Nierenbeteiligung bei leichtketten-assoziierten Erkrankungen

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Berliner DialyseSeminar

Darlegung potentieller Interessenskonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

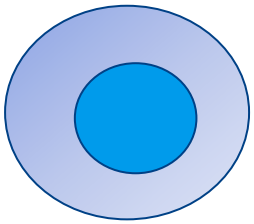
Als Referent versichere ich, dass in Bezug auf den Inhalt des folgenden Vortrags **keine Interessenskonflikte** bestehen, die sich aus einem Beschäftigungsverhältnis, einer Beratertätigkeit oder Zuwendungen für Forschungsvorhaben, Vorträge oder andere Tätigkeiten ergeben.

Inhalt

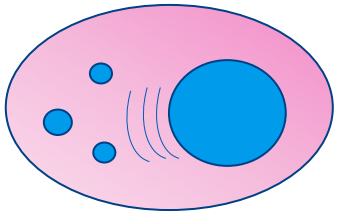
- Was ist eine Monoklonale Gammopathie?
- Proliferative B-Zell- und Plasmazellerkrankungen
- Monoklonale Gammopathie renaler Signifikanz
- Übersicht über Leichtketten-assoziierte Nierenerkrankungen
  - tubulär (CAST Nephropathie, proximale Tubulopathie)
  - glomerulär (Erkrankungen mit und ohne monoklonale Ablagerungen)
- Diagnostik
- Therapie
- Nierentransplantation bei Plasmazelldyskrasien

