Testikkelkreft
Epidemiologi, patologi og behandling

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www.elsevier.com/locate/socscimed

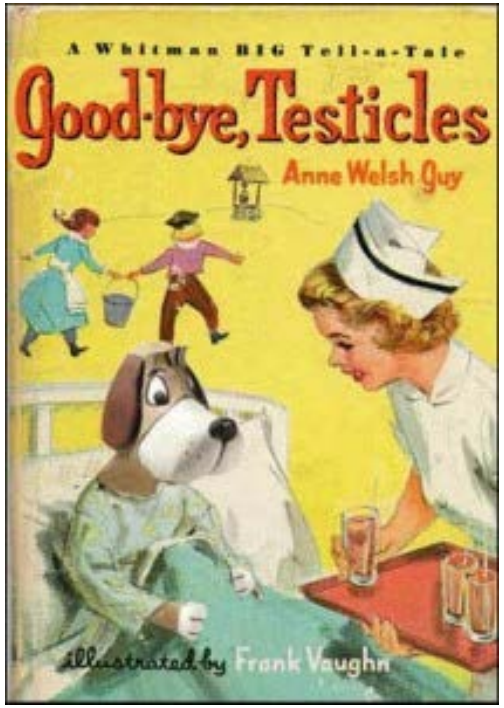
Do diseases have a prestige hierarchy? A survey among physicians and medical students

Dag Album[a,*], Steinar Westin[b]

Table 2
Disease prestige. Rank and mean scores (95% CI) in senior doctor, general practitioner and senior student samples[a]

Samples	Senior doctors $N = 242$			General practitioners $N = 327$			Senior students $N = 317$		
Diseases									
Mean of all diseases		5.0	(4.8–5.2)		5.1	(4.9–5.3)		5.5	(5.3–5.7)
Myocardial infarction	1	6.9	(6.8–7.1)	1	7.2	(7.0–7.4)	2	7.1	(6.9–7.3)
Leukaemia	1	6.9	(6.5–7.0)	2	6.9	(6.7–7.1)	3	7.0	(6.6–7.2)
Spleen rupture	3	6.6	(6.4–6.8)	3	6.6	(6.4–6.8)	4	6.9	(6.7–7.0)
Brain tumour	3	6.6	(6.4–6.8)	3	6.6	(6.4–6.8)	1	7.2	(7.0–7.4)
Testicle cancer	5	6.5	(6.3–6.7)	6	6.5	(6.3–6.7)	6	6.5	(6.3–6.7)
Pulmonary embolism	6	6.3	(6.2–6.5)	3	6.6	(6.4–6.7)	5	6.6	(6.4–6.8)
Angina pectoris	7	6.0	(5.9–6.2)	6	6.5	(6.3–6.6)	7	6.5	(6.3–6.6)
Extrauterine pregnancy	7	6.0	(5.8–6.2)	8	6.0	(5.8–6.2)	9	6.1	(6.0–6.3)
Thyroid cancer	9	5.9	(5.7–6.1)	10	5.9	(5.7–6.1)	16	5.5	(5.3–5.7)
Meniscus rupture	9	5.9	(5.6–6.1)	10	5.9	(5.7–6.1)	10	6.1	(5.9–6.3)
Colon cancer	11	5.7	(5.6–5.9)	12	5.8	(5.6–6.0)	14	5.7	(5.5–5.9)
Ovarian cancer	11	5.7	(5.5–5.9)	12	5.8	(5.6–5.9)	12	5.8	(5.6–6.0)
Kidney stone	13	5.6	(5.4–6.2)	15	5.6	(5.4–5.8)	15	5.6	(5.4–5.7)
Appendicitis	14	5.5	(5.3–5.7)	8	6.0	(5.8–6.2)	8	6.4	(6.2–6.6)
Ulcerative colitis	15	5.4	(5.2–5.6)	17	5.5	(5.3–5.6)	23	5.1	(4.9–5.3)
Kidney failure	15	5.4	(5.2–5.6)	19	5.3	(5.1–5.5)	19	5.3	(5.1–5.5)
Cataract	17	5.3	(5.1–5.5)	21	5.2	(5.0–5.4)	24	5.0	(4.8–5.2)
Duodenal ulcer	18	5.2	(5.1–5.4)	15	5.6	(5.4–5.7)	18	5.4	(5.2–5.6)
Asthma	18	5.2	(5.0–5.4)	12	5.8	(5.6–5.9)	17	5.5	(5.4–5.7)
Pancreas cancer	18	5.2	(5.0–5.4)	18	5.4	(5.2–5.6)	11	5.8	(5.6–6.0)
Ankle fracture	21	5.1	(4.9–5.4)	19	5.3	(5.1–5.5)	13	5.7	(5.5–5.9)
Lung cancer	21	5.1	(4.9–5.3)	21	5.2	(5.0–5.4)	21	5.2	(5.0–5.4)
Sciatica	23	4.9	(4.7–5.1)	23	5.0	(4.8–5.2)	25	5.0	(4.8–5.1)
Bechterew's disease	23	4.9	(4.7–5.1)	23	5.0	(4.8–5.2)	26	4.8	(4.6–5.0)

Primær kirurgisk behandling



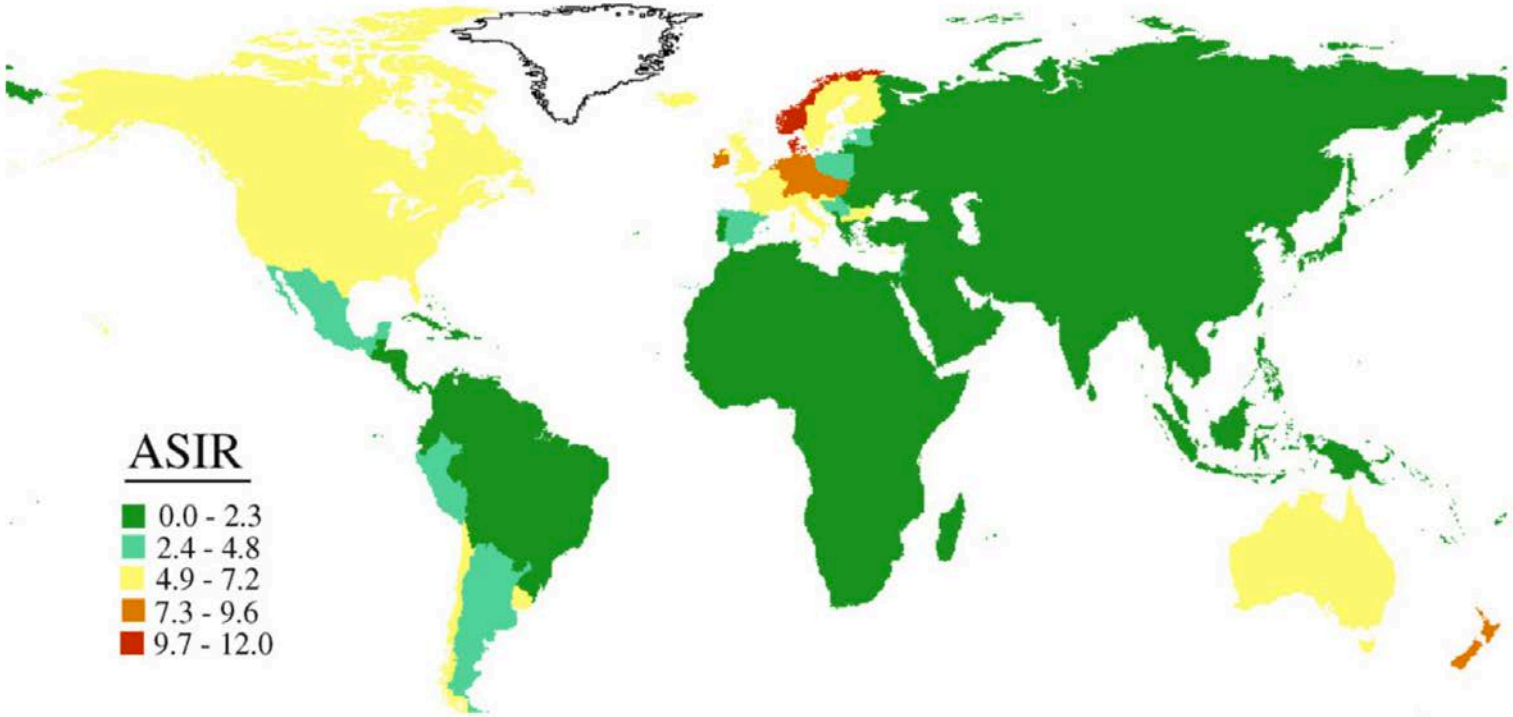
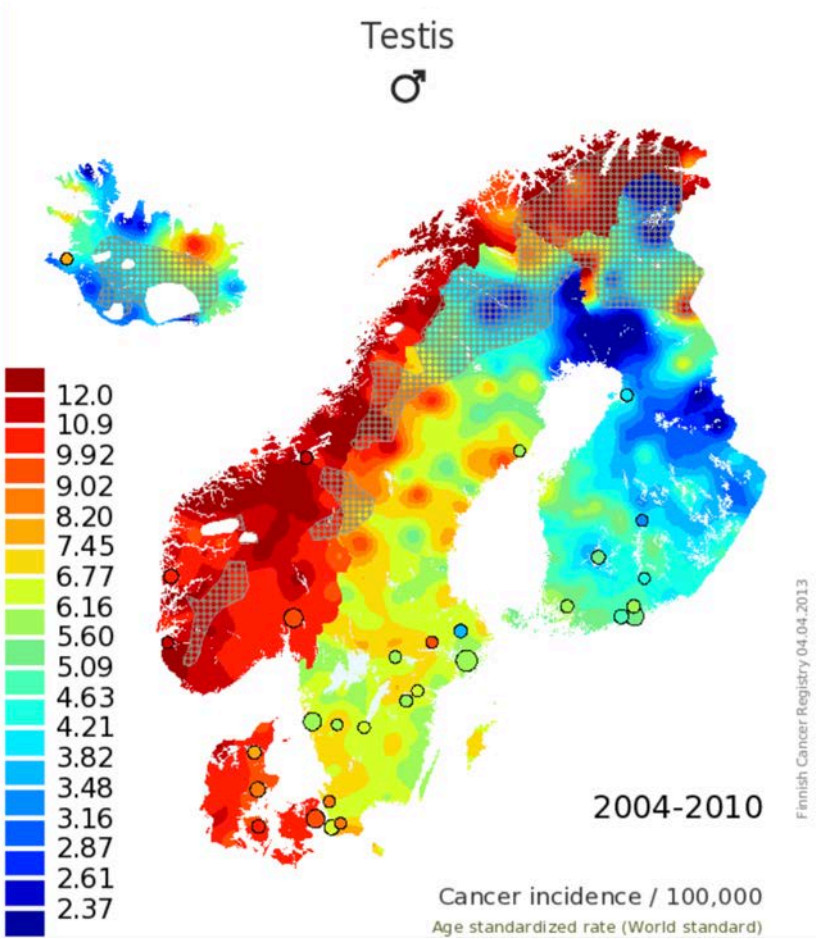


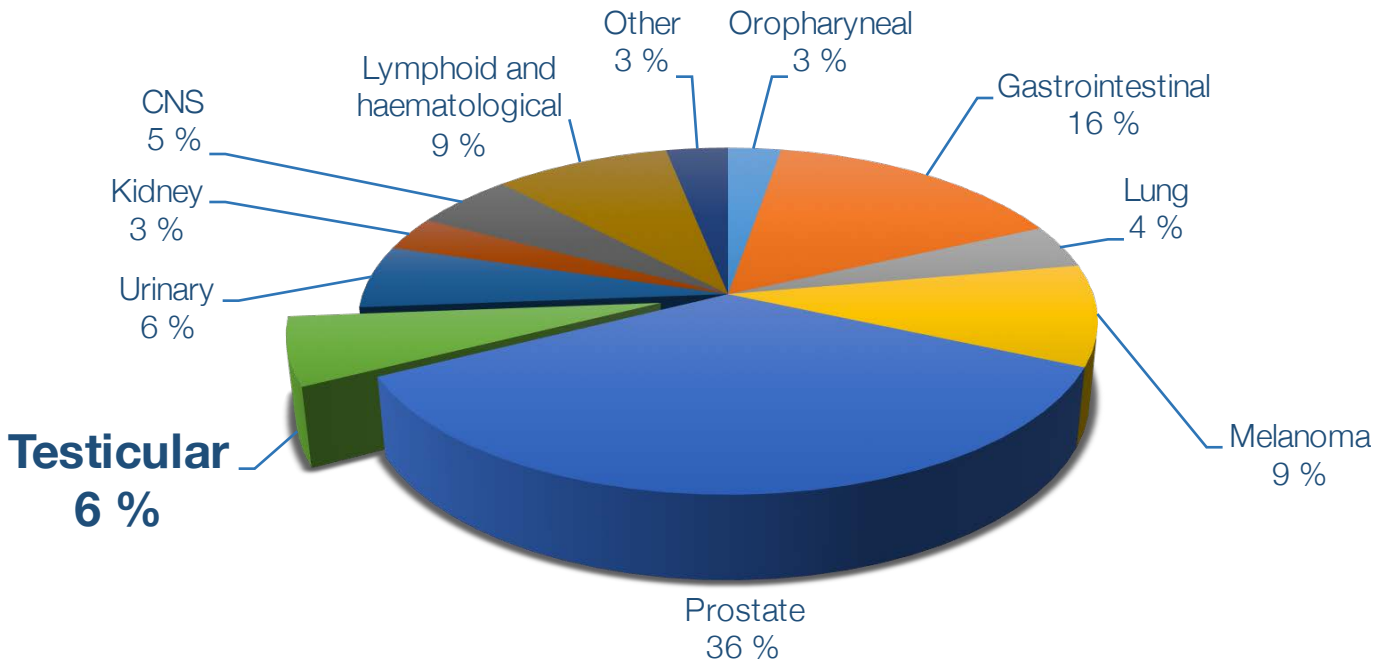
Fig. 2 – Global geographic distribution of testicular cancers by age-standardized incidence rate (ASIR; per 100 000).

Rosen et. Al. Eur Urol 60 (2011) 374-379

- Increasing incidence in all western countries
- Prevalence will continue to increase drastically



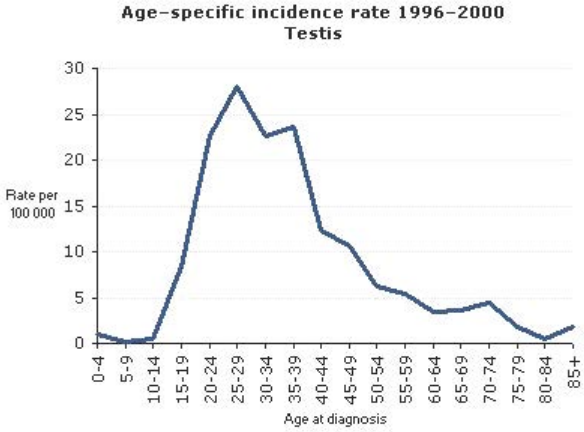
Male Survivors of Cancer



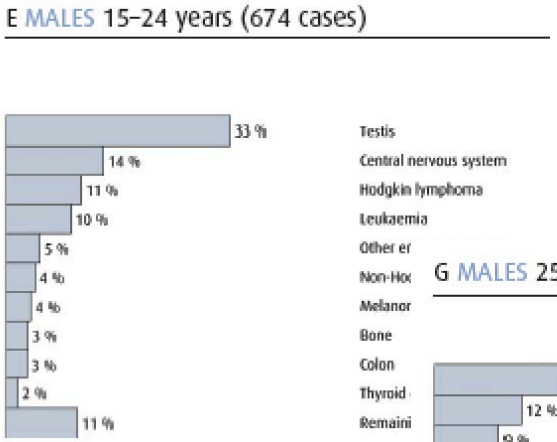
- Although a relatively rare cancer the prevalence of testicular cancer survivors (TCS) have risen sharply the last decades
- 60% of TCS were diagnosed with testicular cancer more then 10 years ago

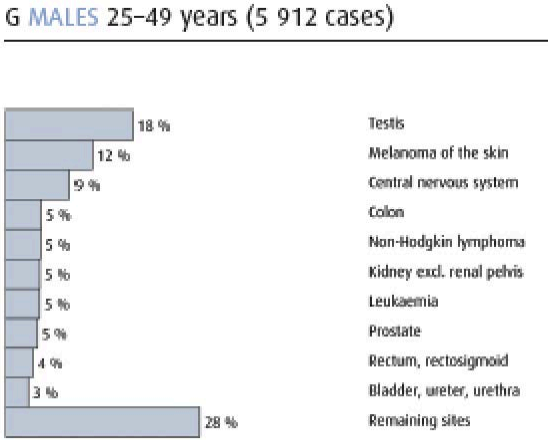
Cancer Registry of Norway, prevalence as of 31.12.2013

Aldersfordeling ca. testis i Norge



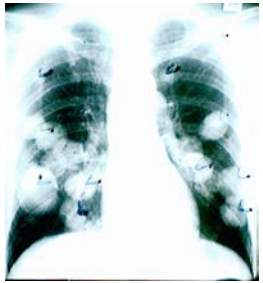
The Cancer Registry of Norway 23.01.2003

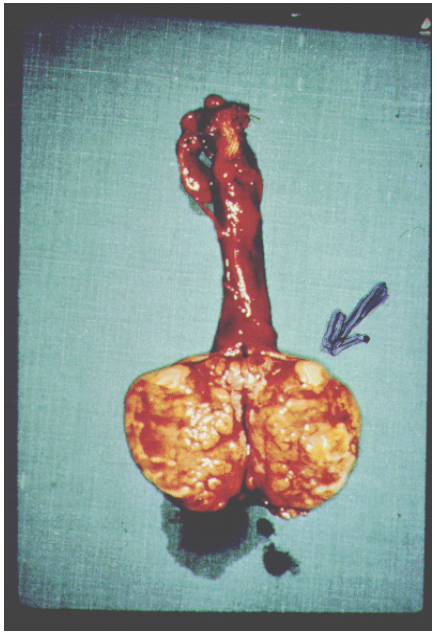




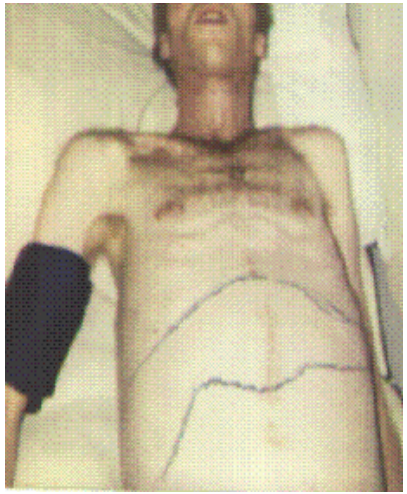
Fra unge menns tragedie til modellsykdom

- I 1960 årene var testikkelkreft hyppigste dødsårsak av enkeltsykdommer i Norge

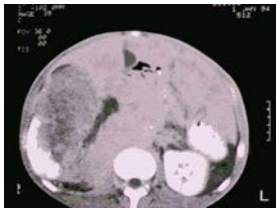


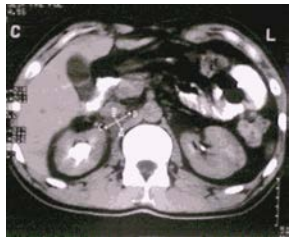


Cisplatinrevolusjonen 1977-1980



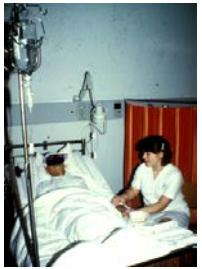
- Sommeren 1978: 28 unge menn nær døden ble behandlet ved Radiumhospitalet, nesten alle responderte
- Ung mann henvist med terminal "pancreas cancer". AFP 200000. Kurert.



