

Från mikroskop till makroskop – när MR och PET möter patologi vid prostatacancer

Tufve Nyholm

Professor

Medicinsk strålningsfysik



UMEÅ UNIVERSITET

Brett samarbetsprojekt

Patologi (Anders Berg, Angsana Lindberg), Onkologi, Urologi, Radiologi och medicinsk strålningsfysik

Upplägg

- Kort om strålbehandling av prostatacancer
- Databaser av MR och PET bilder matchade med histo-patologiska storsnitt
- Urval av resultat

Behandling av prostatacancer

Kirurgi

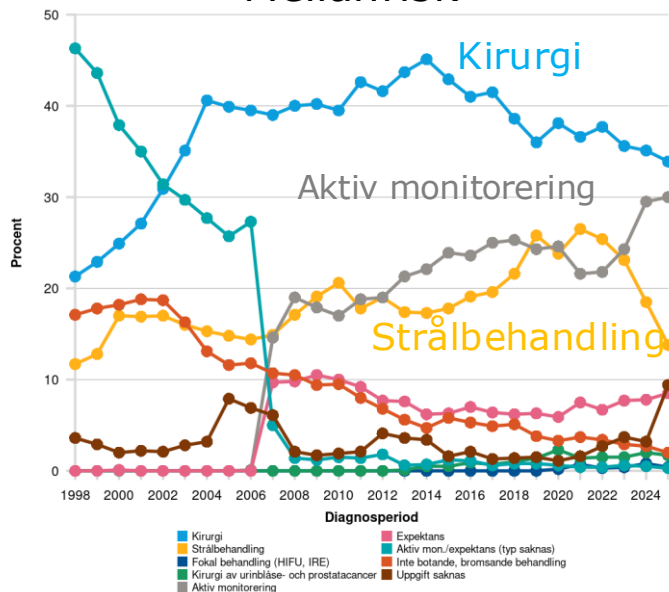


Strålbehandling



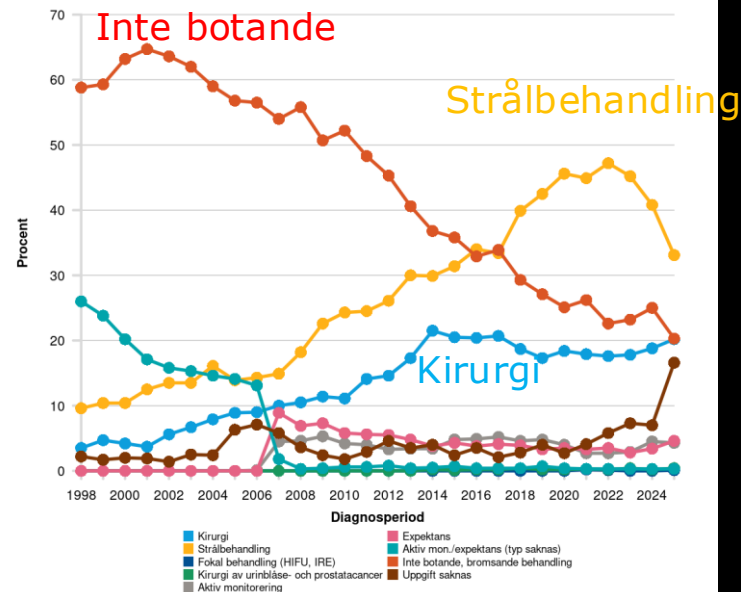
RIKET

Mellanrisk



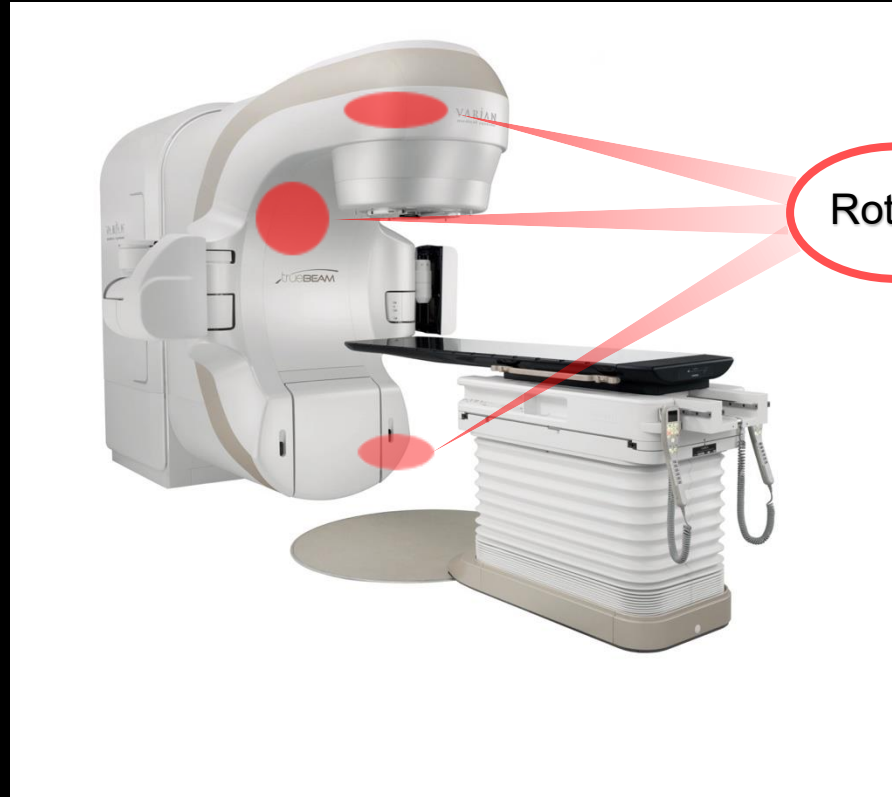
RIKET

Högrisk och mycket högrisk



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Strålbehandling

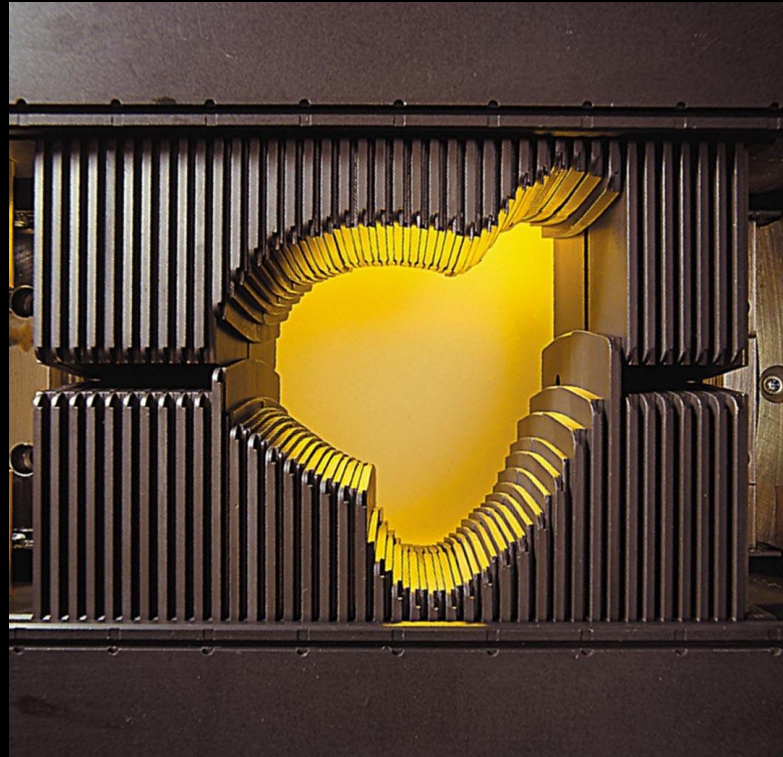


Strålbehandling

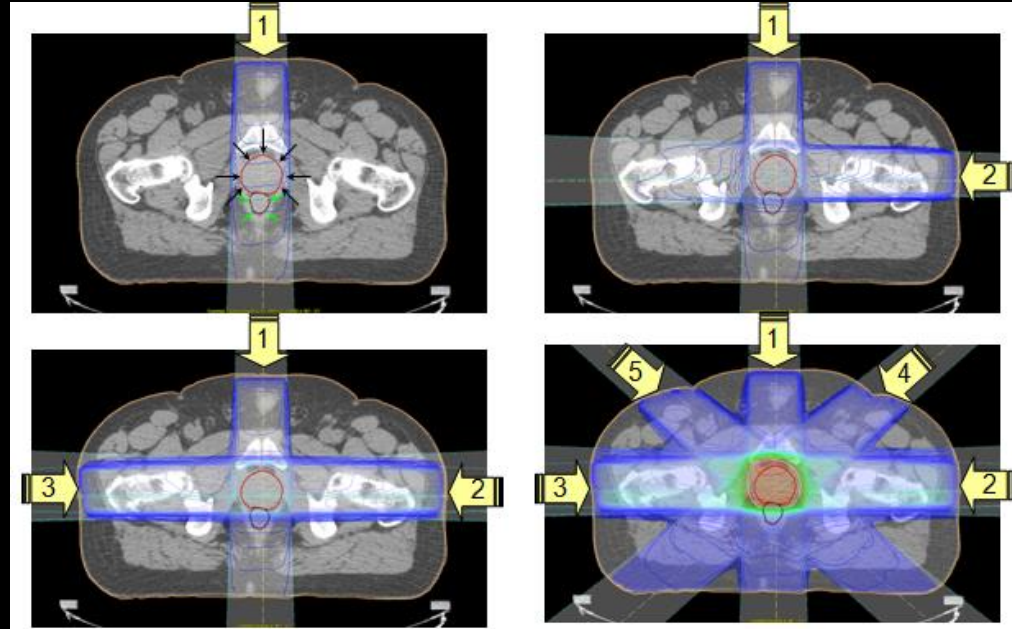


MLC

Multi leaf collimator

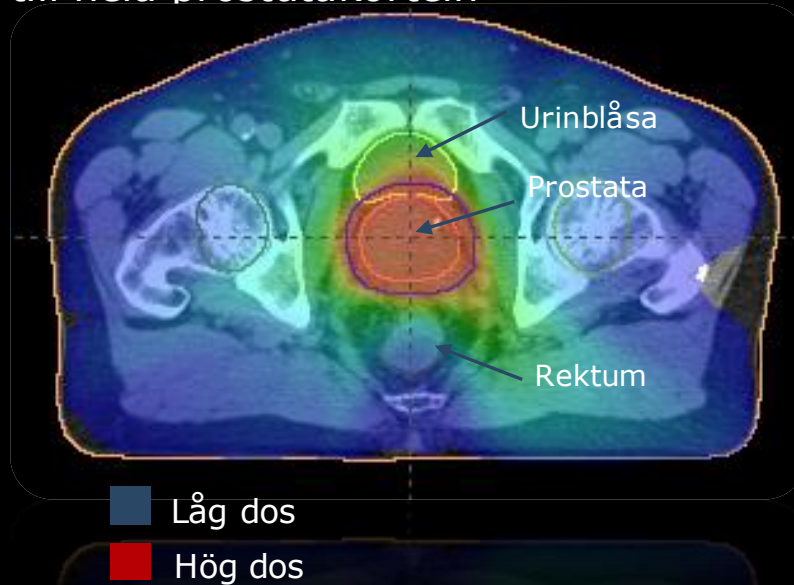


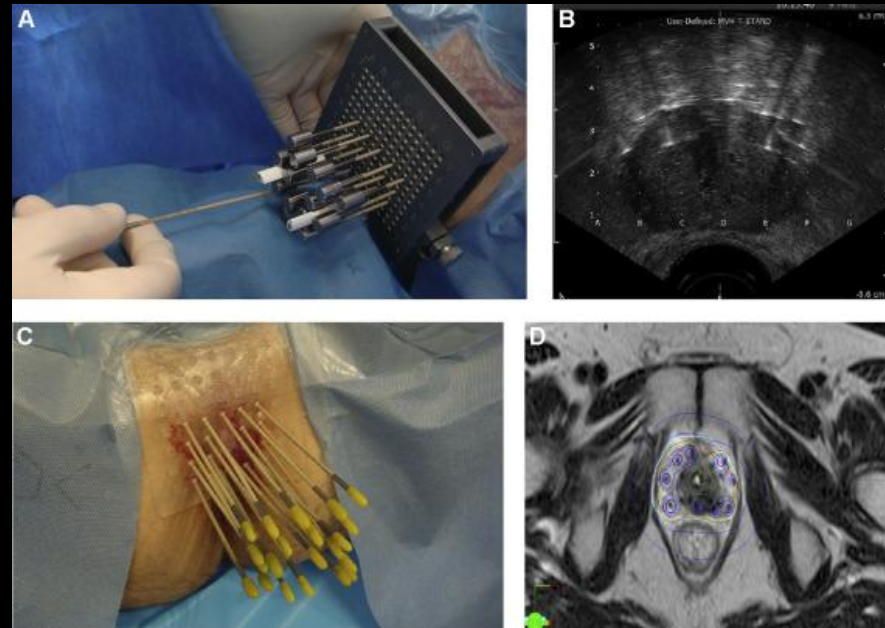
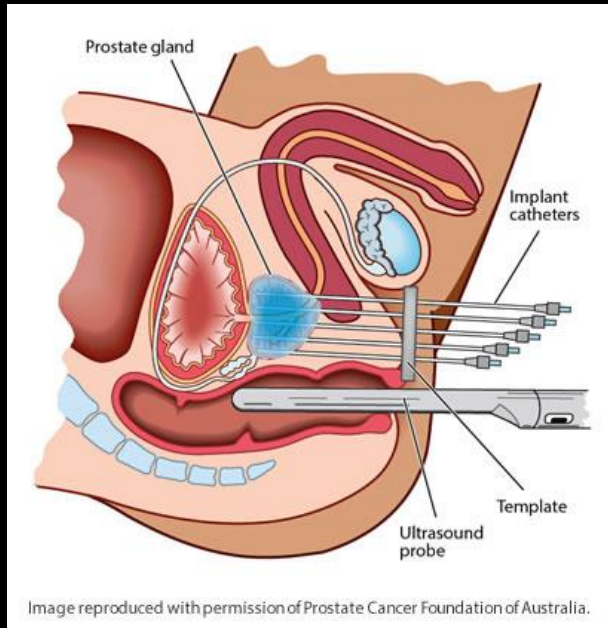
Strålbehandling



