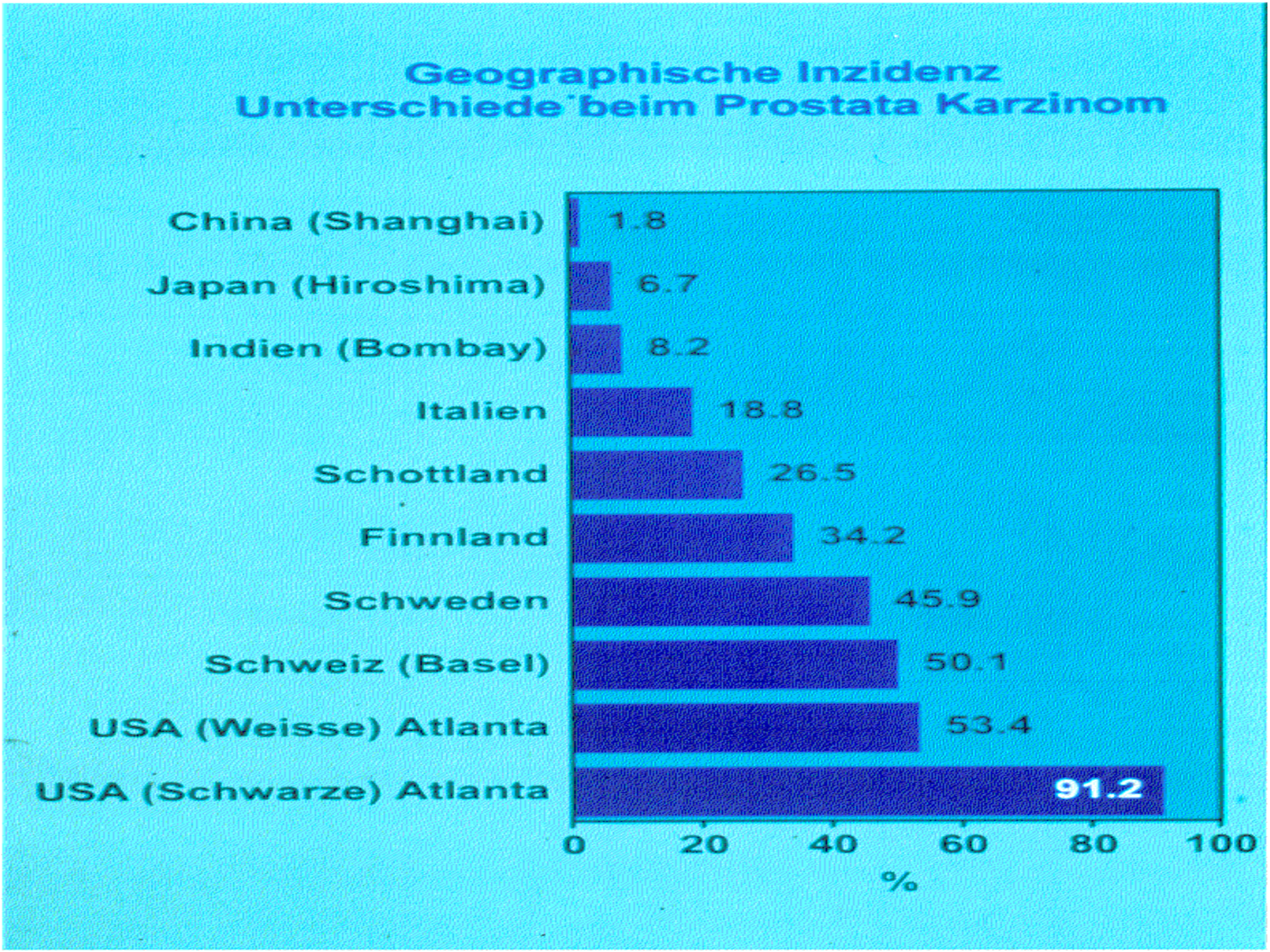
En introduksjon i cancer prostatae verden: om epidemiologi, arvelighet,screening patologi og behandling.

Sophie D. Fosså
OUS-Radiumhospitalet

DISPOSISJON

- Epidemiologi (Verden,Norden, Norge)
- PSA / Screening
- Diagnose / Risikogrupper
- Behandling

Geographische Inzidenz
Unterschiede beim Prostata Karzinom



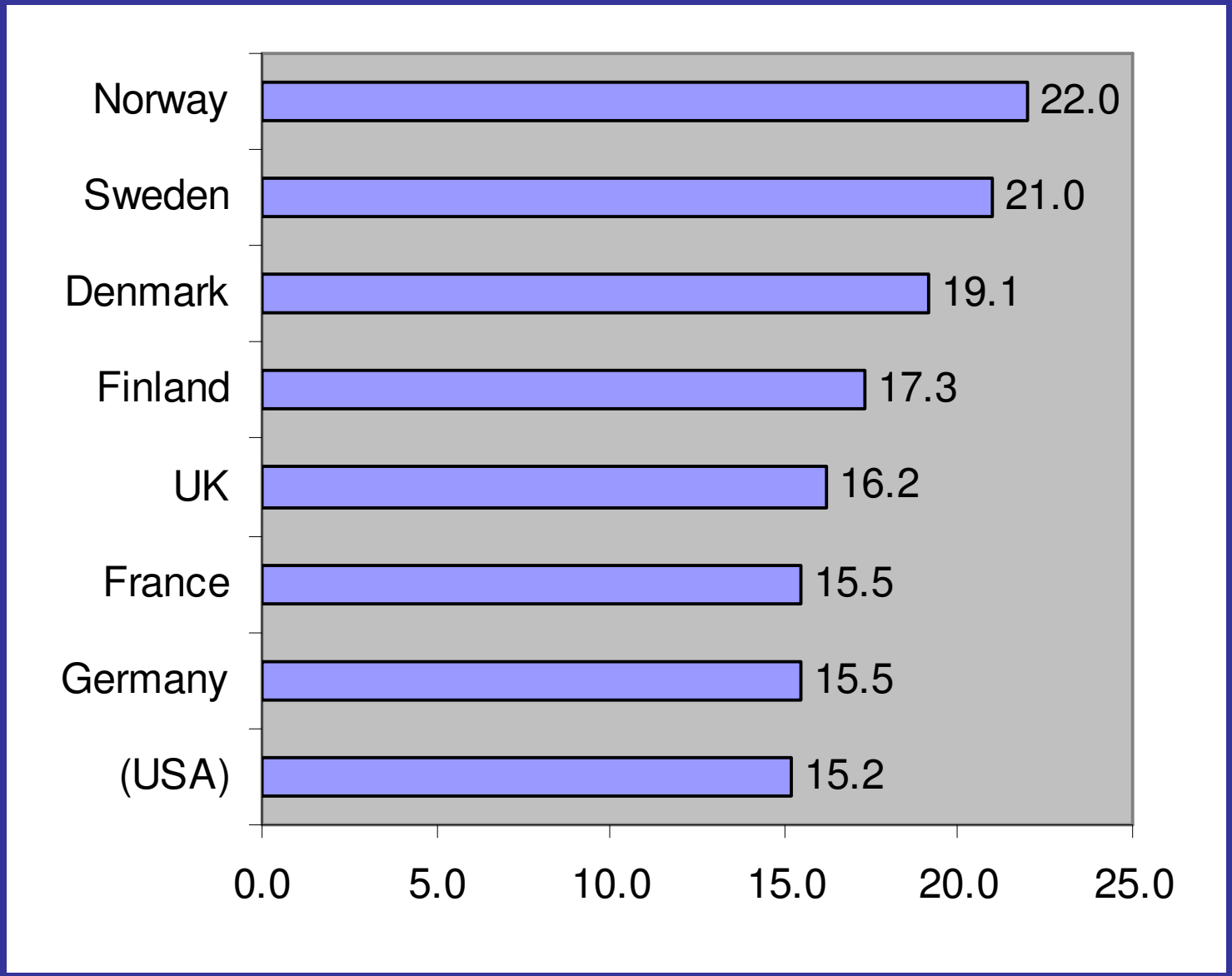
Risikofaktorer

- **Alder**
- **Etnisitet**
- **Familiær opphopning**

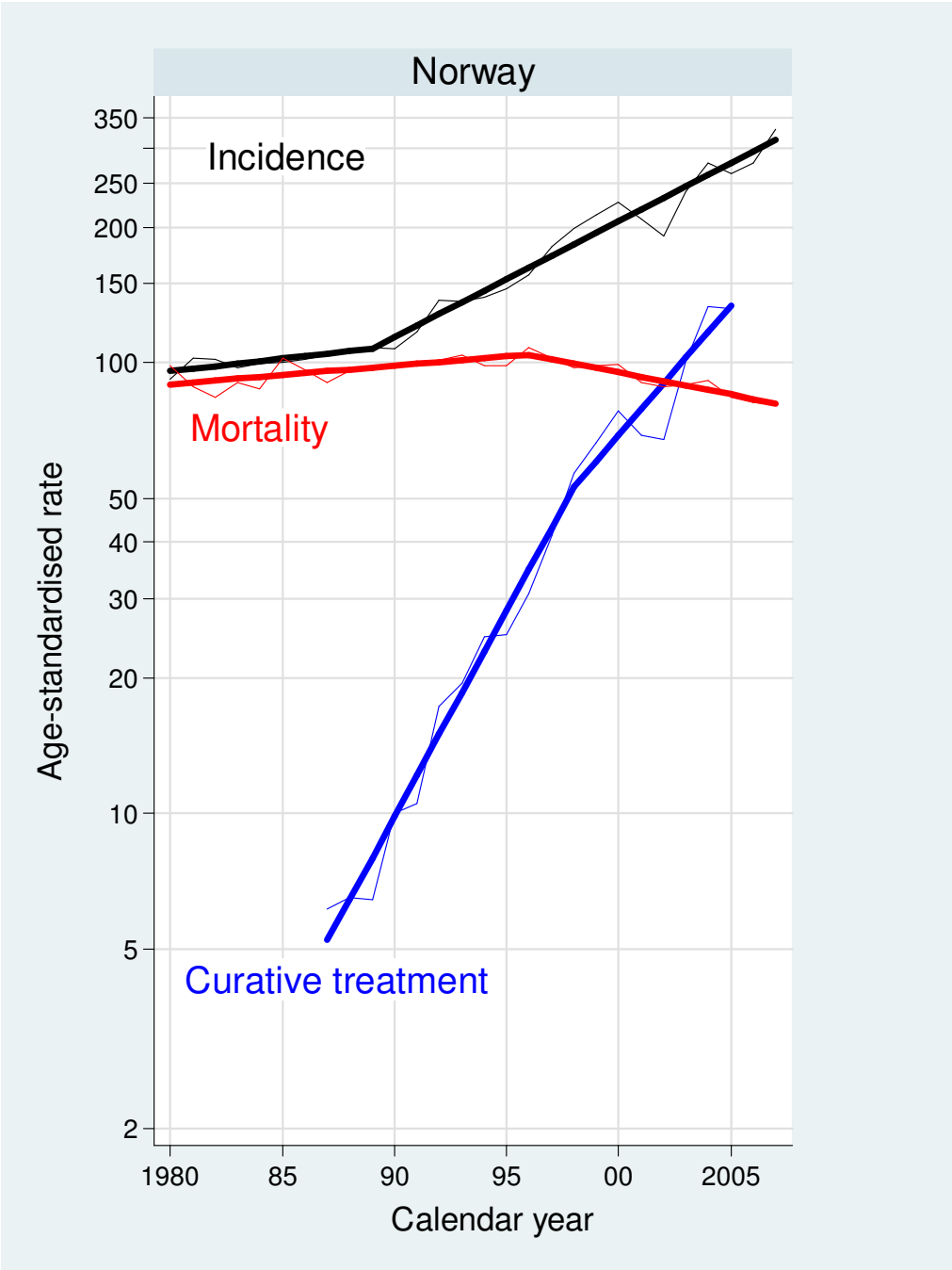
- **Livsstilsfaktorer**
  - **spesielt kosthold**

Prostate cancer mortality

ASR (World pop.) per 100 000 in 1995-1999



Levi et al, Prostate 2004

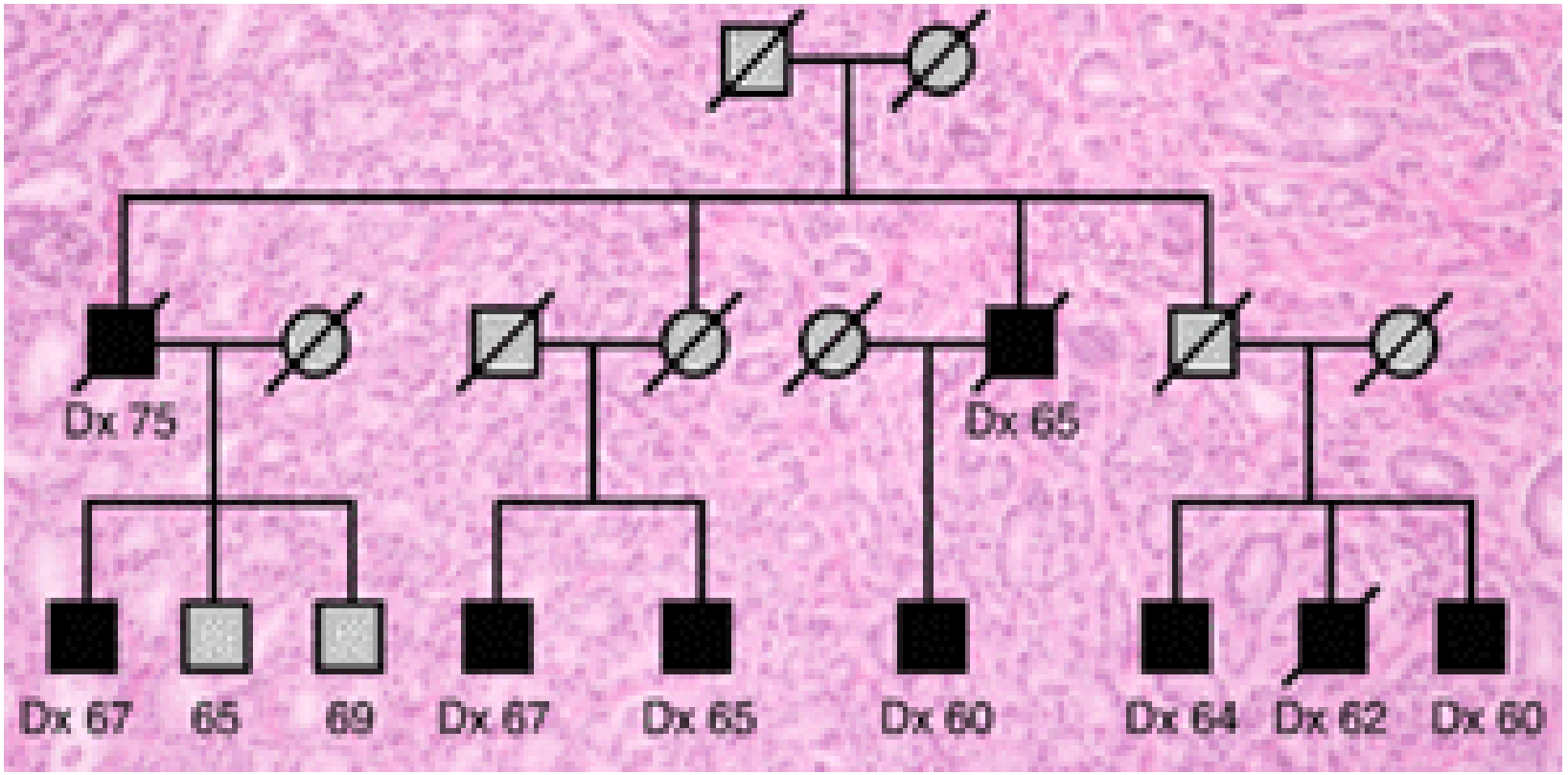


Kvaale, in prep

Prostatakreft

- **1/3 av alle menn over 50 år har områder med kreftceller i prostata**
- **Livstidsrisiko: 1 av 10 (USA: 1 av 6)**
- **Utviklingen fra latent til symptomatisk prostatakreft tar som regel mange år**

Hvem får prostatakreft? Genforskning
Familiær opphopning av prostatakreft



9 av 14 menn i denne familien har fått påvist prostatakreft

Jeffrey Trent and colleges, NIHGR, NIH http://www.ncbi.nlm.nih.gov

Arvelig prostatakreft

Sannsynlig at susceptibilitets-gener for prostatakreft finnes, men per idag defineres arvelig prostatakreft klinisk

- **Alder ved diagnose**
- **Slektskap (førstegrad, annengrad, etc)**
- **Antall slektninger med prostatakreft**

Hereditær Pca
Norsk definisjon

- **Menn med en 1. gradsslektning < 50 år**
- **Menn med to 1.gradsslektninger < 60 år**
- **og alle menn med >2 PC tilfeller hos 1.gradsslektninger uansett alder bør tilbys genetisk veiledning og PSA testing samt informasjon om kosthold ***
- ***modifisert etter EAU Guidelines, 2001/**
- **Familiær brystkreft**

Kriterier for henvisning til genetisk vurdering

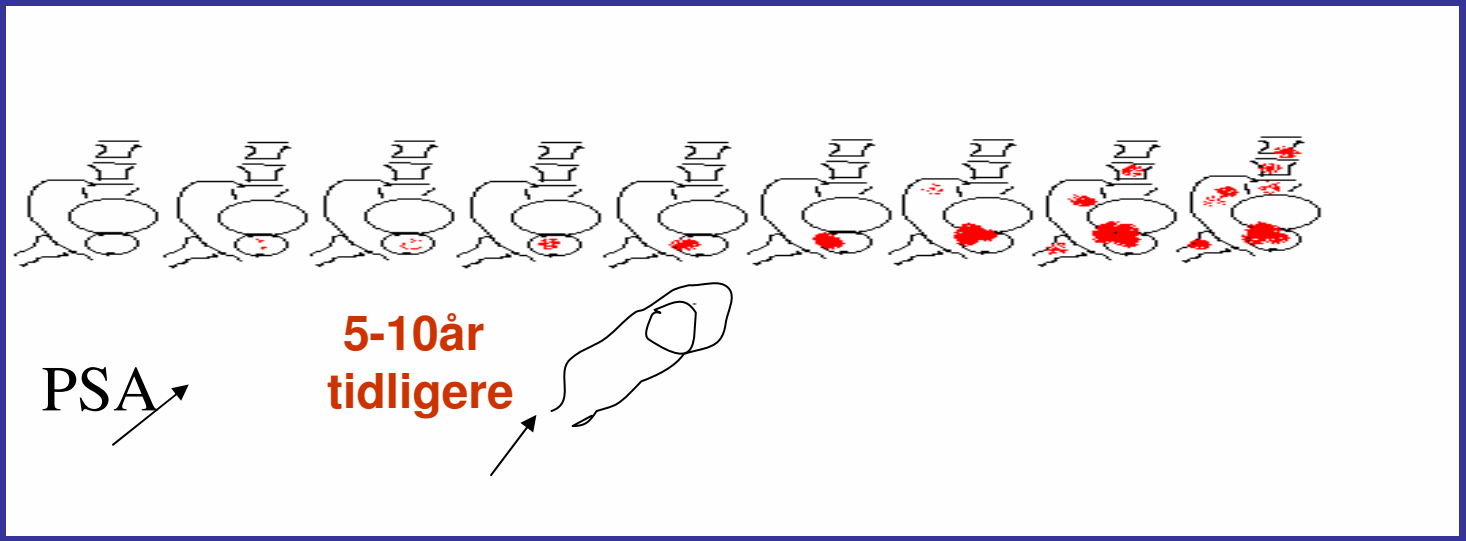
(Seksjon for arvelig kreft, RR)

- Pasient med prostatakreft før 60 år
- Minst to slektninger med prostatakreft,
  én før 65 år
- Opphopning av annen kreft i familien hos pasient med prostatakreft

Prostatakreft: Biologi / Epidemiologi

- Meget langsomt voksende

(7-8 års fordoblingstid (bryst ca.2 år))



- 30-40% av menn >50 år har kreftceller i sin prostata
- Norge (og Norden) har høy PC mortalitet, synkende tendens fra 1996
- PSA diagnostiserer CaP, men sier per se intet om aggressiviteten. (Identifiserer ikke menn med CaP for hvem tidlig behandling er livsreddende)
- DERFOR: INGEN OFENTLIG PSA SCREENING FORELØPIG

PSA (Prostata Spesifikt Antigen)

- **Funksjon**
  - Bidrar til at ejaculatet er flytende
- **Bruksområde**
  - **Diagnose**
  - **Oppfølging av behandling**
- **Problemer**
  - **Skiller dårlig mellom godartet og ondartet vekst ved serum verdier mellom 4-10 ng/ml**
  - **↑PSA ⇒ kreft i biopsi hos 1 av 5, innvirkning på livslengden hos 1 av 16**
  - **For å ”redde” en mann med prostatakreft må det testes PSA hos 1400 menn og 48 menn med paåvist kreft må behandles.(Massiv overbehandling)**
  - **2011: Tallene har forandret seg.**

PSA

- Produseres i benigne og maligne celler fra prostata og påvises i blod

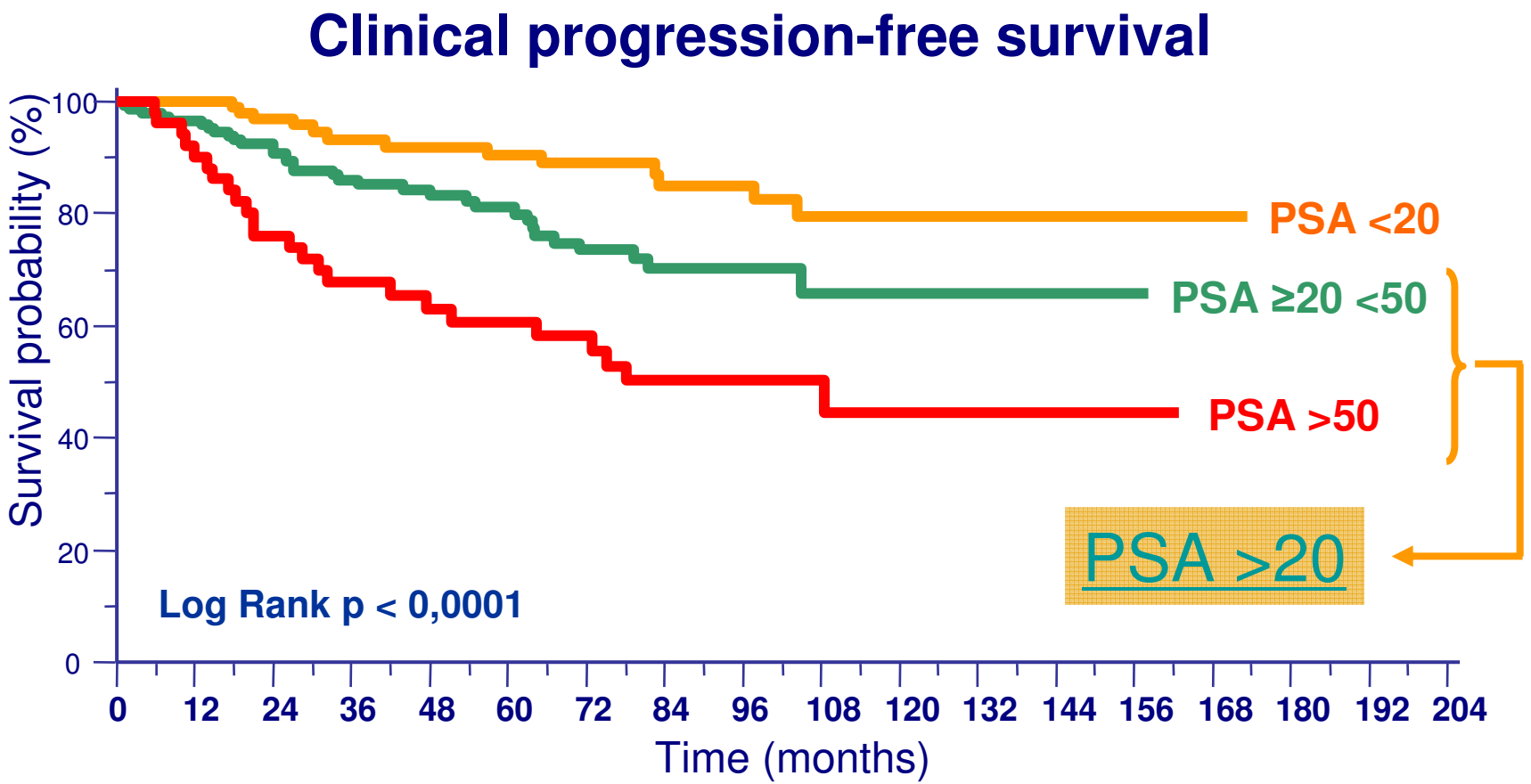
  → økning ved hyperplasia prostata (alder!)
- Lekker ut til blod i økt omfang ved patologiske (abnorme) tilstander
  - Prostatakreft (PC)
  - Prostatitis
  - Intensiv sykling
- Lite differensiert prostatacancer: produserer PSA i mindre grad
- Bruk av samme test/laboratorium og forhør deg om deres normer
- PSA velocity

Age	Normal PSA
40-49	<2.5
50-59	<3.5
60-69	<4.5
70-79	<6.5

PSA velocity

- Prostate-specific antigen doubling time (PSADT) is calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient.
- Calculator på Internet

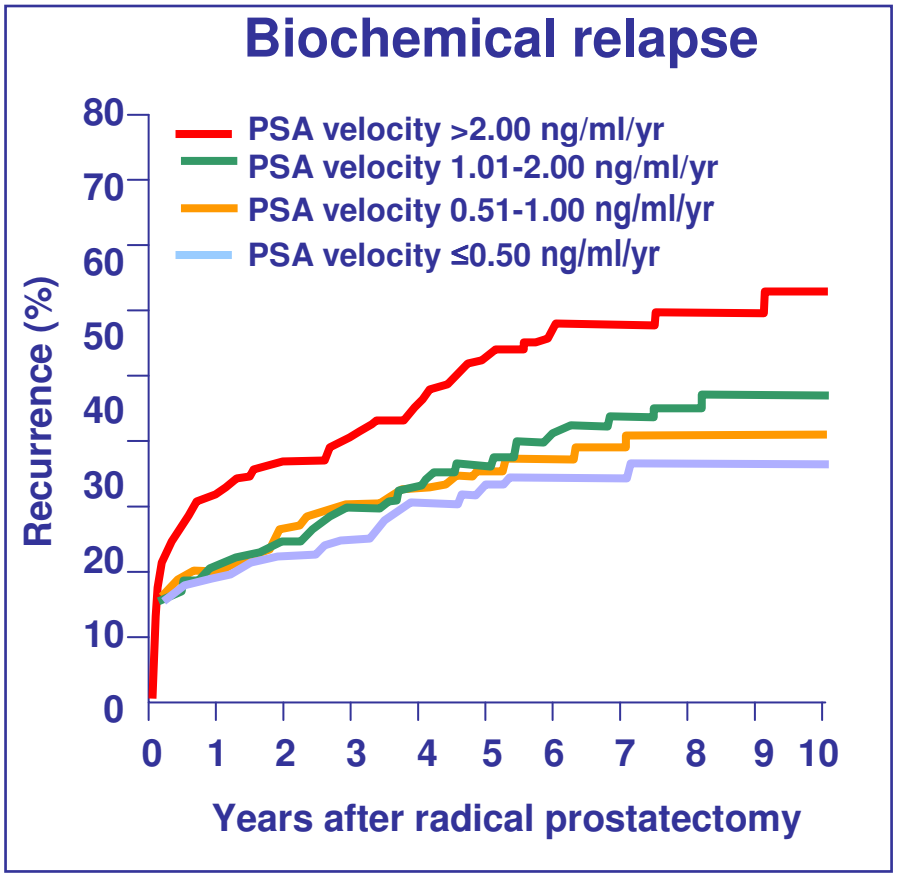
Preoperative PSA

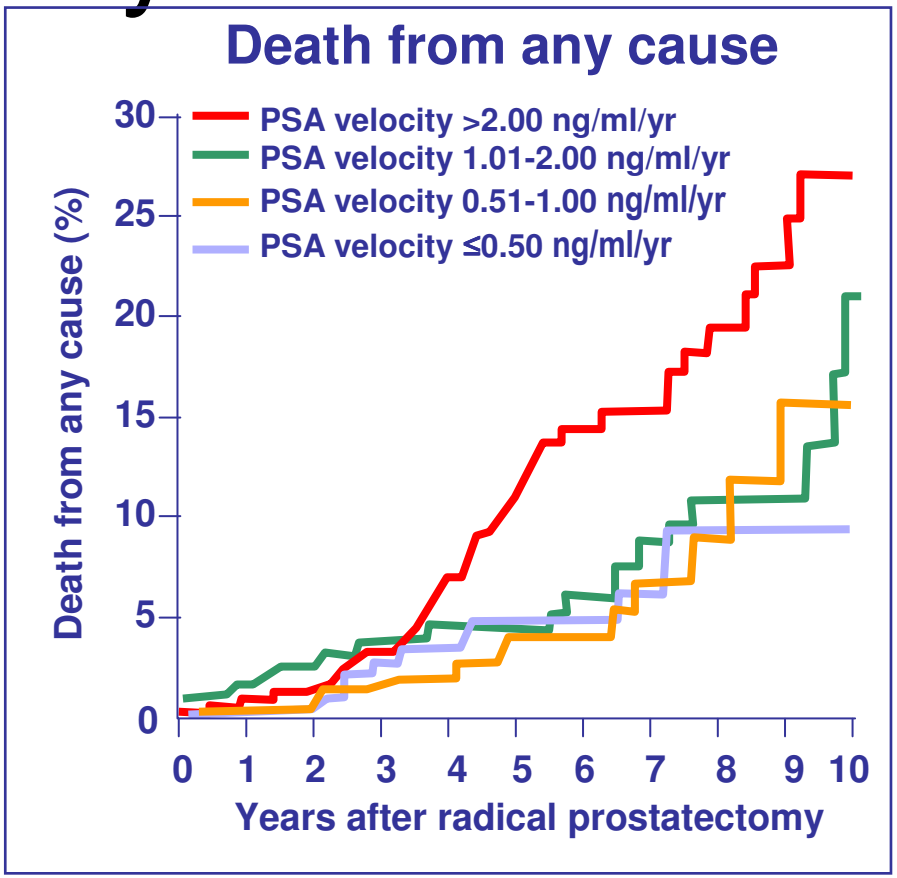


Clinical Progression Free Survival after radical prostatectomy stratified by PSA in 396 high-risk patients (any T, any Gleason, PSA >20 or cT3-4, any Gleason, any PSA)

Joniau, Gontero and Van Poppel, 2008, personal communication

Preoperative PSA and PSA velocity





Men with PSA level increases by more than 2.0 ng/ml during the year before the diagnosis of localized prostate cancer have higher risk of death despite radical prostatectomy

D'Amico et al. N. Engl. J. Med. 2004;351:125-135

Livsforlengende effekt etter PSA-screening med etterfølgende behandling?

” Small effect probable after 7-8years”

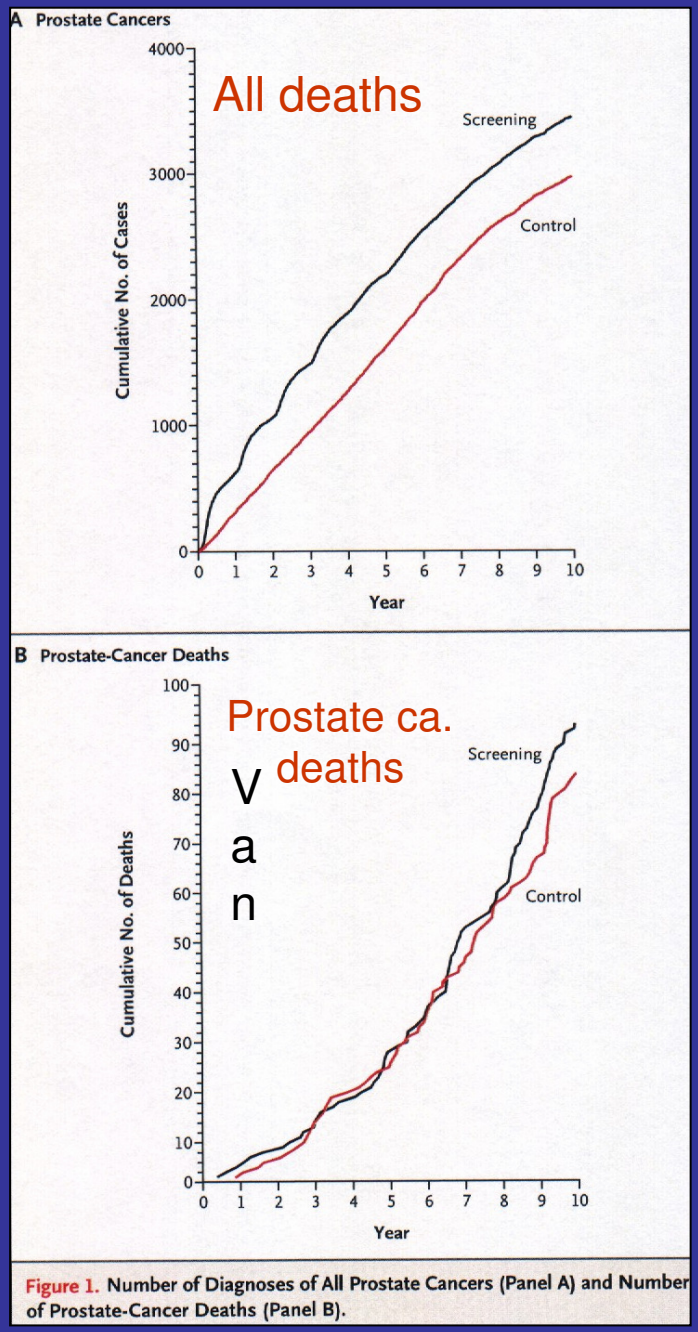


Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

Andriole NEJM 2009;360,1310

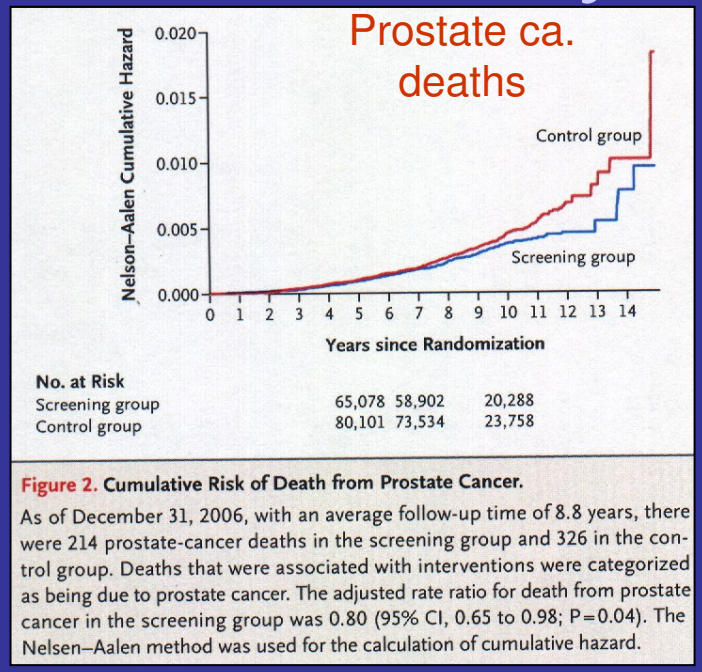


Figure 2. Cumulative Risk of Death from Prostate Cancer.

As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.

Schroeder,NEJM:2009 360;1320

2009

Screening and Prostate-cancer Mortality in a Randomized European Study

Conclusions

PSA-based screening and treatment reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis.

1410 men would need to be screened and 48 cases of prostate cancer would need to be treated to prevent one death from prostate cancer

Schroeder: N. ENGL. J. MED. 2009 March 26

Screening result and Time dependency*

		Numbers to screen (NNS)	Numbers to treat (NNT)
ERSPC	9 years	1254	43[1]
ERSPC (estimated)	10 years	837	29
Gøteborg**	14 years	293	12[2]

** Reduction of prostate cancer mortality from 9 to 5 cases per 1000 men. For each death avoided 11 men are diagnosed without prospect of life Prolongation.

[1] Original publ. NEJM (Schröder 2009); 1410/48
[2] Hugosson, Lancet Oncol 2010;11,725

*Caroll, JCO 2011;29,345

Conclusion

Until more sensitive and more specific screening tools are available that can detect the few cases of prostate cancer with aggressive biological potential among the majority of indolent cases, physicians and patients must understand that most diagnosed prostate cancers will never lead to death and that men can only profit from early detection if local and systemic treatment are limited to those patients who truly need it.

Studer,Urol.Oncol,2010;28:668

PSA SCREENING

1. Reduced risk of prostate cancer death
2. Men with long life expectancy have the highest benefit because screening effect increase with time
3. Significant risk of over-diagnosis
4. The risk of over-treatment can be reduced by “selective treatment” (no treatment to those with the lowest risk)

Caroll, JCO 2011;29,345

PSA screening
American Cancer Society
(ACS 2010)
Similar guidelines in Norway 2010

- Information on uncertainties, risks and potential benefits before PSA testing individually by the family doctor and/or by printed documentation
- No PSA testing without such information
- Start ≥ 50 years (early in high risk patients: family history)
- [~10 års livsforventning (78 år gjennomsnitt i Norge)]

Wolf Ca Cancer J. Clin. 2010, 60:7(

ACS 2010: PSA screening

- With or without rectal palpation
- PSA > 2.5 mg/ml → yearly screening.
- PSA < 2.5 mg/ml → biannual screening.
- PSA ≥ 4 mg/ml → urologist (biopsy)
- PSA 2.5 – 4 mg/ml → individual risk assessment (family history, palpation, previous negative biopsy) PSA doubling time.

- >4 mg/ml ⟶ UROLOG (biopsi)
- PSA doblingstid
- Alder , familiær belastning, livsforventning

PSA testing av menn uten symptomer
Norsk anbefaling i 2010

- Fastlege tar opp spørsmålet om PSA testing hos 50-åringer
- INFORMASJON om PRO og CONTRA (behandlingsmuligheter/bivirkninger)
- Den informerte pasienten avgjør om PSA skal testes

Hvilke menn uten kjent PC skal ha PSA testing?

