bilateral SV (consider entire SV if grossly involved +/- LN regions).

High-Risk Disease with Nodes at Risk

- **CTV1 = prostate and a 2mm margins**
  - The CTV should be expanded for known extracapsular extension determined by DRE, MRI or CT
  - The proximal 2cm of seminal vesicles is included and may also be increased for known clinical extension

- **CTV2 = lymph node volume:**
  - obturator nodes,
  - internal iliac nodes to the body of the sacrum,
  - medial external iliac nodes,
  - common iliac nodes to the sacral promontory
  - Presacral nodes are not included
- **Prostate** is first outlined on the central slice where the gland is clearly demarcated, and on successive caudal slices.
- If MRI is available:
  - Coronal image may help to define the position of the apical extent of the gland.
- The prostate is then outlined on slices cranial to the central slice.
- The pelvic sling muscles should be excluded from the prostate outline.
Radical radiotherapy: prostate ± seminal vesicles

- **Seminal vesicles**
  - Is outlined for all patients

  If the seminal vesicles is *extend predominantly laterally*, then they can be included in their entirety without significantly affecting rectal dose.

  If there is significant *posterior extension of* the seminal vesicles and they are closely to the rectal wall, then the rectal dose constraints may be exceed unless the tips of the seminal vesicles are excluded from the volume.

- The *entire seminal vesicles* is included for stage T3 tumours or if the risk of seminal vesicles involvement is > 15% - provided that the predicted dose to the rectum is acceptable.

- If the rectal dose is unacceptable then the tips of the seminal vesicles are excluded but the proximal 2 cm is treated.
Radical radiotherapy: prostate ± seminal vesicles

- **PTV**
  - Includes additional margins to allow for patient and prostate movement and variations in treatment set-up
  - In practice: margins of 1.0 cm (but not uniform)
    - Tighter margins of 5mm posterior to spare the posterior wall of the rectum

Internal motion of organs - source of concern
Zelefsky et al:
- Median motion for prostate: 4-8 mm in various directions
- Seminal vesicles: 7-11 mm

- DVH - are calculated for PTV, bladder, rectum, femoral heads
Radical radiotherapy: prostate and pelvis

- The pelvic vessels are outlined on each axial CT slice continuity.
- The volume should encompass:
  - the iliac vessels which high in the pelvis lie on its posterior wall
  - the internal iliac / presciatic and external iliac vessel in continuity
  - cover upper pre-sacral area anterior to the upper three sacral segments

- RTOG guidelines suggest:
  - CTV = 7 mm radial margin around the pelvic blood vessels to cover the involved lymph nodes
    - excluding adjacent bowel, bladder, bone and pelvic muscles
  - CTV - begin at the L5/S1 interspace and end at the superior aspect of the pubic bone
  - PTV - applying 5 mm- margin in all directions
LYMPH NODE IRRADIATION (LNI)

- **LNI:**
  - is not standard for low- and intermediate-risk PC
  - is controversial for high-risk PC

- LNI CTV = 7 mm expansion around internal/external iliac vessels, obturator and presacral regions.
CTV\textsubscript{PROS} (purple), CTV\textsubscript{NODES} (red), Bladder (Green), Rectum (Orange), Penile Bulb (dark purple), Seminal Vesicles (cyan), Left Femur and Right Femur (dark blue).

Vikram M Velker et al. Creation of RTOG compliant patient CT-atlases for automated atlas based contouring of local regional breast and high-risk prostate cancers. \textit{Radiation Oncology} 2013, 8:188
4 anterior and posterior oblique fields, one anterior and two lateral fields
Six coplanar fields for high dose treatment
Higher doses > 70-74Gy:
- Improve BDFS at 5, 7 or 8 years
- Determine higher rate of GI late toxicity
- The benefit are important for low-risk and high-risk patients