Prostatacancer och Strålbehandling

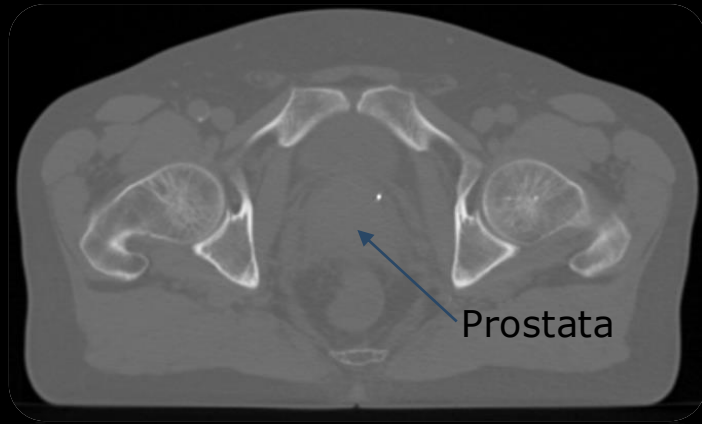
- Behandlingen optimeras för varje patient
- Samma stråldos till hela prostatakörteln



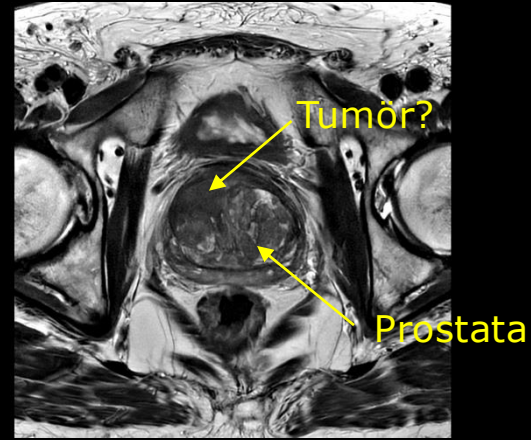


Nya typer av bilder – Ny information

Datortomograf (CT)

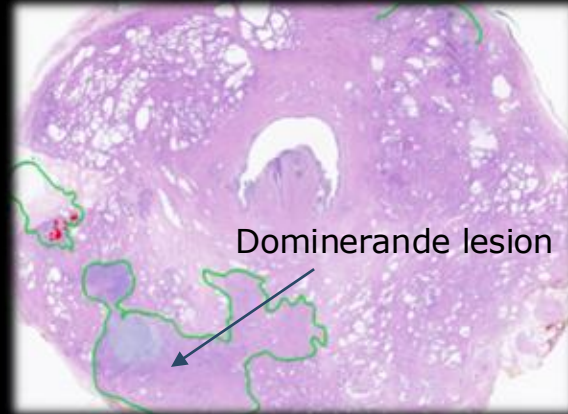


Magnetkamera (MR)



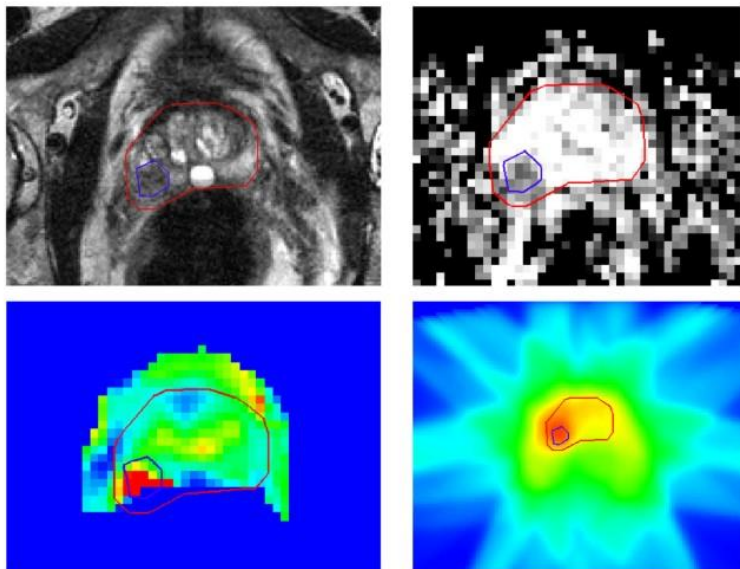
Ska man ge extra dos till den synliga tumören?

- Observation: Lokala återfall kommer ofta i anslutning till dominerade lesion

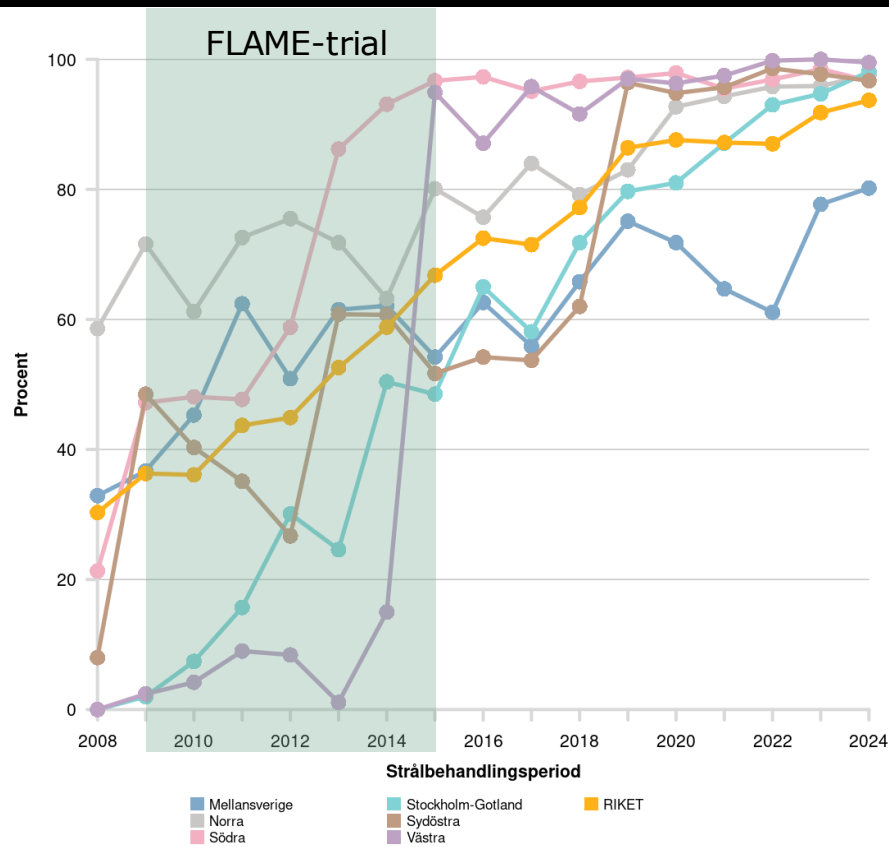


Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial

Linda G. W. Kerkmeijer, MD, PhD^{1,2}; Veerle H. Groen, MD³; Floris J. Pos, MD, PhD⁴; Karin Haustermans, MD, PhD⁵; Evelyn M. Monnikhof, PhD⁶; Robert Jan Smeenk, MD, PhD⁷; Martina Kunze-Busch, PhD⁸; Johannes C. J. de Boer, PhD⁹; Jochem van der Voort van Zijp, MD, PhD¹; Marco van Vulpen, MD, PhD¹; Cédric Draulans, MD, PhD¹; Laura van den Bergh, MD, PhD¹; Sofie Isebaert, PhD¹; and Uulke A. van der Heide, PhD¹