1. Alle som etter informasjon fastholder ønsket om PSA testing
2. Familiær prostatacancer
3. Alle menn som oppsøker legen for vannlatningsbesvær

PSA >4µg/l * → henvisning til urolog, spesielt hvis normalt stor prostata hos menn < 65 år (70 år) og god helse

5. Menn med palpasjonsfunn av prostata

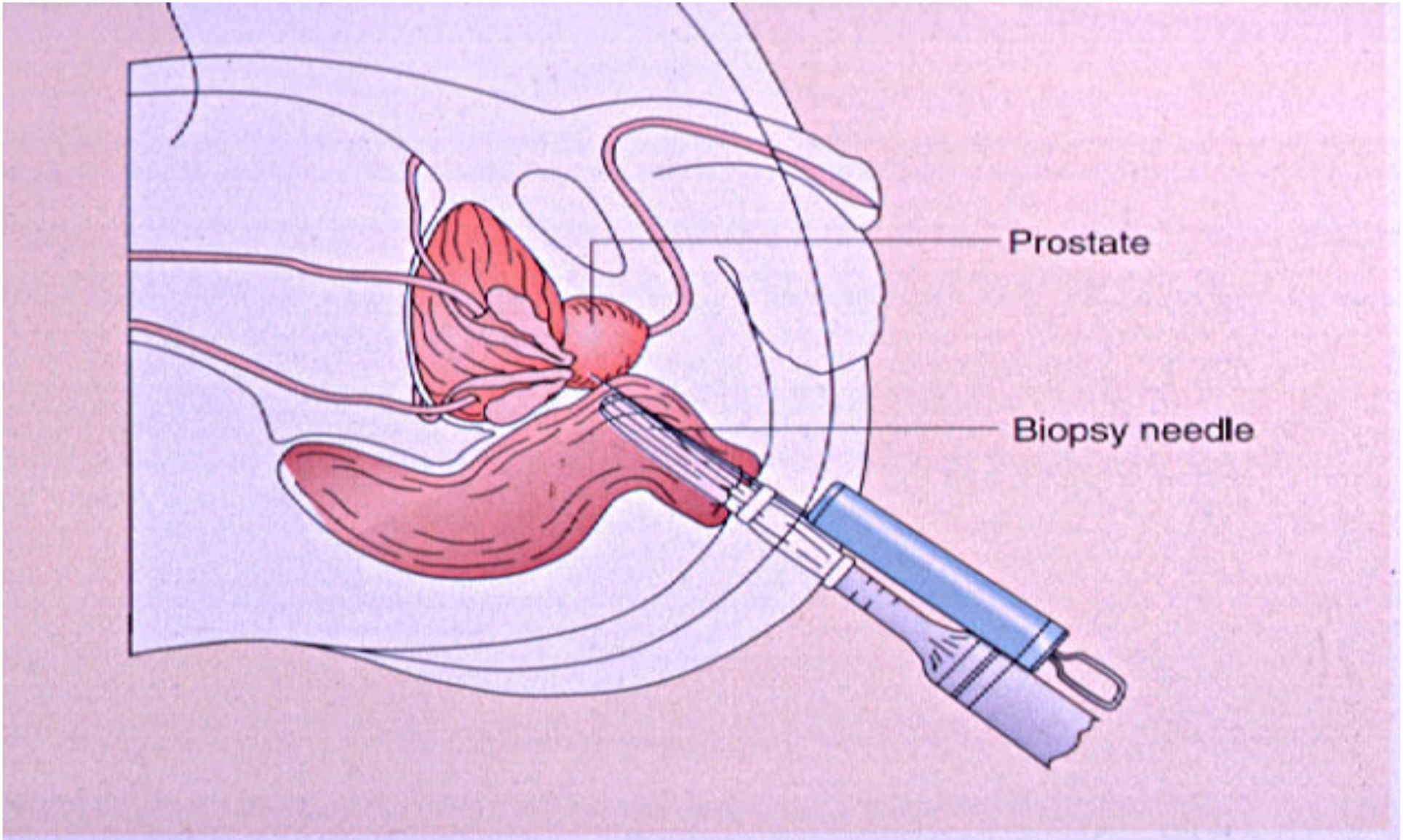
4. Menn med nytilkomne permanente skjelett-smerter eller patologisk lymfeknutesvulst (cancer metastaser ukjent primærtumor)

*kort fordoblingstid; i dag tendens til å bruke >3µg/l

PSA screening (2010)

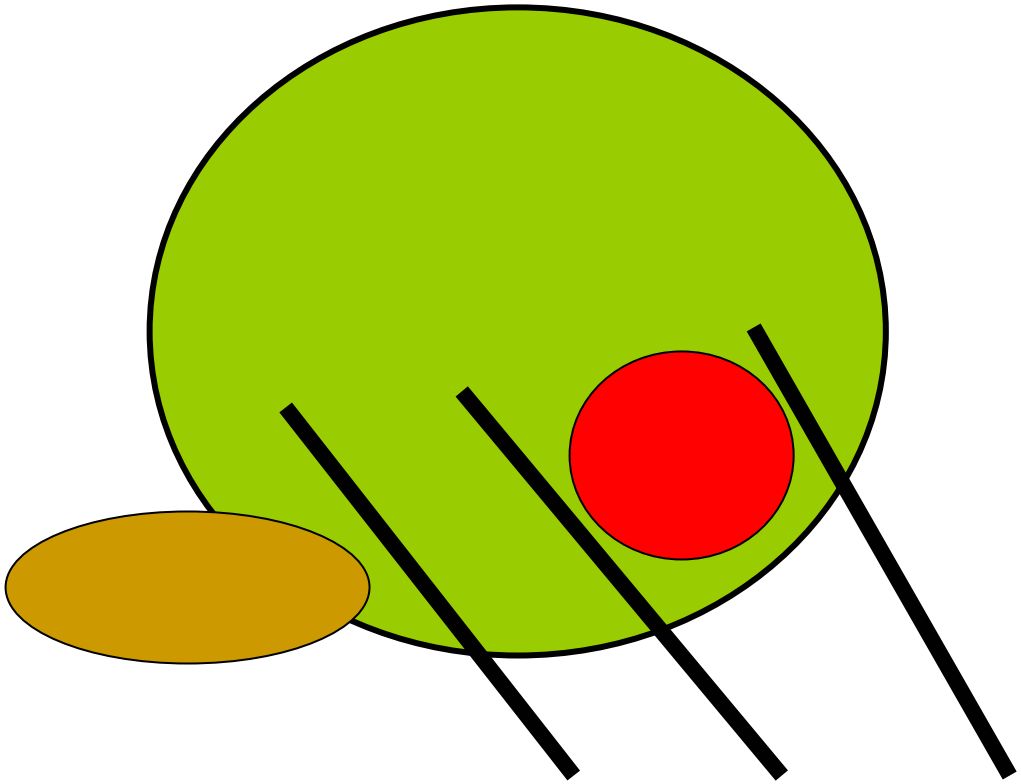
Bakgrunn

- Hos pasienter uten symptomer kan en forhøyet eller raskt stigende PSA være tegn på at det foreligger prostatakreft
- Ingen entydig grenseverdi (tidligere 4 (3)ng/ml)
- PSA skiller ikke mellom ”sinte” og ”snille” kreftformer
- PSA testing har -også i Norge- ført til massiv økning og behandling av menn med tidlig PCa, uten at dette med sikkerhet er årsaken til redusert dødelighet

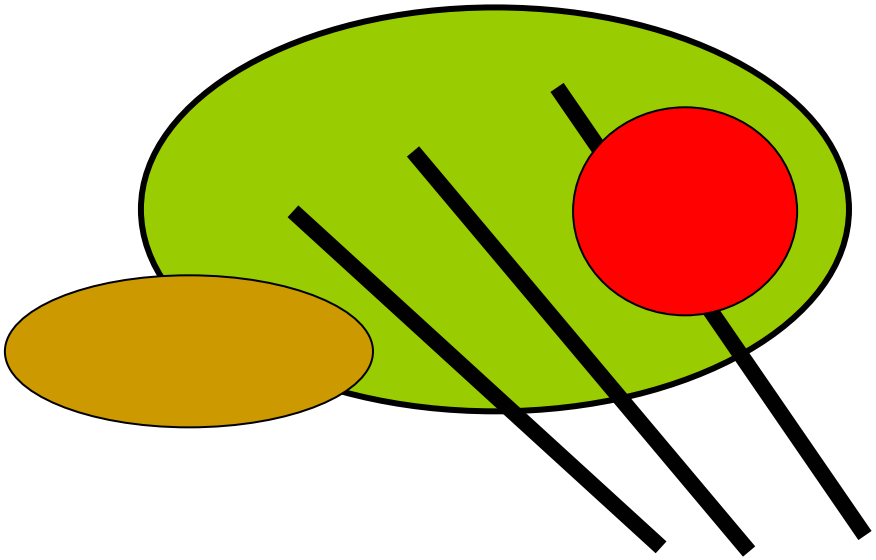


ure 96 The procedure for TRUS-guided biopsy of the prostate should always be car-
d out under antibiotic cover, which should be continued for 3–4 days post-biopsy to
uce the incidence of infective complications. At present, the most common indica-
ns for biopsy is either an elevated PSA or a prostate that feels abnormal on DRE

False negative biopsies

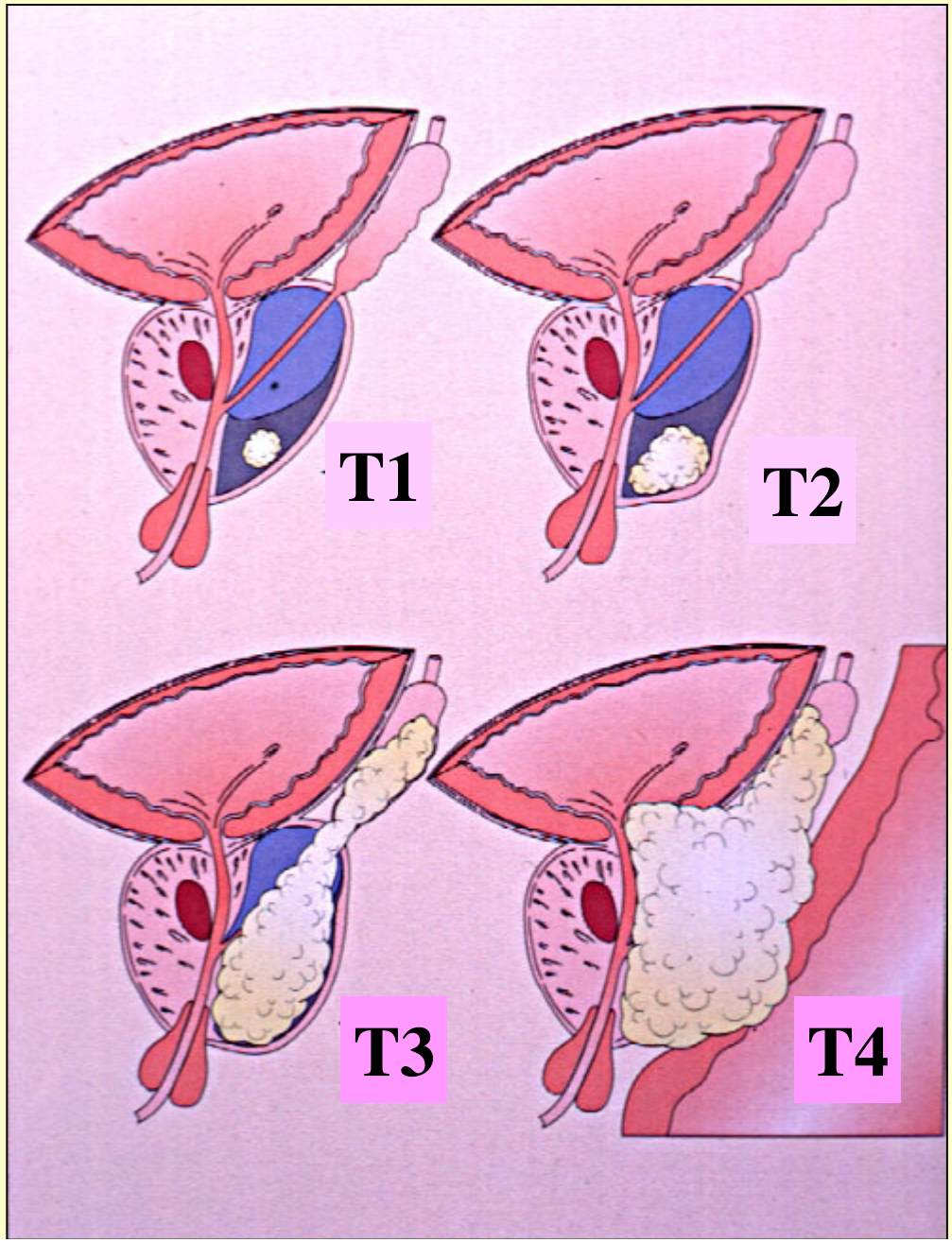


PSA 8.0 ng/ml
volume **80 ml**
PSAD 0.1



PSA 8.0 ng/ml
volume **40 ml**
PSAD 0.2

BEHANDLING og LEVEUTSIKTENE er avhengig av



RISIKOGRUPPER

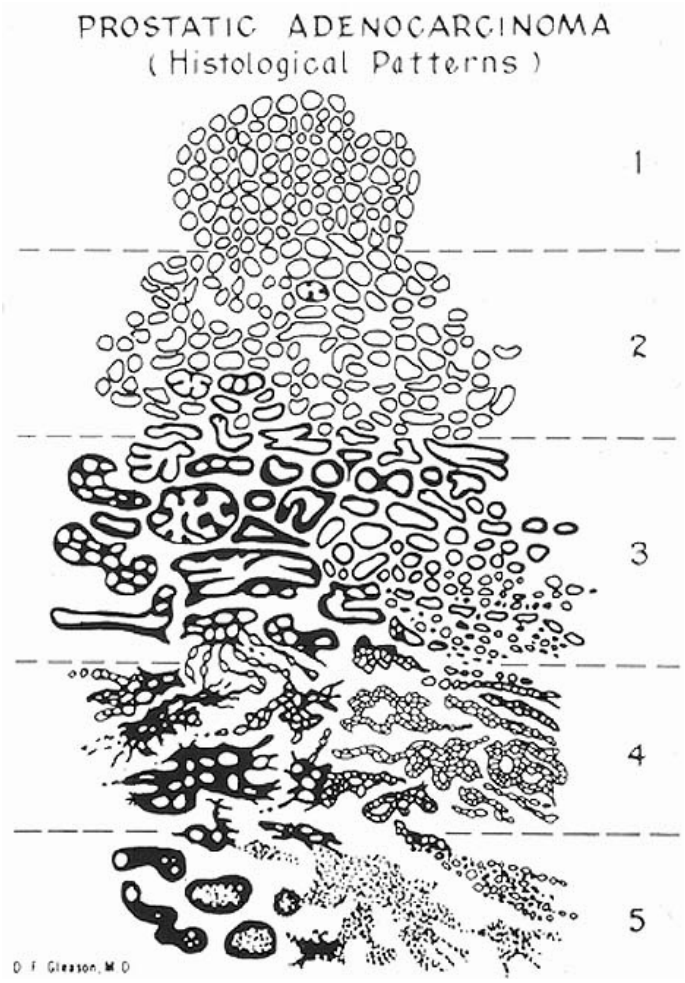
1: T-Kategori
(Utbredelse, vanligvis basert på rektal eksplorasjon)

2: PSA

3:Vekstmønster (Gleason 6-10)

4:Spredning
(Skjelett, Lymkeknuter)

Histologisk gradering - Gleason



<u>GLEASON GRADE</u> (1 - 5)

Som på bildet

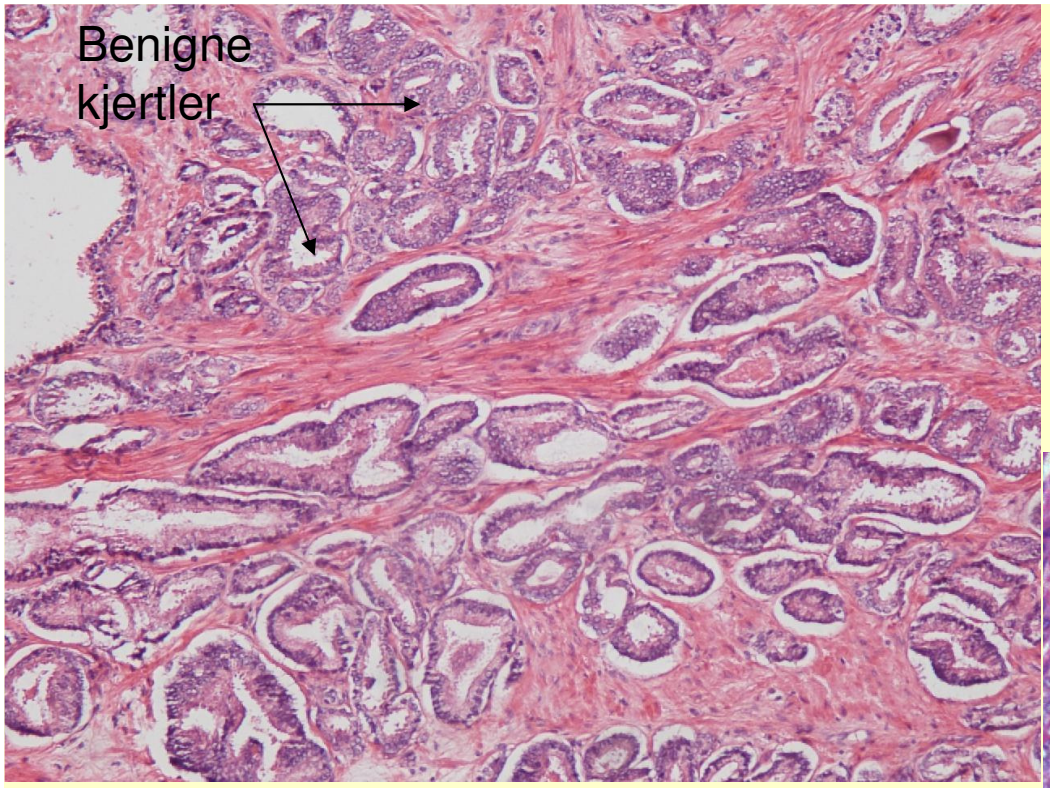
<u>GLEASON SCORE</u> (2 - 10)

Summen av det primære og sekundare "mønsteret" i snittet

<u>PROGNOSTISK FAKTOR</u>

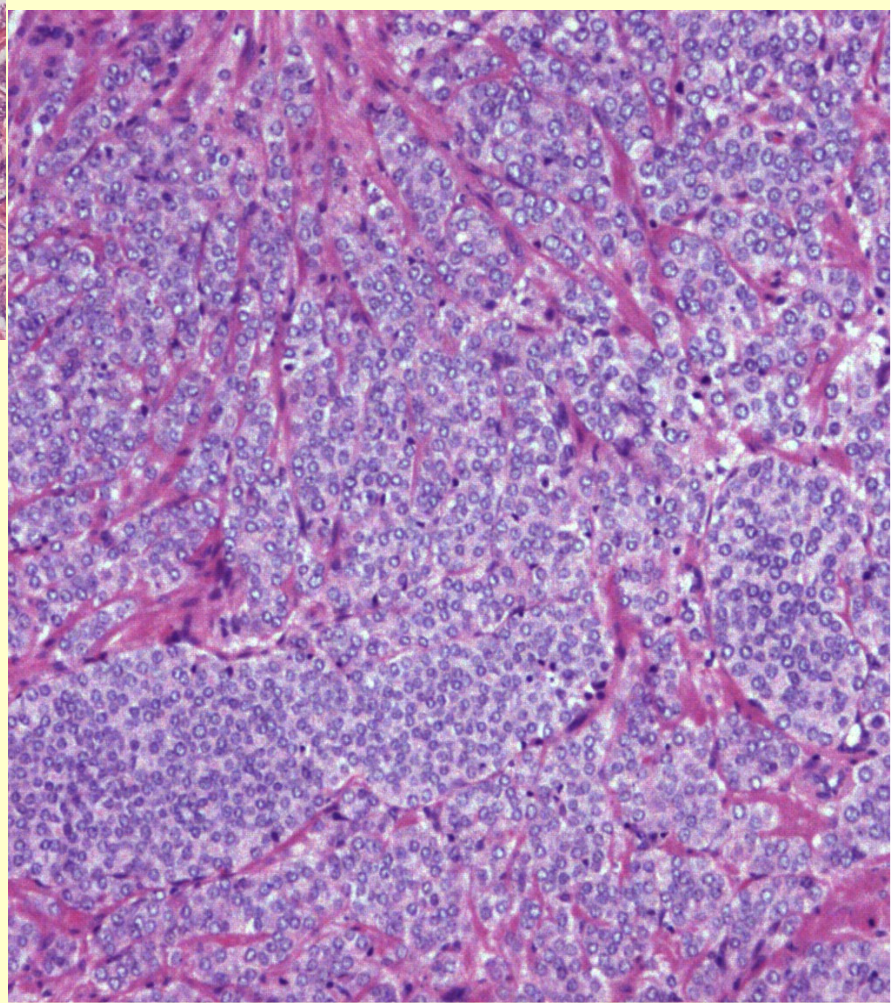
God prognose: <= 3+4

Dårlig prognose: >=4+3



Gleason score 3+3=6

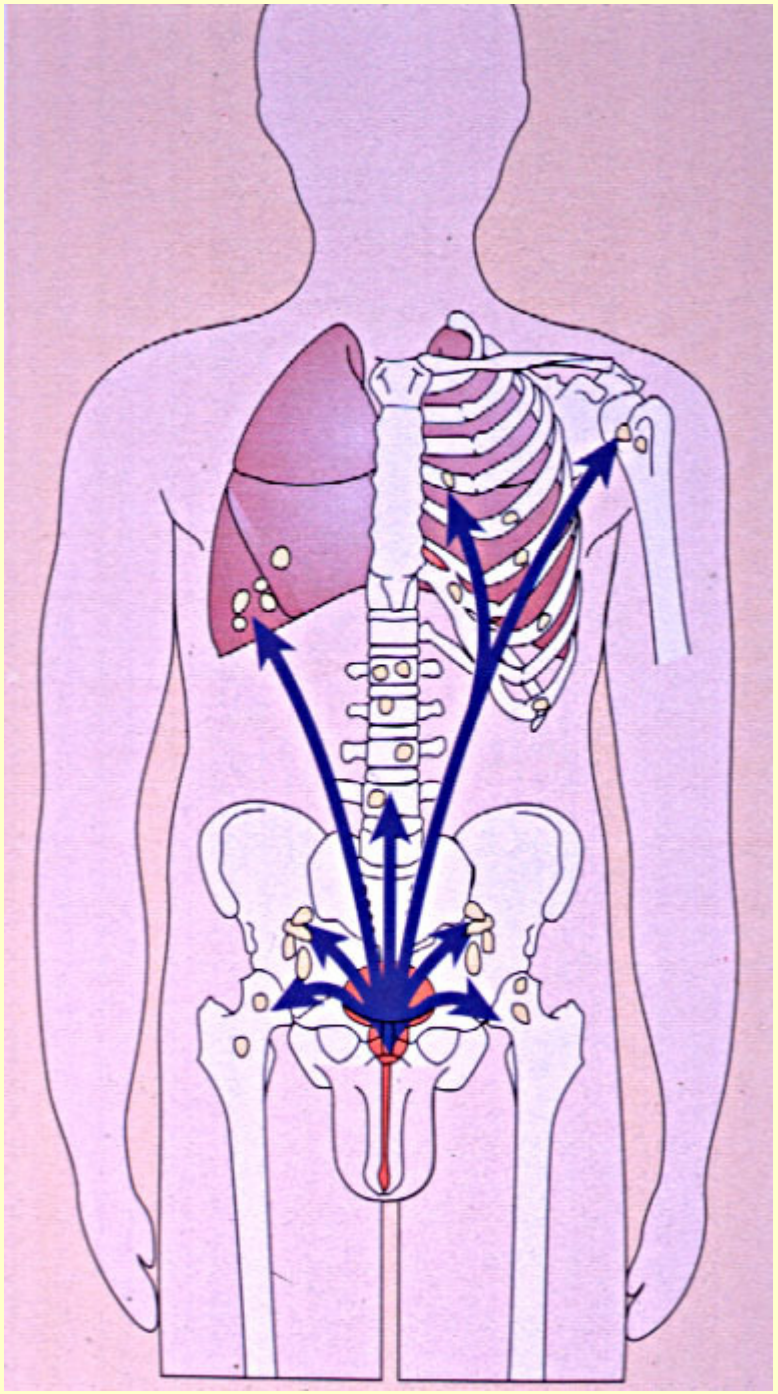
Gleason score 5+5=10



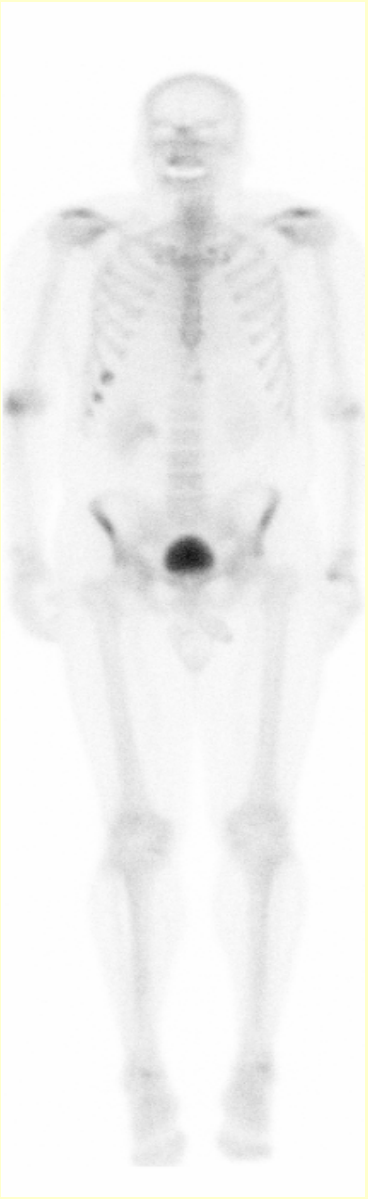
Antagelse

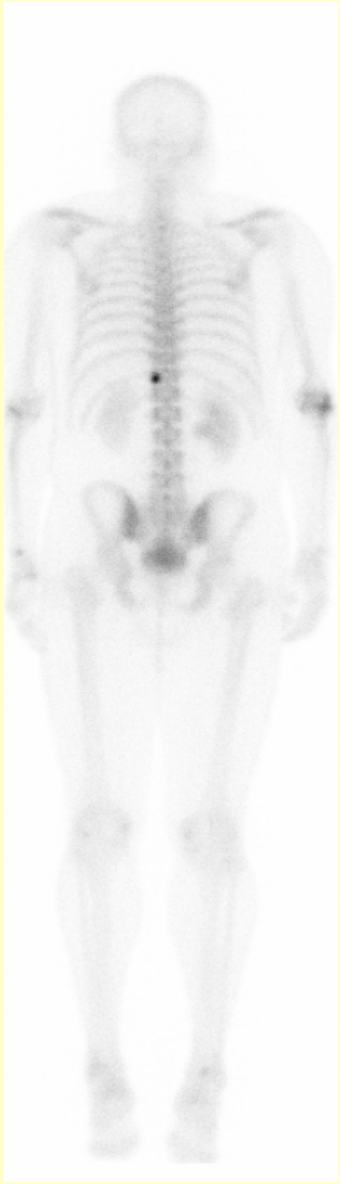
- Jo høyere Gleason score desto mindre er påvirkeligheten av hormoner og desto kortere er responsvarigheten på hormoner
- Gradvis de-differensiering under sykdom

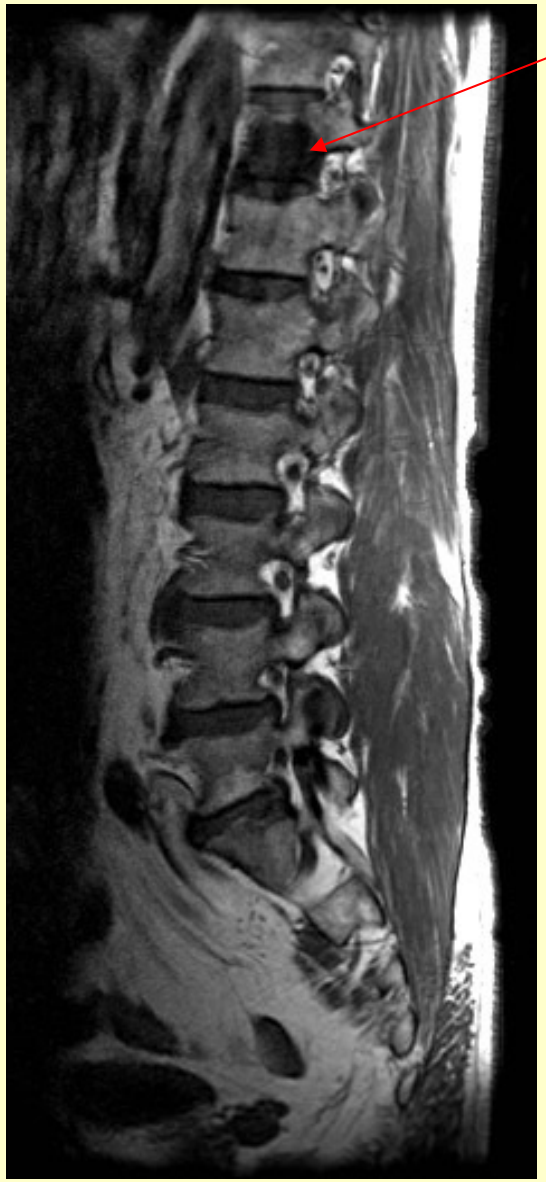
  -og metastaseutvikling
- De-differensiert vev fra prostatakreft produserer mindre PSA enn differensiert vev



Skjelettscintigrafi vs NR av skjelettet







Metastase. Bioptisk verifisert

66 år,

PSA: 34

T2-T3

Skulle ha Prostatekt.

→ Hormoner

Primærdiagnose 1:

63 år gammel : PSA : 8 ng/l ;

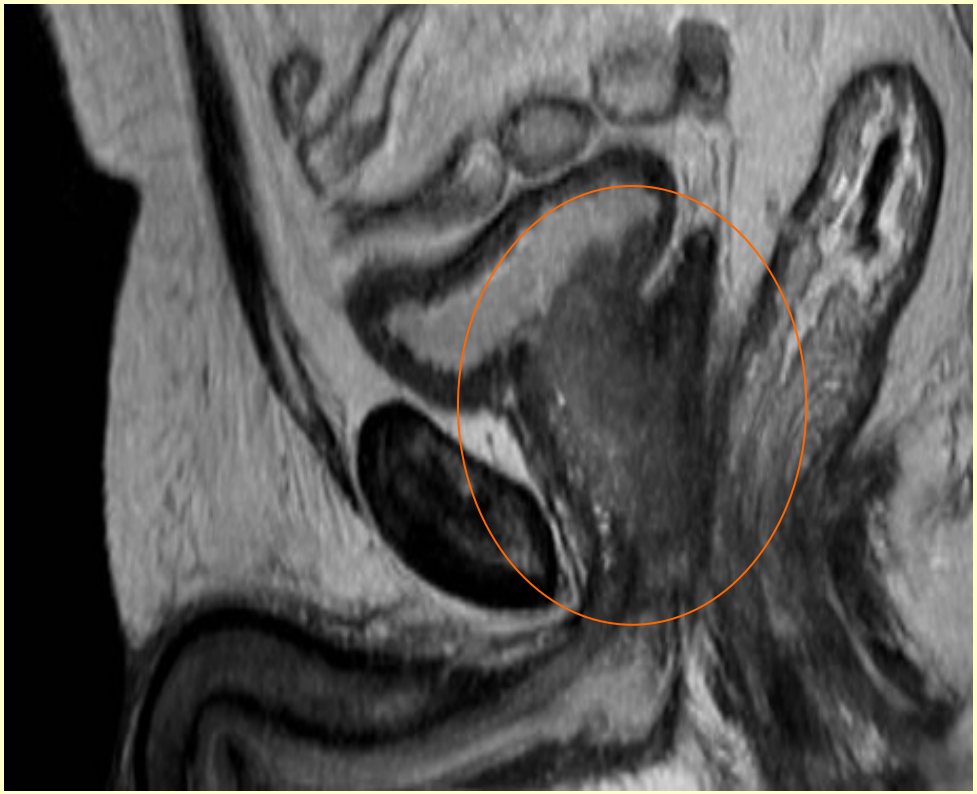
Klinisk vurdering: Prostatakreft innenfor kapselen (T2)

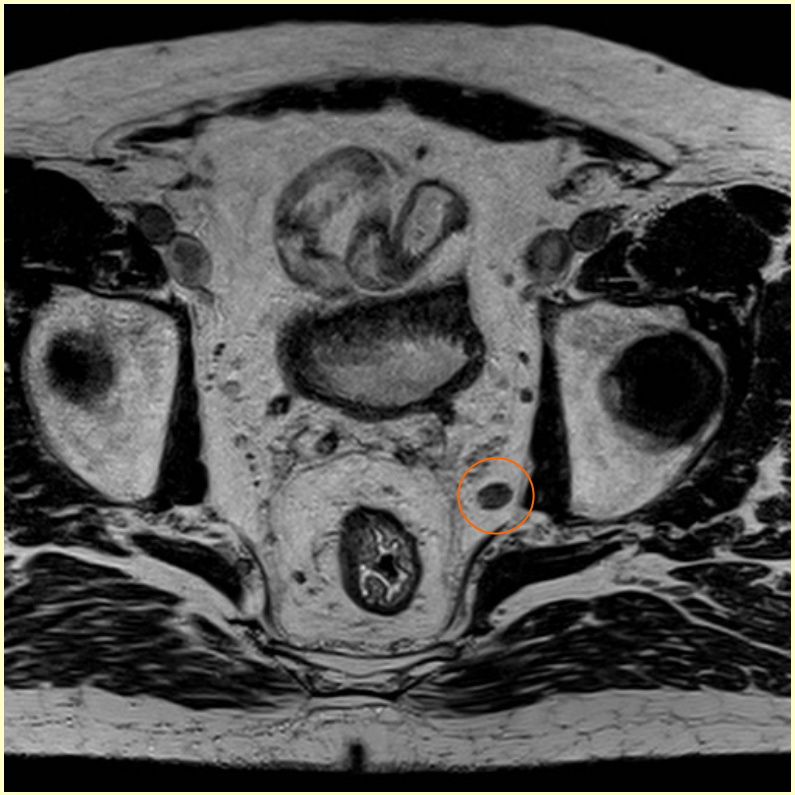
Foreslått **prostatektomi**

MR : Utenfor prostatektomi, Innvekst i urinblæren, Lymfeknutemetasase

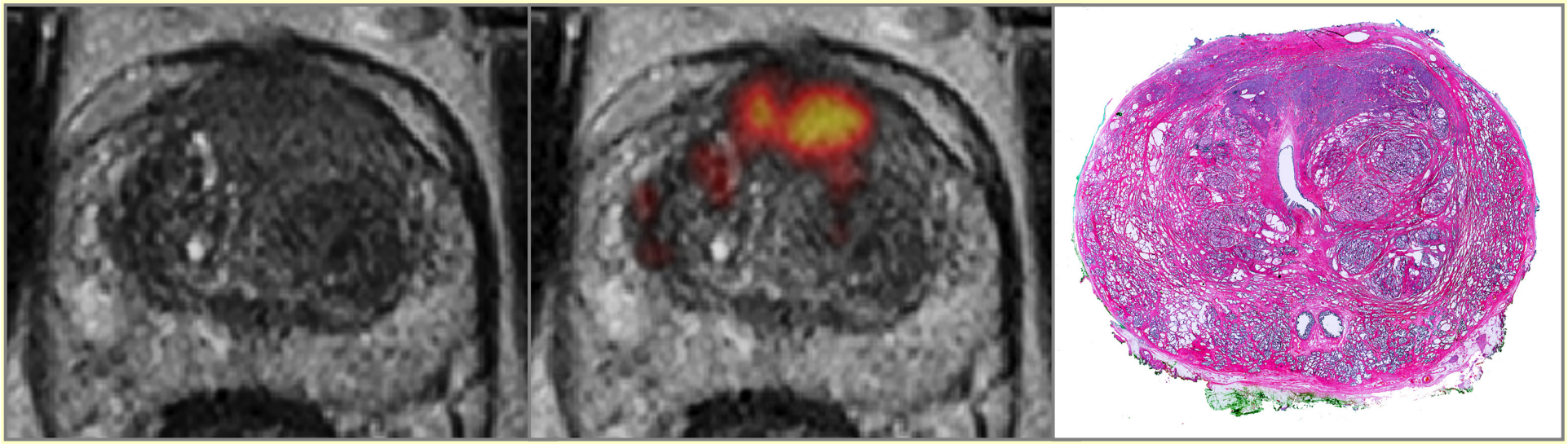
⟶(utenfor det området som man vanligvis fjerner ved "glandelstaging"