Most institutions:
- TD=75,6Gy/42fr, d/fr.=1,8Gy - for prostate
- If pelvic lymph nodes are treated - min.TD=45-50Gy
3DCRT technique
2 anterior oblique fields, 2 lateral fields and one posterior field
DVH
3DCRT technique - Boost
1 anterior field, 2 lateral fields and 2 posterior oblique fields
IMRT technique
2 anterior oblique fields, 2 lateral oblique fields and one posterior field
IMRT technique - Boost
2 anterior oblique fields, 1 anterior field, 2 lateral fields and 2 posterior oblique fields
Dose fractionation for radical EBRT

- TD=75.6-79.2 Gy/42-44 fr., d/fr.=1,8-2Gy

If treating LN:
- Prescribed initial to the pelvis
- TD=45-50.4Gy/25-28 fr., d/fr.=1,8Gy to the pelvis (LN+prostate +SV)

Hypofractionated regimes should be considered:

TD = 70Gy/2.5Gy/fx
TD = 70.2 Gy/2.7Gy/fx
TD=62Gy/3.1Gy/fx (4fx/ week)
TD=51.6Gy/4.3Gy/fx
For SBRT, TD= 36.25Gy/7.25Gy/fx
Radical radiotherapy: prostate ± seminal vesicles

ORGAN AT RISK (OR)

- Rectum
- Bladder
- Sigmoid, small & large bowel
- Urethral bulb
- Femoral heads

OR are outlined as solid organs by defining the outer wall.

Bladder - outlined from base to dome

Rectum - outlined from anus (or 1cm below the lower margin of PTV) to the rectosigmoid junction
- the position is best appreciated on the sagittal CT reconstruction as the level at which is the rectum comes anteriorly

Additional bowel within the PTV is defined separately
## Dose-Volume Constraints for Organ at Risk

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Dose (Gy) at 2-Gy/fr to 100%</th>
<th>Dose volume constraint (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Optimal</td>
</tr>
<tr>
<td>Rectum</td>
<td>V50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>V60</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>V75</td>
<td>3</td>
</tr>
<tr>
<td>Bladder</td>
<td>V50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>V60</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>V70</td>
<td>5</td>
</tr>
<tr>
<td>Sigmoid, small &amp; large bowel</td>
<td>V50</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>V60</td>
<td>0.5</td>
</tr>
<tr>
<td>Urethral bulb</td>
<td>V50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>V60</td>
<td>10</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>V50</td>
<td>5</td>
</tr>
</tbody>
</table>
After RP for localized PC stage T1 -T2, pathological positive margins are described in:

- 10% of patients with T1b,
- 18% of patients with T2a,
- 50%-60% of patients with T2b,

Pathological positive surgical margins have a greater prognostic implication than capsular invasion and are a significant predictor for development of distant metastasis.

Microscopic involvement of the seminal vesicles carries a poor prognosis, with a higher incidence of local recurrence and metastatic spread and lower survival than without such involvement.
ADJUVANT RADIOTHERAPY

- Adjuvant radiotherapy
  - For patients with positive surgical margins
  - pT3/4 disease
- Improve
  - Locoregional control
  - OS
  - Distant metastases-free survival
Retrospective reviews suggest that results are better for patients with pre-radiotherapy:
- PSA < 0.5ng/ml,
- PSA doubling time ≥ 9 months
- Positive surgical margins

It remains under questions:
- Radiotherapy is best given immediately following surgery (adjuvant) for patients at high risk of local recurrence or
- Radiotherapy is reserved for those with a documented PSA relapse (salvage)
ADJUVANT RADIOTHERAPY

- Three trials
- EORTC 22911:
  - 1005 patients
  - pT3pN0 patients and/or positive surgical post prostatectomy who are randomized:
    - Observation or
    - Adjuvant radiotherapy (TD=60Gy/30fr)
- A statistically significant advantage was seen for adjuvant radiotherapy in terms of BPFS and CPFS
- There was no evidence of a difference in OS at 10 years:
  - 76.9% with adjuvant EBRT vs. 80.7% with observation
Identification of Patients With Prostate Cancer Who Benefit From Immediate Postoperative Radiotherapy: EORTC 22911