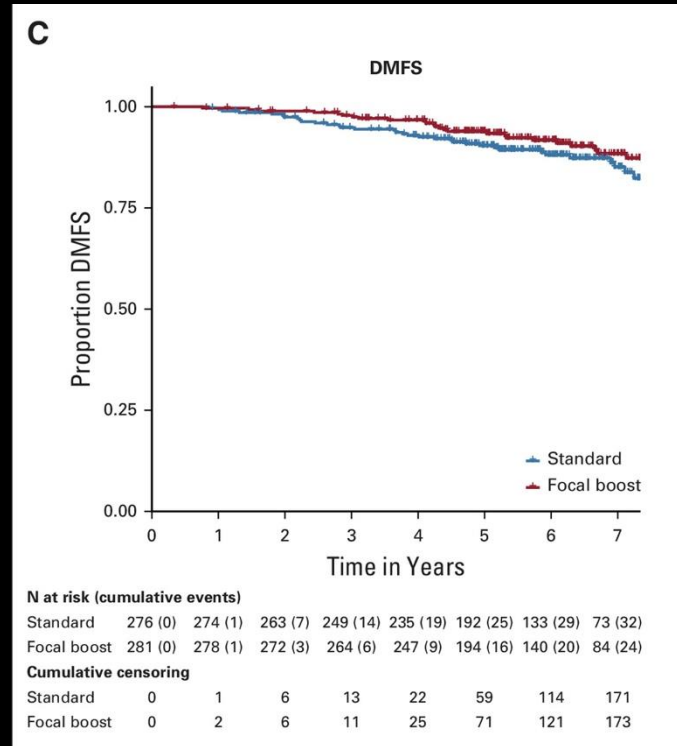
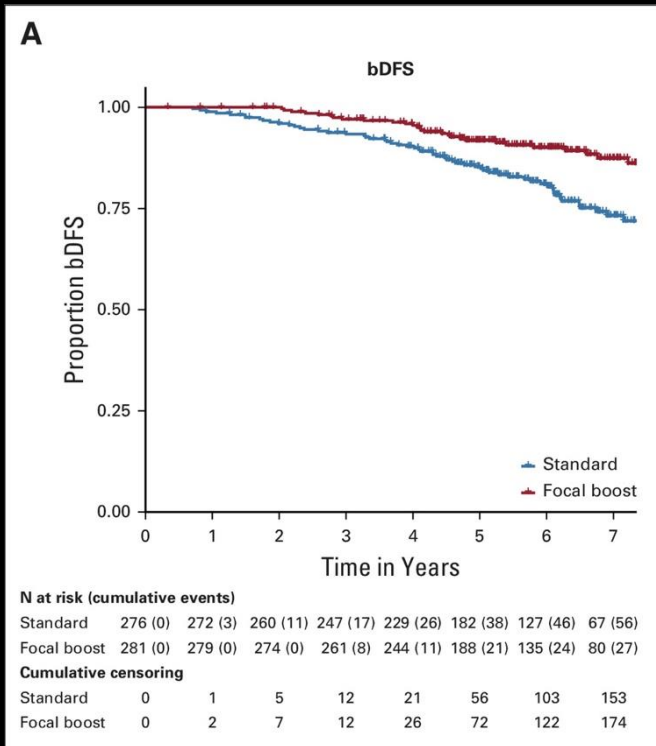
MR eller PET-CT använd vid definition av target vid extern/extern + brachy RT



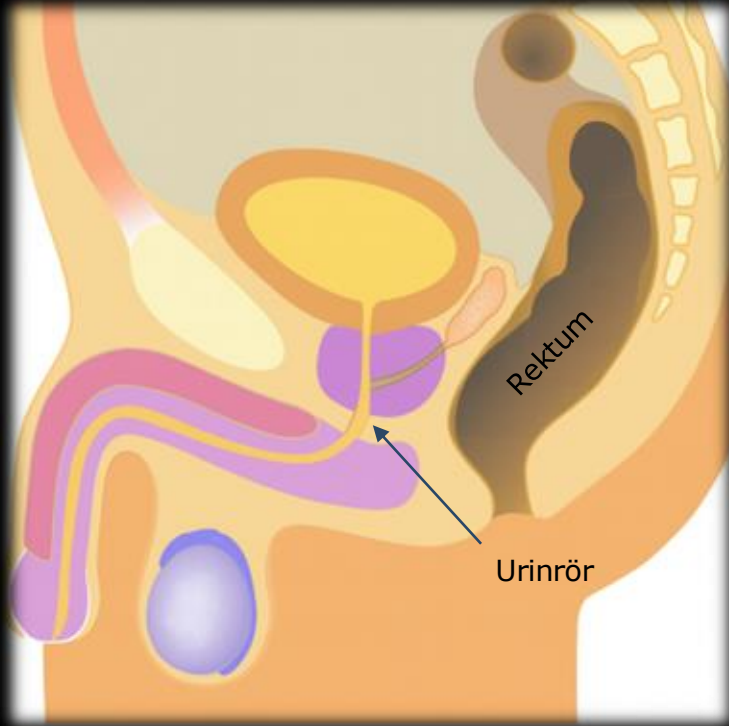
original reports

Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial

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Biverkningar



Urinrör

- Förträngning
- Blödning
- Sveda/smärta

Rektum

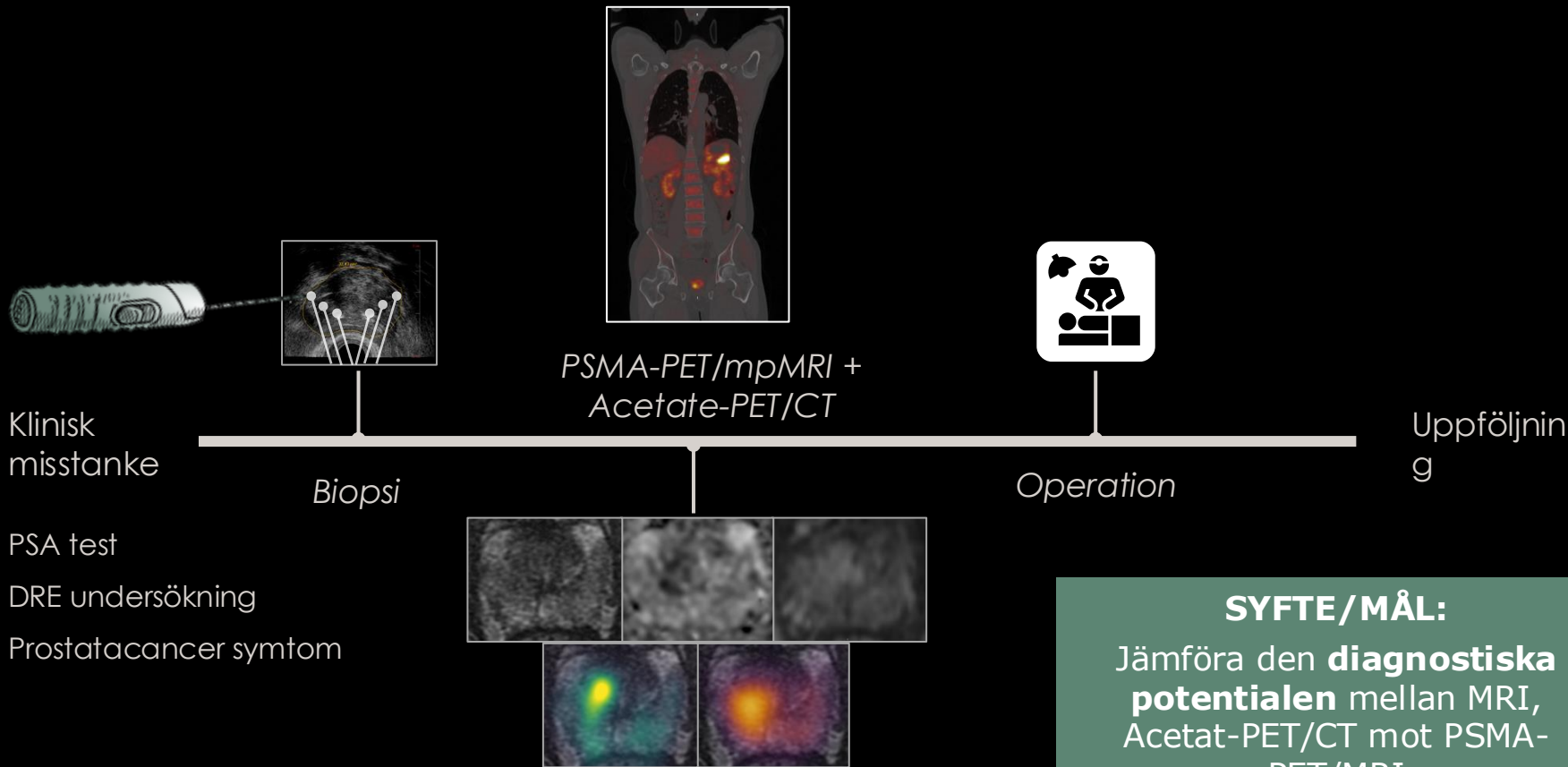
- Trängningar
- Blödning
- Slem
- Smärta

PAMP-studien

-Hur väl presterar våra diagnostiska imaging metoder?



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SYFTE/MÅL:

Jämföra den **diagnostiska potentialen** mellan MRI, Acetat-PET/CT mot PSMA-PET/MRI