Hormonbehandling + strålebehandling





MR av prostata: Tumor fortil

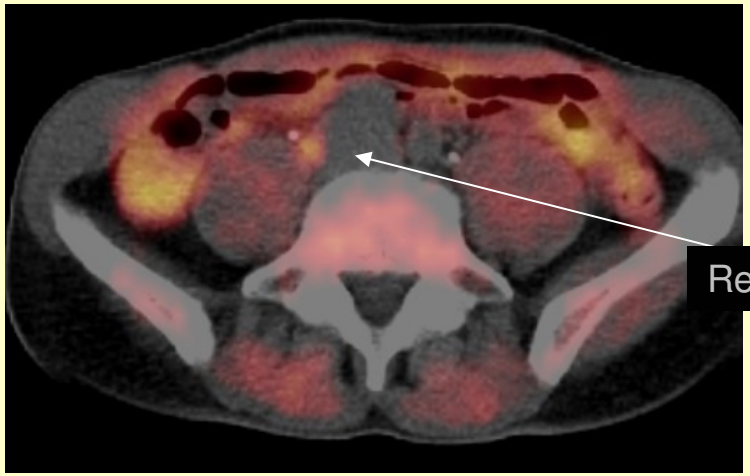


T2W

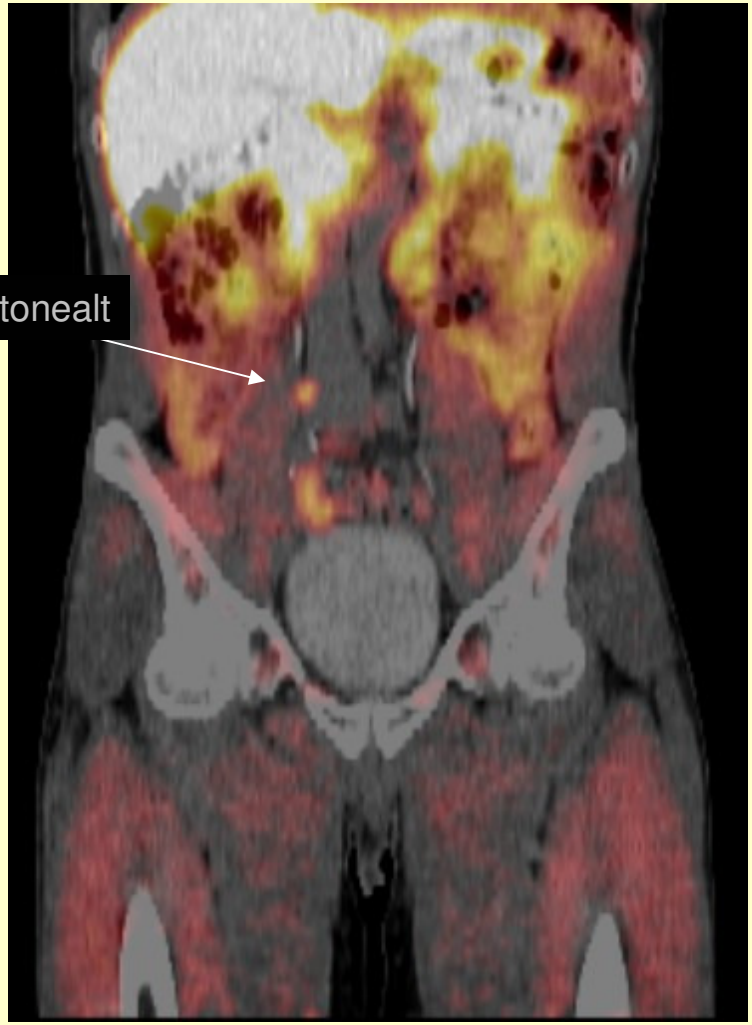
T2W+ DWI b2000

H&E snitt

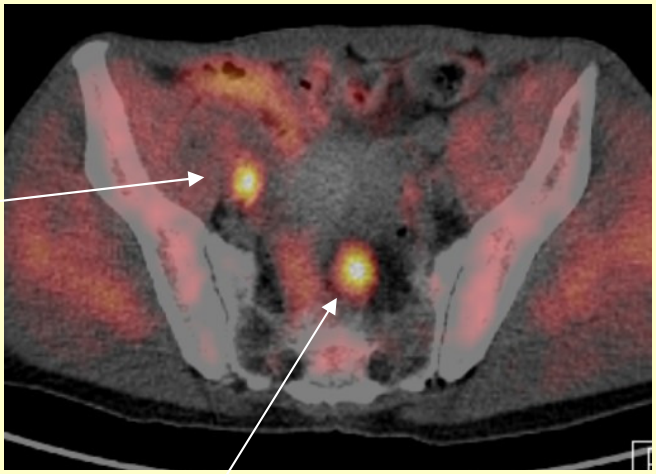
PET:Lymfeknutemetastaser



Retroperitonealt



På bekkenveggen



I mesorectum

Definisjon av risikogrupper

- Lav risiko
- T1-T2a, PSA ≤ 10 ng/ml, Gleason score ≤ 6
- Intermediær risiko
- T2b og/eller PSA >10 - ≤20 ng/ml og/eller Gleason score =7
- Høy risiko
- PSA >20 ng/ml og/eller Gleason score ≥8 **og/eller T3**

D´Amico et al, J Urol 2001

Prostatakreft: Stikkord

- Økende insidens pga aktiv diagnostikk og stigende levealder, median alder ved diagnose: 72 år
- Små områder med cancer (latent) finnes ved obduksjon hos:
  - 10% av 50 åringer
  - 30% av 60 åringer
  - 70% av 80 åringer
- Prostatacancer diagnostiseres hos 1/5 av alle menn i løpet av levetiden, men bare 3% dør av sykdommen
- <5% av tilfellene skyldes arvelig disposisjon. Ingen gode genetiske markører for arvelig prostatakreft

•Slow-growing, dependent on histological differentiation
Doubling time: 3-4 (7) years, (Breast cancer: 1-2 years)

•Risikogrupper: Lav, intermediær, høy riskiko:

Utbredelse i prostata, histologi (Gleason skår), PSA

Cancer prostatae i Norge 2004: 3744

Alder (år)	≤75: 62%
T-kategori	T1-2: 55% T3: 20% T4: 6%
Gleason skår	≤6: 36% 7: 33% ≥8: 23%
PSA	<4: 4% 4-10: 30% >10: 64%
Fjernspredning	18%

Behandling

Målsetning

Kurativ-Helbredende

(Livsforventning >= 10 år)

Palliativ-Symptomlindrende/
livsforlengende

All kreftbehandling har bivirkninger

Behandling av prostatkreft uten spredning

Helbredende

1. Radikal operasjon

2. Høyt-dosert strålebehandling

(med eller uten hormonbehandling)

3. Observasjon og helbredende

behandling ved forverrelse

Livsforl./lindrende

1.Mindre operasjon

2. Lavere dosert strålebehandling

3. Hormoner

4. Observasjon og hormoner ved ved forverrelse

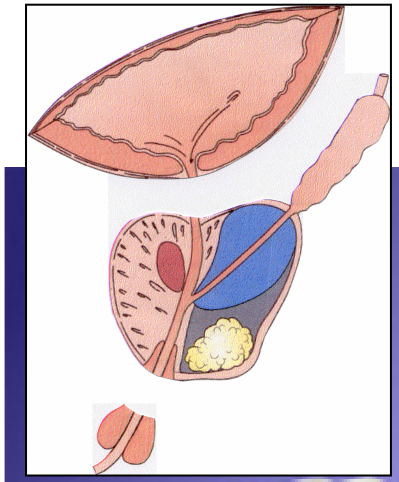
Etablert behandling vs Eksperimentel terapi (Fokal beh . for eksempel HIFU)

Valg av behandling og Effekt av kurativ behandling er avhengig av:

- Utbredelse av svulsten i prostata
  (i eller utenfor prostatakjertelen)
- Spredning til lymfeknuter
- Celledifferensiering (Gleason skår)
- PSA
- Pasientens alder og generell helse (≥ 10år forventet levetid)
  (hormoner, strålebehandling etter operasjon)
- Behandlingstype (operasjon eller strålebehandling)
- Evtl. Tilleggsbehandling
- Tilgjengelighet av en behandlingsform
- Legens tro på en behandling og hans/hennes evne å overbevise pasienten
- Familie / venner / Internet

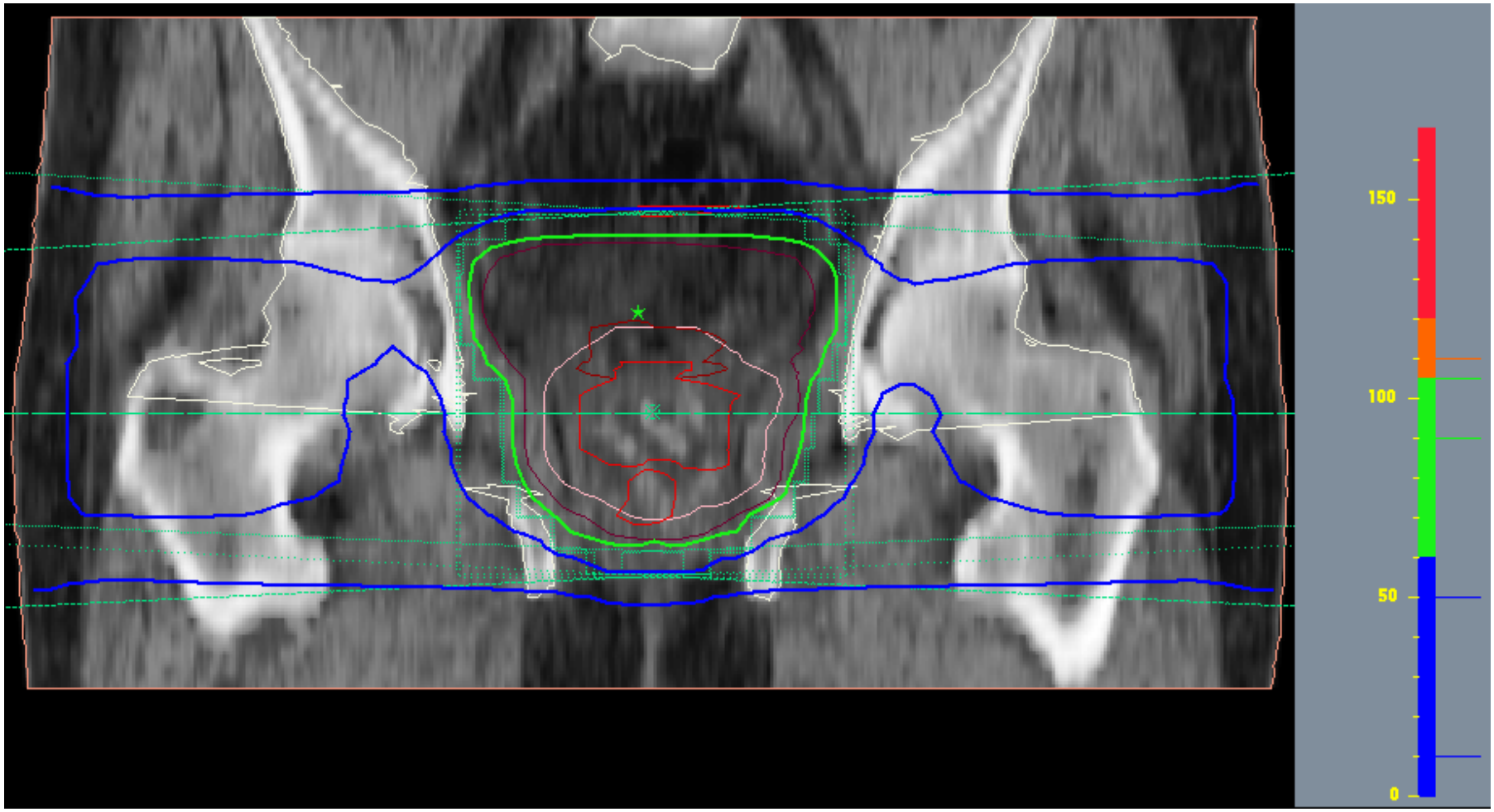
Kandidater for kurativ behandling (2004: n=1650 / 3774 :44%)

- T1-3N0-XM0-X
- T-kategori, Gleason score og PSA rapportert
- Alder ≤75 år
- ECOG 0-1
- Ikke annen kreft
- Ingen informasjon om alvorlige samsykdommer
- Livsforventning >=10år

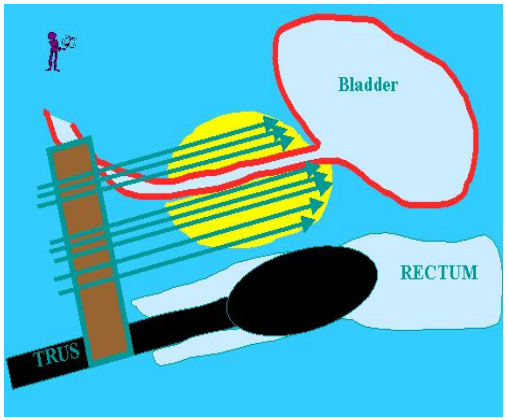


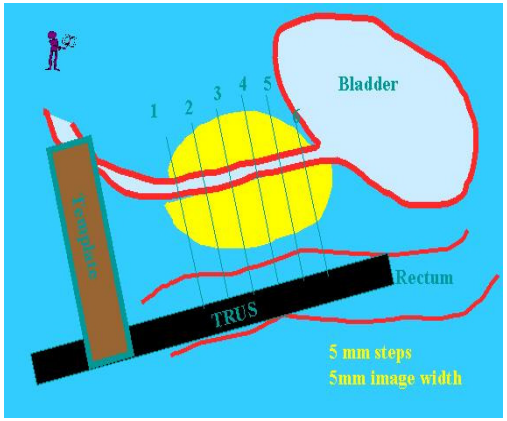
da Vinci®
Surgical System

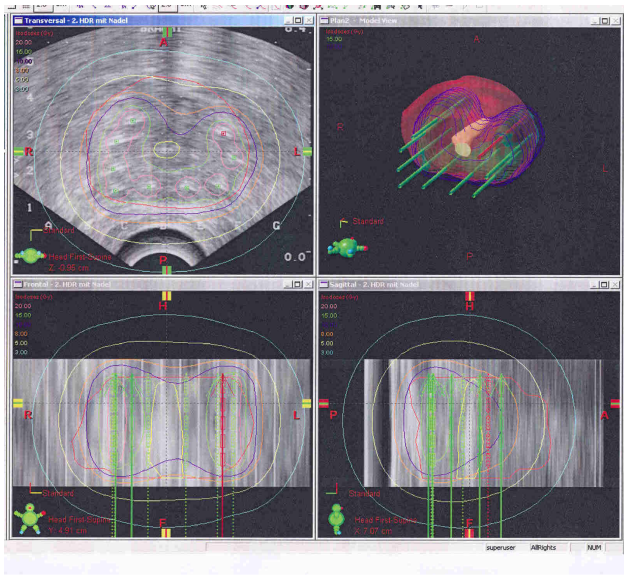
Radiation Treatment

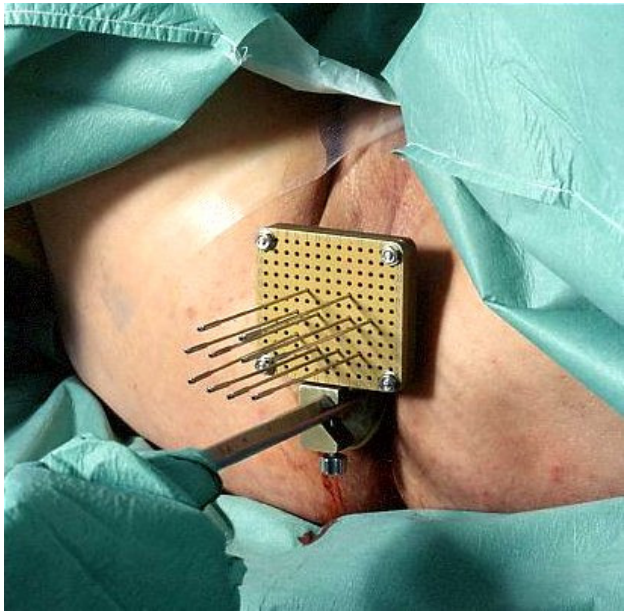


+/- hormone treatment for >= 3 years

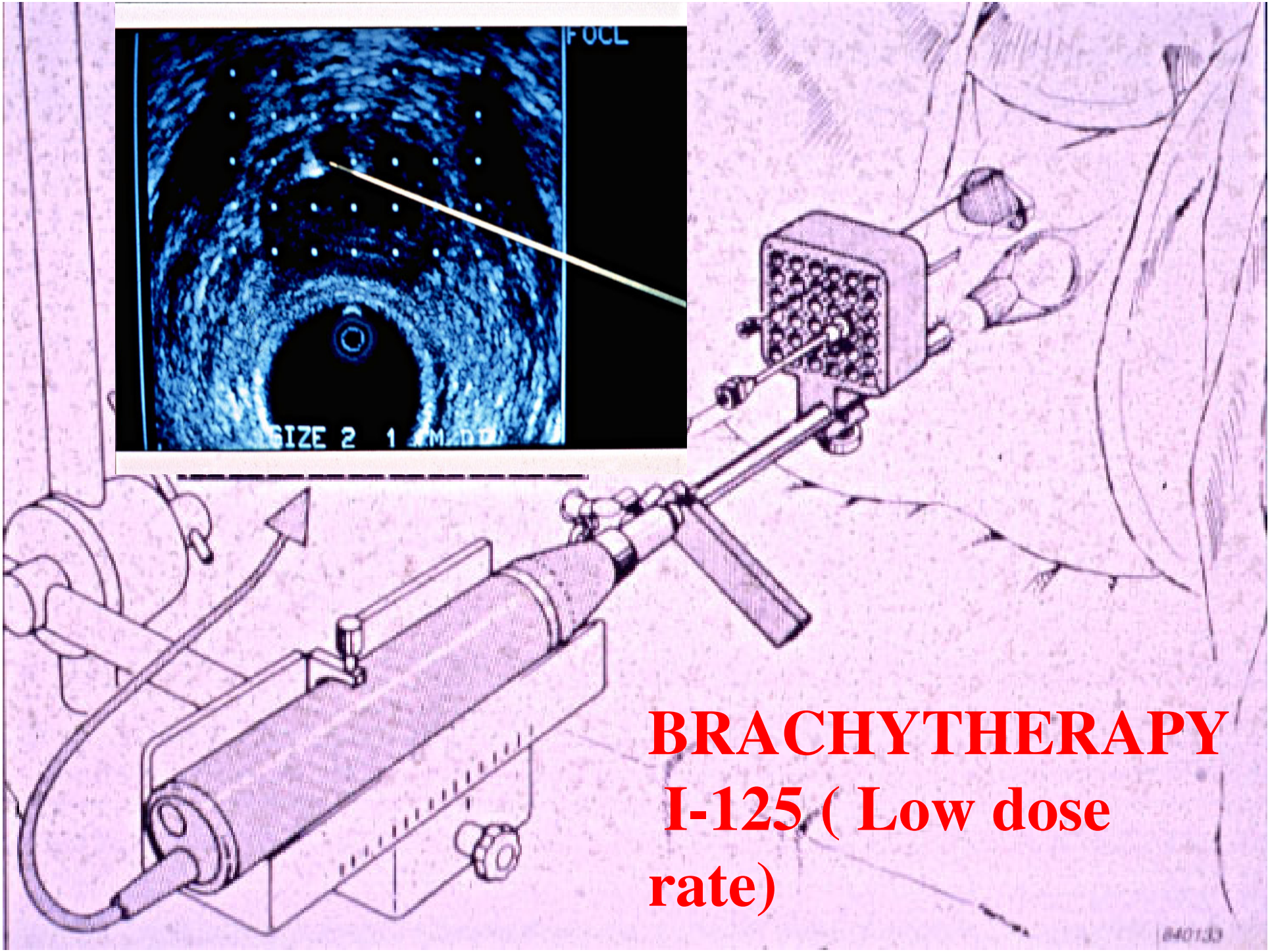






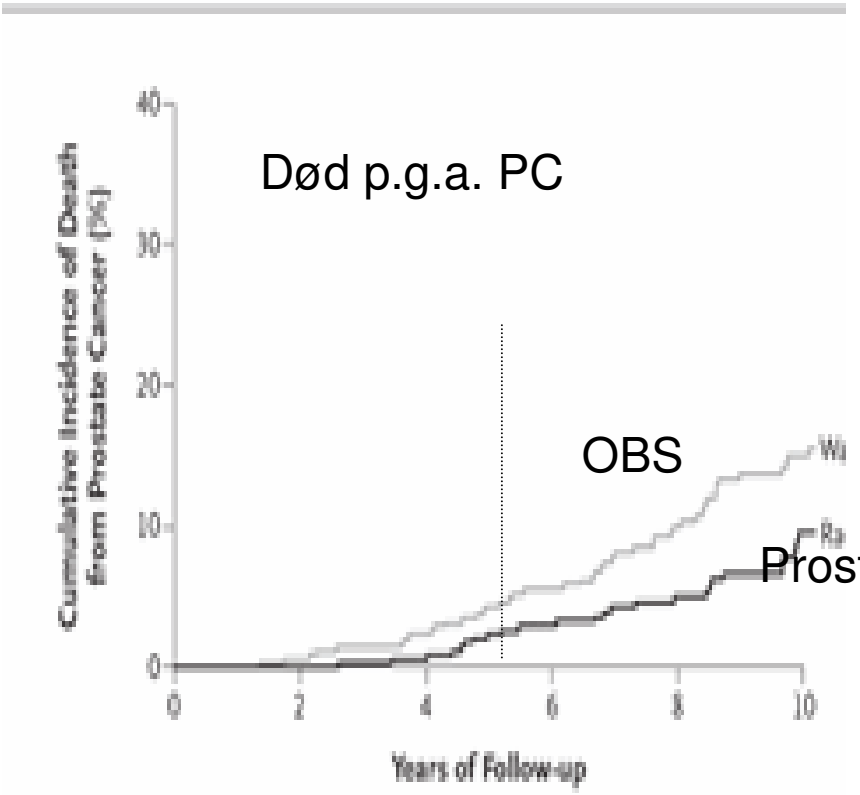


Ir-192 Afterloading: Needle placement (High Dose rate)



BRACHYTHERAPY I-125 (Low dose rate)

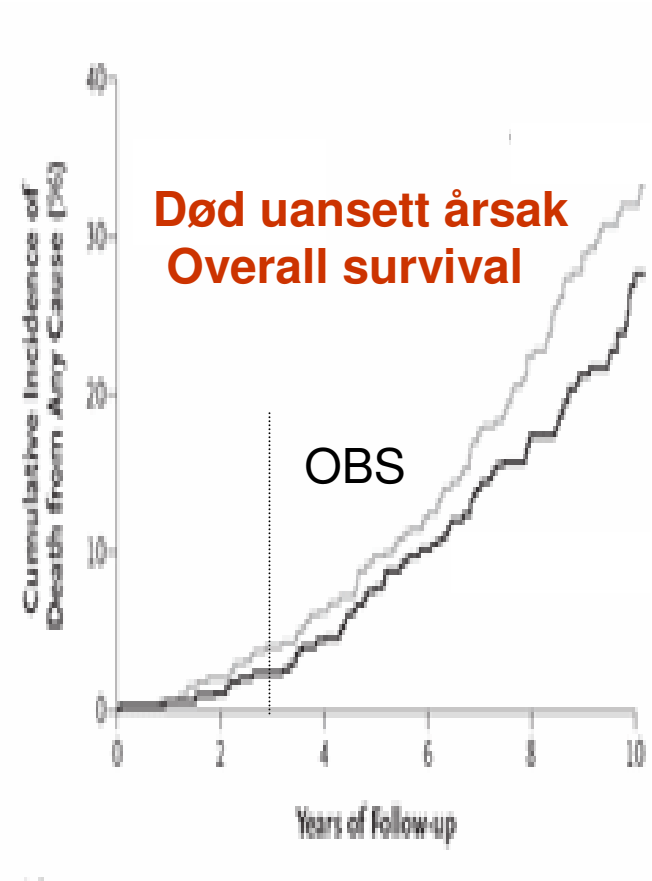
CaP dødsrate etter prostatektomi vs observation (low/intermed. risk patients



Død p.g.a. PC

OBS

Prostat.



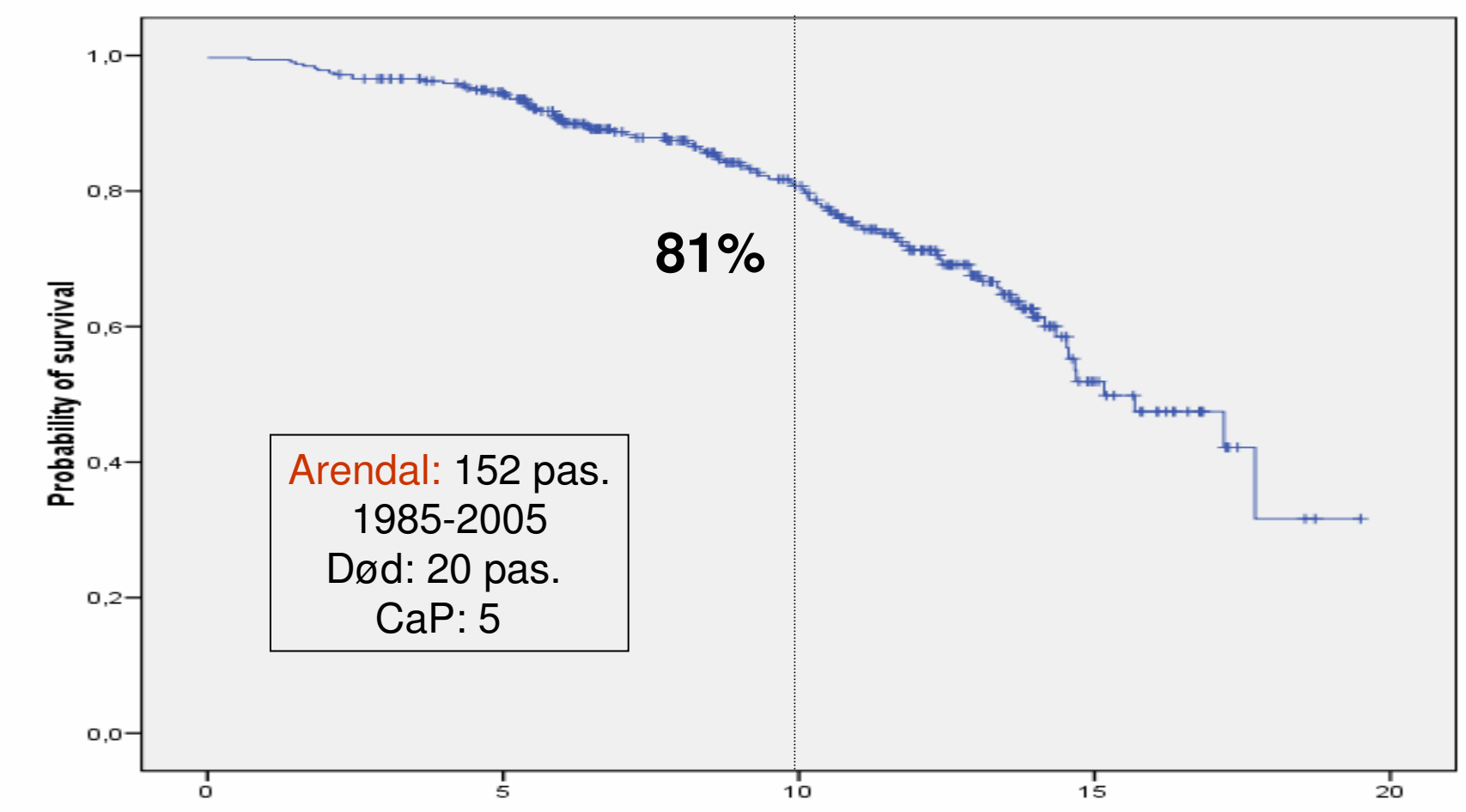
Død uansett årsak
Overall survival

OBS

Prostat.

Bill- Axelson et al., NEJM 352, 1977-1984, 2005

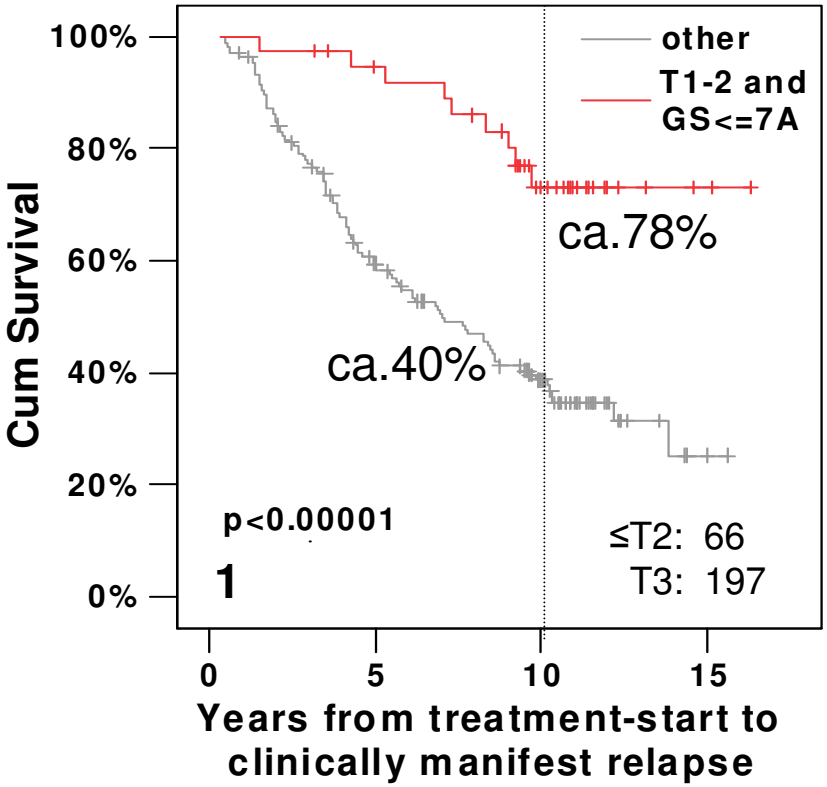
Overall survival after prostatectomy



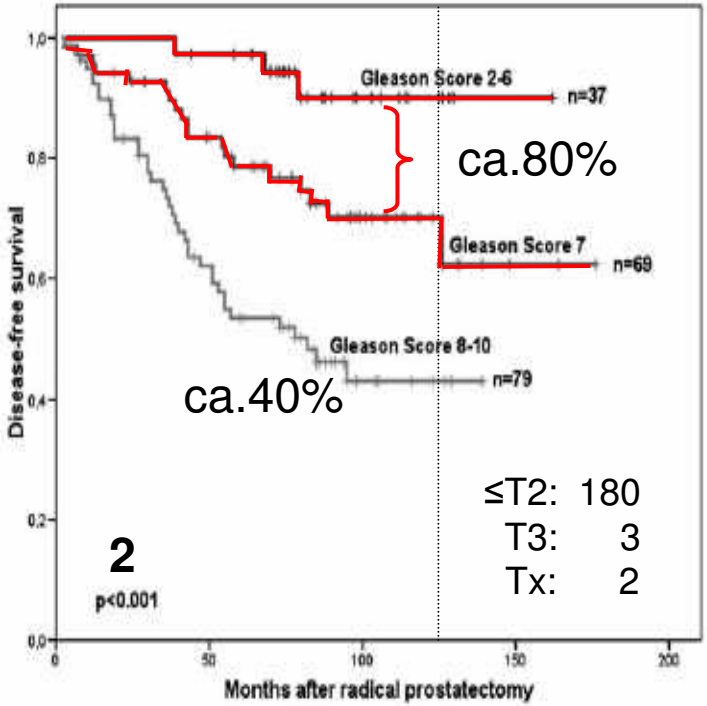
Servoll, in prep

10 year progression-free survival after Radiotherapy (N:203) or Radical Prostatectomy(N:324) in Norway

Radiotherapy

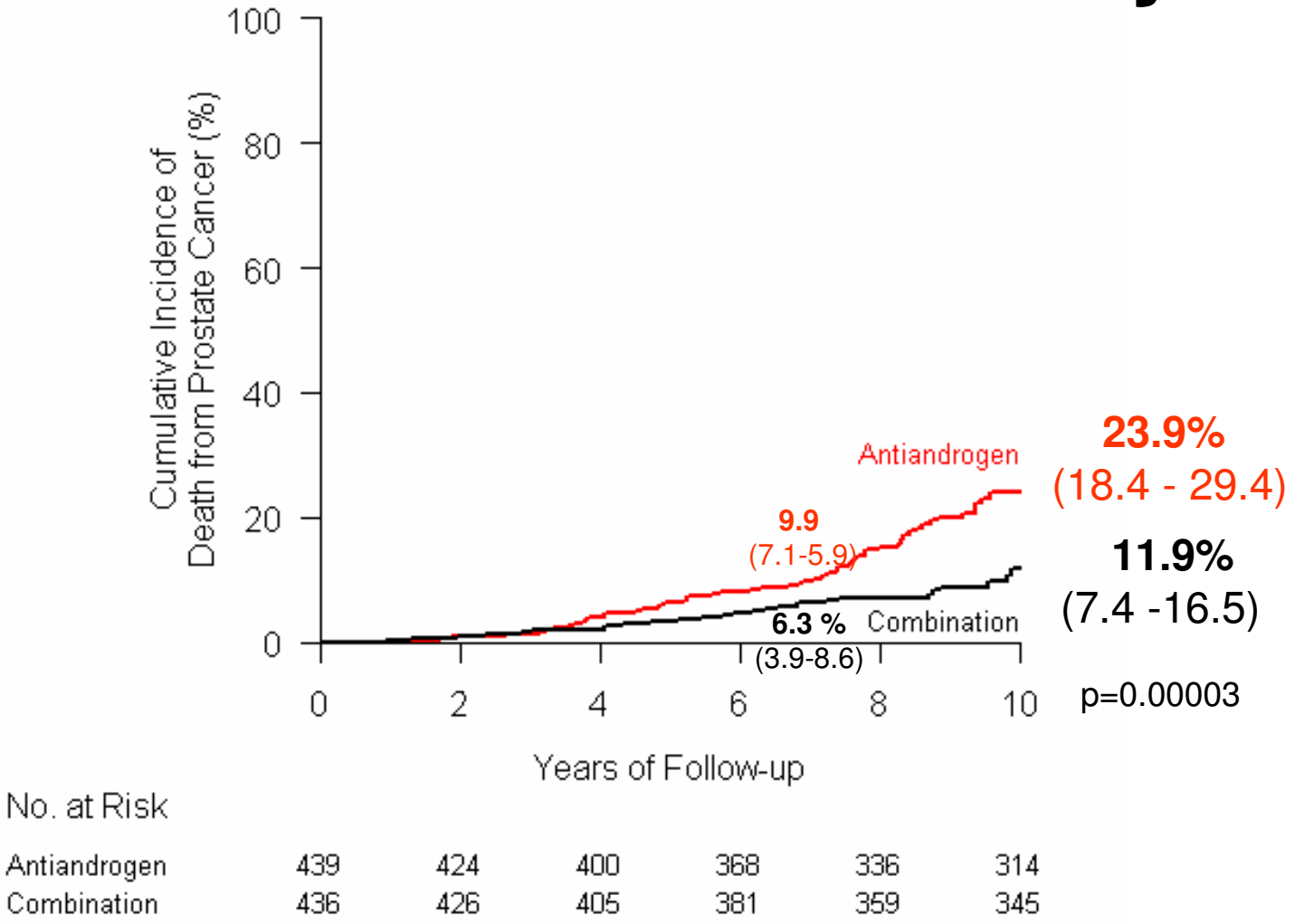


Prostatectomy



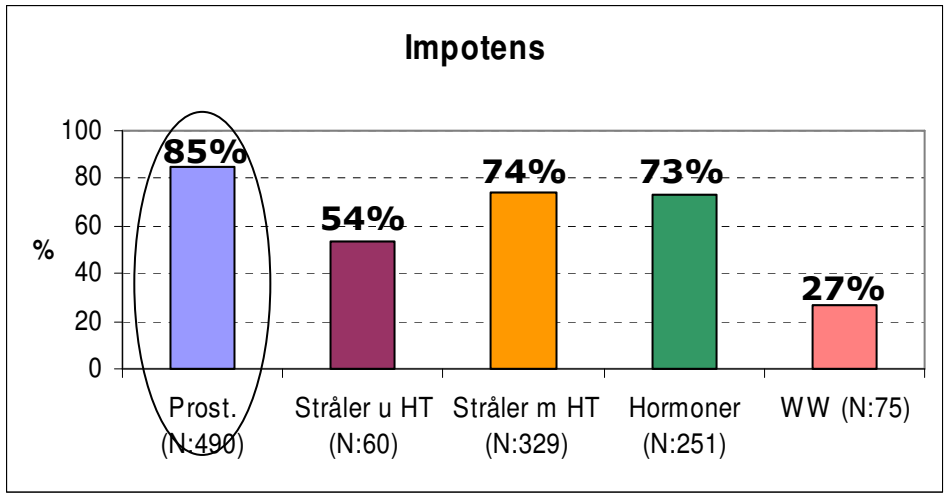
1.Berg IJROBP 2007;69,1074
2.Pretorius CellOncol 2009;31:251

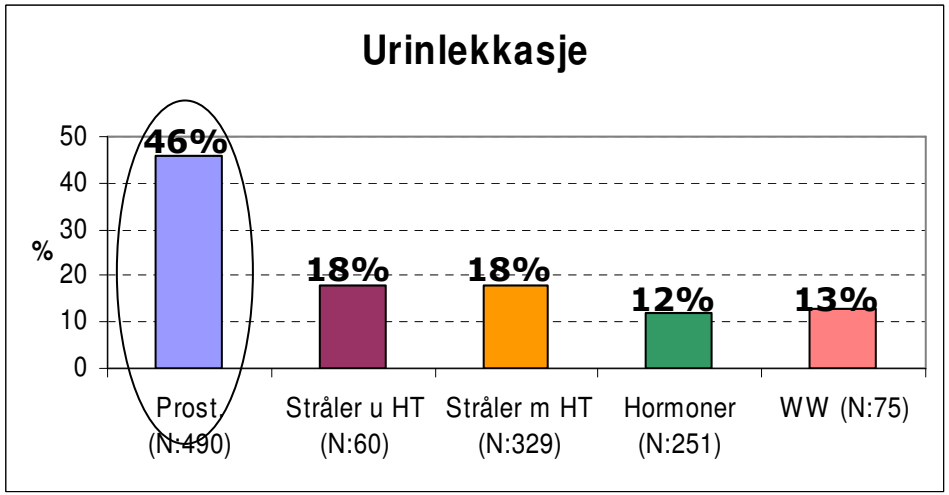
Cumulative incidence of **Prostate Cancer mortality**