Theodorus H. Van der Kwast, Michel Bolla, Hein Van Poppel, Paul Van Cangh, Kris Vekemans, Luigi Da Pozzo, Jean-Francois Bosset, Karl H. Kurth, Fritz I

Figure 3 displays the Kaplan and Meier curves for biochemical progression-free survival according to margin status and treatment arm:

The 5-year biochemical progression-free survival rate was 77.6% (95% CI, 68.8% to 84.2%) for the patients with positive margins in the irradiation arm but was 48.5% (95% CI, 39.6 to 58.9) for the patients with positive surgical margin in the control arm.

**Fig 3.** Biochemical progression-free survival by surgical margin status and allocated treatment. N, number of patients; O, number of events; SM−/+ , surgical margin negative/positive; W&S, wait-and-see group (control); RT, irradiation.
Second trial - SWOG 8794 (NCIC CTG PR-2)

- 425 patients
- Longer follow-up
- Adjuvant radiotherapy was associated with:
- a statistically significant increase in biochemical control and importantly both metastasis-free and OS were improved with HR 0.71 and 0.72 respectively (p=0.02)
- BPRS at 5 years
  - EORTC trial: 74% vs. 52.6% adjuvant EBRT vs. no adjuvant EBRT, p<0.01
  - German trial: 72% vs. 54% adjuvant EBRT vs. no adjuvant EBRT
- Reported urethral stricture: 17.8% with adjuvant EBRT vs. 9.5% with follow-up
Third trial - ARO 96-02

- pT3 disease patients
- Postoperative undetectable PSA
- Adjuvant radiotherapy was associated with a statistically significant improved biochemical control
Each study demonstrated advantages of adjuvant EBRT in PSA relapse, but the impact in OS is not clear.

**Recommendations of ESMO Guides 2014**

- Adjuvant EBRT performed immediate after RP is not routinely recommended
- Patients with positive surgical margins or extracapsular disease after RP must be informed about advantages and disadvantages of adjuvant EBRT
Salvage prostate bed radiotherapy can be administrated to patients post prostatectomy with **biochemical failure**:

- Two consecutive rises of PSA and final PSA > 0.1 ng/ml
- Three consecutive rises of PSA

No randomized data are available showing the benefit of salvage radiotherapy.
**TARGET VOLUME DEFINITION**

**IMRT**

- **CTV1** - prostate bed + the extent of the surgical bed
- **CTV1** should include the surgical clips provided that the normal-tissue dose-constraints are within tolerance.
- The rectum – should not be included in CTV
- **prostate bed** = estimated location of the preoperative prostate volume (including sites of possible microscopic tumor extension)
Adjuvant radiotherapy

CTV1

- **Anterior** border:
  - Caudal (< 2cm above anastomosis) - posterior aspect of symphysis pubis
  - Cranial (> 2cm above anastomosis) - posterior one-third of bladder wall

- **Posterior** border: anterior rectal wall

- **Lateral** border: medial border of obturator internus and levator ani muscle

- **Inferior** border: 5mm cranial to the superior border of the penile bulb
Adjuvant radiotherapy

**CTV1**
- **Superior** border:
  - If SV involvement is low risk and pathologically uninvolved - include base of SV
  - If SV involvement is high risk or are pathologically uninvolved - aim to include tips of SV
  - If SV absent, the superior border should be determined with reference to the estimated position of the preoperative SV

**CTV2** - lymph nodes (high risk factors - incomplete lymph node dissection, high risk factors at the time of recurrence (PSA doubling time < 12 months and persistent PSA following surgery)

