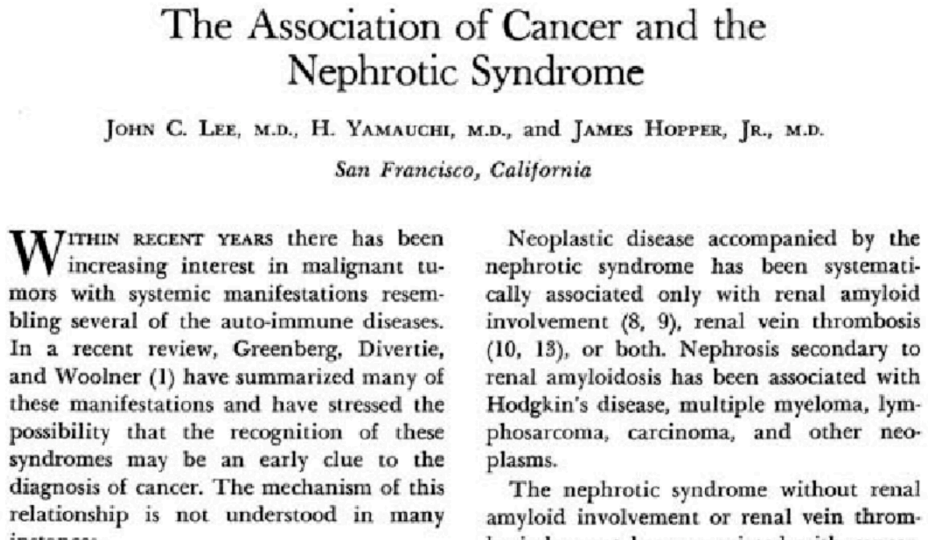
Paraneoplastische Membranöse Nephropathie

PD Dr. med. Andreas D. Kistler
Nephrologische Abteilung, Klinik für Innere Medizin
Kantonsspital Frauenfeld, Schweiz
andreas.kistler@stgag.ch
www.nephrologie-thurgau.ch

Paraneoplastische MN: historisches



The Association of Cancer and the Nephrotic Syndrome

JOHN C. LEE, M.D., H. YAMAUCHI, M.D., and JAMES HOPPER, JR., M.D.
San Francisco, California

WITHIN RECENT YEARS there has been increasing interest in malignant tumors with systemic manifestations resembling several of the auto-immune diseases. In a recent review, Greenberg, Divertie, and Woolner (1) have summarized many of these manifestations and have stressed the possibility that the recognition of these syndromes may be an early clue to the diagnosis of cancer. The mechanism of this relationship is not understood in many

Neoplastic disease accompanied by the nephrotic syndrome has been systematically associated only with renal amyloid involvement (8, 9), renal vein thrombosis (10, 13), or both. Nephrosis secondary to renal amyloidosis has been associated with Hodgkin's disease, multiple myeloma, lymphosarcoma, carcinoma, and other neoplasms.

The nephrotic syndrome without renal amyloid involvement or renal vein throm-

N=100 Patienten mit NS
11 davon mit Tumor
8 davon MN

Lee et al., Ann Int Med 1966

Prävalenz von Tumoren bei MN

Table 2
Prevalence of secondary membranous glomerulonephritis and prevalence of neoplasia in membranous nephropathy

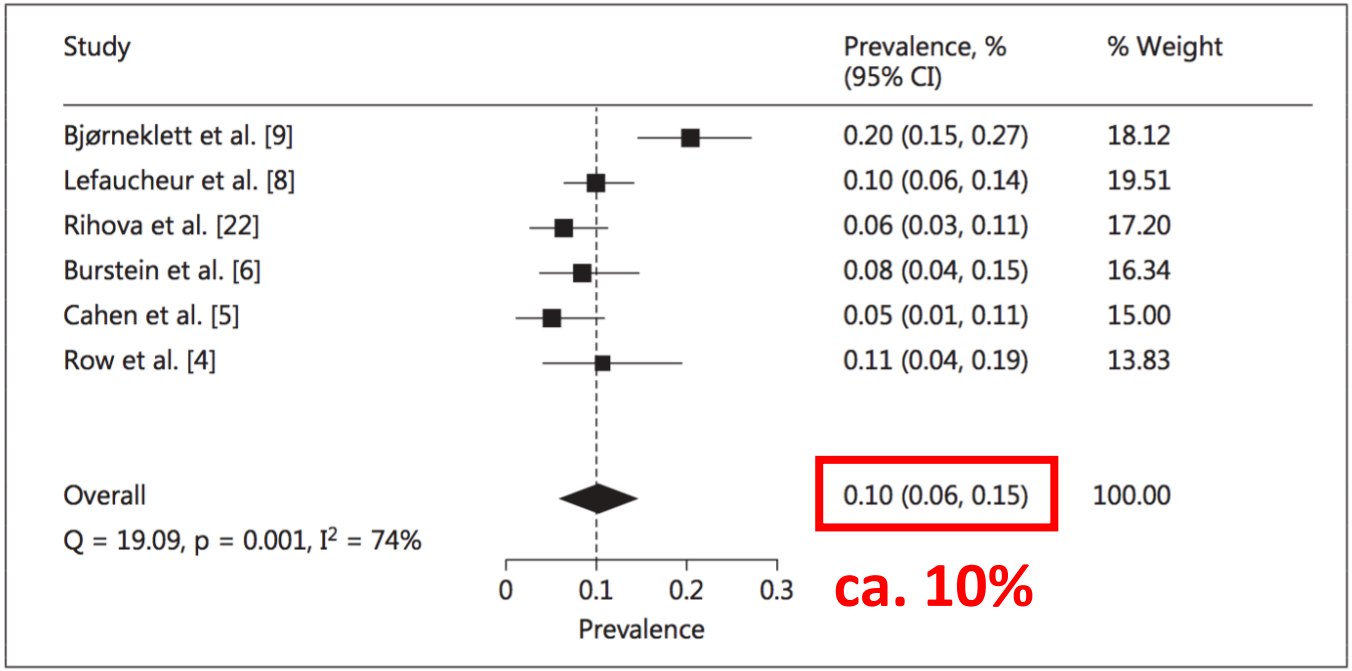
Author	Year	Number of patients	Neoplasia/total (%)
Row et al.	1975	66	11
Chavaz et al.	1977	92	8
Noel et al.	1979	140	1
Zech et al.	1982	30	22
Kingswood et al.	1984	24	12
Cahen et al.	1989	82	5
Burstein et al.	1993	107	8
LeFaucheur et al.	2006	240	10

Bachetta et al., Crit Rev Oncol Hematol 2009

Prävalenz von Tumoren bei MN

Table 2
Prevalence of secor
neoplasia in memb

Author
Row et al.
Chavaz et al.
Noel et al.
Zech et al.
Kingswood et al.
Cahen et al.
Burstein et al.
LeFaucheur et al.
Bachetta et al.



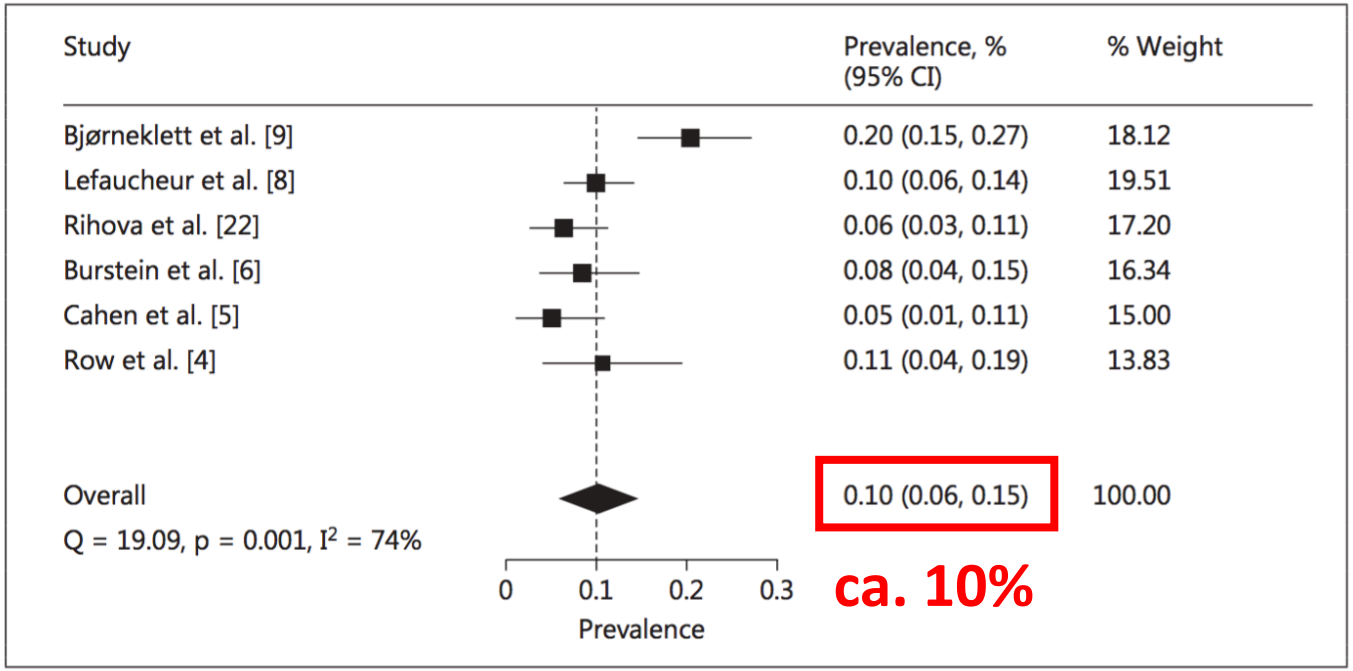
Leeaphorn et al., Am J Nephrol 2014

Prävalenz von Tumoren bei MN

Table 2
Prevalence of secor
neoplasia in memb

Author
Row et al.
Chavaz et al.
Noel et al.
Zech et al.
Kingswood et al.
Cahen et al.
Burstein et al.
LeFaucheur et al.

