JAHRESTAGUNG 2024 BASEL 11.–14. Oktober

Nachsorge bei Keimzelltumoren unter Berücksichtigung von Langzeittoxizitäten

Basel, 11.10.2024

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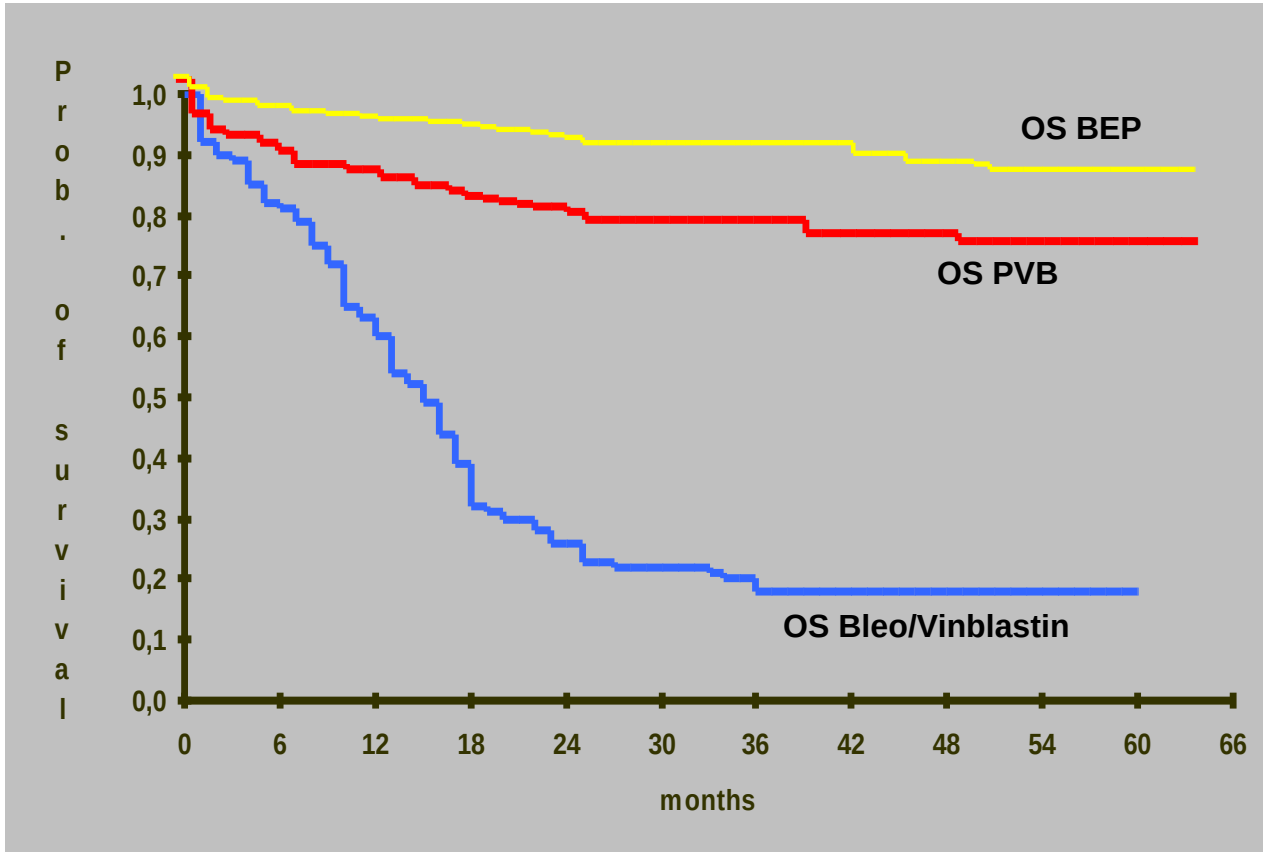
Interdisziplinäre Arbeitsgruppe Hodentumoren

Interessenkonflikte

Financial interest	Company/Organisation
Speaker honoraria	Sandoz, AstraZeneca, Novartis
Consulting/advisory role	Astex Therapeutics (NUPAcT Fellowship Secondment as Clinical Advisor), Sandoz, Pfizer, RareCan
Research Funding (institutional)	Cancer Research UK, JGWP Foundation
Research Funding (personal)	PharmaMar
Travel, accomodation	ESMO, EAU, IGG
Professional Society roles	EAU testicular cancer guideline panel member, ESMO Resilience Task Force member, ESMO Communications Committee member, Onkopedia testicular cancer guideline panel member, DGHO scientific committee member

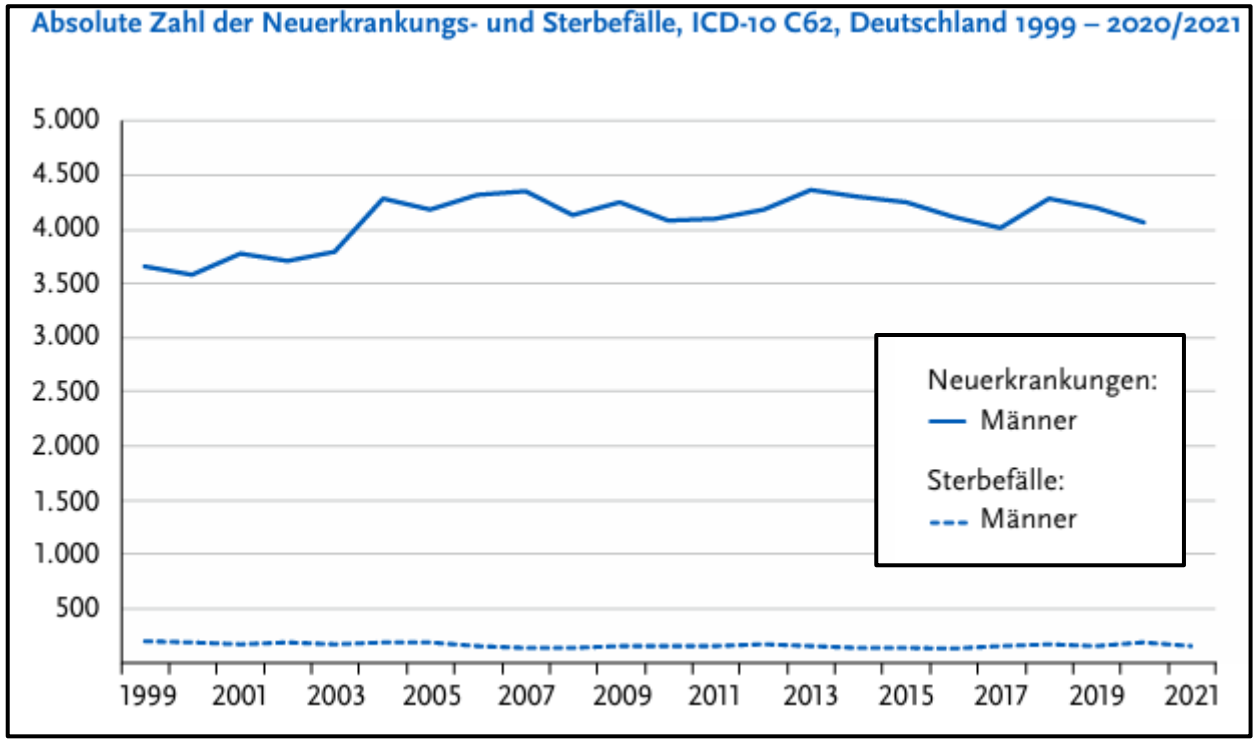
Hintergrund



Samuels et al. Cancer Treat Rev 1976, Williams et al. NEJM 1987, Sonneveld et al. Cancer 2000

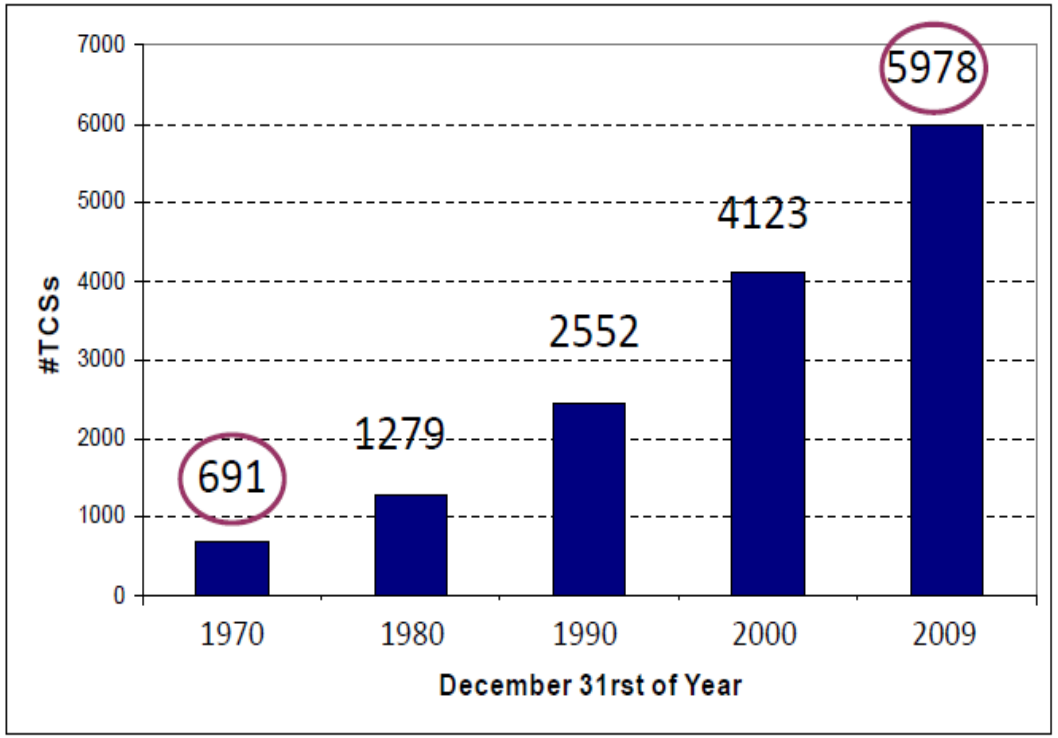
Wachsende Zahl Langzeitüberlebender

Neuerkrankungen und Sterbefälle in Deutschland



RKI, Krebs in Deutschland 2023

Keimzelltumorüberlende ≥ 5 Jahre FU



Cancer Registry of Norway, personal communication

Nachsorge nach erfolgreicher Behandlung

Initial (Jahr 1-3):	Frühzeitige Identifikation eines Rezidivs
Später (Jahr 4-10):	Prävention, Detektion und Behandlung von Langzeitnebenwirkungen

Zeitpunkt von Erkrankungsrezidiven

CS I unter aktiver Überwachung

Histologie	Risikofaktoren	Median time to relapse
Seminom	N/A	14 mos
Nichtseminom[2]	LVI negativ LVI positiv	8 mos 4 mos

Kollmannsberger et al. J Clin Oncol 2015

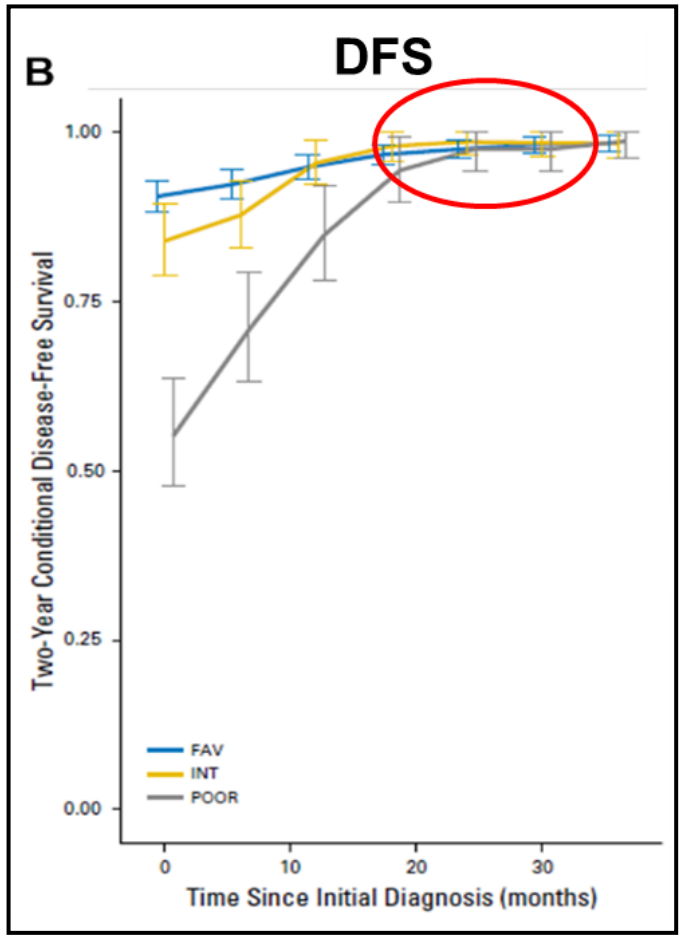
CS I mit adjuvanter Therapie

Histologie	Adjuvante Tx	Median time to relapse
Seminom[1]	Carbo AUC7 x1	23 mos
Nichtseminom[2]	BEP x 1-2	13 mos