**PTV** - add 1.0 cm around CTV
- Posteriorly - toward the rectum the margins may reduced to 5 mm
DOSE FRACTIONATION

- IMRT
- Adjuvant EBRT: TD=64.8Gy - 70 or 70.2 Gy
- Patients with gross disease at recurrence: TD=66-70Gy
- A distinction can be made between adjuvant (absence of detectable disease) and salvage (presence of detectable disease)
- TD (adjuvant) = 64-66Gy
- TD (salvage) = 70Gy
DOSE - VOLUME CONSTRAINTS

- RTOG 0534

- Post prostatectomy EBRT
  - Rectum:  < 25% > 65Gy
    < 45% > 40Gy
  - Bladder:  < 40% > 65Gy
    < 60% > 40Gy
All randomized-controlled:

- Showed no change in BDFS and OS in case of elective node radiotherapy.

Regarding the retrospective analyses, some recent high-quality studies (Seaword et al.) did show a benefit with WPRT, especially in high-risk patients compared to patients who received PORT.

WPRT - whole pelvis radiotherapy, PORT - pelvis only radiotherapy
Dose is prescribed in isocentre (100%)

Clinician should:

- Ensure that volume covers prostate + seminal vesicles with adequate margins in all directions
- Check 95% isodose cover of PTV
- Confirm that no unacceptable “hot spot” occur within or outside the PTV
- Confirm volume of rectum irradiated, particularly avoiding circumferential exposure
- Asses the dose to rectum, bladder and femoral heads, using DVH data
- Verify filed sizes
- Check weighting of different fields
BRACHYTHERAPY

**Indications:**
- Definitive treatment for low- or intermediate-risk patients
- Combination treatment with EBRT
- If prostate volume is too large or pubic arch interference exists, HT can be initiated 2 to 3 months prior to implantation for gland size reduction

**ABS recommends permanent BT as monotherapy:**
- T1-T2a
- Gleason ≤ 6
- PSA ≤ 10 ng/ml

American Brachytherapy Society=ABS
Brachytherapy

**Indications - permanent implant**
- Age < 75 years
- Good general health, fit for anesthesia
- No bleeding disorders
- Life expectancy > 5 years

Carefully select patients for a given technique to maximize its therapeutic efficacy

**Contraindications:**
- Life expectancy < 5 years
- Presence of metastatic disease
- Recent TUR-P
- Prostate volume > 50cc
- No bleeding disorder and anticoagulation that can not be stopped
**Indications - temporary BT**
- T1-T3b
- Any Gleason
- PSA<100 ng/ml and N0M0

**Contraindications:**
- TUR-P within 6 months
- Pubic arch interference
- Obstructive symptoms
- External sphincter infiltration
- Anesthesia not possible
- Lithotomic position not possible
Implants

- permanent with $^{125}\text{I}$ and $^{103}\text{Pd}$
- temporary with $^{192}\text{Ir}$

Dose prescription/fractionation

- $^{125}\text{I}$ BT monotherapy - TD=144Gy
- $^{125}\text{I}$ BT + EBRT (45Gy to pelvis) -TD = 110Gy,
- $^{103}\text{Pd}$ BT monotherapy - TD=125Gy
- $^{103}\text{Pd}$ BT + EBRT (45Gy to pelvis) -TD = 100Gy
BT-HDR advantages vs. BT-LDR

- Overall treatment time HDR:
  - HDR - few minutes vs. LDR - few weeks or months - necessary for delivering of entire dose

- Treatment cost:
  - HDR lower than LDR with 23-29% because the radioactive sources are not purchased for every patient

- Radioprotection
  - HDR - the patient is not “radioactive” vs. LDR

- Radiobiological
  - HDR - repopulation and repairing cells are prevented due the delivering dose in few minutes, \( \alpha/\beta = 1.5 \text{ Gy} \)
BRACHYTHERAPY

