



Faculty of Health and Medical Sciences



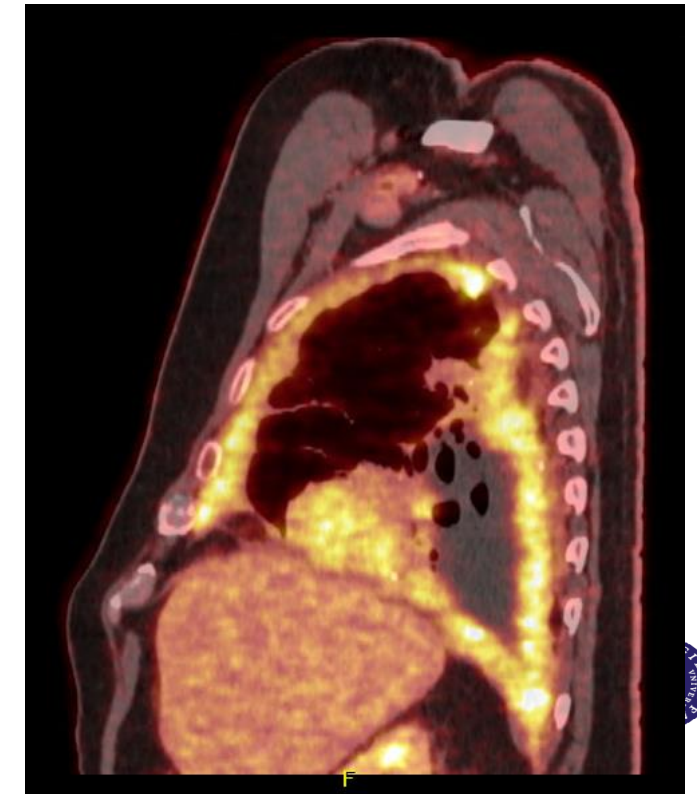
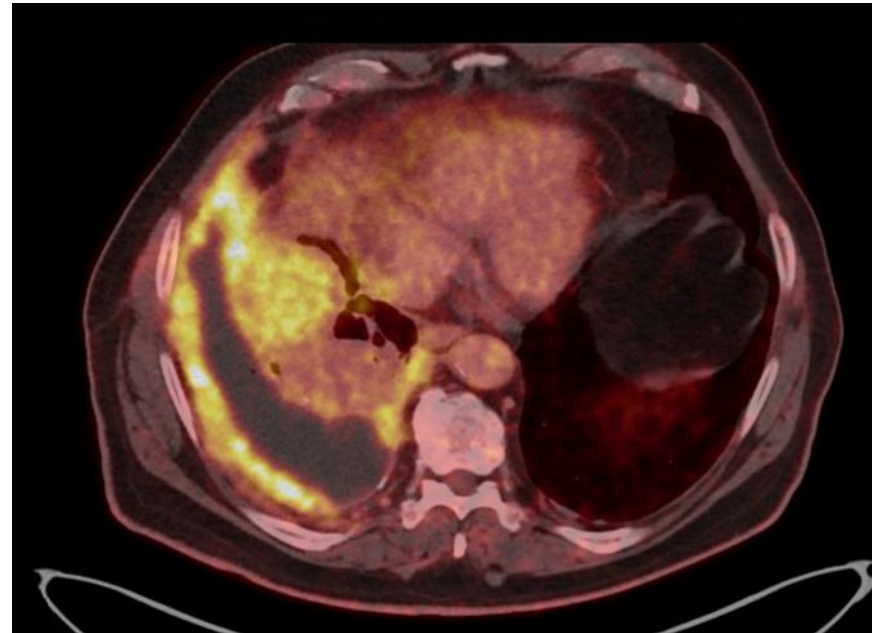
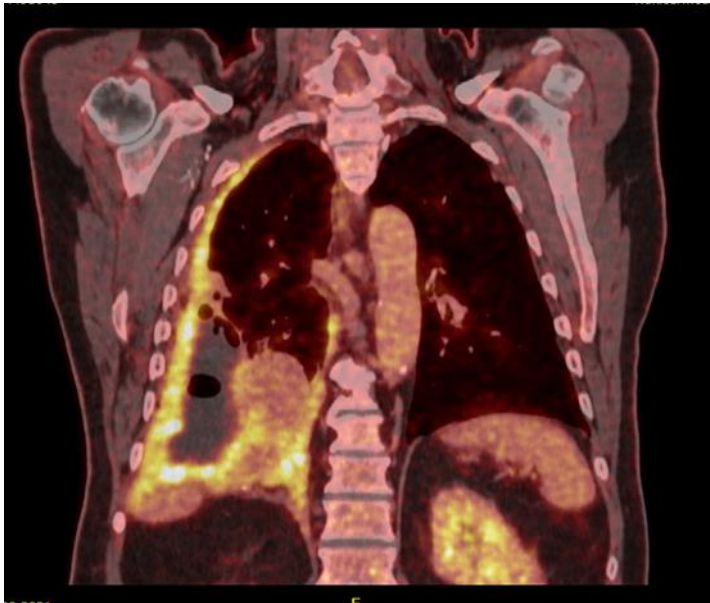
Malignt Pleuralt Mesothelioma

Jens Benn Sørensen
Overlæge, dr.med. Klinisk Lektor
Jens.benn.soerensen@region.dk



76 årig patient , Asbest eksponeret (VVS)

Malignt Pleuralt Mesotheliom dxt, Sarcomatoid type, T4N0M0



ASBESTOS



CHRYSOTILE



AMOSITE



CROCIDOLITE



TREMOLITE



ACTINOLITE



ANTHOPHYLLITE



ASBESTOS

**CANCER & LUNG
DISEASE HAZARD**

**AUTHORIZED
PERSONNEL ONLY**

**RESPIRATORS AND
PROTECTIVE CLOTHING
AREA REQUIRED
IN THIS AREA**

ALL OVER AMERICA...
**MORE SCIENTISTS AND EDUCATORS
 SMOKE KENT with the MICRONITE FILTER**
 than any other cigarette!

BRAND PREFERENCE OF AMERICAN SCIENTISTS WHO SMOKE	
KENT	15.3%
BRAND 'A'	10.8%
BRAND 'C'	7.8%
BRAND 'F'	7.4%
BRAND 'W'	7.3%

BRAND PREFERENCE OF AMERICAN EDUCATORS WHO SMOKE	
KENT	20.2%
BRAND 'C'	8.0%
BRAND 'W'	7.7%
BRAND 'A'	7.7%
BRAND 'F'	7.0%

KENT
 CIGARETTES
 NEW
 EXCLUSIVE MICRONITE FILTER
 KING SIZE

REGULAR SIZE, KING SIZE
 OR CRUSH-PROOF BOX

For good smoking taste,
 it makes good sense to smoke **KENT**

A PRODUCT OF P. LORILLARD COMPANY • FIRST WITH THE FINEST CIGARETTES • THROUGH LORILLARD RESEARCH © 1960, P. LORILLARD CO.

1950'ties

Today



Risikogrupper

Indånding af asbestfibre velkendt årsag til lungehindekræft.

Globalt vurderes det, at ca. 80-90 % af tilfældene af lungehindekræft skyldes asbesteksposition

2/3 skønnes relateret til erhvervsmæssig asbesteksponering

Hyppigere hos mænd end hos kvinder (ratio 5:1)

Tobaksrygning har ingen betydning for udviklingen af lungehindekræft.



Asbestos Ban Nordic Countries

Sverige midt 1970'erne

Island 1982

Norge 1983

Finland ??

DK forbud implementeret i flere tempi:

- 1972 forbudt at bruge asbest eller asbestholdige materialer til termisk-, støj- og fugtisolering.
- 1980 helt forbudt at bruge asbest, bortset fra i tagbeklædning, friktionsbelægninger, pakningsmaterialer og materialer til at fore f.eks. kuglelejer med.
- 1986 skærpet, må kun bruges i eternitbølgepladerne samt pakningsmaterialer og friktionsbelægninger.
- 1988 stoppede al anvendelse af asbest.