1 Chau et al. Ann Oncol 2015

2 Fischer et al. J Clin Oncol 2019

Metastasierte Stadien

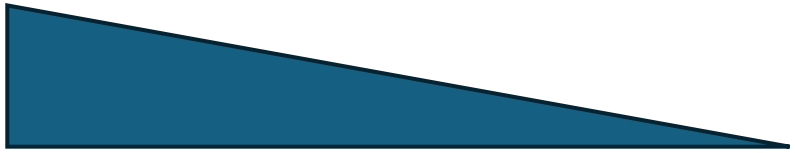


Ko et al., J Clin Oncol 2016

Detektion von Erkrankungsrezidiven

Characteristic	Stage I Nonseminoma				Stage I Seminoma	
	LVI Positive (n = 183)		LVI Negative (n = 935)		Total (n = 1,344)	
	No.	%	No.	%	No.	%
Median time to relapse, months (range)	4 (1-61)		8 (2-77)		14 (2-84)	
Method of first relapse detection						
Abdominal CT scan	31 of 81	38	63 of 132	48	150	87
Tumor markers	49 of 81	61	54 of 132	41	6	3
Chest x-ray	0	0	2 of 132	2	0	0
Physical examination	1 of 81	1	1 of 132	1	0	0
N/a	—		12 of 132	9	17	10

Kollmannsberger et al. J Clin Oncol 2015



CT/STM **CXR/KU**

Diskordanz von Nachsorgeemfpehlungen

Table 2 – Comparison of different follow-up schedules including investigations and their intervals for patients with metastatic testicular germ cell tumour stratified by histology[a]

Histology	STM/CTAP/CXR/CTC interval (mo)			
	EAU/ESMO	NCCN	SWENOTECA	SAGTCCS
Seminoma				
Year 1	3/6–12/6–12/6–12[b]	(3)/at 3 & 9 or 12/6/[b]	6/6[d]/0/0	3/6/6/12[b]
Year 2	3/12/12/12[b]	(6)/12/6/[b]	6/6[d]/0/0	3/12/12/12[b]
Year 3	6/12/12/0	(6)/12/0/0	6/12[d]/0/0	6/12/12/12[b]
Year 4	6/0/0/0	(6)/[c]/0/0	6/12[d]/0/0	6/0/0/0
Year 5	6/12/12/12[b]	(6)/[c]/0/0	12/12[d]/0/0	6/12/12/12[b]
Year >5				
Nonseminoma				
Year 1	Same as for seminoma	2/6/6/[b]	2–3/6[b]/6/0	3/6/6/12[b]
Year 2		3/6–12/6/[b]	3/6[d]/6/0	3/12/12/12[b]
Year 3		6/12/(12)/[b]	6/12[d]/12/0	6/12/12/12[b]
Year 4		6/[b]/(12)/[b]	6/12[d]/12/0	6/0/0/0
Year 5		6/[b]/0/0 (annual STM y5–y10)	6/12[d]/12/0	6/12/12/12[b]
Year >5				

STM = serum tumour markers; CTAP = abdominopelvic computed tomography; CXR = chest X-ray; CTC = chest CT; EAU = European Association of Urology; ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network; SWENOTECA = Swedish and Norwegian Testicular Cancer Group; SAGTCCS = Swiss Austrian German Testicular Cancer Cohort Study; y5 = year 5.

[a] Optional investigations are in parentheses.

[b] CTC in cases with pulmonary metastases at diagnosis (for NCCN: CTC instead of CXR in symptomatic patients or supradiaphragmatic disease at diagnosis).

[c] As clinically indicated.

[d] SWENOTECA explicitly recommends magnetic resonance imaging instead of CT.

Kaufmann, ..., Oing et al. Eur Urol Open Sci 2022

Problem Strahlenbelastung

	Belastung
Rö Thorax	0.02 mSv
CT Kopf	2 - 14 mSv
CT Thorax	8 - 22 mSv
CT Abdomen	10 - 31 mSv

Smith-Bindman et al. Arch Intern Med 2009

Strahlenbelastung	Effektive Dosis	Risiko Krebsmortalität
Rx Thorax pa	0.02 mSv	1 : 1'000'000
Rx Thorax pa/lat	0.1mSv	1: 200'000
Transatlantik Flug	0.1 mSv	1 : 200'000
Background/Jahr	2.5 mSv	1 : 8'000
CT Thorax (Standard)	7-8 mSv	1: 2'857 – 2'500
CT Thorax „low dose"	4 mSv	1: 5'000
CT Abdomen	8 mSv	1: 2'500
CT Becken	6 mSv	1: 3'333

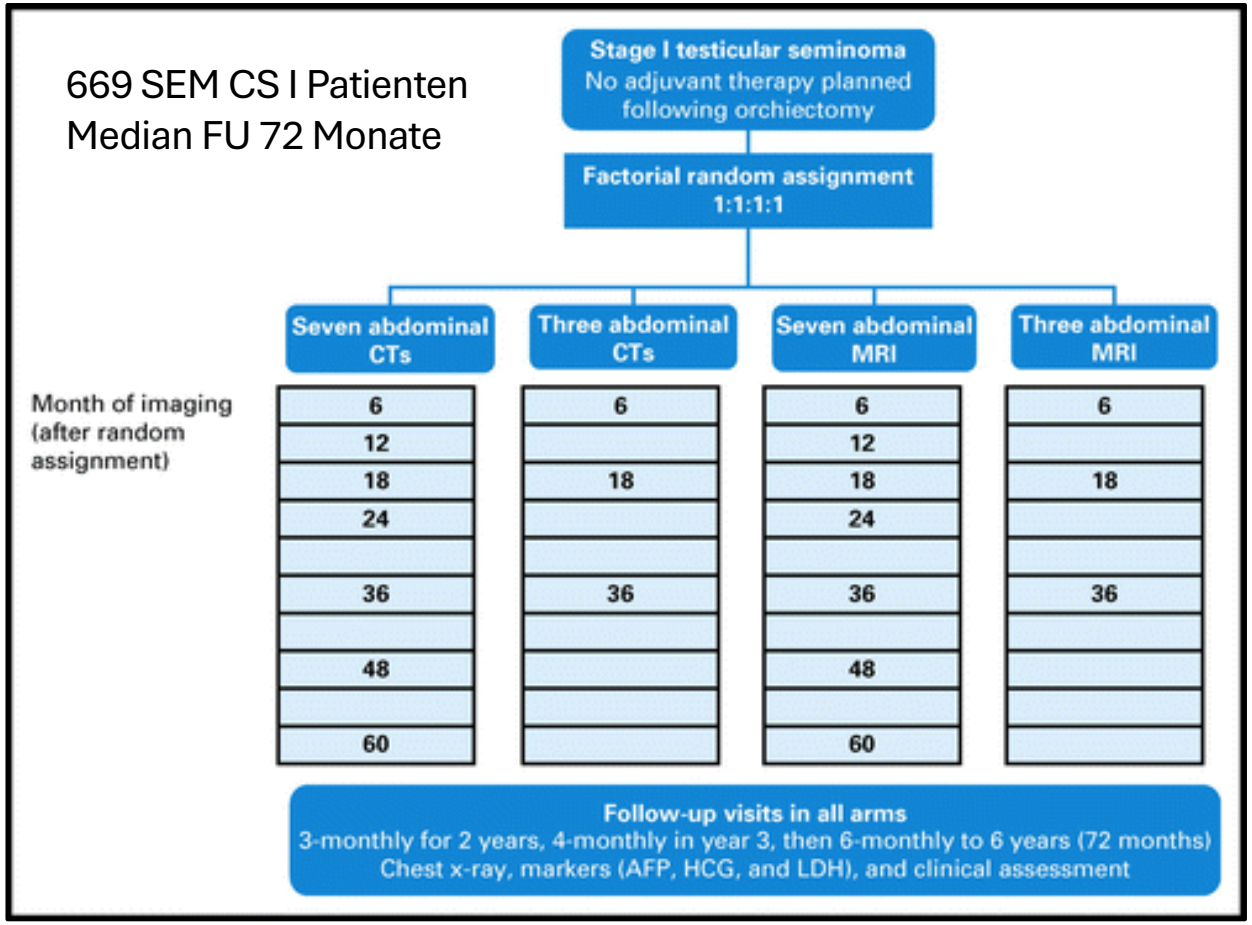
Mettler et al. Radiology 2008

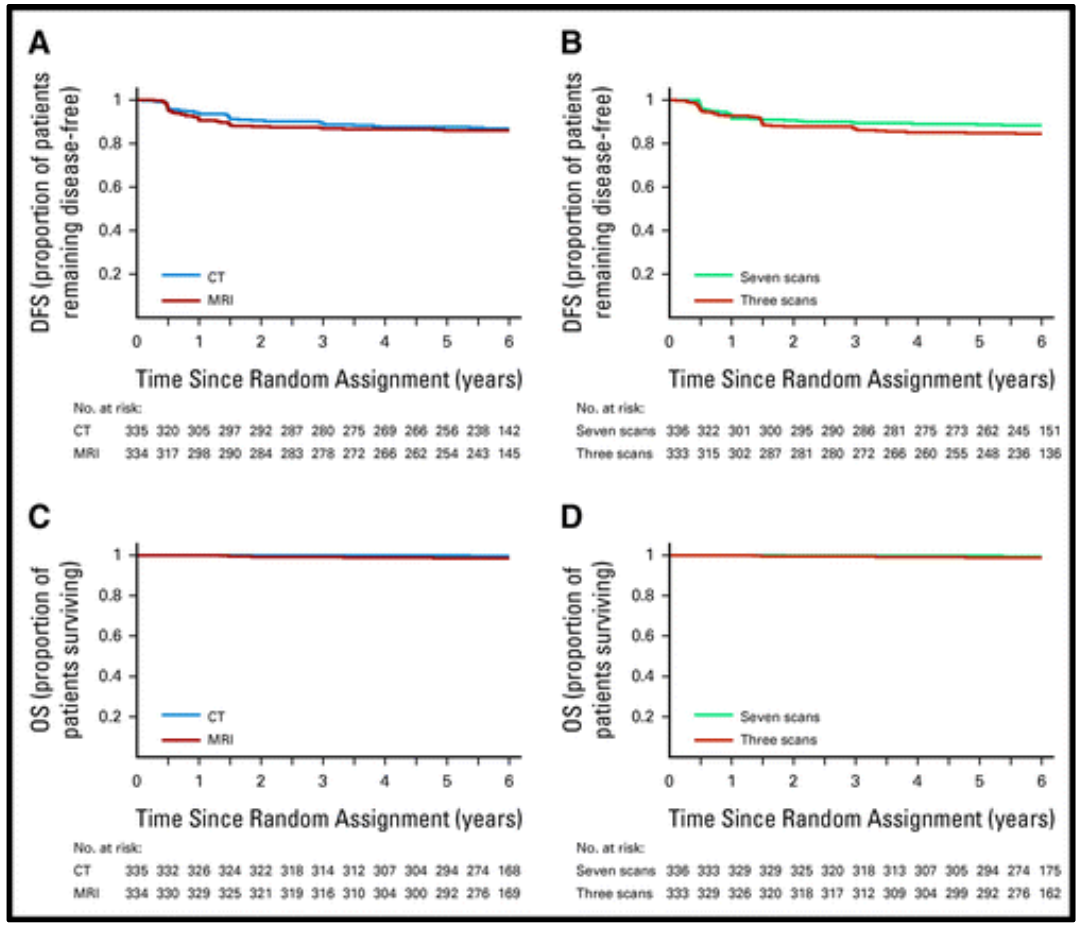
Ca. 1,5-2% aller Tumorerkrankungen durch (unnötige) CT-Untersuchungen

Brenner NEJM 2007

MRT AP statt CT AP?