- **BT-HDR advantages vs. BT-LDR**
  - BT-HDR can be performed as monotherapy, in localized disease or combined with EBRT
  - BT-HDR as monotherapy is recommended for:
    - T1-T2a, Gleason ≤ 7, PSA ≤ 10ng/ml.
  - Big prostate volume (60cc) do not represent a contraindication for HDR
  - Urinary toxicity grade 3: 4% for HDR vs. 15% for LDR

- **Dose/ fractionation schema for HDR:**
  - TD = 34Gy/4 fr., d/fr.=8.5Gy
  - TD = 38Gy/4 fr., d/fr.=9.5Gy
  - TD = 31.5Gy/3 fr., d/fr.=10.5Gy
After 4 weeks - postimplant
The patient returns for CT scan to evaluate of the seeds implant

Ideally:
95% of prostate volume should received 100% of prescribed dose (V100>95%)
D90 > 90-100%
V150 < 70%
Patient setup and preparation for prostate BT
Isodose distribution of target volume, organ at risk and seeds position inside the target volume:
green - prostate,
center yellow - prostatic urethra
blue cyan - rectal mucous
purple - SV
red curve - 145Gy isodose
DVH for prostate (black), urethra (red), rect (blue) SV (purple)
3D organ reconstruction
Seed and needle positions
Green - prostate
Yellow - prostatic urethra
Blue - rectal mucous
Purple - SV
Red - I125 sources
# BRACHYTHERAPY
## ACUTE SIDE EFFECTS

<table>
<thead>
<tr>
<th>Genitourinary</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disuria</td>
<td>Rectities</td>
</tr>
<tr>
<td>Nicturia</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Acute urinary retention (5-15%)</td>
<td>Constipation</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>Rectal bleeding</td>
</tr>
<tr>
<td></td>
<td>Tenesmus</td>
</tr>
</tbody>
</table>

Predictive factors of AUR:
- prostate volume,
- neoadjuvant HT,
- D90,
- number of seeds,
- number of needles
### BRACHYTHERAPY LATE SIDE EFFECTS

<table>
<thead>
<tr>
<th>Genitourinary</th>
<th>Gastrointestinal</th>
<th>Erectile function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Especially in combined treatment BT+EBRT</td>
<td>Erectile dysfunction occurs in 10-70% of cases</td>
</tr>
<tr>
<td>Incontinency (&lt;1%)</td>
<td>- diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- rectal tenesmus,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ulcerations, fistulas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- intermittent rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>Urethral strictures</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Predictive factors of urethral strictures:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dosimetric factors: D90, V100, mean urethral dose, maximum urethral dose, HT, age, IPSS score</td>
<td></td>
</tr>
</tbody>
</table>
EBRT ACUTE SIDE EFFECTS

Occur during and up to 6 months after radiotherapy

<table>
<thead>
<tr>
<th>Genitourinary Obstructive and irritative prostatic symptoms:</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Proctitis</td>
</tr>
<tr>
<td>Urgency</td>
<td>- tenesmus,</td>
</tr>
<tr>
<td>Haematuria - rarely</td>
<td>- rectal bleeding,</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>- pain,</td>
</tr>
<tr>
<td>Poor stream</td>
<td>- mucous discharge</td>
</tr>
<tr>
<td></td>
<td>- diarrhea</td>
</tr>
</tbody>
</table>

Other acute toxicities
Skin erythema
Dry or moist desquamation
Fatigue
Lethargy
Pubic hair loss
### EBRT Late Side Effect

<table>
<thead>
<tr>
<th>Genitourinary</th>
<th>Gastrointestinal</th>
<th>Erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis</td>
<td>Tenesmus (17% at 5 years, after 74 Gy)</td>
<td>- Prevalent in the first 6 months</td>
</tr>
<tr>
<td>Haematuria</td>
<td>Rectal bleeding (32% at 5 years)</td>
<td>- Is influenced by HT</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>Diarrhoea (15% at 5 years)</td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>Mucosal loss</td>
<td></td>
</tr>
<tr>
<td>Irritative bladder symptoms</td>
<td>Rectal-anal stricture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel frequency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel obstruction</td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>Rectal-anal stricture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
<td></td>
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</tbody>
</table>