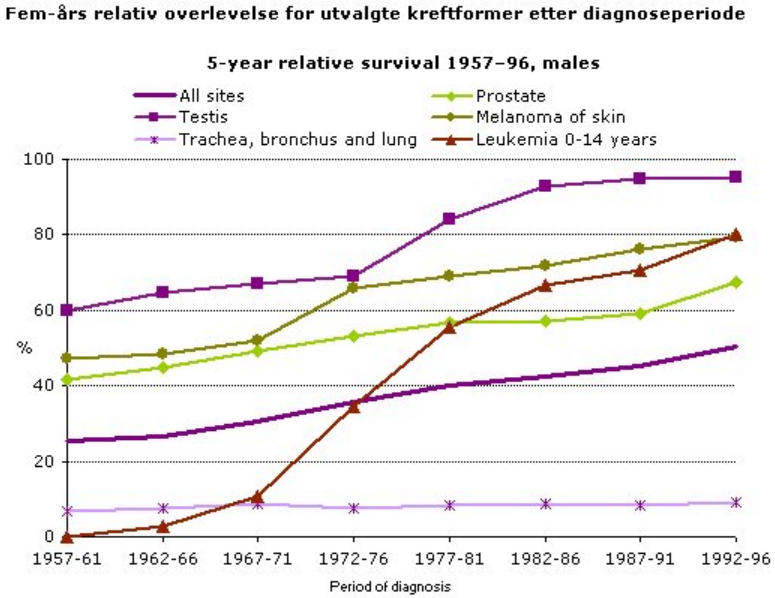


SWENOTECA

- Swedish Norwegian Testicular Cancer Group
- Etablert i 1981
- Utarbeider retningslinjer for testikkelkreft
- Onkologer og urologer

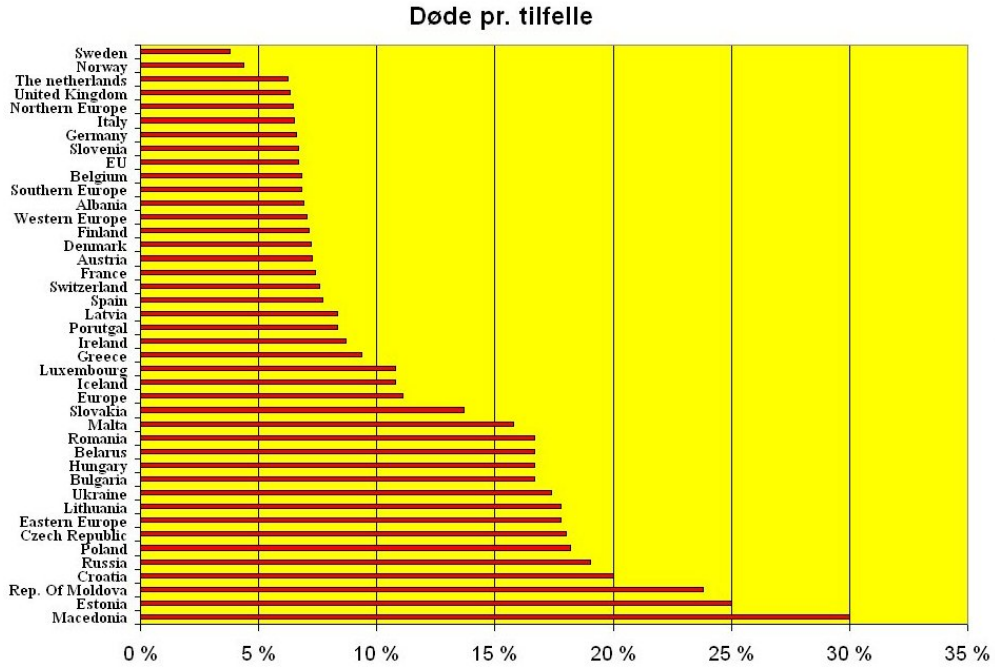


Best prognose av alle kreftformer



Incidens og mortalitet, testikkelkreft

Etter Bray et al, Eur J Cancer 38 (2002) 99 - 166



Seminom vs. nonseminom

Seminom

- Medianalder 35-37 år
- Senere spredning
- Mest lymfogen spredning
- Ekstremt straleføIsom
- Kjemosensitiv
- AFP alltid normal (NB: noen har habituelt forhøyet AFP)
- ⇧hCG 20 - 40%

Nonseminom

- Medianalder 25-29
- Tidlig spredning
- Ofte hematogen spredning
- Ofte flere typer histologi
  - Embryonalt carcinom
  - Yolk sac tumor
  - Choriocarcinom
  - Teratocarcinom
  - Seminom
- Stråleresistent
- Kjemosensitiv
- ⇧AFP og/eller hCG hos >70%

Utredning
av pasienter med testikkelkreft

VED DIAGNOSETIDSPUNKT (før orkiektomi):

- Ultralyd begge testikler
- CT thorax/abd/bekken (metastaser?)
- Tumormarkører **AFP, hCG og LD**
- Hormonanalyser (testosteron, FSH, LH, SHBG)

Cryopreservering av sæd

- Tilbys pasienten før orkiektomi om mulig
- Redusert fertilitet hyppig ved testiscancer
- Spesielt viktig ved kontralateral atrofisk testikkel
- Pasienten skal tilbys testikkelprotese

Tumormarkører

- hCG

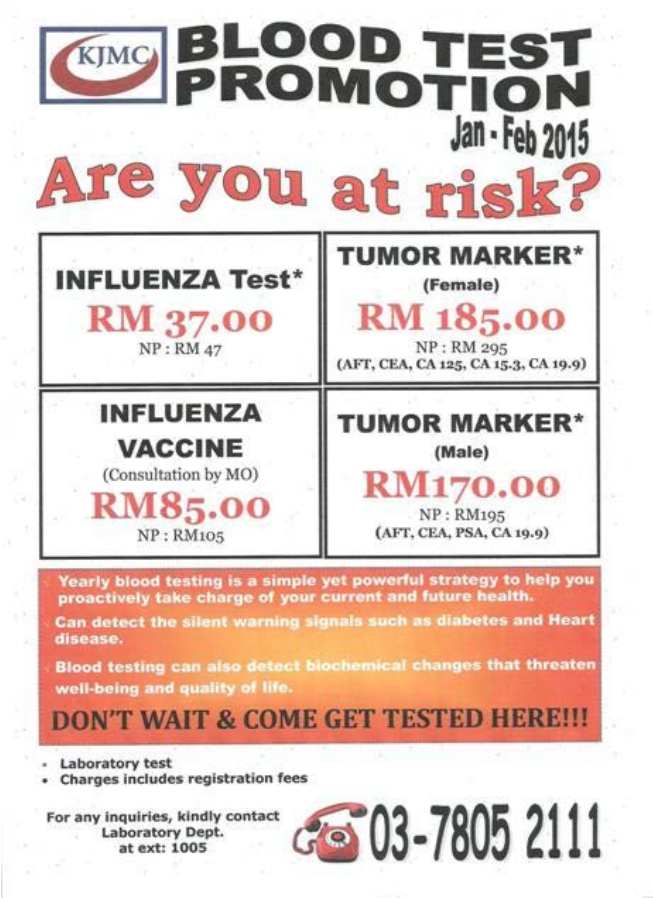
  Halveringstid ≤ 3 døgn

- AFP

  Halveringstid ≤ 7 døgn

- Beregnet halveringstid er beste mål på behandlingsrespons

- Skal følges til normalisering etter orkiektomi, og under eventuell kjemoterapi (metastatisk sykdom)



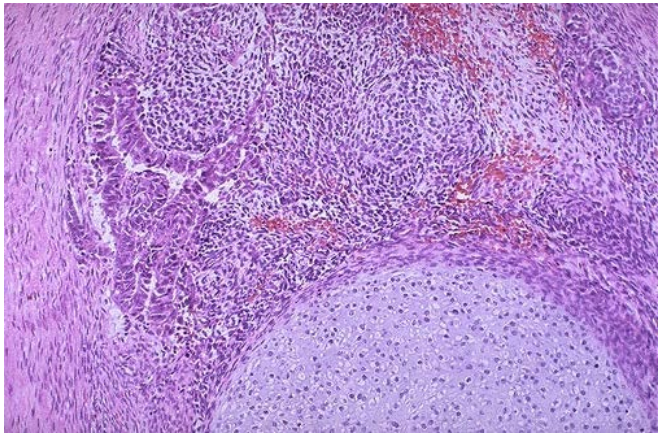
Histopatologi

- ***Germinalcelletumor?***
- ***Seminom eller nonseminom?***

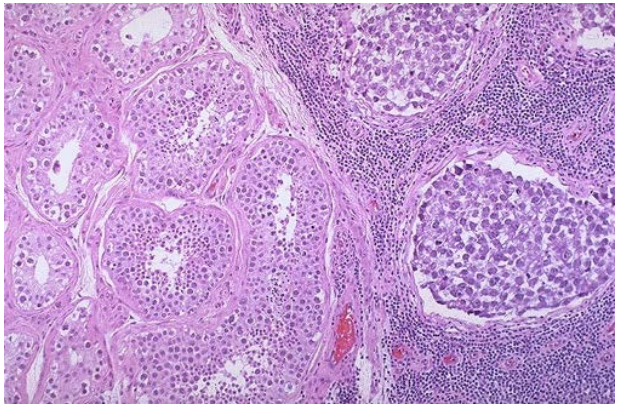
  Bare rene seminomer er seminomer

  Spermatocytisk seminom?
- ***Største tumordiameter***
- **Invasjon av tumorceller i karstrukturer**
- **Innvekst i rete testis**

Nonseminom (embryonalt karsinom og teratom)



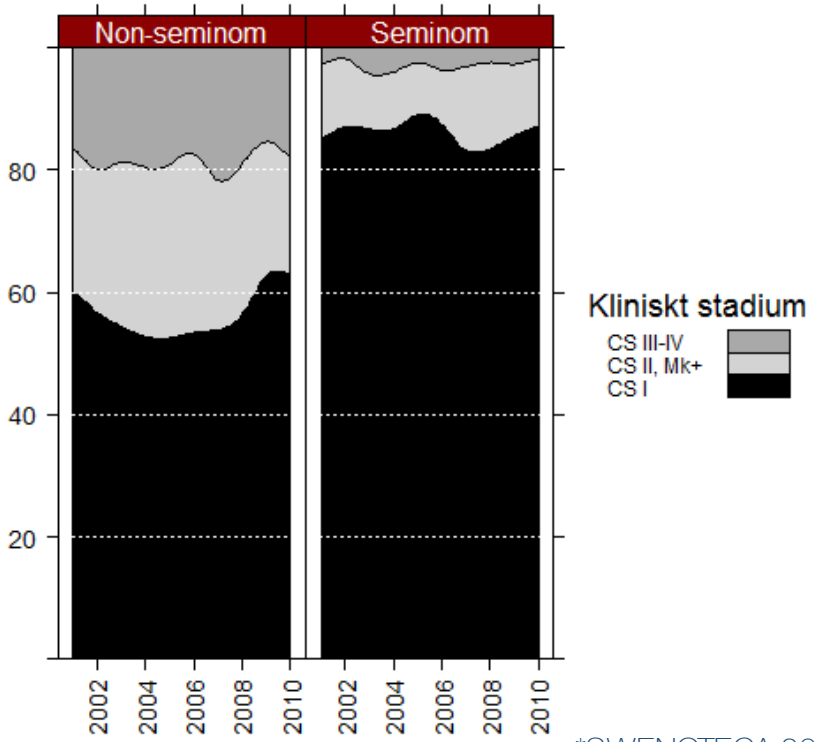
Rent seminom



Stadieinndeling, SWENOTECA / RMH

- CS I:
  - Ingen kliniske/radiologiske tegn til metastaser
- CS Mk+:
  - Forhøyde serum tumormarkører (AFP og/eller hCG) som eneste tegn til metastaser
- CS II:
  - Spredning til lymfeknuter under diafragma
- CS III
  - Spredning til lymfeknuter over diafragma
- CS IV
  - Ekstralymfatiske metastaser

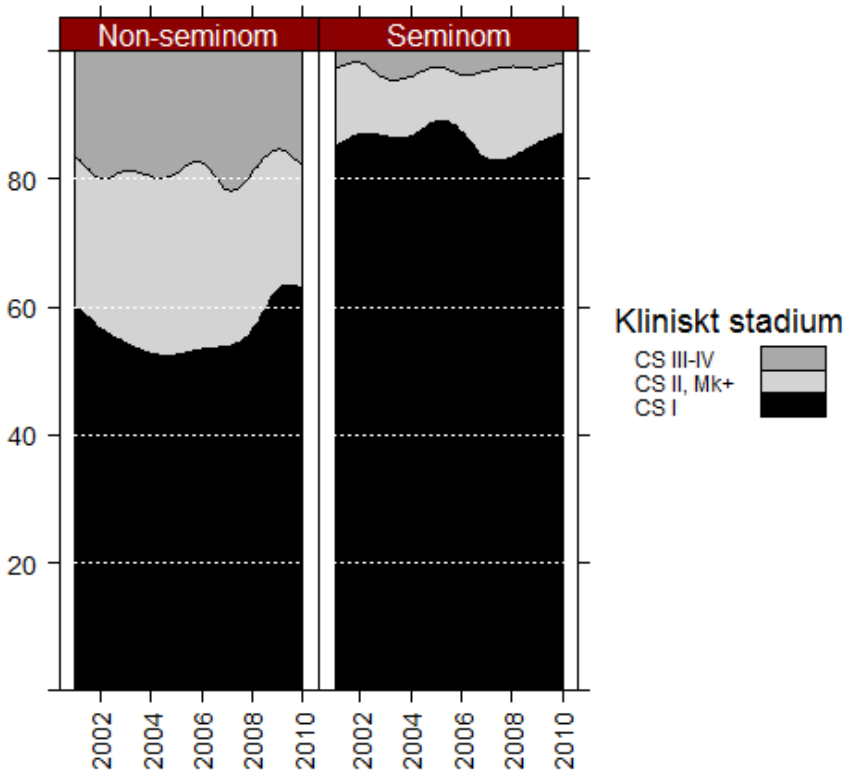
➢ A: Lymfeknuter i buken < 2 cm
➢ B: Lymfeknuter i buken 2-5 cm
➢ C: Lymfeknuter i buken > 5 – 10 cm
➢ D: Lymfeknuter i buken > 10 cm



*SWENOTECA 2001-2010

Stadium og type

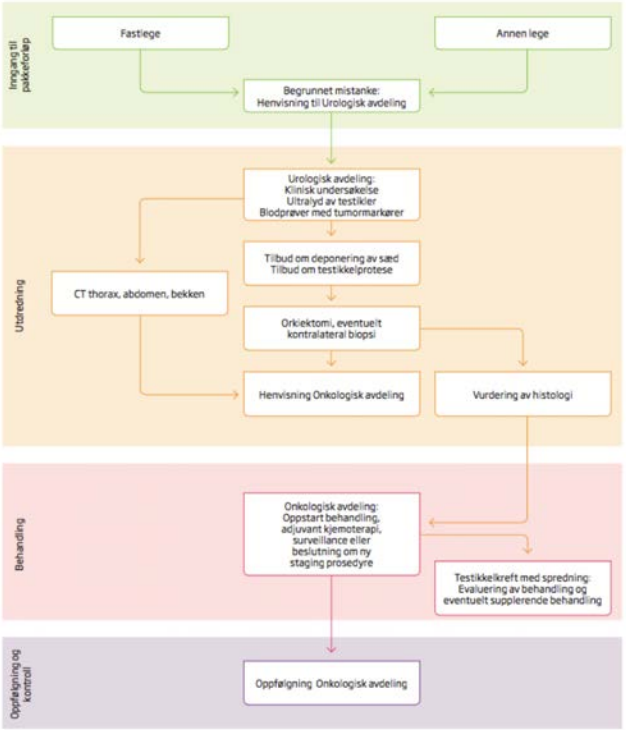
- Seminom (54%*)
  - 86% CS I
  - Median alder 37 år
- Non-seminom (46 %*)
  - 57% CS I
  - Median alder 29 år