Men eksponering kan fremdeles ske da asbest fortsat findes fuldt lovligt mange steder (gamle tagplader, installationer isoleret med asbest mm).



Malignant Mesothelioma

Malignant Mesotheliomas:

Pleural 85%

Peritoneal 15%

Pericardial ???

Tunica vaginalis testis:

Rare (DK 2-3 cases/year)

Current status DK

Rare Disease, DK 168 New Cases/year 2018 (pop. 5.7 Million)

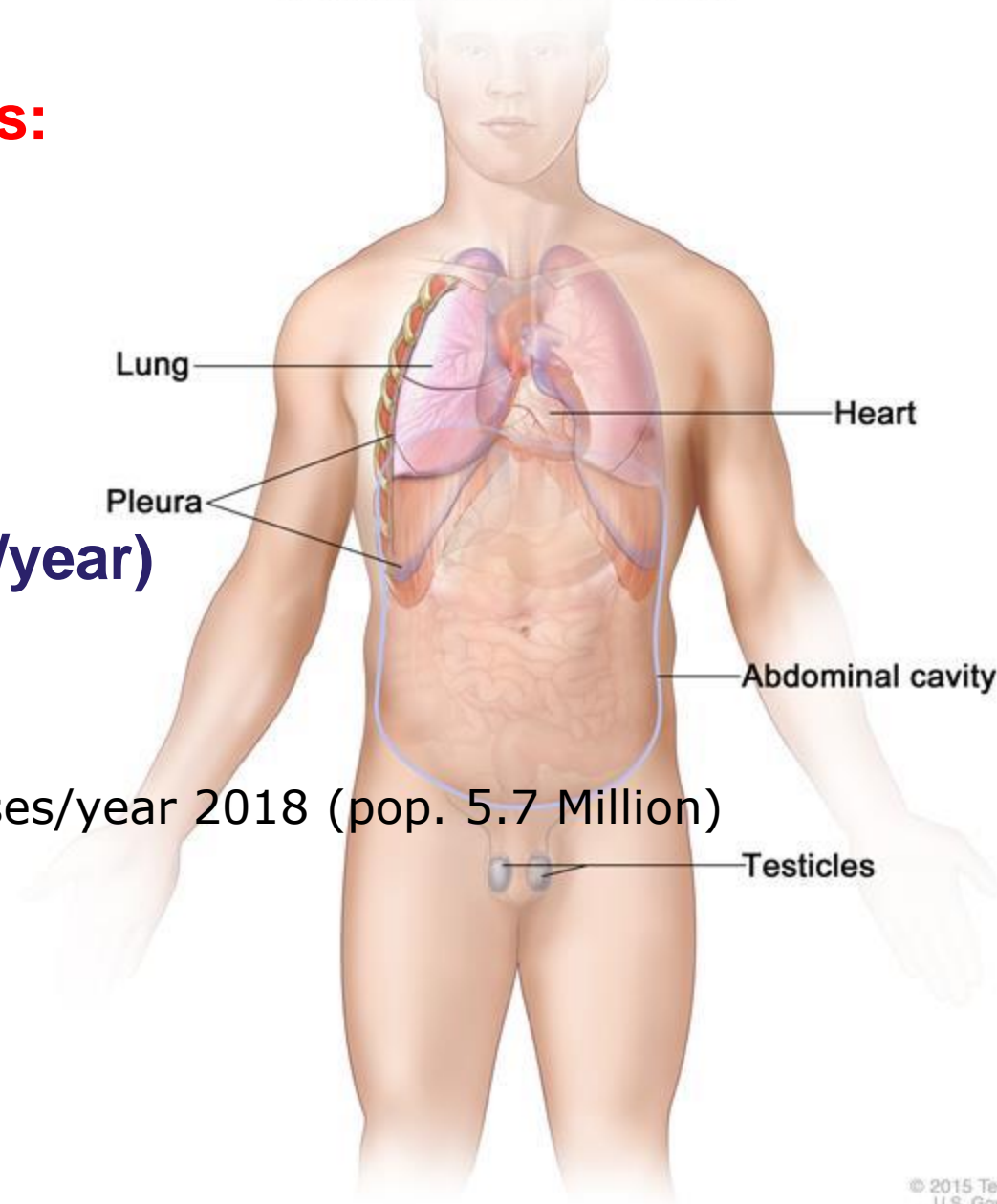
Pleural 140

Peritoneal 25

Pericardium ???

Tunica vaginalis testis 3

Ref.: Nordcan May 2020



	Male	Female
Number of new cases per year (incidence 2015-2019)	121	24
Proportion of all cancers (%)	0.5	0.1
Proportion of all cancers except non-melanoma skin (%)	0.6	0.1
Risk of getting the disease before age 75 (%)	0.2	0.0
Age-standardized rate (Nordic)	3.9	0.7
– Estimated annual change latest 10 years (%)	-0.1	0.4
Number of deaths per year (2015-2019)	89	22
Proportion of all cancer deaths (%)	1.1	0.3
Risk of dying from the disease before age 75 (%)	0.1	0.0
Age-standardized rate (Nordic)	3.0	0.6
– Estimated annual change latest 10 years (%)	-1.7	0.7
Persons living with the diagnosis at the end of 2019 (prevalence)	227	46
Number of persons living with the diagnosis per 100 000	7.8	1.6
Relative survival (%) with [95% CI] (2015-2019)		
1-year	62.2 [57.0-66.9]	62.4 [50.9-71.9]
5-year	14.1 [10.2-18.5]	11.3 [5.4-19.7]