Side effects depend of dose, EBRT technique, comorbidities, age

- The risk of GI complications is reduced by using IMRT rather than 3D CRT or conventional radiotherapy techniques.
Various devices have been developed to spare rectal structure:

- **endorectal balloons** - increase the distance from the dorsal rectal wall to the prostate

- relatively novel spacers that separate the anterior rectal wall from the prostate by injecting an absorbable hydrogel or saline-filled balloon that naturally biodegrades within 6 months after implantation

*Fig. 1. Axial T2 magnetic resonance images of a patient with a spacer before injection (a) and after injection (b).*
The objective of study is to look at the cost-effectiveness of a toxicity-reducing spacer for prostate cancer patients by comparing IMRT therapy with a spacer (IMRT+S) versus IMRT only without a spacer (IMRT-O). It gives an overview of the economic consequences before introducing this new approach into standard practice.

The results:
- confirm a decrease of rectal dose when using an absorbable spacer and a decrease of rectal toxicity.
- presented in this paper are valuable for decision-making in terms of policy making and future research.
Dose-escalated IMRT > 78 Gy prescription dose increased rates of acute and chronic grade ≥ 2 rectal toxicity from 3% to 20% and 5% to 21%, respectively.

The risk of rectal toxicity depends on the volume of the rectum that receives a high radiation dose.

In a large prospective series, the percentage volume of rectum receiving >70 Gy (V70 rectum) correlated with the occurrence of chronic rectal toxicity.

Grade ≥ 2 chronic rectal toxicity occurred in 54% and 13% of patients in whom the V70 rectum was >26.2% and ≤ 26.2%, respectively.
Pelvic radiation disease (PRD) also widely known as “radiation proctopathy” is a well recognized late side-effect following conventional prostate radiotherapy.

102 patients who had radical prostate IMRT/IGRT and who had new or ongoing bowel symptoms

4 patients who were treated after radical prostatectomy received TD = 64-66 Gy in 2 Gy/fraction, 5 times/week.

98 patients TD = 73.8-78 Gy in 1.8-2 Gy/fraction, 5 times/week.
Endoscopic examination:
- gastric/colonic/rectal polyps (56%),
- diverticular disease (49%),
- haemorrhoids (38%),
- radiation proctopathy (29%),
- gastritis/oesophagitis (8%),
- bowel cancer (3%),
- radiation proctopathy without associated pathology (4%),
- more than one diagnosis (63%).

- In patients presented with rectal bleeding, the percentage found to have PRD - 35%, was equal to or lower than the previously reported range of 35–75% in the literature.
- This strongly supports - any symptomatic patient under the above circumstances should be investigated for gastrointestinal pathology.
This study showed that bowel symptoms following prostate IMRT/IGRT are due to numerous diagnoses other than PRD, including malignancy was one of the causes of late onset bowel symptoms in these patients.

Most patients treated with prostate IMRT who have late bowel symptoms or positive FOBT (faecal occult blood tests), have non-radiotherapy related etiology; many patients have premalignant or malignant causes.

Symptoms or signs of late PRD cannot be distinguished from those of other bowel diseases without visual inspection.
Patients who present with new or persisting bowel symptoms more than 90 days after EBRT for PC (whether IMRT or 3D conformal)

Should be investigated with endoscopic examination (with consideration of a full colonoscopy)

To establish a diagnosis and to guide further management
Advances in imaging technology, such as the development of hybrid imaging systems (e.g., PET/CT), which provide both structural and metabolic information, as well as geographical mapping have contributed to more accurate imaging assessments.

11C-choline and 18F-labeled choline analogs such as FCH PET are helpful for the assessment of regional lymph node involvement after prostatectomy or radiation therapy.