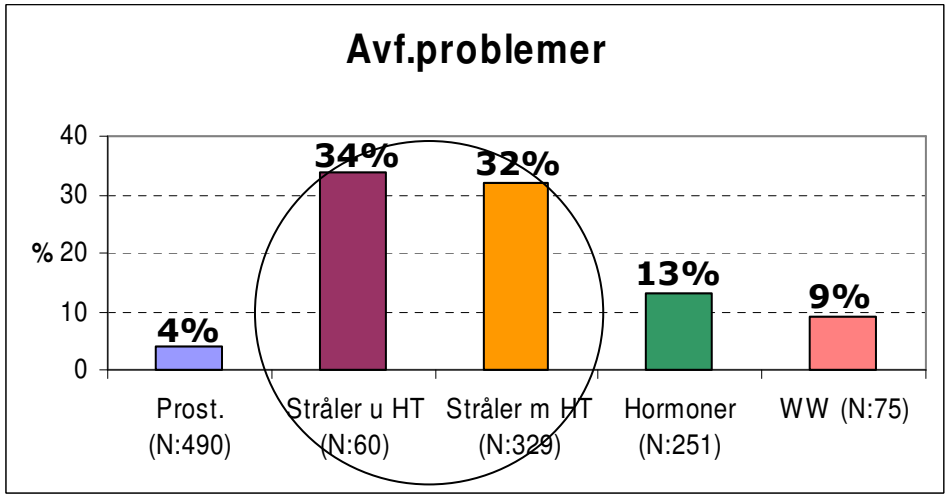


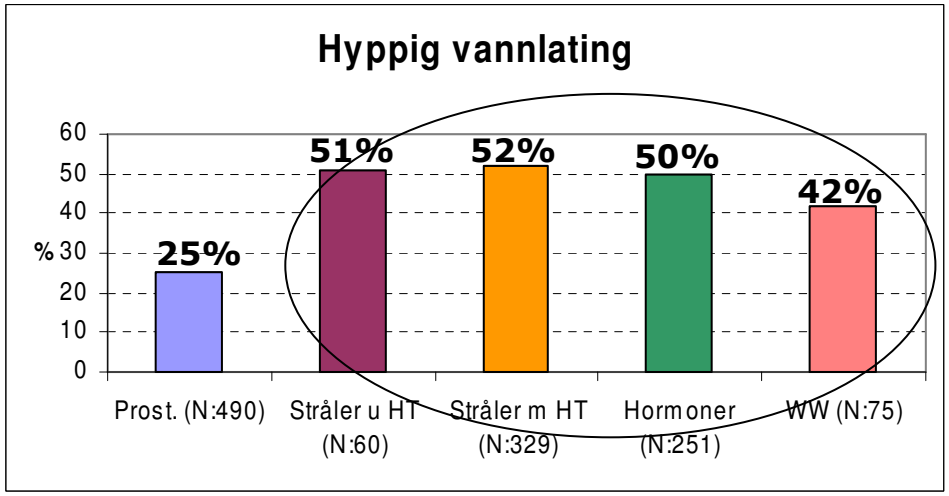
ASTRO, 2008, Plenary Session

Bivirkninger av behandling
(No2008+Da2009)









Prostatektomi Rad u/HT Rad m/HT Hormoner Watchfull Waiting

Maximal suppression of serum testosterone

Surgical castration : Orchiectomy

Medical castration : Hormones

LHRH agonister

LHRH Antagonister

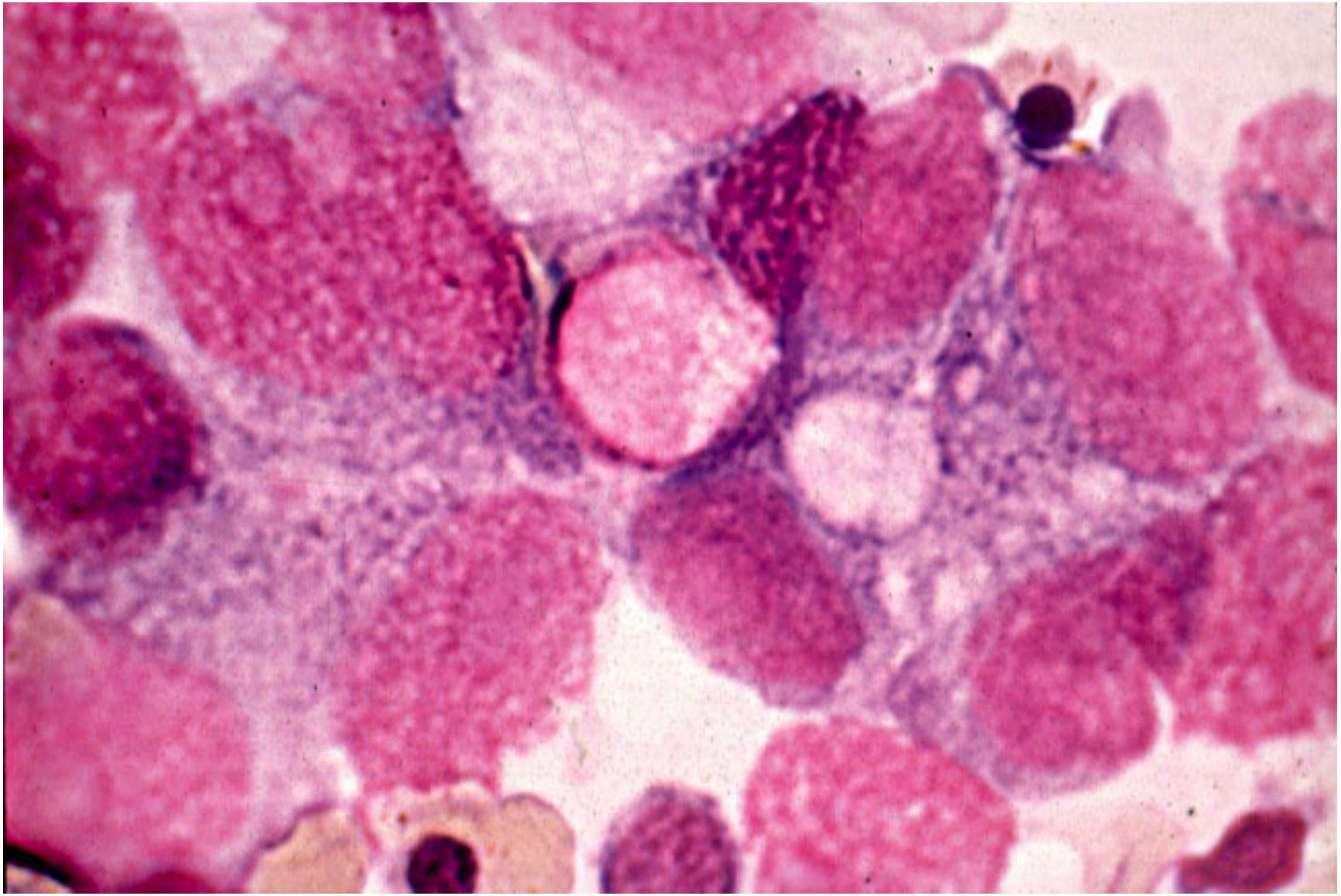
(Orale Anti-Androgener)

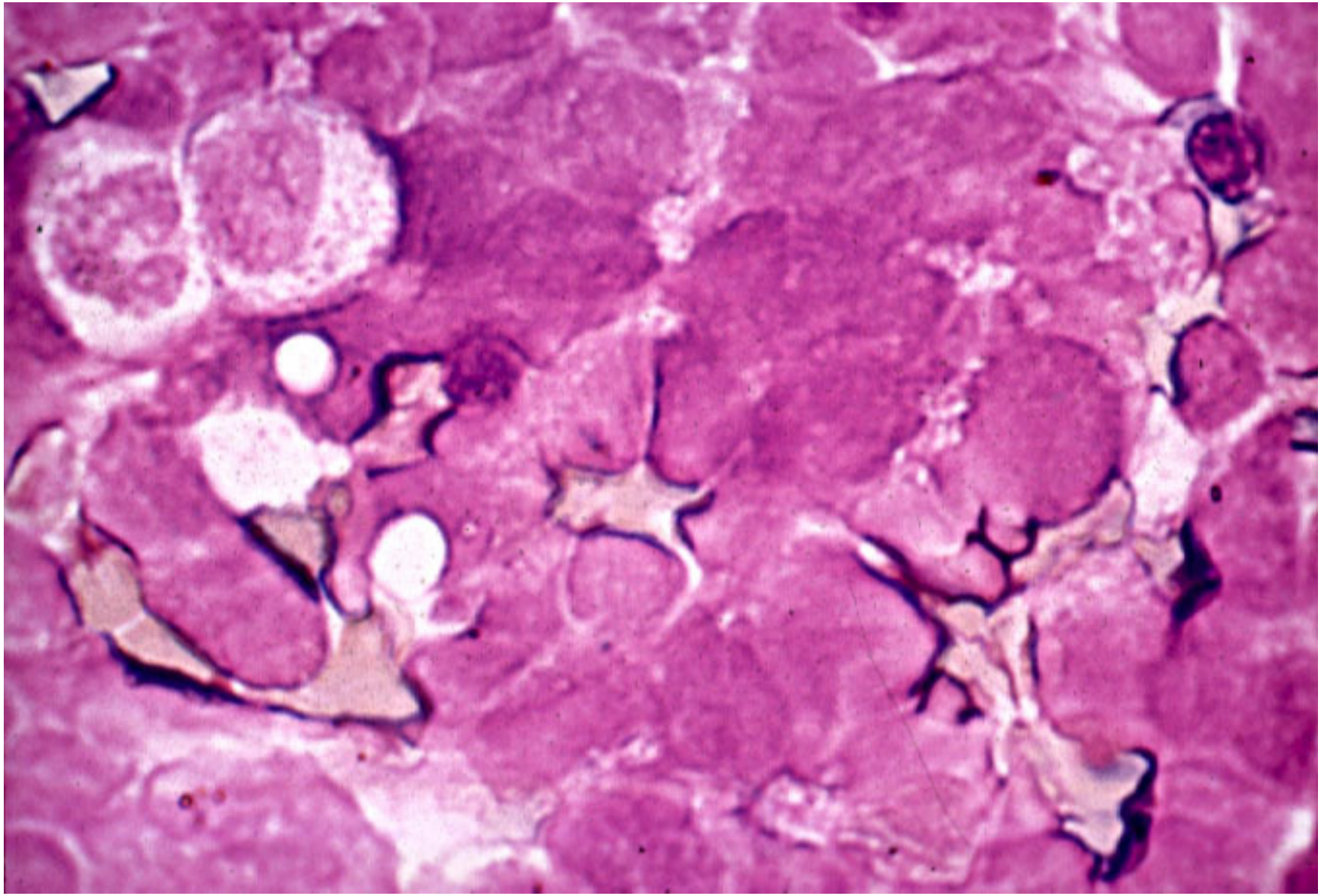
Total androgenblokkade

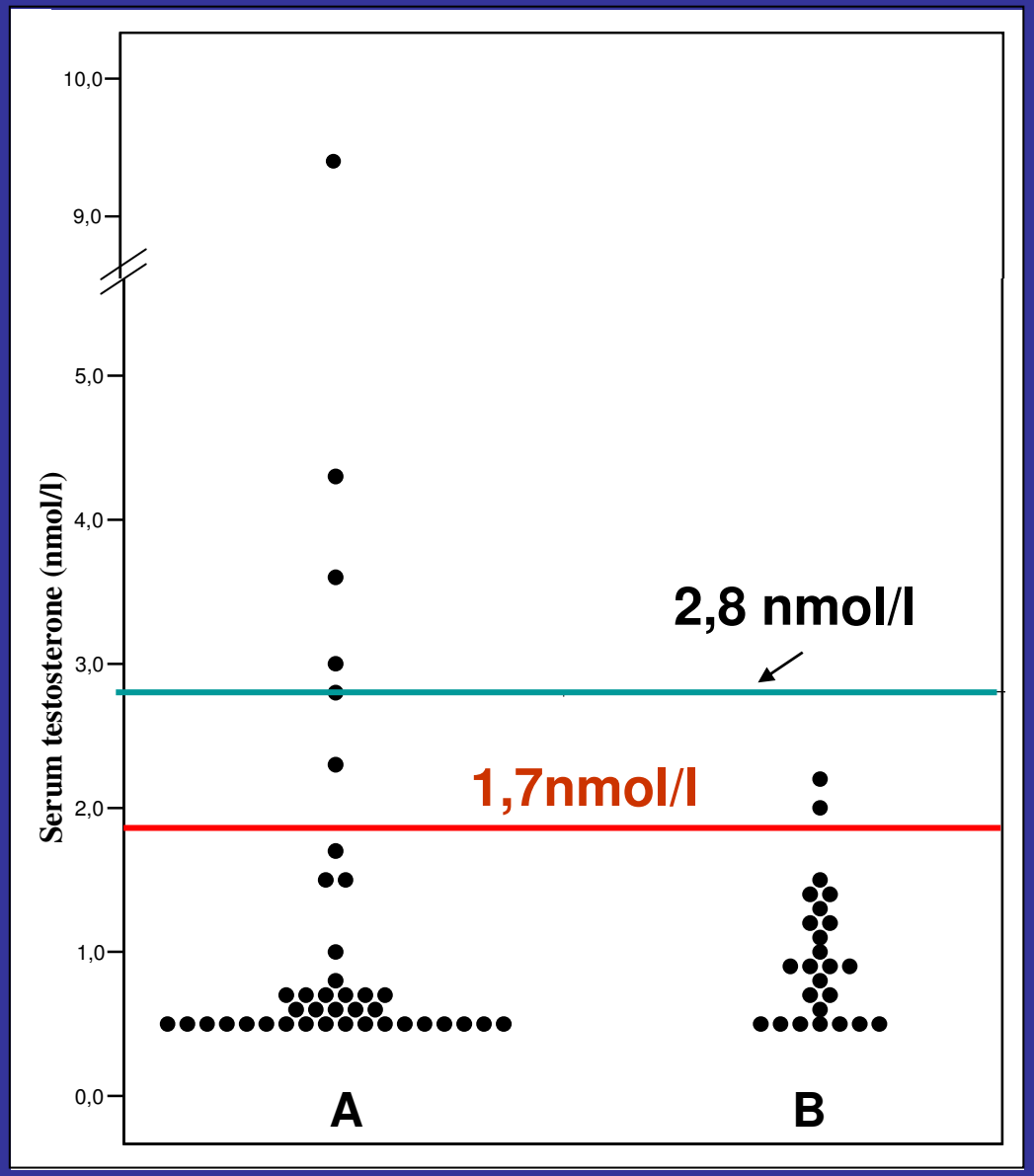
Estrogens

Suppression of serum testosterone below 0.7nmol/L

Zlotta (2006): Eur.Urol.suppl 5 ,369







A: Leu group (n=40) B: Gos group (n=25)

Serum testosterone levels in patients during the last 2 weeks of a 3-monthly cycle of treatment with an LHRH analogue

A: Procren Depot

B: Zoladex Depot

Yri et al, Eur. Urol.2005

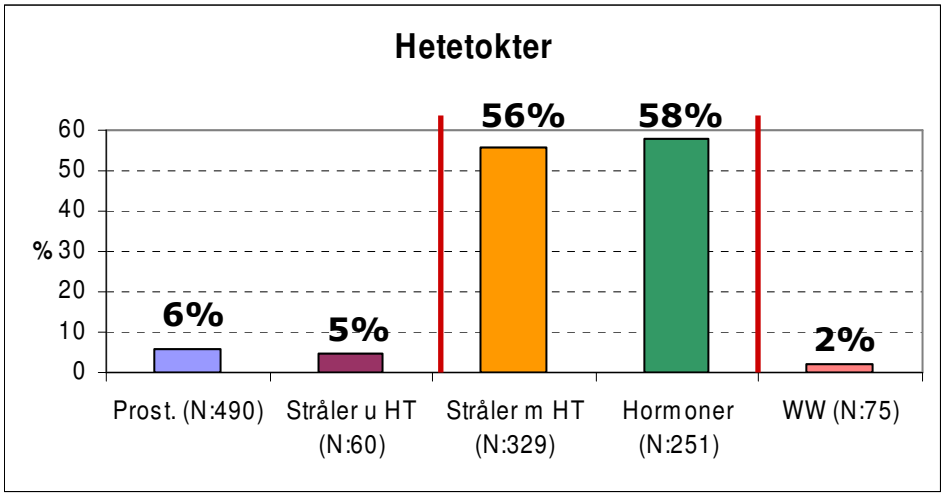
TREATMENT AND SIDE EFFECTS

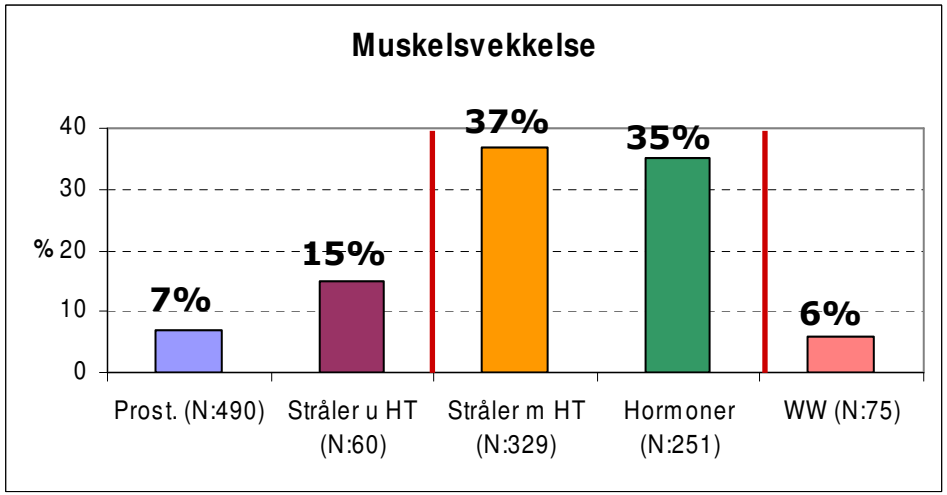
Table 1
Potential complications of androgen deprivation therapy

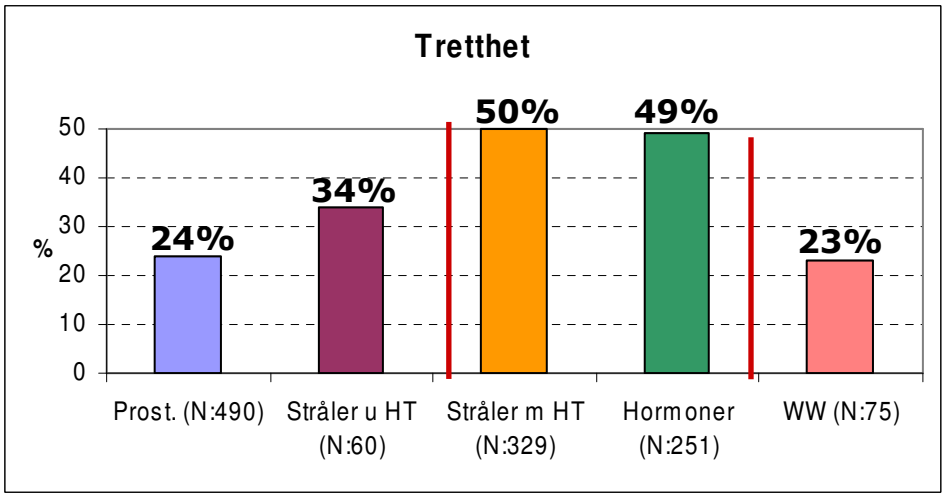
The "Big Three"	What you feel	What you see	What you don't see
Loss of libido	Fatigue	Weight gain	Loss of bone density
Erectile dysfunction	Lack of energy	Gynecomastia	Anemia
Hot flashes	Lack of initiative	Loss of muscle mass	Metabolic changes: Alterations of serum lipids, Exacerbation of hypertension, diabetes, heart disease
	Aches and pains	Loss of strength	
	Depression	Decreased size in testicles and penis	
	Emotional lability	Hair changes	
	Cognitive changes		

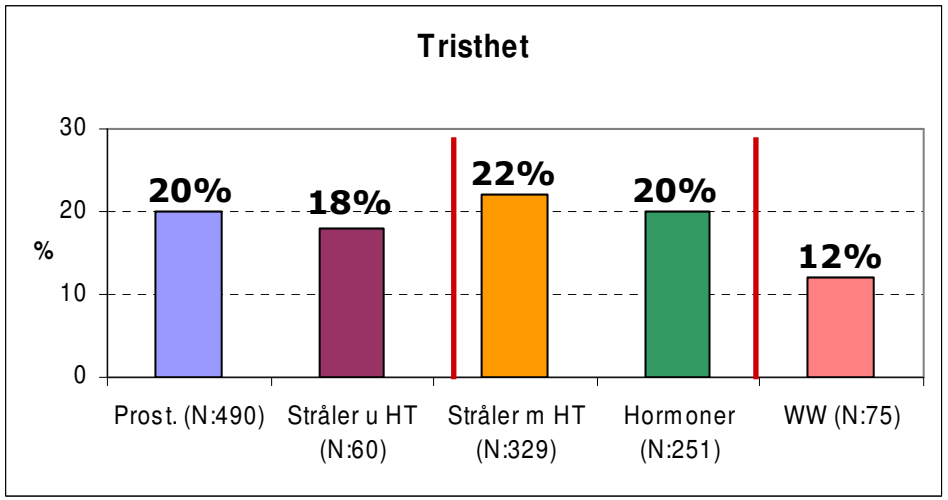
Higano C, Hematol Oncol Clin N Am, 2006

Bivirkninger av behandling forts. PROFO unders.





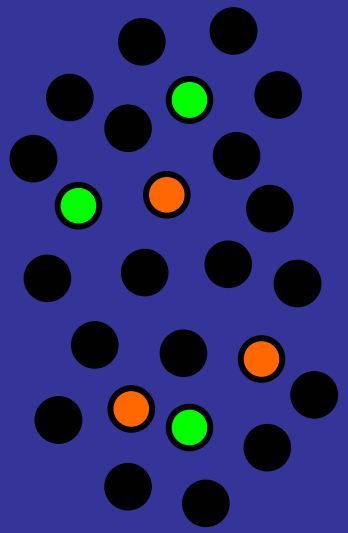




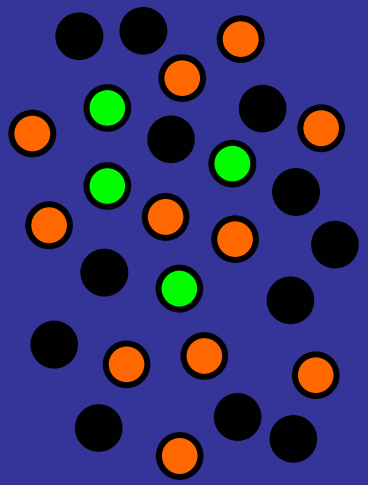
Prostatektomi Rad u/HT Rad m/HT Hormoner Watchfull Waiting

Metastatic Disease: Hormone Sensitivity

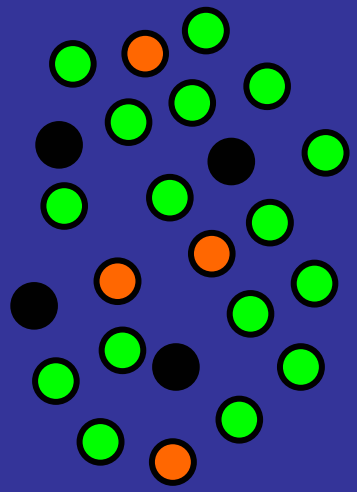
Hormone Sensitive



Hormone Responsive



Hormone Refractory



- Hormone-dependent cells
- Partially hormone-dependent cells
- Hormone-independent cells

Schematic provided by Drs. T. Smith and H. Vogelzang.

Utvikling av CRPC
(Serum testosteron <1.7nmol/l)

1. Økning av androgenreseptorer (ARs)
2. Mutasjon av AR genet

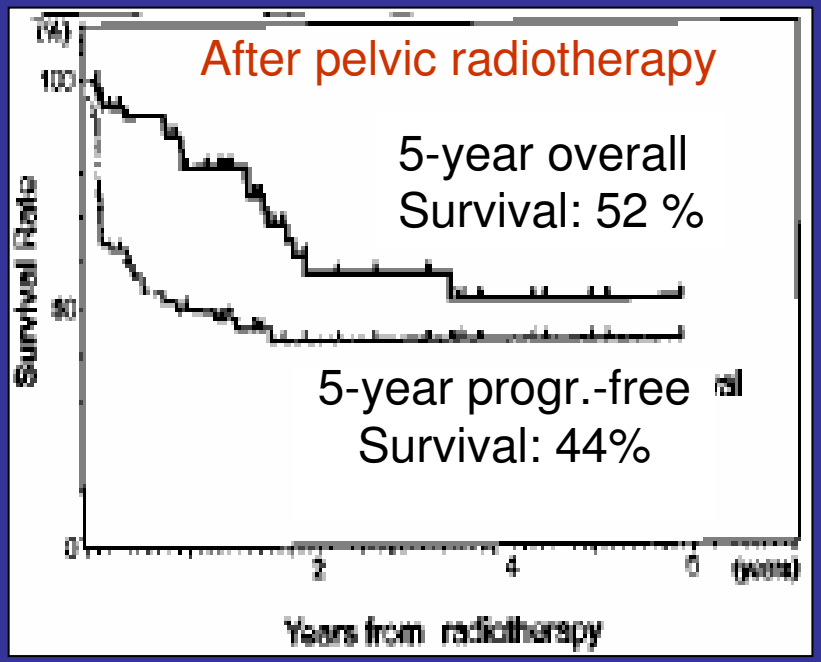
   → Hypersensitivitet for lave nivåer av serum testosteron, som finnes i serum
3. Intra-cellulær androgen produksjon

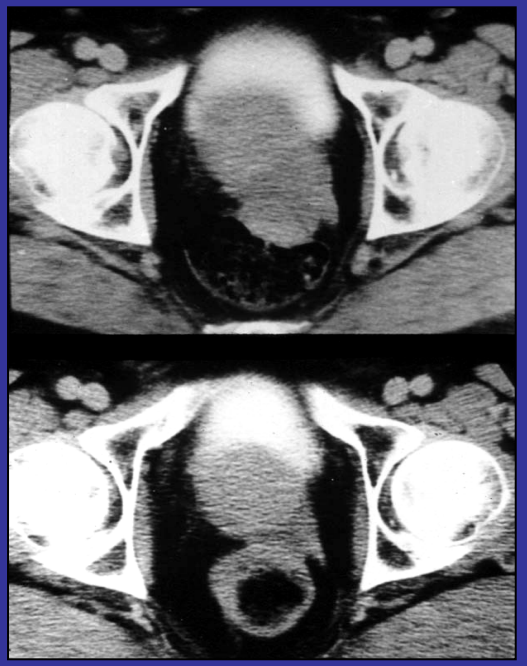
   → Fortsatt androgen påvirkelig ved ytterligere androgen deprivasjon på cellenivå
4. Mutasjoner i onkogent virksomme signalveier (vekststimulasjon ved BCL-2, neuropeptider etc.)

   ⇒ Hormon-refraktar PC

   AIPC (androgen independent PC)

HRPC with advanced loco-regional tumor manifestations and no or minimal metastatic burden

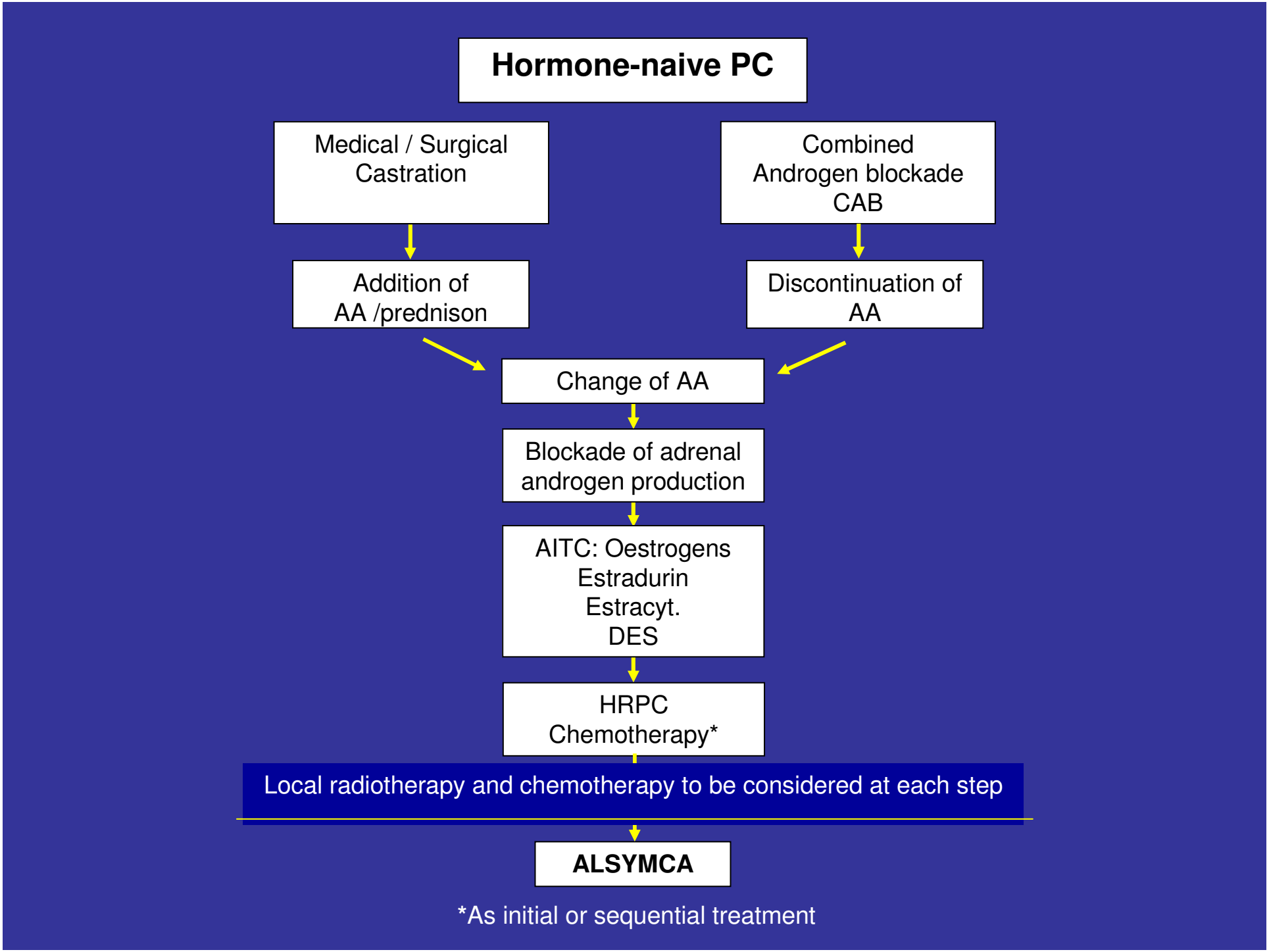




Conclusion: More clinical research needed

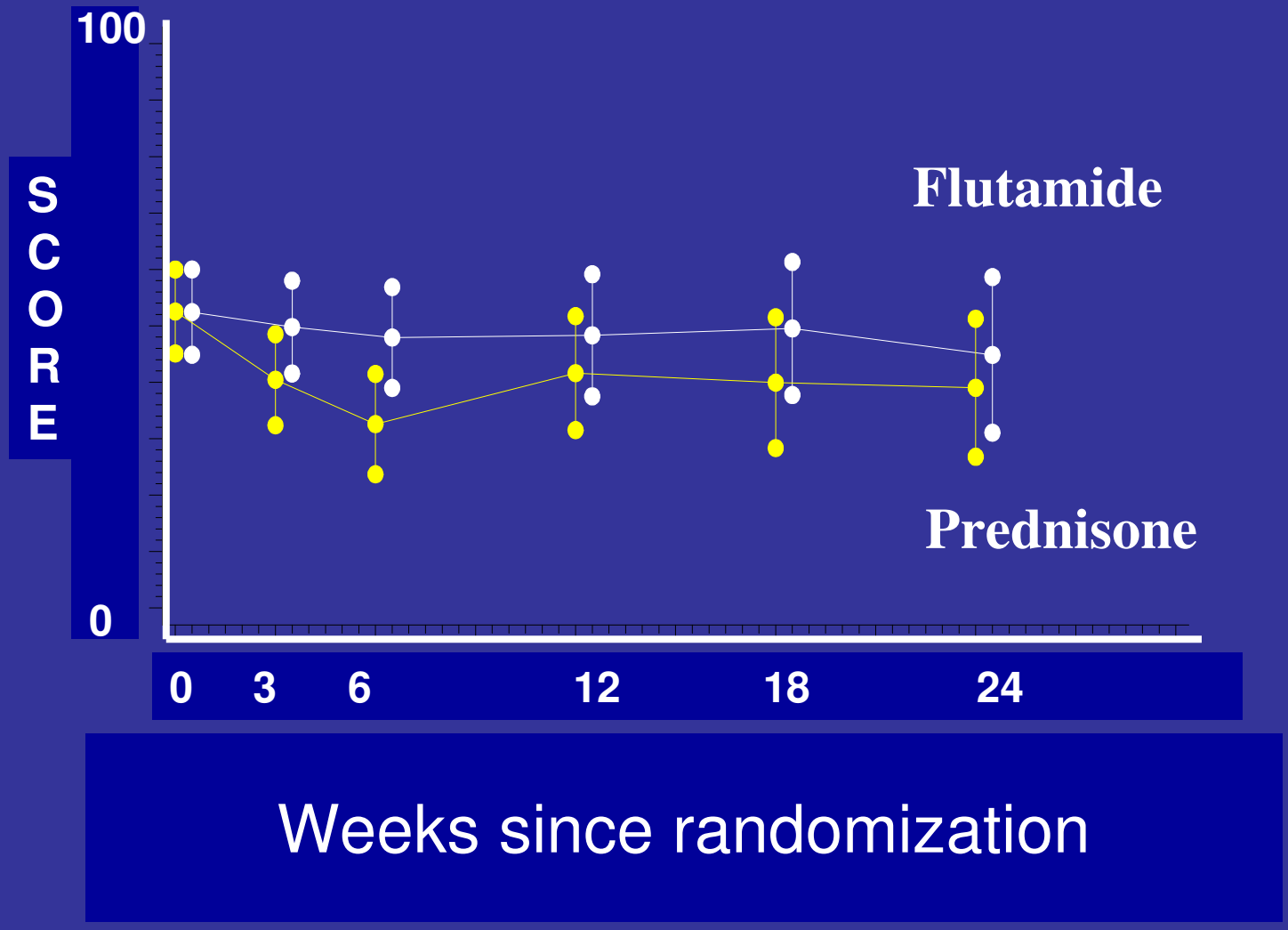
•20% of HRPC patients
• Palliative surgery with undocumented effect
• Early radiotherapy is effective
• Long-term survival possible

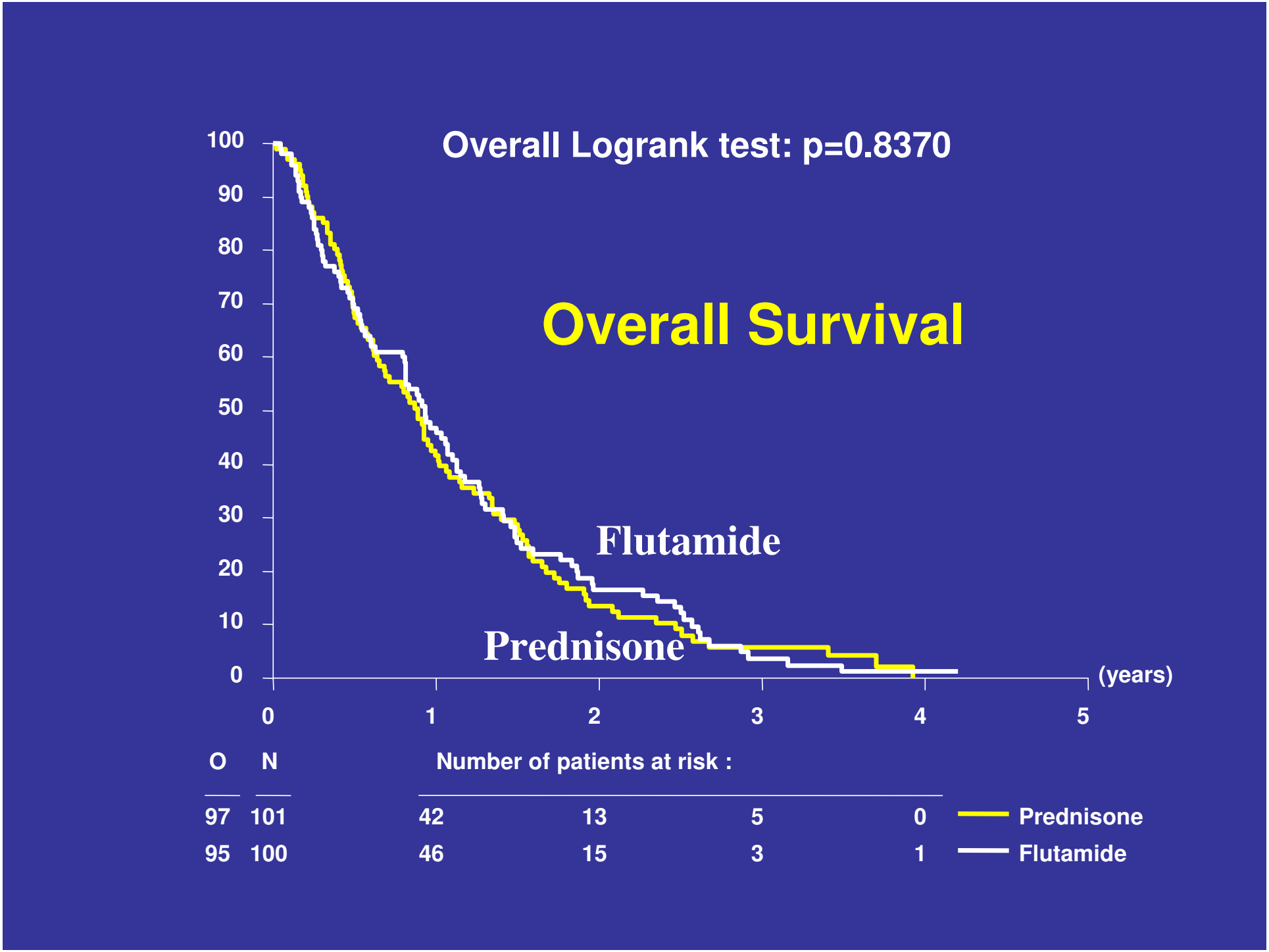
Nakamura,Anticancer research (2004) 24,3141


Hormone-naive PC
Medical / Surgical Castration
Combined Androgen blockade CAB
Addition of AA /prednison
Discontinuation of AA
Change of AA
Blockade of adrenal androgen production
AITC: Oestrogens Estradurin Estracyt. DES
HRPC Chemotherapy*
Local radiotherapy and chemotherapy to be considered at each step
ALSYMCA
*As initial or sequential treatment

Palliation by systemic treatment

Pain




Overall Logrank test: p=0.8370
Overall Survival
100
90
80
70
60
50
40
30
20
10
0
Flutamide
Prednisone
(years)
0
1
2
3
4
5
O
N
Number of patients at risk :
97
101
42
13
5
0
Prednisone
95
100
46
15
3
1
Flutamide

Nye cellegifter og behandlingsprinsipper når hormoner ikke lengre er effektive.
Hvem har effekt? Hvem får bivirkninger Gener? Hvilke gener ?