*SWENOTECA 2001-2010

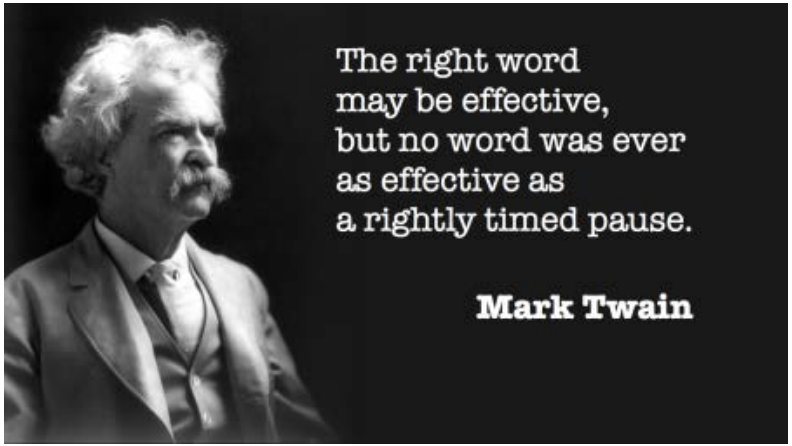
Henvisningsrutiner urolog-onkolog
Klinisk Stadium 1 (ikke sikre metastaser)

- Henvis til kreftavdeling, ikke vent på histologisk svar!
- Organiser kontroller av tumormarkører ved utreise
- Non-seminom: Endelig staging 6-8 uker etter orkiektomi
- Seminom inn elektivt for videre oppfølging og evt. adjuvant behandling
- Info-skriv til pasient om testikkelkreft vedlegges
- Samtykke SWENOTECA



Utredning av pasienter med testikkelkreft CS I Endelig staging 6-8 uker etter orkiektomi (non-seminom)

- Klinisk us.
- CT thorax/abdomen/bekken
- Tumormarkører/hormonanalyser
- Evt. regranskning av histologi



Seminom CS I terapimuligheter

- Strålebehandling
  - Adjuvant RT mot paraaortale ± iliacale lymfeknuter
- Adjuvant kjemoterapi
  - 1 kur karboplatin reduserer tilbakefall av sykdom med ca 60-70 %, dvs fra 15 % til 5-6 %
- Surveillance
  - Kun tette kontroller i 10 år, 15 % tilbakefall

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Management of Seminomatous Testicular Cancer: A Binational Prospective Population-Based Study From the Swedish Norwegian Testicular Cancer Study Group (SWENOTECA)

Torgrim Tandstad, Rune Smaaland, Arne Solberg, Roy M. Bremnes, Carl W. Langberg, Anna Laurell, Ulrika K. Stierner, Olof Ståhl, Eva K. Cavallin-Ståhl, Olbjørn H. Klepp, Olav Dahl, and Gabriella Cohn-Cedermark

From St. Olavs University Hospital, Trondheim; Stavanger University Hospi-

A B S T R A C T

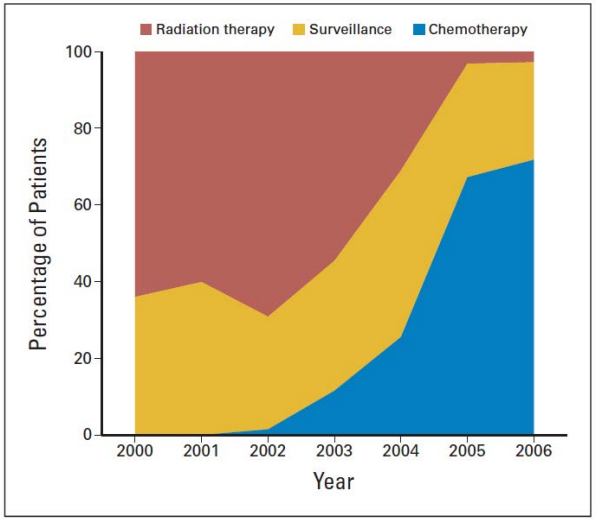


Fig 1. Development in the treatment of clinical stage 1 seminoma, 2000 to 2006.

Seminom CS I terapimuligheter

- Alle modaliteter gir samme overlevelse på kort sikt 98-99 %
- Ulike bivirkninger
- Ulike senbivirkninger

Seminom CS I Strålebehandling

- Strålebehandling: Øker risiko for annen dødelig kreft senere i livet
- Ikke lenger standard behandling

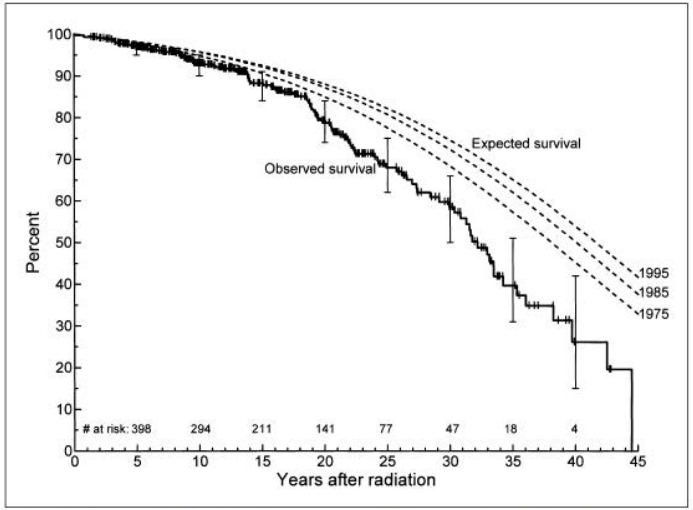
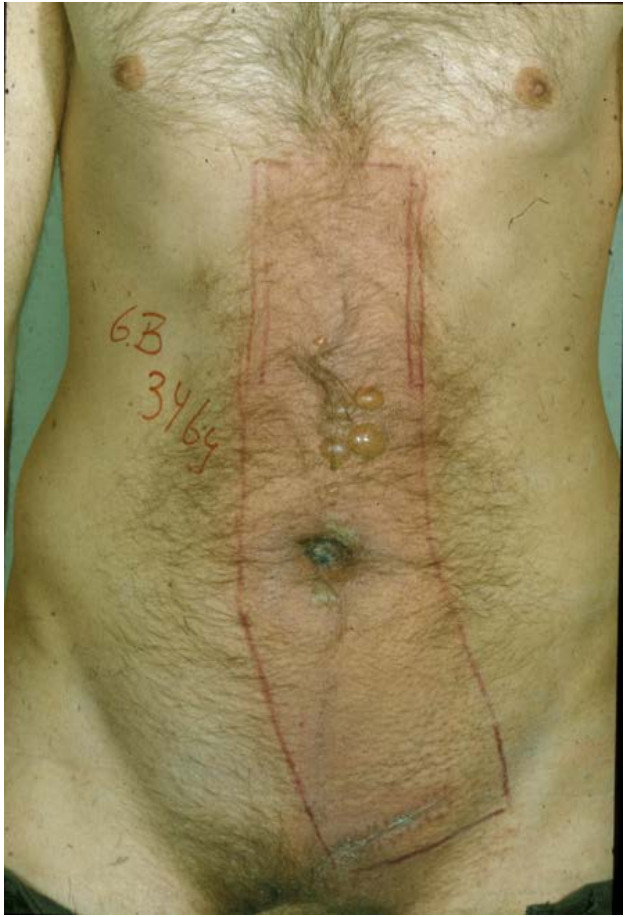


Fig 1. Survival of all 453 patients. Vertical bars are 95% CIs. The number of men at risk is shown above the abscissa. The individually age- and race-adjusted expected survival curves from life-tables for the male US population in 1975, 1985, and 1995 are also shown. These survival curves give the age- and race-adjusted expected survival rates for individuals subjected to the force of mortality in the US male population for that year.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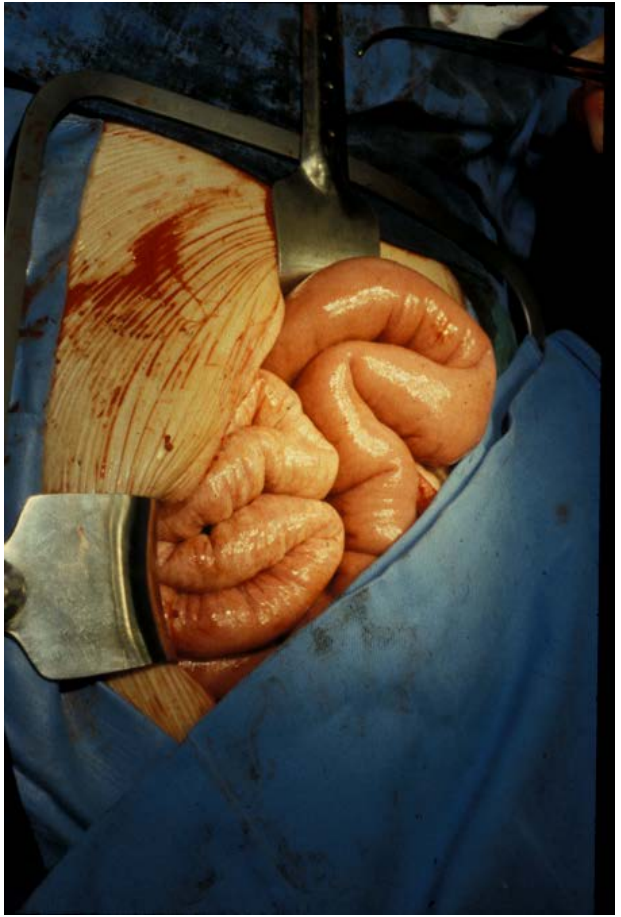
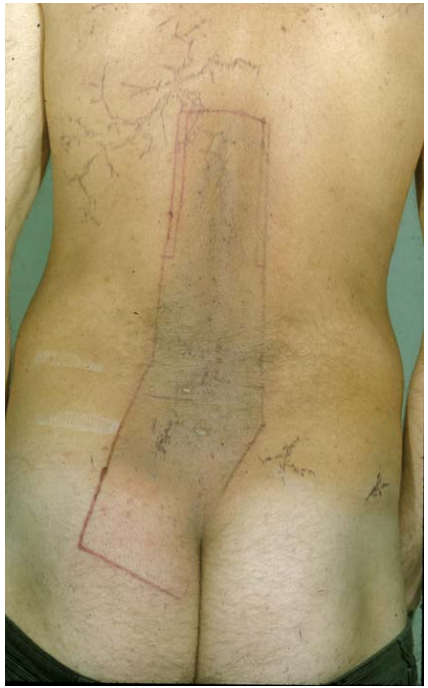
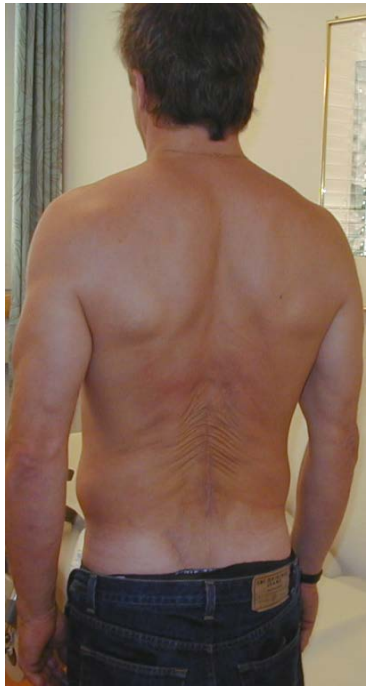
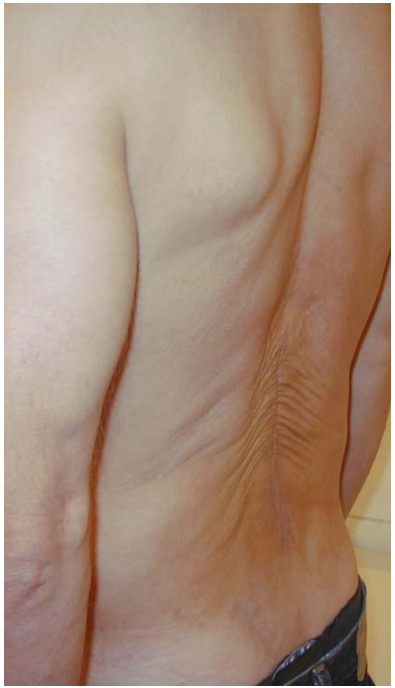






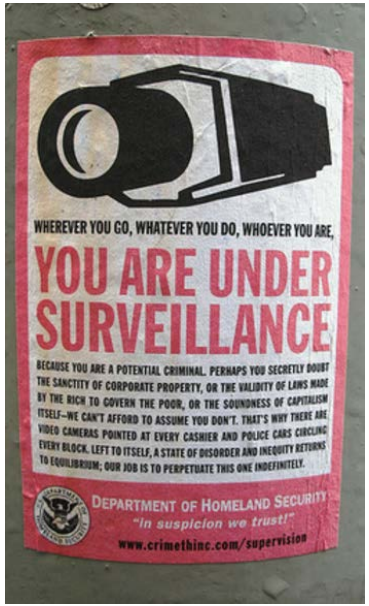


Seminom CS I Adjuvant Karboplatin

- 88 % ingen nytte av behandling
- 12 % slipper tilbakefall (3 kurer kjemoterapi, 98 % overlevelse)

Seminom CS I Surveillance

- 85 % kurert av orkiektomi alene
- 15 % får tilbakefall (3 kurer kjemoterapi, 98 % overlevelse)



Seminom CS I

- Risikofaktorer
  - Innvekst i rete testis
  - Tumor > 4 cm

- Risiko for recidiv
  - 5-8 % ved 0 risikofaktorer
  - 20 % ved 2 risikofaktorer

Seminom CS I anbefalinger

SWENOTECA / Nasjonalt handlingsprogram

Pas deltar i beslutningen etter muntlig/skriftlig informasjon

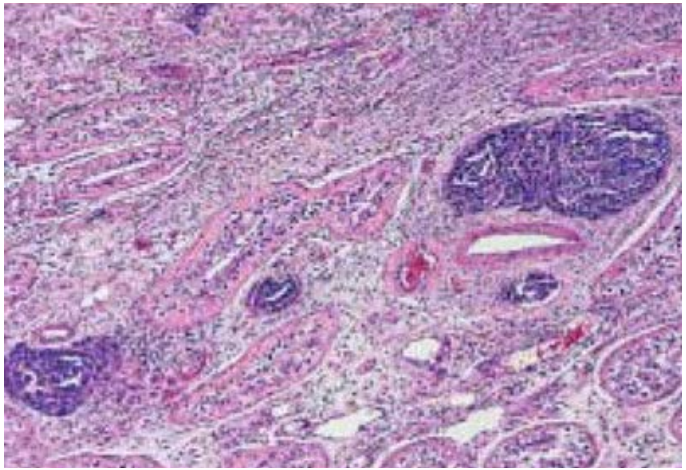
- 0 risikofaktorer:
  - Surveillance
- 1-2 risikofaktorer:
  - Anbefalt en kur adjuvant karboplatin
- Stråleterapi kan vurderes i individuelle tilfeller, men er ikke anbefalt som noen standard behandling

Adjuvant behandling anbefales også til pas. som med stor sannsynlighet vil falle ut av kontrollopplegg (narkomane, alkoholikere….)

Non-seminom CS I

- Risiko for tilbakefall ved surveillence:
  - VASC+: 50% (30 % av pasienter)
  - VASC-: 15% (70 % av pasienter)

- 90 % av tilbakefall kommer de første to år etter orkiektomi
- Ca 2/3 av alle recidiv kommer retroperitonealt



Non-seminom CS I terapimuligheter

- RPLND
  - Unilateralt
- Adjuvant kjemoterapi
  - 1 kur BEP, reduserer risiko for tilbakefall med 90-95 %
- Surveillance
  - Kun tette kontroller i 5 år, 25 % tilbakefall (15 % hos VASC– og 50 % hos VASC+)

Non-seminom CS I Surveillance

- 75 % er kurert ved orkiektomi alene
- 25 % vil få tilbakefall (3 kurer BEP ± (kirurgi)
  - Kun 15 % med VASC-
  - Hele 50 % med VASC+

Non-seminom CS I Adjuvant BEP

- Reduserer risiko for tilbakefall med 90-95 %
- Kun 15 % av pasienter med VASC- har nytte av behandlingen
- 50 % av pasienter med VASC+ har nytte av behandlingen

VOLUME 27 · NUMBER 13 · MAY 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Risk-Adapted Treatment in Clinical Stage I Nonseminomatous Germ Cell Testicular Cancer: The SWENOTECA Management Program

Torgrim Tandstad, Olav Dahl, Gabriella Cohn-Cedermark, Eva Cavallin-Stahl, Ulrika Stierner, Arne Solberg, Carl Langberg, Roy M. Bremnes, Anna Laurell, Hans Wijkstrøm, and Olbjørn Klepp

From the Department of Oncology, St Olavs University Hospital, Trondheim;

A B S T R A C T

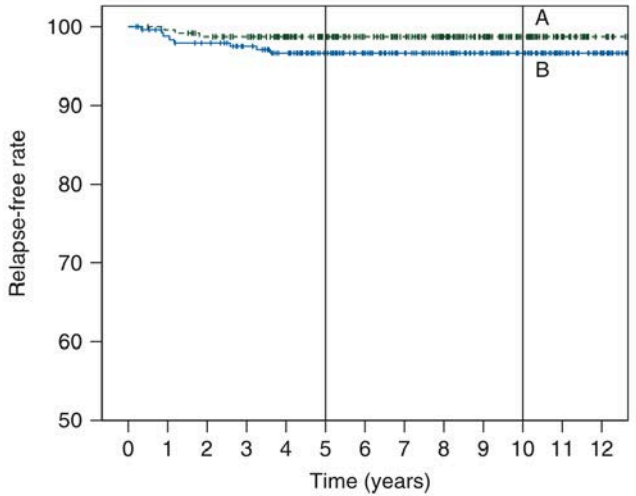


Figure 1. Kaplan–Meier curves for relapse-free rates by risk group; (A) patients without lymphovascular invasion; (B) patients with lymphovascular invasion.