Bachetta et al.



Leeaphorn et al., Am J Nephrol 2014

Hoxha et al., JASN 2016: *Hamburg: 25/345 (7.2%) Boston: 18/242 (7.4%)*

Zeitpunkt der Tumordiagnose

Gleichzeitiges Auftreten
NS + Tumorsymptome

Vorbekannter
Tumor

Tumordiagnose
durch Screening
nach MN-Diagnose

Tumordiagnose
im Verlauf

Diagnosestellung MN

Zeitpunkt der Tumordiagnose

Gleichzeitiges Auftreten
NS + Tumorsymptome

Biopsiepraxis?
Einschlusskriterien?

Vorbekannter
Tumor

Tumordiagnose
durch Screening
nach MN-Diagnose

Tumordiagnose
im Verlauf

Diagnosestellung MN

Zeitpunkt der Tumordiagnose

Gleichzeitiges Auftreten
NS + Tumorsymptome

Screeningpraxis?

Vorbekannter
Tumor

Tumordiagnose
durch Screening
nach MN-Diagnose

Tumordiagnose
im Verlauf

Diagnosestellung MN

Zeitpunkt der Tumordiagnose

Gleichzeitiges Auftreten
NS + Tumorsymptome

Follow up?

Vorbekannter
Tumor

Tumordiagnose
durch Screening
nach MN-Diagnose

Tumordiagnose
im Verlauf

Diagnosestellung MN

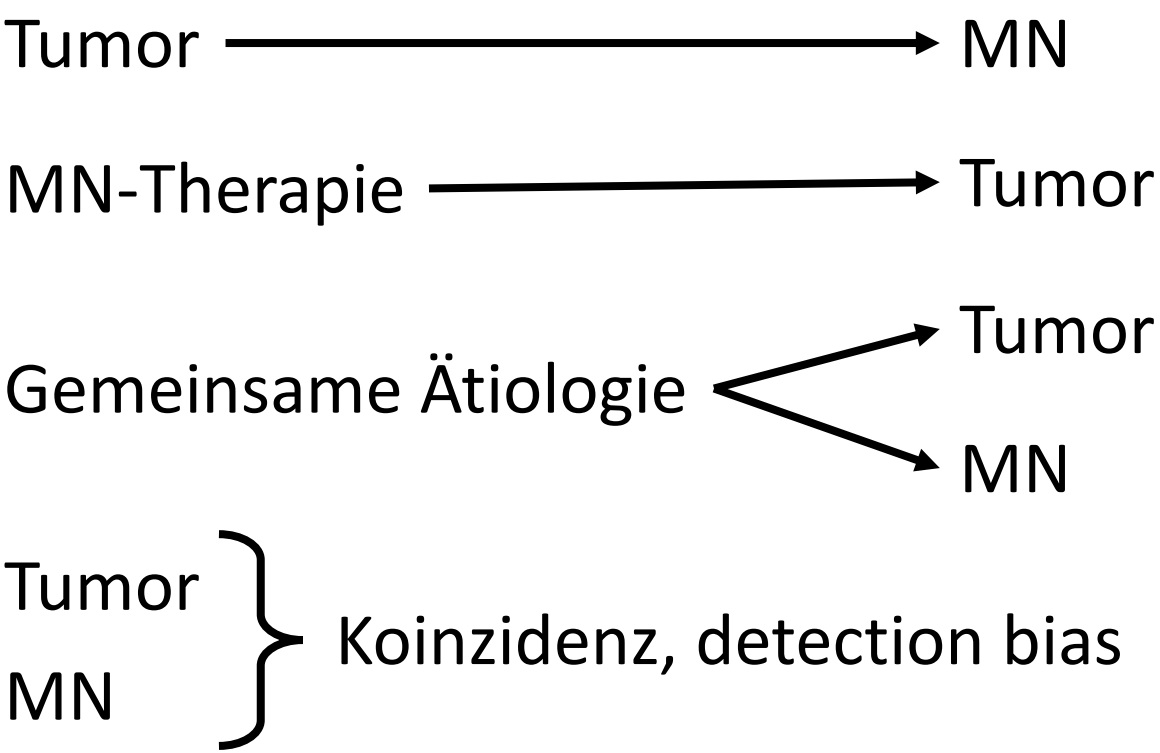
Mögliche Kausalität

Paraneoplastisches Syndrom

Tumor ⟶ MN

- Durch Tumor verursachte Begleiterkrankung
- weder durch Raumbedarf noch durch invasives Wachstum des Tumors / Metastasen verursacht
- sondern durch vom Tumor sezernierte Wachstumsfaktoren, Hormone, Antigene, etc.
- ***Kriterien:***
  - Zeitliche Korrelation von Tumor und paraneoplastischem Syndrom, inkl. Therapieansprechen / Rezidiv
  - Plausibler pathophysiologischer Zusammenhang

Mögliche Kausalität



Überblick

- Gibt es die paraneoplastische MN überhaupt?
- Pathogenese und Pathophysiologie
- Was den Kliniker interessiert:
  - ➤ Sollen Patienten mit MN auf Malignome gescreent werden?
  - ➤ Falls ja: welche?
  - ➤ ... und wie?

Standardisierte Inzidenz (SIR)

Age	Men SIR (95 %CI)	Women SIR (95 %CI)
18–54	10.2 (1.1–36.7)	9.5 (0.1–52.7)
55–64	8.6 (1.0–31.1)	13.0 (0.2–72.4)
⩾65	10.0 (5.0–17.9)	13.2 (3.5–33.7)
Total	9.8 (5.5–16.2)	12.3 (4.5–26.9)

Zum Zeitpunkt der NBX symptomatisch bei 52%
Dx durch Screening bei 48%

Lefaucheur et al., Kidney Int 2006
(GN-PROGRESS study group)

SIR = ca. 10

Standardisierte Inzidenz (SIR)

Table 3. Cancers in relation to the glomerular diseases subdivided into subgroups after WHO classification

	Males					Females				
140–205 All malignant neoplasms	obs	exp	O/E	CI low	CI high	obs	exp	O/E	CI low	CI high
1 Minor change	3	1.2679	2.37	0.48	6.91	**5**	**1.2287**	**4.07**	**1.31**	**9.5**
2 Focal segm. prolif.	8	4.7391	1.69	0.73	3.33	1	2.4635	0.41	0.01	2.26
3 Focal segmental sclerosis	4	1.4343	2.79	0.75	7.14	1	0.3806	2.63	0.03	14.62
4 Membranoproliferative	2	1.5874	1.26	0.14	4.55	2	1.257	1.59	0.18	5.74
5 Extracapillary	10	5.4802	1.82	0.87	3.36	5	2.3432	2.13	0.69	4.98
6 Endocapillary	**4**	**1.0128**	**3.95**	**1.06**	**10.11**	1	0.4963	2.02	0.03	11.21
7 Diffuse membranous	**13**	**7.28**	**1.79**	**0.95**	**3.05**	7	3.5455	1.97	0.79	4.07
8 Diffuse mesangial proliferative	**13**	**7.1**	**1.83**	**0.97**	**3.13**	8	4.5713	1.75	0.75	3.45
9 Diffuse sclerosis	3	1.5139	1.98	0.4	5.79	—	0.5198	—	—	5.76
10 Unclassified	**9**	**4.3373**	**2.08**	**0.95**	**3.94**	3	2.5837	1.16	0.23	3.39
Total	**69**	**35.753**	**1.93**	**1.5**	**2.44**	**33**	**19.3897**	**1.7**	**1.17**	**2.39**

Bold script indicates significant excess. Abbreviations are: obs, observed; exp, expected; CI, 95% confidence interval (low-high).