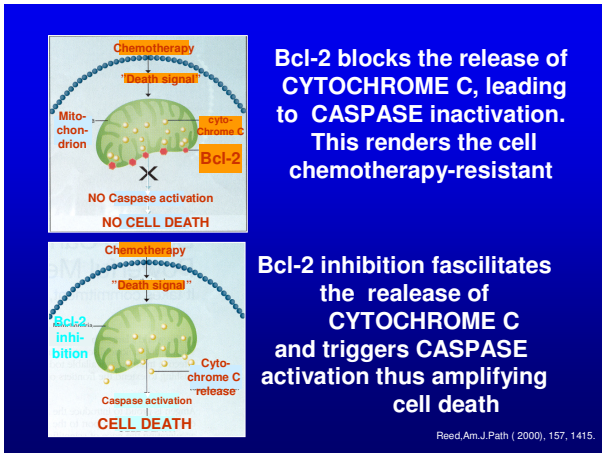
Nye former av hormon- og cellegift- Behandling/ Målsøkende medikamenter

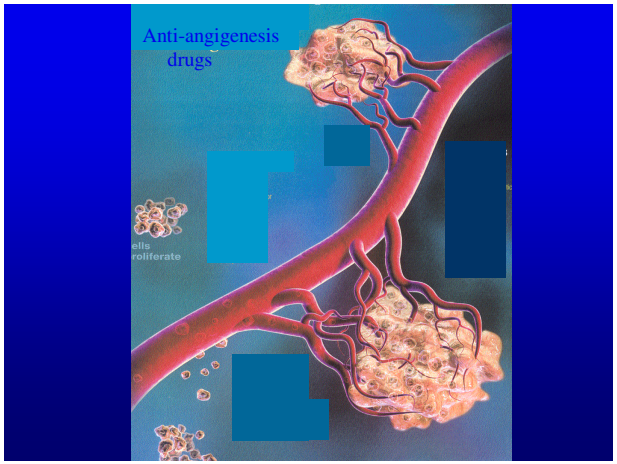
TAXOTERE

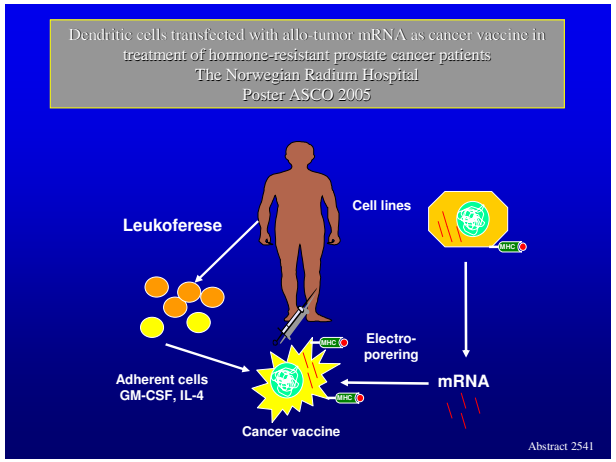
Cabazitaxel

ABIRATERONE

Vaccine



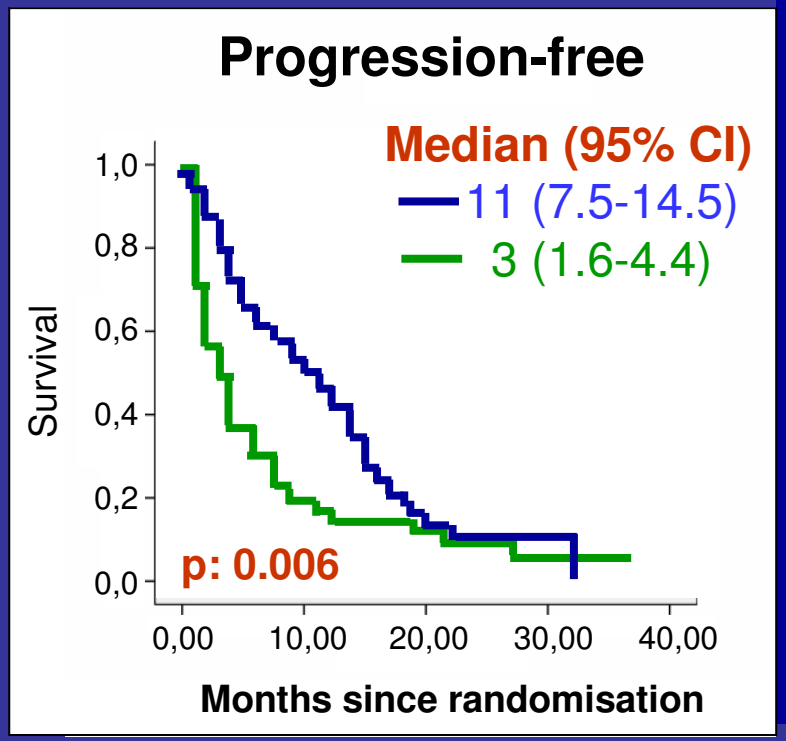


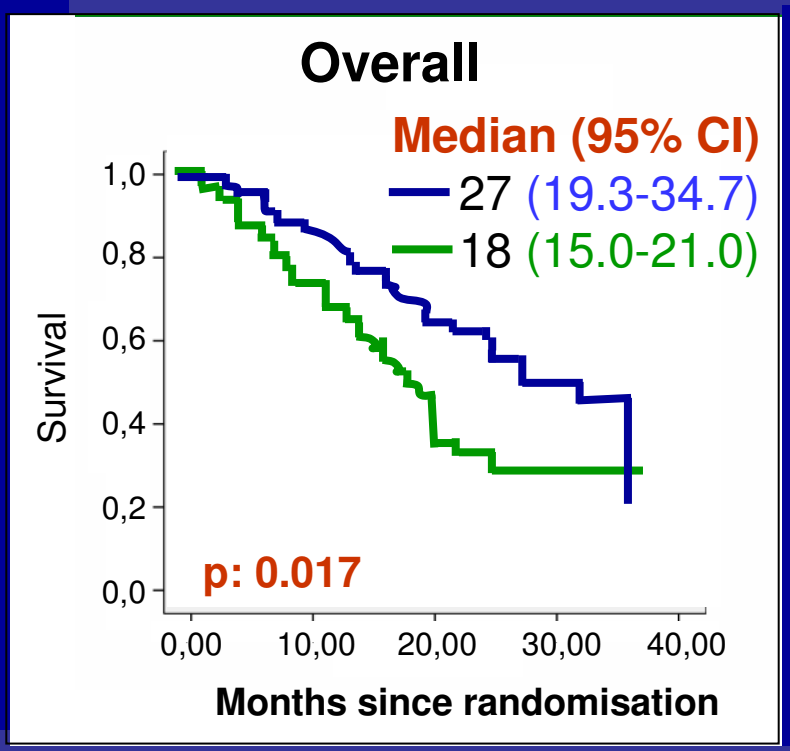


Kjemoterapi (Taxotere)

- God palliativ effekt
- Biokjemisk respons (≥50%)
- Livsforlengende
- Kan gjentas

Survival

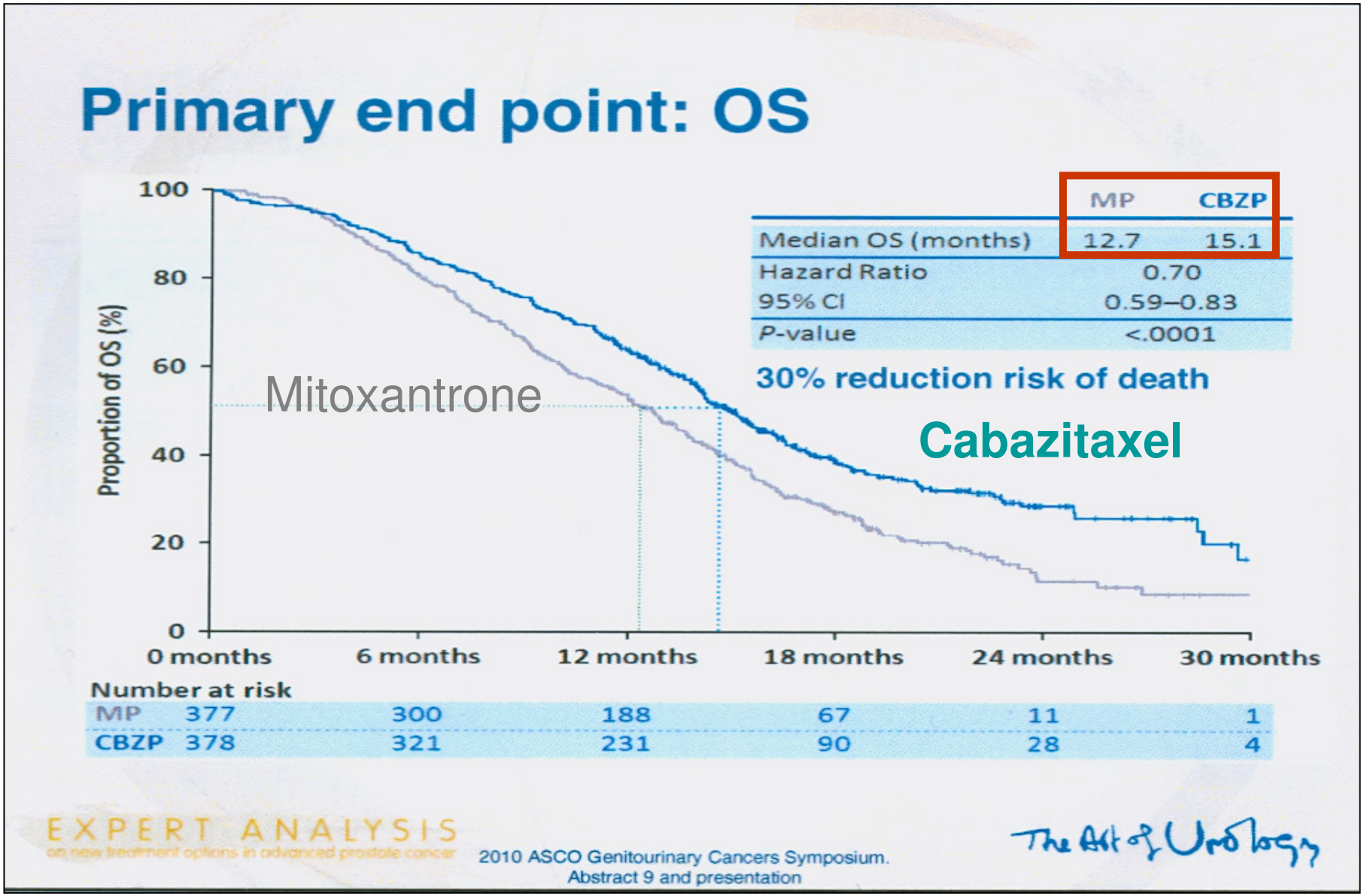




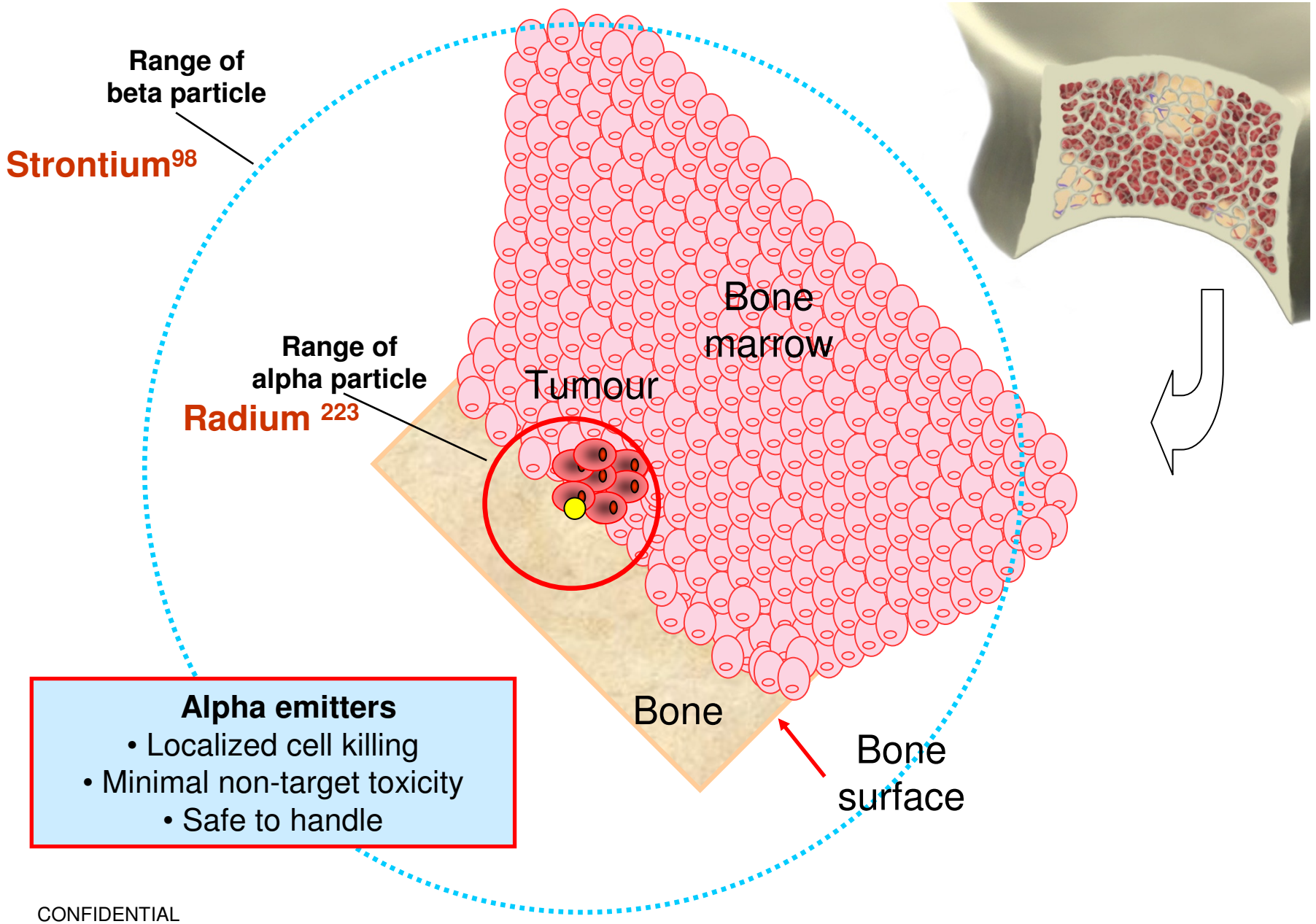
TAX + P P

ETTER TAXOTERE:

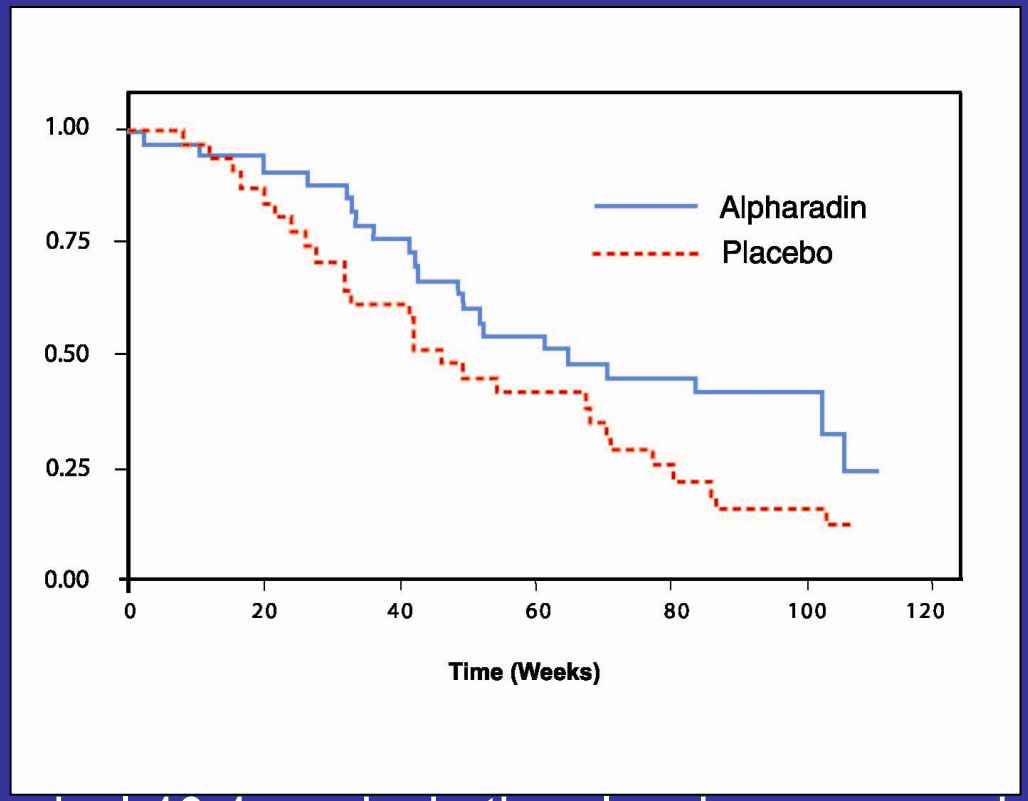
HRCP:Totaloverlevelse etter Cabazitaxel vs Mitoxantrone



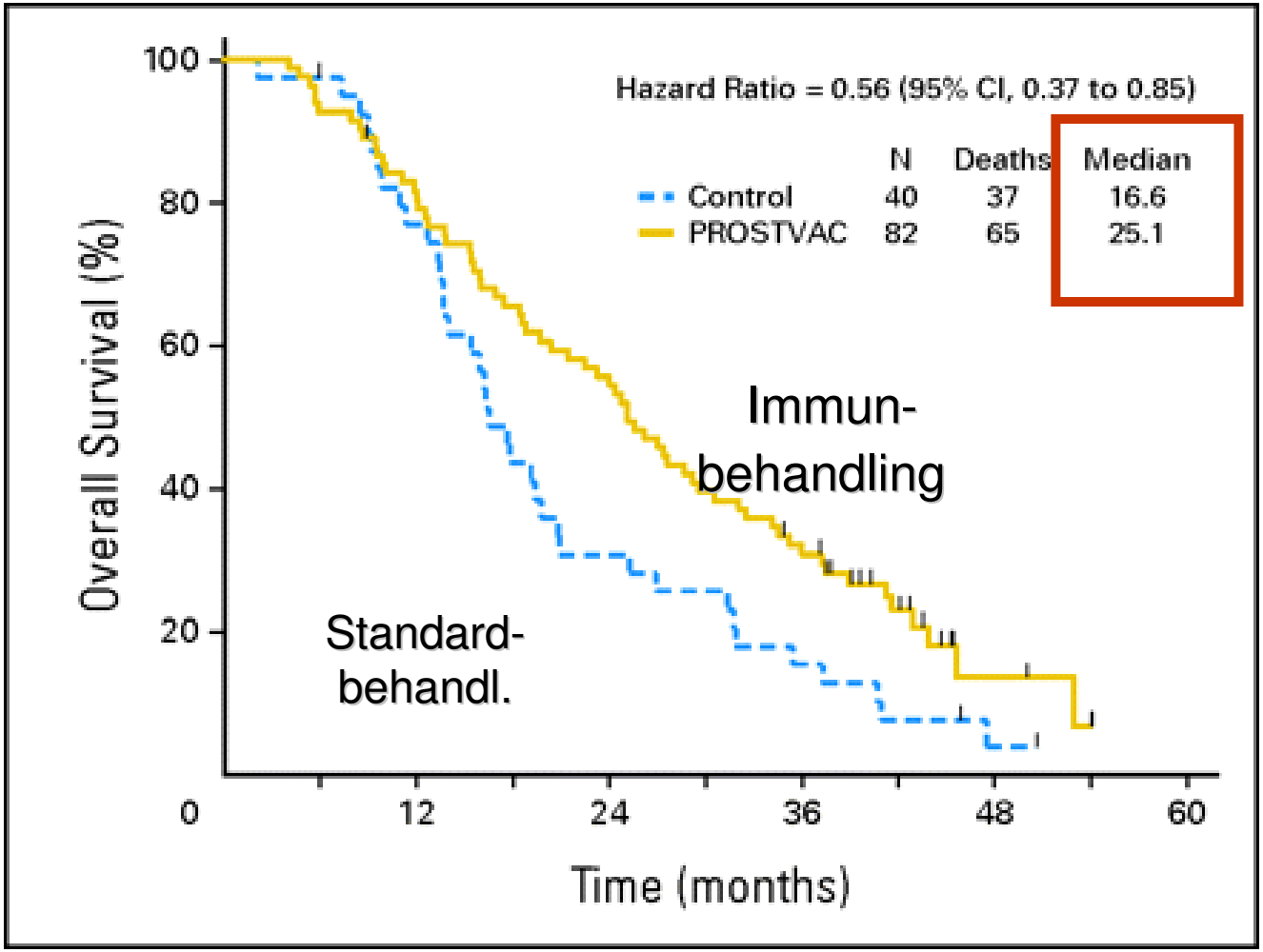
Alfaradin: Short path length = Localised Action



Overall survival 24 months follow up (ITT population)

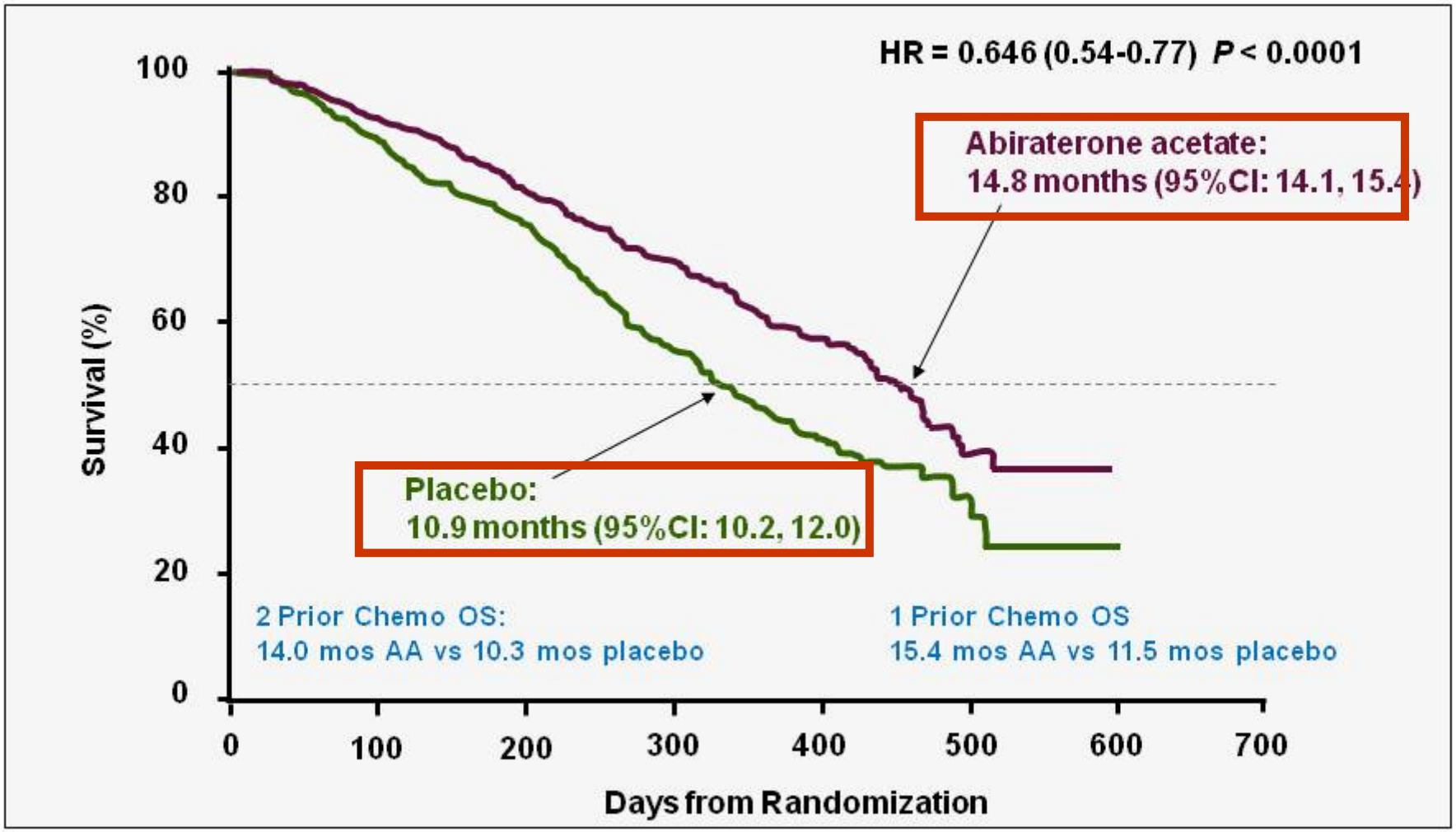


- Median overall survival 46.4 weeks in the placebo group and 65.3 weeks in the Alpharadin group. Hazard ratio 2.103, p = 0.017. 4.5 months difference
- 30% (10pts) of the patients were alive at 24 months in the Alpharadin group versus 13% (4 pts) in the placebo group



PROSTVAC: Overall survival. The estimated median overall survival is 25.1 months for the PROSTVAC arm and 16.6 months for the control arm.

COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC



AA	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

Konklusjon

1. Mulig med fortsatt hormonbehandling ved progresjon av prostatakreft under initial androgen suppresjon
   - Sjekk serum testosteron
   - Vurder palliativ strålebehandling av primærtumor
2. Flere muligheter avhengig av primærbehandling, pasientens tilstand (alder, almentilstand, symptomer), progresjonshastighet
3. Sekundær hormonbehandling med Prednison/ Anti-androgener : Ofte ”PSA kosmetikk” (BUT: ABIRATERONE)
4. Ikke forspill muligheten for effektiv kjemoterapi, Ikke utsett start av kjemoterapi for lenge
5. Alsympca: Annen linjes non-hormonal behandling (eksperimentell)

TAKK

Clinical T-category of the cases curatively treated in the periods 1993-95 and 2002-04

	1993-95	2002-04
T1ab	17 (3%)	79 (3%)
T1c	46 (9%)	842 (34%)
T2	235 (44%)	931 (37%)
T3	170 (32%)	551 (22%)
TX/unknown	68 (13%)	103 (4%)
Total	536 (100%)	2506 (100%)

Kvaale, in prep

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

CONCLUSIONS and treatment

PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. (Current Controlled Trials number, ISRCTN49127736.)

1410 men would need to be screened

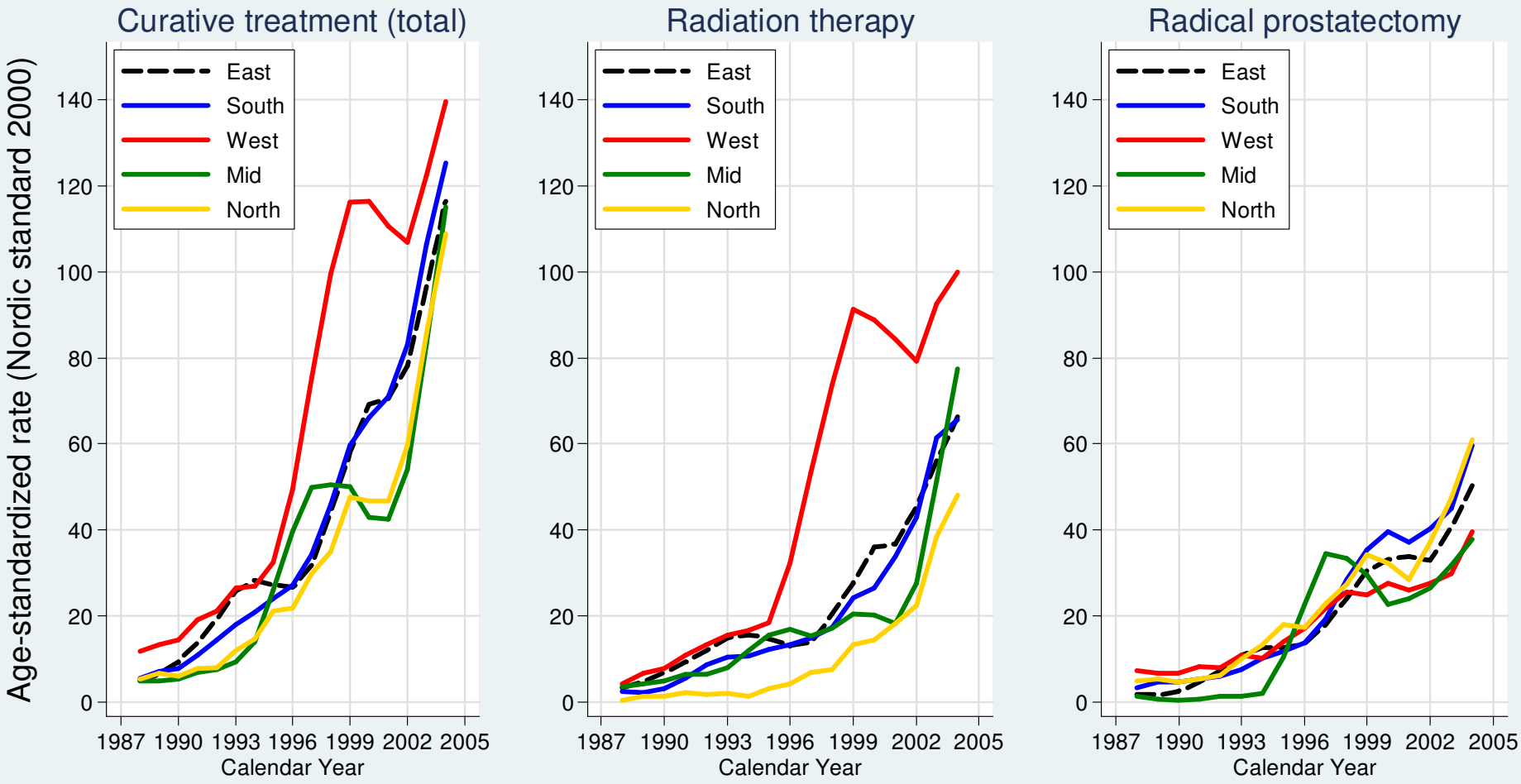
48 additional cases of prostate cancer would need to be treated

to prevent one death from prostate cancer.

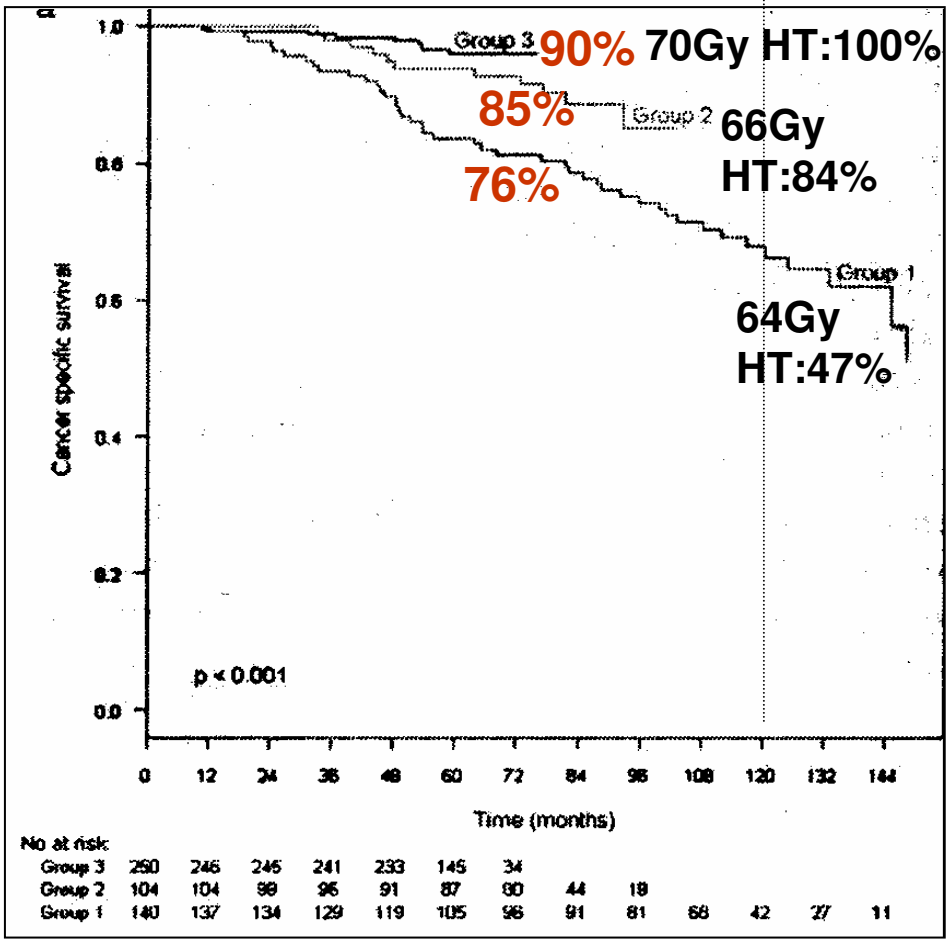
N. ENGL. J. MED. 2009 March 26

Senere behandling

	No2005	**No2008** N: 242	**Da2009** N:344
Hormonbehandling	37%	50%	77%
Strålebehandling	10%	42%	20%
Kirurgi	6%	12%	19%
Kjemoterapi	3%	16%	11%
Vaksinebehandling	0%	1%	6%
Bifosfanater	2%	15%	16%

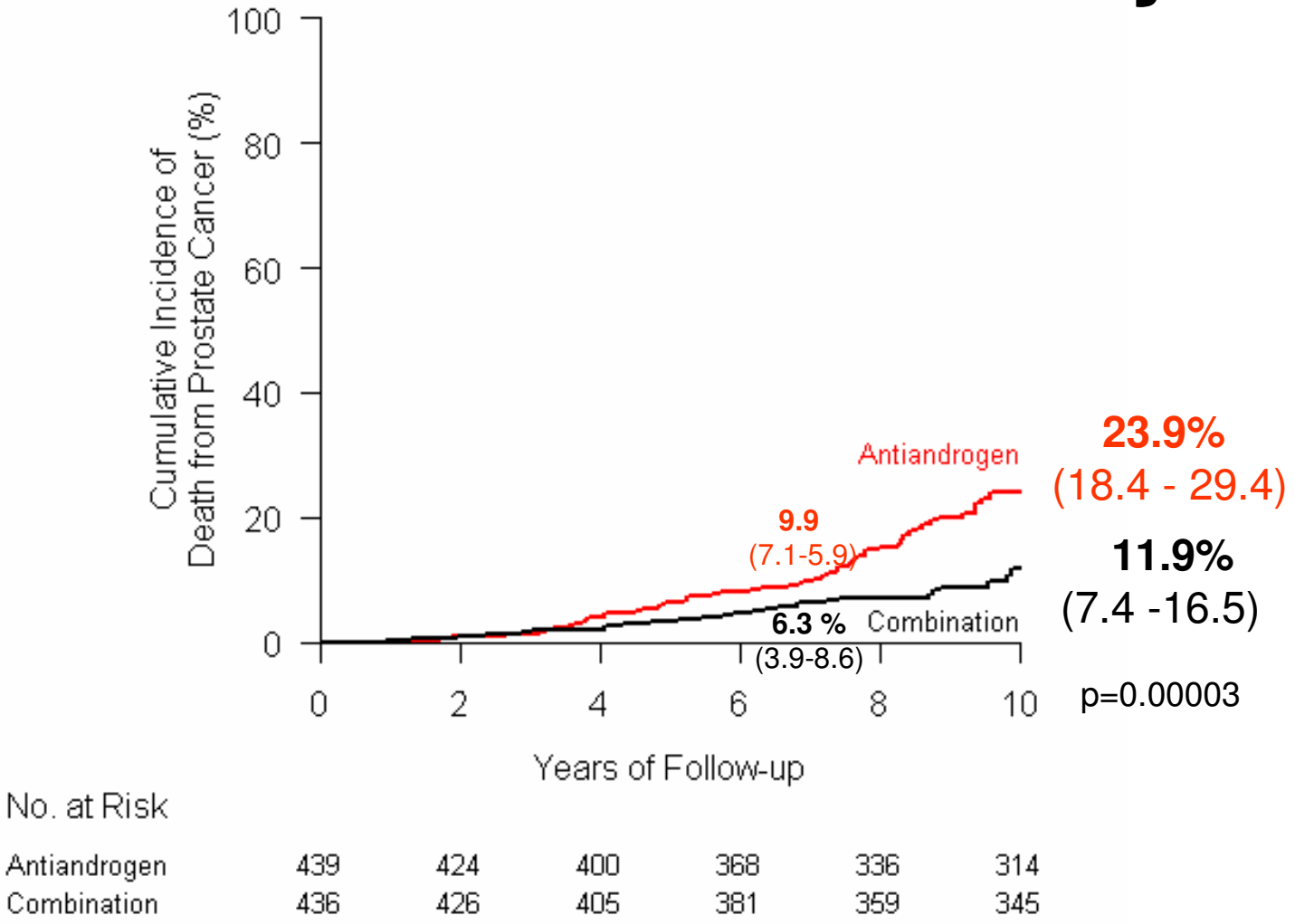

Curative treatment (total)
Radiation therapy
Radical prostatectomy
Age-standardized rate (Nordic standard 2000)
East
South
West
Mid
North
0
20
40
60
80
100
120
140
1987 1990 1993 1996 1999 2002 2005
Calendar Year

Importance of Target dose and Combination with HormoneTreatment (HT)