- med histopatologi som referensstandard

Klinisk
misstanke



Biopsi

*In vivo
MR + PET*



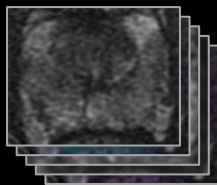
Operation

Uppföljning

PSA test

DRE undersökning

Prostatacancer symptom



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Klinisk
misstanke

PSA test

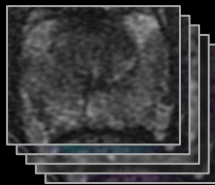
DRE undersökning

Prostatacancer symptom



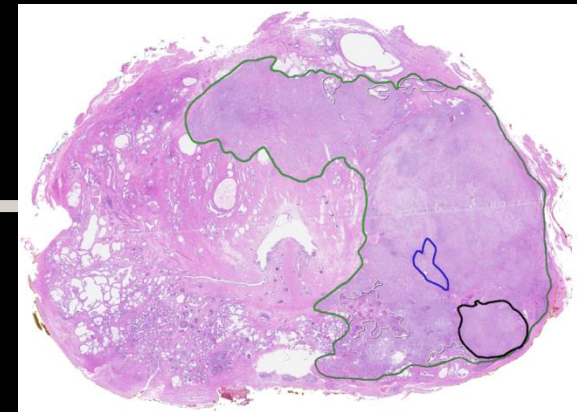
Biopsi

*In vivo
MR + PET*



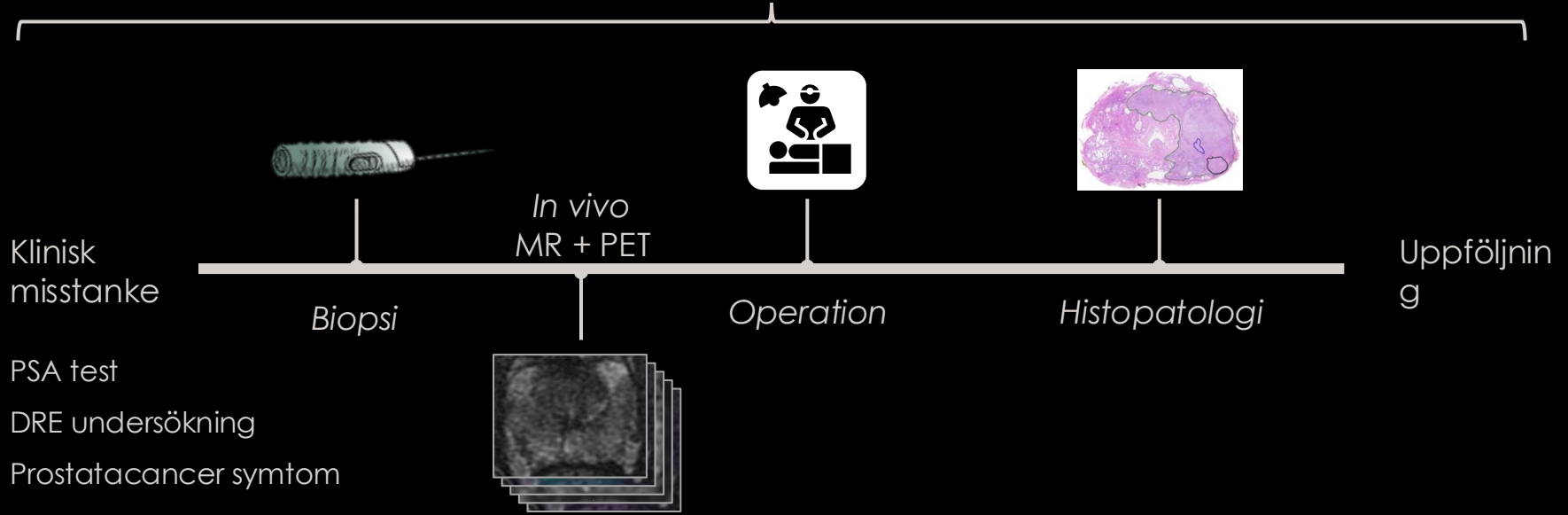
Operation

Histopatologi

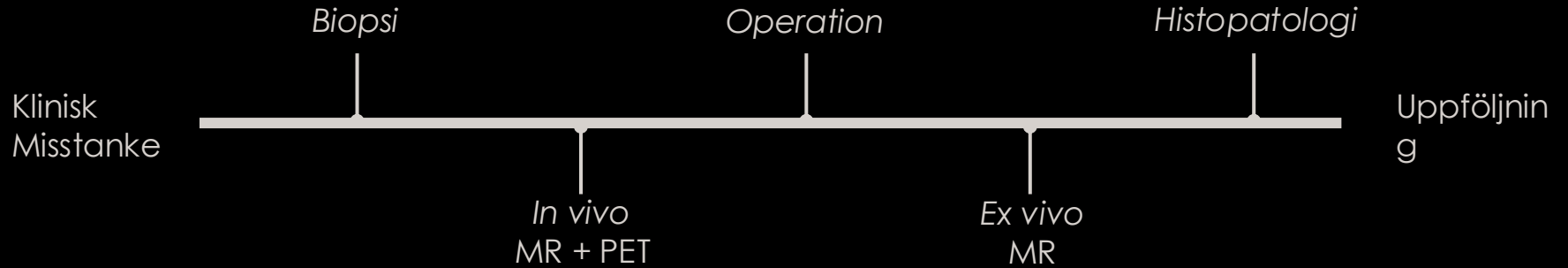


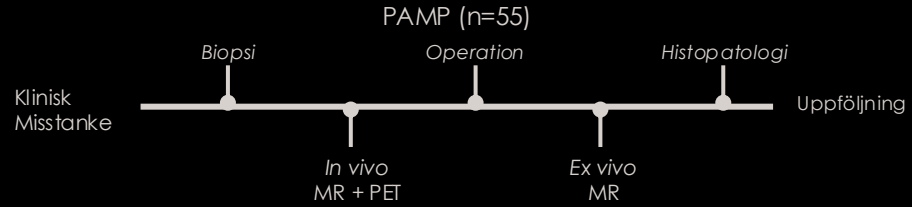
PAMP (n=55)

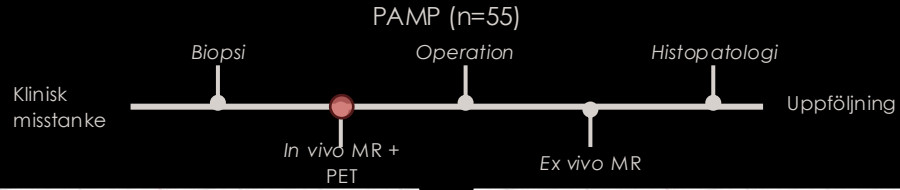
PSMA-PET, Acetat-PET, MRI, Patologi



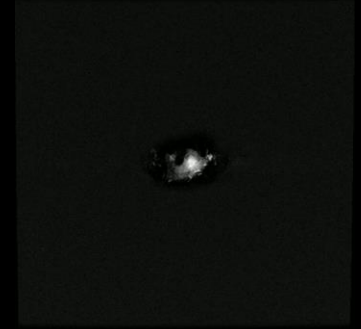
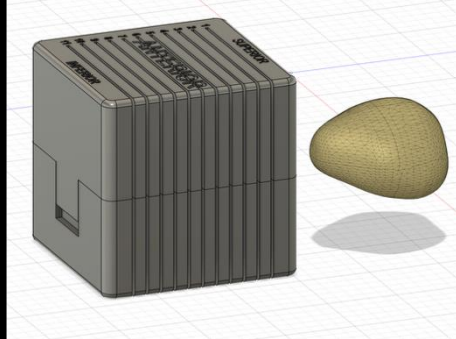
PAMP (n=55)



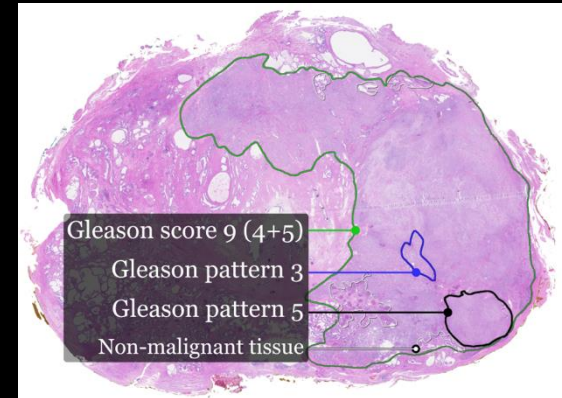


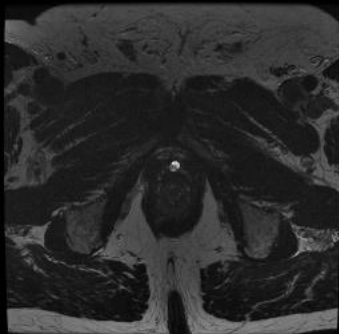
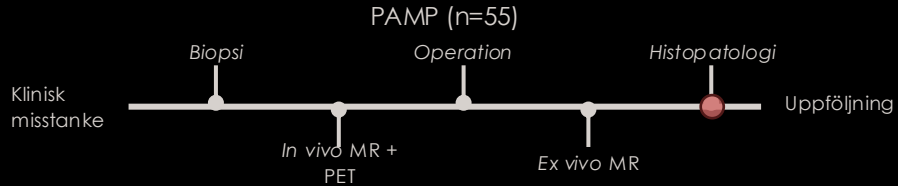


In vivo MR

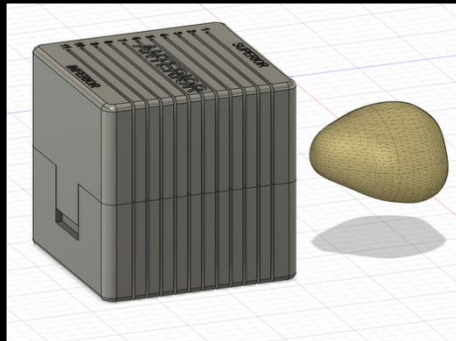


Ex vivo MR

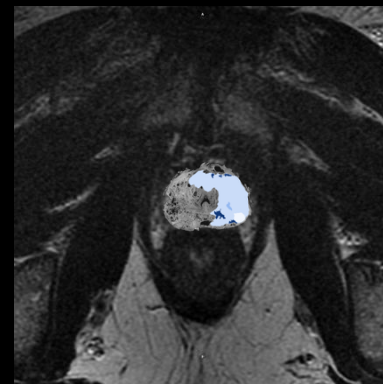
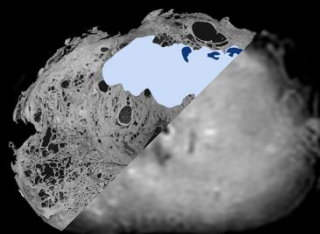
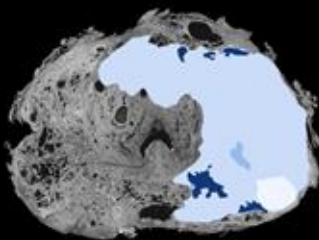




In vivo MR



Ex vivo MR



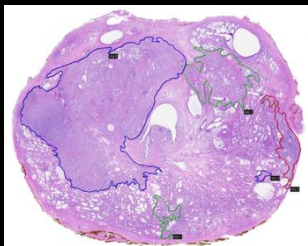
- Gleason pattern 5
- Gleason pattern 4
- Gleason pattern 3
- Non-malignant tissue

