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Gelocalizeerd prostaatkanker: radiotherapie of heelkunde?

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Disclosure slide: I am a radiation oncologist

This last part of surgery, namely, operations, is a reflection on the healing art; it is a tacit acknowledgement of the insufficiency of surgery.

It is like an armed savage who attempts to get that by force which a civilized man would get by stratagem.

John Hunter (1728 – 1793)

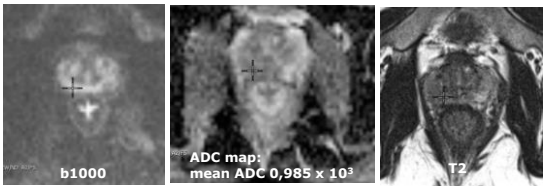
Clinical case example: pt X, °1946

- No co-morbidities, CCE in 2002, no medication, no ED
- Consults urologist in 2016 for elevated PSA & very mild LUTS
- Current PSA of 8,27 µg/L (was 4,11 µg/L in 10/2014)
- DRE: V = 50 cc, not suspect
- TRUS: V = 44 cc, not suspect

What would you recommend?

1. Reassure the patient and perhaps monitor PSA
2. mpMRI
3. Random biopsies

Patient underwent mpMRI



PI-RADS 3: intermediate (the presence of clinically significant cancer is equivocal)

What would you do now?

1. Reassure the patient and perhaps monitor PSA
2. mpMRI-guided biopsies +/- random biopsies
3. Random biopsies

Patient received MRI-guided (TRUS-fusion) biopsies

- In MRI-visible lesion: 3+4=7 in 1/3 cilinders
- Random biopsies: HPIN

- Conclusion:
  - Healthy 70-year old,
  - Localized prostate cancer (cT1c), iPSA < 10 µg/L, grade group 2 (3+4=7)

What would you now recommend?

1. Active surveillance
2. RALP
3. EBRT +/- ADT
4. Other: (focal) brachytherapy, HIFU, cryotherapy, photodynamic therapy,…

A fateful choice

The comparative effectiveness of contemporary treatment options for localized prostate cancer is one of the highest priority research questions according to the US National Academy of Medicine.

Sandro Botticelli, Judgement of Paris

The ProtecT trial

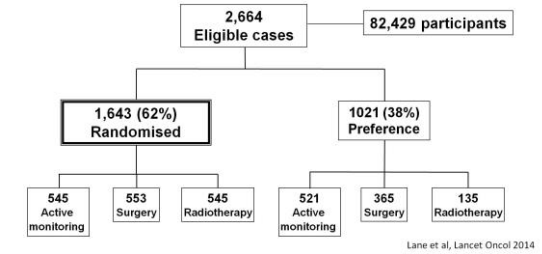
(Prostate testing for cancer and Treatment)

1999 – 2008

82,429 men PSA-tested
2,965 prostate cancers

To date, largest RCT comparing active monitoring, surgery and radiotherapy for PSA-detected localised prostate cancer
1ry endpoint: 10-y disease-specific mortality
2ry endpoints: all-cause mortality, progression, PROMs

ProtecT study flow chart



Lane et al, Lancet Oncol 2014

www.nihr.ac.uk

Presented By Freddie Hamdy at 2017 Genitourinary Cancers Symposium

ProtecT study options

- **Active Monitoring** is a surveillance programme. Men were followed up with PSA-testing and re-evaluation of their disease. They were offered radical treatments if the disease appeared to progress. The purpose was to **avoid unnecessary treatment**, but to keep them in a '**window-of-curability**' if treatment became necessary. *= PSA evaluation every 3m/1yr and 6-12m after*
  - Triggers (PSA rise >50%/12m; symptoms; changes in DRE; patient anxiety)
  - Investigations (imaging, repeat biopsies)
  - Change of management (suggestion of disease progression, patient/physician anxiety)
- **Surgery** was performed as radical prostatectomy with routine follow-up and additional treatments as necessary *= majority open retropubic but nerve-sparing*
- **Radiotherapy** with neoadjuvant androgen deprivation therapy and 74 gray 3-D conformal external beam, regular follow-up, and additional interventions as necessary *= 3-6 months of NACT, 3D-CRT technique, bRec = nadir + 2*

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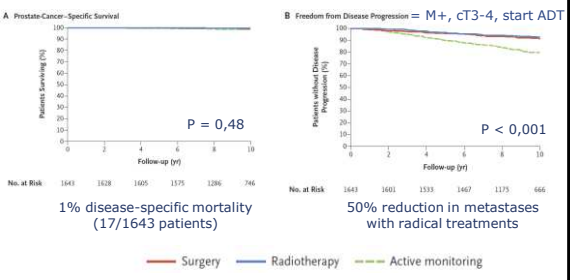
ProtecT: 10-year clinical outcomes