Annals of Oncology

original articles

Annals of Oncology 25: 2167–2172, 2014
doi:10.1093/annonc/mdu375
Published online 11 August 2014

One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group

T. Tandstad[1*], O. Ståhl[2], U. Håkansson[3], O. Dahl[4,5], H. S. Haugnes[6,7], O. H. Klepp[8], C. W. Langberg[9], A. Laurell[10], J. Oldenburg[9], A. Solberg[1], K. Söderström[11], E. Cavallin-Ståhl[2], U. Stierner[12], R. Wahlquist[13], N. Wall[14] & G. Cohn-Cedermark[15,16] on behalf of SWENOTECA

Non-seminom CS I anbefalinger

SWENOTECA / nasjonalt handlingsprogram

Pas deltar i beslutningen etter muntlig/skriftlig informasjon

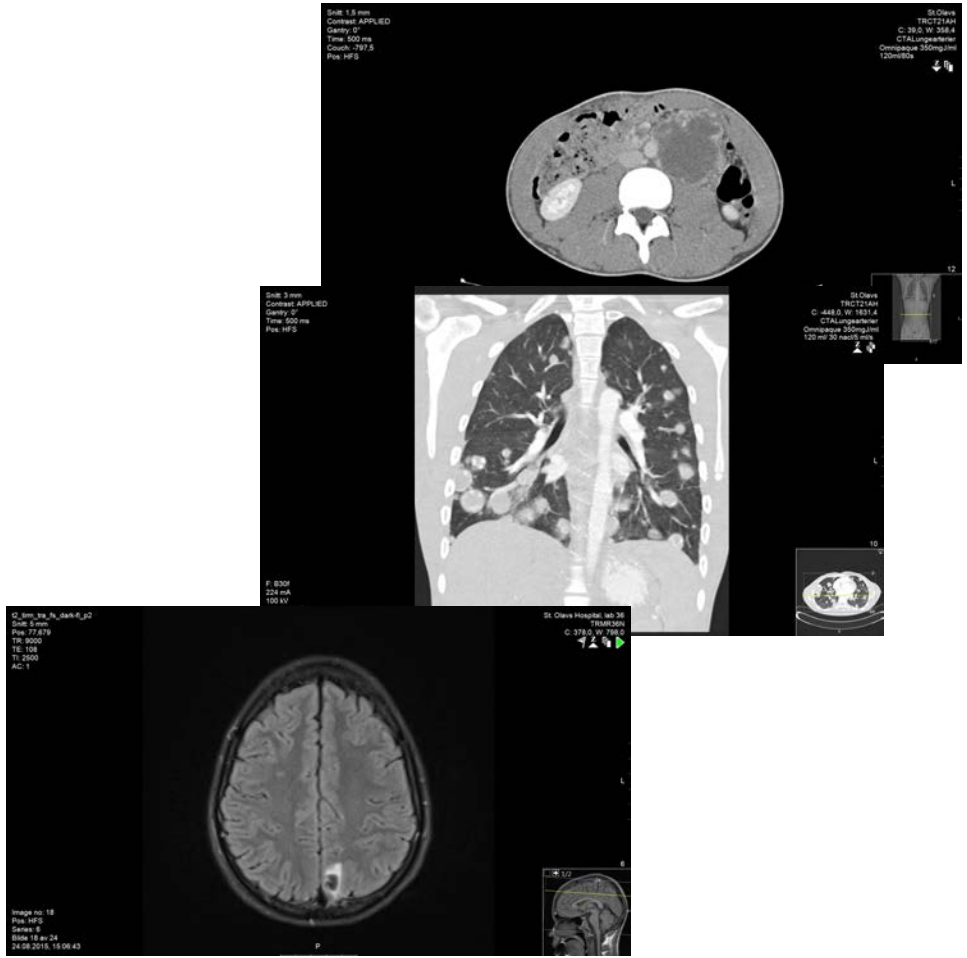
- VASC +: 1 kur adjuvant BEP
- VASC - : Surveillance, men mulighet for 1 kur adjuvant BEP etter pasientens ønske

Metastatisk sykdom

Metastaser på diagnosetidspunkt:

- 15 % ved seminom
- 45 % ved non seminom

- Helbredelse oppnås hos >90%
- Prognose er avhengig av stadium og tumormarkører



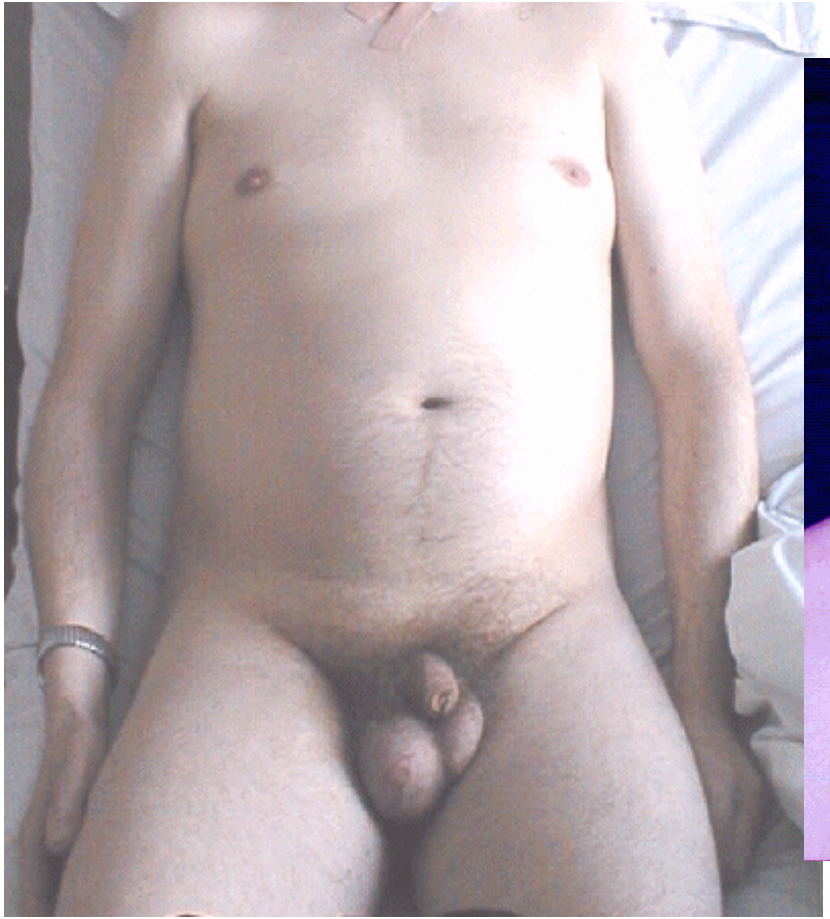
Henvisningsrutiner urolog-onkolog

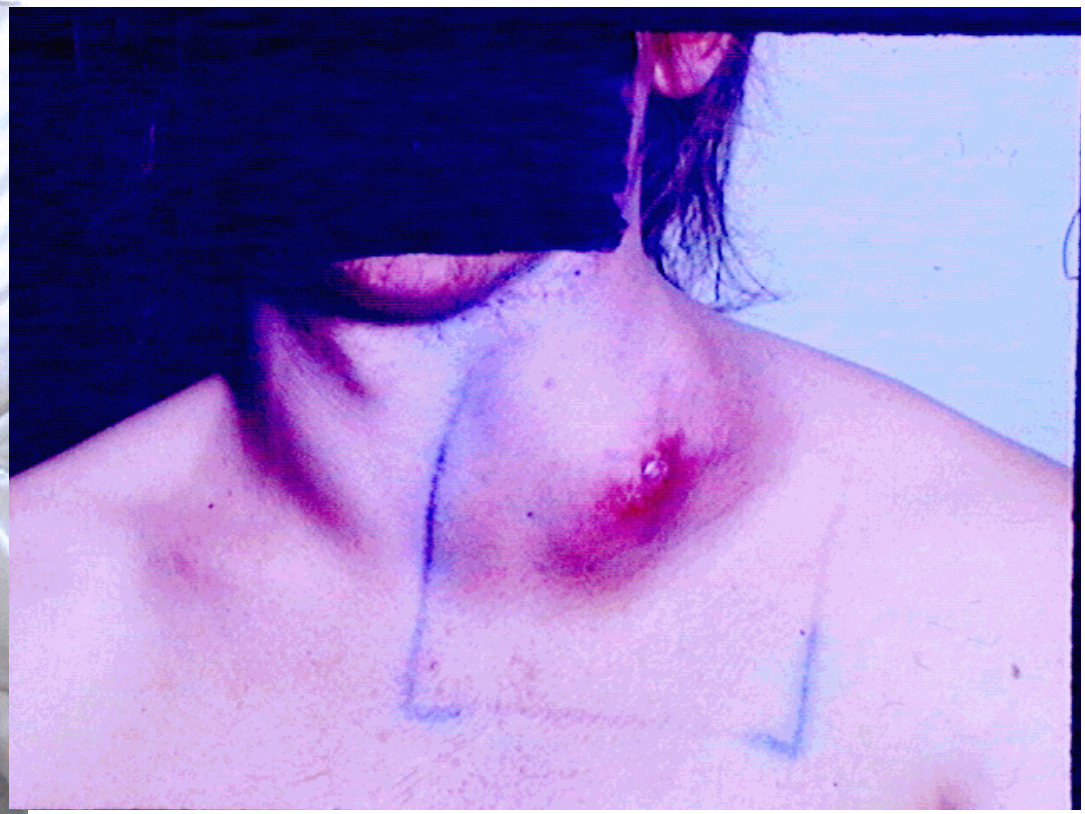
- Ved metastaser **skal** pasienten utredes og behandles snarest ved Universitetssykehus (Oslo, Bergen, Trondheim, Tromsø)
- Henvis pasienten direkte, enten ved intern henvisning eller kontakt (telefon, fax). Ikke avvent til epikrise!
- Utbredt metastasering, klinisk sikker testikkelkreft og patologiske verdier av hCG eller AFP og kritisk syk pasient:
  - Start av kjemoterapi høyeste prioritet ofte uten forutgående orkiektomi

IGCCCG Prognostic Groups

J. Clin Oncol 15:594-603, 1997

- **Tar hensyn til:**
- Primært utgangspunkt (gonadal / ekstragonadal)
- Histologisk type (seminom / non-seminom)
- Lokalisering av evt. ekstragonadal primærtumor
- Lokalisering av viscerale metastaser (lunge-metastaser versus andre ikke-nodale metastaser)
- Serum-verdi av AFP, hCG, LDH



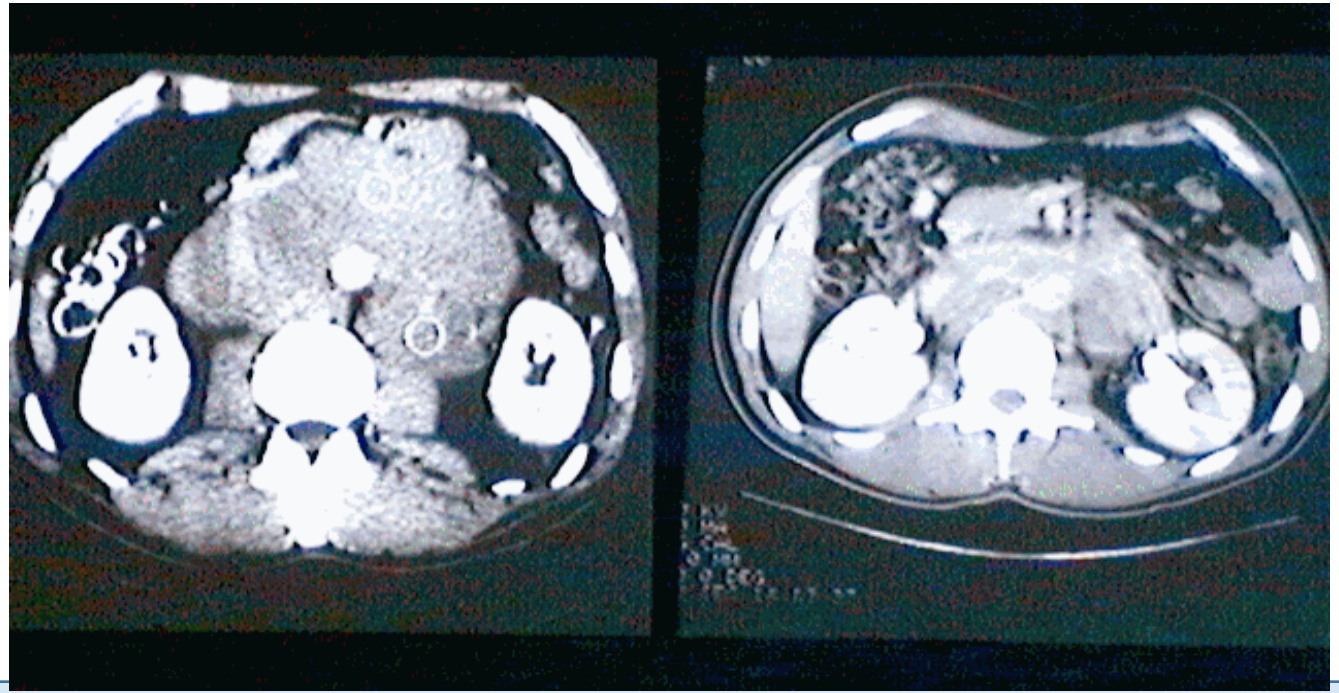


Metastatisk sykdom-seminom

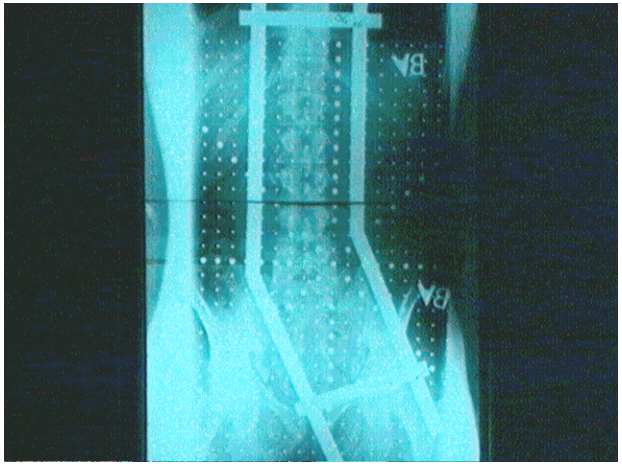
CS II A (glandelmetastaser retroperitonealt<2 cm)

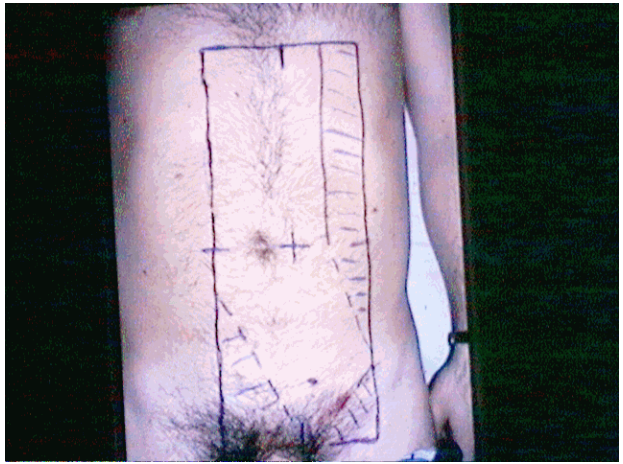
- Kjemoterapi BEP x 3 (3 uker mellom hver kur)
- Strålebehandling mot retroperitoneale lymfeknuter er et alternativ 2Gy x 15, dvs. totalt 30 Gy. Dvs 3 ukers behandling
- PET-CT kan være nyttig

Seminom-metastaser før og etter en abdominal CT…

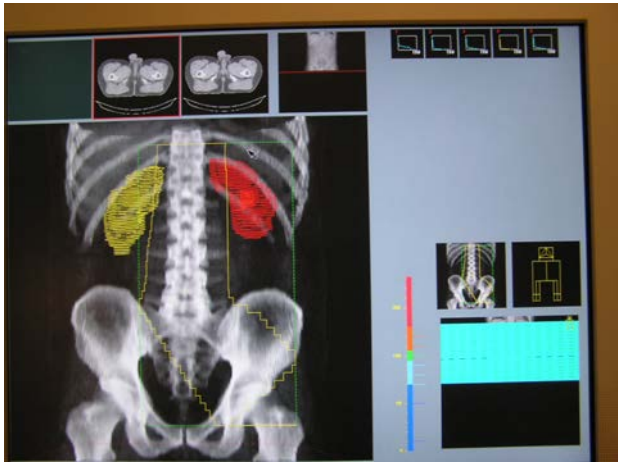


Klassisk L-felt for profylaktisk stråleterapi ved seminom CSIIA, dekker retroperitoneale lymfebaner