Histopatologi

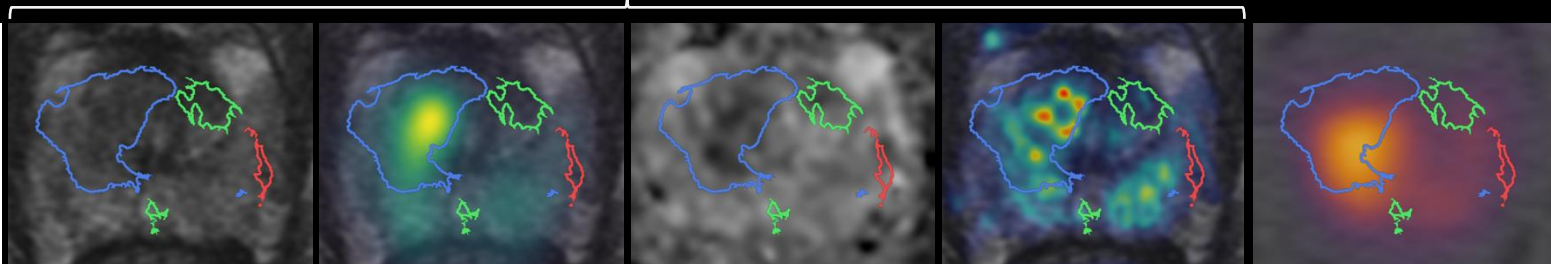
Ex vivo MR

In vivo MR

PSMA-PET/mpMRI



Histopathology



T2w

PSMA-PET

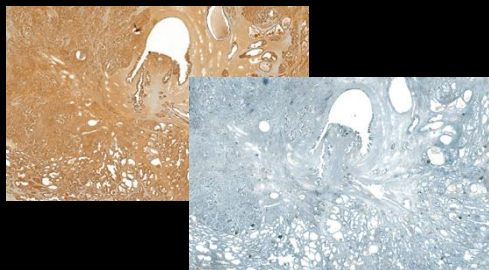
ADC

K^{trans}

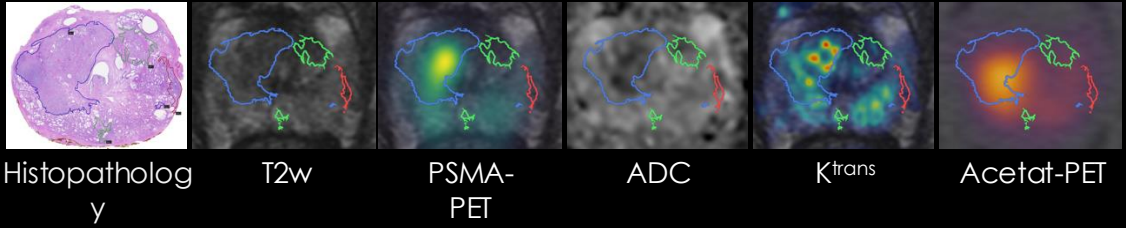
Acetat-PET

H&E

- Ki-67
- PSMA
- PSA
- FactorVII



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1. Hur många av tumörerna kan vi detektera med MR och PET?
2. Hur väl kan MR och PET avgöra tumörstadiet?
3. Vilka tumörer hittar vs missar vi?
4. Hur väl kan MR och PET avgöra lesionernas utbredning?
5. Vad behandlas vid strålbehandling med tumörboost?

"Data characteristics"

Table 1 Characteristics of the 55 included study participants

| Characteristics | Median (min, max) |
|--|-------------------|
| Age [years] | 63 (45, 76) |
| PSA [ng/ml] | 6.3 (2.9, 13.3) |
| Days between imaging and surgery | 26 (2, 138) |
| Injected activity PSMA [MBq] | 163 (121, 201) |
| Post RP ISUP | N (%) |
| 2 | 29 (52.7) |
| 3 | 17 (30.9) |
| 4 | 5 (9.1) |
| 5 | 4 (7.3) |
| pT status | |
| T2 | 25 (45.5) |
| T3 | 30 (54.5) |
| pN status | |
| Not removed | 44 (80.0) |
| Lymph nodes removed without metastasis | 9 (16.4) |
| Lymph nodes removed with metastasis | 2 (3.6) |
| Surgical margin | |
| Positive | 14 (25.5) |
| Negative | 41 (74.5) |
| Seminal vesicle involvement | |
| None | 51 (92.7) |
| Right | 0 (0) |
| Left | 2 (3.6) |
| Both | 2 (3.6) |

N=number of patients, RP=radical prostatectomy.

| Gleason | ISUP | >0.05 cc | >0.1 cc | >0.5 cc |
|-------------|------|----------|---------|---------|
| Alla grader | | 130 | 88 | 43 |
| 3+3 | 1 | 34 | 14 | 1 |
| 3+4 | 2 | 50 | 33 | 14 |
| 4+3 | 3 | 23 | 20 | 11 |
| 4+4 | 4 | 19 | 17 | 13 |
| > 4+4 | 5 | 4 | 4 | 4 |

42 kliniskt signifikanta lesioner (38 patienter)

Klinisk signifikant lesion utifrån PI-RADS v2.1s definition:

- Gleason score $\geq 3+4$, och/eller
- Volume > 0.5 cc, och/eller
- *Extraprostatisk extension (EPE)*.

1. Hur många av tumörerna kan vi detektera med MR och PET?

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Modality

Mean detection rate

mpMRI

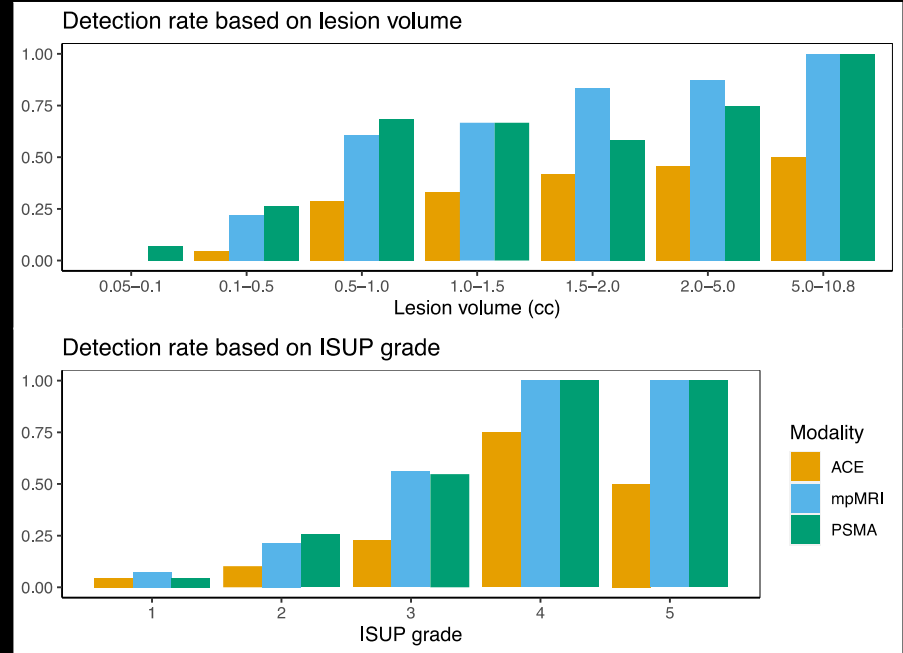
74 % (31/42)

PSMA

70 % (29.5/42)

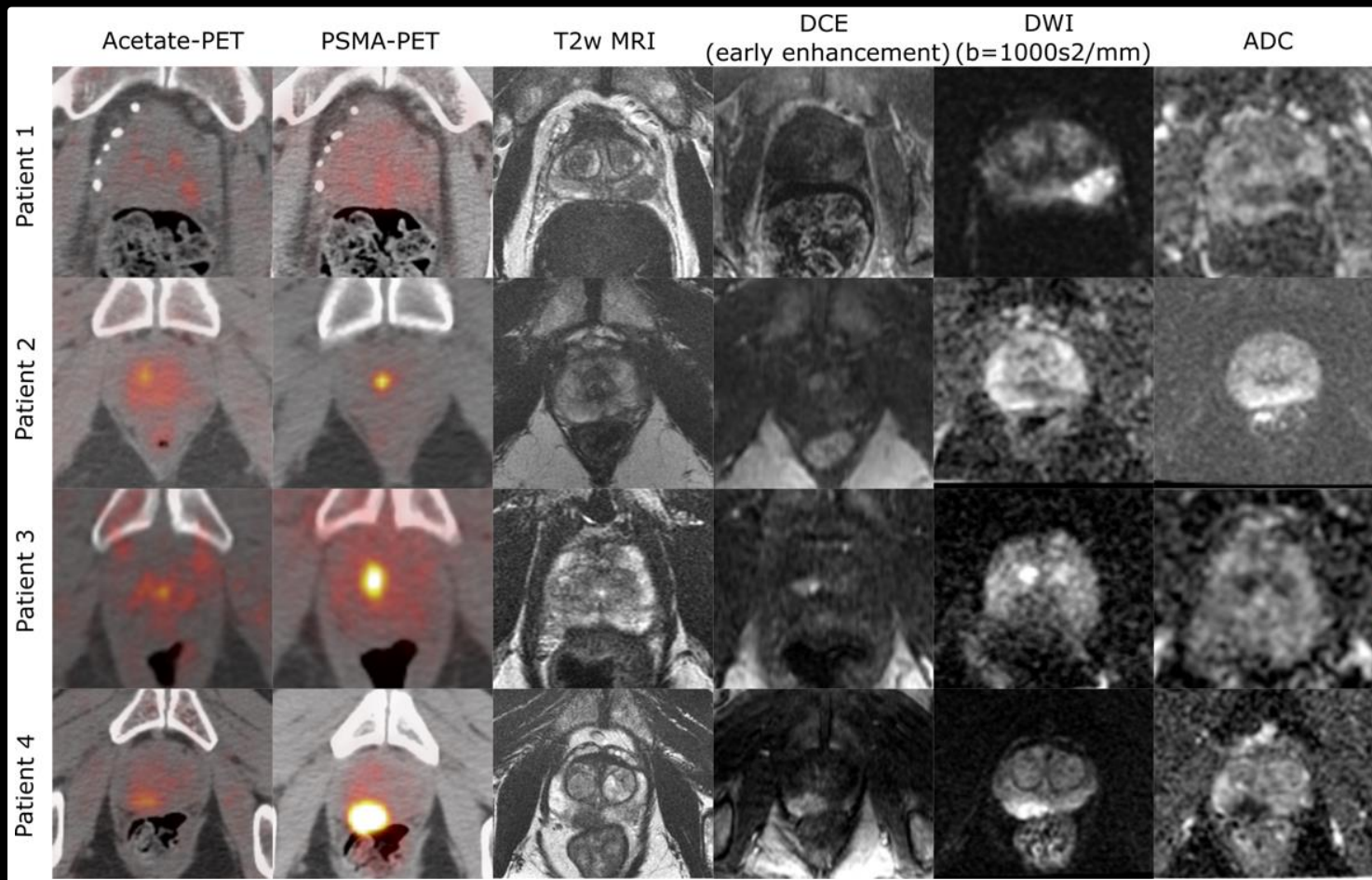
ACE

37 % (15.5/42)