Monoklonale Gammopathie

Klon

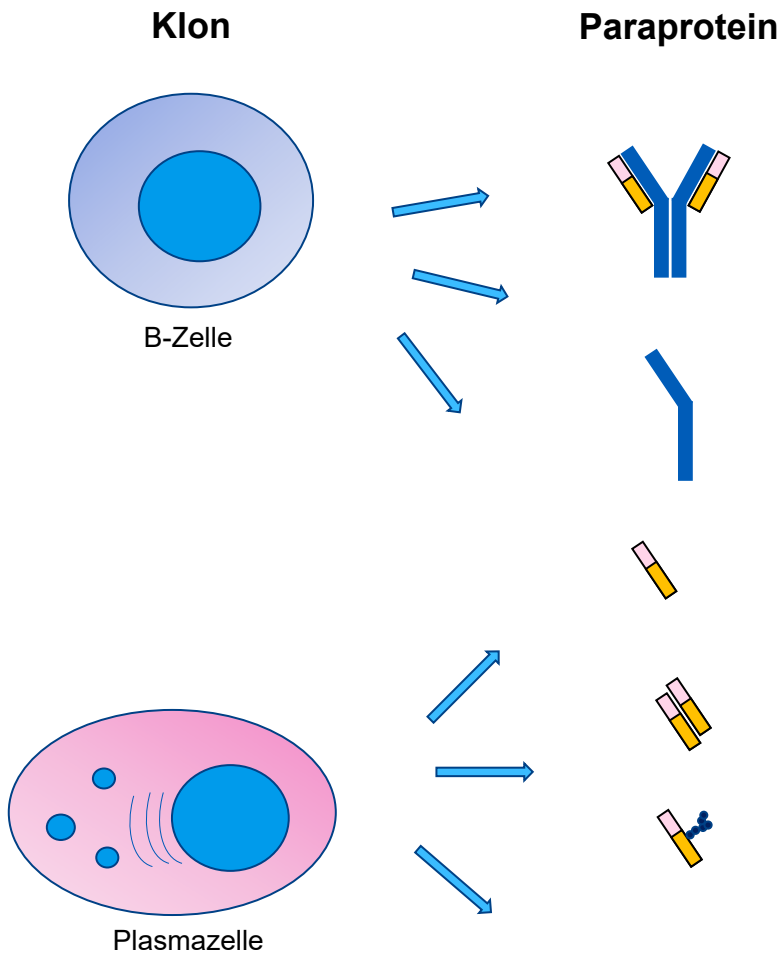


B-Zelle

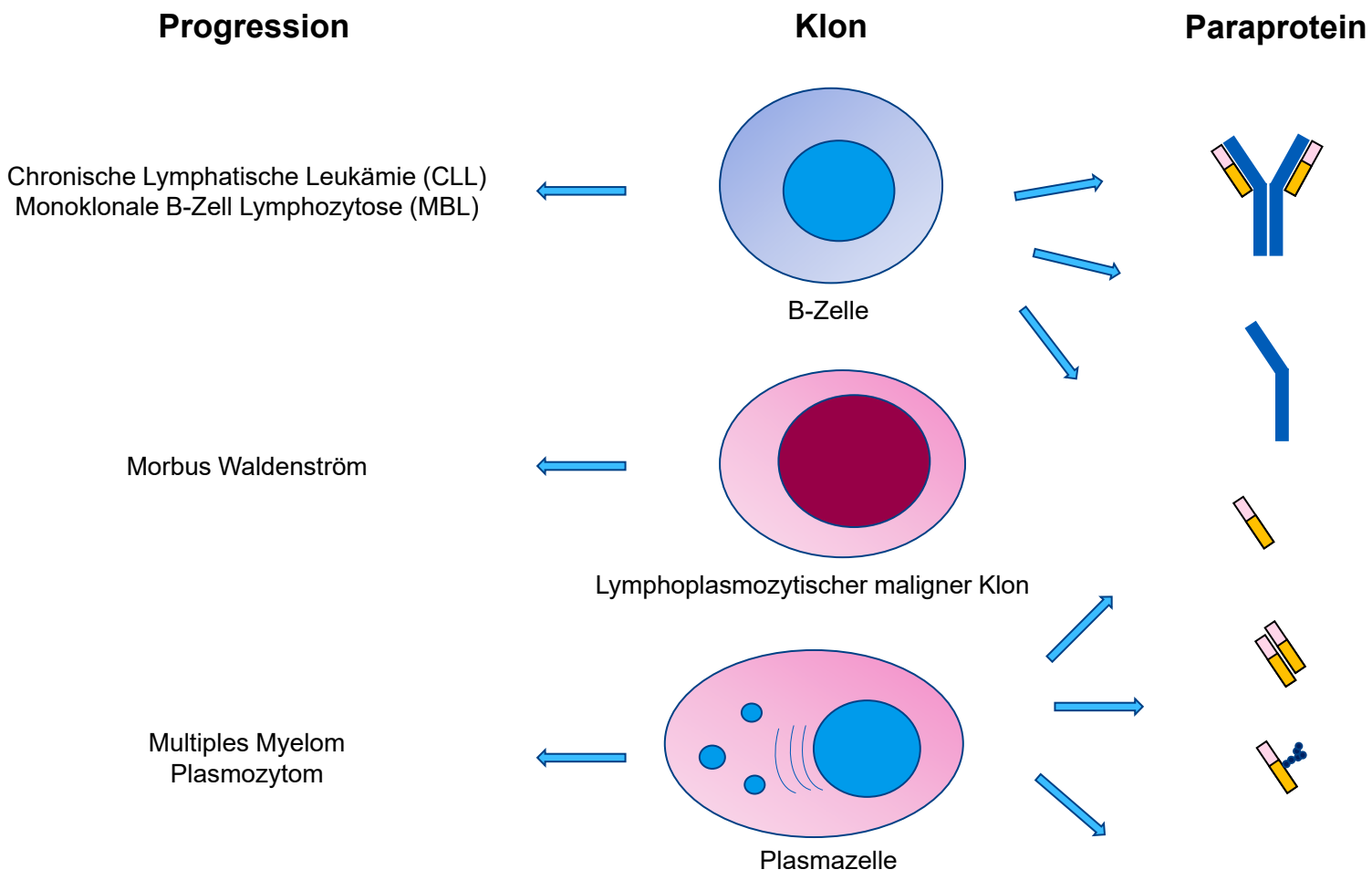


Plasmazelle

Monoklonale Gammopathie



Progression der Monoklonalen Gammopathie



Proliferative B-Zell- und Plasmazellerkrankungen

Disease	Clone	Bone marrow involvement	Immunoglobulin	M-spike	Organ damage and/or involvement
MGUS	Any	<10%	Any	<30 g/l	None
Smouldering MM[a]	Plasma cell	10–60%	Any	≥30 g/l	None
MM[a]	Plasma cell	≥10%	Any	≥30 g/l	SLiM CRAB: 60% bone marrow plasma cells, involved:uninvolved free light-chain ratio >100, >1 bone lesion on MRI, hypercalcaemia, renal impairment, anaemia and lytic bone lesions