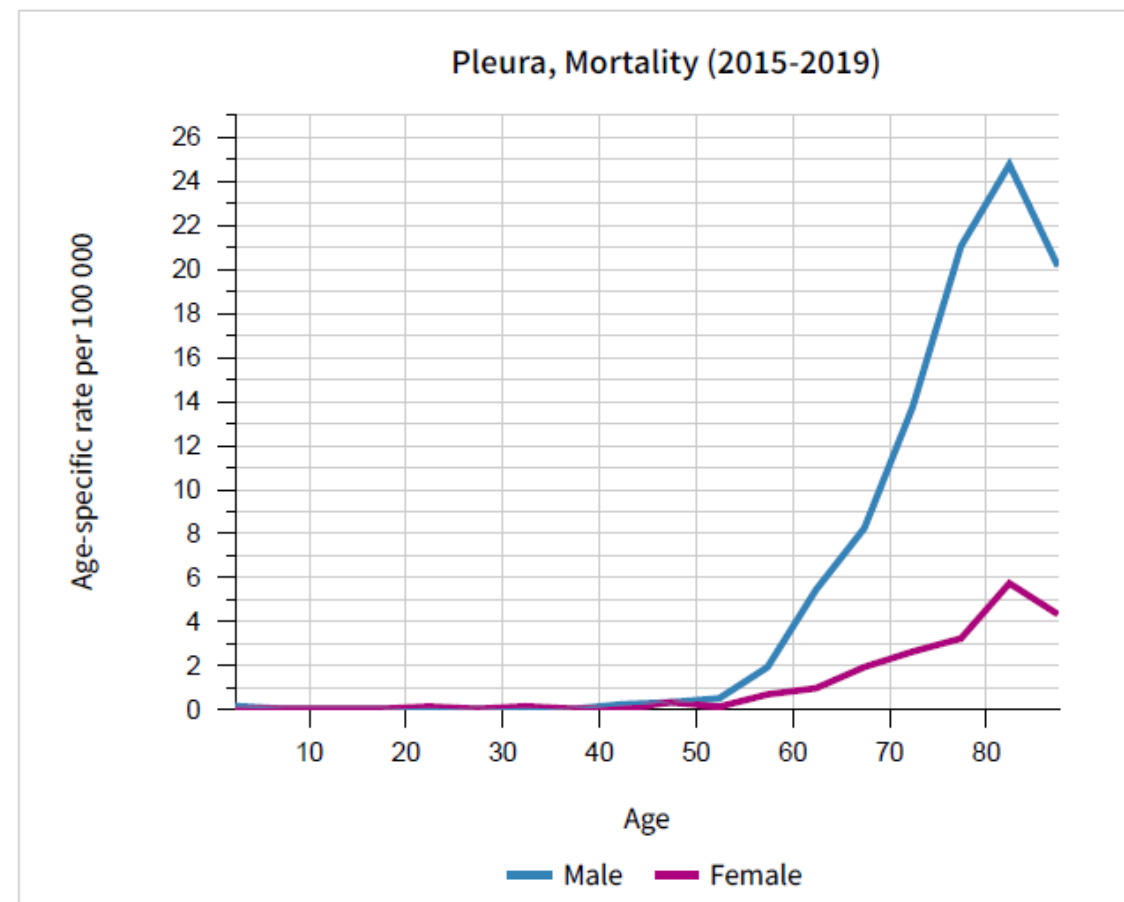
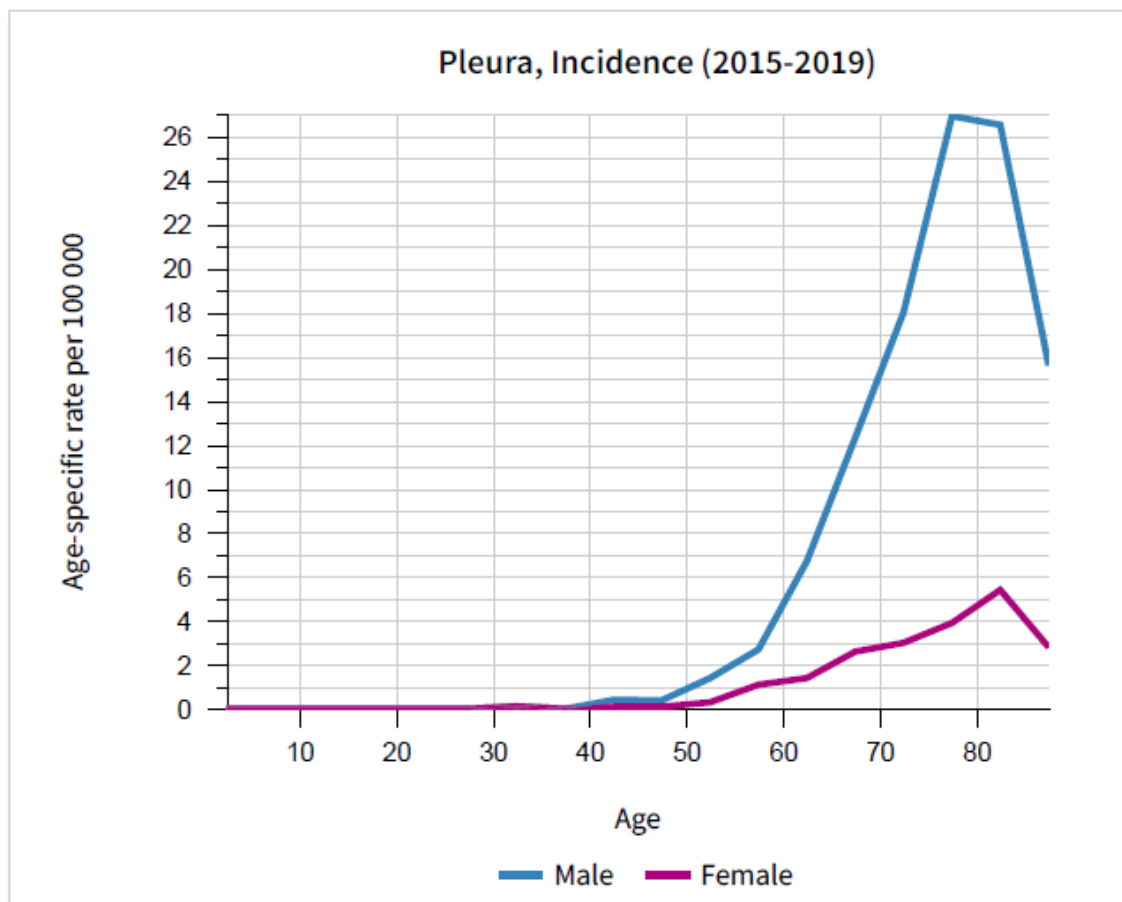
Denmark