669 SEM CS I Patienten
Median FU 72 Monate

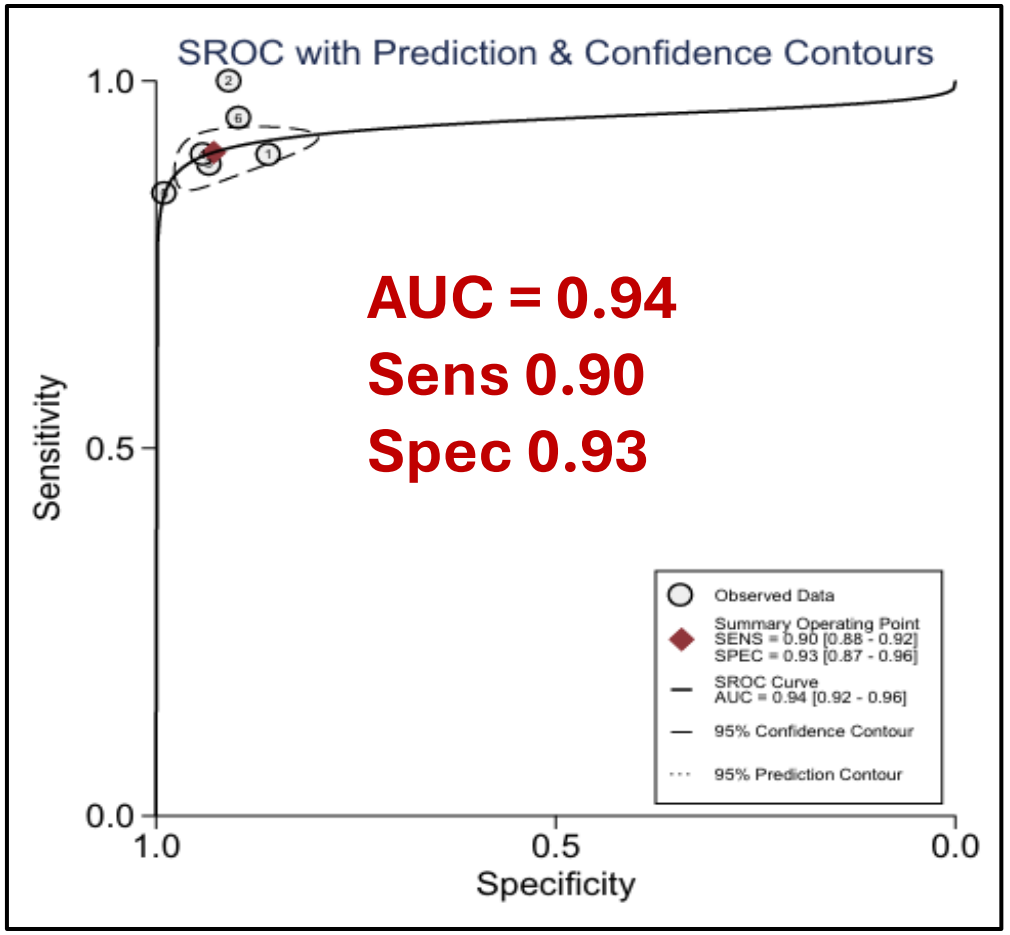




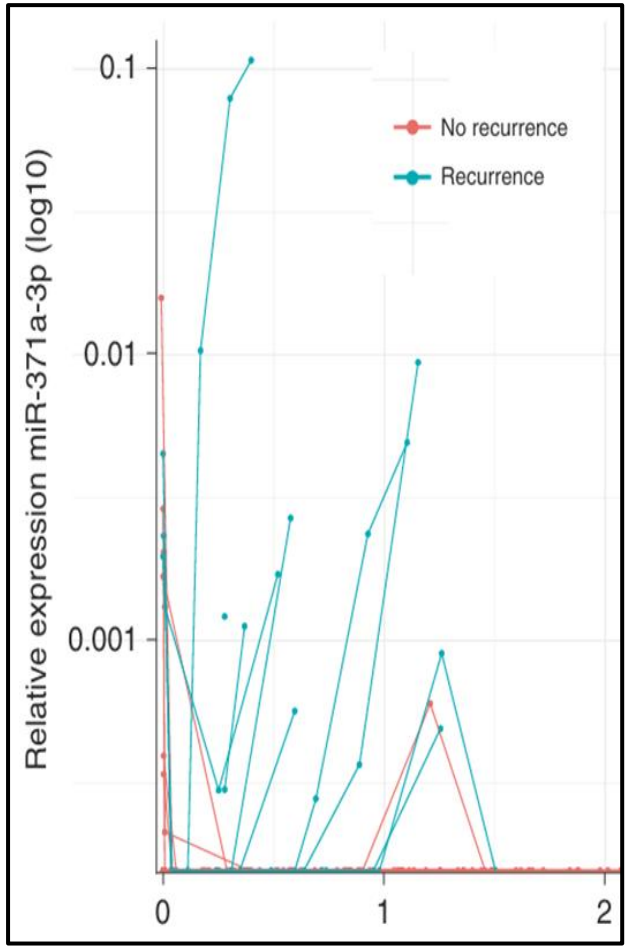
CT 88% / MRT 78% der Rezidive per Bildgebung entdeckt.

Joffe et al. J Clin Oncol 2022

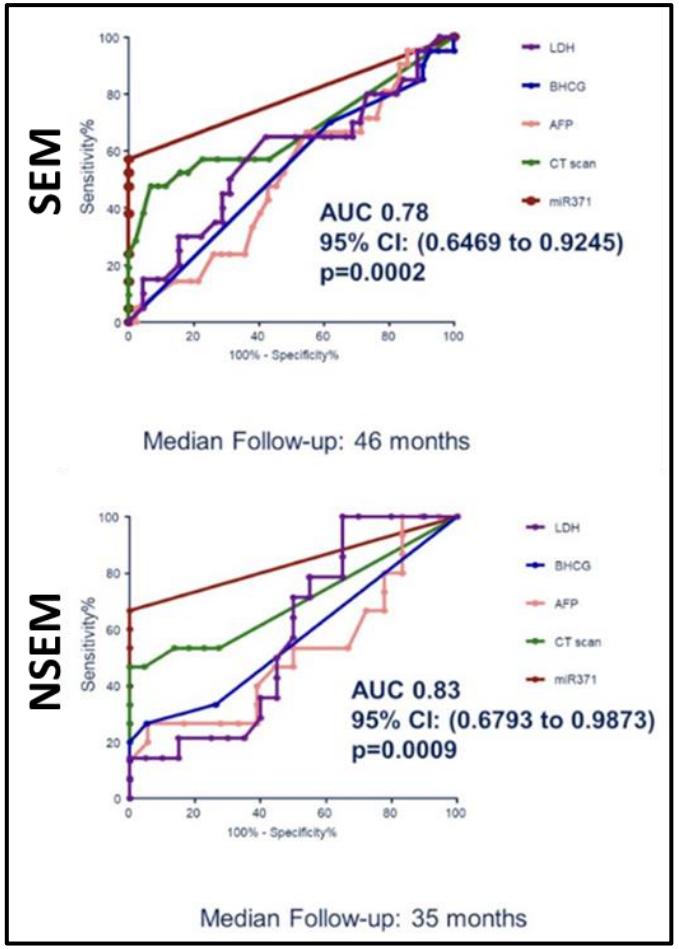
miR-371a-3p statt Bildgebung?