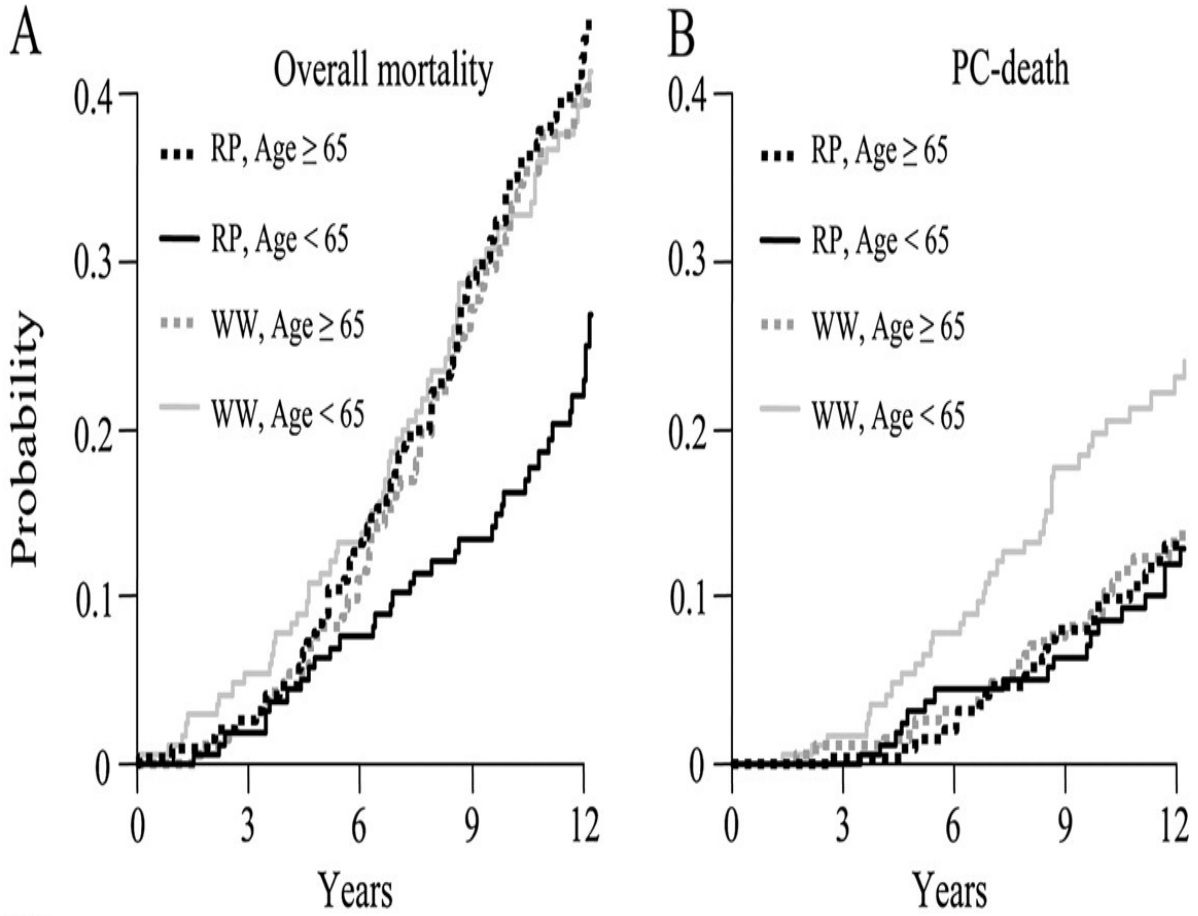
Karlsdottir ActaOnc.(2006) 45:454

Cumulative incidence of **Prostate Cancer mortality**



ASTRO, 2008, Plenary Session

Cumulative incidence of endpoints by age group



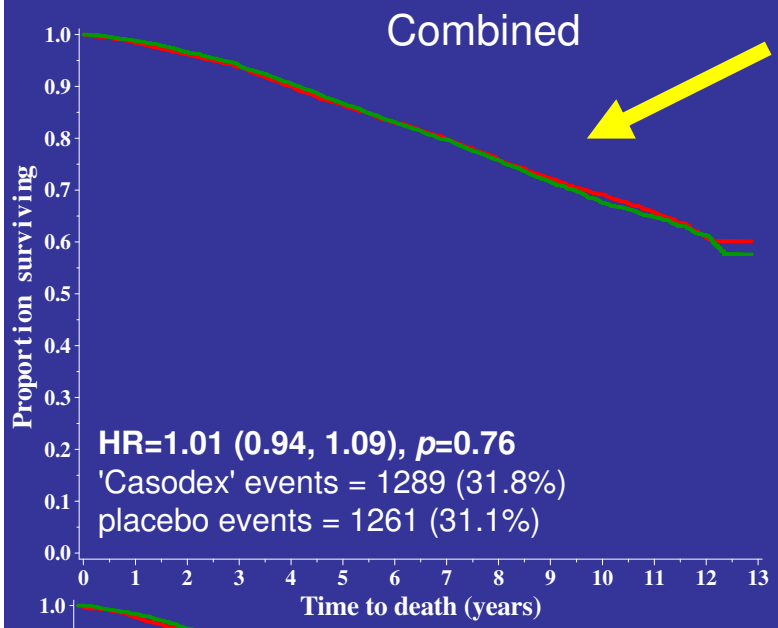
No. At Risk

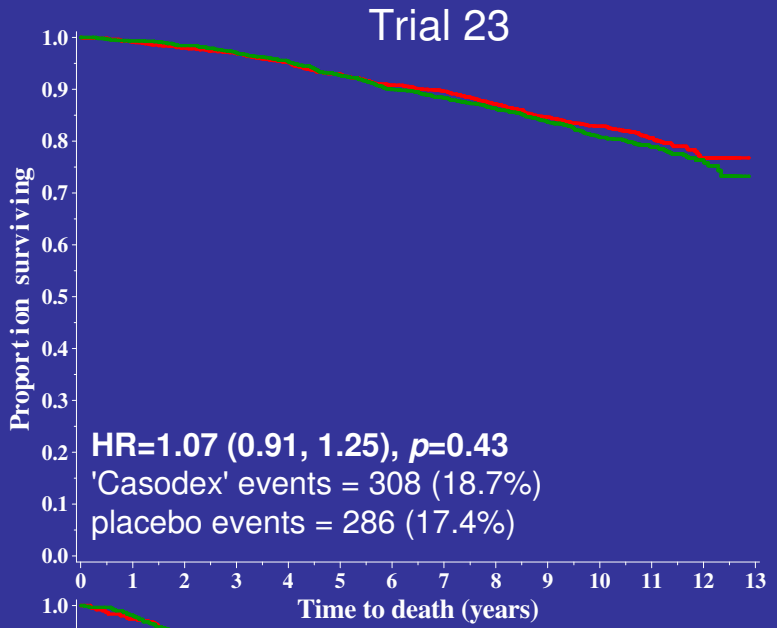
RP, Age ≥ 65	190	185	166	121	59	190	185	166	121	59
RP, Age < 65	157	154	145	127	83	157	154	145	127	83
WW, Age ≥ 65	182	177	162	123	64	182	177	162	123	64
WW, Age < 65	166	157	144	105	63	166	157	144	105	63

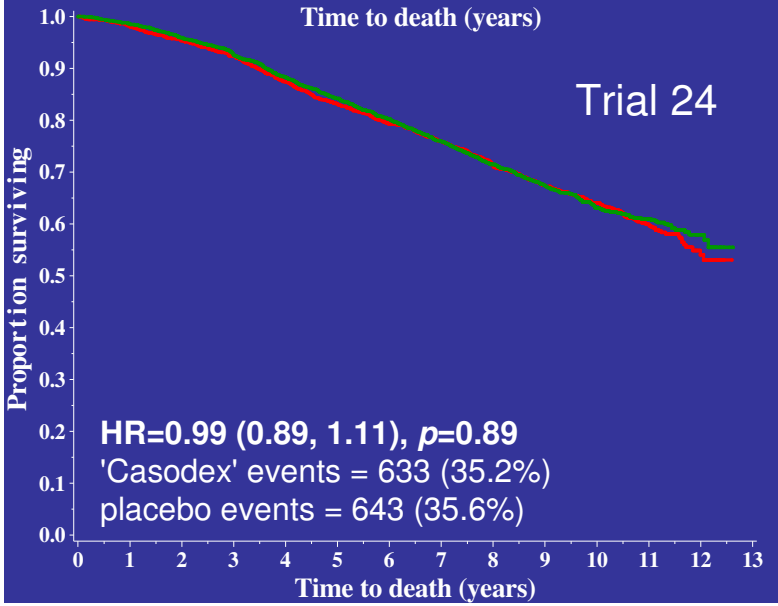
Bill-Axelson JNCI(2008)100;1144

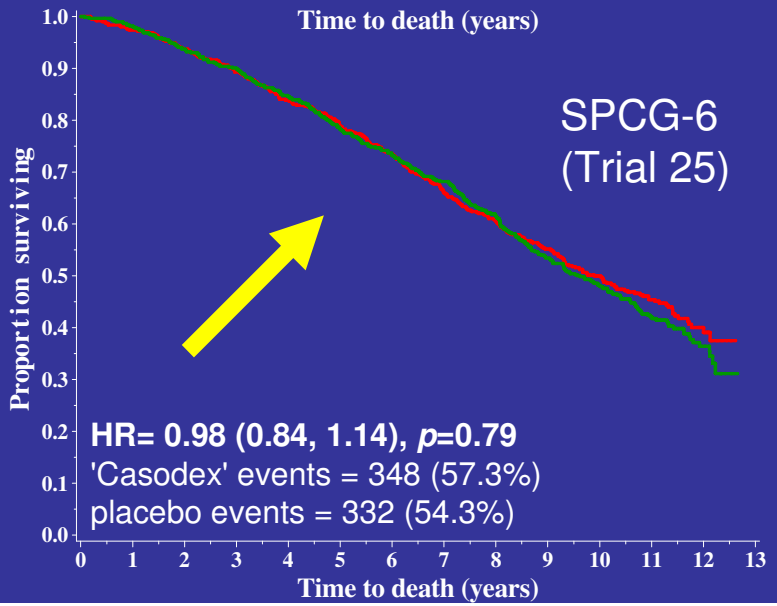
Overall Survival — 4th Analysis

Casodex Placebo









Conclusion so far

- Local treatment of non-metastatic prostate cancer with curative intention prolongs life.

- Hormone monotherapy or observation only* represents undertreatment

*excluding strict surveillance strategy

Kandidater for kurativ behandling, n=1650

	Lav n=500	Intermediær n=453	Høy n=697
Kurativ behandling	**57%**	**68%**	**61%**
- RP	36%	28%	7%
- RAD	21%	40%	54%
Hormon behandling	0,2%	3%	21%
Observasjon	35%	23%	14%
-Kurativ	6%	6%	2%
-Palliativ	5%	7%	5%
Annet	2%	3%	0,6%
Ukjent	5%	3%	3%

Får ikke prostata-behandling

Flere enn hver tredje mann i Norge som har moderat til alvorlig prostatakreft uten spredning, får ikke helbredende strålebehandling eller operasjon.

Aftenposten 02.10.2009

Oppsummering og konklusjon (E.Hernes (2004):

- I store trekk er beh. gitt i samsvar med retningslinjer, men…

  -57% av lavrisiko-pas fikk aktiv kurativ behandling. For mange?

  -64% av intermediær/høyrisiko-pas fikk aktiv kurativ behandling. For få?

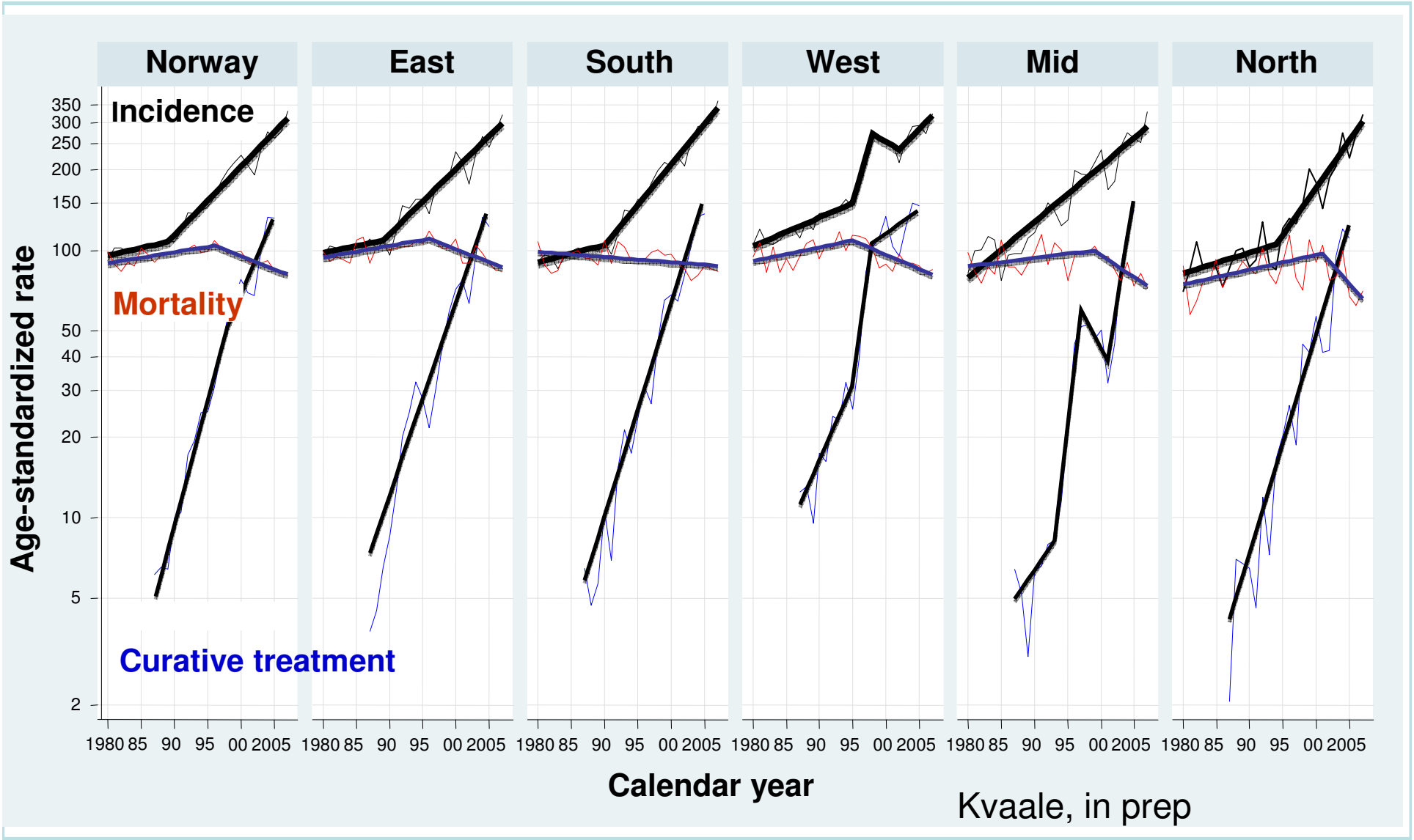
Prostate cancer incidence (age 40-74), curative treatment (age 40-74) and mortality (age 40-84) in Norway

- Observed numbers in 2005: Curative treatment per Health Region in men aged 40-74 years diagnosed with prostate cancer (all stages) in 2005

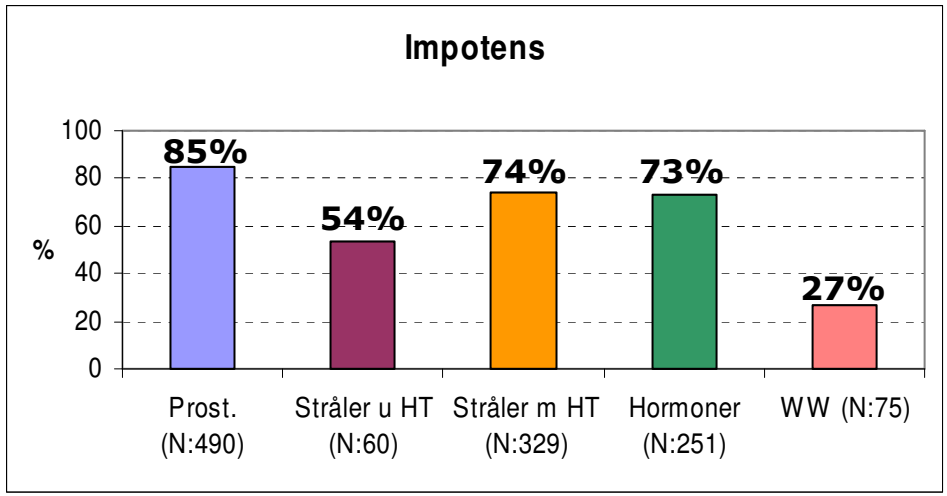
		Type of curative treatment[a] (% of total numbers)		
Region	**Incident cases**	**# of curative treatment (% of incident cases)**	**Radiotherapy**	**Prostatectomy**
East	716	375 (52%)	187 (50)	188 (50)
South	500	243 (49%)	99 (41)	144 (59)
West	467	241 (52%)	151 (63)	90 (37)
Mid	318	175 (55%)	114 (65)	65 (35)
North	200	104 (52%)	43 (41)	61 (59)
Total	2201	1138 (52%)	594 (52)	544 (48)

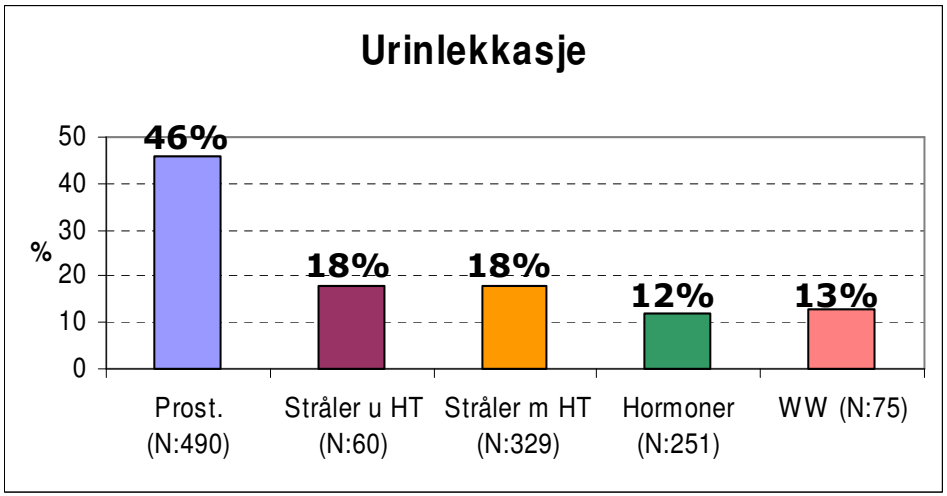
[a] **Year of diagnosis: 2005. Treatment within 12 months after diagnosis**

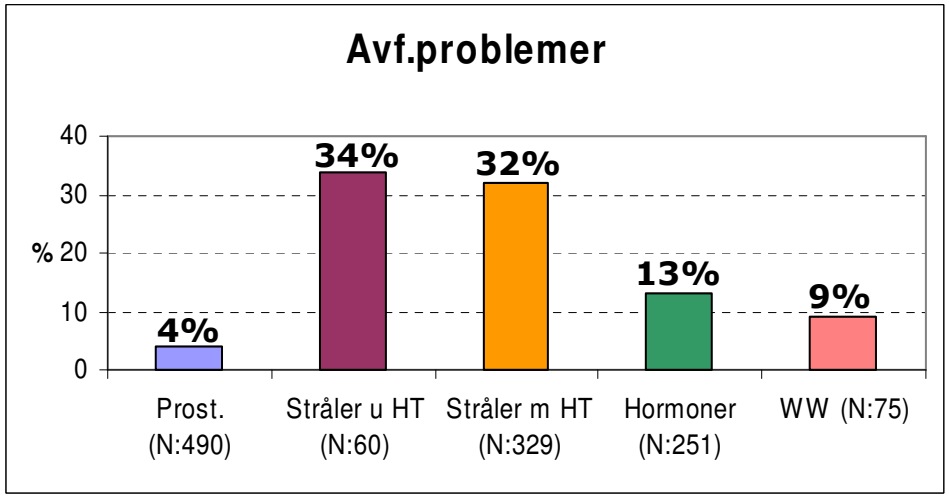
Fitted trends from joinpoint regression (bold lines) of incidence, curative treatment and mortality in Norway

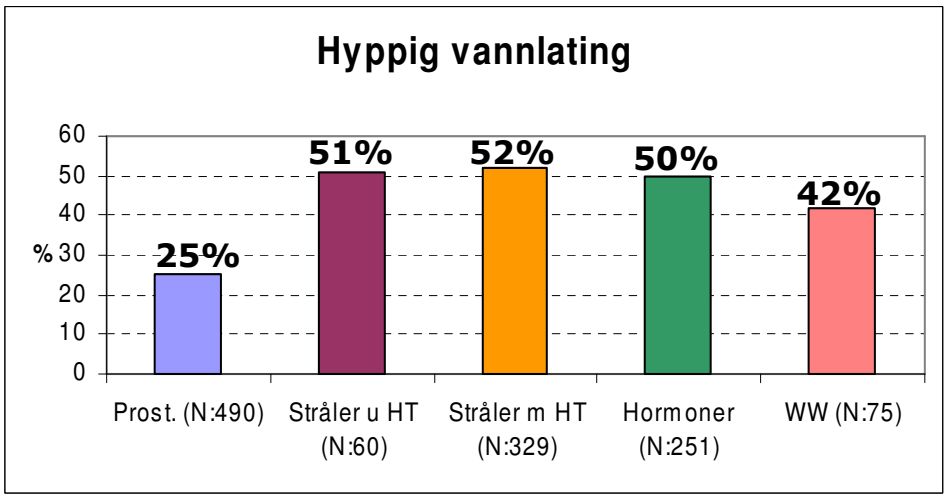


Bivirkninger av behandling
(No2008+Da2009)









Prostatektomi Rad u/HT Rad m/HT Hormoner Watchfull Waiting

Impotensproblemer hos pasienter som er **operert for prostatakreft** uten senere tilbakefall.

År	N	Impotenspr obl.	Aldri istand til samleie
≤2005	294	86% (253)	71%* (180)
≥2006	248	85% (211)	76%* (160)

*Pre-operativ rådgiving: <20% ?

Kandidater for kurativ behandling -definisjon av risikogrupper

- Lav risiko (n=500)

  T1-T2a, PSA ≤ 10 ng/ml, Gleason score ≤ 6

- Intermediær risiko (n=453)

  T2b og/eller PSA >10 - ≤20 ng/ml og/eller Gleason score =7

- Høy risiko (n=697)

  T2c og/eller PSA >20 ng/ml og/eller Gleason score ≥8
  og/eller T3

D´Amico et al, J Urol 2001

Summary and Conclusions

- Incidence of prostate cancer and the use of treatment with curative intent have increased significantly in all five geographical regions since the early 1990s
    - In recent years there are only minor differences in incidence rates and in the use of curative treatment between the regions
- Declines in prostate cancer mortality can be observed in all regions
- Our results indicate that:
    - The earliest declines in mortality are seen in regions with the most frequent use of curative treatment
    - The strongest decrease in mortality is found in the counties with the highest increase in curative treatment

CANCER Registry of Norway
INSTITUTE OF POPULATION-BASED CANCER RESEARCH

Summary and Conclusions

- The results from this ecologic study are consistent with the results from the recent European randomised trial

- However, the increases in incidence and curative treatment are highly correlated
  - Difficult to separate the possible effect on mortality of early diagnosis followed by early treatment from the impact of improved and more active treatment of other cases, including clinically detected cases

- Other and/or additional explanations for the favourable mortality trends should be considered

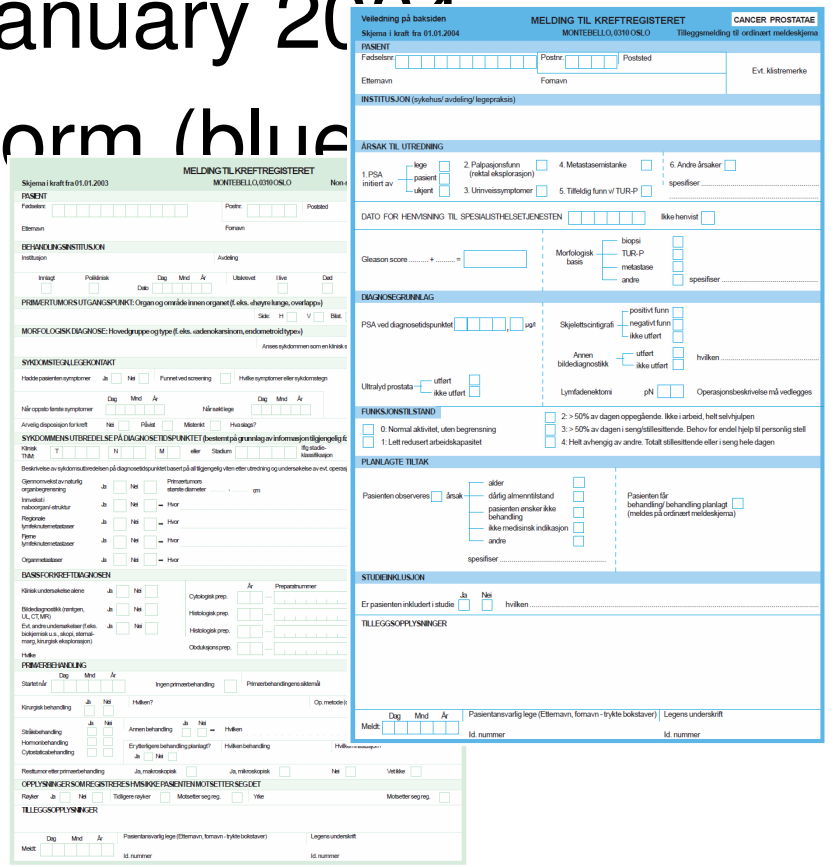
- Since the introduction of PSA-testing we have observed more than a doubling of the cumulative risk of prostate cancer. Much of the excess incidence may represent overdiagnosis

CANCER Registry of Norway
INSTITUTE OF POPULATION-BASED CANCER RESEARCH

NoPCR

- Location: Cancer Registry of Norway (CR)
- Start of registration 1 January 2004
- Additional registration form (blue)

- Clinical T category
- Gleason score
- PSA



Initial management – definitions

- **Curative local therapy**
  - Radical prostatectomy (**RP**), **within 6 months**
  - Definite radiotherapy +/- horm. (**RAD**), **within 14 months**
- **Palliative hormonal therapy**
  - Within 4 months
- **Observation**
  - **Curative**: later curative local therapy (”active surveillance”/AS)
  - **Palliative**: later hormonal therapy

Risikogrupper

- **Lav risiko:** T1 eller liten T2, Gleason 6 & PSA <10
- **Middels risiko:** Alle andre
- **Høy risiko:** Stor T2C/T3 eller Gleason 8-10 eller PSA >20

Behandling

- Helbredende: Ingen spredning

- Livsforlengende
  lindrende

  Spredning
  Høy alder
  Livsforventning <5-10 år

- Pasientens ønsker

Behandling

Helbredende

Radikal operasjon

Høy-doset strålebehandling
(med eller uten hormonbehandling)

Observasjon og behandling ved forverrelse

Livsforl./lindrende

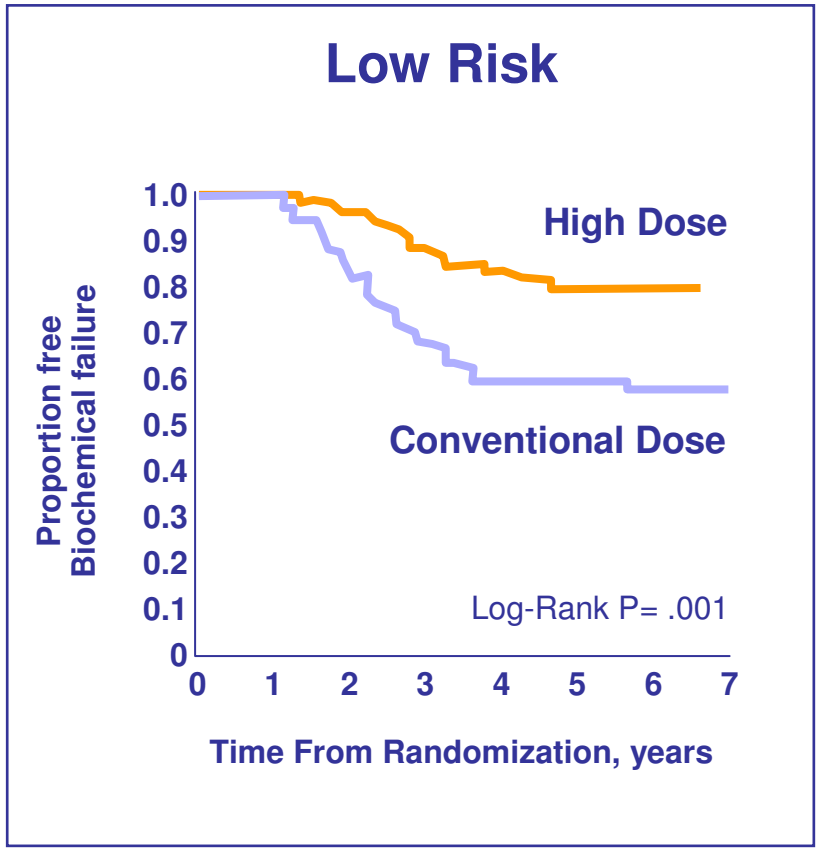
Mindre operasjon

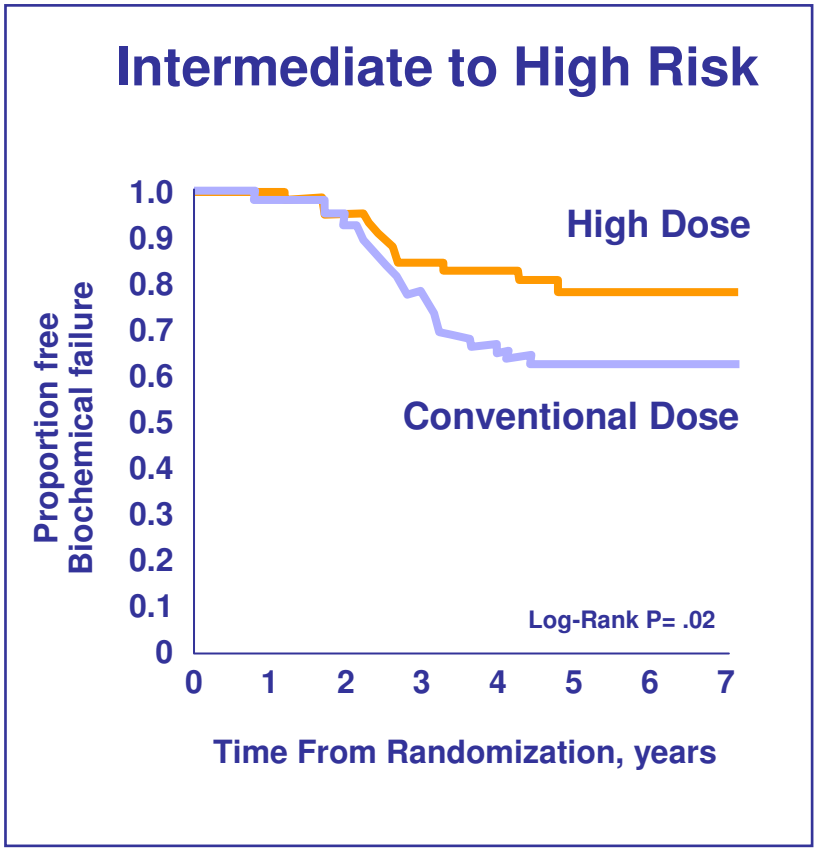
Lavere dosert strålebehandling

Observasjon og hormonbehandling
ved forverrelse

Hvis riktig anvendt er helbredelsen/-overlevelsen avhengig av om pasienten opereres, strålebehandles eller følger observasjonsstrategien.

Dose escalation in modern radiation therapy

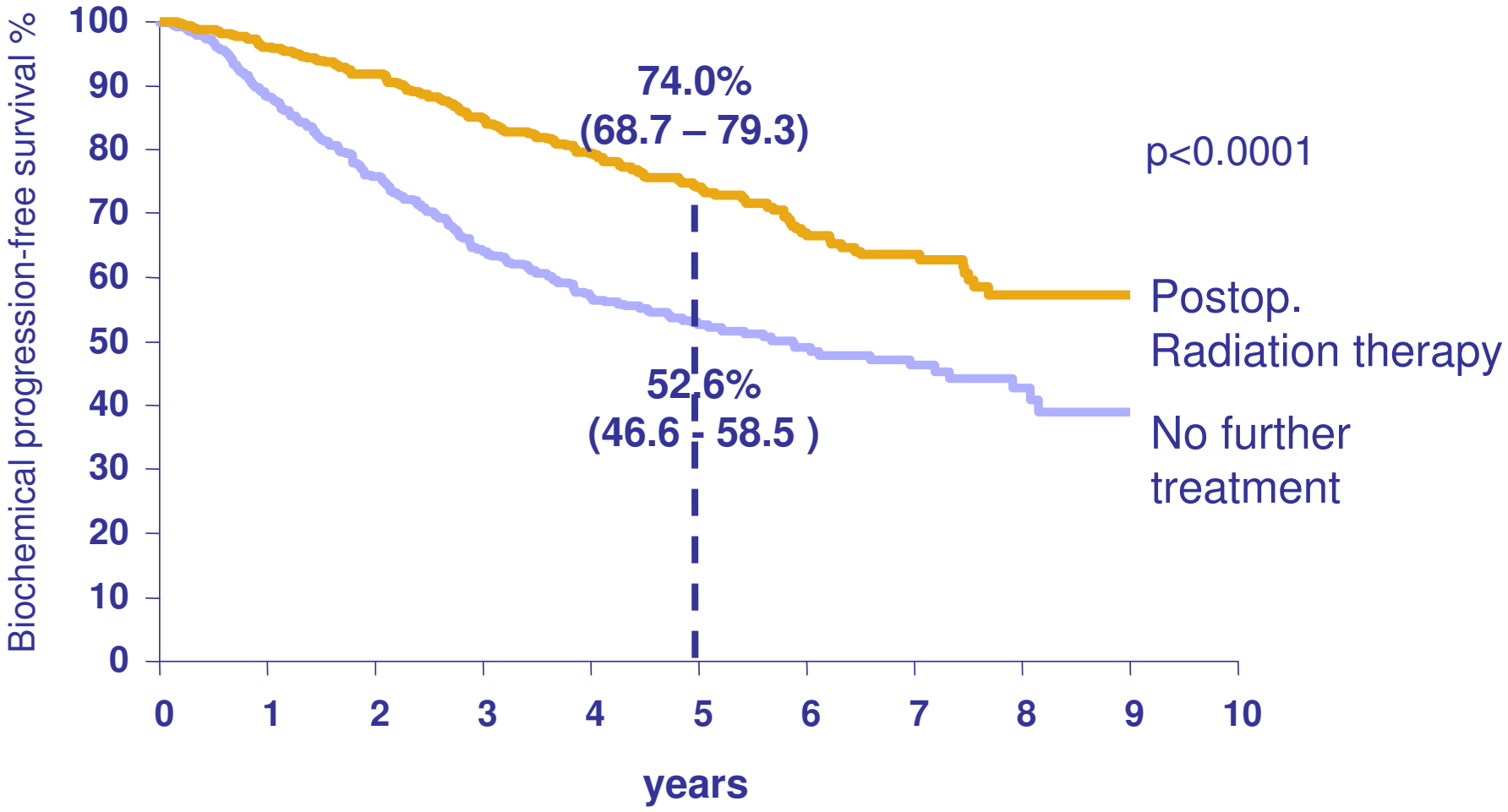




Peeters et al., JCO 2006;24(13):1990-1996

Post-operative radiotherapy:

EORTC trial: biochemical progression-free survival (Patients with tumor-positive margins)



Bolla et al. Lancet 2005;366:572-8

Behandling av prostatkreft uten spredning

Helbredende

Radikal operasjon

- Høyt-dosert strålebehandling

strålebehandling

(med eller uten hormonbehandling)

Observasjon og helbredende hormoner

behandling ved forverrelse forverrelse

Livsforl./lindrende

Mindre operasjon

Lavere dosert strålebehandling

Observasjon og

ved

Hvis riktig anvendt er helbredelsen/-overlevelsen uavhengig av om pasienten i første omgang opereres, strålebehandles eller følger observasjonsstrategien.

Pasientens betraktninger etter at lokalisert prostatkreft er påvist

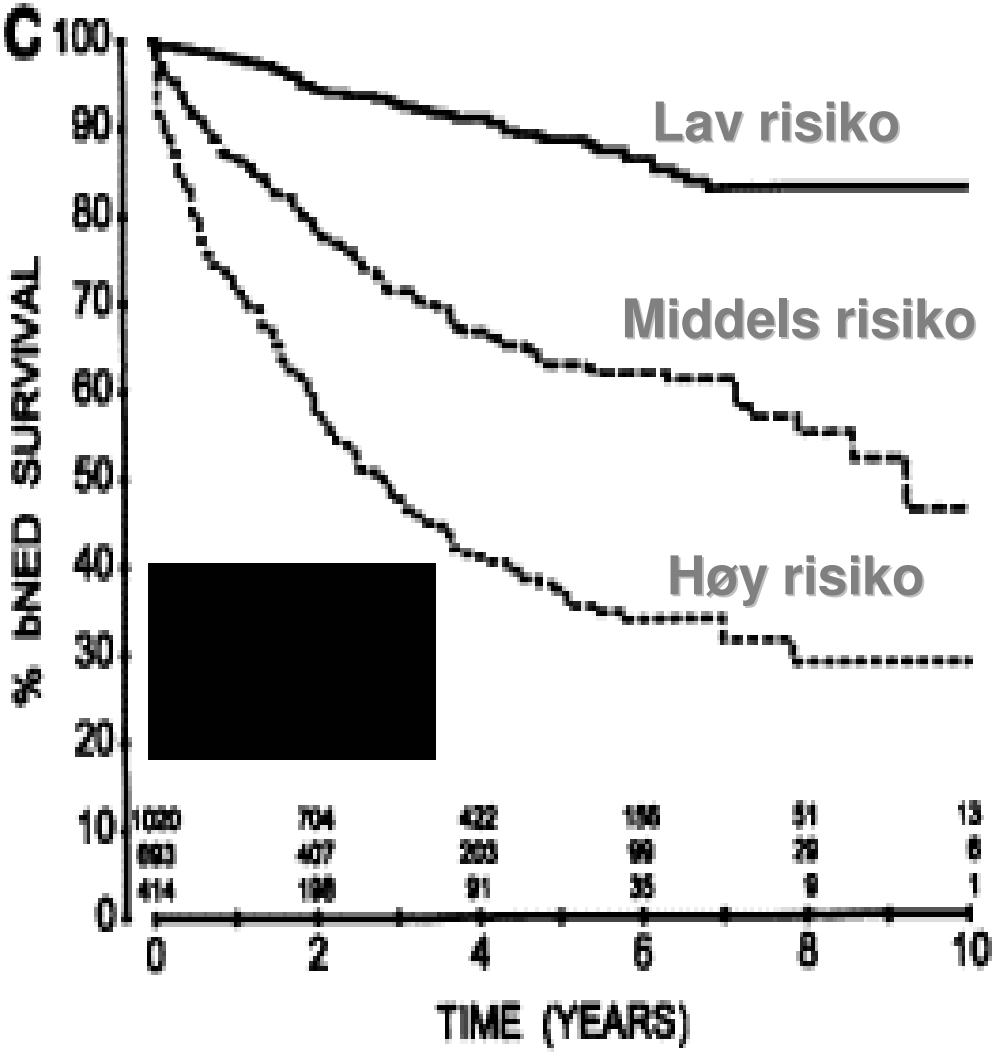
- Ønsker jeg behandling – hvilken behandling?