L-felt ved seminoma testis



Metastatisk sykdom-seminom

- CS > IIA: Kjemoterapi

- BEP 3 kurer (God prognose), BEP 4 kurer (Intermediær prognose)

Metastatisk sykdom-seminom

- Ofte restforandringer (fibrose) etter avsluttet Kjemoterapi ved seminom
- PET-CT ved residual tumor $\geq$ 3cm (min 2 mnd etter beh)
- Ikke kirurgi/strålebehandling rutinemessig. Kun ved voksende restforandringer/pos PET

BEP: Internasjonal gullstandard kjemoterapi ved testikkelkreft

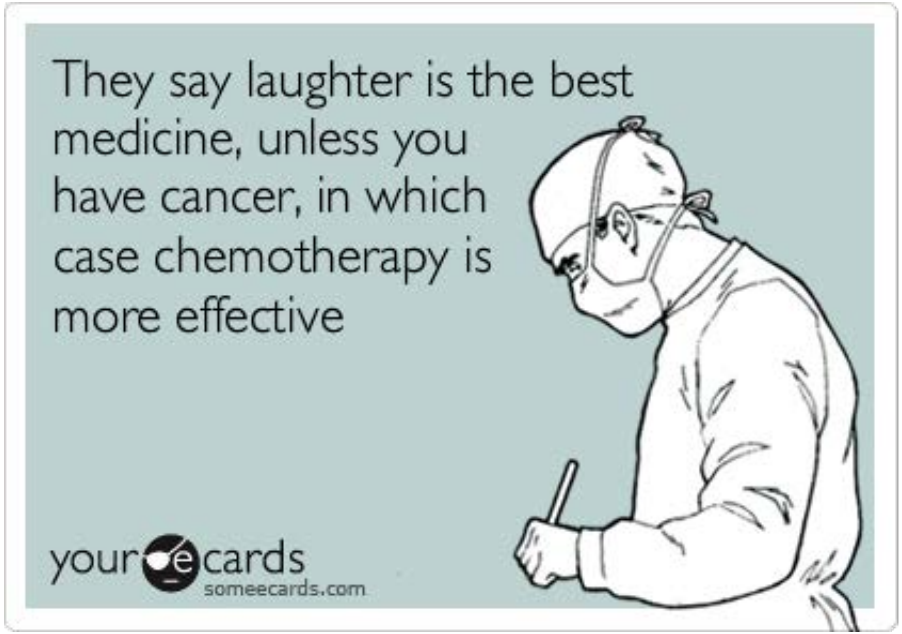
- Cisplatin 20 mg/m^2 Dag 1 – 5
- Etoposid 100 mg/m^2 Dag 1 – 5
- Bleomycin 30 000IE Dag 1, 5, 15

- God prognose: BEP x 3
- Intermediær og dårlig prognose: BEP x 4

- Intensivering ved utilfredsstillende respons. (Tumormarkører/CT)

BEP

- Høyemetogen
- Nefrotoksisk
- Ototoksisk
- Nevrotoksisk
- Myelotoksisk



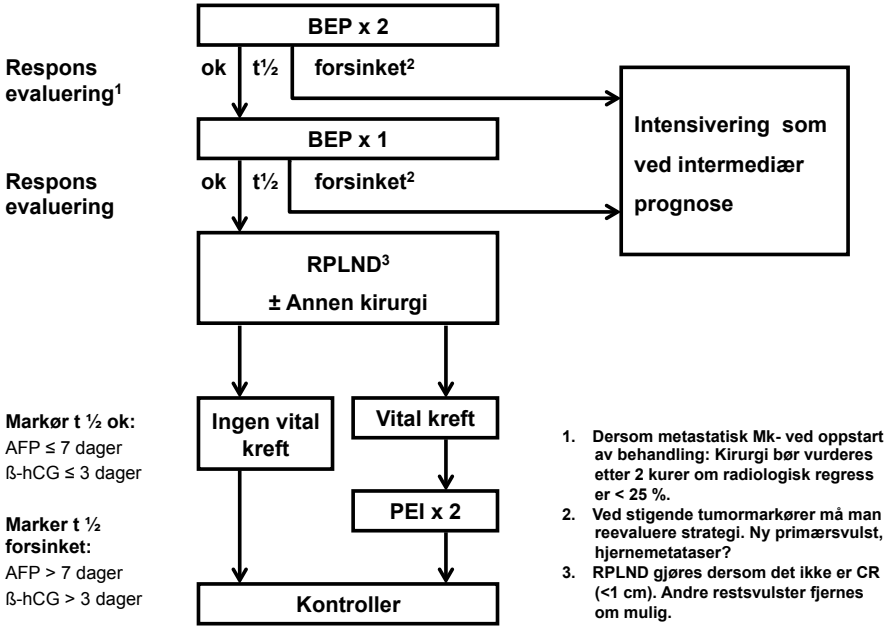
BEP

- Aldri dosereduser
- Hold intervaller
- Alltid bleomycin til tross for nøytropeni

Non-seminom-metastatisk sykdom

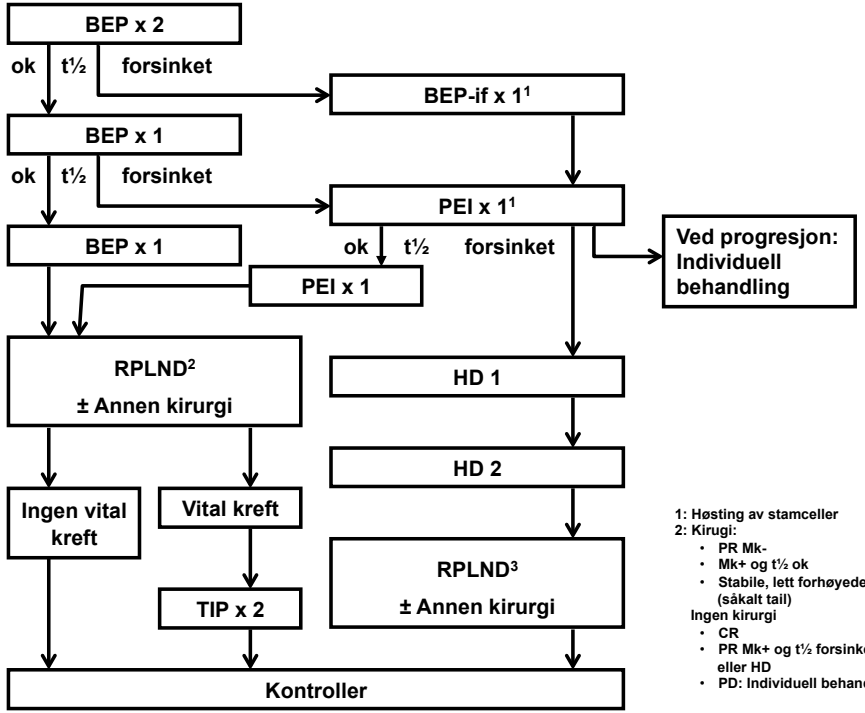
- **Standard kjemoterapi med BEP** x 3(-4)
- Evaluere behandlingsrespons etter 2 kurer
  - Adekvat fall av tumormarkører
  - Billeddiagnostikk
- Ved suboptimal respons intensivere kjemoterapi
  - Trinn1: Legg til ifosfamid
  - Trinn2: HMAS

Flytskjema 2: Non-seminom CS Mk+, IIA Mk+ , IIB-D, III, IV
God prognose



1. Dersom metastatisk Mk- ved oppstart av behandling: Kirurgi bør vurderes etter 2 kurer om radiologisk regress er < 25 %.
2. Ved stigende tumormarkører må man reevaluere strategi. Ny primærsvulst, hjernemetataser?
3. RPLND gjøres dersom det ikke er CR (<1 cm). Andre restsvulster fjernes om mulig.

Flytskjema 3: Non-seminom CS Mk+, IIA Mk+ , IIB-D, III, IV
Intermediær prognose og pasienter med dårlig prognose grunnet kun "dårlige" markører



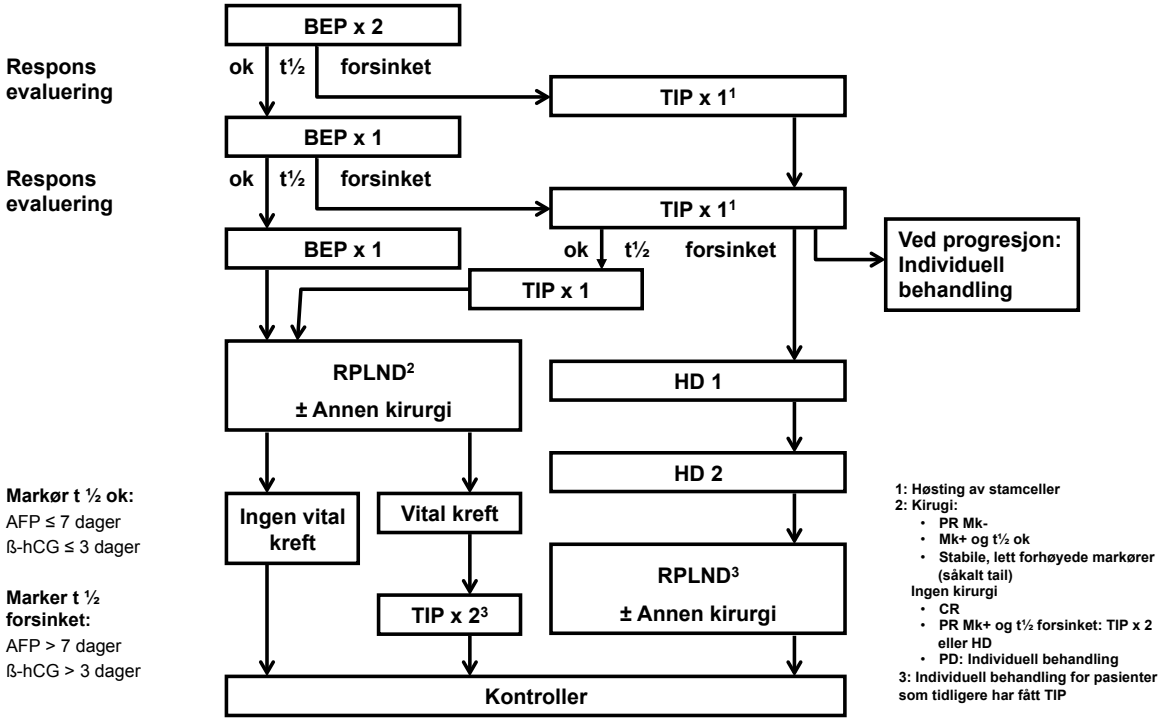
Markør t ½ ok:
AFP ≤ 7 dager
ß-hCG ≤ 3 dager

Marker t ½ forsinket:
AFP > 7 dager
ß-hCG > 3 dager

1: Høsting av stamceller
2: Kirugi:
- PR Mk-
- Mk+ og t½ ok
- Stabile, lett forhøyede markører (såkalt tail)

Ingen kirurgi
- CR
- PR Mk+ og t½ forsinket: TIP x 2 eller HD
- PD: Individuell behandling

Flytskjema 4: Non-seminom CS Mk+, IIA Mk+ , IIB-D, III, IV
Dårlig prognose med ikke-pulmonelle viscerale metastaser



Markør t ½ ok:
AFP ≤ 7 dager
ß-hCG ≤ 3 dager

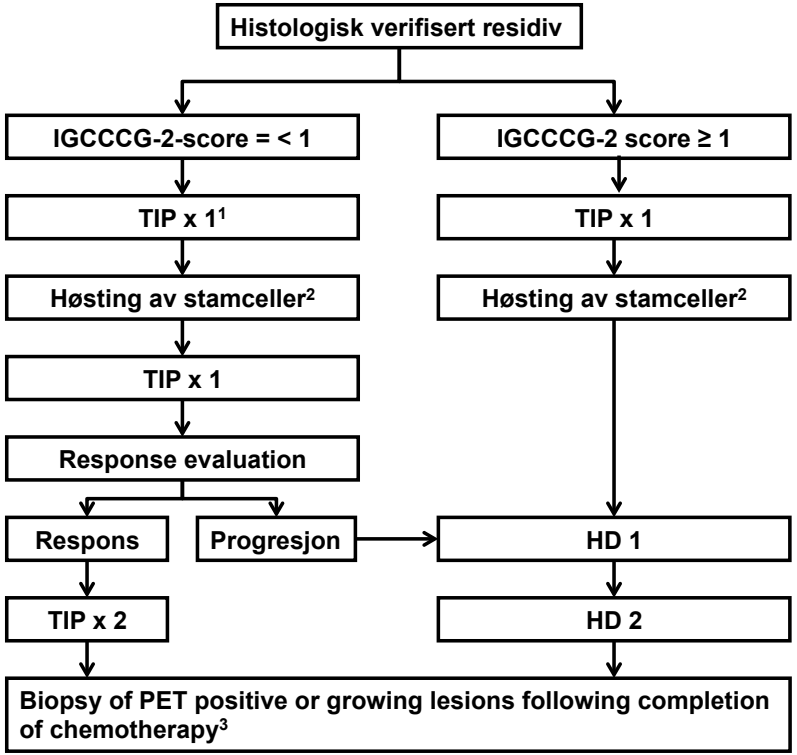
Marker t ½ forsinket:
AFP > 7 dager
ß-hCG > 3 dager

1: Høsting av stamceller
2: Kirugi:
- PR Mk-
- Mk+ og t½ ok
- Stabile, lett forhøyede markører (såkalt tail)

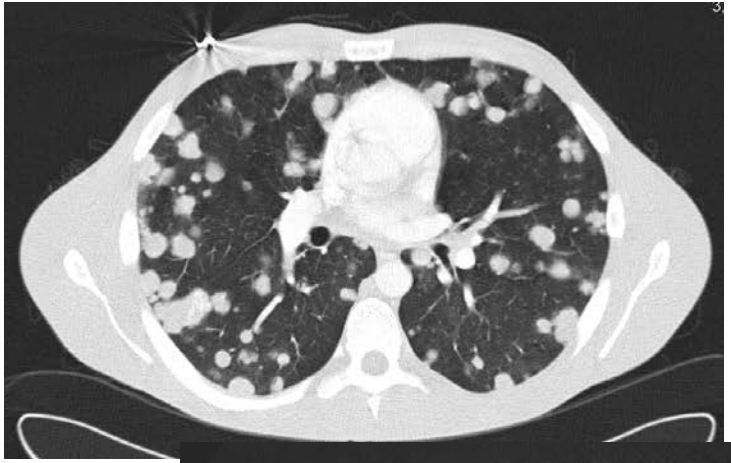
Ingen kirurgi
- CR
- PR Mk+ og t½ forsinket: TIP x 2 eller HD
- PD: Individuell behandling

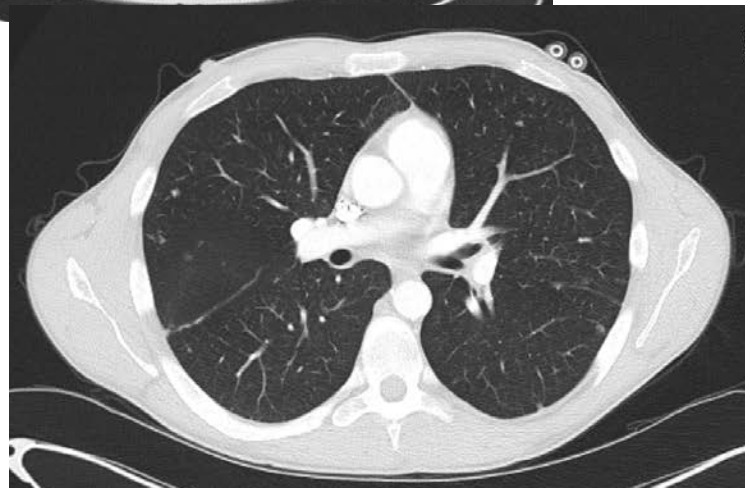
3: Individuell behandling for pasienter som tidligere har fått TIP

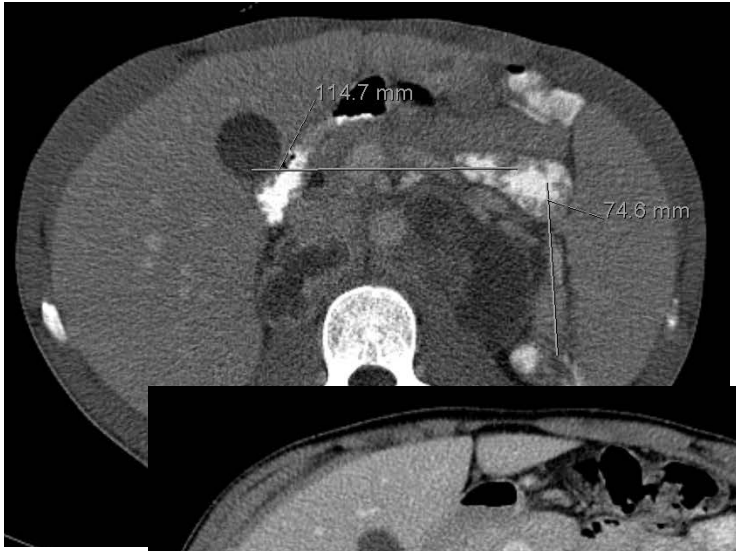
Flytskjema 5: Residivbehandling etter tidligere behandling for metastatisk sykdom

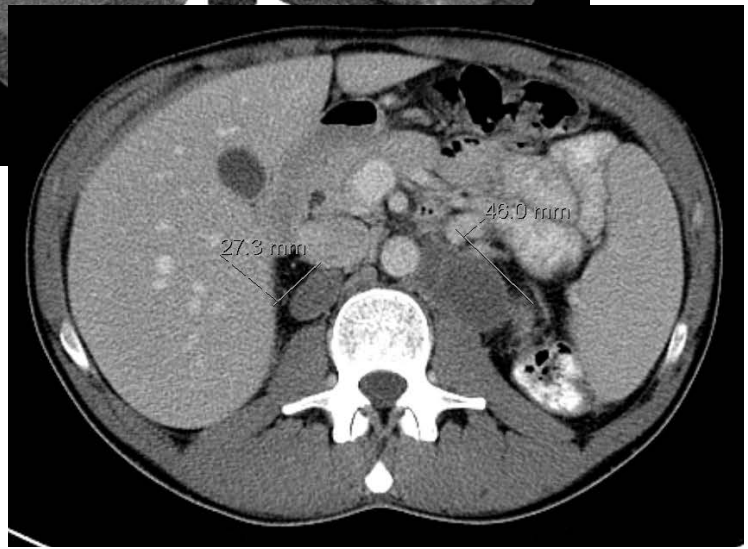


1: Ved små lokaliserte seminomresidiv kan strålebehandling være en behandlingsmulighet
2: Dersom høsting ikke tidligere er utført
3: Dersom funn av vital kreft, er kirurgi anbefalt behandling.