Quingzhao et al. Mol Diagn Ther 2021



Fankhauser et al. Br J Cancer 2019

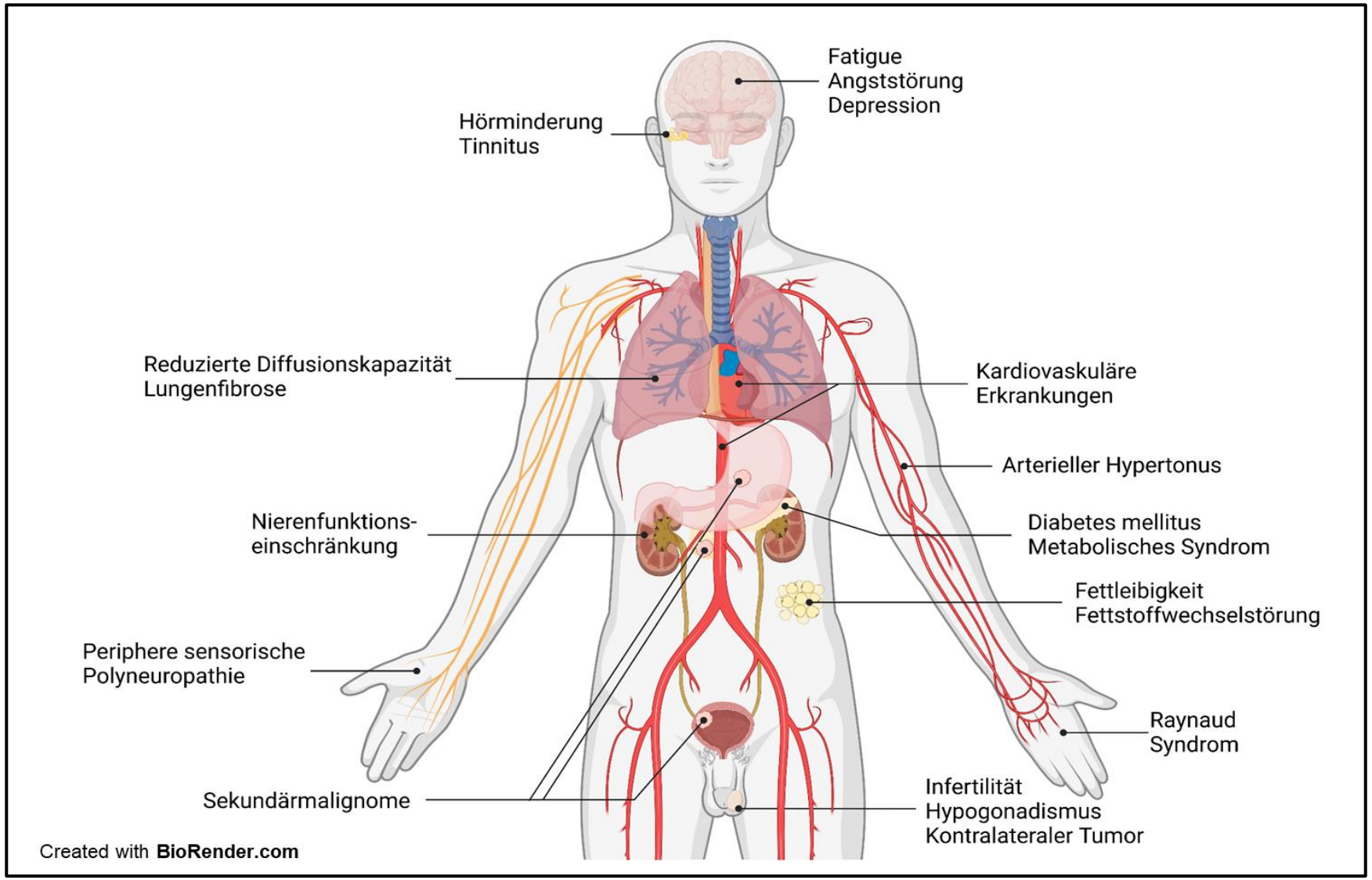


Nappi et al. ASCO 2023

Fazit und Ausblick

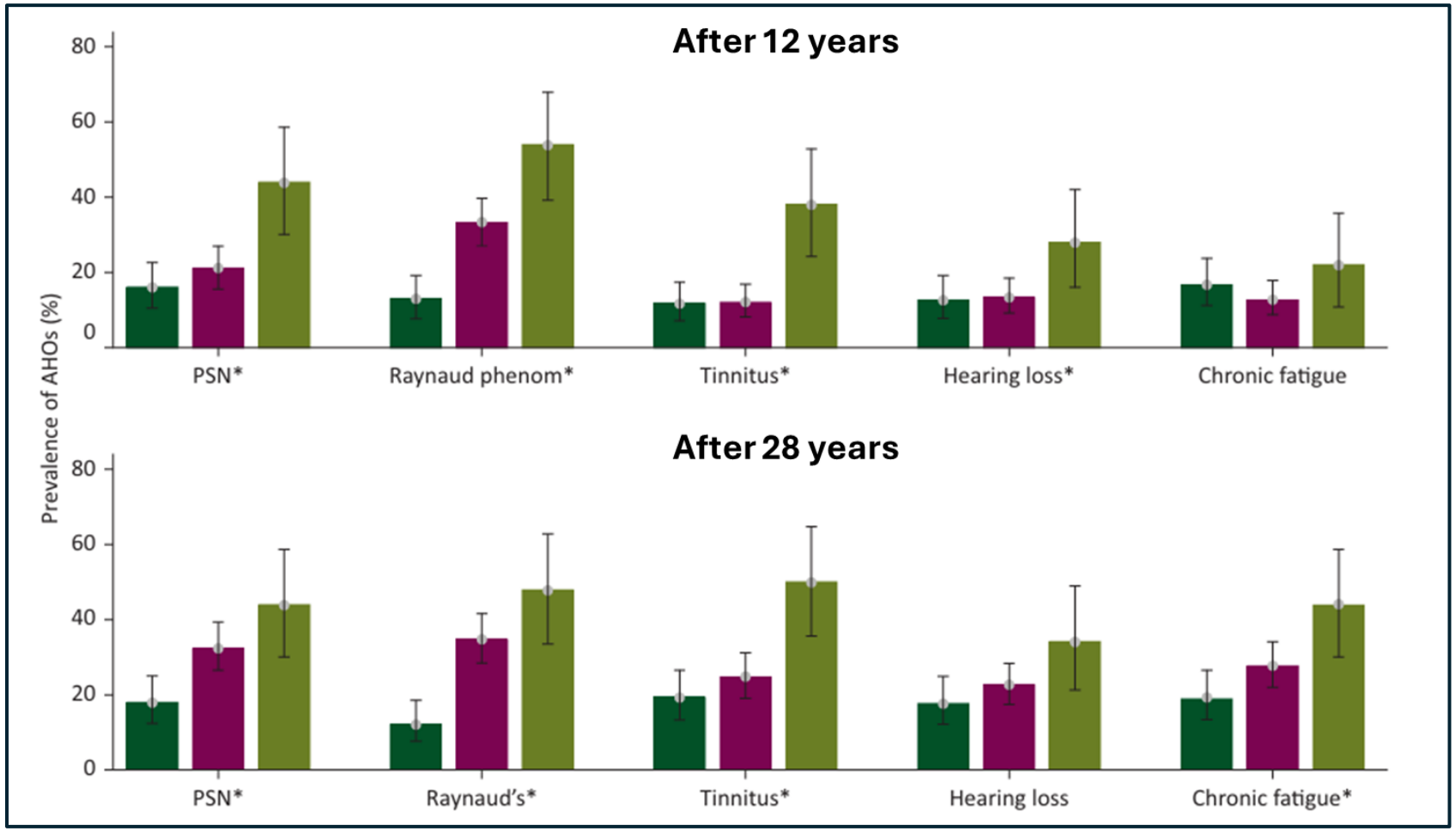
- Zahl der CT-graphischen Bildgebungen bereits dramatisch reduziert (aktuell 5x CT/MRT AP binnen 5 Jahren)
- MRT beim CS I Seminom der CT AP nicht unterlegen
  - 3 Schnittbildgebungen äquieffektiv zu 7 Untersuchungen binnen 5 Jahren
  - Möglicher *Stage shift* hin zu späteren Stadien
  - MRT der CT wann immer möglich vorzuziehen insb. bei AS
- miR-371a-3p detektiert Rezidive zuverlässig und früher als konventionelle Nachsorgemaßnahmen
  - Cave: Teratome miR-371a-3p negativ
  - Kosten bisher deutlich höher als konventionelle STM
  - Kann die miR-371a-3p die Bildgebung (insb. beim Seminom) ersetzen?

Langzeitfolgen der Therapie



Krege, Oing, Bokemeyer et al. Dt Ärztebl Intl 2023

Adverse health related outcomes



Fosså et al. Ann Oncol 2023

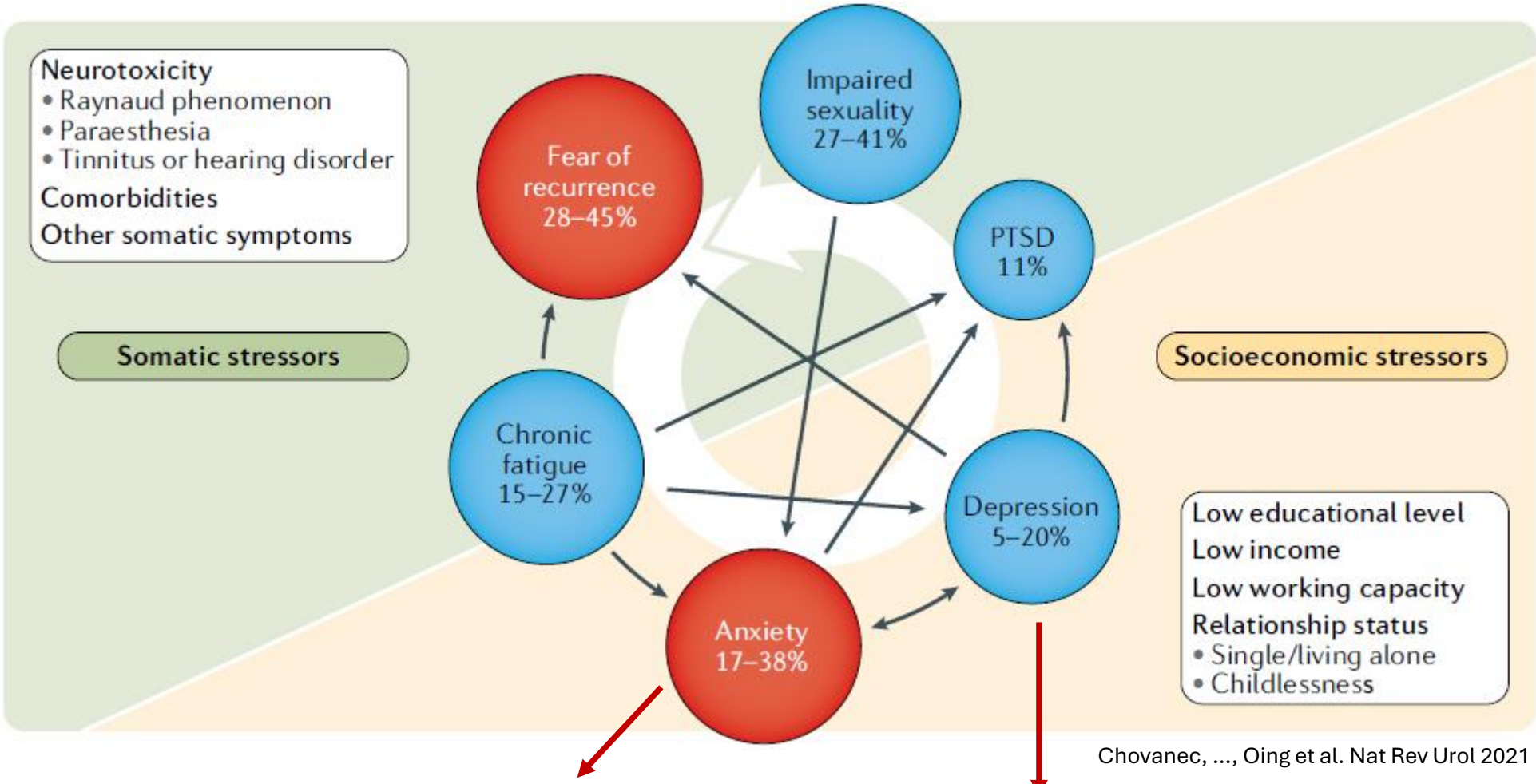
Klassische CDDP-assoziierte Nebenwirkungen mit langer Persistenz nach Therapieende

Surgery only

PBCT-standard ≤850mg/m² CDDP

PBCT-high >850mg/m² CDDP

Psychosoziale Langzeitfolgen



Chovanec, ..., Oing et al. Nat Rev Urol 2021

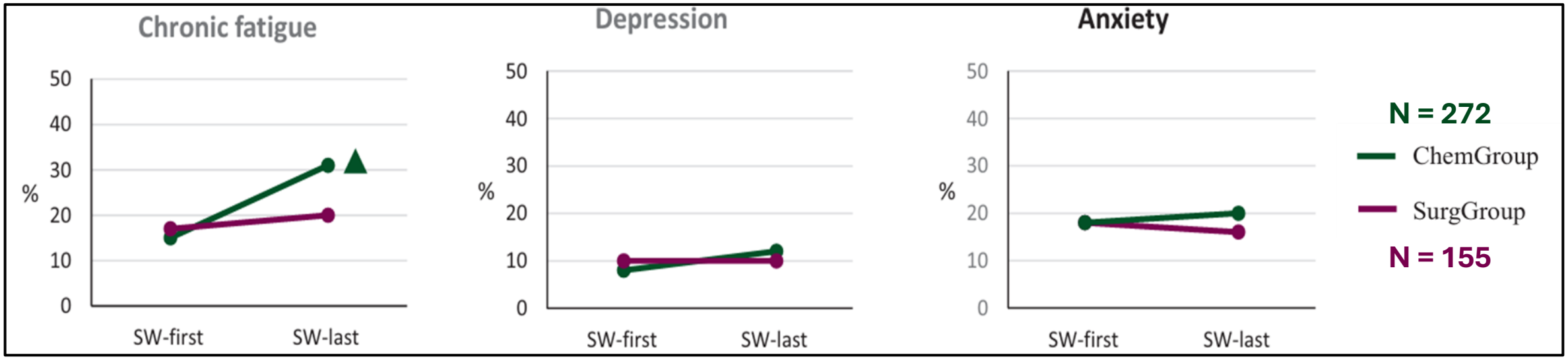
Prevalence significantly higher compared to age-matched healthy controls in most studies

Smith et al. Psychooncology 2018

Prevalence **not** significantly different from age-matched healthy controls in most studies