Leung N, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019

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MBL	B-cell clone[c]	Peripheral B-cell count $<5 \times 10^9$/l	Any	Any	Absence of lymph node involvement
CLL	B-cell clone[c]	Peripheral B-cell count $>5 \times 10^9$/l	Any	Any	Adenopathy, anaemia and thrombocytopenia
Other B cell lympho-proliferative disorders	Pan B-cell markers ($CD19^+CD20^+CD79^+CD22^+PAX5^+$)	Presence or absence	Any	Any	Adenopathy and splenomegaly

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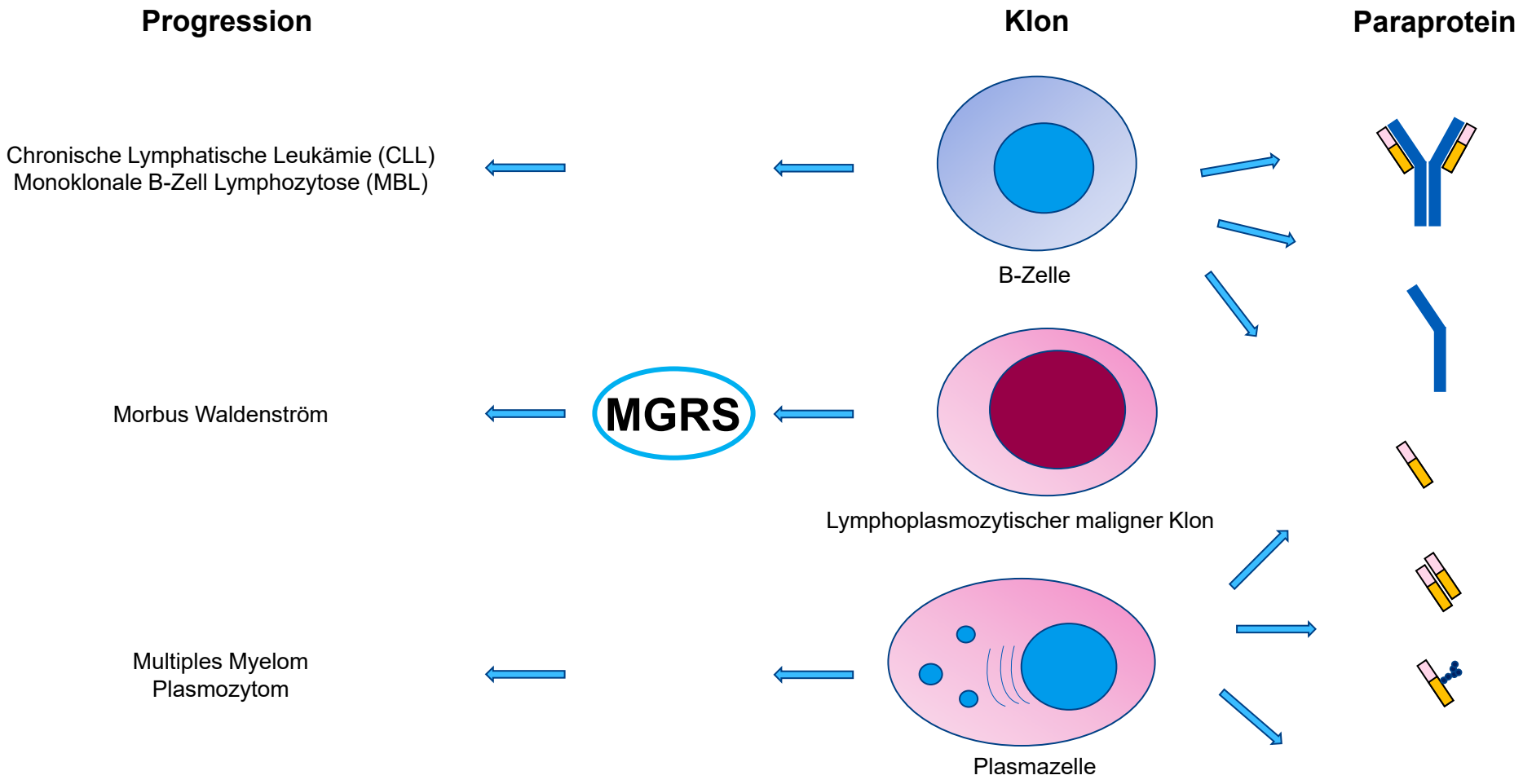
Monoklonale Gammopathie renaler Signifikanz (MGRS)