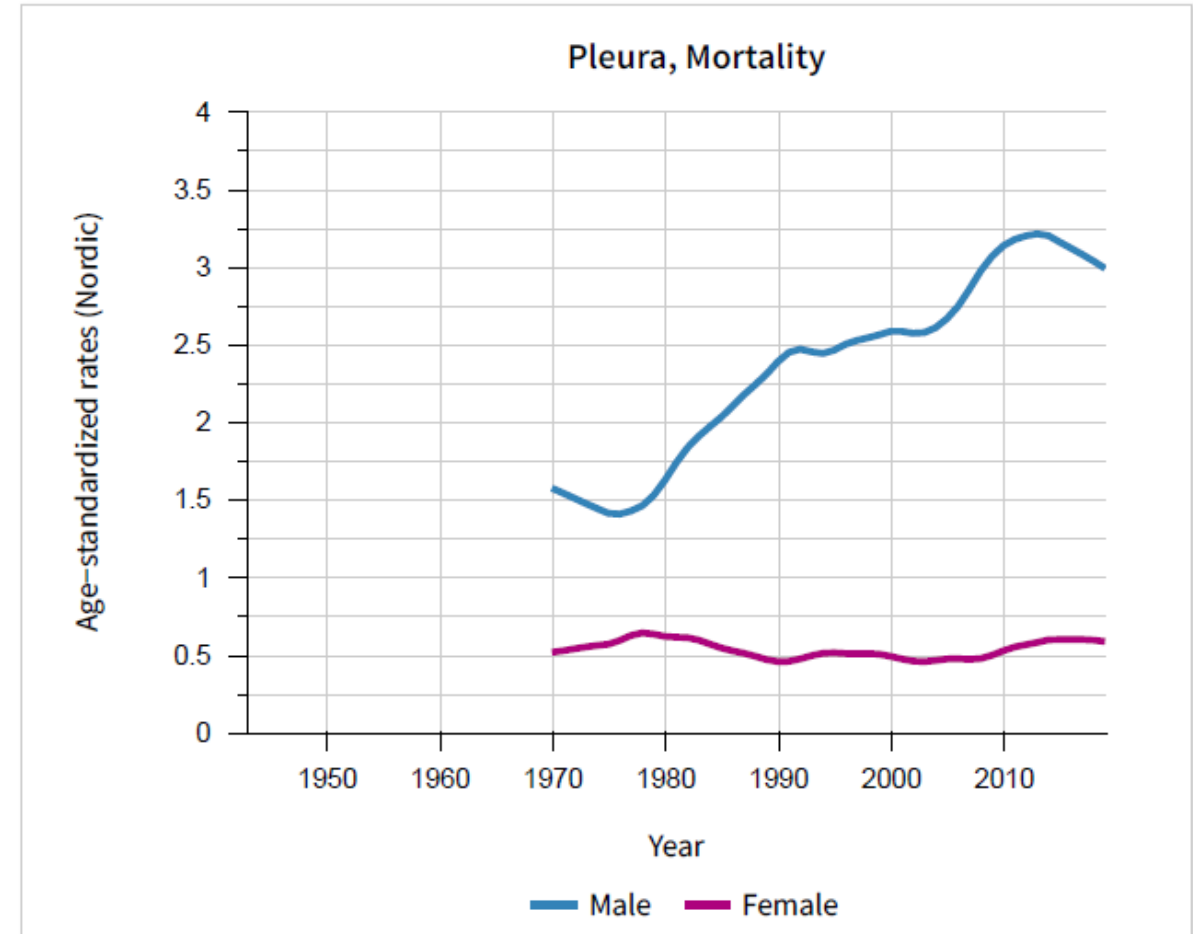
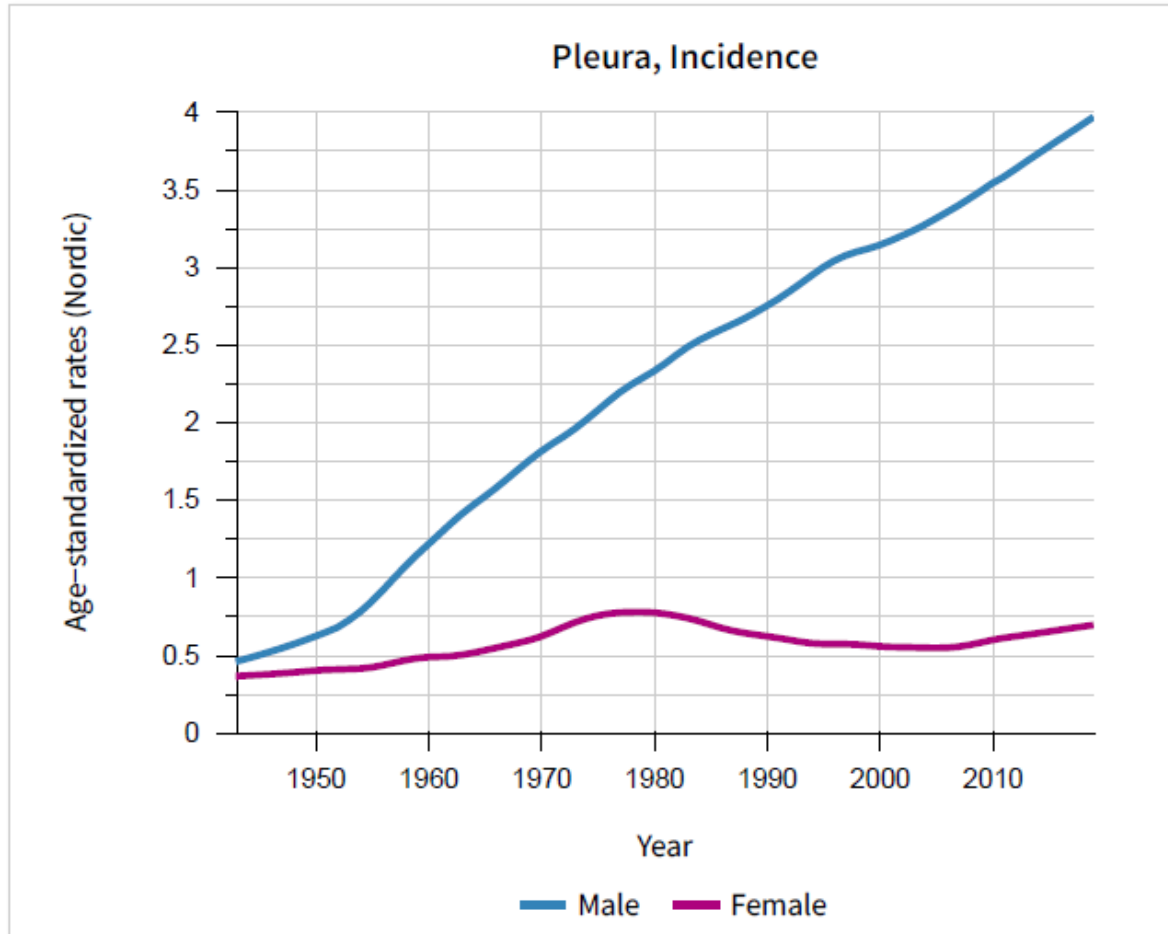
Pleura