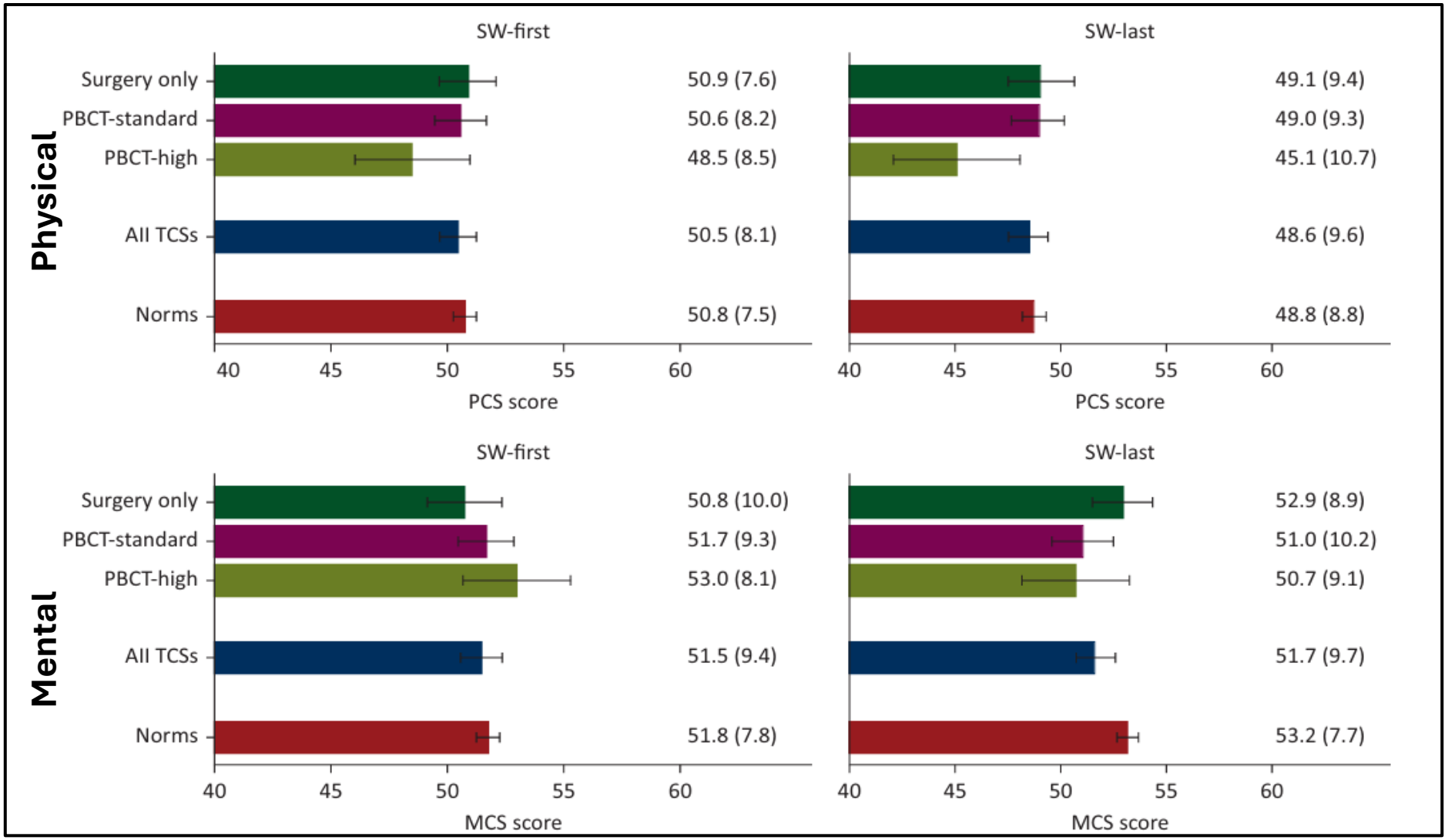
Smith et al. Psychooncology 2018

Psychosoziale Langzeitfolgen



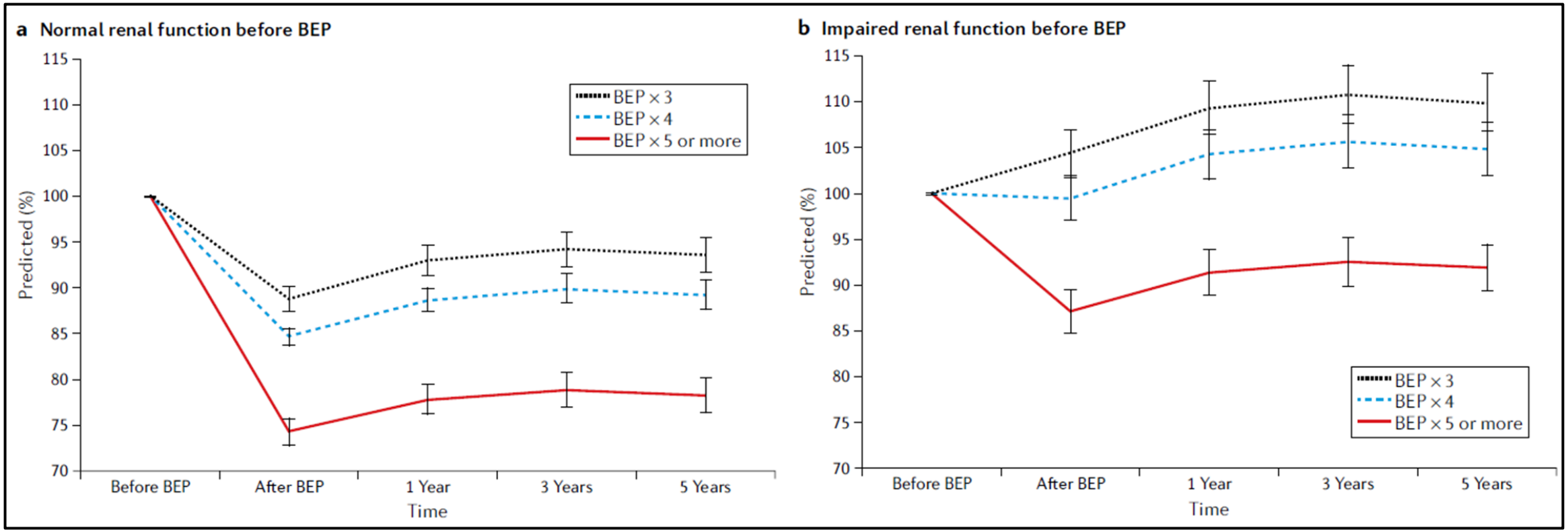
Fosså et al. Ann Oncol 2023

HRQoL in der Langzeitperspektive



Fosså et al. Ann Oncol 2023

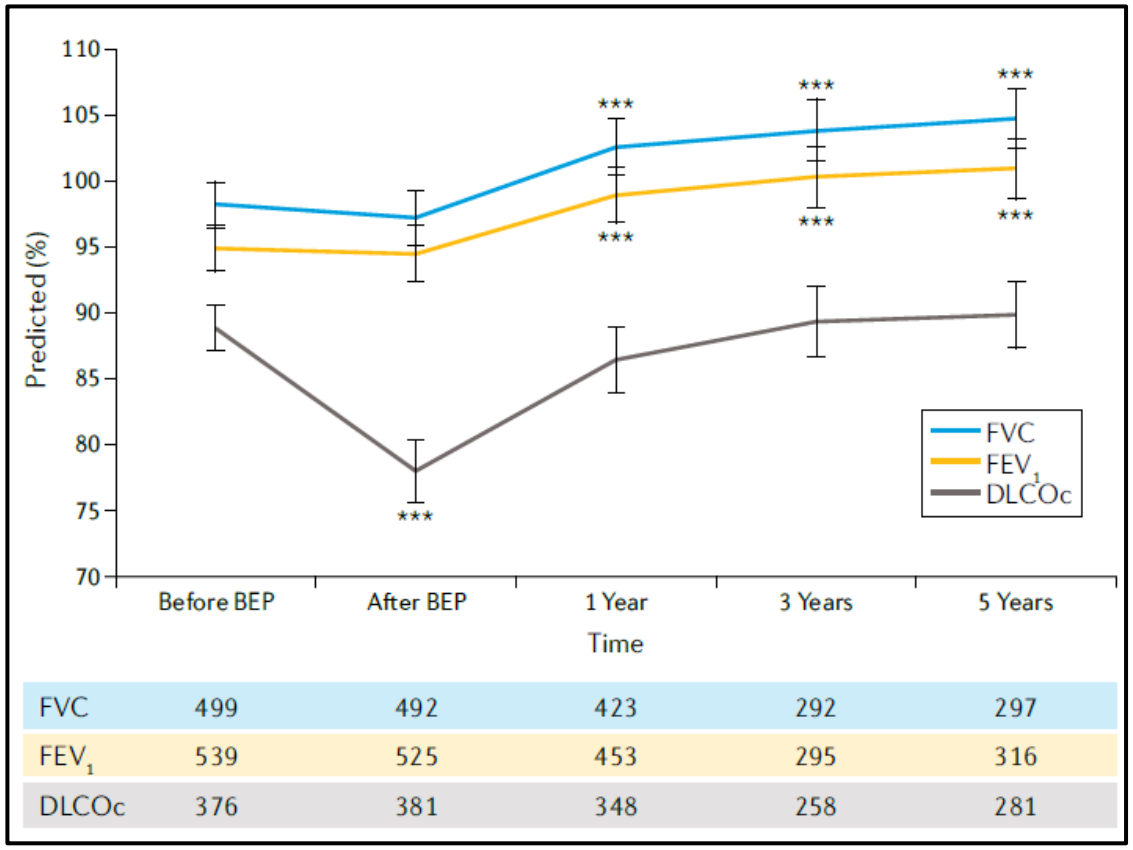
Renale Funktionsstörung



Laurtisen et al. Ann Oncol 2015

I.d.R. Rasche Normalisierung der Nierenfunktion binnen 1 Jahr nach BEP.
Hypertonus vor Therapiestart und CDDP ≥400mg/m^2: Risiko CKD ↑

Pulmonale Funktionsstörung



FVC	499	492	423	292	297
FEV_1	539	525	453	295	316
DLCOc	376	381	348	258	281

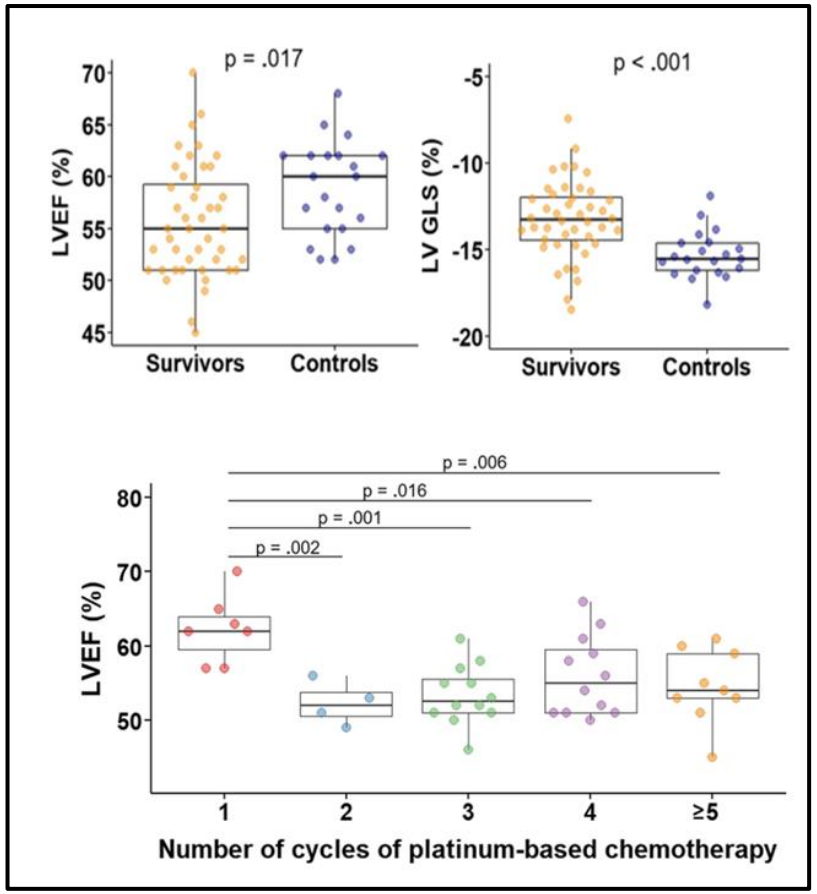
Laurtisen et al. JCO 2016

Bleomycin kurzfristig negativen Einfluss Lungenfunktion.