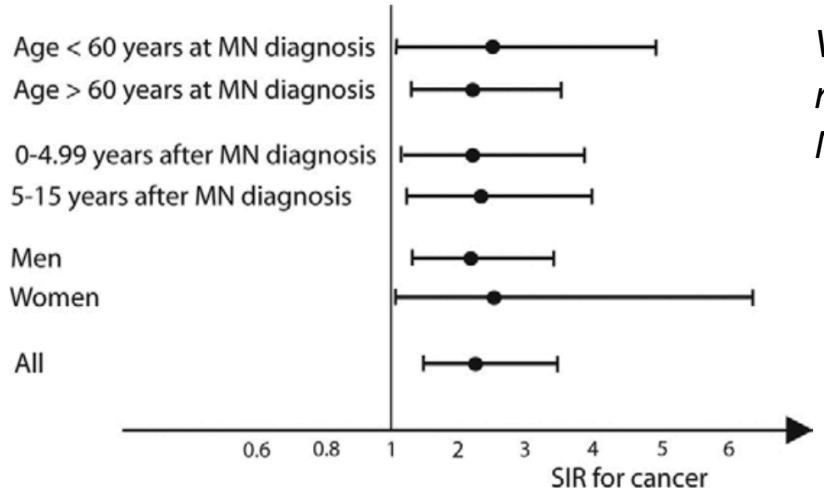
Verknüpfung von Nierenbiopsieregister mit Krebsregister (Zeitpunkt ab Nierenbiopsie)

Birkeland und Storm, Kidney Int 2003

SIR = ca. 2

Standardisierte Inzidenz (SIR)

Table 3. Cancers in relation to the glomerular diseases subdivided into subgroups after WHO classification

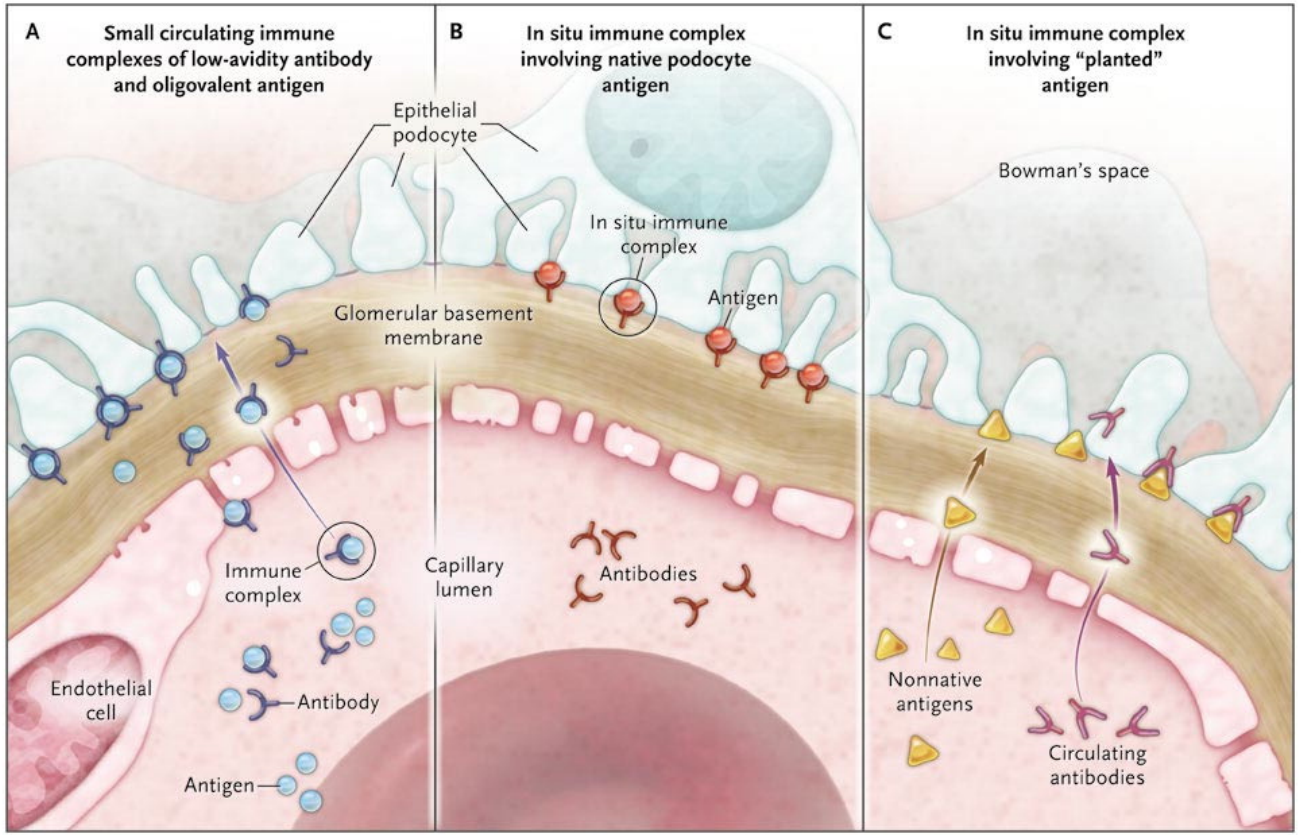


Verknüpfung von Nierenbiopsieregister mit Krebsregister (Zeitpunkt ab Nierenbiopsie)

Biorneklett et al., AJKD 2007

SIR = ca. 2,5

Pathophysiologie



Glassock, NEJM 2009

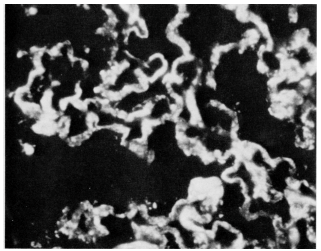
Pathophysiologie

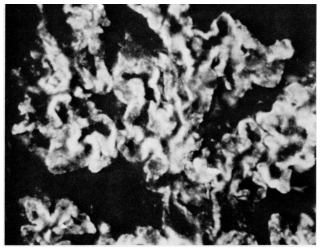
- Nachweis glomerulärer Ablagerung von Tumorantigenen gelang in einigen Fällen

THE NEW ENGLAND JOURNAL OF MEDICINE Sept. 6, 1973

CARCINOEMBRYONIC ANTIGEN-ANTIBODY COMPLEXES IN A PATIENT WITH COLONIC CARCINOMA AND NEPHROTIC SYNDROME

MARY E. COSTANZA, M.D., VIVIAN PINN, M.D.,
ROBERT S. SCHWARTZ, M.D., AND
LARRY NATHANSON, M.D.





Adenocarcinoma of the Palate Associated with Nephrotic Syndrome and Epimembranous Carcinoembryonic Antigen Deposition

DENNIS BOROCHOVITZ, MB, BCH, FF PATH (SA), WING K. KAM, MD, PHD, MARTHA NOLTE, MD, SCOTT GRANER, BS, AND JOSEPH KISS, MD

A 42-year-old male presented with adenocarcinoma of the palate and nephrotic syndrome. Renal biopsy demonstrated membranous glomerulopathy in which carcinoembryonic antigen was demonstrated. Carcinoembryonic antigen was also found in the palatal tumor. This is the first instance of this association with this particular tumor.

***Cancer* 49:2097–2102, 1982.**

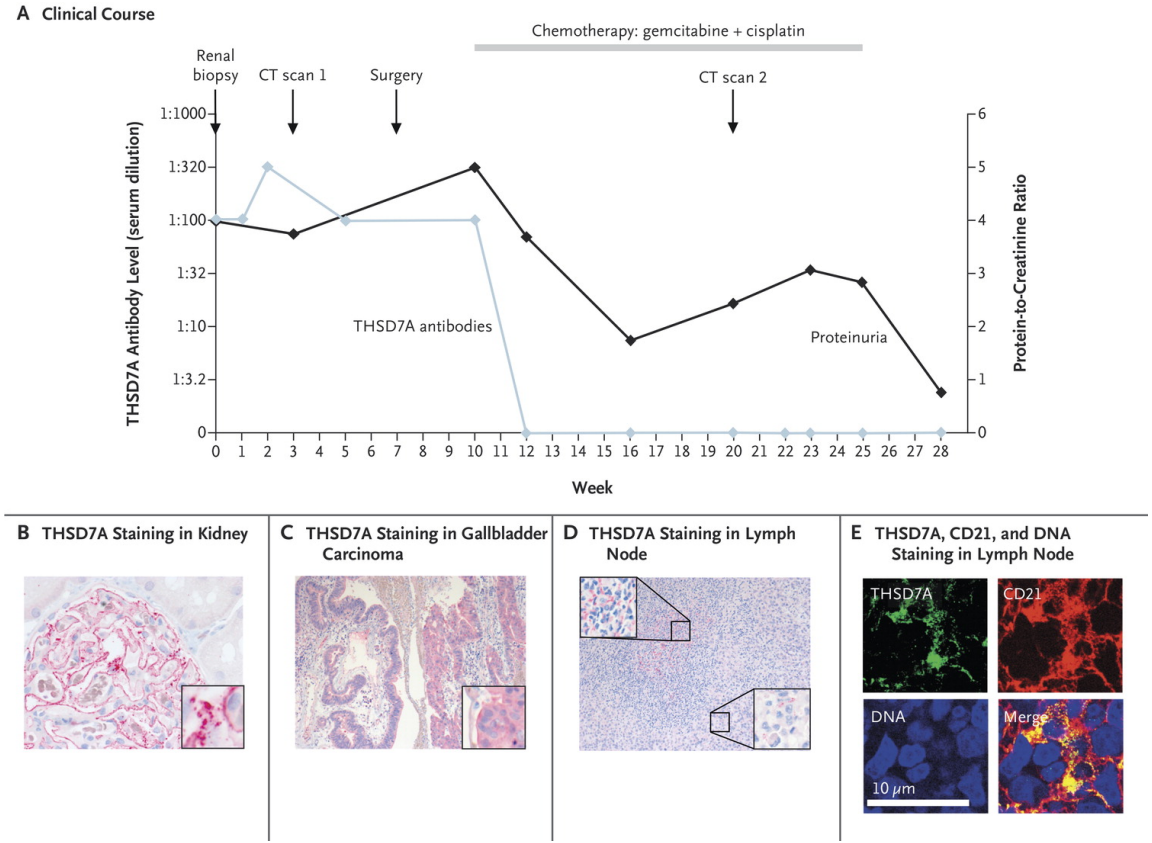
Pathophysiologie

- ***Aber:***
  - Kein Tumorantigen-Nachweis gelungen in anderen Fällen
  - Zirkulierende Immunkomplexe sind häufig nachweisbar bei Tumorpatienten
  - Glomeruläre Depots können oft nachgewiesen werden bei Tumorpatienten; diese Depots liegen aber meist mesangial / subendothelial und sind oft klinisch stumm (Pascal et al. Cancer Res 1976; Beaufils et al. Nephron 1985)

➤ Zusätzlicher Faktor nötig für subepitheliale Ablagerung?