NORDCAN

Association of the Nordic Cancer Registries



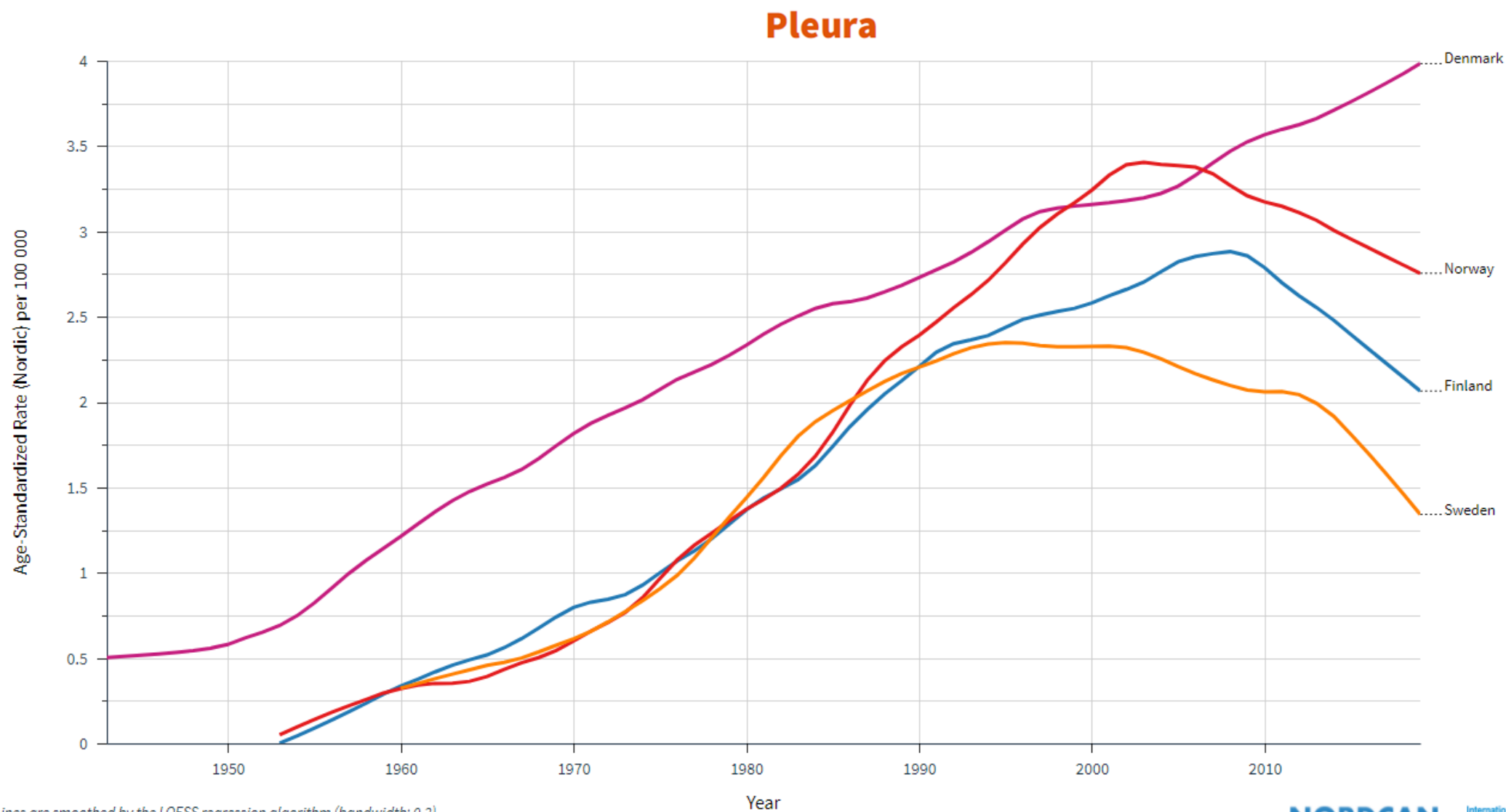
Denmark
Pleura

Denmark
Pleura

Age-Standardized Rate (Nordic) per 100 000 , Incidence, Males

Pleura

Denmark - Finland - Norway - Sweden



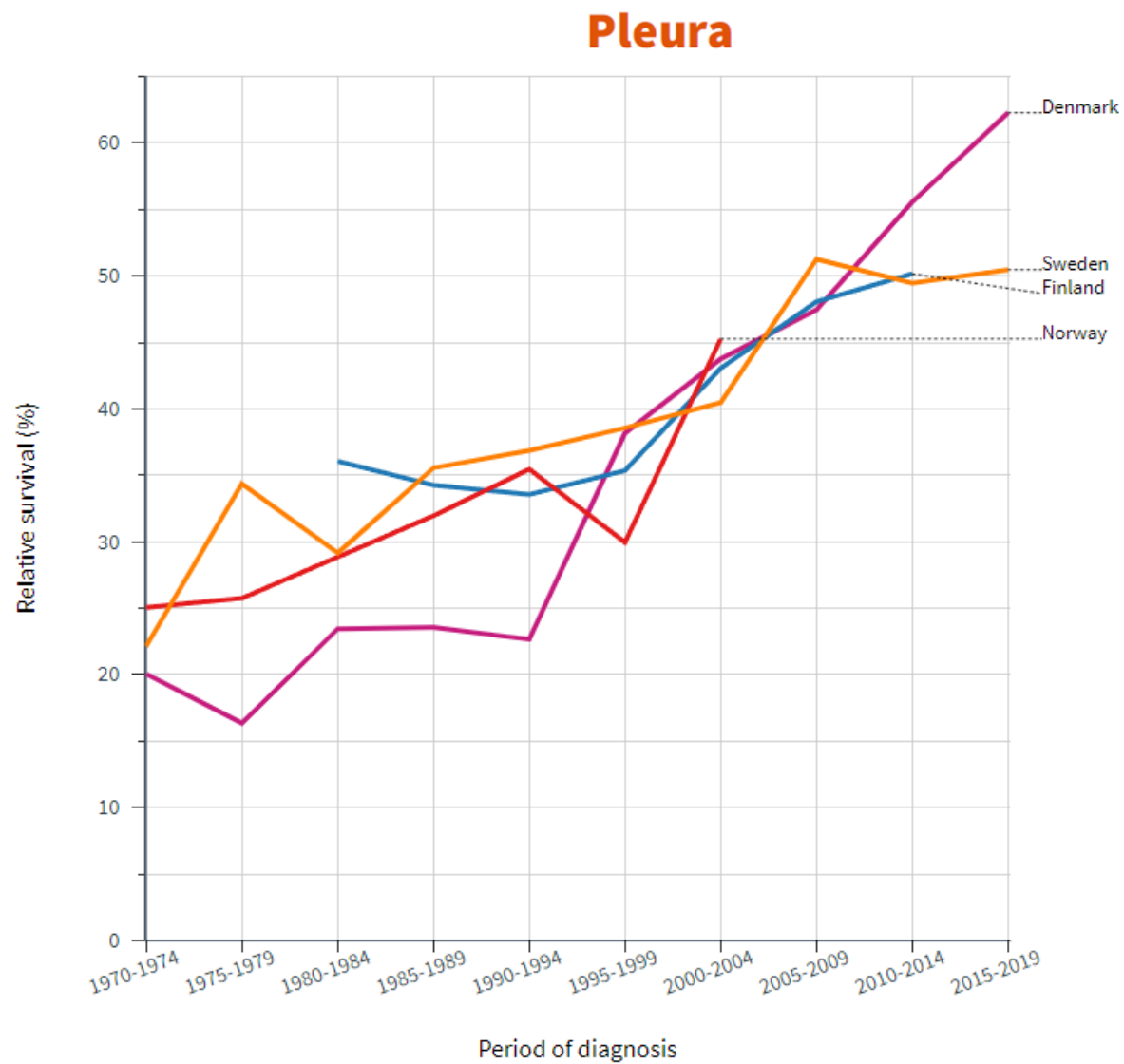
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.2)