1% disease-specific mortality (17/1643 patients)

= M+, cT3-4, start ADT

50% reduction in metastases with radical treatments

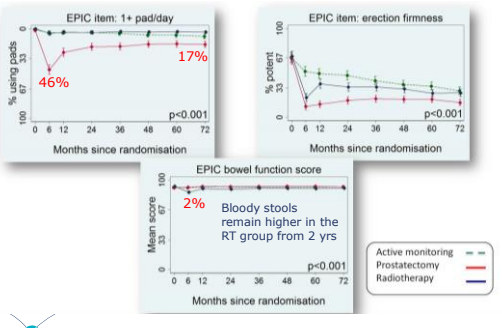
Hamdy F. et al. NEJM 2016.

ProtecT: primary treatment failure

- Active surveillance (545 assigned, 482 (88%) started):
  - 291 (53%) received radical treatment
- Surgery (553 assigned, 391 (71%) started):
  - 18 men had PSA > 0,2 ng/ml at least 3 months after RP
  - 9 men received adjuvant RT
  - Pathology: **29% had ECE (pT3)** and 24% had SM+
- Radiotherapy (545 assigned, 405 (74%) started):
  - 55 (14%) men had PSA nadir + 2,0 ng/ml after RT
- NNT: +/- 30 to avoid M+, and +/- 9 to avoid clinical progression

Hamdy F. et al. NEJM 2016.

ProtecT: patient-reported outcomes

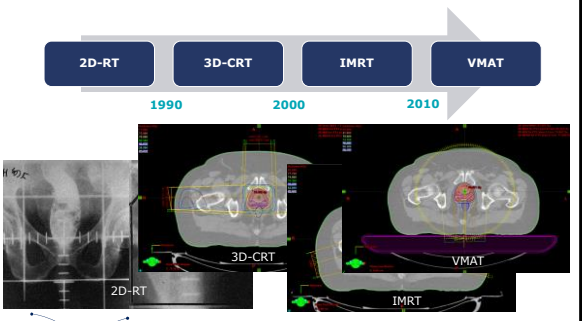


Donovan J.L. et al. NEJM 2016.

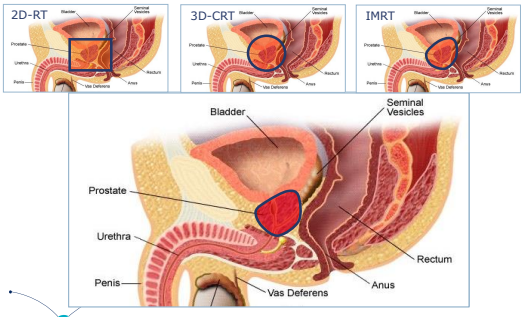
Conclusions from ProtecT trial

- No difference in long-term oncological outcome between RT and RP.
- Toxicity profile is significantly different:
  - RP: incontinence in +/- 50% of patients immediately after surgery and +/- 20% long-term. There is no evidence that this rate is less with RALP!
  - RT: acute GI toxicity in +/- 5% of patients, late radiorectitis in 1-2%.
  - Impotence is seen in both, erectile function is probably "first casualty".
- These QoL data are confirmed by other cohorts: POCS, CAESAR, NC ProCESS etc.