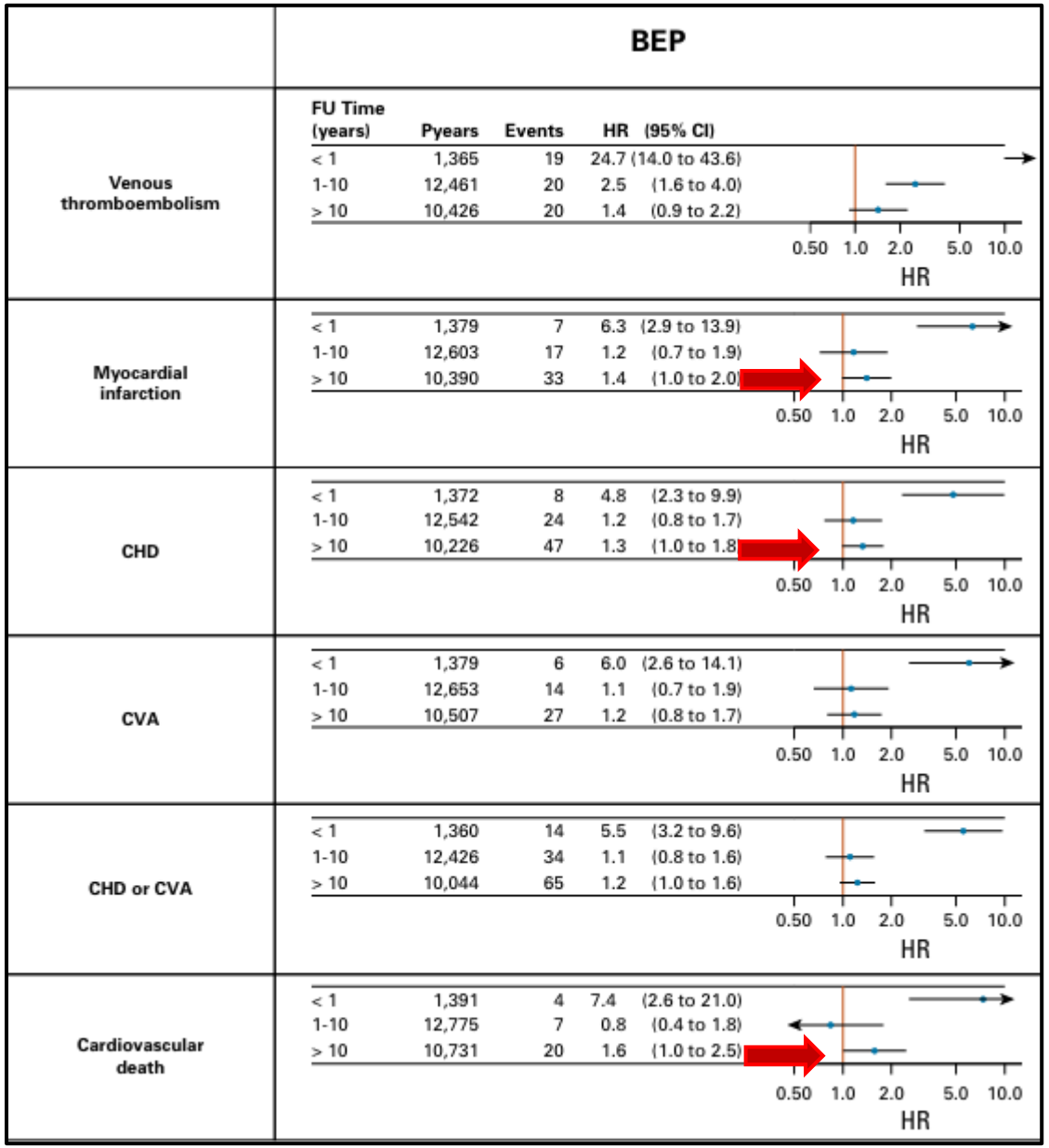
Kaum Langzeitfolgen ausser bei pulmonaler Resektion oder Rauchen.