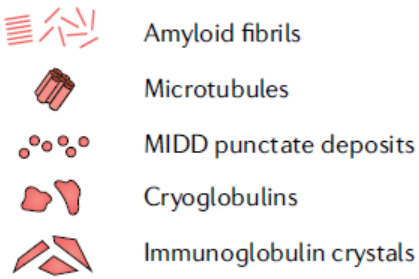


Monoklonale Gammopathie renaler Signifikanz (MGRS) - Definition

- Klonale B- oder Plasmazell-Lymphoproliferation mit
  - einer oder mehrere Nierenmanifestationen, die auf das produzierte monoklonale Immunglobulin zurückzuführen ist
  - ohne dass der Klon systemische Tumorkomplikationen auslöst oder die hämatologischen Kriterien für eine spezifische Therapie erfüllt

Leung N, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019

Leichtketten-assoziierte Nierenerkrankungen



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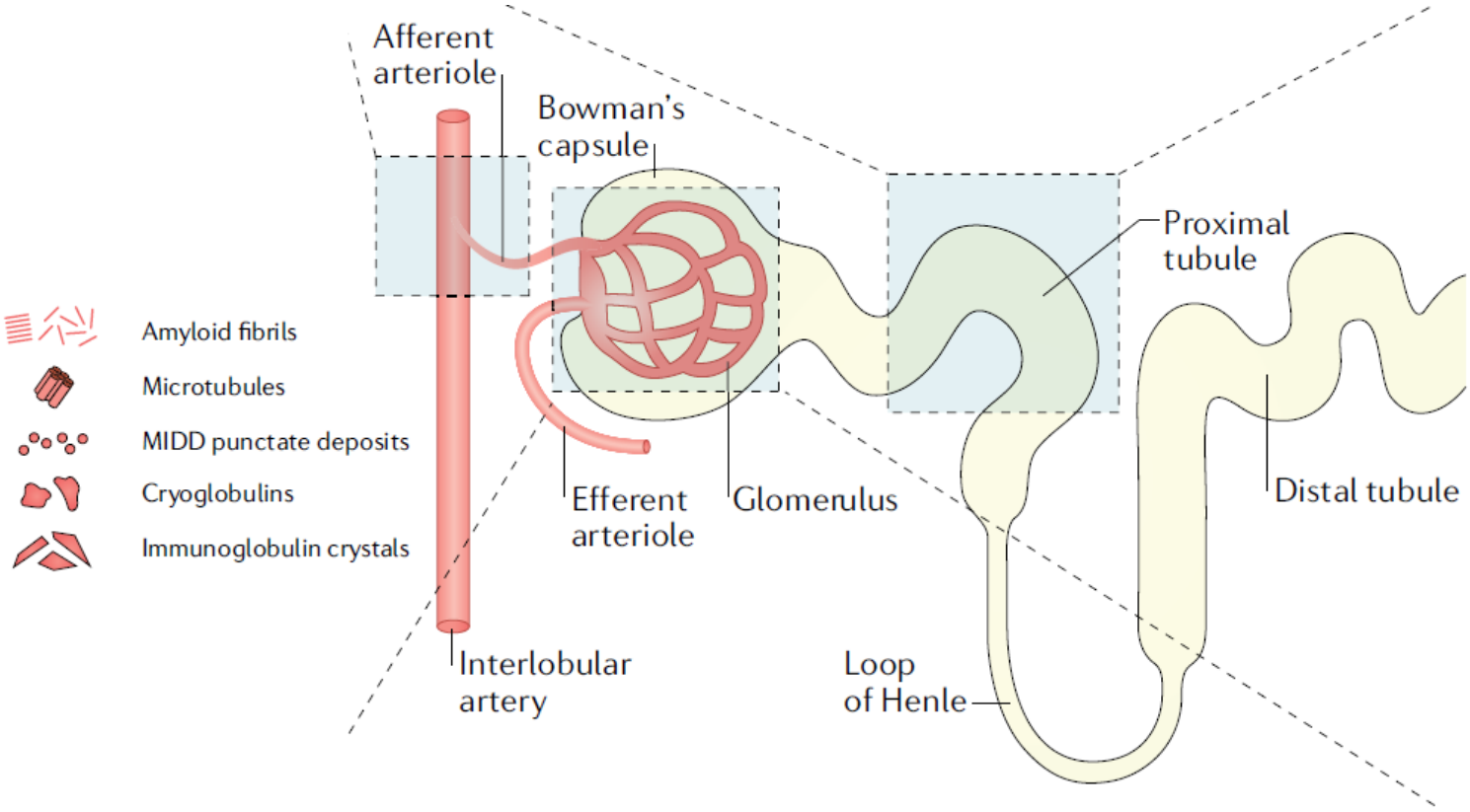