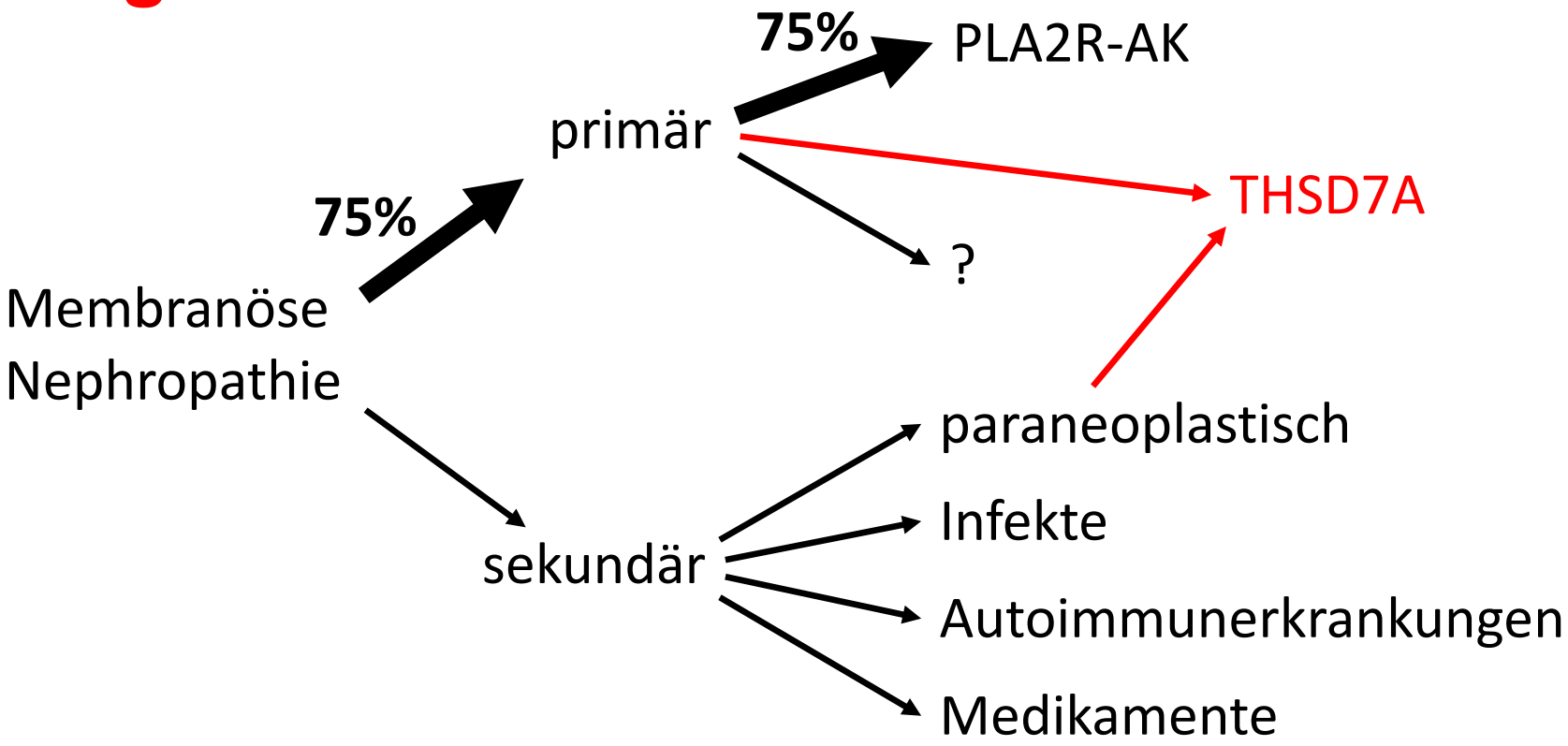
➤ Sind die Antigenablagerungen „innocent bystanders“?

Pathophysiologie



Hoxha et al., NEJM 2016

Ätiologie der MN



Überblick

- Gibt es die paraneoplastische MN überhaupt?
- Pathogenese und Pathophysiologie
- Was den Kliniker interessiert:
  - ➤ Sollen Patienten mit MN auf Malignome gescreent werden?
  - ➤ Falls ja: welche?
  - ➤ ... und wie?

Mögliche Argumente für Tu-Screening

- Verbesserung des Outcomes des Tumors (Präsymptomatische Detektion von Tumoren im Frühstadium)
- Verbesserung des Outcomes des nephrotischen Syndroms (Remission des NS mit Therapie des Tumors)
- Kontraindikation für Immunsuppression

Mögliche Argumente für Tu-Screening

- Verbesserung des Outcomes des Tumors (Präsymptomatische Detektion von Tumoren im Frühstadium)
  - ➤ *Keine robusten Daten*
- Verbesserung des Outcomes des nephrotischen Syndroms (Remission des NS mit Therapie des Tumors)

- Kontraindikation für Immunsuppression

Mögliche Argumente für Tu-Screening

- Verbesseru
  (Präsympt
  Frühstadiu
  ➤ *Keine ro*
- Verbesseru
  (Remissior
  ➤ *Fallserie*
- Kontraindi

Lefaucheur et al.,
Kidney Int 2006

Localization of tumor	Histology	*N*	M/F	Stage	Treatment of tumor	Remission	
						Tumor	Nephrotic-range proteinuria
C34 Bronchus and lung	Adenocarcinoma	4	3/1	T2N1M0	S	+	C
				T2N2M0	S+R	–	–
				T2N2M1	R	–	–
				T2N2M1	—	–	–
	Squamous cell carcinoma	4	4/0	T1N0M0	S	+	C
				T2N1M0	S+R+Ch	+	C
				T2N2M0	S+R	+	P
				T2N2M0	S+R	–	–
C61 Prostate	Adenocarcinoma	5	5/0	T2NxM0	H	+	C
				T2NxM0	H+Cs+R	+	P
				T3NxM0	H+R	–	–
				T3NxM0	S+H+Cs	–	–
				T3NxM1	H	–	–
C16 Stomach	Adenocarcinoma	2	1/1	T1N0M0	S	+	–
				T2N1M1	—	–	–
C18 Colon	Adenocarcinoma	1	1/0	Dukes D	Ch	–	–
C32 Larynx	Squamous cell carcinoma	1	1/0	T2N2M0	R	–	–
C37 Thymus	Micronodular thymoma	1	0/1	Masoaka II	S+R	+	C
C38 Mediastinum	Liposarcoma	1	1/0	T3N0M0	S	+	P
C67 Bladder	Transitional cell carcinoma	1	1/0	T4N1M0	S+R	–	–
C53 Cervix uteri	Squamous cell carcinoma	1	0/1	T2N0M0	R	+	–
C50 Breast	Infiltrating duct carcinoma	1	0/1	T2N0M0	S+R+H	+	–
C83 Diffuse non-Hodgkin's lymphoma	Follicular B-cell lymphoma	1	0/1		Cs+Cy	+	C
C92 Chronic myeloid leukaemia		1	0/1		Ch	–	–

Mögliche Argumente für Tu-Screening

- Verbesseru
  (Präsympt
  Frühstadiu
  ➤ *Keine ro*
- Verbesseru
  (Remissior
  ➤ *Fallserie*
- Kontraindi

Lefaucheur et al.,
Kidney Int 2006

Localization of tumor	Histology	*N*	M/F	Stage	Treatment of tumor	Remission: Tumor	Remission: Nephrotic-range proteinuria
C34 Bronchus and lung	Adenocarcinoma	4	3/1	T2N1M0	S	+	C
				T2N2M0	S+R	–	–
				T2N2M1	R	–	–
				T2N2M1	—	–	–
	Squamous cell carcinoma	4	4/0	T1N0M0	S	+	C
				T2N1M0	S+R+Ch	+	C
				T2N2M0	S+R	+	P
				T2N2M0	S+R	–	–
C61 Prostate	Adenocarcinoma	5	5/0	T2NxM0	H	+	C
				T2NxM0	H+Cs+R	+	P
				T3NxM0	H+R	–	–
				T3NxM0	S+H+Cs	–	–
				T3NxM1	H	–	–
C16 Stomach	Adenocarcinoma	2	1/1	T1N0M0	S	+	–
				T2N1M1	—	–	–
C18 Colon	Adenocarcinoma	1	1/0	Dukes D	Ch	–	–
C32 Larynx	Squamous cell carcinoma	1	1/0	T2N2M0	R	–	–
C37 Thymus	Micronodular thymoma	1	0/1	Masoaka II	S+R	+	C
C38 Mediastinum	Liposarcoma	1	1/0	T3N0M0	S	+	P
C67 Bladder	Transitional cell carcinoma	1	1/0	T4N1M0	S+R	–	–
C53 Cervix uteri	Squamous cell carcinoma	1	0/1	T2N0M0	R	+	–
C50 Breast	Infiltrating duct carcinoma	1	0/1	T2N0M0	S+R+H	+	–
C83 Diffuse non-Hodgkin's lymphoma	Follicular B-cell lymphoma	1	0/1		Cs+Cy	+	C
C92 Chronic myeloid leukaemia		1	0/1		Ch	–	–