114.7 mm
74.6 mm


46.0 mm
27.3 mm

Metastasekirurgi etter kjemoterapi non-seminom

- Non-seminom

  RPLND ved restglandler > 1 cm.

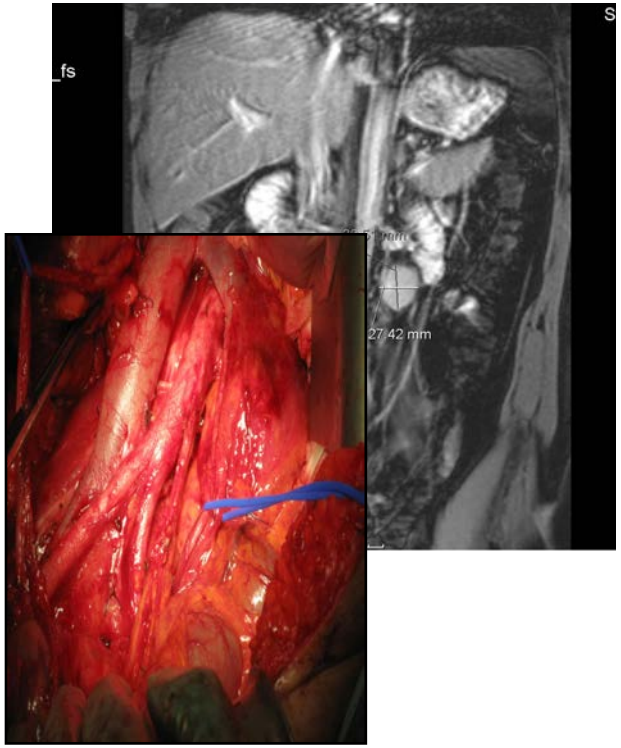
  1/3 av pasientene har vitalt tumorvev,

  1/3 har teratom, som må fjernes radikalt

  1/3 har kun nekrose/fibrose

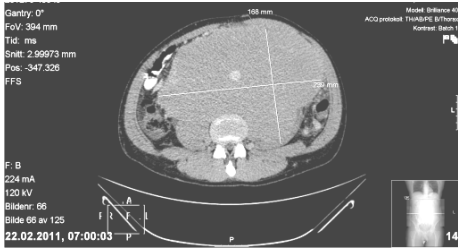
  Kirurgi ved øvrige restforandringer

  (lunge, lever, hjerne…)

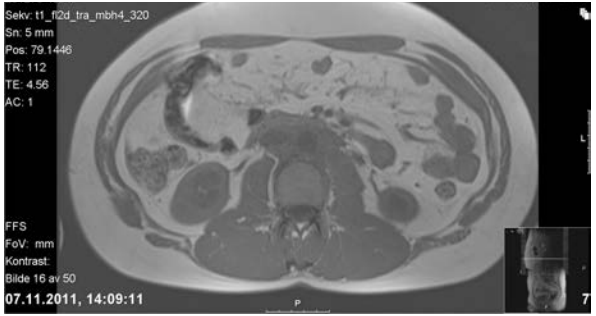


Etterkontroll ved testikkelkreft

- Ved recidiv ”alltid” kurativ behandlingsintensjon
- Hyppighet avhenger av
  Histologisk type
  Klinisk stadium
- I Norge sentralisert til regional onkologisk avdeling



- Etterkontroller **spesielt** viktig der man har ”valgt bort” adjuvant behandling



Etterkontroll ved testikkelkreft, prinsipper

- Regelmessige kontroller

  hver 3-6. mnd første 1-2 år

  hver 6-12 mnd til 5 år

  Årlig til 5-10 år

- Innhold
  - Klinisk status (obs gjennværende testis)
  - Rtg thorax
  - MR abd/bekken
  - Tumormarkører

"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."

After treatment – During follow-up

- Secondary cancer from medical imaging?
  - CT abdomen 10 mSv
  - CT abdomen /pelvis 14 mSv
  - CT whole body 20-25 mSv

- Abdominal imaging during follow-up
  - SWENOTECA CSI nonseminom:
    - 1998: 14 CT abdomen/pelvis
    - 2012: 6 MRI abdomen/pelvis

- MRI
  - No ionizing radiation

- Whole body PET-CT
  - Up to 32 mSv[1], i.e.0.032 Gy
    - Bladder 80 mSv

[1]Huang et al. Radiology 2009

Background radiation: 2.4 mSv

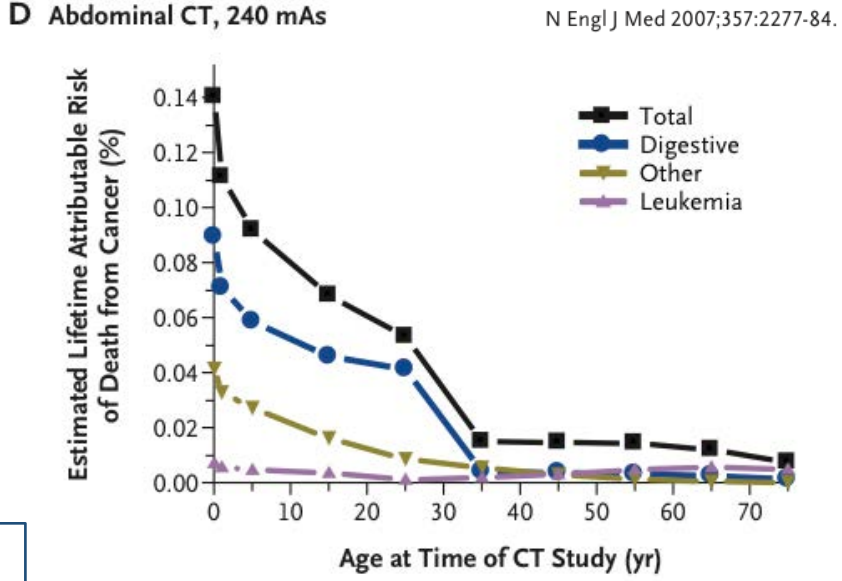
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Computed Tomography — An Increasing Source of Radiation Exposure

N Engl J Med 2007;357:2277-84.



Etterkontroller, eksempel metastatisk non-seminom

SWENOTECA IX

Follow-up schedule for seminoma patients

Name: _____ Civic registration number: _____
Orchiectomy, date: _____ side: right / left tumor size_____ growth in rete testis: yes/no
Date definitive staging: _____ Stage/prognostic group:_____ Date end of treatment: _____

This is a MINIMUM follow-up schedule.
FOLLOW-UP EVERY 3 MONTHS FOR INTERMEDIATE PROGNOSIS PATIENTS, AND PATIENTS WITH RESIDUAL TUMORS YEAR 1
Other examinations depending on primary metastatic locations, and/or any residual tumors.

Control type **Tm**: Tumor markers, AFP, β-HCG and LDH, (PLAP optional). *(List the patient for a telephone appointment)*
Control type **B**: Clinical examination, AFP, β-HCG, LDH, S-creatinine, (PLAP optional), **MRI of the retroperitoneum**/(abdominopelvic CT).
Control type **C**: Like B with addition of Testosterone, SHBG, LH, FSH. Chest X-ray for patients with primary metastatic disease.

Metabolic screening (lipids, fasting glucose, HbA1c), and blood pressure at 1-, 5- and 10-year visit.

Inform the Swedish patients at 1-, 5- and 10- year visit that a quality of life questionnaire will be sent out from RCC Syd, Sweden.

	B	**C**	**Check-ups** year 1
0	**6**	**12**	*Months from end of treatment*
	B	**B**	**Check-ups** year 2
12	**18**	**24**	*Months from end of treatment*
	Tm	**C**	**Check-ups** year 3
24	**30**	**36**	*Months from end of treatment*
	Tm	**B**	**Check-ups** year 4
36	**42**	**48**	*Months from end of treatment*
		C	**Check-ups** year 5
48		**60**	*Months from end of treatment*

Patients in CS I treated with RT: *only checkups for six years, and only abdominal imaging at the 2 yr check-up.*

Year 6 from end of treatment: Visit (clinical examination and Tm), radiology if residul tumours. Check-up type B if CS I.
Year 8 from end of treatment: Visit (clinical examination and Tm), radiology if residul tumours. Check-up type B if CS I.
Year 10 from end of treatment: Check-up type C. Patient care plan to be given to the patient (Sammanfattning av sjukdomsförlopp och behandling).
Ultrasound of contralateral testicle when clinically indicated.

2015-03-12

www.swenoteca.org

Etterkontroll ved testikkelkreft

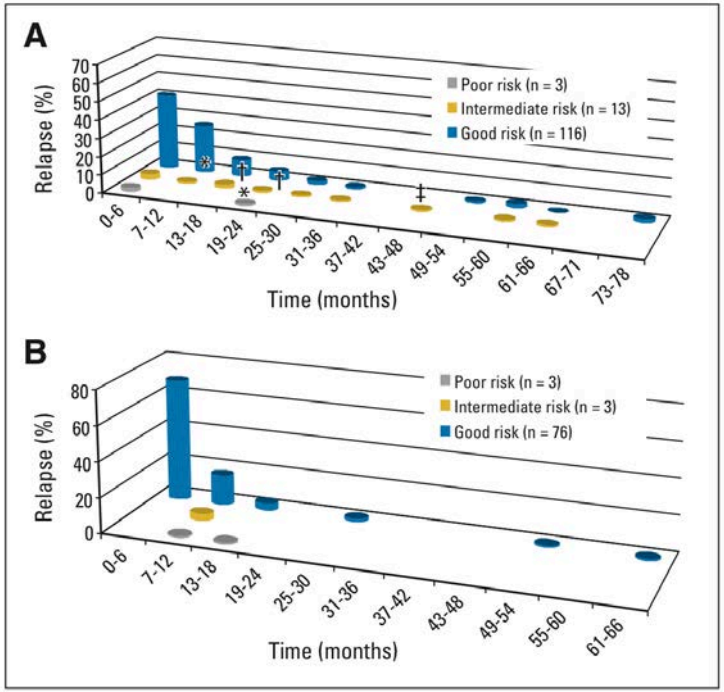
- De fleste residiv kommer innen 18 måneder
- Oftere sene residiv ved seminom
- 60 - 70% av residivene først retroperitonealt
- Ved nonseminom 60 - 70% forhøyet AFP/hCG v. residiv

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patterns of Relapse in Patients With Clinical Stage I Testicular Cancer Managed With Active Surveillance

Christian Kollmannsberger, Torgrim Tandstad, Philippe L. Bedard, Gabriella Cohn-Cedermark, Peter W. Chung, Michael A. Jewett, Tom Powles, Padraig R. Warde, Siamak Daneshmand, Andrew Protheroe, Scott Tyldesley, Peter C. Black, Kim Chi, Alan I. So, Malcom J. Moore, and Craig R. Nichols

Peter C. Black and Alan I. So, University of British Columbia, The Vancouver



Prognose ved testikkelkreft

- Kurasjonsrate ca. 95-97% totalt
- Klinisk stadium 1: Minst 98-99%, seminom og nonseminom
- Minst 90% kurasjon av alle med manifeste metastaser, men
- Prognosen ved svært utbredt sykdom fortsatt utfordring
- Største utfordring nå:

  Beholde høye kurasjonsrate

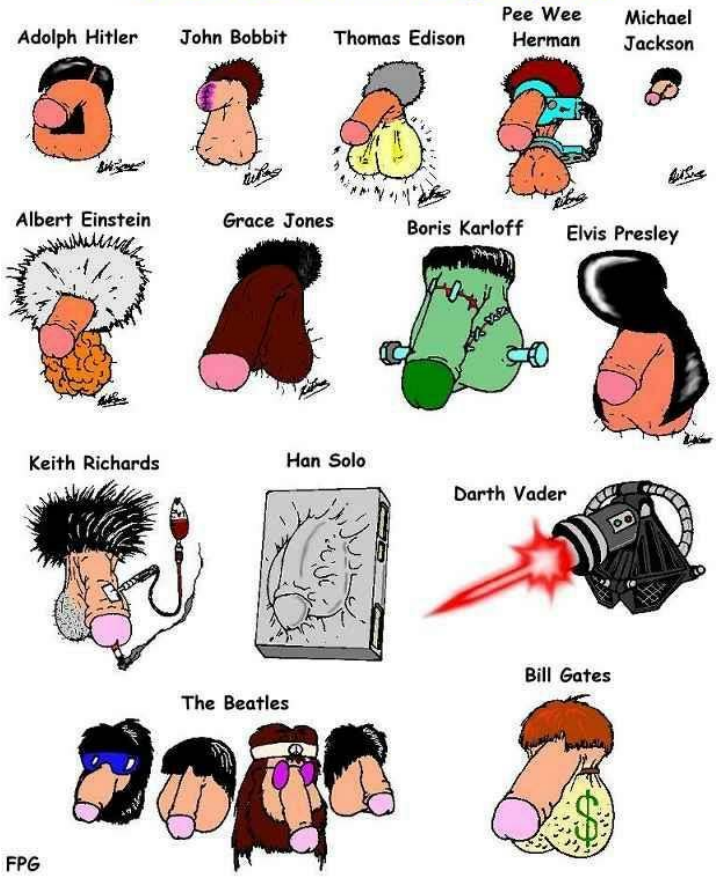
  Redusere risiko for langtidsbivirkninger

  Optimalisere behandling ved poor risk

Carcinoma in situ (CIS) testis

- Nesten alle tilfelle av invasiv germinalcelle-tumor i testis utgår fra CIS
- Ofte CIS i testis ved extragonadal germinacelletumor
- 2-5% CIS i begge testis ved cryptorchisme
- Ved CIS i kontralaterale testis utvikler 50% testiscancer i løpet av 5 år (?)
- CIS er strålefølsomt (16 – 20 Gy)
- Bør kontralaterale testis biopseres, og bestråles hvis CIS påvises???

Testicles of famous people...

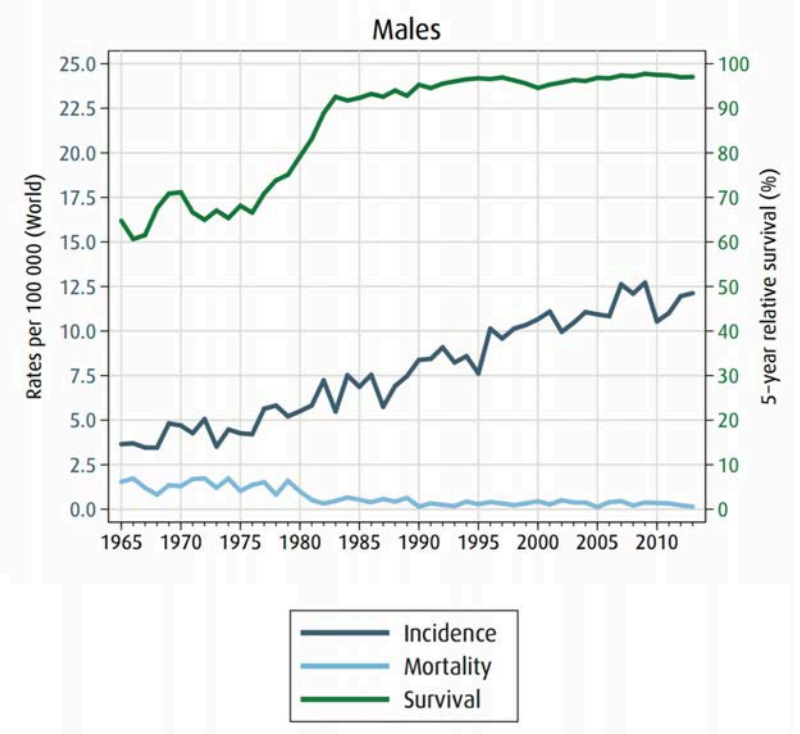


Why is long-term toxicity important in testicular cancer survivors (TCS)?