CVD

LVEF



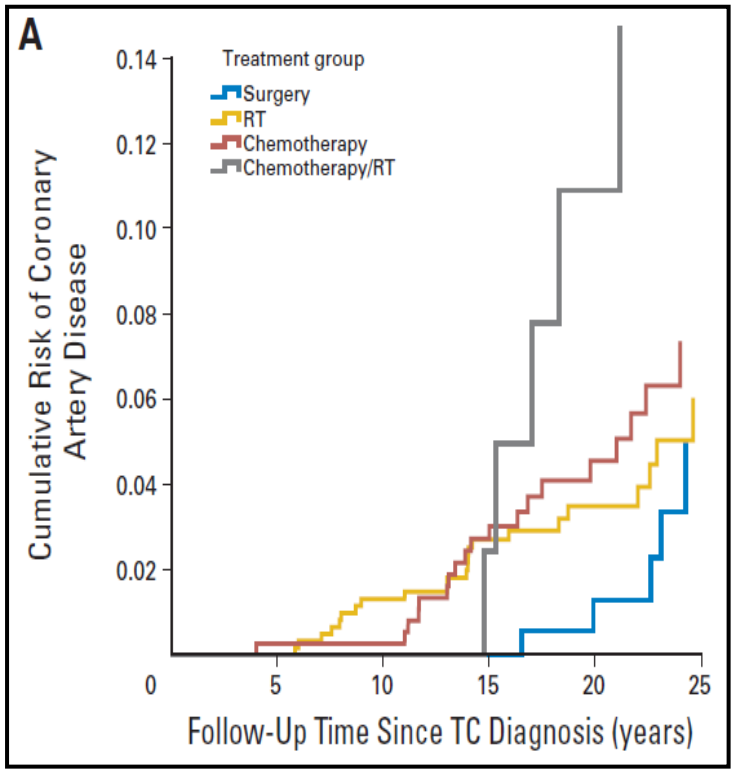
BeitzenHeinecke et al. Eur Radiol 2024



Lauritsen et al. J Clin Oncol 2019

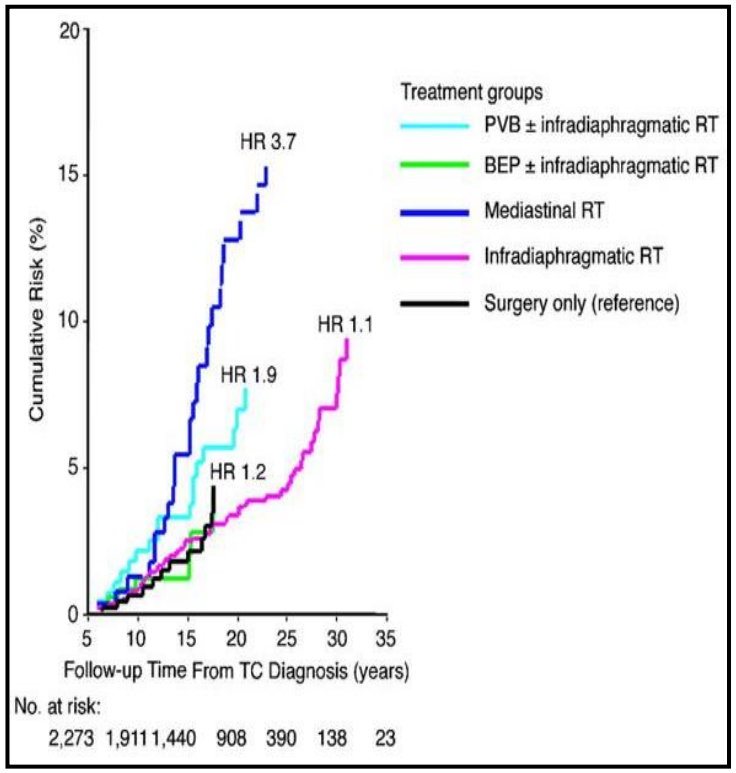
Kardiovaskuläre Ereignisse

CAD

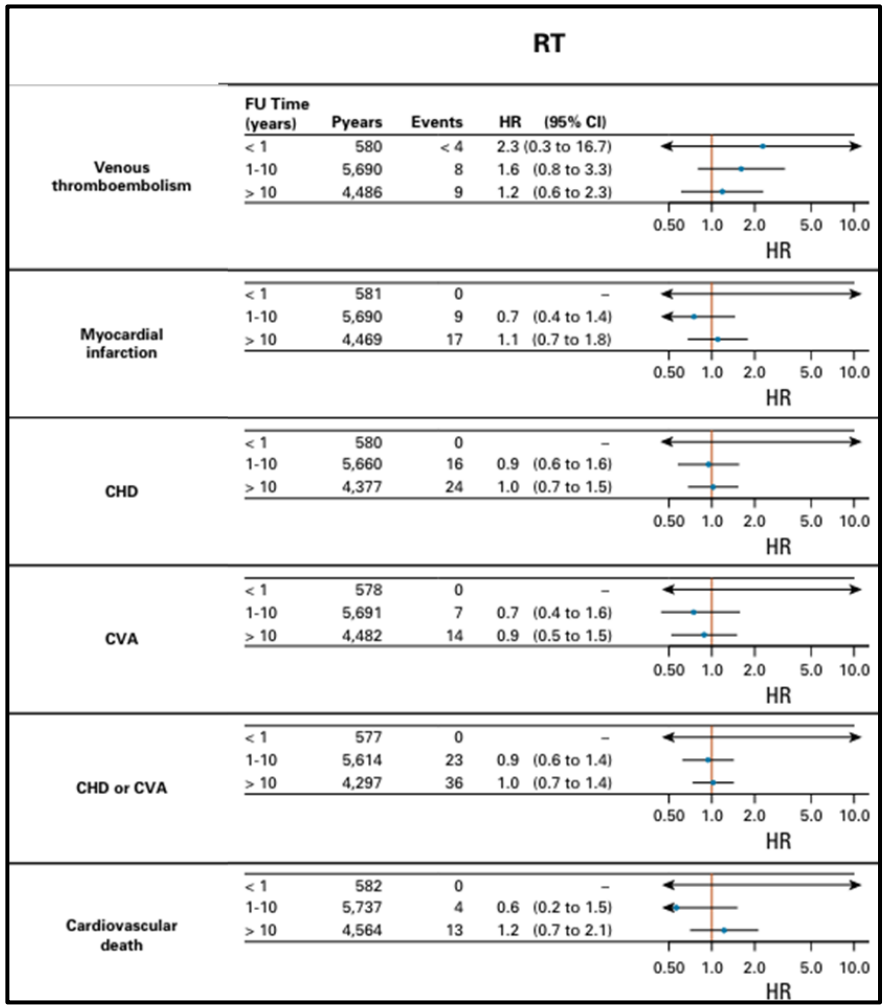


Haugnes et al. JCO 2010

MI

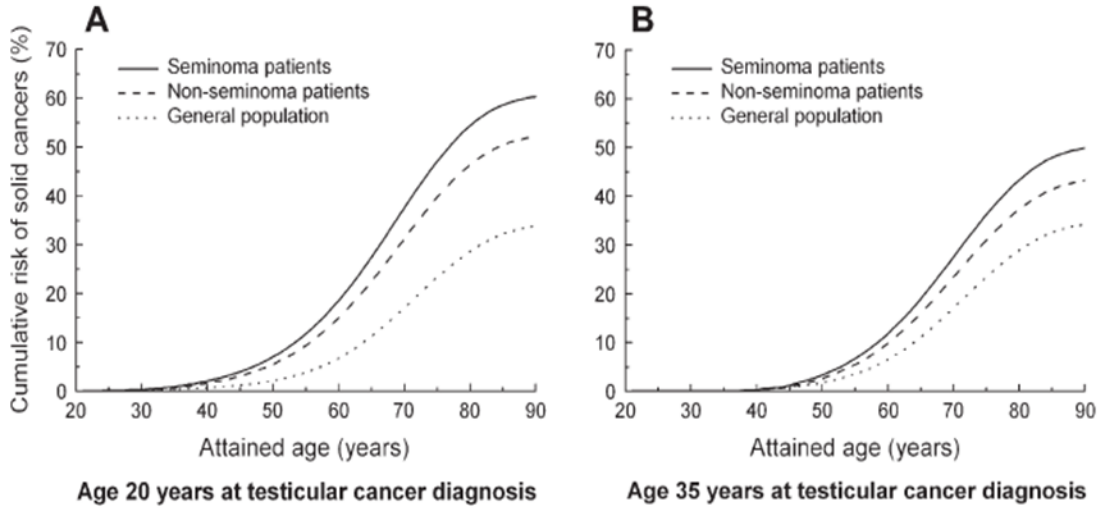


Van den Belt-Dusebout et al. JCO 2006



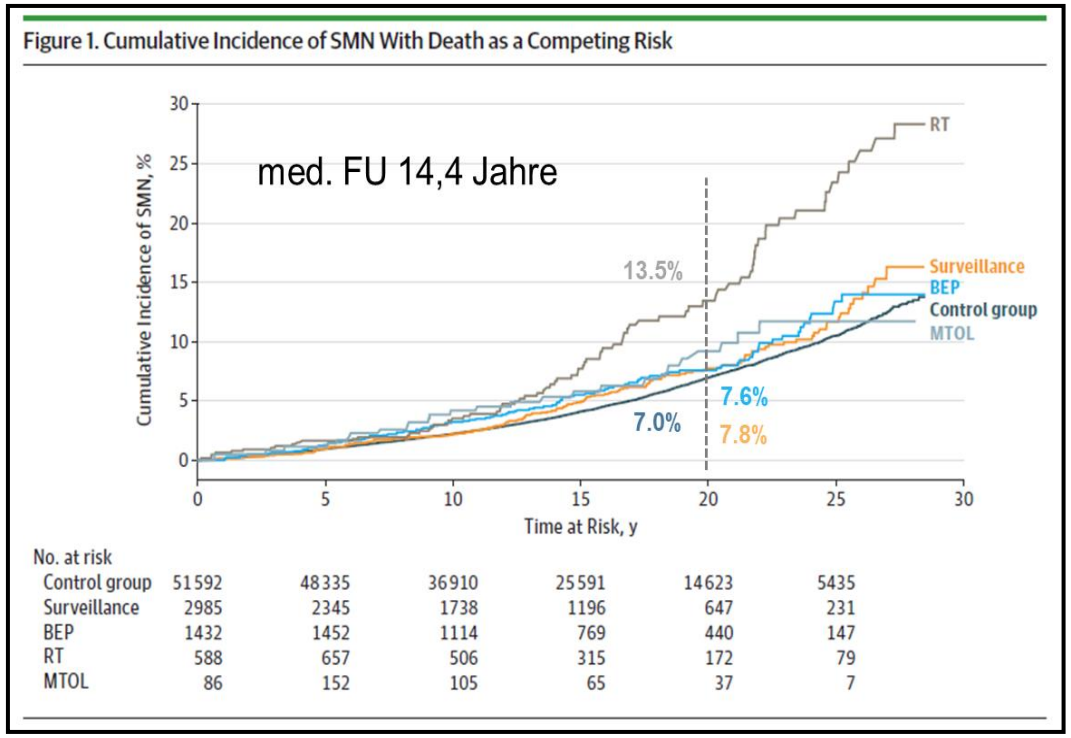
Lauritsen et al. J Clin Oncol 2019

Sekundärmalignome

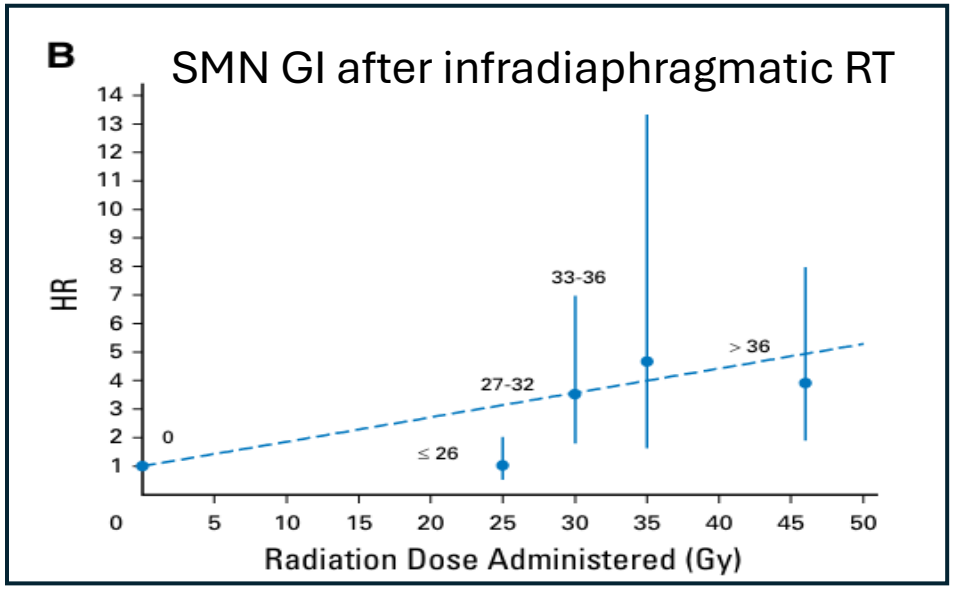


SMN risk is age-related and higher in younger GCT patients

Travis et al J Natl Cancer Inst 2005



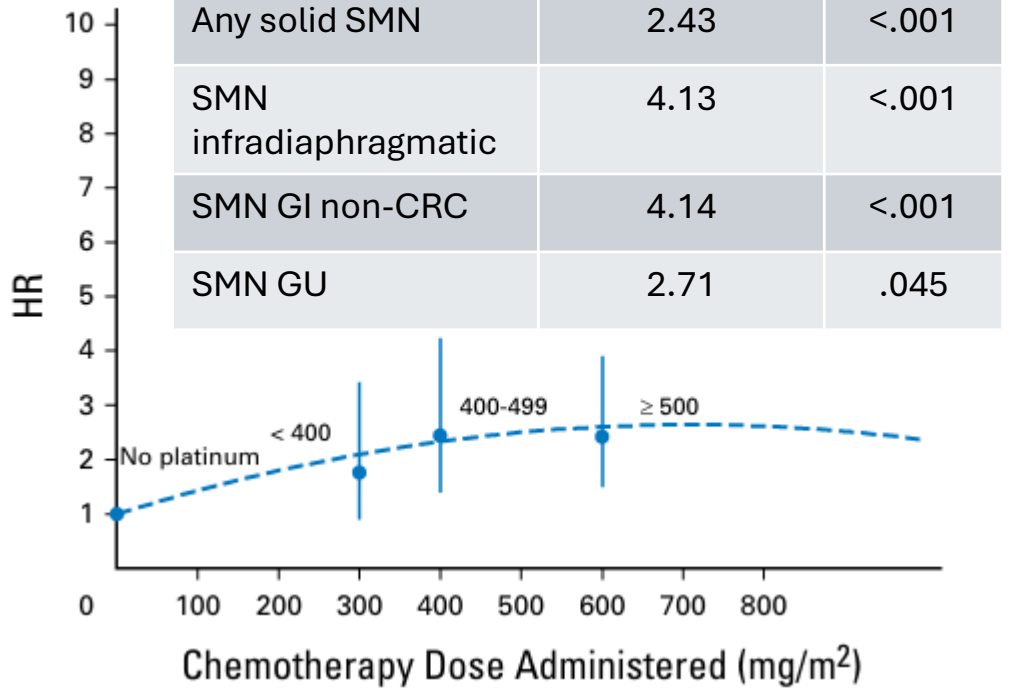
Kier et al., JAMA Oncol 2016



Groot et al., J Clin Oncol 2018

Sekundärmalignome nach PBCT

CDDP 400-499mg/m²	HR	P
Any solid SMN	2.43	<.001
SMN infradiaphragmatic	4.13	<.001
SMN GI non-CRC	4.14	<.001
SMN GU	2.71	.045



Groot et al., J Clin Oncol 2018

Anstieg der Gesamt- und Krebsmortlität nach >10 Jahren.

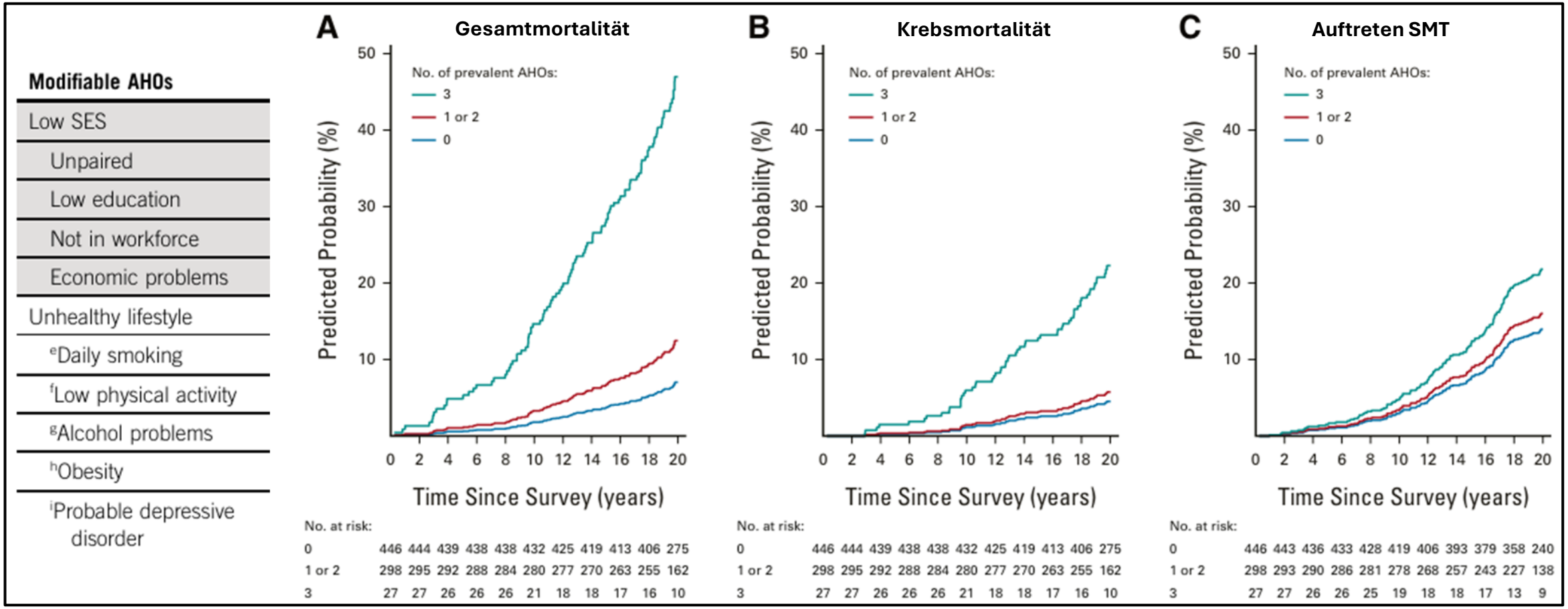
50% der Todesfälle Krebs-assoziiert (71% PBCT-high).

Surgery only

PBCT-standard ≤630mg/m² CDDP

PBCT-high >630mg/m² CDDP

Modifizierbare Risikofaktoren



Fosså et al., J Clin Oncol 2022

Testosteronmangel

Study or Subgroup	CT Events	CT Total	Orchiectomy alone Events	Orchiectomy alone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Standard treatment						
Leitner et al 1986	1	22	0	6	1.3%	0.91 [0.03, 25.05]
Fossa et al 1990	1	25	1	23	1.8%	0.92 [0.05, 15.56]
Stuart et al 1990	0	27	0	11		Not estimable
Eberhard et al 2008	7	19	2	4	3.8%	0.58 [0.07, 5.11]
Palmieri et al 1996	3	28	2	16	4.2%	0.84 [0.13, 5.64]
Nuver et al 2005.	18	86	3	44	5.7%	3.62 [1.00, 13.04]
Gerl et al 2001	13	117	3	58	6.5%	2.29 [0.63, 8.39]
Willemse et al 2013	35	176	3	58	6.6%	4.55 [1.34, 15.41]
Aas et al 1991	6	42	5	31	9.0%	0.87 [0.24, 3.15]
Nord et al 2003	38	373	12	251	23.6%	2.26 [1.16, 4.41]
Huddart et al 2005	35	272	19	169	37.4%	1.17 [0.64, 2.11]
Subtotal (95% CI)		**1187**		**671**	**100.0%**	**1.79 [1.28, 2.51]**
Total events	157		50			