Ca. 50% potentiell kurativ

Mögliche Argumente für Tu-Screening

- Verbesseru
  (Präsympto
  Frühstadiu
  ➤ *Keine ro*
- Verbesseru
  (Remissior
  ➤ *Fallserie*
- Kontraindi

Lefaucheur et al.,
Kidney Int 2006

Localization of tumor	Histology	*N*	M/F	Stage	Treatment of tumor	Remission	
						Tumor	Nephrotic-range proteinuria
C34 Bronchus and lung	Adenocarcinoma	4	3/1	T2N1M0	S	+	C
				T2N2M0	S+R	–	–
				T2N2M1	R	–	–
				T2N2M1	—	–	–
	Squamous cell carcinoma	4	4/0	T1N0M0	S	+	C
				T2N1M0	S+R+Ch	+	C
				T2N2M0	S+R	+	P
				T2N2M0	S+R	–	–
C61 Prostate	Adenocarcinoma	5	5/0	T2NxM0	H	+	C
				T2NxM0	H+Cs+R	+	P
				T3NxM0	H+R	–	–
				T3NxM0	S+H+Cs	–	–
				T3NxM1	H	–	–
C16 Stomach	Adenocarcinoma	2	1/1	T1N0M0	S	+	–
				T2N1M1	—	–	–
C18 Colon	Adenocarcinoma	1	1/0	Dukes D	Ch	–	–
C32 Larynx	Squamous cell carcinoma	1	1/0	T2N2M0	R	–	–
C37 Thymus	Micronodular thymoma	1	0/1	Masoaka II	S+R	+	C
C38 Mediastinum	Liposarcoma	1	1/0	T3N0M0	S	+	P
C67 Bladder	Transitional cell carcinoma	1	1/0	T4N1M0	S+R	–	–
C53 Cervix uteri	Squamous cell carcinoma	1	0/1	T2N0M0	R	+	–
C50 Breast	Infiltrating duct carcinoma	1	0/1	T2N0M0	S+R+H	+	–
C83 Diffuse non-Hodgkin's lymphoma	Follicular B-cell lymphoma	1	0/1		Cs+Cy	+	C
C92 Chronic myeloid leukaemia		1	0/1		Ch	–	–

Mögliche Argumente für Tu-Screening

- Verbesserung des Outcomes des Tumors (Präsymptomatische Detektion von Tumoren im Frühstadium)
  - ➤ *Keine robusten Daten*
- Verbesserung des Outcomes des nephrotischen Syndroms (Remission des NS mit Therapie des Tumors)
  - ➤ *Fallserien und -berichte*
- Kontraindikation für Immunsuppression
  - ➤ *Keine robusten Daten, aber plausibel*

Wen soll man screenen?

a) Klinische Prädiktoren (Lefaucheur et al., Kidney Int 2006)

- Alter

Age	MN	T	%
18–54	135	3	2.2
55–64	32	3	9.4
⩾65	73	18	24.7
Total	240	24	10.0

- Rauchen (68% MN-Patienten mit vs. 29% ohne Tumor haben >20 PY)
- Thrombosen (?)

Wen soll man screenen?

b) Histologie

- Mesangiale und subendotheliale Depots

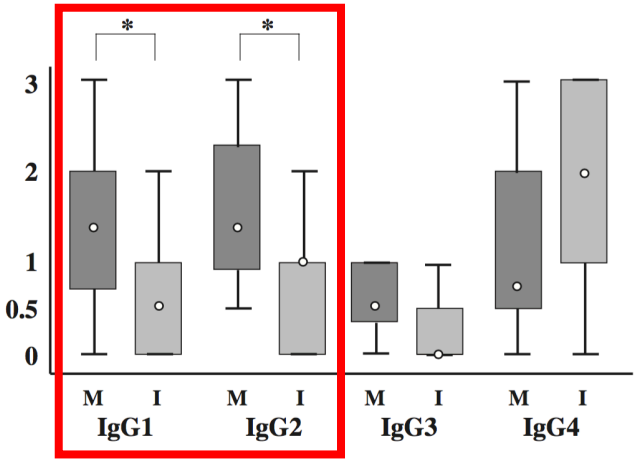
  Wenige Daten bei paraneoplastischer MN

  Sensitivität und Spezivität gering

  (Larsen et al., Mod Path 2013: mesangiale Depots bei 6/12 mMN vs. 25/85 iMN)
- Endokapilläre Leukozyten (>8 / Glom)

  Lefaucheur et al., Kidney Int 2006: Sensitivität 92%, Spezifität 75%
- IgG-Subklassen:

Wen soll man screenen? IgG-Subklassen



Ohtani et al., NDT 2004
M-MN: n=10
I-MN: n=15

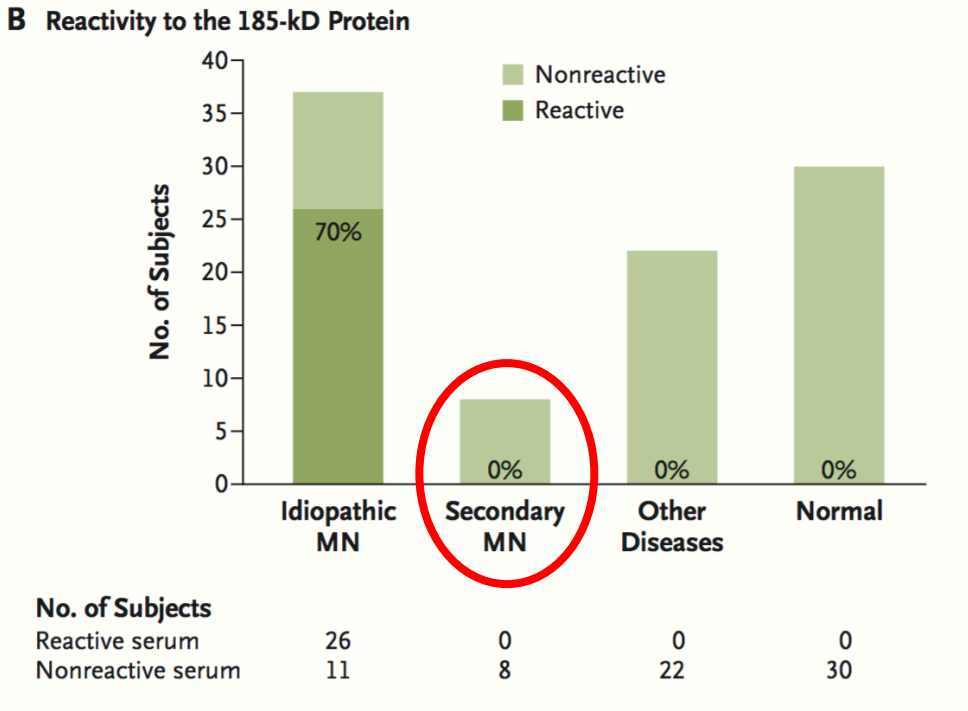
Parameters	M-MN ($n = 8$)	I-MN ($n = 42$)	P-value
IHC score of IgG1 (Scores: 0/1/2/3)	4/0/3/1	31/7/4/0	0.066
IHC score of IgG2 (Scores: 0/1/2/3)	1/0/6/1	20/4/16/2	0.030
IHC score IgG3 (Scores: 0/1/2/3)	4/1/1/2	10/3/18/11	0.248
IHC score IgG4 (Scores: 0/1/2/3)	7/0/1/0	6/4/14/18	<0.001

Qu et al., NDT 2012

	Idiopathic MN ($n = 69$)	Malignancy-associated MN ($n = 16$)	
	% Positive	% Positive	Difference between groups, P-value
IgG4	65	31	<0.05
IgG3	22	19	NS
IgG2	81	94	NS
IgG1	1	6	NS
PLA_2R	56	19	<0.05

Lunnbrö-Widgren et al., CKJ 2015

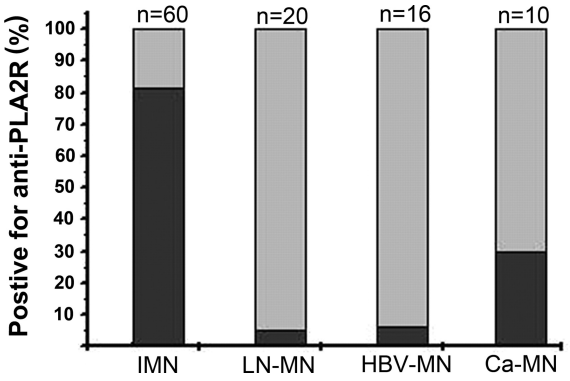
Wen soll man screenen? PLA2R-Ak



N=0 Patienten mit Tumoren

Beck et al., NEJM 2009

Wen soll man screenen? PLA2R-Ak



Qin et al., JASN 2011

7/10 PLA2R-Ak negativ:

- IF IgG4-negativ bei allen
- 3 † , 3 ohne Tumor-Th, 2 CR nach Tumor-Resektion

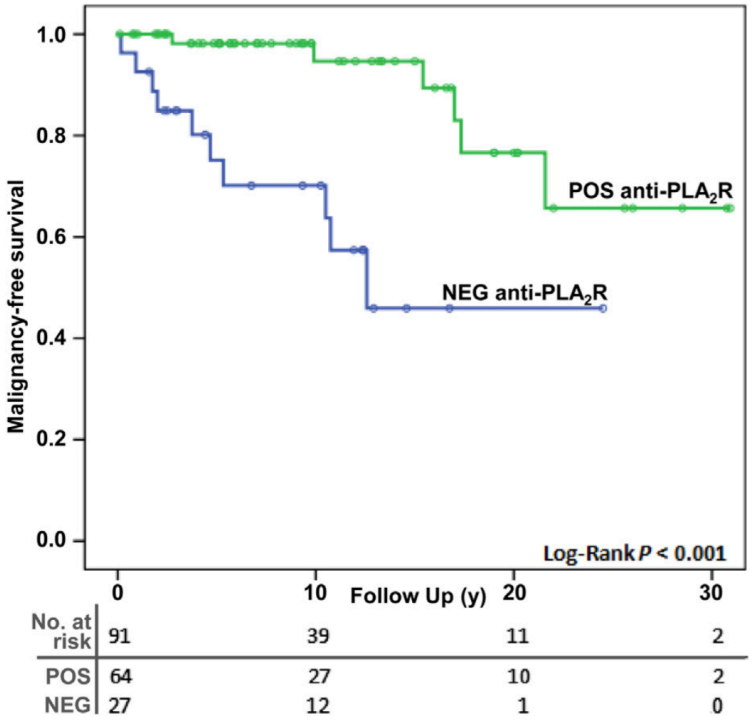
3/10 PLA2R-Ak positiv:

- IF IgG4-positiv bei 2 Pat
- Alle 3 mit persistierendem NS trotz Tumor-Resektion

PLA2R-Ak bei Patienten mit Tumor-assoziierter MN

Referenz	Serum	Biopsie
Qin, JASN 2011	3/10	
Hoxha, NDT 2011	0/3	
Hoxha, KI 2012	0/7	0/7
Larsen 2013		3/12
Segarra-Medrano 2014	1/2	1/2
Lunnbrö-Widgren 2015		3/16
Total	**4/22 (18%)**	**5/37 (14%)**
Hoxha, JASN 2016 *Hamburg* *Boston*	 14/25 (56%) 8/18 (44%)	

PLA2R-Ak und Malignomrisiko



N=91 Patienten mit „idiopathischer“ MN (kein klinischer Verdacht auf sekundäre MN; negative Serologien auf Hepatitis, HIV, Auto-Ak, Kryo)

Table b. Multiple Cox regression analysis of malignancy in iMN.

Parameter	Hazard ratio	95% CI	*P*
Negative anti-PLA_2R*	9.705	2.324 – 40.537	0.002
Age* (per 1-y older)	1.080	1.029 – 1.132	0.002
Male gender	4.795	1.271 – 18.089	0.021
Immunosuppression†	2.220	0.527 – 9.356	0.277

Timmermans et al., AJKD 2013

PLA2R-Ak und Malignomrisiko

An Indirect Immunofluorescence Method Facilitates Detection of Thrombospondin Type 1 Domain–Containing 7A–Specific Antibodies in Membranous Nephropathy

Elion Hoxha,* Laurence H. Beck Jr.,† Thorsten Wiech,‡ Nicola M. Tomas,* Christian Probst,§ Swantje Mindorf,§ Catherine Meyer-Schwesinger,* Gunther Zahner,* Phillip R. Stahl,‡ Ruth Schöpper,* Ulf Panzer,* Sigrid Harendza,* Udo Helmchen,‖ David J. Salant,† and Rolf A.K. Stahl*

J Am Soc Nephrol **28:** ●●●–●●●, 2016

Kohorte	PLA2R^{+}	PLA2R^{-}
Hamburg	14/259 (5.4%)	11/86 (12.8%)
Boston	8/153 (5.2%)	10/89 (11.2%)
Total	22/412 (**5.3%**)	21/175 (**12.0%**)

THSD7A-Ak und Malignomrisiko

Table 2. Clinical baseline characteristics of patients with THSD7A-associated MN

Clinical Characteristics	Prospective Hamburg Cohort: 345 Patients	Retrospective Hamburg Cohort: 689 Patients	Boston Cohort: 242 Patients	Combined Patient Cohorts: 1276 Patients
No. of patients with THSD7A-associated MN (% of the respective cohort population)	9 (2.6)	20 (2.9)	11 (4.5)	40 (3.1)
Age, yr, median, IQR	47, 39–61	67, 55.25–76	51, 33–66	60.5, 46–73.25
Men (%)	3 (33)	11 (55)	3 (27)	17 (43)
Proteinuria, g/24 h, median, IQR	5.4, 4.0–6.9	7.2, 4.3–9.9 (*n*=16)	5.9, 3.0–7.7 (*n*=11)	6.7, 3.7–8.6 (*n*=36)
Serum creatinine, mg/dl, median, IQR	0.8, 0.6–0.9	1.3, 1.0–2.0 (*n*=16)	0.8, 0.8–1.5 (*n*=9)	1.0, 0.8–1.5 (*n*=34)
Time from renal biopsy to study inclusion, mo, median, IQR	0.75, 0.5–0.8	1.0, 0.0–12.3	1.0, 0.3–25.5	1.0, 0.0–11.6
No. of patients with THSD7A-associated MN and malignancy (% of the respective THSD7A–associated MN population)	3 (33.3)	4 (20.0)	1 (9.1)	8 (20.0)

Data on proteinuria and serum creatinine were available for 36 and 34 patients, respectively. In 29 patients, the time between renal biopsy (and diagnosis of MN) and study inclusion (and serum collection for PLA_2R1-Ab and THSD7A-Ab measurement) was <6 months. IQR, interquartile range.

Hoxha et al., JASN 2016

Wen soll man screenen

- Kosteneffizienz unklar, keine prospektiven Studien
- Kein klinischer, histologischer oder Laborparameter unterscheidet klar zwischen iMN und pMN
- Verschiedene Parameter können aber helfen, die Vortestwahrscheinlichkeit abzuschätzen:
  - Alter, Nikotin
  - Histologie (IgG-Subklassen, mesangiale / subendotheliale Depots, endokapilläre Leukozyten)
  - PLA2R, THSD7A

Wie soll man screenen?

Type of malignancy	Bjørneklett et al. [9]	Lefaucheur et al. [8]	Rih et al	Total
Lung	6 (18.18)	8 (33.33)	3 (3	22 (25.88)
Prostate	7 (21.21)	5 (20.83)	1 (1	13 (15.29)
Hematologic	5 (15.15)	2 (8.33)	0 (0	12 (14.11)
Colon/rectal	4 (12.12)	1 (4.16)	1 (1	9 (10.58)
Breast	4 (12.12)	1 (4.16)	0 (0	6 (7)
Stomach/esophagus	1 (3)	2 (8.33)	0 (0	5 (5.8)
Bladder	2 (6)	1 (4.16)	0 (0	4 (4.7)
Renal cell carcinoma	0 (0)	0 (0)	0 (0	2 (2.35)
Larynx	0 (0)	1 (4.16)	0 (0	1 (1.17)
Thymus	0 (0)	1 (4.16)	0 (0	1 (1.17)
Mediastinum	0 (0)	1 (4.16)	0 (0	1 (1.17)
Cervix/uterus	1 (3)	1 (4.16)	1 (1	3 (3.5)
Hepatocellular	0 (0)	0 (0)	1 (1	1 (1.17)
Cholangiocarcinoma	0 (0)	0 (0)	1 (1	1 (1.17)
Melanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Skin, nonmelanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Disseminated, unknown	1 (3)	0 (0)	0 (0	1 (1.17)
Wilms' tumor	0 (0)	0 (0)	0 (0	1 (1.17)

Values are number of cases (percentage). Number and percent c

Leeaphorn et al., Am J Nephrol 2014

Bachetta et al., Crit Rev Oncol Hematol 2009

Table 3
Membranous nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal carcinoma	10
Justaglomerular cell tumor	1
Gastro – intestinalcancers	
Esophagus carcinoma	2
Gastric carcinoma	15
Pancreatic or Vater ampulla carcinoma	3
Colorectal carcinoma	5
Liver cell adenoma	1
Hepatocellular carcinoma	1
Uro-genital cancer	
Breast cancer	5
Small cell carcinoma of the endometrium	1
Squamous cell carcinoma of the cervix uteri	1
Choriocarcinoma	1
Bladder carcinoma	2
Prostatic carcinoma	9
Melanoma	1
Brain tumor	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Bronchial carcinoid tumor	2
Small cell carcinoma	6
Lung and bronchus carcinoma	13
Mesothelioma	2
Laryngeal cancer	2
Thymoma	7
Other tumors	
Solid tumors without details	57
Squamous cell carcinoma of the mandible	1
Sarcoma	3
Carotid body tumor	1
Chordoma of sacro-coccygeal region	1
Spinal schwannoma	1
Testicular seminoma	1
Adenolymphoma of the parotid	1
Adrenal ganglioneuroma	1
Hematological	23

Wie soll man screenen?