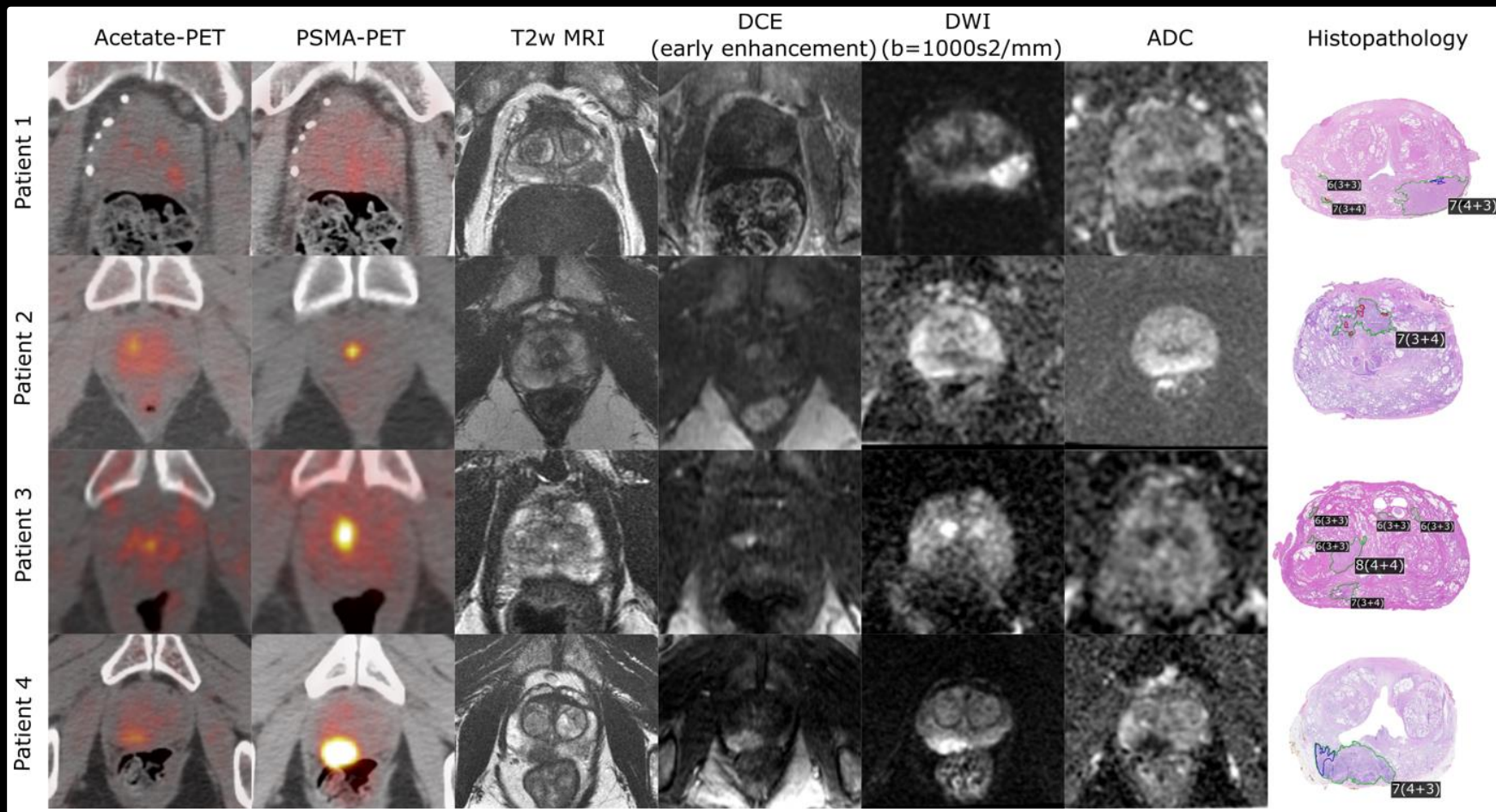


| ISUP 1 | ISUP 2 | ISUP 3 | ISUP 4 | ISUP 5 |
|--------|--------|--------|----------------------------|----------------------------|
| GS 3+3 | GS 3+4 | GS 4+3 | GS 4+4 GS 3+5 GS 5+3 | GS 4+5 GS 5+4 GS 5+5 |

1. Hur många av tumörerna kan vi detektera med MR och PET?

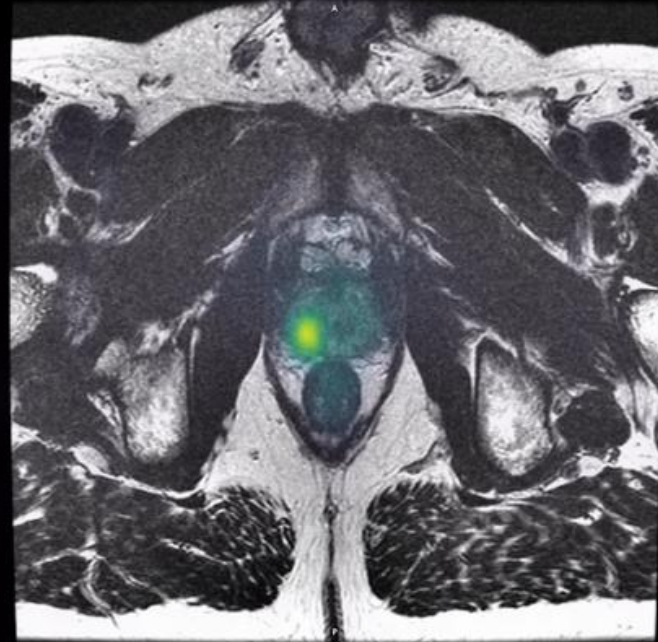


1. Hur många av tumörerna kan vi detektera med MR och PET?



1. Hur många av tumörerna kan vi detektera med MR och PET?

| Modality | Mean detection rate |
|-----------------------|----------------------|
| mpMRI | 74 % (31/42) |
| PSMA | 70 % (29.5/42) |
| ACE | 37 % (15.5/42) |
| PSMA-PET/mpMRI | 85% (35.5/42) |

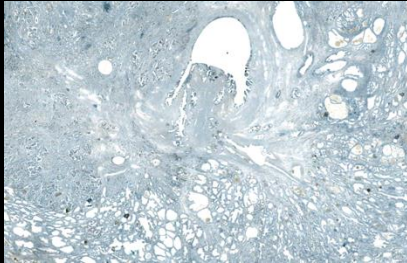


2. Hur väl kan MR och PET avgöra tumörstadiet?

| Modality | Sensitivity EPE | Specificity EPE | Modality | Sensitivity SVI | Specificity SVI |
|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| mpMRI | 37 % | 96 % | mpMRI | 38 % | 95 % |
| PSMA | 7 % | 98 % | PSMA | 38 % | 97 % |
| PSMA- PET/mpMRI | 32 % | 100 % | PSMA- PET/mpMRI | 50 % | 100 % |

3. Vilka tumörer hittar vs missar vi?

Ki-67: Proliferation



Score: % Positiva



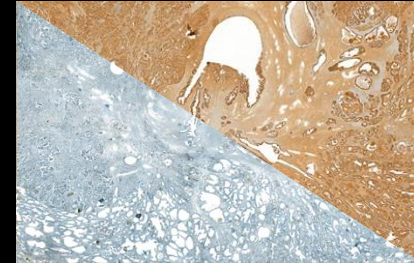
Vävnads-PSA:
Differentiation



Score: % Positiva ×
intensiteten



Riskgrupper



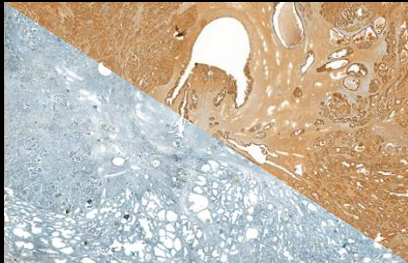
IHC subgroup B: högt Ki-67 & lågt PSA
IHC subgroup A: lågt Ki-67 & högt PSA



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3. Vilka tumörer hittar vs missar vi?

IHC subgroup B: högt Ki-67 & lågt PSA
IHC subgroup A: lågt Ki-67 & högt PSA



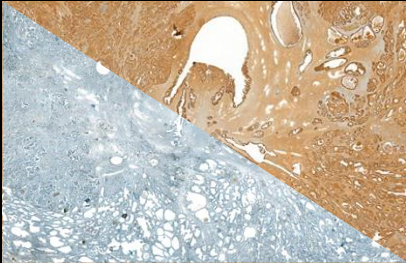
| | IHC subgroup A | IHC subgroup B |
|-----------|----------------|----------------|
| Detektion | | |
| MR+ | 2 | 24 |
| MR- | 11 | 14 |
| PET+ | 4 | 22 |
| PET- | 9 | 16 |
| PET/MR+ | 7 | 26 |
| PET/MR- | 6 | 12 |

Bland de 38 lesioner som tillhörde **IHC-subgrupp B** kunde:

63% detekteras med mpMRI,
58% med PSMA-PET och
69% med PSMA-PET/mpMRI

3. Vilka tumörer hittar vs missar vi?

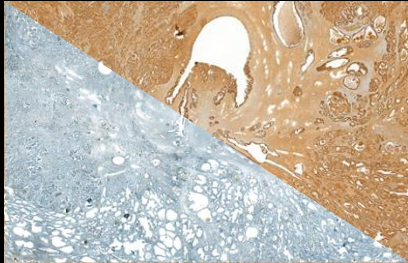
IHC subgroup B: högt Ki-67 & lågt PSA
IHC subgroup A: lågt Ki-67 & högt PSA



| Detektion | IHC subgroup A | | IHC subgroup B | |
|---------------------|----------------|--------------|----------------|--------------|
| | IGG \leq 2 | IGG \geq 3 | IGG \leq 2 | IGG \geq 3 |
| MR ⁺ | 0 | 2 | 5 | 19 |
| MR ⁻ | 9 | 2 | 8 | 6 |
| PET ⁺ | 1 | 3 | 5 | 17 |
| PET ⁻ | 8 | 1 | 8 | 8 |
| PET/MR ⁺ | 3 | 4 | 5 | 21 |
| PET/MR ⁻ | 6 | 0 | 8 | 4 |

3. Vilka tumörer hittar vs missar vi?

IHC subgroup B: högt Ki-67 & lågt PSA
IHC subgroup A: lågt Ki-67 & högt PSA

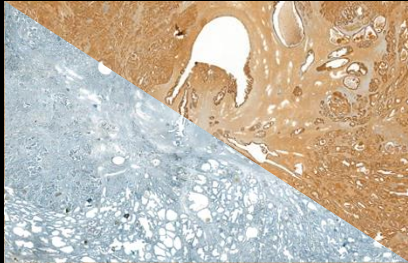


| Detektion | IHC subgroup A | | IHC subgroup B | |
|---------------------|----------------|--------------|----------------|--------------|
| | IGG \leq 2 | IGG \geq 3 | IGG \leq 2 | IGG \geq 3 |
| MR ⁺ | 0 | 2 | 5 | 19 |
| MR ⁻ | 9 | 2 | 8 | 6 |
| PET ⁺ | 1 | 3 | 5 | 17 |
| PET ⁻ | 8 | 1 | 8 | 8 |
| PET/MR ⁺ | 3 | 4 | 5 | 21 |
| PET/MR ⁻ | 6 | 0 | 8 | 4 |