Another advantage of choline-based PET/CT is that it may be better able than MRL (MR lymphangiography) or sentinel node SPECT to detect distant nodes and/or bone metastases.
When a patient treated with curative intent several years before has an isolated nodal relapse, it is crucial to determine whether the recurrence is regional and inside or outside the \( \text{CTV}_{\text{RTOG}} \).

The purpose of this study was

1. To describe the pattern of nodal relapse in prostate cancer patients with biochemical failure after prostate-only radiotherapy.

2. To determine if patients with treatment failure + FCH PET/CT positive had invaded nodes within the \( \text{CTV}_{\text{RTOG}} \).
Selection of patients

Eighty-three patients with pathologically-proven prostate adenocarcinoma had a FCH PET/CT for biochemical failure after radiotherapy. All of the patients had negative bone scintigraphy and abdominal CT. FCH PET/CT was performed when the PSA increased to a value of ≥2 ng/mL. For patients who had a PSA value below 2 ng/mL, a PSA doubling time <6 months was required [8]. Sixty-five patients had positive PET scans (78.3%).

Characteristics of the patients and treatments at baseline and at time of Choline PET-based relapse.

<table>
<thead>
<tr>
<th>PET-based relapses</th>
<th>All PET + (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>24 (36.9%)</td>
</tr>
<tr>
<td>Regional</td>
<td>26 (40.2%)</td>
</tr>
<tr>
<td>Distant</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td>Local + Regional</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td>Regional + Distant</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Local + Distant</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Local + Regional + Distant</td>
<td>2 (3.1%)</td>
</tr>
</tbody>
</table>

Topography of involved nodes

- Distal common iliac: 3 (9.7%)
- Internal iliac: 3 (9.7%)
- External iliac: 9 (29.0%)
- Ilio-obturator: 5 (16.1%)
- Presacral: 2 (6.4%)
- Proximal common iliac: 6 (19.3%)
- Perirectal: 2 (6.4%)
- Perivesical: 2 (6.4%)
- Inguinal: 2 (6.4%)
- Periaortic: 6 (19.3%)
- Mediastinum: 2 (6.4%)
(A) Sagittal view: the white arrow shows an enlarged PET positive common iliac node above the L5-S1 limit.
(B) Axial view: the white arrow shows the same enlarged common iliac node as in 1A.
(C) Sagittal view: the white arrow shows a smaller PET positive peri-aortic node at the L2–L3 limit.
(D) Axial view: the white arrow shows the same enlarged common iliac node as in 1C. The maximal

$^{18}$Fluoro-choline PET/CT of a prostate cancer patient with a rising PSA after prostatectomy and radiotherapy.
The common iliac nodes are only included beyond the L5/S1 space - **distal common iliac region**.

Nodal stations **inside the CTV_{RTOG}** included:
- obturator nodes,
- internal iliac nodes,
- external iliac nodes,
- distal common iliac nodes.
Six regions outside the $\text{CTV}_{\text{RTOG}}$ are defined:

1. proximal common iliac,
2. para-aortic,
3. paravesical,
4. pararectal,
5. inguinal,
6. mediastinal stations.
Patterns of FCH PET-based lymph node relapse

- 17 patients (54.8%) had FCH-positive nodal failures inside the CTV_{RTOG},
- 10 patients (32.3%) outside the CTV_{RTOG} and
- 4 patients (12.9%) had nodal relapses which occurred inside and outside CTV_{RTOG}. 
3D mapping of occult nodal relapses evaluated by $^{18}$F-choline PET/CT in patients with biochemical failure after prostate-only radiotherapy with or without a prior radical prostatectomy ($n=31$).

3D mapping of nodal relapses evaluated with FCH PET/CT suggests that with IMRT the upper field limit of pelvic radiotherapy could be extended to L2-L3 safely to cover 95% of nodal stations at risk of an occult relapse.
Incurable PC represents a spectrum of clinical scenarios where the cancer has spared beyond the prostate gland.