Very high cure rate

- CS I
  - 5 years OS: >98%[1,2]
- Metastatic
  - Nonseminoma: 5 years OS: >90%[3]
  - Seminoma: 5 years OS: >96%[2]

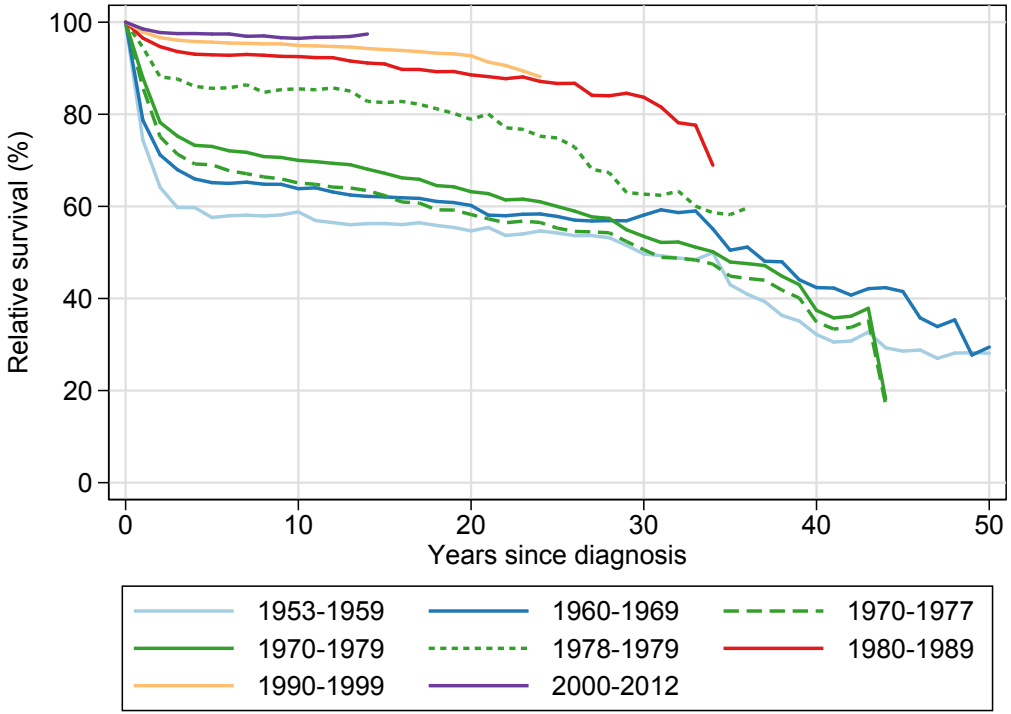
Long life-expectancy following treatment (40-70 years)



[1]Tandstad et al. JCO 2009; [2]Tandstad et al. JCO 2011; [3]Olofsson et al. JCO 2011

Cancer in Norway 2013, Cancer Registry of Norway, 2015

The Past - Consequences



- Relative survival of TCS (graph should be flat if survival was comparable with general population)
- Late effects affecting mortality does not show until 20+ of follow-up

Kvammen & Tandstad et al. (in press)

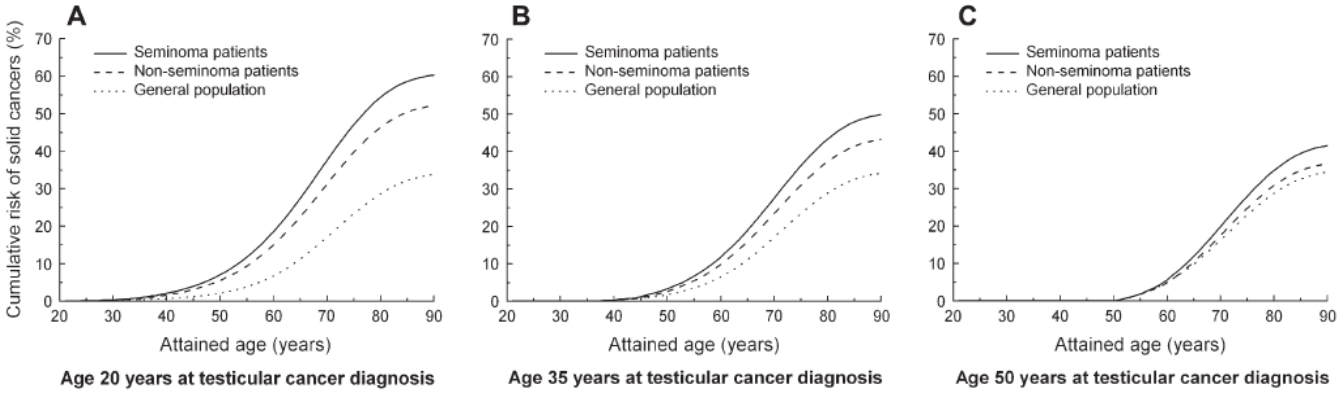
SWENOTECA
Swedish Norwegian Testicular Cancer Group

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

NTNU
Norwegian University of
Science and Technology

Torgrim Tandstad OnkoLiS
2016 Gardermoen 4. februar

Second cancers I

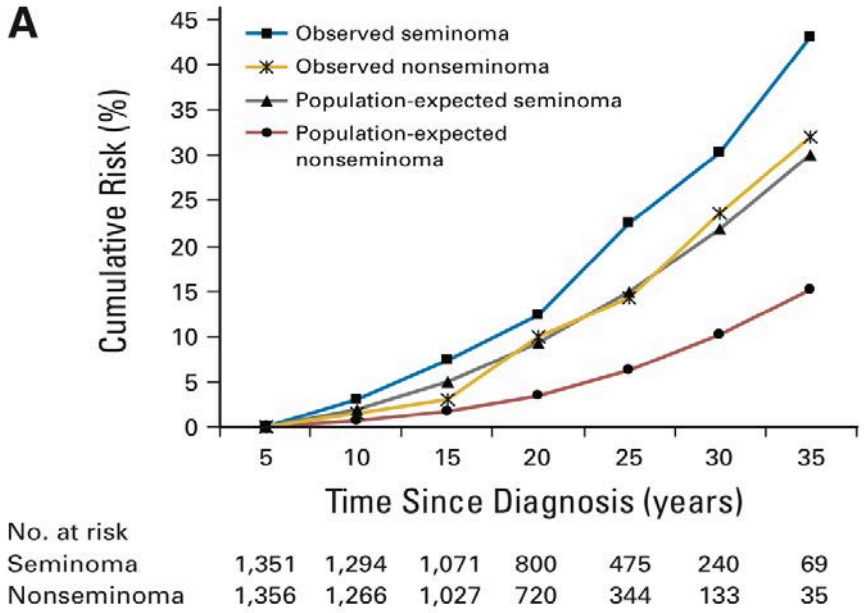


- 55-70% elevated risk for second cancers in TCS[1,2,3]
- Highest risk for secondary cancers in patients diagnosed with TC at a young age
- Long latency, 20-30 years
- Slightly higher risks for seminoma than non-seminoma patients

[1]Travis et al J Natl Cancer Inst 2005; [2]Richiardi et al Int J Cancer 2007; [3]Van den Belt-Dusebout et al JCO 2007

Second cancers II

- Treatment:[1,2]
  - RR at 2.0-2.6 after RT
  - RR at 1.8-2.1 after chemo
  - RR at 2.9-3.0 after RT/chemo
- Fung et al:[3]
  - Metastatic nonseminoma, modern treatment chemotherapy (55% treated after 2000)
  - No increased risk after surgery
  - SIR 1.43 after chemotherapy
  - Median time 12.5 y (short follow-up)

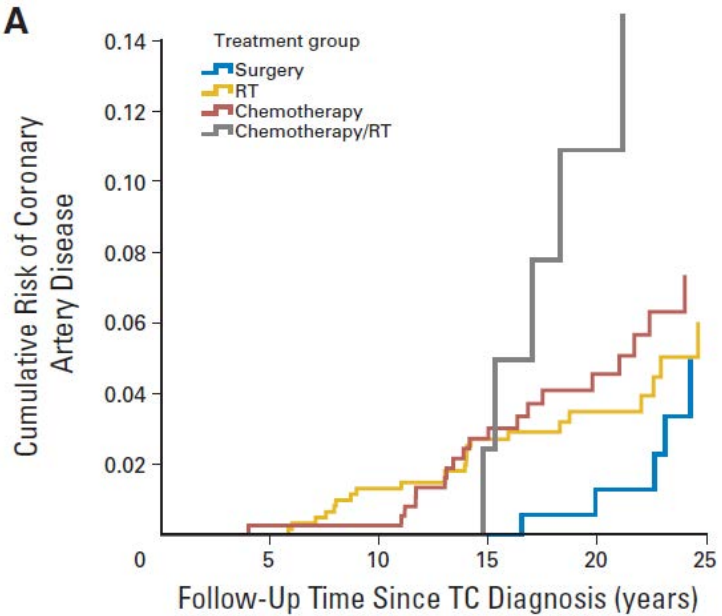


[1]Travis et al J Natl Cancer Inst 2005; [2]Van den Belt-Dusebout et al JCO 2007; [3]Fung et al JCO 2013

Cardiovascular disease (CVD)

- Coronary artery disease (stroke and peripheral artery disease)
- Typically develops several years after treatment
- Increased risk after RT or chemotherapy
- Combination of RT and chemotherapy yields the highest risk

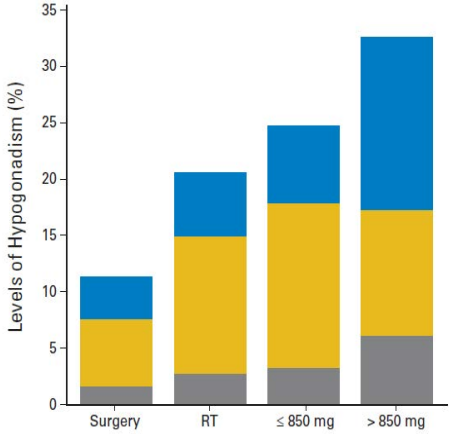
Treatment	Relative R	Absolute R[3]
Surgery	1[1,2,3]	2.5%
RT	2.1-2.4[1,3]	6.4%
Chemotherapy	1.9-2.6[1,2,3]	5.6%
RT/chemo	2.3-4.8[1,2,3]	17%

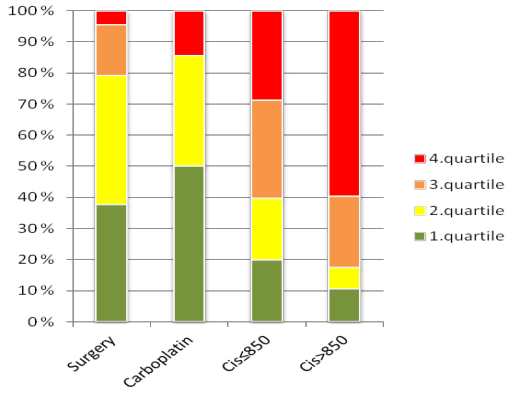


[1]Huddart et al JCO 2003; [2]Van den Belt-Dusebout et al JCO 2006; [3]Haugnes et al JCO 2010

CVD Mechanisms?

- Predictors for CVD[1]
  - Hypertension
  - Obesity
  - Hypercholesterolemia
  - Hypogonadism
- Residual serum platinum detectable decades following treatment[2]
  - Continuous endothelial stimulation?
- Long term platinum associated with hypogonadism, hypercholesterolemia, hypertension and paraesthesia[3]





[1]Haugnes et al. JCO 2009; [2]Hjelle et al. Anticancer Res 2015; [3]Boer et al. Ann Oncol 2015

Pulmonary disease

- The risk of death due to respiratory disease is nearly 3-fold after chemotherapy compared to the normal population[1]
- Decreased pulmonary function in patients receiving high doses of cisplatin or pulmonary surgery yields the highest risk[2]

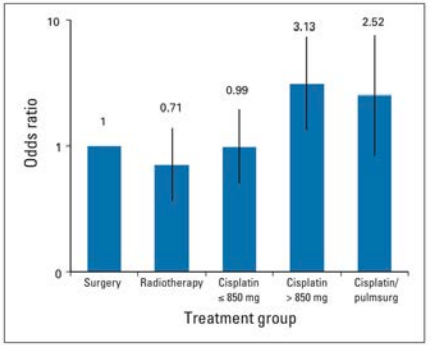


Fig 2. Odds ratios (OR) for having a restrictive lung disease in different treatment groups when the surgery group is used as reference. Bars indicate 95% CIs for ORs.

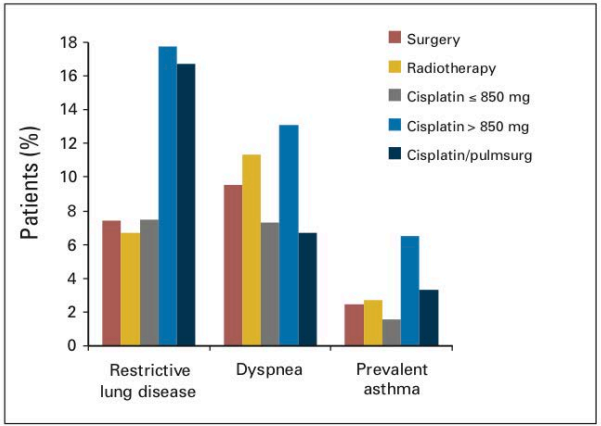


Fig 1. Percentage of patients with restrictive lung disease, dyspnea, and prevalent asthma at follow-up according to treatment group.

[1]Fossa et al. JNCI 2007; [2]Haugnes et al. JCO 2009

Fatigue

- More prevalent in TCS than in general population (16% vs. 10%)
  - Survey I: Median follow-up of 12 years
  - 16% prevalence of fatigue
- Increases with additional follow-up
  - Survey II: Median follow-up of 20 years
  - 27% prevalence of fatigue
- Associated with physical inactivity, low testosterone, neuropathy, Raynaud´s phenomenon, depression and anxiety

Fatigue, Anxiety, and Depression in Long-Term Survivors of Testicular Cancer

By Sophie D. Fossà, Alv A. Dahl, and Jon H. Loge

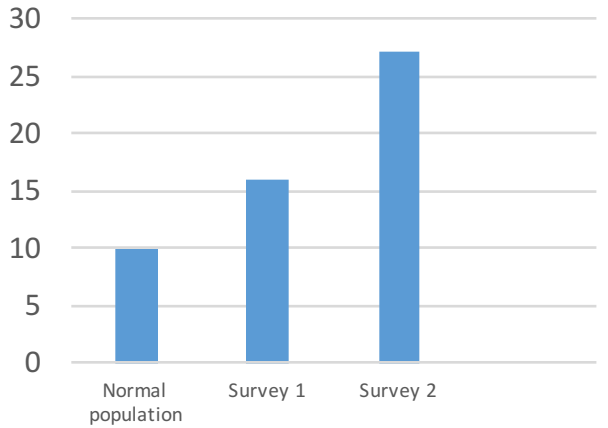
Annals of Oncology

original articles

Annals of Oncology 26: 2133–2140, 2015
doi:10.1093/annonc/mdv328
Published online 11 August 2015

Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: increasing prevalence and risk factors

M. Sprauten[1], H. S. Haugnes[2,3], M. Brydøy[4], C. Kiserud[1], T. Tandstad[5], T. Bjøro[6,7], J. Bjerner[8], M. Cvancarova[1], S. D. Fossà[1] & J. Oldenburg[9,10]*



Other toxicities

- Neurotoxicity
- Ototoxicity
- Nephrotoxicity
- Fertility

Long-Term Complications After Testicular Cancer Treatment

JANUARY 8, 2016

By Jan Oldenburg, MD, PhD; Hege S. Haugnes, MD, PhD; Silke Gillessen, MD; and Torgrim Tandstad, MD, PhD

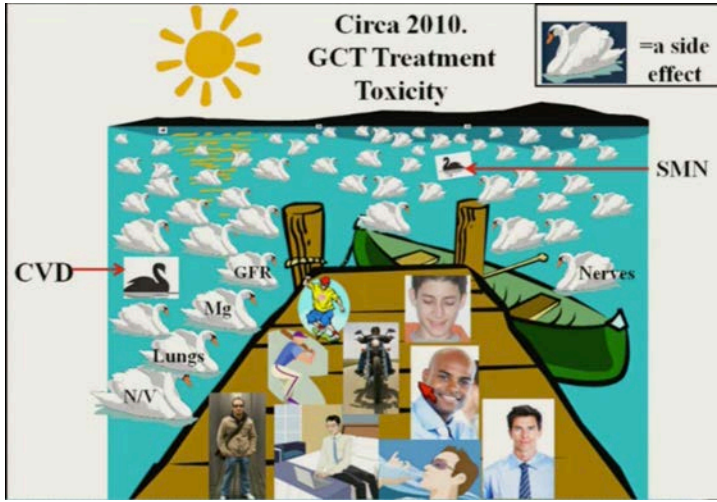
Article Highlights

- *Survivorship research and long-term side effects are areas of particular importance for testicular cancer survivors because of the high cure rate and the young median age at diagnosis.*
- *Long-term side effects in this population include secondary malignant neoplasms, pulmonary complications, cardiovascular toxicity, and fertility issues.*
- *Preventive measures, such as smoking cessation, a healthy diet, and an active lifestyle, may play an important role in reducing the risk of several treatment-related toxicities.*

Issues with the current knowledge

- ”Old” data
  - Retrospective
  - Based on patients treated years ago (even decades ago)
  - Few patients with metastatic disease received less than 4 courses of cisplatin-based chemotherapy
- Sparse data on long-term toxicity of adjuvant chemotherapy in stage I TC
- But
  - Best data available
  - Primum non nocere

- Long-term toxicity of testicular cancer impacts survival for remainder of life
- In good/intermediate prognosis metastatic GCT the risk of death due to long-term toxicity may be higher than the risk of dying due to testicular cancer
- Not only ”black swan” events, but are relatively frequent



Bosl G: Educational Session, ASCO Annual Meeting 2010

Prevention of late effects – Clinical implications

- **Long-term toxicity is related to the burden of treatment**

- **Minimize burden of treatment**
  - Avoid dual therapy (chemotherapy/radiotherapy)
  - Always know what you treat
  - Reduce risk for relapse

Do not compromise cure!!!!

Lege Artis 1st century BC. Staatliche Museen zu Berlin, Antikensammlung

CS I?