Större sannolikhet att detektera höggradiga än låggradiga

3. Vilka tumörer hittar vs missar vi?

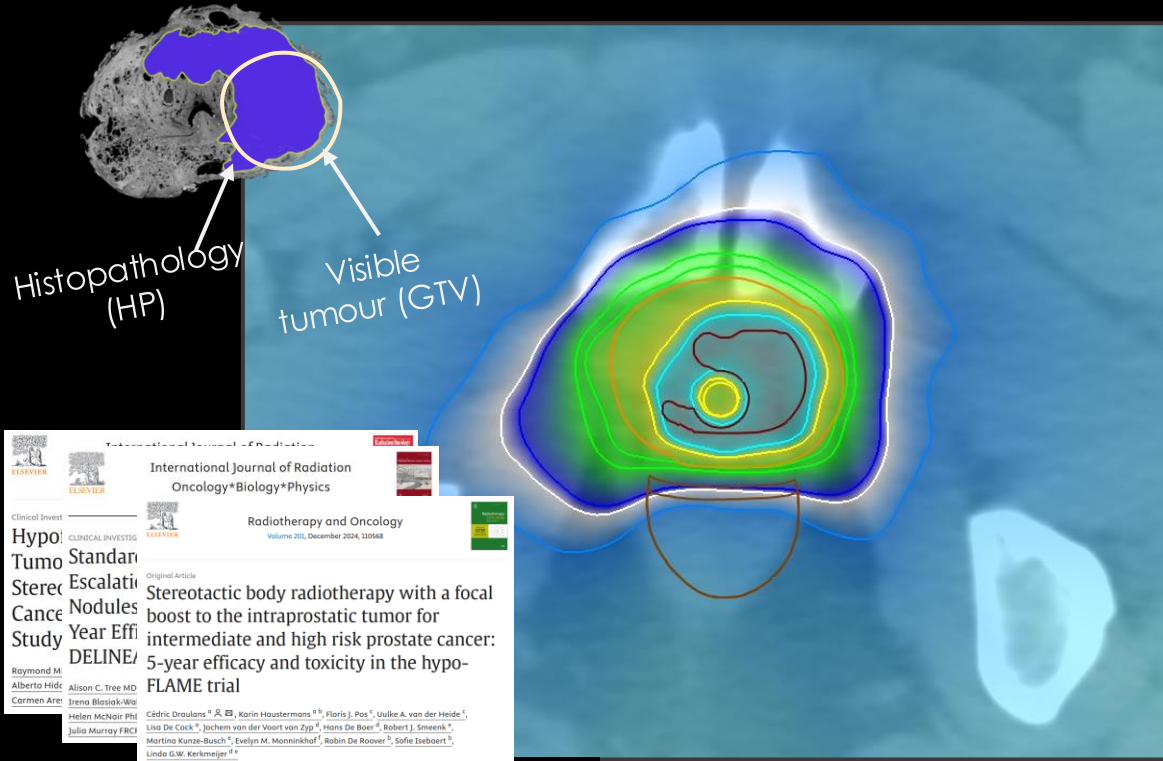
IHC subgroup B: högt Ki-67 & lågt PSA
IHC subgroup A: lågt Ki-67 & högt PSA



| Detektion | IHC subgroup A | | IHC subgroup B | |
|---------------------|----------------|--------------|----------------|--------------|
| | IGG \leq 2 | IGG \geq 3 | IGG \leq 2 | IGG \geq 3 |
| MR ⁺ | 0 | 2 | 5 | 19 |
| MR ⁻ | 9 | 2 | 8 | 6 |
| PET ⁺ | 1 | 3 | 5 | 17 |
| PET ⁻ | 8 | 1 | 8 | 8 |
| PET/MR ⁺ | 3 | 4 | 5 | 21 |
| PET/MR ⁻ | 6 | 0 | 8 | 4 |

Odetekterade lesioner kan vara av **högrisk**
(IHC subgroup B)

4. Hur väl kan MR och PET avgöra lesionernas utbredning?



Att kombinera fokal dosökning mot tumören och hypo-fraktionering har visat lovande resultat¹⁻³

Betydande skillnader i GTV definition har dock visats⁴

Svårt att verifiera då den **verkliga targettäckningen och tumörbördan är okänd**

International Journal of Radiation Oncology*Biolog*Physics

Radiotherapy and Oncology

Volume 201, December 2024, 119568

Original Article

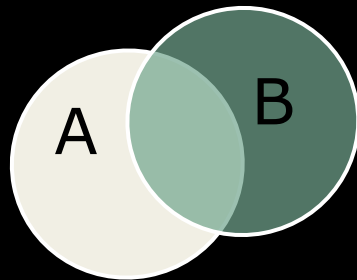
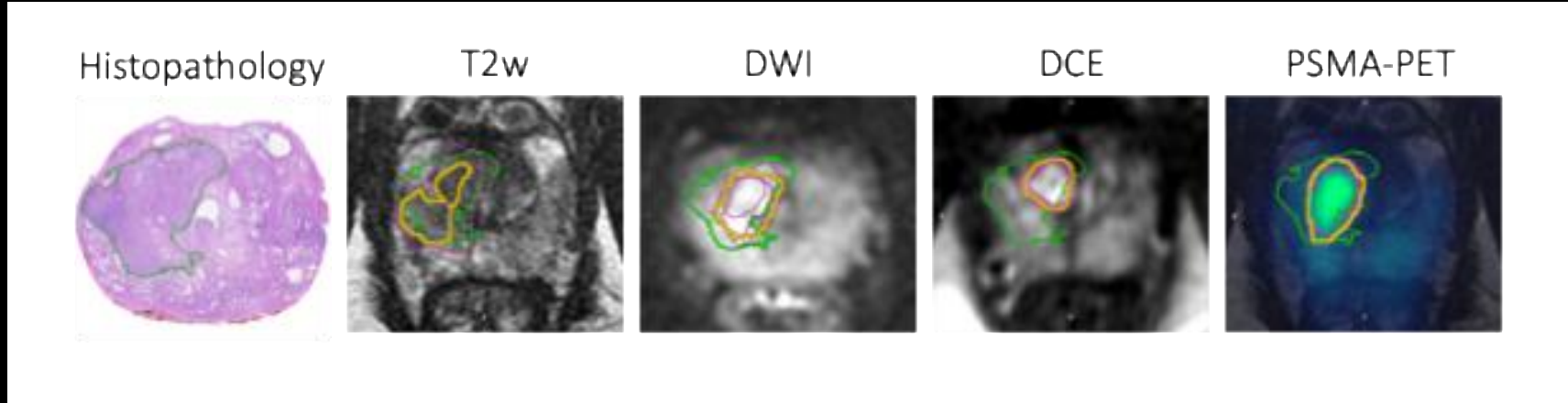
Stereotactic body radiotherapy with a focal boost to the intraprostatic tumor for intermediate and high risk prostate cancer: 5-year efficacy and toxicity in the hypo-FLAME trial

Cédric Draulans^{a,*,}, Karin Houstermans^{a,*,}, Floris J. Pos^{b,}, Usulke A. van der Heide^{c,}, Lisa De Cock^{d,}, Jochem van der Voort van Zipp^{e,}, Hans De Boer^{f,}, Robert J. Smeenk^{g,}, Martina Kurus-Busch^{h,}, Evelyn M. Manninkhof^{i,}, Robbin De Roover^{j,}, Sofie Isebaert^{k,}, Linda G.W. Kerkmeijer^{l,*}

Raymond M. Alberto Hidalgo Cermen Are Helen McNaair Phd Julia Murray FRCS Alison C. Tree MD Irene Blasiak-Wu

1. Miralbell R, et al. (2010)
2. Tree AC, et al. DELINEATE trial (2016)
3. Draulans C et al. Hypo-FLAME (2024)
4. Van Schie MA, et al. (2018)

4. Hur väl kan MR och PET avgöra lesionernas utbredning?



$$DSC = \frac{2 * |A \cap B|}{|A| + |B|}$$

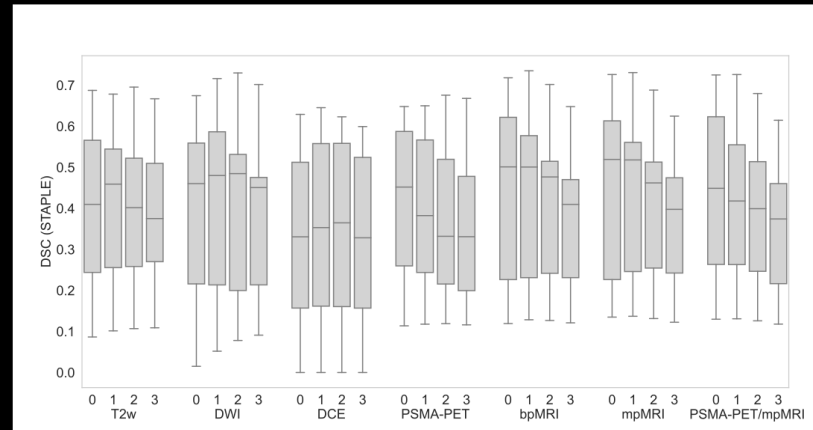
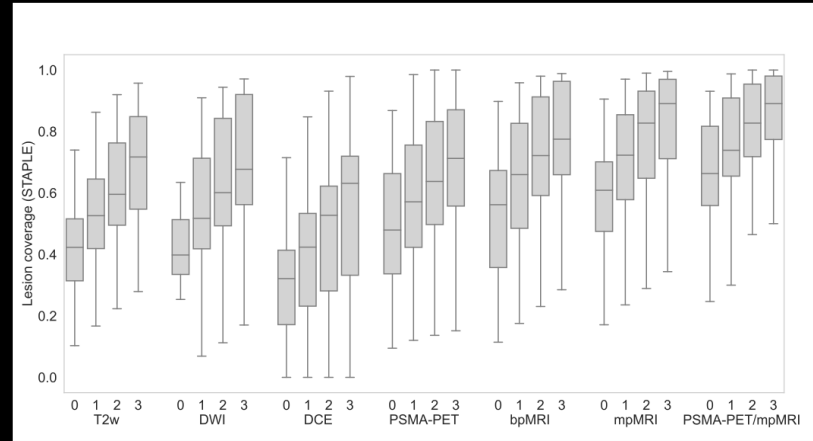
$$Lesion\ coverage = \frac{|A \cap B|}{|A|}$$

4. Hur väl kan MR och PET avgöra lesionernas utbredning?

mpMRI och PSMA-PET/mpMRI hade bäst "lesion coverage" med minst frisk vävnad i targetvolymen

Marginal på enskild modalitet gav motsvarande "lesion coverage" men resulterade i mer exponerad "icke-lesion"

Genomgående svårt att definiera hela lesionen utan att inkludera för mycket friskvävnad!