Type of malignancy	Bjørneklett et al. [9]	Lefaucheur et al. [8]	Rih… et al	Total
Lung	6 (18.18)	8 (33.33)	3 (3	22 (25.88)
Prostate	7 (21.21)	5 (20.83)	1 (1	13 (15.29)
Hematologic	5 (15.15)	2 (8.33)	0 (0	12 (14.11)
Colon/rectal	4 (12.12)	1 (4.16)	1 (1	9 (10.58)
Breast	4 (12.12)	1 (4.16)	0 (0	6 (7)
Stomach/esophagus	1 (3)	2 (8.33)	0 (0	5 (5.8)
Bladder	2 (6)	1 (4.16)	0 (0	4 (4.7)
Renal cell carcinoma	0 (0)	0 (0)	0 (0	2 (2.35)
Larynx	0 (0)	1 (4.16)	0 (0	1 (1.17)
Thymus	0 (0)	1 (4.16)	0 (0	1 (1.17)
Mediastinum	0 (0)	1 (4.16)	0 (0	1 (1.17)
Cervix/uterus	1 (3)	1 (4.16)	1 (1	3 (3.5)
Hepatocellular	0 (0)	0 (0)	1 (1	1 (1.17)
Cholangiocarcinoma	0 (0)	0 (0)	1 (1	1 (1.17)
Melanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Skin, nonmelanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Disseminated, unknown	1 (3)	0 (0)	0 (0	1 (1.17)
Wilms' tumor	0 (0)	0 (0)	0 (0	1 (1.17)

Values are number of cases (percentage). Number and percent c…

Leeaphorn et al., Am J Nephrol 2014

Bachetta et al., Crit Rev Oncol Hematol 2009

Table 3
Membranous nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal carcinoma	10
Justaglomerular cell tumor	1
Gastro – intestinalcancers	
Esophagus carcinoma	2
Gastric carcinoma	15
Pancreatic or Vater ampulla carcinoma	3
Colorectal carcinoma	5
Liver cell adenoma	1
Hepatocellular carcinoma	1
Uro-genital cancer	
Breast cancer	5
Small cell carcinoma of the endometrium	1
Squamous cell carcinoma of the cervix uteri	1
Choriocarcinoma	1
Bladder carcinoma	2
Prostatic carcinoma	9
Melanoma	1
Brain tumor	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Bronchial carcinoid tumor	2
Small cell carcinoma	6
Lung and bronchus carcinoma	13
Mesothelioma	2
Laryngeal cancer	2
Thymoma	7
Other tumors	
Solid tumors without details	57
Squamous cell carcinoma of the mandible	1
Sarcoma	3
Carotid body tumor	1
Chordoma of sacro-coccygeal region	1
Spinal schwannoma	1
Testicular seminoma	1
Adenolymphoma of the parotid	1
Adrenal ganglioneuroma	1
Hematological	23

Wie soll man screenen?

Type of malignancy	Bjørneklett et al. [9]	Lefaucheur et al. [8]	Rih… et al	Total
Lung	6 (18.18)	8 (33.33)	3 (3	22 (25.88)
Prostate	7 (21.21)	5 (20.83)	1 (1	13 (15.29)
Hematologic	5 (15.15)	2 (8.33)	0 (0	12 (14.11)
Colon/rectal	4 (12.12)	1 (4.16)	1 (1	9 (10.58)
Breast	4 (12.12)	1 (4.16)	0 (0	6 (7)
Stomach/esophagus	1 (3)	2 (8.33)	0 (0	5 (5.8)
Bladder	2 (6)	1 (4.16)	0 (0	4 (4.7)
Renal cell carcinoma	0 (0)	0 (0)	0 (0	2 (2.35)
Larynx	0 (0)	1 (4.16)	0 (0	1 (1.17)
Thymus	0 (0)	1 (4.16)	0 (0	1 (1.17)
Mediastinum	0 (0)	1 (4.16)	0 (0	1 (1.17)
Cervix/uterus	1 (3)	1 (4.16)	1 (1	3 (3.5)
Hepatocellular	0 (0)	0 (0)	1 (1	1 (1.17)
Cholangiocarcinoma	0 (0)	0 (0)	1 (1	1 (1.17)
Melanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Skin, nonmelanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Disseminated, unknown	1 (3)	0 (0)	0 (0	1 (1.17)
Wilms' tumor	0 (0)	0 (0)	0 (0	1 (1.17)

Values are number of cases (percentage). Number and percent c…

Leeaphorn et al., Am J Nephrol 2014

Bachetta et al., Crit Rev Oncol Hematol 2009

Table 3
Membranous nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal carcinoma	10
Justaglomerular cell tumor	1
Gastro… intestinal cancers	
Esophagus carcinoma	2
Gastric carcinoma	15
Pancreatic or Vater ampulla carcinoma	3
Colorectal carcinoma	5
Liver cell adenoma	1
Hepatocellular carcinoma	1
Uro-genital cancer	
Breast cancer	5
Small cell carcinoma of the endometrium	1
Squamous cell carcinoma of the cervix uteri	1
Choriocarcinoma	1
Bladder carcinoma	2
Prostatic carcinoma	9
Melanoma	1
Brain tumor	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Bronchial carcinoid tumor	2
Small cell carcinoma	6
Lung and bronchus carcinoma	13
Mesothelioma	2
Laryngeal cancer	2
Thymoma	7
Other tumors	
Solid tumors without details	57
Squamous cell carcinoma of the mandible	1
Sarcoma	3
Carotid body tumor	1
Chordoma of sacro-coccygeal region	1
Spinal schwannoma	1
Testicular seminoma	1
Adenolymphoma of the parotid	1
Adrenal ganglioneuroma	1
Hematological	23

Wie soll man screenen?

Type of malignancy	Bjørneklett et al. [9]	Lefaucheur et al. [8]	Rih… et al	Total
Lung	6 (18.18)	8 (33.33)	3 (3	22 (25.88)
Prostate	7 (21.21)	5 (20.83)	1 (1	13 (15.29)
Hematologic	5 (15.15)	2 (8.33)	0 (0	12 (14.11)
Colon/rectal	4 (12.12)	1 (4.16)	1 (1	9 (10.58)
Breast	4 (12.12)	1 (4.16)	0 (0	6 (7)
Stomach/esophagus	1 (3)	2 (8.33)	0 (0	5 (5.8)
Bladder	2 (6)	1 (4.16)	0 (0	4 (4.7)
Renal cell carcinoma	0 (0)	0 (0)	0 (0	2 (2.35)
Larynx	0 (0)	1 (4.16)	0 (0	1 (1.17)
Thymus	0 (0)	1 (4.16)	0 (0	1 (1.17)
Mediastinum	0 (0)	1 (4.16)	0 (0	1 (1.17)
Cervix/uterus	1 (3)	1 (4.16)	1 (1	3 (3.5)
Hepatocellular	0 (0)	0 (0)	1 (1	1 (1.17)
Cholangiocarcinoma	0 (0)	0 (0)	1 (1	1 (1.17)
Melanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Skin, nonmelanoma	1 (3)	0 (0)	0 (0	1 (1.17)
Disseminated, unknown	1 (3)	0 (0)	0 (0	1 (1.17)
Wilms' tumor	0 (0)	0 (0)	0 (0	1 (1.17)