- Slightly enlarged lymph nodes are often not cancer

- Difference between 3 course of BEP or surveillance/one adjuvant course of chemotherapy

Annals of Oncology 1: 281–288, 1990.

Original article

Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer

Value of pre- and post-orchiectomy serum tumor marker information in prediction of retroperitoneal lymph node metastases

O. Klepp, P. Flodgren, H. Maartman-Moe, C.E. Lindholm, B. Unsgaard, H. Teigum, S.D. Fosså & E. Paus, for the Swedish-Norwegian Testicular Cancer Project (SWENOTECA)

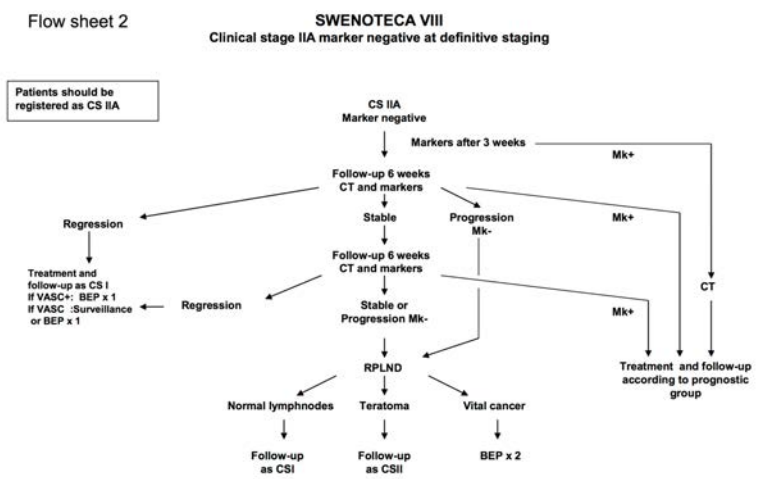
Table 2. **Distribution of early clinical stages (CS) and result of pathological staging (PS) of the retroperitoneum.**

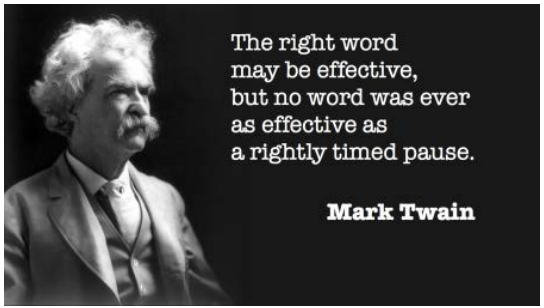
CS	All patients included (%)*	Evaluable for PS	PS2 cases (% of evaluable)
CS1	295 (50.2)	279	75 (26.9)
CS1Mk+	32 (5.4)	28	28 (100)
CS2A	43 (7.3)	38	25 (65.8)
Early stages	370 (62.9)	345	128 (37.1)

*Per cent of all the 588 cases (including advanced stages) in the SWENOTECA study.

Delayed staging

- CS I nonseminoma[1]
  - Second staging procedure 6-8 weeks after orchiectomy
- CS IIA Mk- nonseminoma[1]
  - Observation algorithm
- CS IIA Mk- seminoma[2]
  - Second staging 8 weeks after orchiectomy
  - Treatment is not initiated unless metastatic disease is unequivocal, (e.g. growth, rising markers or positive biopsy)

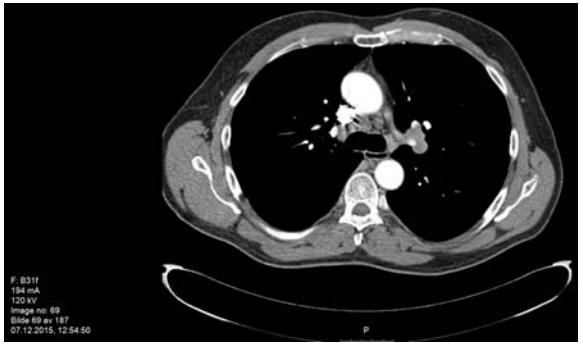


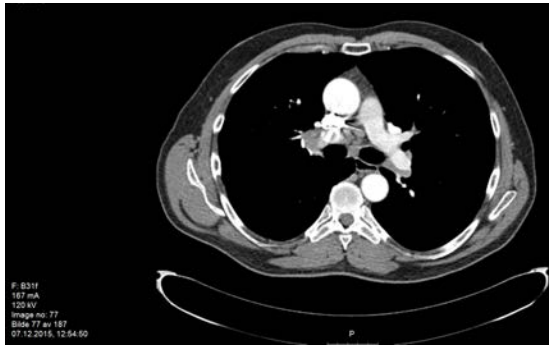


[1]SWENOTECA VIII; [2]SWENOTECA IX (www.swenoteca.org)

Correct stage and prognostic group

- Sarcoidosis
  - Relatively frequent finding
  - Never treat patients with pathologically lymph nodes only above the diaphragm without histological verification
  - Unexpected distribution of lymph nodes?
- IGCCCG prognostic group[1]
  - Good: BEP x 3
  - Intermediate/poor: BEP x 4





Nonseminoma "Intermediate markers"

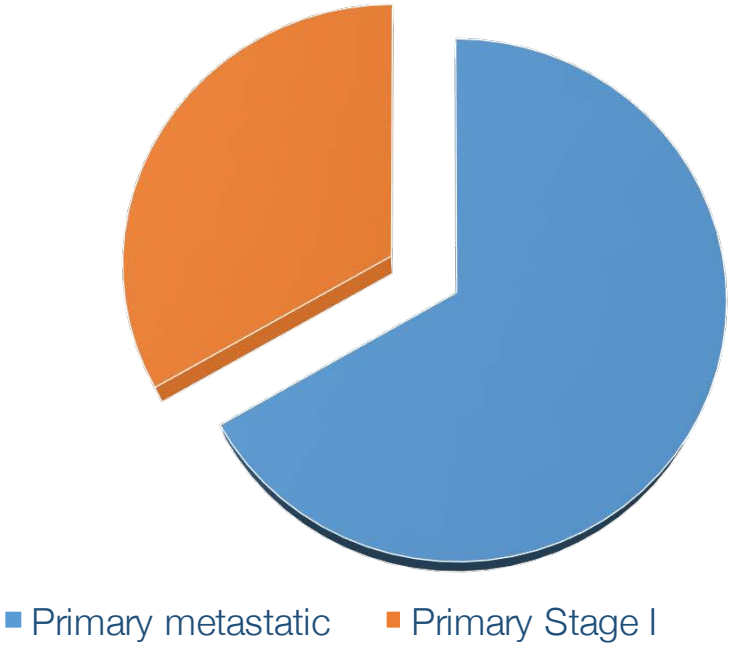
- AFP > 1000 ng/ml and <10 000 or
- hCG > 5000 iu/l and < 50 000
- (LDH > 1.5 x N and < 10 x N)

Prognostic group should always be based on markers at start of chemotherapy, i.e. always after orchiectomy

[1]IGCCCG, JCO 1997

Patients needing therapy for metastatic disease, i.e. BEP x 3 or more

- Metastatic nonseminoma and seminoma
  - 95% chemotherapy
- Relapsed CS I patients (non risk-adapted)
  - Nonseminoma 25%
  - Seminoma 15%
- Reducing the number of patients in need of full chemotherapy



Risk-adapted treatment CS I

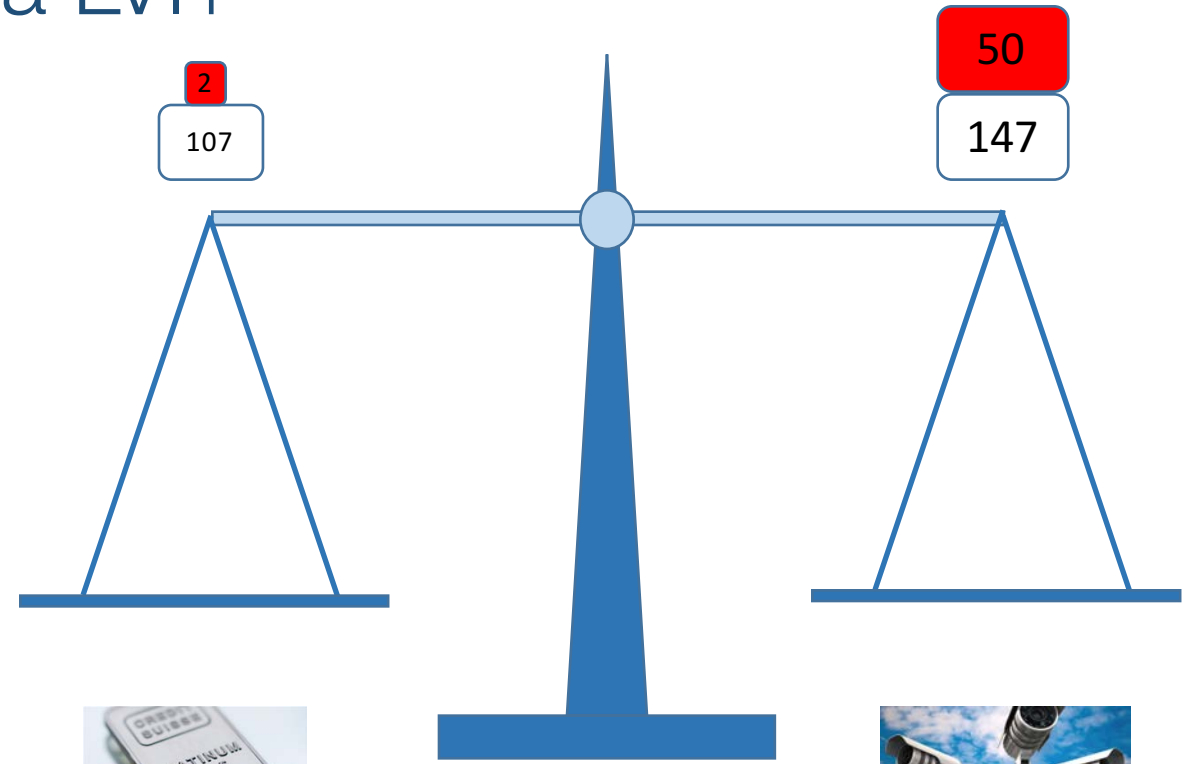
- Nonseminoma[1-4]
  - LVI+: 50%
  - LVI- : 15%

- Seminoma[5]
  - Stromal invasion rete testis
  - Tumor diameter >4cm
  - 0 risk factor: 5%
  - 1-2 risk factors: 20%

[1]Daugaard et al; AMPIS 2003, [2]Tandstad et al; JCO 2009, [3]Kollmannsberger et al; Ann Onc 2009, [4]Sturgeon et al; Eur Uro 2010, [5]Tandstad et al; In press 2016

CS I nonseminoma LVI+

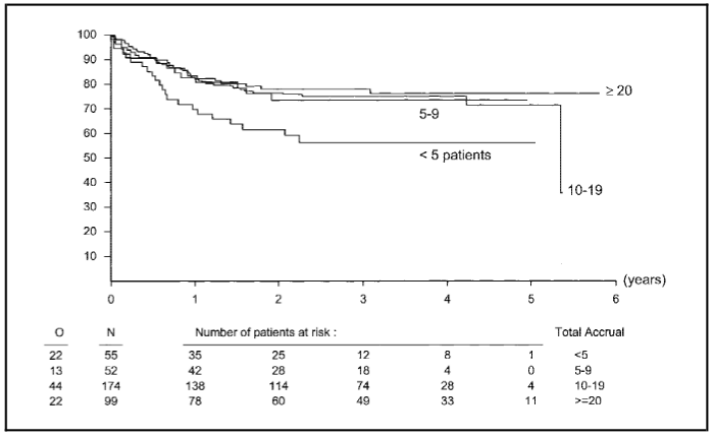
- BEP x 1
  - All receive chemotherapy
  - only 2% are in need of salvage chemotherapy
- Surveillance
  - Only patients relapsing receive chemotherapy
  - ~50% need salvage chemotherapy
- Overtreat 50% with one course of BEP, or overtreat 50% with three courses of BEP



Experience or cooperation

Impact of the Treating Institution on Survival of Patients With "Poor-Prognosis" Metastatic Nonseminoma

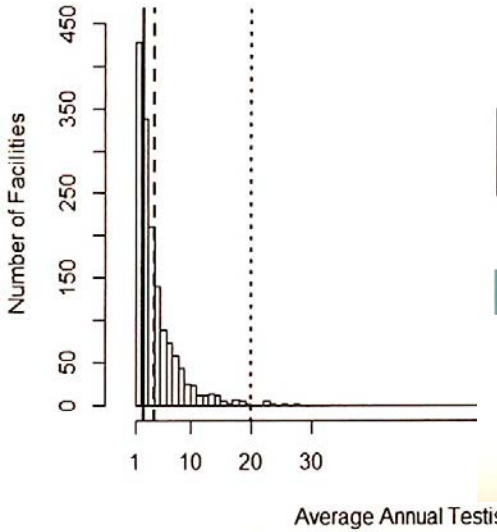
Laurence Collette, Richard J. Sylvester, Sally P. Stenning, Sophie D. Fossa, Graham M. Mead, Ronald de Wit, Pieter H. M. de Mulder, Niels Neymark, Eric Lallemand, Stanley B. Kaye

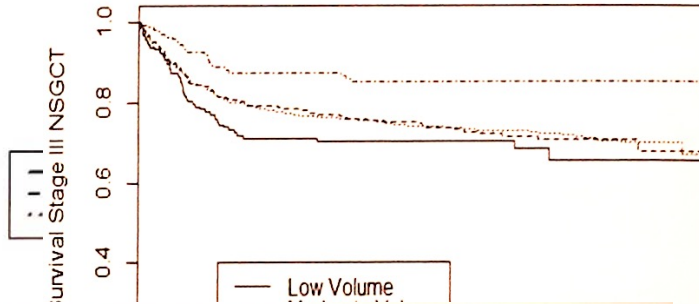


High annual hospital volume is associated with improved overall survival in clinical stage III non-seminoma testicular cancer: Results from the National Cancer Data Base (1998-2011)

Claudio Jeldres[1,2,3], Khanh Pham[1,2,3], Sia Daneshmand[3,4], Christian Kollmannsberger[3,5,6], Brandon Hayes Lattin[3,7], Erika Wolff[1], Katherine Odem-Davis[8], Christopher R. Porter[1,2,3] and Craig R. Nichols[2,3,7]

[1]Section of Urology and Renal Transplantation and [2]Multidisciplinary Testicular Cancer Program, Virginia Mason Medical Center, Seattle, WA; [3]SWOG Genitourinary and Adolescent and Young Adult Oncology Committees; [4]Department of Urology, University of Southern California Norris Cancer Center, Los Angeles, CA; [5]Department of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC; [6]Testicular Cancer Commons; [7]Division of Hematology/Oncology, Oregon Health and Sciences University, Portland, OR; [8]Center for Biomedical Statistics, Seattle, WA





CONCLUSIONS

93% of patients with clinical stage III non-seminoma in the US are treated facilities with annual hospital volumes of ≤20 cases/year.

Hospitals with an annual hospital volume of >20 case/year exhibit the best overall survival rates.

Further investigation of centralization of care to improve outcomes in patients with clinical stage III non-seminoma is warranted.

Cooperative Groups

- Management program
- Continuous quality improvement
- Low threshold peer network

Life style

- Lifestyle is a modifiable variable
  - Smoking
  - Healthy diet
  - Active lifestyle

- Long term follow-up
  - Oncologist or GP?
  - Treat late effects such as hypogonadism and hypertension

- Patients care plans
  - e.g. www.swenoteca.org

Patient care plan to be delivered to the patient and general practitioner at termination of uro-oncological follow-up

You were operated year_____for testicular cancer, subtype:

□ Seminoma □ Non-seminoma

□ No dissemination of disease were confirmed
□ Dissemination of disease were confirmed to_____

Additional treatment
□ No
□ Chemotherapy (number of cycles :____)
□ Radiotherapy
□ Surgery in addition to removal of the testicle_____

Date for last follow-up:_____ Hospital:_____
Responsible doctor:_____Telephone:_____

You have completed the last oncological follow-up after previous treatment for testicular cancer. The risk for relapse of the disease is very low, and you will be taken care of at your general practitioner in the future. This patient care plan should be shown in case of future contact with the health services.

You are at risk of a new tumor in the remaining testicle and regular self-exams are important. Further, another cancer type may develop after treatment with chemotherapy and/or radiotherapy. Some side-effects from testicular cancer treatment may emerge several years after treatment, e.g. sub-normal values of male sex hormone (testosterone). In addition, men previously treated with chemotherapy and/or radiotherapy have an increased risk for hypertension, overweight, elevated cholesterol levels and cardiovascular disease. Thus, it is advisable to keep away from smoking, avoid overweight and exercise regularly.

We recommend that the following are controlled by the general practitioner:

1) Blood pressure, height, weight, waist circumference
2) Blood samples including fasting lipids (total cholesterol, HDL and LDL-cholesterol, triglycerides), fasting glucose and hormones (testosterone, FSH and LH)
3) Clinical examination in case of any symptoms

The purpose of these controls is to prevent, identify and possibly treat risk factors which might lead to complications, e.g. cardiovascular disease. We recommend controls every 2.-3. years. If abnormal values are detected at these controls, further follow-up at the general practitioner is initiated.

Conclusions

- TCS have a lifelong increased risk of dying from long term toxicity of treatment

- Long term toxicity is related to treatment burden
  - Correct treatment to correct stage administered by the correct physician (i.e. experienced physician)
  - Need of more accurate prognostic factors to predict relapse (microRNA?)

- Follow-up
  - Survivorship care plans (Does is work?)
  - Life style interventions
  - Imaging (MRI?)