6. Vad behandlas vid strålbehandling med tumörboost?

Protocol characteristics

Prostate PTV (PTVT1): 42.7 Gy in 7 fractions

GTV: Up to 49.0 Gy prioritizing OARs

Seminal vesicles (PTVT2): 31.2 Gy

Lymph nodes (PTVTN): 29.4 Gy

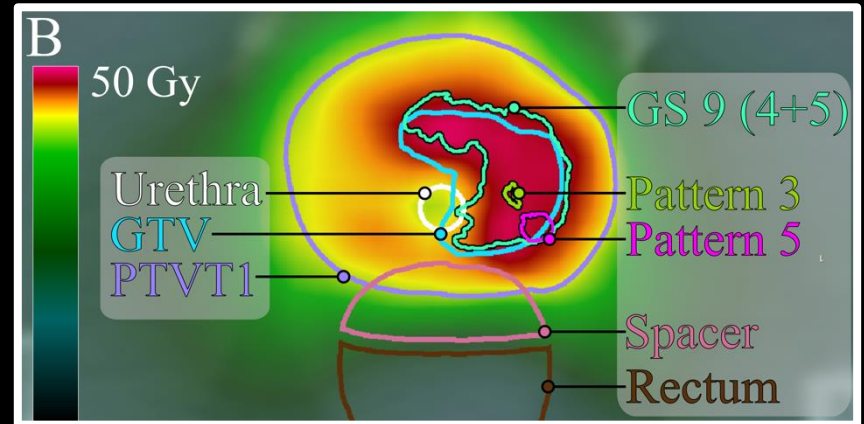
Urethra: $D_{0.05cc} < 44.8$ Gy

GTV: Visible tumour on PSMA-PET/mpMRI

CTVT1: Prostate gland + GTV

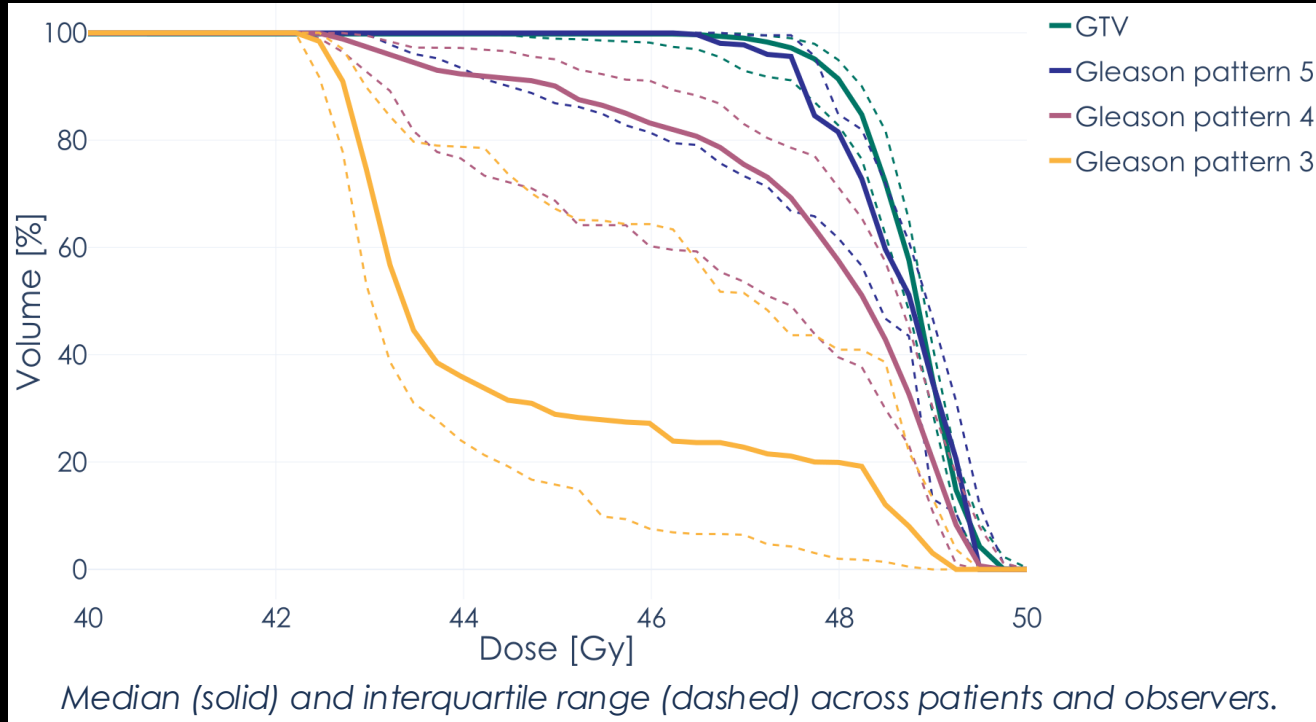
PTVT1: CTVT1 + 5 mm

Rectum spacer: 10 mm separation between prostate CTV and Rectum



15 patienter x 4 planer (med olika GTVn)


6. Vad behandlas vid strålbehandling med tumörboost?




Sammanfattning

- Vi hittar ca 70% av de klinisk signifikanta tumörerna med MR eller PSMA-PET
 - **PSMA-PET/mpMRI ger bättre detektion** (70% -> 85%)
 - Bättre detektion av större och höggradiga lesioner
 - Icke-detekterade lesioner kan vara av höggrad och/eller högrisk (IHC-group B)
- **PSMA-PET/mpMRI ger bäst bild av utbredningen**
 - Marginal på enskild modalitet gav motsvarande tumörtäckning men resulterade i att mer frisk vävnad inkluderades
 - Delar av lesioner är ofta inte synliga på varken MR eller PET
- **Höggradiga tumörområden får högre dos** vid strålbehandling med extern-boost
 - trots icke optimal interobserver-agreement vid tumörutritning

Referenser använda i denna presentation

 Physics and Imaging in Radiation Oncology
Volume 18, April 2021, Pages 19–25



Registration of histopathology to magnetic resonance imaging of prostate cancer

Kristina Sandgren ^{a,*,} Erik Nilsson ^{a,} Angsana Keeratjarat Lindberg ^{a,} Sara Strandberg ^{b,} Lennart Blomqvist ^{c,} Anders Bergh ^{d,} Bengt Friedrich ^{e,} Jan Axelsson ^{a,} Margareta Ögren ^{b,} Mattias Ögren ^{b,} Anders Widmark ^{f,} Camilla Thellenberg Karlsson ^{f,} Karin Söderkvist ^{f,} Katrine Riklund ^{g,} Joakim Jonsson ^{a,} Tufve Nyholm ^a

Article | [Open access](#) | Published: 09 November 2023

The grade of individual prostate cancer lesions predicted by magnetic resonance imaging and positron emission tomography

Erik Nilsson ^{a,} Kristina Sandgren, Josefine Grefve, Joakim Jonsson, Jan Axelsson, Angsana Keeratjarat Lindberg, Karin Söderkvist, Camilla Thellenberg Karlsson, Anders Widmark, Lennart Blomqvist, Sara Strandberg, Katrine Riklund, Anders Bergh & Tufve Nyholm


Communications Medicine 3, Article number: 164 (2023) | [Cite this article](#)


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ORIGINAL ARTICLES

Histopathology-validated lesion detection rates of clinically significant prostate cancer with mpMRI, [⁶⁸Ga]PSMA-11-PET and [¹¹C]Acetate-PET

Sandgren, Kristina^{a,1}; Strandberg, Sara N.^{b,2}; Jonsson, Joakim H.^c; Grefve, Josefine^d; Keeratjarat Lindberg, Angsana^e; Nilsson, Erik^b; Bergh, Anders^f; Söderkvist, Karin^f; Thellenberg Karlsson, Camilla^f; Friedrich, Bengt^g; Widmark, Anders^h; Blomqvist, Lennartⁱ; Berg Loegager, Vibeke^h; Axelsson, Jan^h; Ögren, Mattias^h; Ögren, Margareta^h; Nyholm, Tufve^h; Riklund, Katrine^h


Author information 


Nuclear Medicine Communications 44(11):997–1004, November 2023. | DOI: 10.1097/MNM.0000000000001743 

▶ *Acta Oncol.* 2025 Oct 27;64:44211. doi: [10.2340/1651-226X.2025.44211](https://doi.org/10.2340/1651-226X.2025.44211) 

Ultra-hypofractionated radiotherapy with focal boost for high-risk localized prostate cancer (HYPO-RT-PC-boost): *in silico* evaluation with histological reference

Erik Nilsson ^{a,*,} Anneli Nilsson ^{a,} Joakim Jonsson ^{a,} Kristina Sandgren ^{a,} Josefine Grefve ^{a,} Jan Axelsson ^{a,} Angsana K Lindberg ^{a,} Karin Söderkvist ^{b,} Camilla T Karlsson ^{b,} Björn Zackrisson ^{b,} Sara Strandberg ^{c,} Katrine Riklund ^{c,} Anders Bergh ^{d,} Mathieu Moreau ^{e,} Adalsteinn Gunnlaugsson ^{e,} Lars E Olsson ^{e,f,} Tufve Nyholm ^a


 Physics and Imaging in Radiation Oncology
Volume 31, July 2024, 100633



Original Research Article

Histopathology-validated gross tumor volume delineations of intraprostatic lesions using PSMA-positron emission tomography/multiparametric magnetic resonance imaging

Josefine Grefve ^{a,*,} Erik Nilsson ^{a,} Karin Söderkvist ^{b,} Adalsteinn Gunnlaugsson ^{c,} Kristina Sandgren ^{a,} Joakim Jonsson ^{a,} Angsana Keeratjarat Lindberg ^{a,} Erik Nilsson ^{a,} Jan Axelsson ^{a,} Anders Bergh ^{d,} Björn Zackrisson ^{b,} Mathieu Moreau ^{e,} Camilla Thellenberg Karlsson ^{b,} Lars E. Olsson ^{f,} Anders Widmark ^{h,} Katrine Riklund ^{d,} Lennart Blomqvist ^{d,} Vibeke Berg Loegager ^{g,} Sara N. Strandberg ^{d,} Tufve Nyholm ^a

▶ *Acta Oncol.* 2024 Jun 23;63:39041. doi: [10.2340/1651-226X.2024.39041](https://doi.org/10.2340/1651-226X.2024.39041) 

Accuracy of gross tumour volume delineation with [⁶⁸Ga]-PSMA-PET compared to histopathology for high-risk prostate cancer

Maryam Zarei ^{a,*,} Elin Wallsten ^{a,} Josefine Grefve ^{b,} Karin Söderkvist ^{b,} Adalsteinn Gunnlaugsson ^{c,} Kristina Sandgren ^{a,} Joakim Jonsson ^{a,} Angsana Keeratjarat Lindberg ^{a,} Erik Nilsson ^{a,} Anders Bergh ^{d,} Björn Zackrisson ^{b,} Mathieu Moreau ^{e,} Camilla Thellenberg Karlsson ^{b,} Lars E. Olsson ^{f,} Anders Widmark ^{h,} Katrine Riklund ^{d,} Lennart Blomqvist ^{d,} Vibeke Berg Loegager ^{g,} Jan Axelsson ^{a,} Sara N Strandberg ^{d,} Tufve Nyholm ^a

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PhD Joakim Jonsson (Strålningsfysik)

PhD Elin Wallsten (Strålningsfysik)

PhD Erik Nilsson (Strålningsfysik)

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