NORDCAN | IARC - All Rights Reserved 2021 - Data version: 9.1

1-year age standardised relative survival (%), Males

Pleura

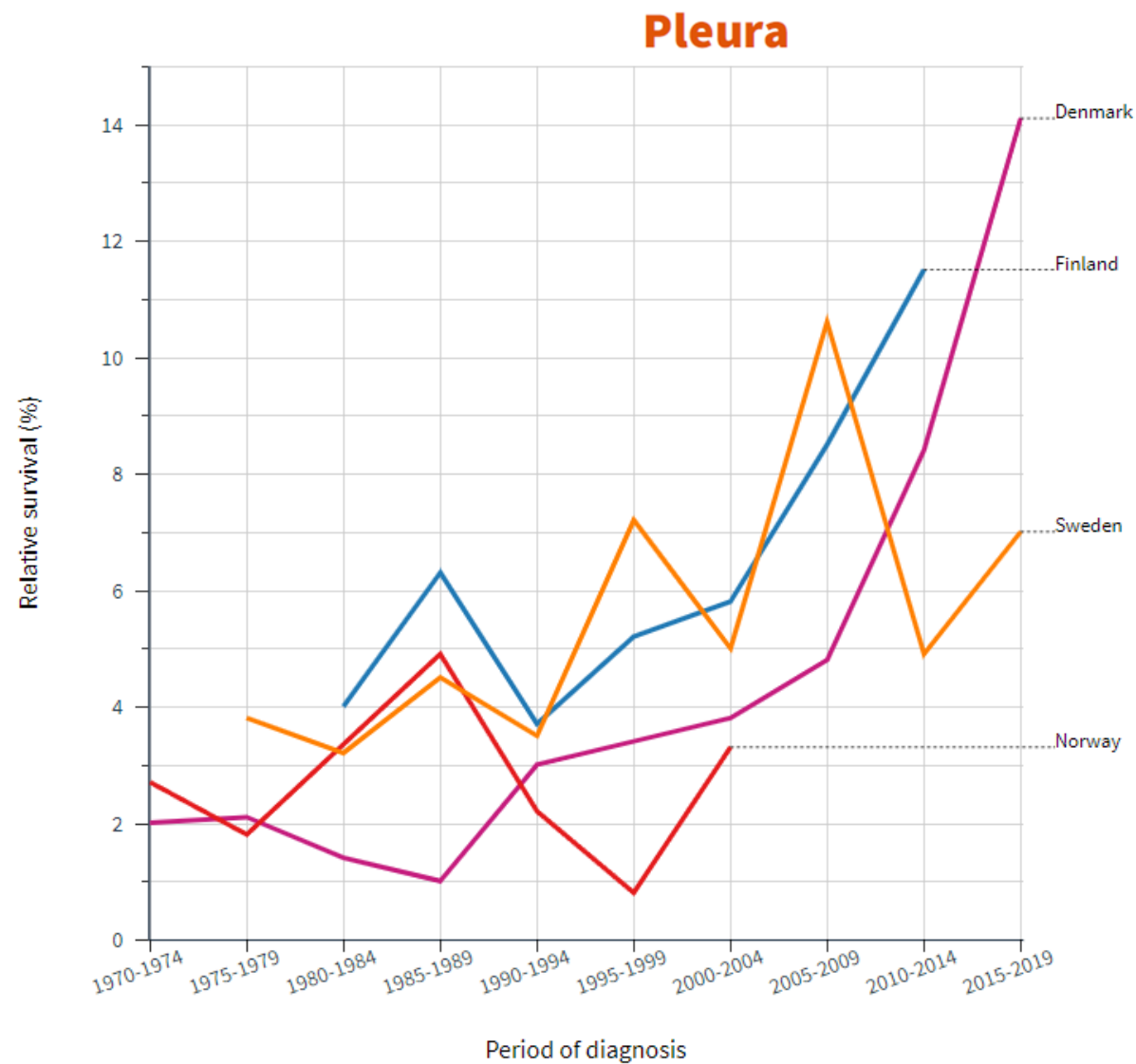
Denmark - Finland - Norway - Sweden



5-year age standardised relative survival (%), Males

Pleura

Denmark - Finland - Norway - Sweden

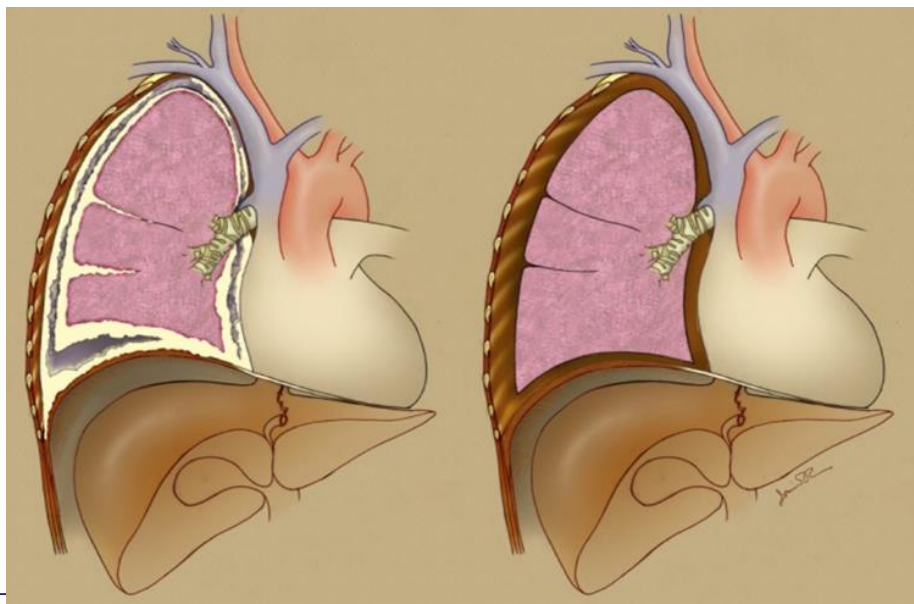


Malignant Pleural Mesothelioma Surgery

Surgical candidates: T1-3N0-1M0
Approx. 25% of all M_{Pleu}M, i.e. 25-35/year in DK

Age limit: ≤ 75 yrs (76-80 yrs???)
Histology: Epitheloid, biphasic $\leq 50\%$ sarcomatoid ($>50\%$ sarcomatoid???)
PS0-1, LFU and comorbidity acceptable

Pleurectomy/decortication P/D

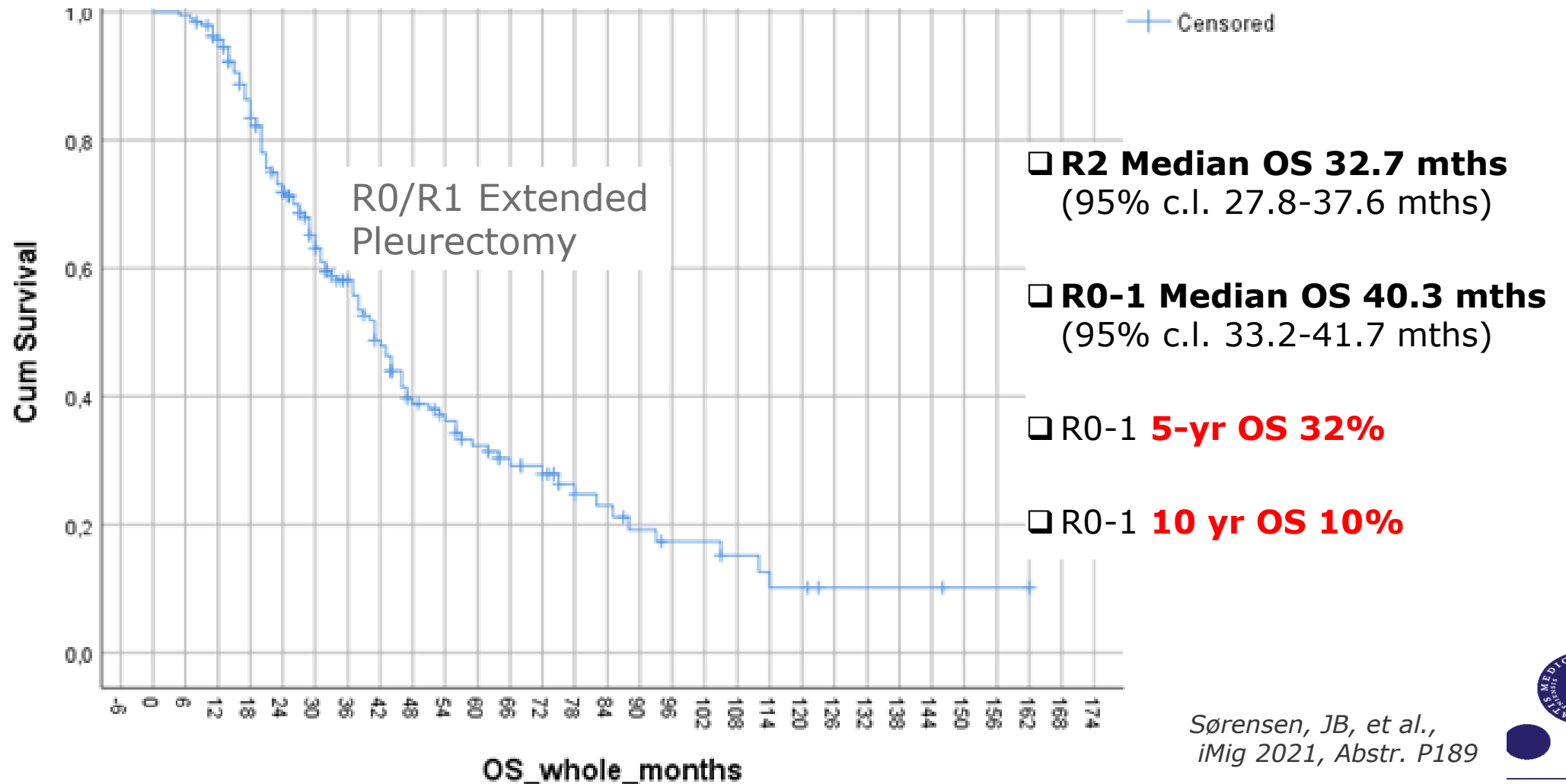


Treatment Strategy:

- 3 courses Neoadjuvant Platinum + Pemetrexed
- Pleurectomy/Decortication
- 3 courses Adjuvant Platinum + Pemetrexed

Peri-operative Chemo + P/D 2006-2021

Overall Survival in R0/R1 Extended Pleurectomy (n=186, ~13/year)



Men 75% af patienterne er inoperable, hvad med dem?