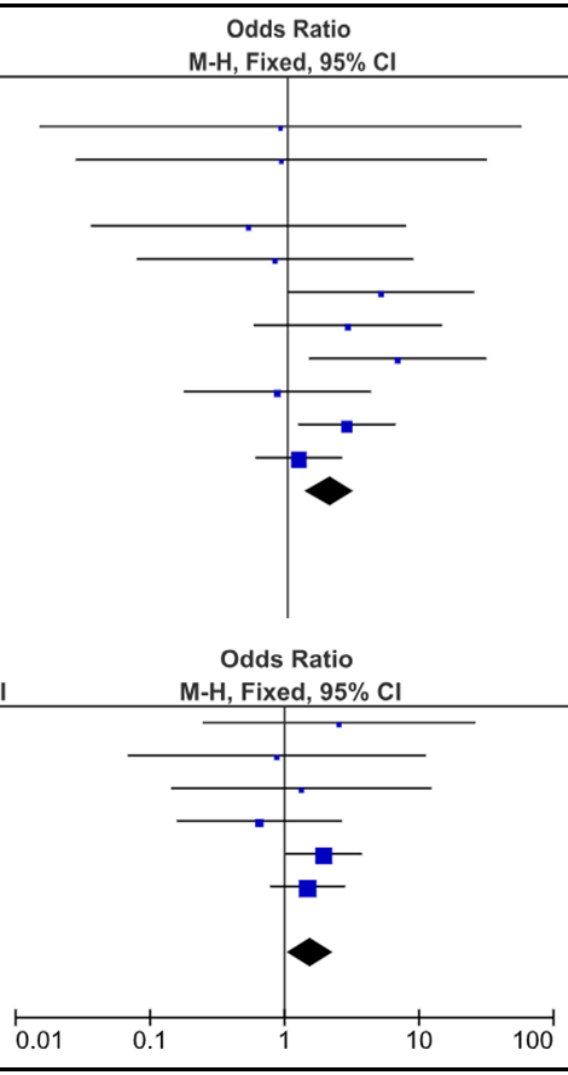
Heterogeneity: $\chi^2 = 9.23$, df = 9 ($p = 0.42$); $I^2 = 2\%$

Test for overall effect: Z = 3.38 ($p = 0.0007$)

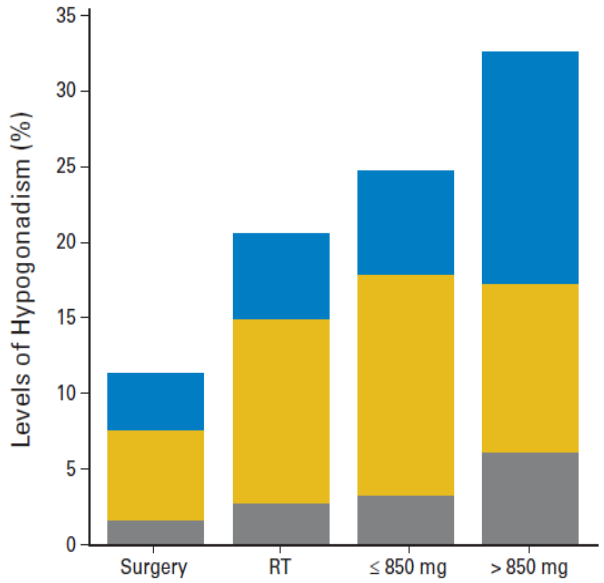
Study or Subgroup	RT Events	RT Total	Orchiectomy only Events	Orchiectomy only Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fossa et al 1990	3	29	1	23	2.6%	2.54 [0.25, 26.18]
Palmieri et al 1996	1	9	2	16	3.3%	0.88 [0.07, 11.24]
Eberhard et al 2008	8	14	2	4	3.5%	1.33 [0.14, 12.37]
Aas et al 1991	4	36	5	31	12.4%	0.65 [0.16, 2.67]
Nord et al 2003	46	515	12	251	38.1%	1.95 [1.02, 3.76]
Huddart et al 2005	25	158	19	169	40.1%	1.48 [0.78, 2.82]
Total (95% CI)		**761**		**494**	**100.0%**	**1.56 [1.04, 2.35]**
Total events	87		41			

Heterogeneity: $\chi^2 = 2.34$, df = 5 ($p = 0.80$); $I^2 = 0\%$

Test for overall effect: Z = 2.14 ($p = 0.03$)



Bandak et al. Andology 2016



Elevated LH, normal TEST

Serum-TEST < 10nmol/l

TEST replacement

Haugnes et al. J Clin Oncol 2012

Sexualleben

IIEF-15 Outcomes	OR (95% CI) Adjustment for Age	Adjustment for Neurotoxicity	Adjustment for Anxiety or Depression	Multivariable Adjustment*
Erectile dysfunction:				
Surveillance (referent)	1	1	1	1
Bleomycin, etoposide + cisplatin alone	1.5 (1.0–2.1)†	1.2 (0.8–1.8)	1.5 (1.1–2.2)†	1.3 (0.9–1.8)
Bleomycin, etoposide + cisplatin, + post-chemotherapy surgery	2.1 (1.4–3.4)‡	1.8 (1.1–2.8)†	2.2 (1.4–3.4)‡	1.8 (1.1–2.8)†
Radiotherapy	1.7 (1.1–2.5)†	1.6 (1.1–2.5)†	1.7 (1.1–2.6)†	1.6 (1.1–2.5)†
More than 1 treatment line	3.2 (1.6–6.3)‡	2.4 (1.2–4.9)†	3.2 (1.6–6.5)‡	2.4 (1.2–5.1)†
Orgasmic dysfunction:				
Surveillance (referent)	1	1	1	1
Bleomycin, etoposide + cisplatin alone	1.2 (0.9–1.6)	1.0 (0.8–1.4)	1.2 (0.9–1.6)	1.1 (0.8–1.4)
Bleomycin, etoposide + cisplatin, + post-chemotherapy surgery	1.5 (1.0–2.1)†	1.3 (0.9–1.9)	1.5 (1.0–2.1)†	1.4 (1.0–2.0)
Radiotherapy	1.4 (1.0–1.9)†	1.3 (1.0–1.8)	1.5 (1.1–2.0)†	1.4 (1.0–1.9)
More than 1 treatment line	2.8 (1.6–4.7)‡	2.1 (1.2–3.6)‡	2.9 (1.7–5.0)‡	2.2 (1.2–3.8)†
Decreased overall satisfaction:				
Surveillance (referent)	1	1	1	1
Bleomycin, etoposide + cisplatin alone	1.1 (0.9–1.4)	0.9 (0.7–1.1)	1.1 (0.8–1.4)	0.9 (0.7–1.2)
Bleomycin, etoposide + cisplatin, + post-chemotherapy surgery	1.0 (0.8–1.4)	0.8 (0.6–1.1)	1.0 (0.7–1.4)	0.8 (0.6–1.2)
Radiotherapy	1.4 (1.1–1.9)†	1.3 (1.0–1.8)†	1.4 (1.1–1.9)†	1.4 (1.0–1.8)†
More than 1 treatment line	1.6 (1.0–2.6)	1.1 (0.7–1.9)	1.5 (0.9–2.6)	1.2 (0.7–2.0)
Decreased intercourse satisfaction:				
Surveillance (referent)	1	1	1	1
Bleomycin, etoposide + cisplatin alone	1.2 (0.9–1.6)	1.0 (0.7–1.4)	1.1 (0.8–1.6)	1.0 (0.7–1.7)
Bleomycin, etoposide + cisplatin, + post-chemotherapy surgery	1.3 (0.8–1.9)	1.0 (0.7–1.6)	1.2 (0.8–1.9)	1.1 (0.7–1.7)
Radiotherapy	0.9 (0.6–1.4)	0.8 (0.5–1.3)	0.9 (0.6–1.3)	0.8 (0.5–1.3)
More than 1 treatment line	1.7 (0.9–3.4)	1.3 (0.6–2.6)	1.6 (0.8–3.3)	1.3 (0.7–2.7)
Decreased sexual desire:				
Surveillance (referent)	1	1	1	1
Bleomycin, etoposide + cisplatin alone	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Bleomycin, etoposide + cisplatin, + post-chemotherapy surgery	1.1 (0.7–1.7)	1.1 (0.8–1.7)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
Radiotherapy	1.0 (0.7–1.5)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	1.0 (0.7–1.5)
More than 1 treatment line	1.2 (0.6–2.3)	1.1 (0.5–2.1)	1.1 (0.6–2.2)	1.1 (0.5–2.2)

* Neurotoxicity, anxiety or depression, Charlson comorbidity index and smoking.
† $p < 0.05$.
‡ $p < 0.005$.

Bandak et al., J Urol 2018

Aufklärung über Risiko der erektilen Dysfunktion obligat.

Fazit und Ausblick

- HRQoL nicht signifikant verschieden von Gesamtpopulation
- CDDP-assoziierte Langzeitfolgen sind vielfältig und dosisabhängig
- Überproportional Zunahme ab CDDP Kumulativdosis ≥400mg/m^2
- Reduktion der CDDP-Kumulativdosis wann immer möglich
  - Vermeidung adjuvanter Therapie im CS I
  - De-Eskalation der Therapie beim CS IIA/B
  - CS IIA/B: Primäre RPLND vermeidet jegliche Chemotherapie bei 70-80%
  - Vermeidung von 4x EP anstatt 3x BEP bei IGCCCG good risk disease
  - Keine adjuvante Therapie nach post-Chemo RPLND ungeachtet des vitalen Keimzelltumor-Anteils
- **Holistische Nachsorge mit Fokus Spätfolgen weit über 5 Jahre hinaus**

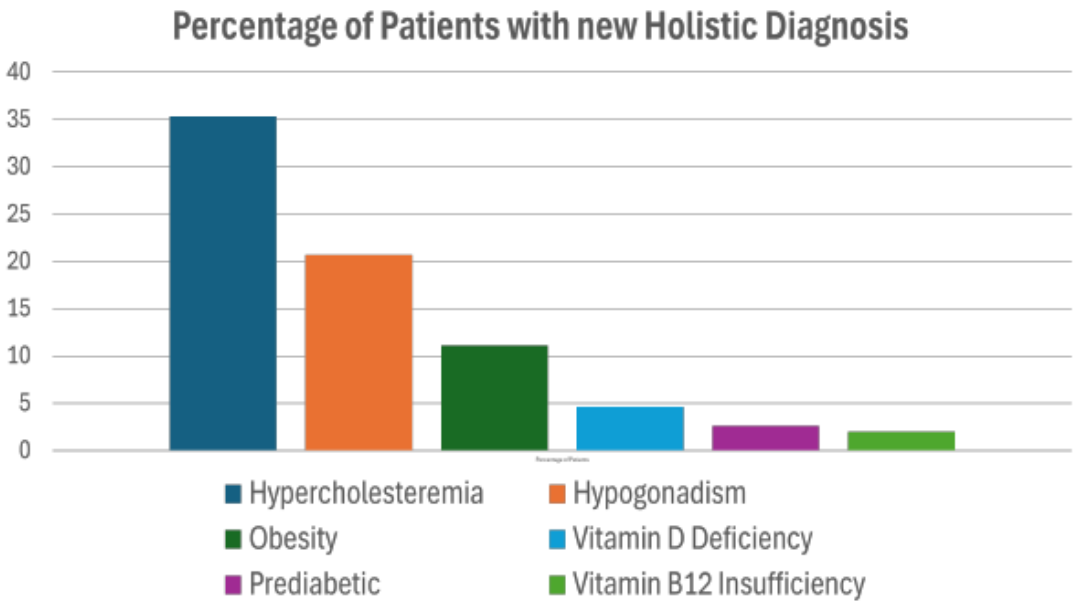
RMH care pathway EMPOWER

	Pre Empower Pathway (EP) survey		Post pathway survey
Issue	% that felt this was important	% that felt this was addressed in CLC	% that felt this was addressed
Lifestyle and exercise	80	9.6	87.5
Mental Health	70	18.1	100
Sexual Health and well-being (including fertility)	50	13.5	80.5
Effort made to understand health concerns	NA	50	100
Effort made to listen to health concerns	NA	64	100
Effort made to involve what mattered to them within their care	NA	68	100

Holwell et al. ESMO 2024

Results

88 patients (58.6%) had a new holistic diagnosis



- **100% patients had a shared care plan.**
- 38/150 patients (25.3%) reported symptoms of anxiety, and 8 (5.3%) reported symptoms of depression.
- Three internal referrals were made to the adult psychological support service with 9.4% being signposted to local primary care services.
- 0.6% of patients required an onward GP referral request.

Champion et al. ESMO 2024

Survivorship care

- Einfaches Nachsorgeschema adaptiert an das primäre Therapiekonzept
- Patientenedukation und Motivation
- Einbindung der hausärztlichen Versorgung

- Spättoxizitäten erklären
- Beeinflussung *Life style factors* (Sport, Nikotin, Gewicht)
- Kontrolle kardiovaskulärer Risikofaktoren
- Kontrolle der Sexualhormone
- Kontrolle Zweittumore (lebenslang)

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