Values are number of cases (percentage). Number and percent c…

Leeaphorn et al., Am J Nephrol 2014

Bachetta et al., Crit Rev Oncol Hematol 2009

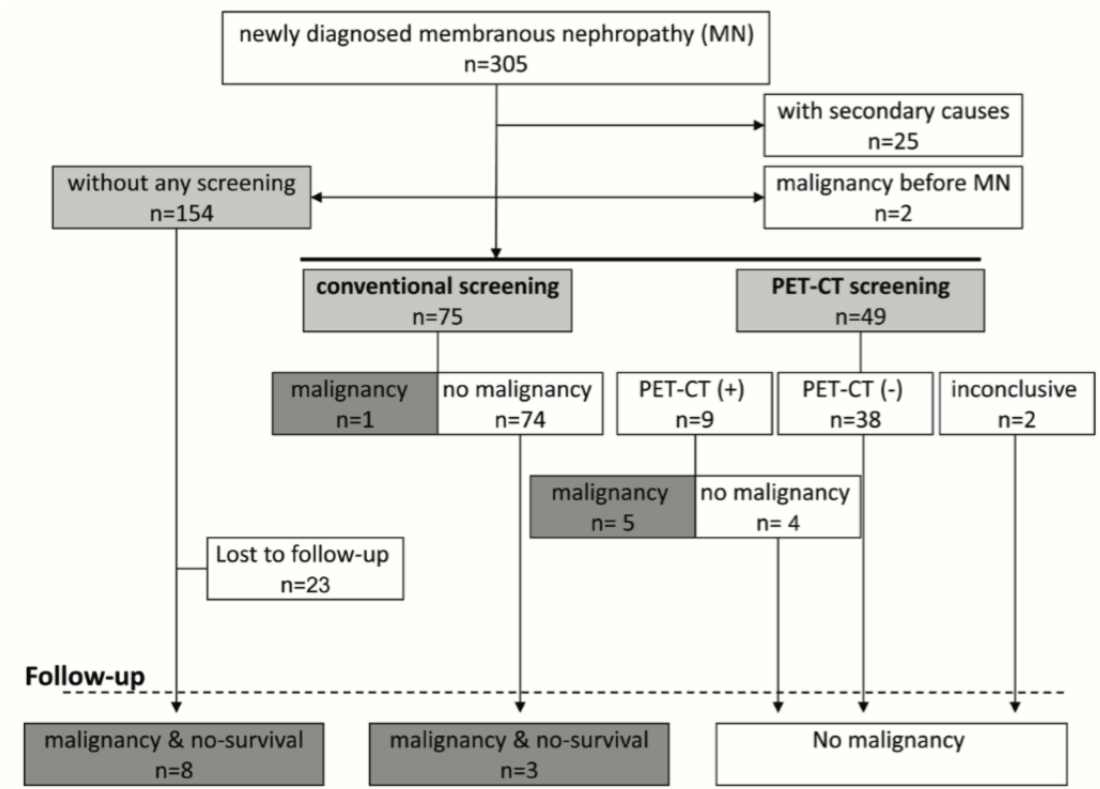
Table 3
Membranous nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal carcinoma	10
Justaglomerular cell tumor	1
Gastro – intestinalcancers	
Esophagus carcinoma	2
Gastric carcinoma	15
Pancreatic or Vater ampulla carcinoma	3
Colorectal carcinoma	5
Liver cell adenoma	1
Hepatocellular carcinoma	1
Uro-genital cancer	
Breast cancer	5
Small cell carcinoma of the endometrium	1
Squamous cell carcinoma of the cervix uteri	1
Choriocarcinoma	1
Bladder carcinoma	2
Prostatic carcinoma	9
Melanoma	1
Brain tumor	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Bronchial carcinoid tumor	2
Small cell carcinoma	6
Lung and bronchus carcinoma	13
Mesothelioma	2
Laryngeal cancer	2
Thymoma	7
Other tumors	
Solid tumors without details	57
Squamous cell carcinoma of the mandible	1
Sarcoma	3
Carotid body tumor	1
Chordoma of sacro-coccygeal region	1
Spinal schwannoma	1
Testicular seminoma	1
Adenolymphoma of the parotid	1
Adrenal ganglioneuroma	1
Hematological	23

Wie soll man screenen?

- Praktisch alle Malignome können potentiell mit MN assoziiert sein
- Screening auf häufige Neoplasien:
  - Koloskopie, ggf. Gastroskopie
  - CT Thorax bei Rauchern
  - PSA / Mammographie
  - ggf. Sonographie Abdomen

Wie soll man screenen?



Feng et al, Oncotarget 2016

Wie soll man screenen?

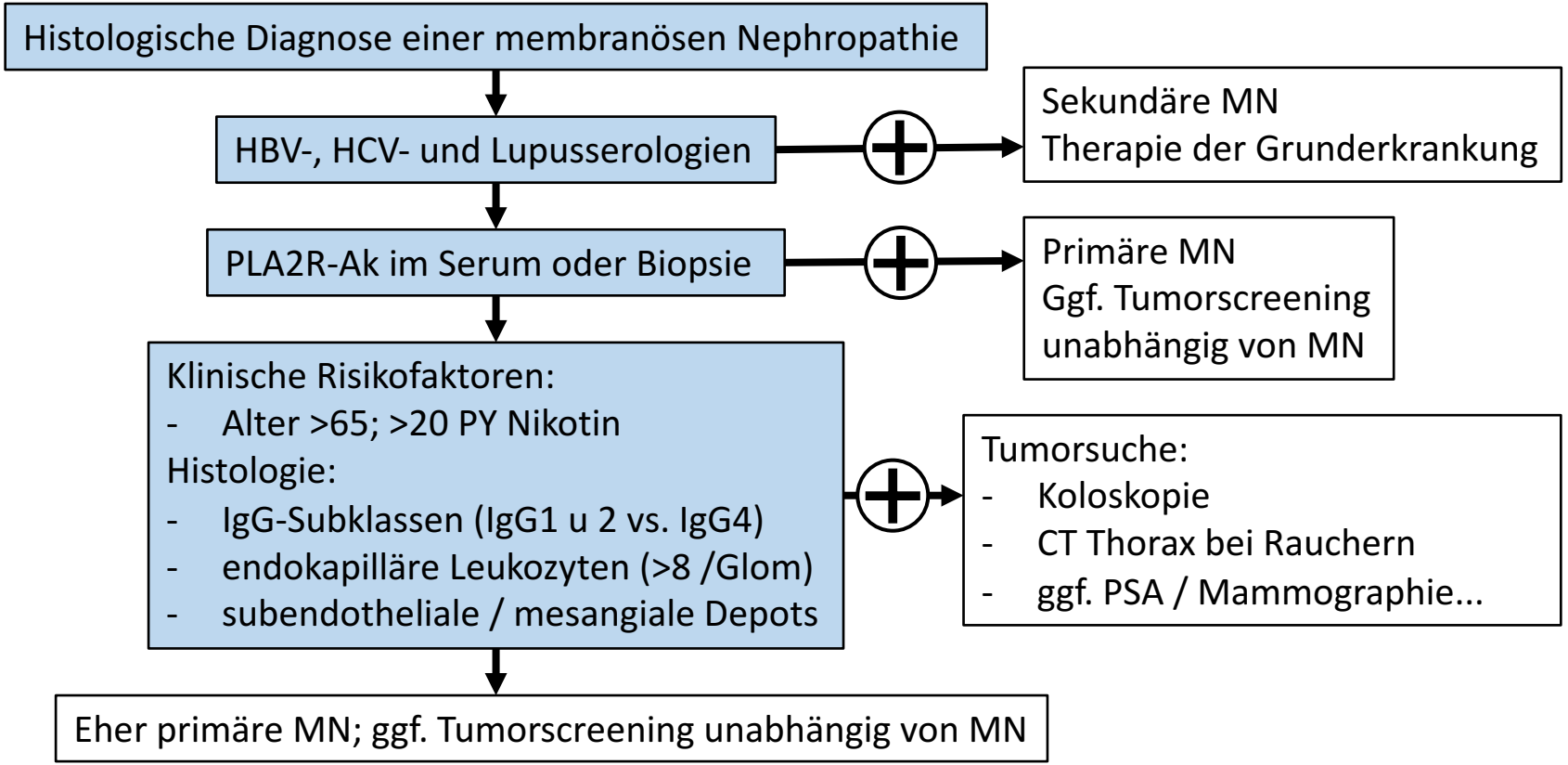
	age/ gender	screening	malignancy	pathology /stage	follow-up (mo)	survival	surgical resection	proteinuria (g/24 h)	proteinuria after resection*
1	49/M	Conventional(+)	colon	adenocarcinoma /T3N2M1	74	yes	yes	3.14	disappearance
2	73/M	PET-CT(+)	prostate	adenocarcinoma /Gleason score 4+3	35	yes	yes	2.87	reduction
3	65/M	PET-CT(+)	lung	adenocarcinoma / T1N0M0	35	yes	yes	15.43	reduction
4	50/F	PET-CT(+)	thyroid	adenocarcinoma / T1N0M0	28	yes	yes	5.25	reduction
5	78/M	PET-CT(+)	lung	adenocarcinoma / T1N0M0	46	yes	yes	1.51	disappearance
6	69/M	PET-CT(+)	stomach	adenocarcinoma / T1N1M0	81	yes	yes	8.15	disappearance
7	75/F	Conventional(-)	breast	N/A	28	no	no	4.56	no remission
8	54/M	Conventional(-)	colon	N/A	36	no	no	1.40	no remission
9	74/M	Conventional(-)	lung	N/A	51	no	no	3.59	no remission
10	69/F	no	lung	N/A	15	no	no	3.95	no remission
11	66/M	no	stomach	N/A	19	no	no	4.46	no remission
12	64/F	no	lung	N/A	32	no	no	3.9	no remission
13	31/M	no	lung	adenocarcinoma / T2N1M1	18	no	yes	1.62	no remission
14	76/M	no	colon	N/A	73	no	no	2.88	no remission
15	74/F	no	N/A	N/A	77	no	no	2.14	no remission
16	74/M	no	N/A	N/A	58	no	no	7.4	no remission
17	89/M	no	prostate	N/A	58	no	no	1.84	no remission

Feng et al, Oncotarget 2016

Zusammenfassung

- Genauso wie die Membranöse Nephropathie eine morphologische Beschreibung ist und mehrere Ätio-Pathogenesen umfasst, ist auch die Tumor-assoziierte MN heterogen
- Zumindest in einigen dieser Fälle handelt es sich um ein paraneoplastisches Syndrom
- Kein klinischer, histologischer oder Laborparameter unterscheidet klar zwischen primärer und paraneoplastischer MN, aber verschiedene solche Parameter erlauben ein fokussiertes Screenen

Möglicher Screeningalgorithmus



PD Dr. med. Andreas D. Kistler
andreas.kistler@stgag.ch
www.nephrologie-thurgau.ch