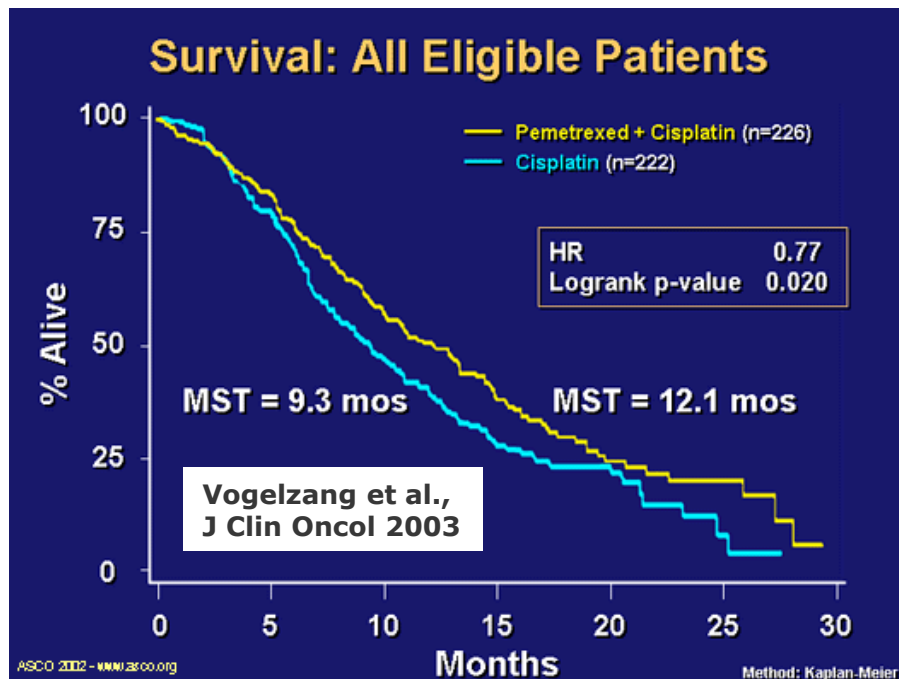
- Standard behandlingen er 1. linie Platin + Pemetrexed
- 2. Linie behandling er Vinorelbine

MPM Chemotherapy Status and Limitations

1st Line

Overall Response rates 20-40%, OS 12-17 mths

Improves QoL , PFS, and Overall Survival



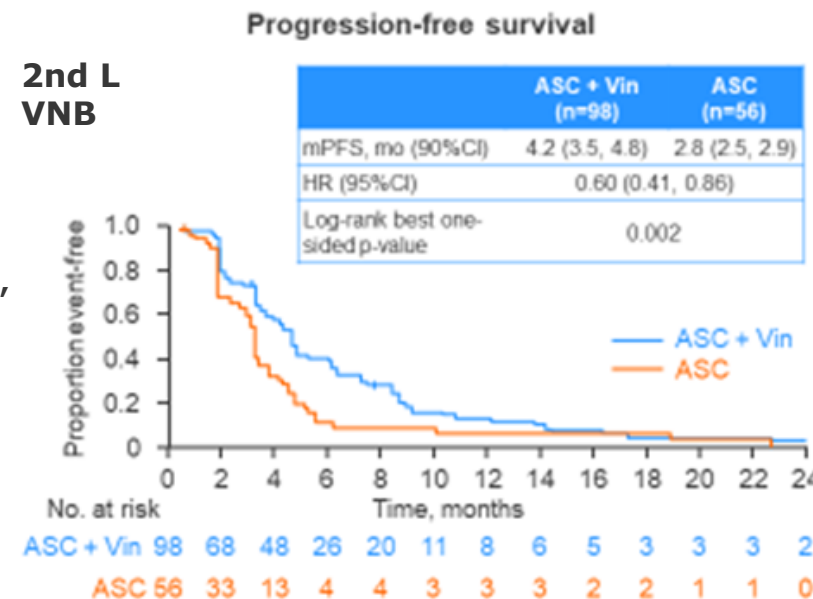
Platinum + Pemetrexed
FDA and EMA Approved

No combo compared to another combo

2nd Line

Overall Response rates 8-18%, OS 4-9 mths

Survival benefit not proven, PFS improved



No standard defined, common options:

If 1L with Pem. → Vinorelbine 2L

If 1L without Pem. → Pemetrexed 2L



Newer medical antineoplastic treatments

Antiangiogenic treatments

- **Bevacizumab**
- Two randomized trials: one neg., one positive
- Not EMA approved
- **Nintedanib**
- One pos. random. Phase II, one neg. random. Phase III trial
- Not FDA or EMA approved

Kindler J Clin Oncol 2012,
Zalcman Lancet 2016,
Grosso J Clin Oncol 2017,
Scagliotti Lacet Respir Med 2019

Targeted Treatments

Targeted treatments

- Fewer genomic alterations than in e.g. NSCLC
- Most alterations are mutated regulatory genes:
BAP1 (*BRCA1*-associated protein 1) (47.6%)
NF2 (38.1%)
CDKN2A/B (loss) (35.7%)
- Mutations in Driver Genes rare
- No genomic treatments with confirmed efficacy

Immunotherapy

Encouraging Activity reported

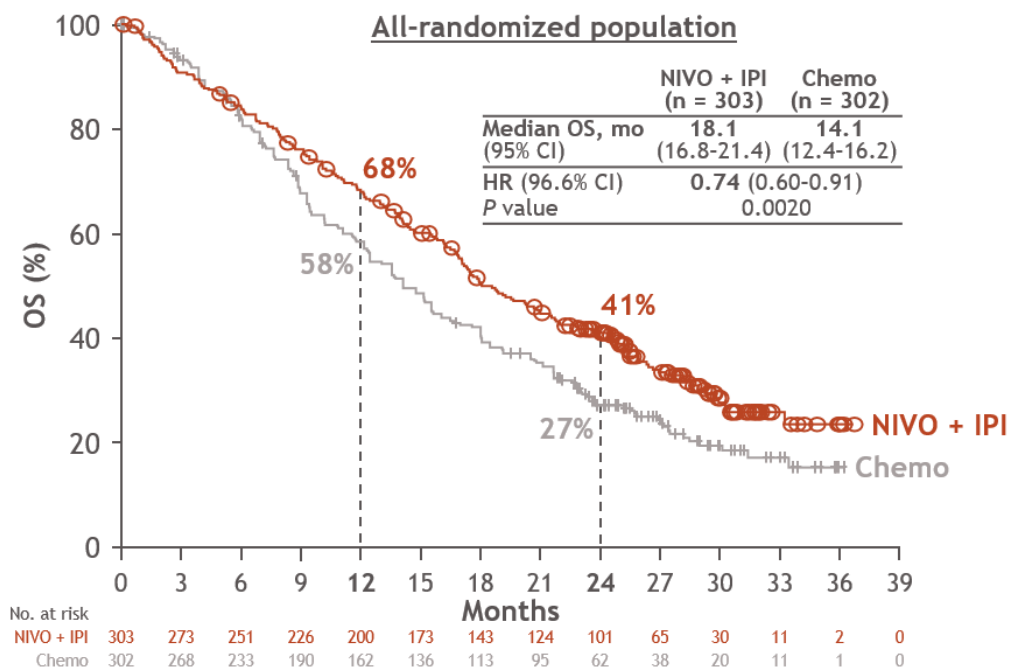
- Randomized trials completed and ongoing
- More on following slides

1st L Immunotherapy in MPlEuM

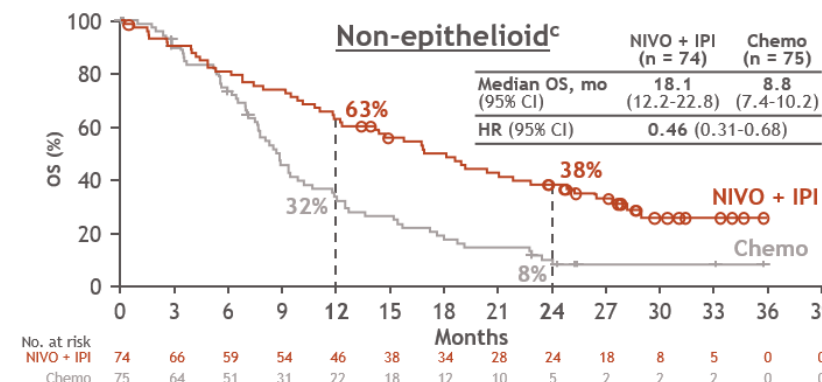
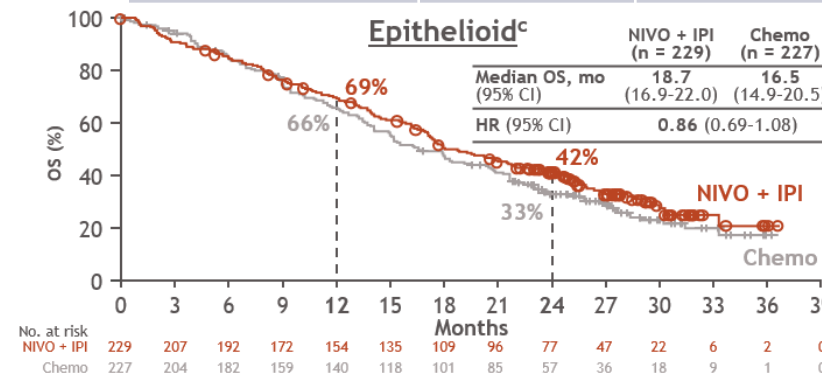
CheckMate 743: Nivo + Ipi vs Chemo, 1st Line unresectable MPM

