Clinical case: prostate cancer

Marco van Vulpen, MD, PhD

Prostate cancer: is treatment necessary? (OS + DSS)

- N=731, prostatectomy versus observation; median FU 10.0 years

Prostate cancer: is treatment necessary? (tox)

- Many severe side effects from the intervention (surgery)

Contents

- Brachytherapy (BT): 1 fraction outpatient LDR permanent seed implant
  - Outcome
  - Toxicity and quality of life
  - Developments

- External beam radiotherapy (EBRT): ±35 fractions outpatient
  - Outcome
  - Toxicity and quality of life
  - Developments

- What will the future hold for BT and EBRT

Brachytherapy (DSS)

- n=921, I-125, 144 Gy, 1989-2004

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Brachytherapy (OS)

- n=921, I-125, 144 Gy, 1989-2004

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(Wilt, NEJM 2012;367(3):203)
Toxicity and quality of life

- Urinary Grade ≥ 3 (severe) toxicity rates:
  - Acute urinary retention: ≤ 10% (5-34%) = highest incidence
  - Urinary incontinence: ≤ 1.5% (0-17%)
  - Urinary bother: ≤ 1-3%
  - Hemorrh. cystitis: <=1%
  - Infection: <=1%
  - Fistula: <=1%
- Quality of life: No change with baseline

bNED in time (< and > 2000)

- There seems to be a trend for improved outcome in time
- Cause: technique? (intra-operative planning), patient selection?, learning curve?, other factors?

External beam radiotherapy > 10 years ago

- Success of I-125 brachytherapy:
  - Image guidance: needle update
  - High dose
  - Locking needles
  - 100%
  - 150%
  - 200%= 288 Gy
  - Ablative tumor dose

• There seems to be a trend for improved outcome in time
• Cause: technique? (intra-operative planning), patient selection?, learning curve?, other factors?

Improve outcome

What was done to improve outcome:
- Adding to the irradiation: by adding androgen suppression
  (Bolla, Lancet 2002;360:103)
- Improve the irradiation: by increasing the dose
  (Al-Mamgani IJROBP 2008;72:980)

But, what should have been done first:
- Improve the delivery accuracy
  A. Imaging the tumor
  B. Compensate for movement
  (van Vulpen, BJU Int 2008;101:944)
Delineation and imaging explain earlier results

Required for delineation:
1. Need for sufficient delineation tools
2. Need for MRI delineation guidelines (Villeirs 2005; McLaughlin 2005)

Guidelines seem poorly read (even by experts)

Contouring interobserver study to determine effect contouring on D90
- Questioned: delineate according to Villeirs 2005 (added to set)
- Delineators: ESTRO Probate members (8) (considered experts)
- Conclusion: guideline seemed not used (not read?)
- Possible solutions:
  - Automatic contouring on MRI (nearly solved)
  - Training

Detection and delineation limit?

- For radiotherapy a decision must be made per voxel to include it in the target or not
- Prostatectomy PA delineation study
- Tumors up to app 1 cc seem detectable and delineable
- Smaller prob. not clinically relevant

Validation with pathology

- For radiotherapy per voxel a decision must be made to include it in the target or not
- For radiotherapy patients no pathology of the entire prostate can be obtained
- Results can be compared to radiology studies on patients scheduled for prostatectomy

In practice: prostate tumor delineation

Map of the probability of tumor

- Combine eg DCE and DWI
- Automatic contouring of GTV and high-risk CTV
- = high-risk CTV
- = GTV
Hypoxic tumors determine outcome

Goal: delineate and boost hypoxic tumor areas

(Movsas 2002)

MR in hypoxia imaging

Chaotic and dysfunctional vasculature
Perfusion deficits
Angiogenesis
Hypoxia
Increased vascular permeability
Tumor proliferation
Molecular MRI
BOLD MRI
Diffusion-weighted MRI
T1-weighted MRI
Post-contrast T1-weighted MRI

(Dijkhuizen 2005)

Hypoxia imaging: BOLD

- Deoxyhaemoglobin is paramagnetic (iron particle)
- Is within red blood cells
- Cave: is correlated to blood volume and perfusion
- \( R^2 \) correlates with eppendorf pO2 and biopsies

(Alessi 2009)

Translational hypoxia studies required

- All prostates are hypoxic pO2 seems less reliable
- Hypoxia-aggressiveness: intrinsic and extrinsic markers more reliable?
- Human prostate hypoxia staining cumbersome (formalin, hours to fixate)

Required: Correlate functional MRI values in hypoxia animal model to functional MRI values in humans (VIDI)

Top whole block, H&E, DCE, DWI
Bottom: HIF1a, VEGF, CA-IX

Many and fast developments in MRI

- Functional imaging: higher Tesla, more possibilities in MRS, BOLD, DWI
- E.g. MRS in 7T using endocoil: phosphate and/or proton coil

B. Compensate for movement

Ways of position verification

(Courtesy: Marcel van Herk)
Toxicity and quality of life

Toxicity in earlier radiotherapy (no IMRT, no position verification):

- GI: grade > 3: 68Gy: 4% 78Gy: 5%
- GU: grade > 3: 68Gy: 12% 78Gy: 13%

(Proten F Clin Oncol 2006;24:190)

Toxicity in current radiotherapy (with IMRT, with position verification):

- GI: grade > 3: 78Gy: 1%
- GU: grade > 3: 78Gy: 4%

(very low compared to grade > 3 toxicity in RP and BT)