- Hvis jeg blir behandlet – hvilke bivirkninger vil jeg få?

Behandling av avansert prostatkreft

- **Hormoner: Fjerne virkning av mannlige kjønnshormon (testosteron)** fra prostatakreftcellen. Fjerne testikler, sprøyter som stopper testosteronproduksjonen,
- Tabletter som forhindrer at testosteron tas opp av kreftcellen.
- **Strålebehandling:** Utvendig: mot plagsomme spredningsfoci; Innvendig: med systemisk virkning (Alsympca)
- **Cellegift:** Taxotere og ”målsøkende medikamenter”
- **Benstyrkende medikamenter:** Zometa

Total overlevelse og risikogrupper hos pasienter med prostatakreft uten spredning



1.Hvilke Gener/ Molekyler er relatert til gunstig/ ugunstig overlevelse i hver risikogruppe ?

2. Bedret behandling i middels / høy risiko gruppen

D'Amico J.Urol.2001

Prostate Cancer Pathway

1900 Hormonavhengig cancer

1950 Effekt av kastrasjon

(Familiær opphopning)

1990 LHRH analoger

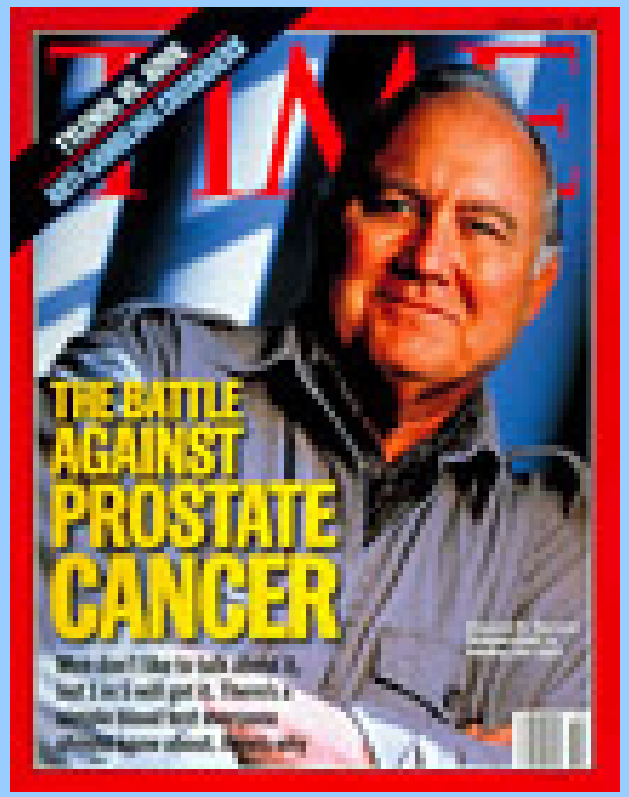
Serum PSA

Holdningsendring

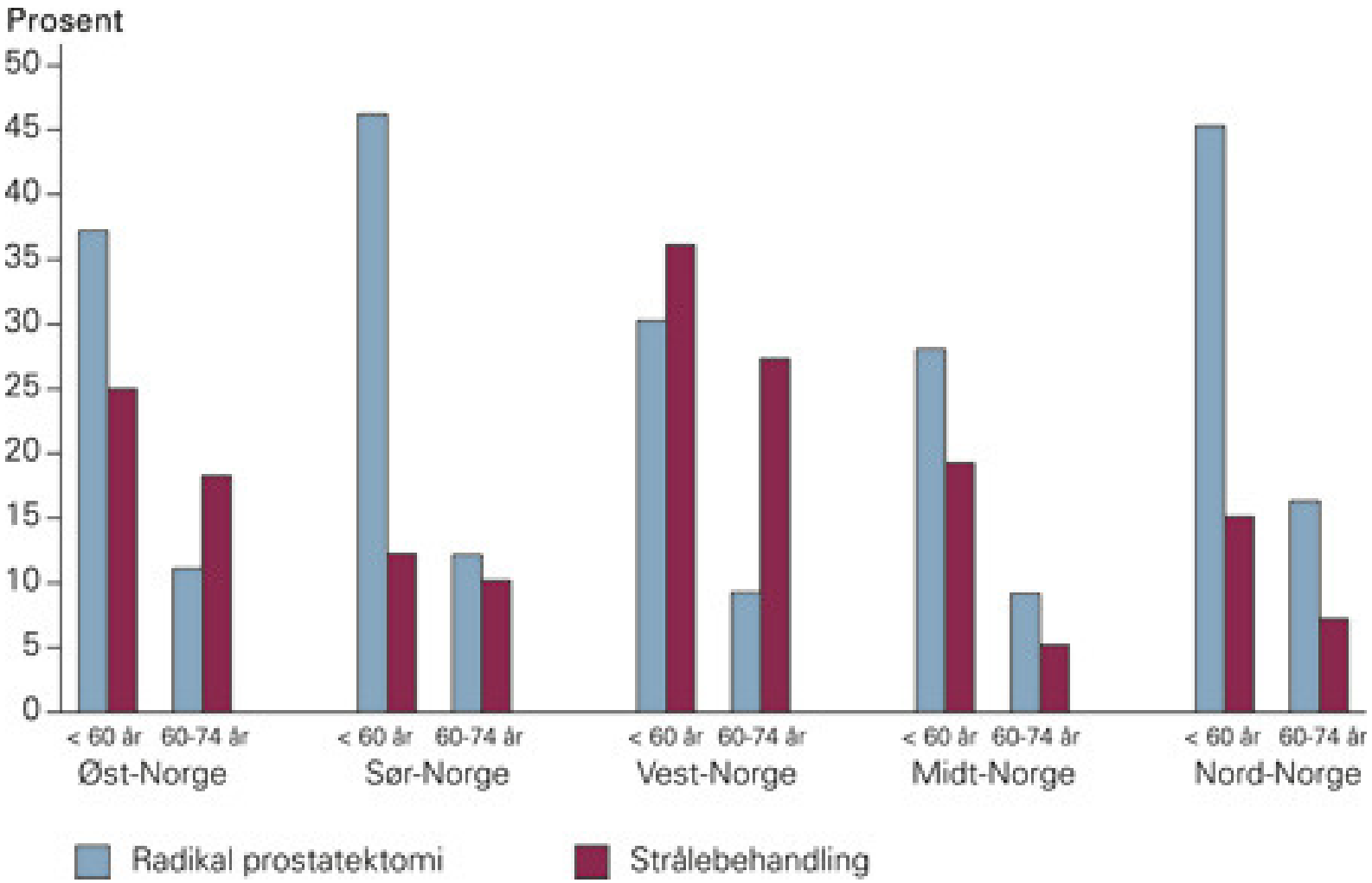
2000 Livsforlengende effekt av helbredende behandling

Livsforlengende effekt av kjemoterapi (docetaxel)

”The man’s cancer”



April 01 1996

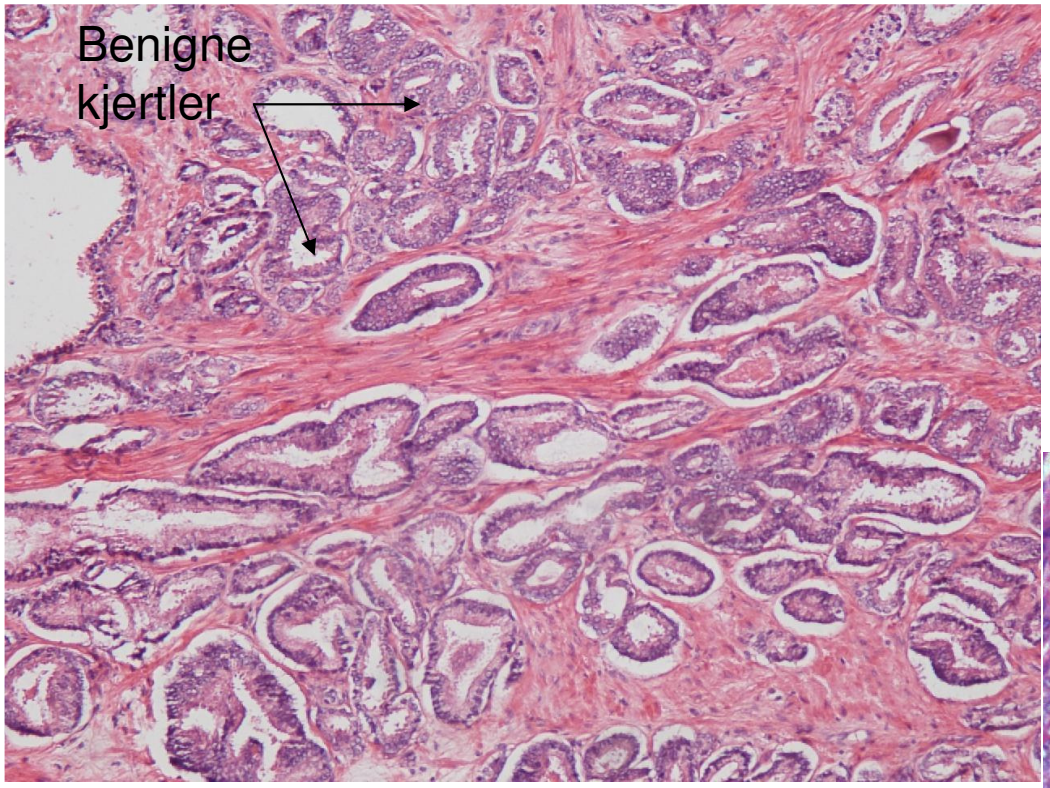


Kvåle et al, Tidsskriftet nr 7;912-6,2006

Adverse effects 1 year after curative treatment of prostate cancer

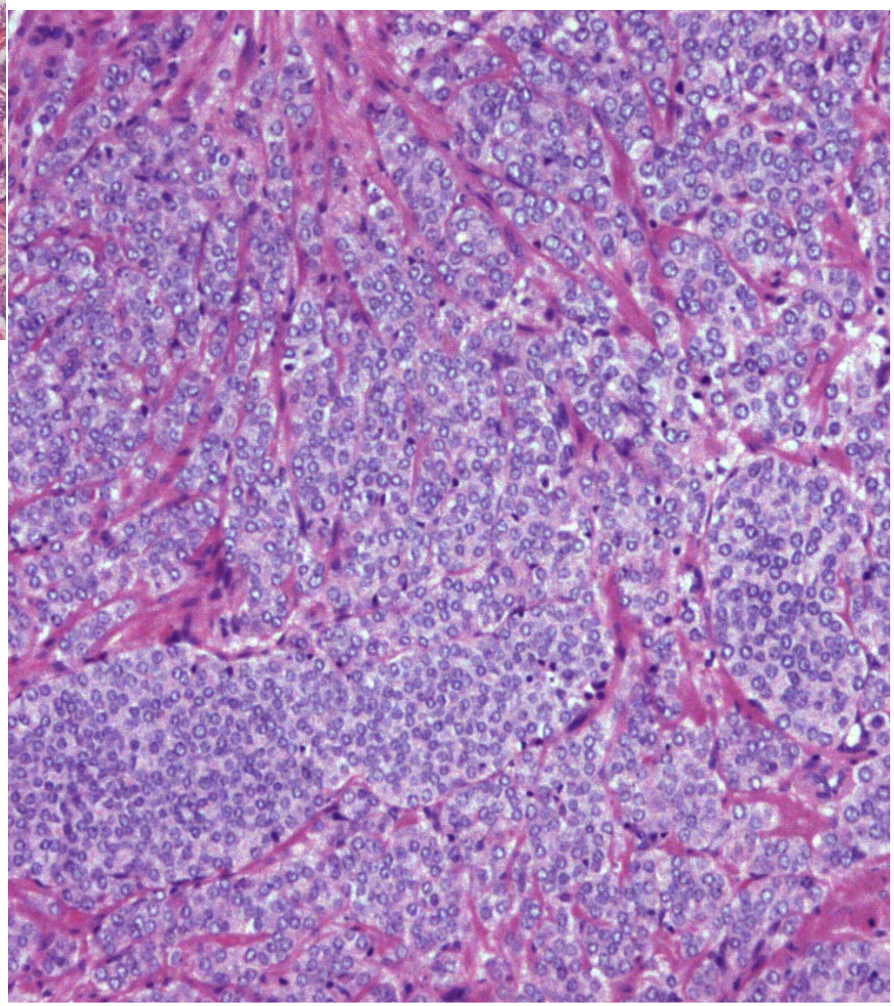
	Prostatectomy	Radiotherapy
Urinary incontinence		
Any pad use	24 %	3 %
Leakage problem	8 %	4 %
Sexual function problems (erection, orgasm)	50 %	29 %
Bowel problems (urgency, frequency, blood, pain, leakage)	2 %	9 %

Sanda NEJM (2009) 358,1250



Gleason score 3+3=6

Gleason score
5+5=10



Prostatakreft

- **1/3 av alle menn over 50 år har områder med kreftceller i prostata**
- **Livstidsrisiko: 1 av 10 (USA: 1 av 6)**
- **Utviklingen fra latent til symptomatisk prostatakreft tar som regel mange år**

Behandling
Målsetning

Kurativ-Helbredende
(Livsforventning >= 10 år)

Palliativ-Symptomlindrende/
livsforlengende

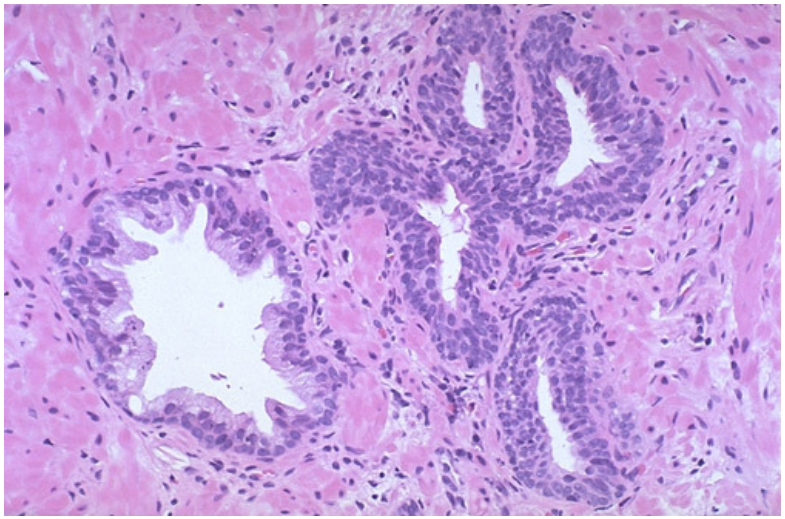
All kreftbehandling har bivirkninger

Pasientens betraktninger før PSA testing ETTER informasjon fra fastlegen

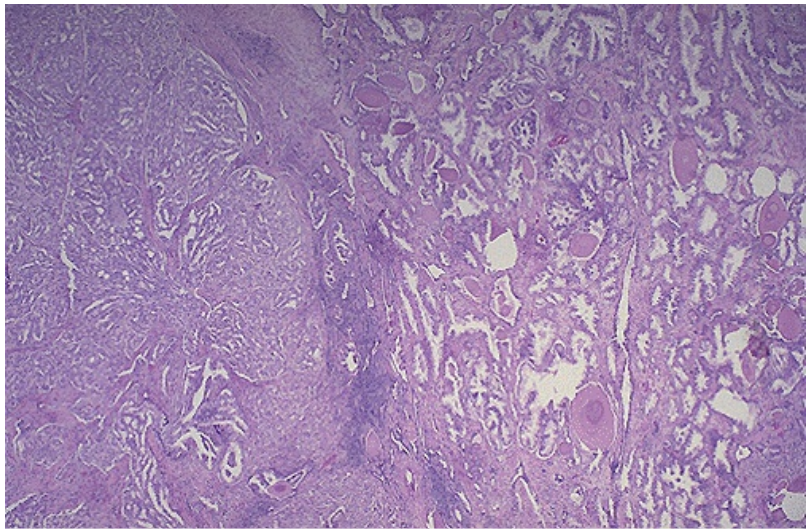
- Vil jeg ha en PSA-test med evtl. prøvetagning etterpå?
- Hvis det påvises PCa – vil jeg ha behandling?

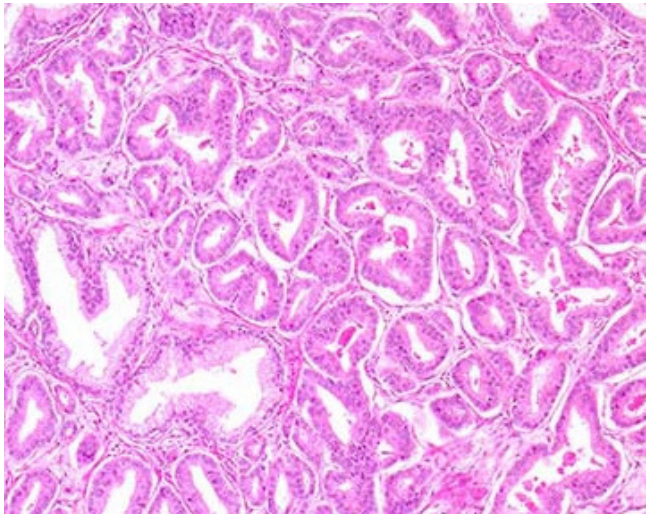
Prostatakreft - Histologi

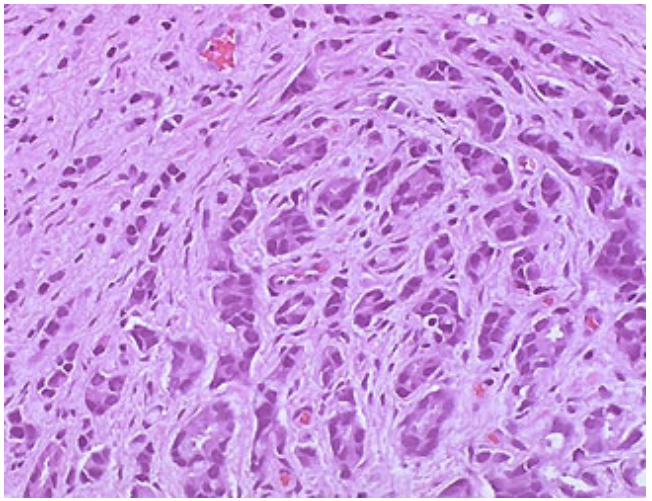
Normalt epitel vs PIN
(PIN:prostata intraepitelial neoplasi)



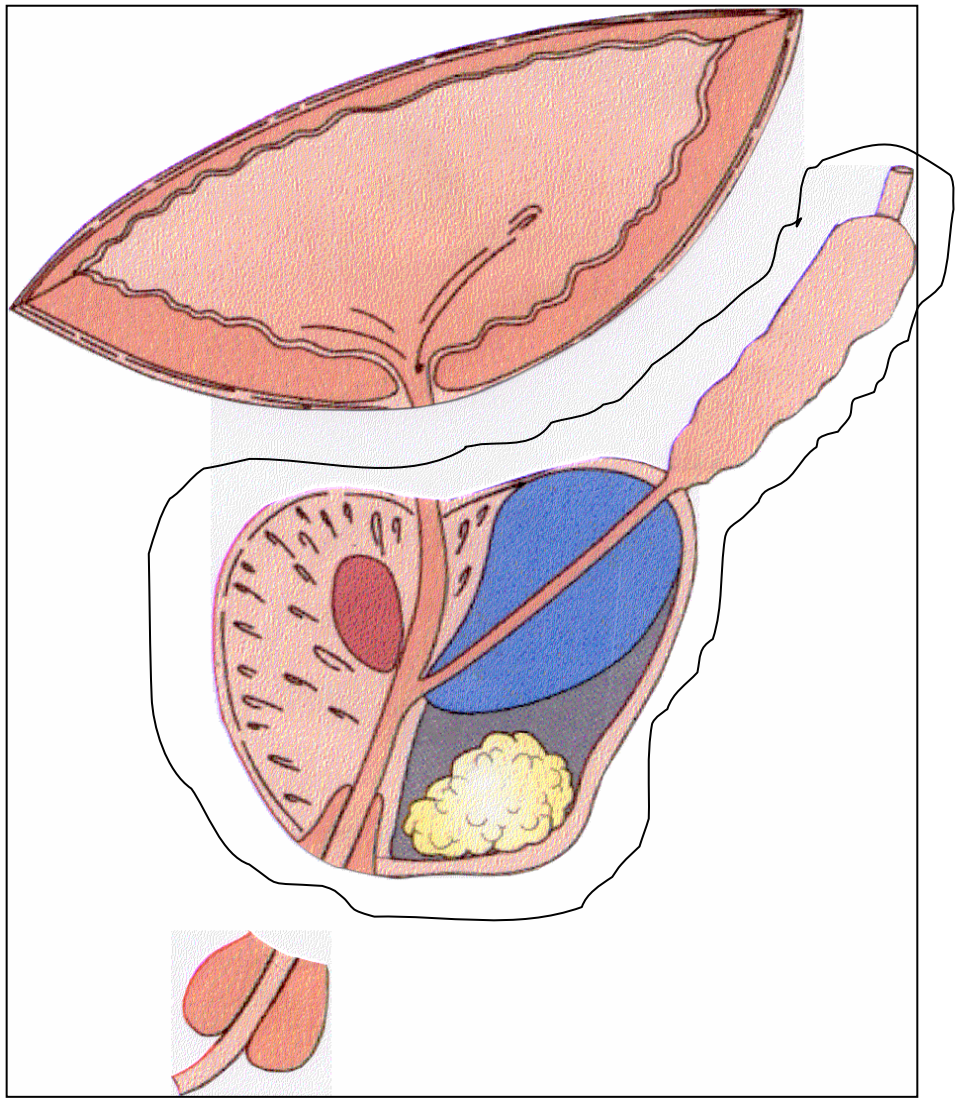
Adenocarcinom







Radical prostatectomy RP

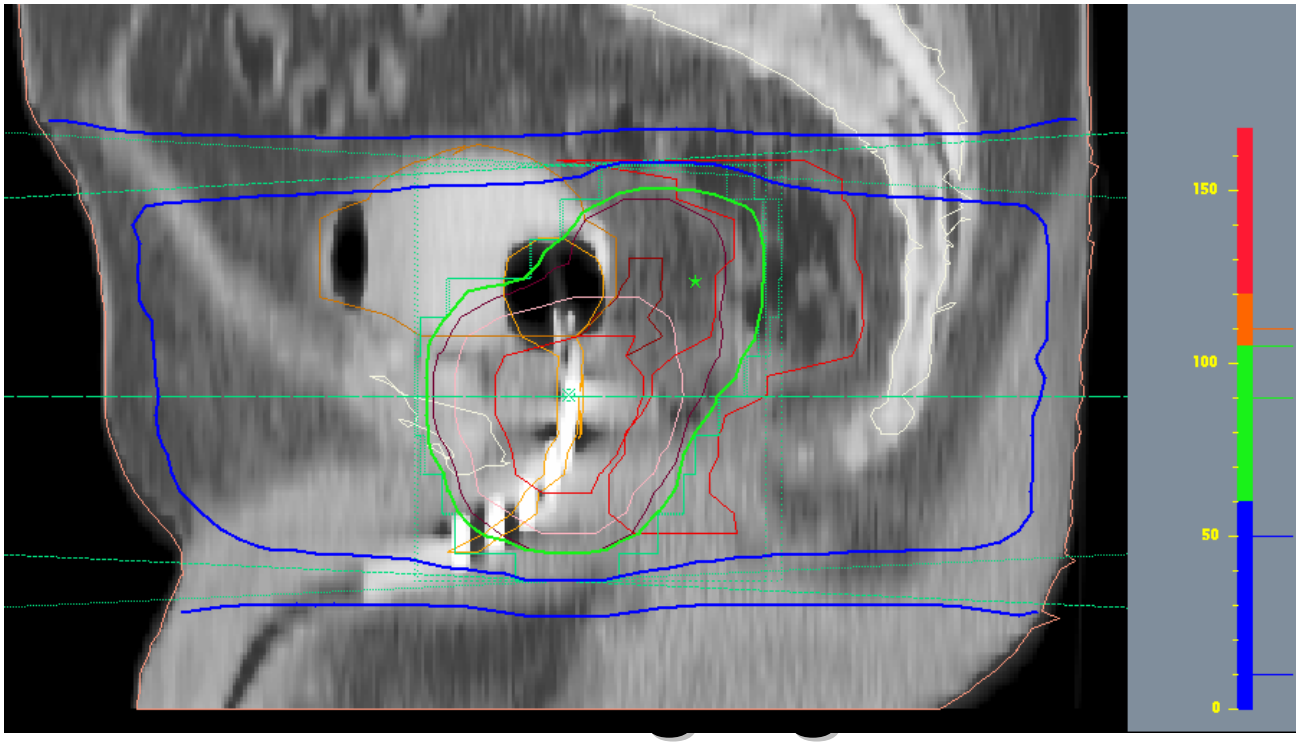


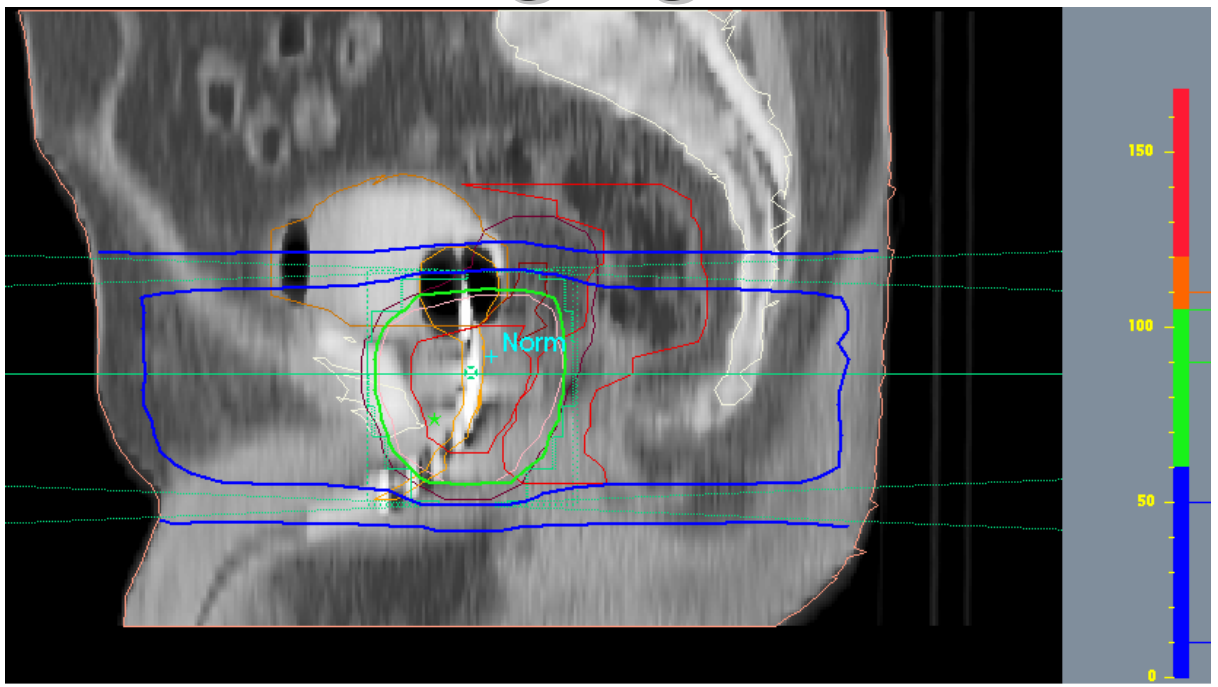
Open RP

Laparoscopic RP

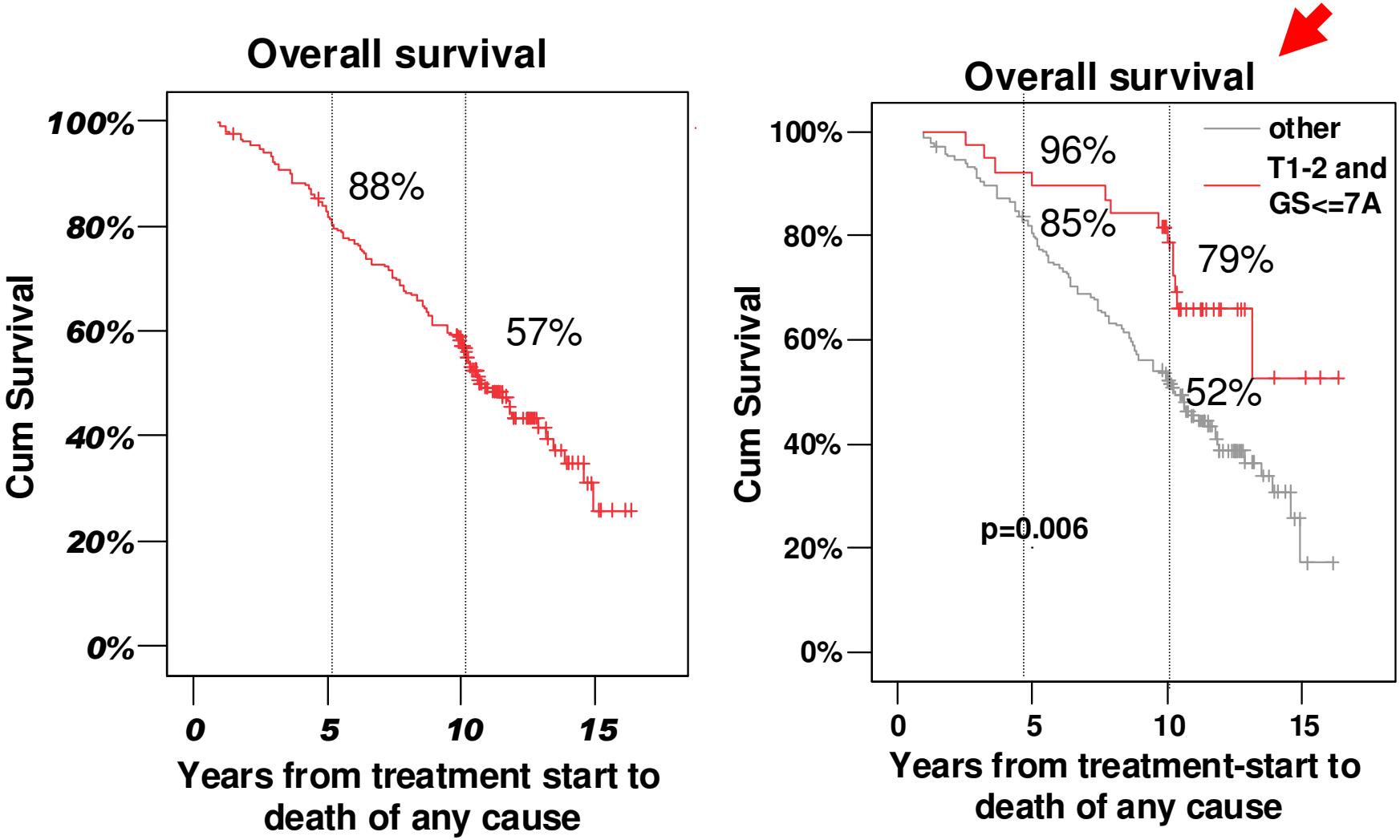
Robot-Surgery

SPCG-7/SFUO-3





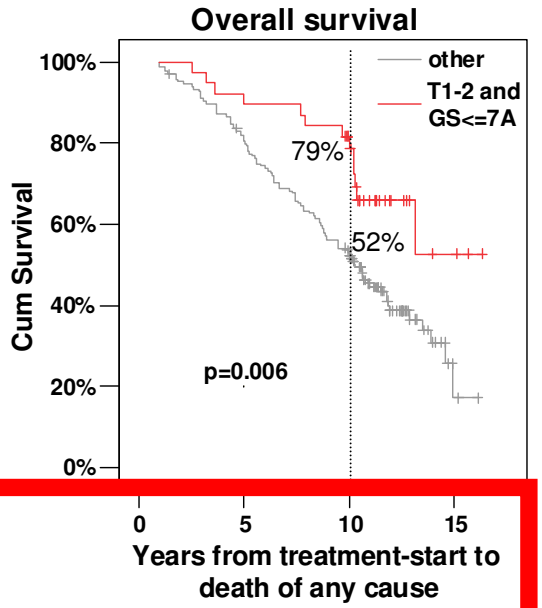
Overall survival after radiotherapy (66-70Gy) without hormones

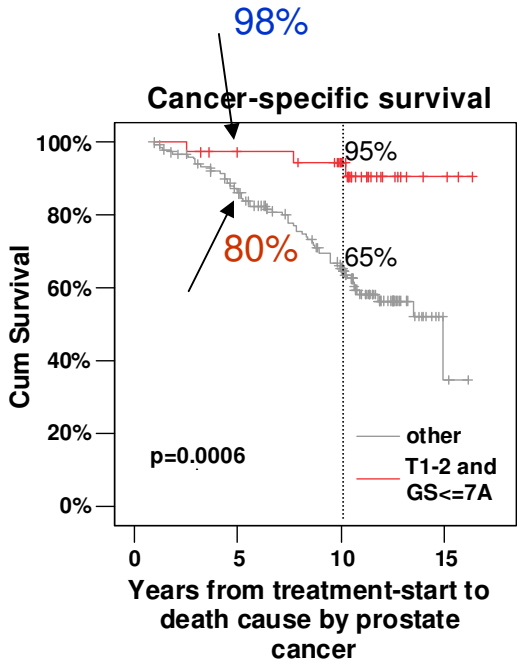


Behandlingsresultatet er avhengig av pasientutvalget

Berg, 2007

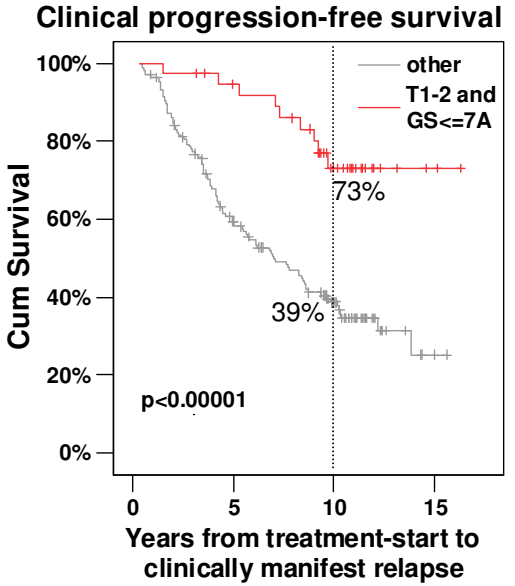
Klinisk utfall ”lav-/interm, risk vs. high-risk prostate cancer





Paper II:
5år CSS.:
Lav/interm.risiko: 95%
Høy risiko: 78%

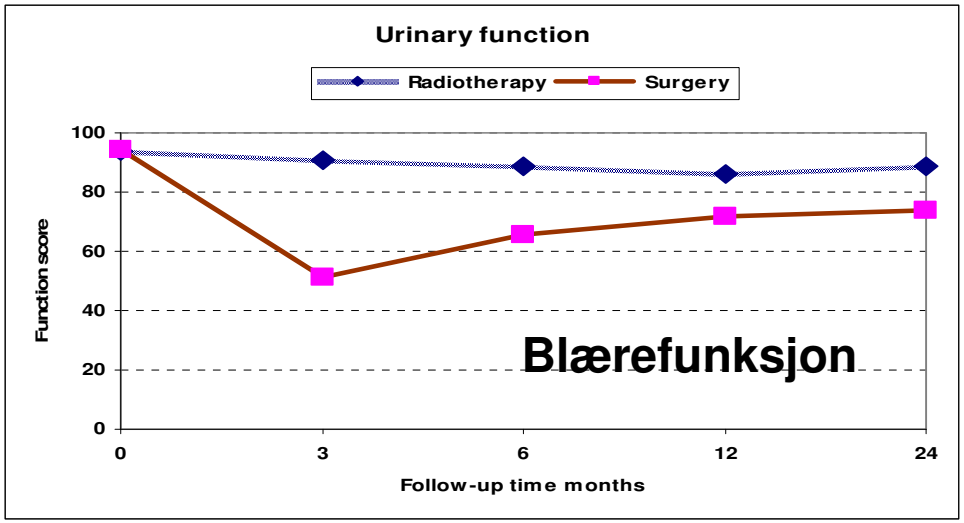
64 Gy ingen horm.