Baas P, et al. *Lancet*. 2021;397:375-386

Primary endpoint: OS



ARM		Non-Epithelioid	Epithelioid
IPI-NIVO	OS (months)	18.1	18.7
CHEMO	OS (months)	8.8	16.5
HR (95%CI)		0.47 (0.35-0.63)	0.93 (0.68-1.28)



- Median PFS was 6.8 months with NIVO + IPI^a and 7.2 months with chemo^b

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

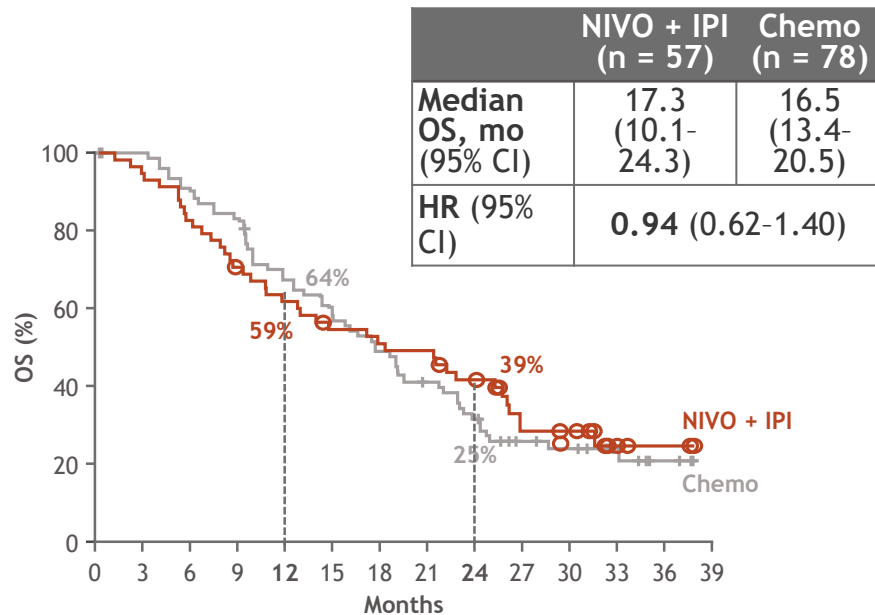
Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively. ^a95% CI, 5.6-7.4 months; ^b95% CI, 6.9-8.0 months; ^cPatients were stratified by tumor histology: epithelioid vs non-epithelioid. OS HRs (95% CI) for epithelioid vs non-epithelioid were: NIVO + IPI, 0.93 (0.68-1.28); chemo, 0.47 (0.35-0.63). Histology per CRF source.

Baas P, et al. *Lancet*. 2021;397:375-386.



Overall Survival by PD-L1 expression level

PD-L1 < 1%



No. at risk

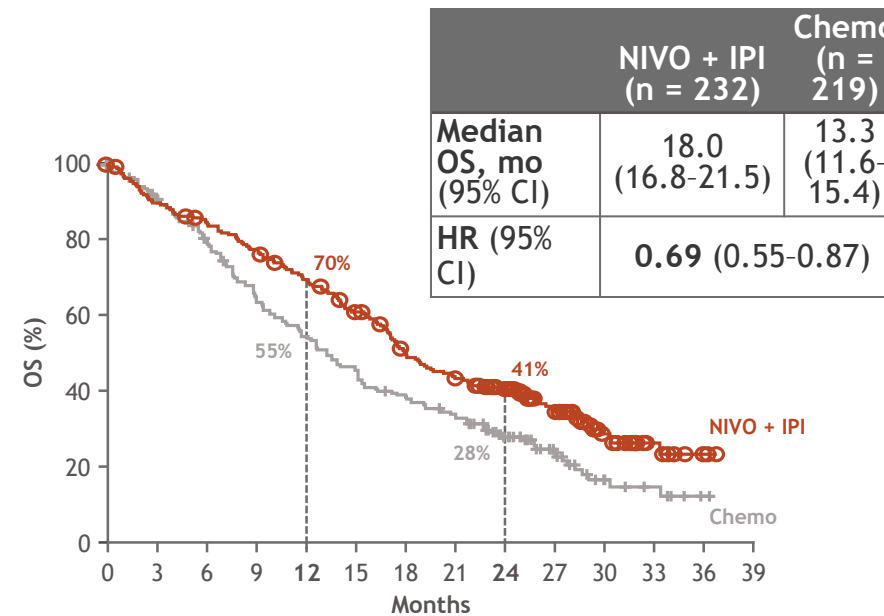
NIVO + IPI	57	53	46	38	33	29	26	22	18	12	6	2	0	0
Chemo	78	75	67	56	48	41	33	27	17	13	10	5	0	0

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Patients were not stratified by PD-L1 expression level.
OS HR (95% CI) for PD-L1 ≥ 1% vs < 1% were: NIVO + IPI, 0.87 (0.61-1.23); chemo, 1.18 (0.87-1.60).

Baas et al. Oral presentation at WCLC 2020. Abstract 3.

PD-L1 ≥ 1%



No. at risk

NIVO + IPI	232	207	194	177	157	135	108	93	76	50	24	9	2	0
Chemo	219	188	162	131	111	92	78	66	44	24	9	6	1	0



Nivolumab + Ipilimumab approved for 1st Line unresectable MPM by FDA and EMA

02 OCT 2020

FDA NEWS RELEASE

FDA Approves Drug Combination for Treating Mesothelioma

22 APR 2021

First approval in 16 years for mesothelioma a type of cancer caused by inhaling asbestos fibers



For Immediate Release: October 02, 2020

Today, the U.S. Food and Drug Administration approved Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for the first-line treatment of adults with malignant pleural mesothelioma that cannot be removed by surgery. This is the first drug regimen approved for mesothelioma in 16 years and the second FDA-approved systemic therapy for mesothelioma.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA RECOMMENDS EXTENSION OF THERAPEUTIC INDICATIONS FOR NIVOLUMAB AND IPIILIMUMAB

Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

First approval in 15 years for Mesothelioma



Malignant Pleural Mesothelioma, Key points:

- **Incidence** still increasing in DK
- **Survival** is improving, 1-yr OS 62%, 5-yrs OS 11-14%
- **Surgery** (Pleurectomy/Decortication) with perioperative chemo:
R0/R1: 5-yrs OS 32%, 10-yrs OS 10%.
- Majority of pts (75%) non-resectable.
- **Non-resectable** pts:
Standard is Platinum doublet (increase OS, improve QoL),
no new drugs approved in DK since 2004
- **Immunotherapy:**
1st L Nivolumab+Ipilimumab vs Chemo:
Improved OS, mOS 4.0 mths increase,
2 yrs OS increase from 27% (Chemo) to 41% (Immuno),
Approved by FDA (US) and EMA (EU)