Palliative pelvic radiotherapy:
- may relieve exiting symptoms: hemorrhage, bladder and urethra obstructions, rectal symptoms
- prevent progression and delay local extension.

It is addressed, also for treatment of metastatic disease.
Many schedules:
- TD=60-65 Gy/30-33fr./6 weeks, d/fr.=2Gy (Perez 1992)
- TD=40-56 Gy/20-28fr./4-5 weeks, d/fr.=2Gy
- TD=40-50 Gy/22-27fr./4-5 weeks, d/fr.=1.8Gy
- TD= 20Gy/5fr/5days, d/fr.=4Gy**

Palliative EBRT to metastases

- Commonly used for M1OSS
  - Single dose, TD=8Gy/1 fr./1 day can be repeated if required
  - TD=20Gy/5-4fr/5-4 days, d/fr.=4-5Gy
  - TD=30Gy/10fr/10days, d/fr.=3Gy

- Symptomatic nodal disease and visceral metastases - palliative EBRT

** [Din OS, Thanvi N, Ferguson CJ, Kirkbride P. Palliative prostate radiotherapy for symptomatic advanced prostate cancer. Radiother Oncol 2009;93:192-6]
There are no published reviews that summarized its palliative treatment effects.

The optimal dose and fractionations regimens still need to be defined.

Based on the current literature, it is impossible to draw reliable conclusion regarding the magnitude, onset or duration of the beneficial and detrimental effect.
Stratification of localized prostate cancer into 4 risk groups with corresponding 5-years biochemical failure-free survival (BFFS) after radiotherapy. Median TD=69.4Gy and no HT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>5-year BFFS (%)</th>
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<tbody>
<tr>
<td>PSA &lt;10 ng/ml, any Gleason</td>
<td>81</td>
</tr>
<tr>
<td>PSA 10-20 ng/ml, any Gleason</td>
<td>69</td>
</tr>
<tr>
<td>PSA &gt;20 ng/ml, Gleason 2-6</td>
<td>47</td>
</tr>
<tr>
<td>PSA &gt;20 ng/ml, Gleason ≥ 7</td>
<td>29</td>
</tr>
</tbody>
</table>

Shipley et al. 1999
FUTURE DEVELOPMENTS

- **Volumetric-modulated arc therapy (VMAT)**
  - Novel form IMRT optimization that allows the radiation dose to be delivered in a single gantry rotation of up to 360°
  - Reduce treatment delivery time,
  - Reduce the number of MUs
  - Offer a better OAR sparing with comparable target dose coverage to IMRT

- **Tomotherapy**

- **Stereotactic radiotherapy**
  - Delivers highly conformal, dose sculpting radiotherapy treatment.
  - Results from a number of trails using extreme hypofractionation including patients with low- or intermediate risk PC suggest that the technique is feasible

- **Proton beam therapy**

- **IGRT**
CONCLUSIONS

- The treatment is a challenge for radiation oncologist.
- Prostate cancer has been and still is one of the major battlegrounds in clinical oncology.

- In the past decade IMRT has become a widely used treatment for localized prostate cancer.
  - In order to obtain the local control is necessary to deliver a high dose: > 76-80Gy
- We have to balance toxicities related treatment, life expectancy, stage, risk factors, comorbidities, patient's preference
- There is no general consensus regarding what represents optimum management
Excellent 5-years control rates suggest that RP, 3DCRT, IMRT, BT are relatively equally effective for the treatment of favorable risk disease.

Patient should have the opportunity to consult with both a Surgical Oncologist and Radiation Oncologist.

Patient should be:
➢ informed of the potential benefits and risk of the different available options
➢ warned that the treatment of prostate cancer may cause sexual dysfunction, infertility and incontinency
Patient and physician preference usually influence treatment selection based on critical assessment of relative sides effects profiles and quality of life evaluation.
Thank you for attention!


9. ESTRO-EAU teaching course on Brachytherapy for prostate cancer. Nice, France 2008