Comparing Quality of Life (QoL):
Significantly better QoL in current EBRT compared to earlier EBRT
(Lips IJROBP 2008;69(3):656)

Development of radiotherapy

Technical radiation delivery approaches:
- Conventional radiotherapy
- Conformal radiotherapy
- Intensity Modulated RadioTherapy (IMRT)
- VMAT, Cyberknife, etc
- Next: Protons / Carbon Ions/ etc

Treatment approach (concept):
- Image Guided RadioTherapy (IGRT)
- Inhomogeneous dose distribution
- Based on the biological target volume
- Individualized treatment

FLAME trial: randomized, ablative boost

FLAME trial: Focal Lesion Ablative boost
Randomized Phase III trial
- GTV 95Gy, 35 fractions
- prostate 77Gy, 35 fractions
Up to now: n= 70, severe toxicity < 1%

Overview studies hypofractionation

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<th>Number</th>
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Concern: quality in developments

- How about the lessons we learned from EBRT?
  - Look while you treat (iceball? / TRUS versus MRI?)
  - Dose-effect knowledge (thaw freeze cycles?)
  - Placing of needles (operator dependant versus e.g. BT knowledge)
  - Thermometry (safety) (hyperthermia knowledge)

Why not combine developments with existing knowledge?

Concern: Current staging

- Finding capsula infiltration large consequences with regard to:
  - Choice of treatment / Outcome (hormonal therapy)
    (Bhiti, Lancet 2002;360:163)
  - Differentiate between stage 2 and 3: specificity
    - Ultrasound: 42%
    - MRI: 90 – 50 %
    (Hsu BJU Int 2006;98:982)
    (Fütterer Radiol 2006;241:449)
- Currently: ultrasound still common practice, why?
  (urology practice, MR availability, radiology knowledge)
Concern: Current tumor characterization

- Biopsies: random systematic
  - (Montironi Eur Urol 2008;53:111)
- Gleason score: poor biopsy agreement with prostatectomy:
  - Gleason 5-6 undergrading: 35%, Gleason 8-10 overgrading: 35% (n=1670)
  - (Rajinikanth Urol 2008;72:177)
- PSA: poor correlation with the amount of tumor

Concluding: multidisciplinary approach essential

Innovation: computerized tumor detection

- MRI is able to:
  - localize tumor
  - show tumor aggressiveness
  - Show amount of tumor
  - Reliably predict tumor location
  - (Vilim RO 2005;99:106)
  - (Taube Radiol 2005:234:804)
  - (Esseniatal RO 2008;91:145)
  - (Groenendaal IJROBP 2012;82:537-44)

- MRI is able to:
  - localize tumor
  - show tumor aggressiveness
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Response assessment: PSA?

- PSA rise: not clear whether bounce, local or distant failure
  - Difficult to assess local control rate (blinded biopsies)
  - Difficult to assess dose-effect relationship
  - Other ways of follow-up required
  - Bounce:
    - 40 – 80% of patients bounce during follow-up
    - Bounce correlated with and survival: n=975; p=0.001
  - (Hinnen 2011)

Response assessment: MRI

- MRI and F18-choline PET promising to detect recurrences
  - (Haider 2008, Moman 2009)

Salvage results Netherlands

- Collaboration: AvL (RP), Nijmegen (Cryo), Groningen (Cryo, Utrecht (BT)
  - Poor outcome if PSA>10 and PSA-DT<12mths
  - Much severe toxicity

Focal salvage

- Many focal salvage possibilities: HDR, I-125, Cryo, HIFU, Etc.
  - Focal salvage seems possible:
    - Focal salvage: n=15: 1 patient grade 3 toxicity
    - But, is salvage clinically relevant?
Innovation: recurrence detection and treatment

- Current follow-up: PSA, evtl. “blinded biopsies”
- Imaging available for early detection: Choline-PET + MRI
- Salvage to entire prostate: appr. 30% grade 3-4 toxicity
- Focal salvage possible, e.g. by HIFU, Cryo, HDR, LDR seeds, etc.

Haider et al. 2008;70:425-30
Meintal et al. 2010;76(3):741-6

Establish a dose effect relationship

Local recurrence after IMRT 77Gy, 35x2.2Gy
Local recurrence after I125 144Gy

(van Vulpen 2009)

Establish dose-effect relationship

Necessary: spread dose points
- Brachytherapy: all 144Gy, but 100% to 200% within implants
- EBRT: FLAME provides dose spread

Example 95Gy plan

What will the future hold for EBRT?

- Extreme hypofractionation
  - E.g. 5x7Gy study, toxicity grade≥3: 1%
  - Goal: less fractions (1-3) with MRI-linac
- Towards focal treatment (in the MRI)
- Selective hypofractionated lymph node irradiation
  - E.g. Meerleer (Ghent) trial: 5x10Gy

ClinicalTrials.gov: NCT01558427

(Lips Trials 2011;12:235)

What will the future hold for Brachytherapy?

- Less treatments: only clinical relevant cases
- From LDR to HDR
- In the MRI

Primary Focal HDR
Salvage Focal HDR
MRI-compatible Robotics

Conclusions

- Current radiotherapy:
  - High quality
  - Image guidance
  - Many technical developments in next decade
    - Safe hyp-fractionated image guided ablation
- Quality assurance:
  - >20 patients per year?
  - Sufficient imaging (CT + MRI)
  - Sufficient position verification (markers, CT-linac)

(NVI quality guidelines)