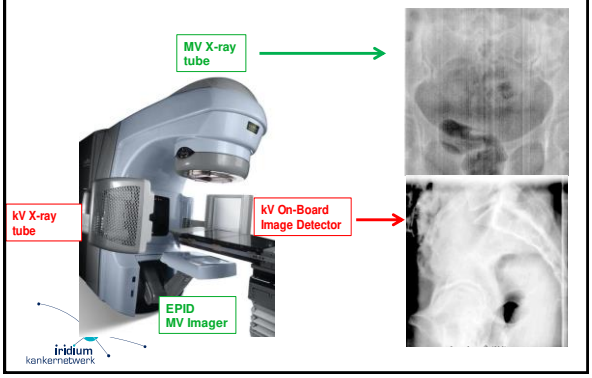
IMRT



IGRT

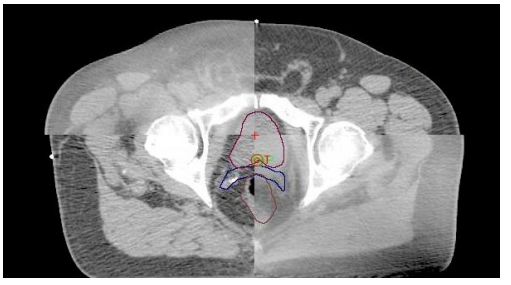


OBI



kV-MV "matching" on fiducial (= gold) markers

CB-CT "matching" on soft tissue



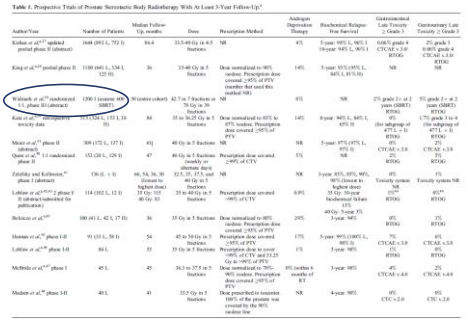
"moderate" hypofractionation

	n	Population	RT dose	Outcome	Toxicity
CHHiP Dearnaley D. et al. Lancet Oncol 2016	3216	cT1b-3aN0	74/37 Gy vs. 60/20 Gy	88% vs. 90% 5-yr bDFS, p = NS	No significant differences in late toxicity
RTOG 04-15 Lee W.R. et al. JCO 2016	1115	LR only	73,8/41 Gy vs. 70,8/28 Gy	85% vs. 86% 5-yr bDSF, p = NS	Late grade 2-3 GU & GI toxicity significantly worse
HYPRO Incrocci L. et al. Lancet Oncol 2016	820	IR-HR	78/39 Gy vs. 64,6/19 Gy	77% vs. 80% 5-yr bDFS, p = NS	Late grade ≥ 3 GU but not GI toxicity significantly worse
PROFIT Catton C.N. et al. Ontario Clinical Oncology Group JCO 2017	1204	IR only	78/39 Gy vs. 66/20 Gy	79% 5-year bDFS in both arms	No significant differences in late toxicity

Typically 15-25 fractions with 2,5-3,5 Gy per fraction

Brenner D.J. et al. Transl Cancer Res 2018.

"extreme" hypofractionation

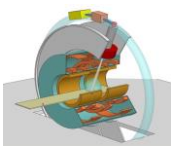


Kothari G. et al. Technol Cancer Res Treat 2018.

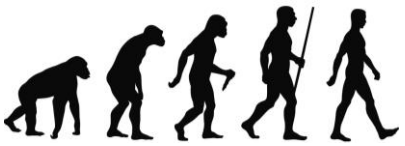
RT is after all the natural evolution of Pca treatment

Open surgery

Minimally invasive surgery



Non-invasive radiosurgery



Remember our patient?

- In MRI-visible lesion: 3+4=7 in 1/3 cilinders
- Random biopsies: HPIN
- Conclusion:
  - Healthy 71-year old, no ED
  - Localized prostate cancer (cT1c), iPSA < 10 µg/L, grade group 2 (3+4=7)

What would you now choose?

1. Active surveillance
2. RALP
3. EBRT +/- ADT
4. Other: (focal) brachytherapy, HIFU, cryotherapy, photodynamic therapy,…

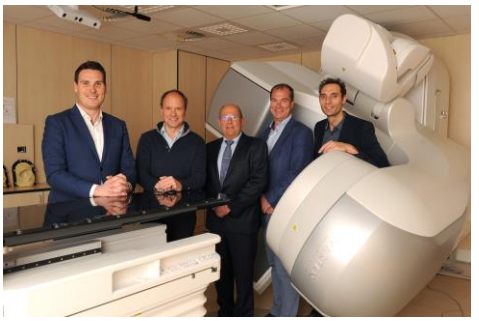
Patient had bilateral NS RALP in March 2017

- Definitive pathology: pT2c pN0 R0, Gleason 3+4=7
- Current status after 2,5 years:
  - PSA < 0,01 µg/L
  - good continence, no pads
  - erectile dysfunction, uses Sildenafil with little effect

Conclusions

- Overall and prostate cancer-specific survival rates are probably equivalent for the 3 major options in localized prostate cancer and are therefore insufficient to allow sound clinical decisions to be made.
- However, there is robust evidence that the choice of primary treatment results in a particular short- and medium-term adverse event profile. This should be discussed in detail with patients during pretreatment counselling.
- Generally, active surveillance has the lowest impact on cancer-specific QoL, although symptoms appear with changes of treatment and ageing. Surgery has a negative impact on urinary and sexual function when compared with active surveillance and EBRT. EBRT has a negative impact on bowel function when compared with active surveillance and surgery.
- Quality of life, anxiety and depression are probably equivalent on surveillance compared with active treatments.

Lardas M. et al. Eur Urol 2017.



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