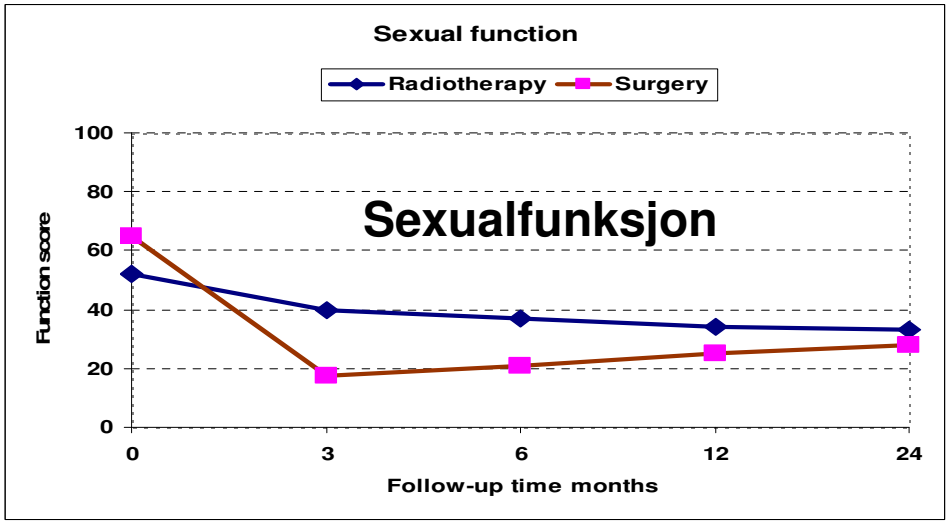


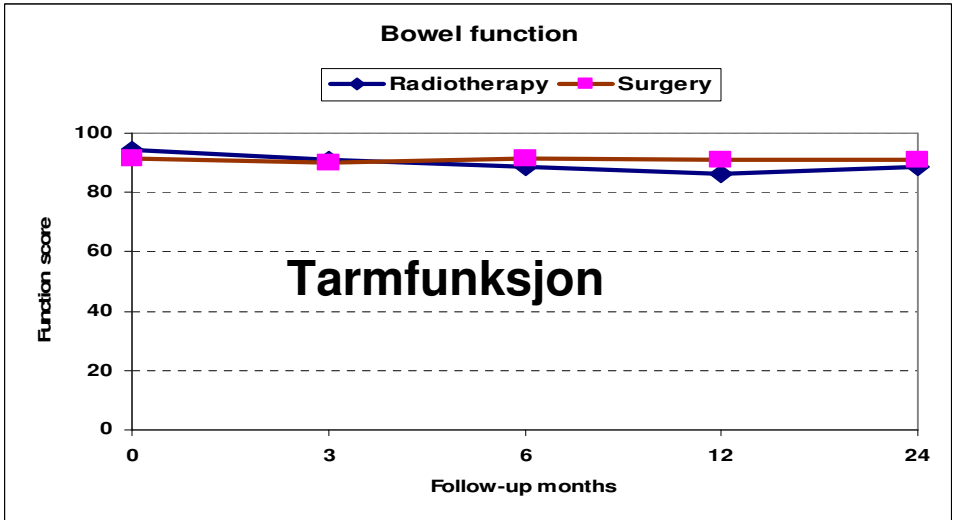
Berg IRROBP (2007)15:69

Longitudinal skår (0: verrst 100: best)

Radioterapi Prostatektomi







Alternativer for Kurativ behandling

1. **Aktiv surveillance** → Små tumores
   PSA <10
   Gleason 6 (7a=3+4)
   Behandling ved progresjon

Lokalisert / lokalavansert CaP

PSA Gleason T-kategori

Radikal prostatektomi

Radioterapi

Urolog

Kurativ behandling

2. Operasjon ± Fjerning av lymfeglandler

→ Små tumores (vanligvis)

→ PSA <20? <40?

→ I dag: Større svulster (utenfor prostata) i kombinasjon med strålebeh, hormoner/cellegift?

→ Omfanget av lymfeknutefjerning?

→ Robot versus åpen operasjon:

- mindre blødning
- kortere sykehusopphold
- kortere sykmelding (?)
- mindre bivirkninger ???

Kurativ behandling

3. Strålebehandling ± bestråling av lymfeknuter

Uten hormoner: Lavrisiko pasienter

Med hormoner: Middels[1] eller høy[1] risiko

Varighet: 0,5 – 3 år

Tabletter[2] Sprøyter[2]

(hvilken type?)

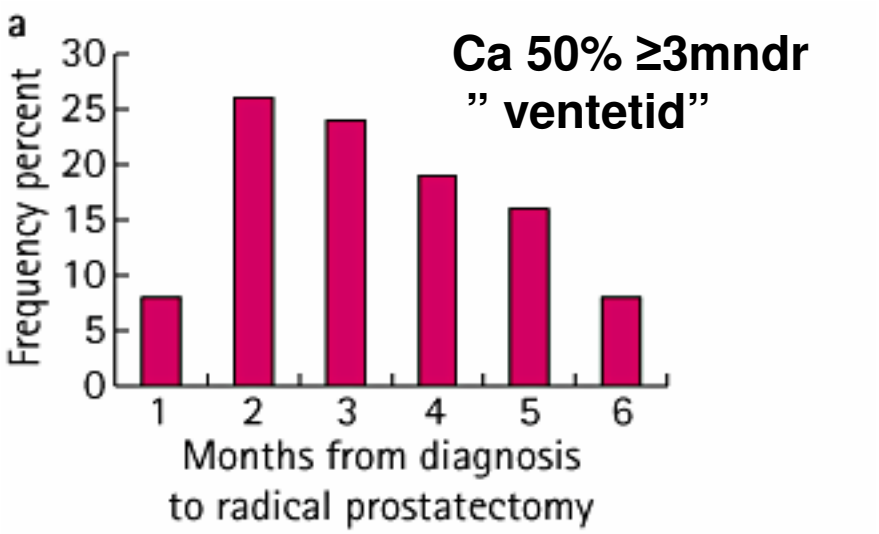
Høye stråledoser: ≥74 Gy avhengig av risiko

---

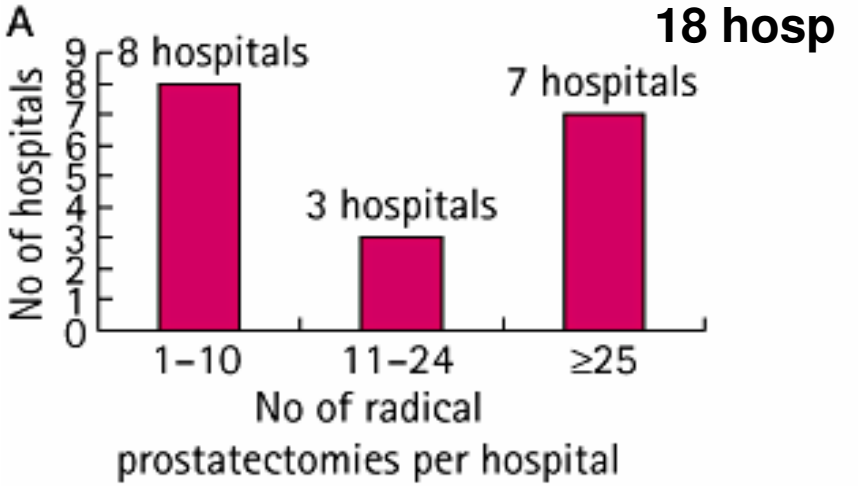
[1]Utbredelse (T) / Gleason / PSA

[2]Testosteron <0.7 ng/l

Norway 2004 and prostate cancer: Interval from initial diagnosis and local treatment and number of responsible institutions

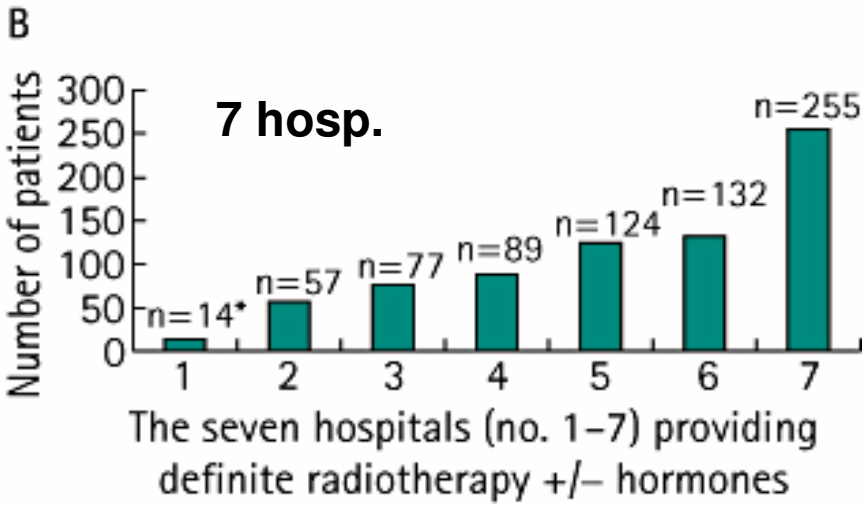


Ca 50% ≥3mndr
" ventetid"



18 hosp

For lang "ventetid"
For mange sykehus som opererer
Bedre for strålebhandling



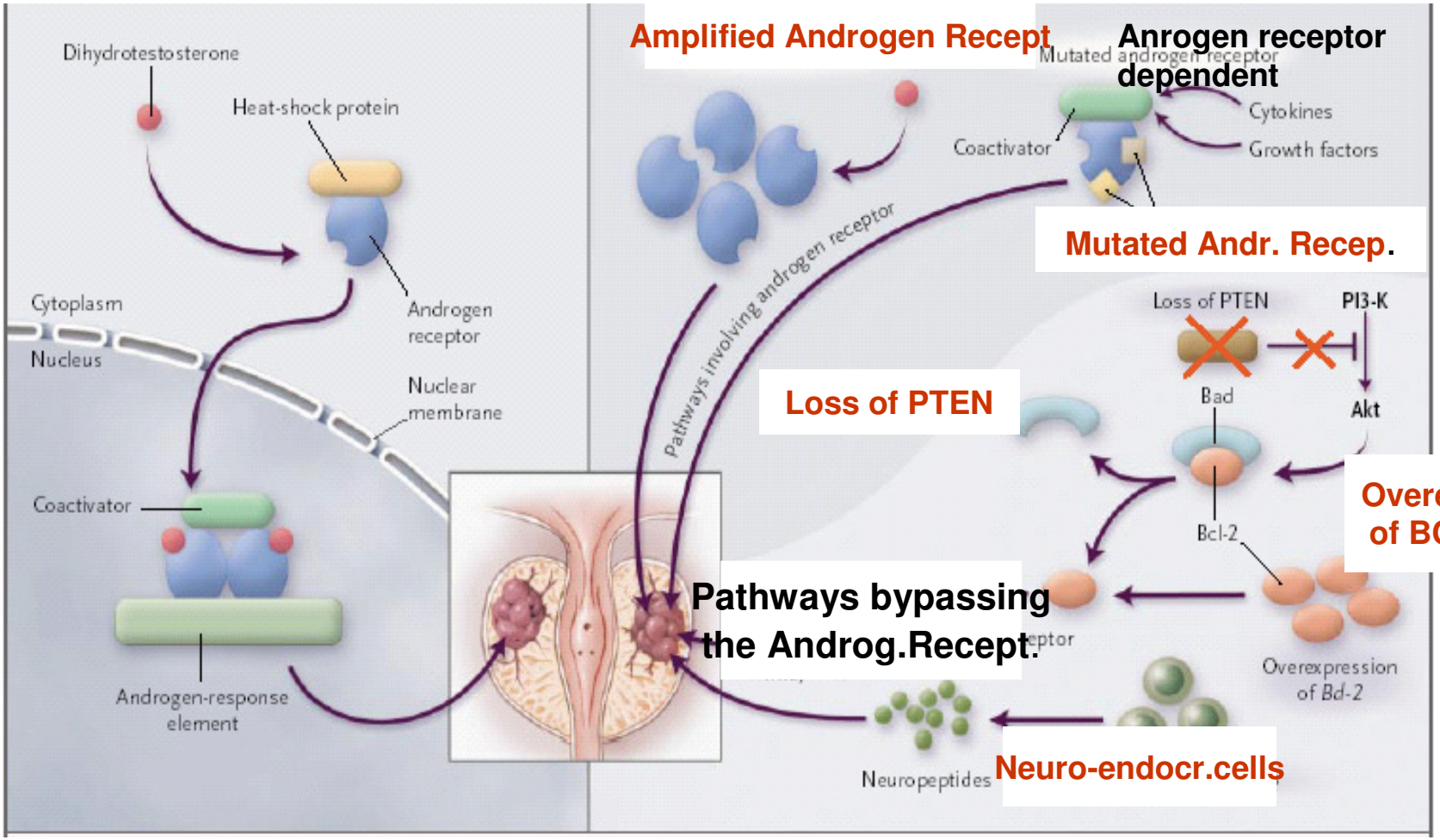
7 hosp.

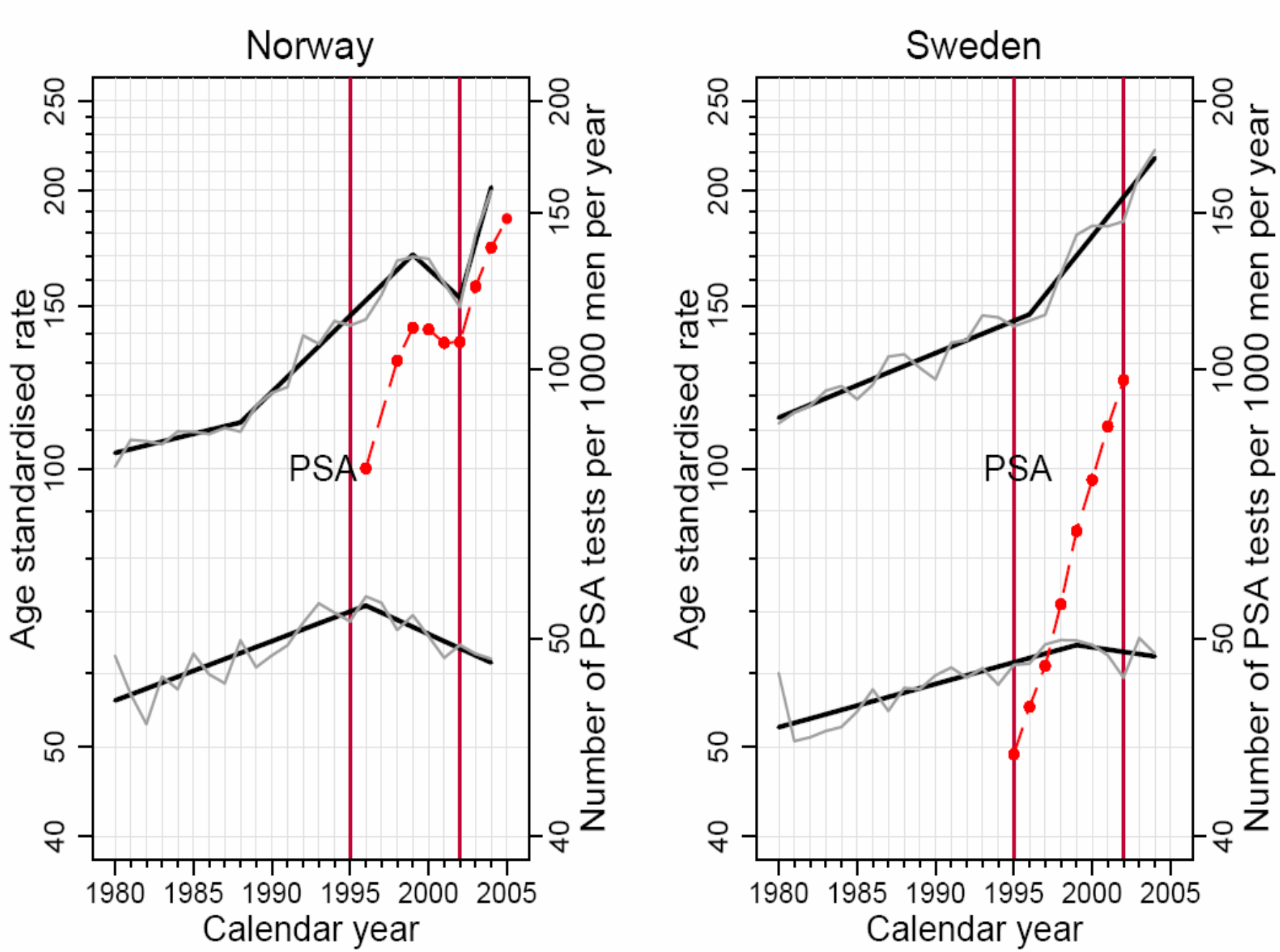
Hernes (2010) , 105;805

Bakgrunn

Hva skal man velge?

Development of AIPC (New insight)




Norway
Sweden
Age standardised rate
Number of PSA tests per 1000 men per year
Calendar year
PSA
40
50
100
150
200
250
1980
1985
1990
1995
2000
2005

Cellenivå: Addition of AA
(ingen profylaktisk mammabestråling)

Flutamide:

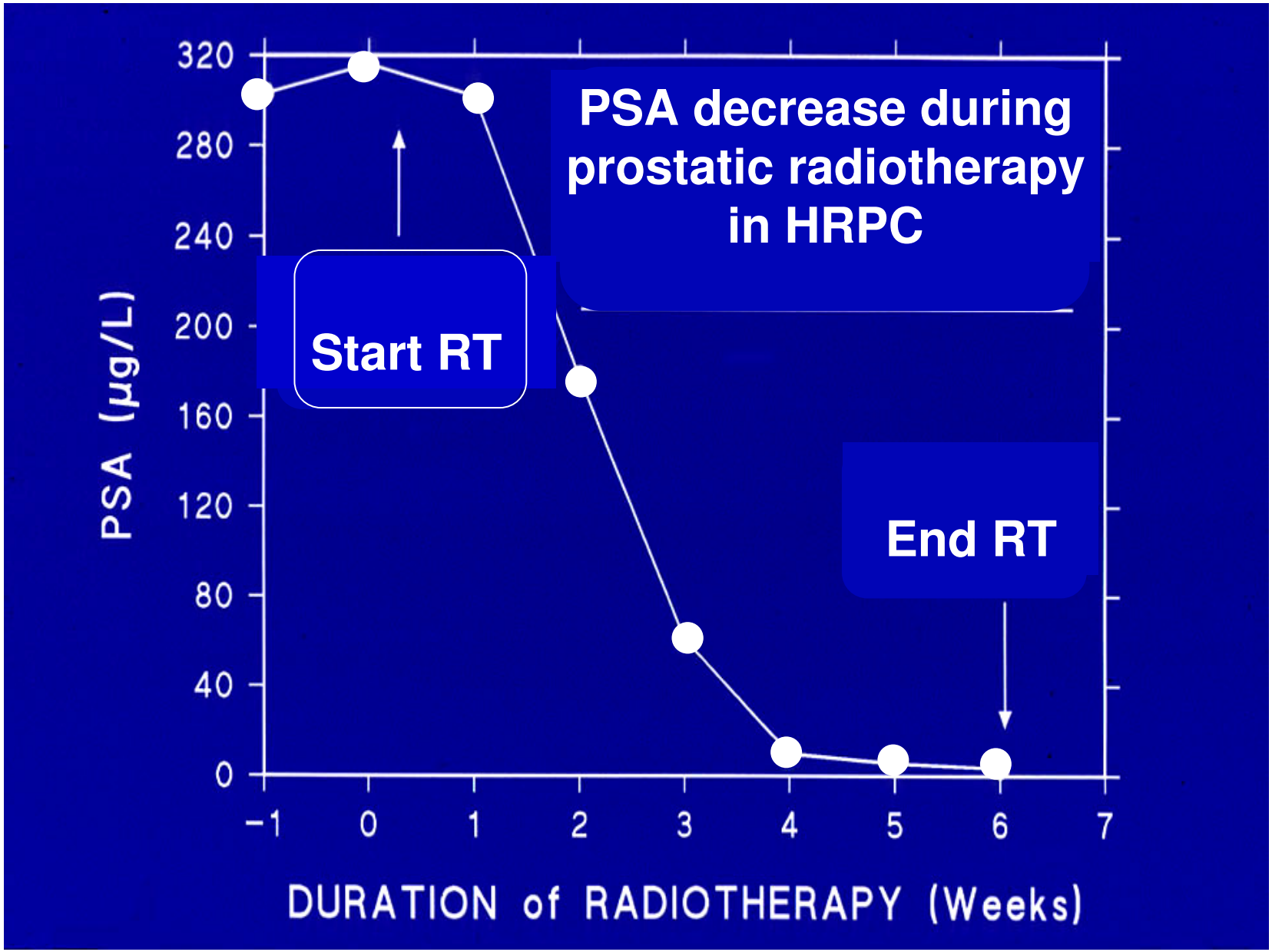
Casodex:

Arbiterone:

Cellenivå: Anti-Androgen Withdrawal

Bakgrunn:

PSA respons:


PSA decrease during prostatic radiotherapy in HRPC
Start RT
End RT
PSA (µg/L)
320
280
240
200
160
120
80
40
0
−1
0
1
2
3
4
5
6
7
DURATION of RADIOTHERAPY (Weeks)

Serumnivå: Blockade of adrenal androgen production

1. Prednisolone:

2. Dexamethasone:

3. Ketaconazole (+ Hydrocortison)
4. Arbiterone

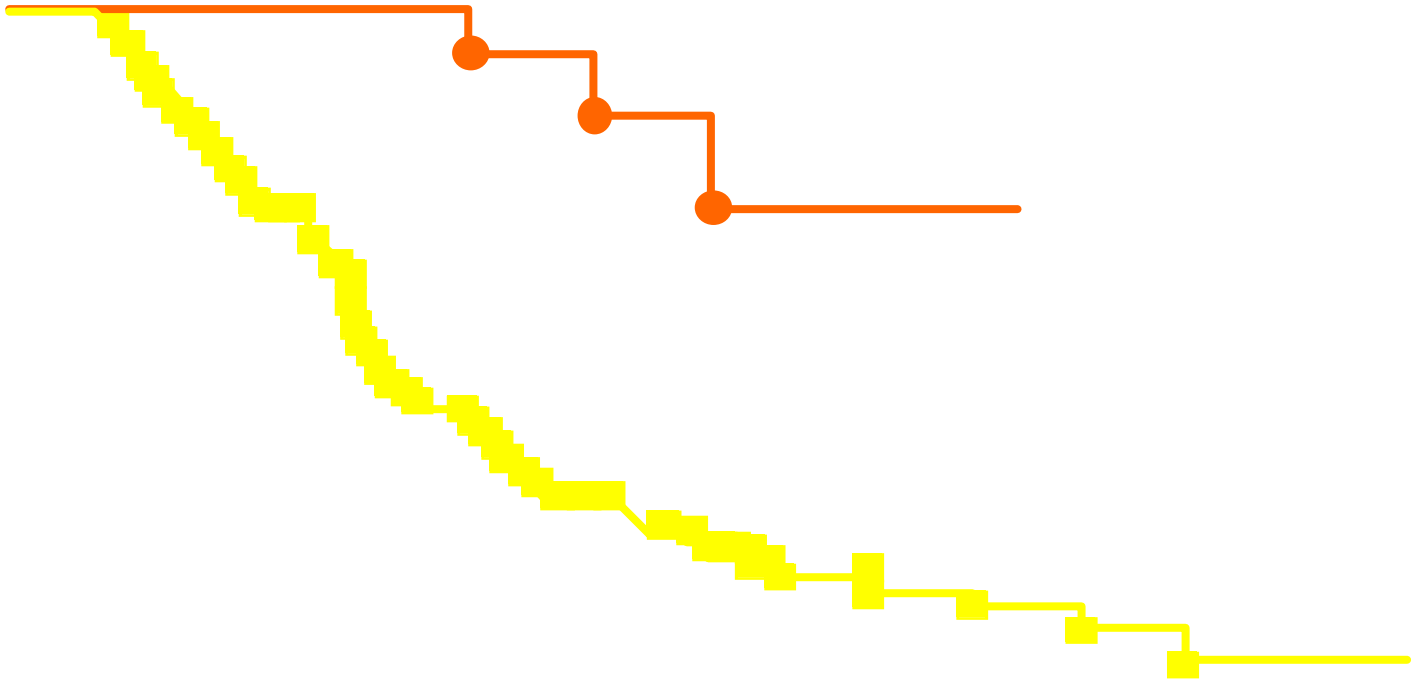
Corticosteroids

Estrogens

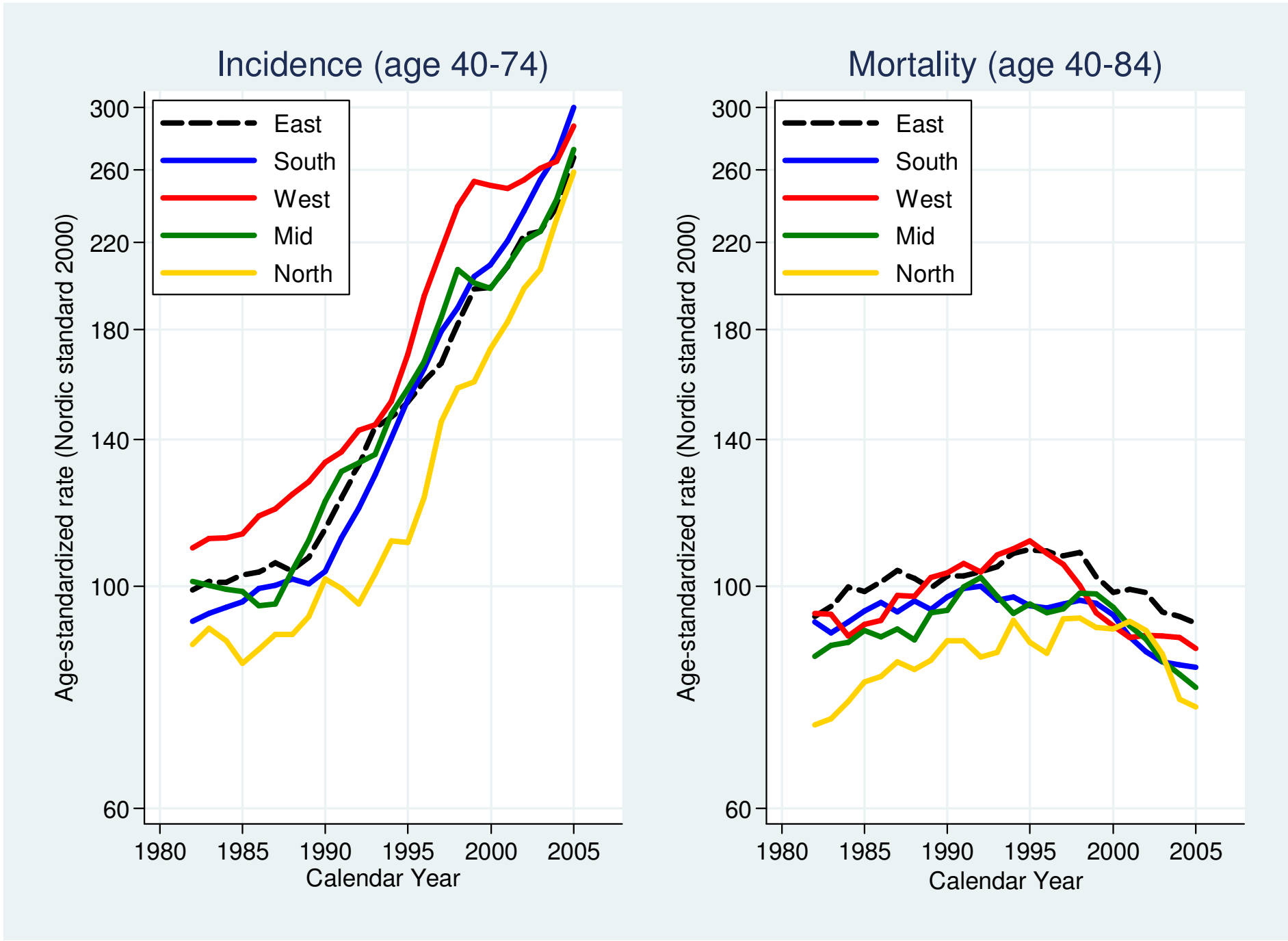
Estrogens

Sekundær hormonbehandling av kastrasjonuavhengig prostatakreft

Prostate-Specific Antigen as a Predictor of Overall Survival in Prostate Cancer



Adapted with permission from *J Clin Oncol*. 1993;11:607-615.


Incidence (age 40-74)
Mortality (age 40-84)
Age-standardized rate (Nordic standard 2000)
300
260
220
180
140
100
60
East
South
West
Mid
North
1980
1985
1990
1995
2000
2005
Calendar Year

Demografi, n=3744

		Missing
Alder	≤65 år =27%, >65-75 år =35%, >75 år =38%	
Fjernspredning	M+ =18%, M0 =73%	9%
T-kategori	T1-2 =55%, T3 =20%, T4 =6%	9%
Gleason score	≤6 =36%, 7 =33%, ≥8 =23%	8%
PSA	<4 =4%, 4-10 =30%, >10-20 =22%, >20 =42%	2%

Kandidater for kurativ behandling,

2004:n=1650 av 3774 (44%)

	Lav n=500	Intermediær n=453	Høy n=697
Kurativ behandling	57%	68%	61%
- RP	36%	28%	7%
- RAD	21%	40%	54%
Hormon behandling	0,2%	3%	21%

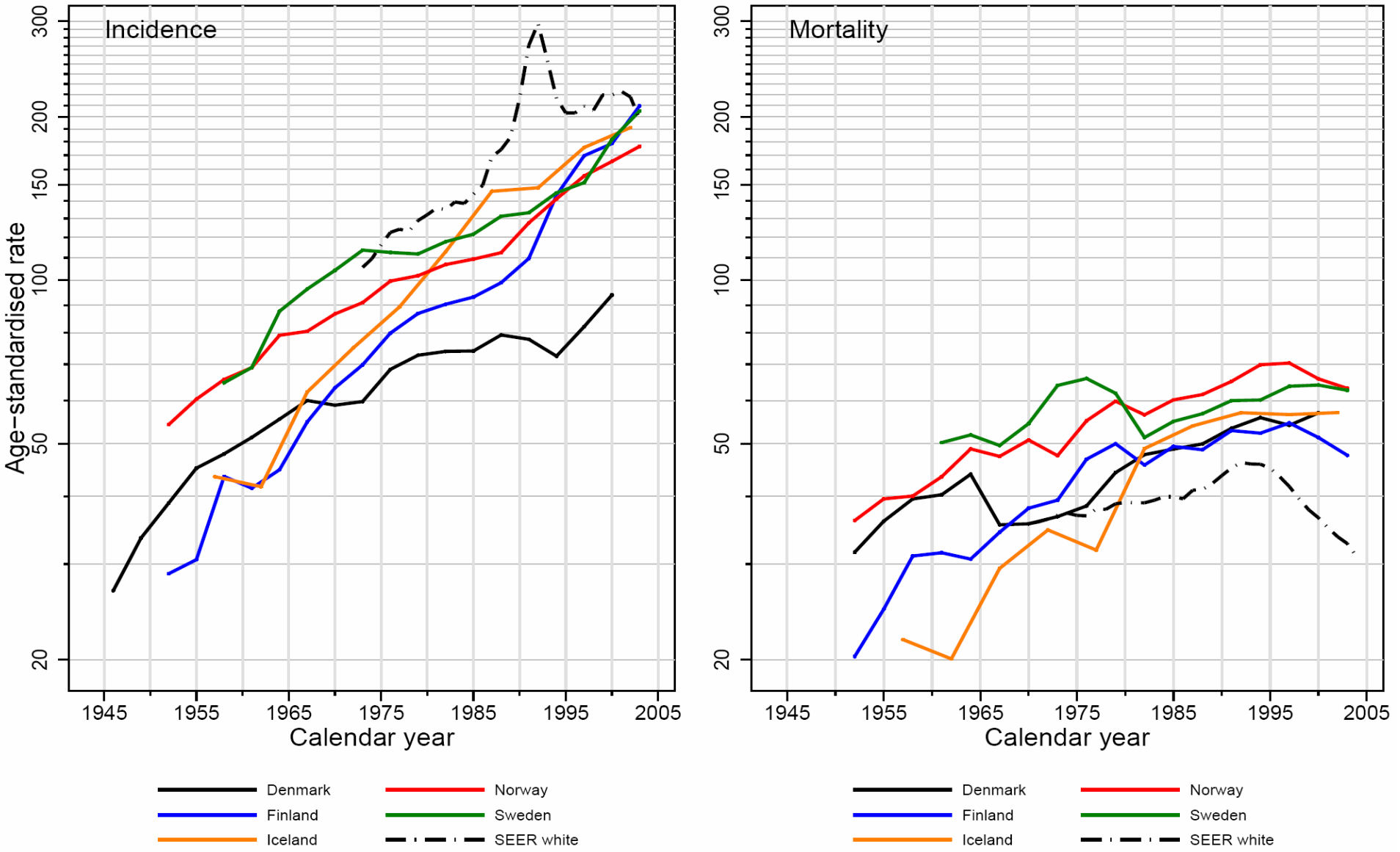
64% av intermediær/høyrisiko-pas fikk aktiv kurativ behandling. For få?

57% av lavrisiko-pas fikk aktiv kurativ behandling. For mange?

Primærbehandling, n=3744

	n	%
Kurativ behandling	1151	31
Palliativ behandlindling	1328	36
Observasjon	1019	27
Annet	33	1
Ukjent	213	6

Fig. 1. Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States, all ages.



Kvåle et al. JNCI 2007

Doubling Time of PSA Level from Four PSA Assays

To find the doubling time of the psa level of a pre-operative patient, enter the dates and results of his assays (in ng/ml) and click the submit button at the bottom of the page.

Patient`s nickname NorskMann (May be left blank.)

Enter the date 25 January 1998 and the result 2.0 of the first psa test

Enter the date 23 March 1999 and the result 3.0 of the first psa test

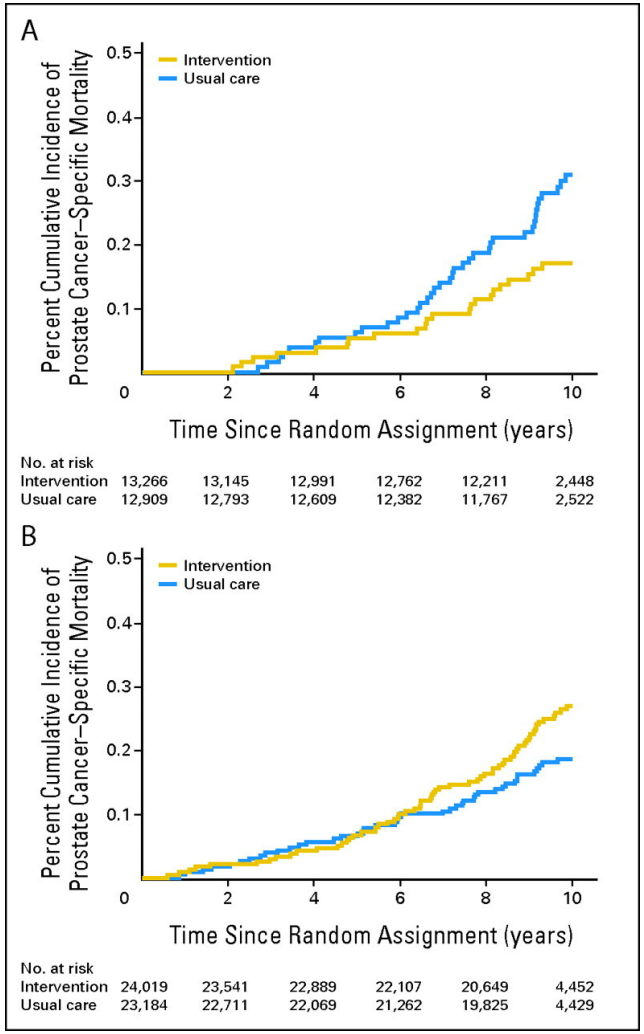
Enter the date 16 June 2000 and the result 4.0 of the first psa test

Enter the date 12 October 2001 and the result 5.0 of the first psa test

Submit

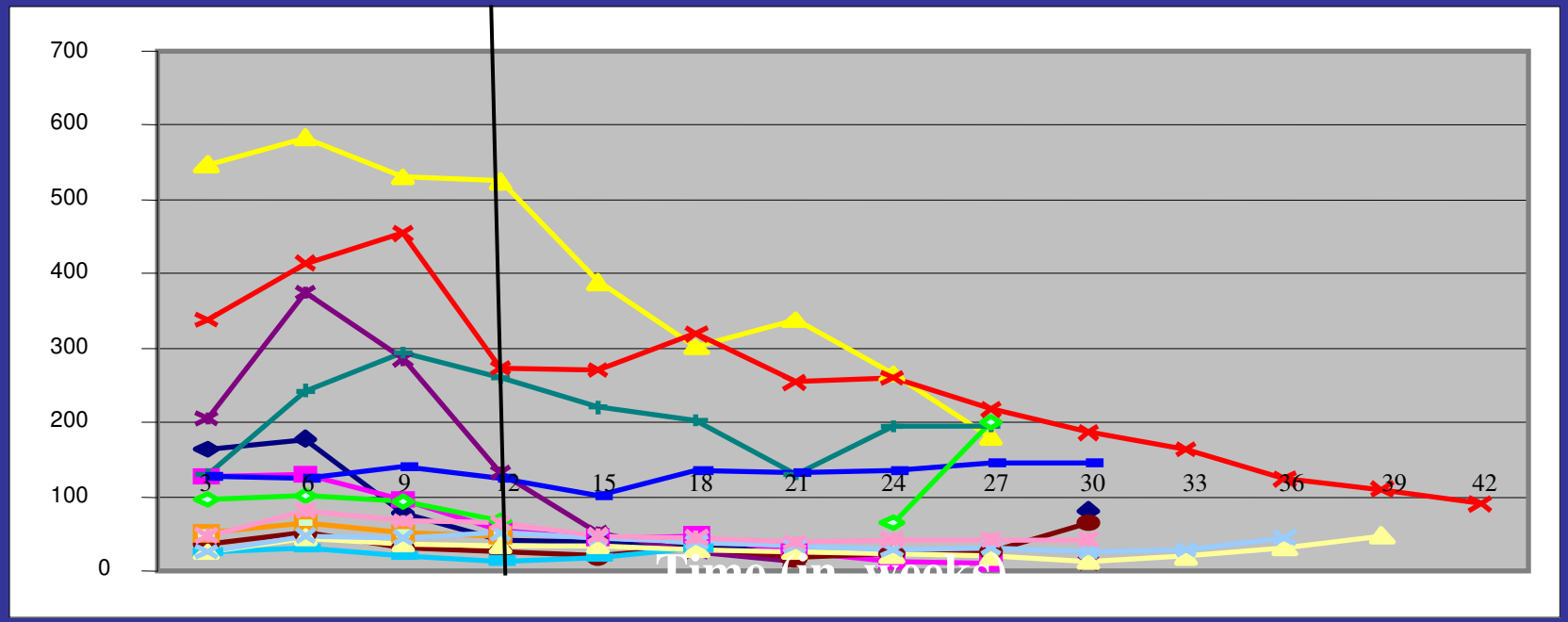
Doubling time

(A) Unadjusted cumulative incidence estimates14 of prostate cancer–specific mortality in men with no or minimal comorbidity randomly assigned to usual care or intervention.



Crawford E D et al. JCO 2011;29:355-361

PSA values for patients during treatment with Taxotere



Conclusion: Minimum treatment time 12 weeks

Fiazzi ESMO 2004