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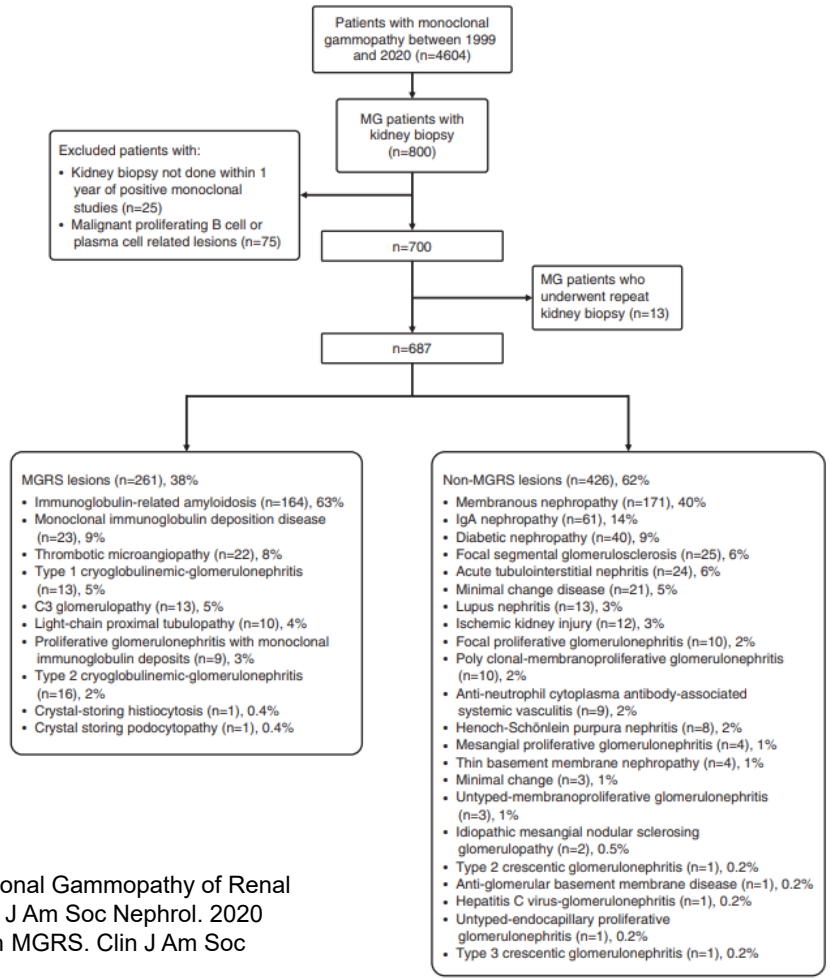
Leichtketten-assoziierte Nierenerkrankungen - Klinik

- Proteinurie
- nephrotisches Syndrom
- Hämaturie
- AKI
- CKD
- C3-Verbrauch
- C4-Verbrauch
- Hypertonie
- renales Fanconi Syndrom
- Extrarenale Manifestationen (u.a. Purpura, Livedo, Raynaud, Gangrän, Arthralgien, Kardiomyopathie, Makroglossie, PNP, Osteomalazie)

Bridoux F, Nasr SH, Arnulf B, Leung N, Sirac C, Jaccard A. Renal manifestations of MGUS. Hematology Am Soc Hematol Educ Program. 2024

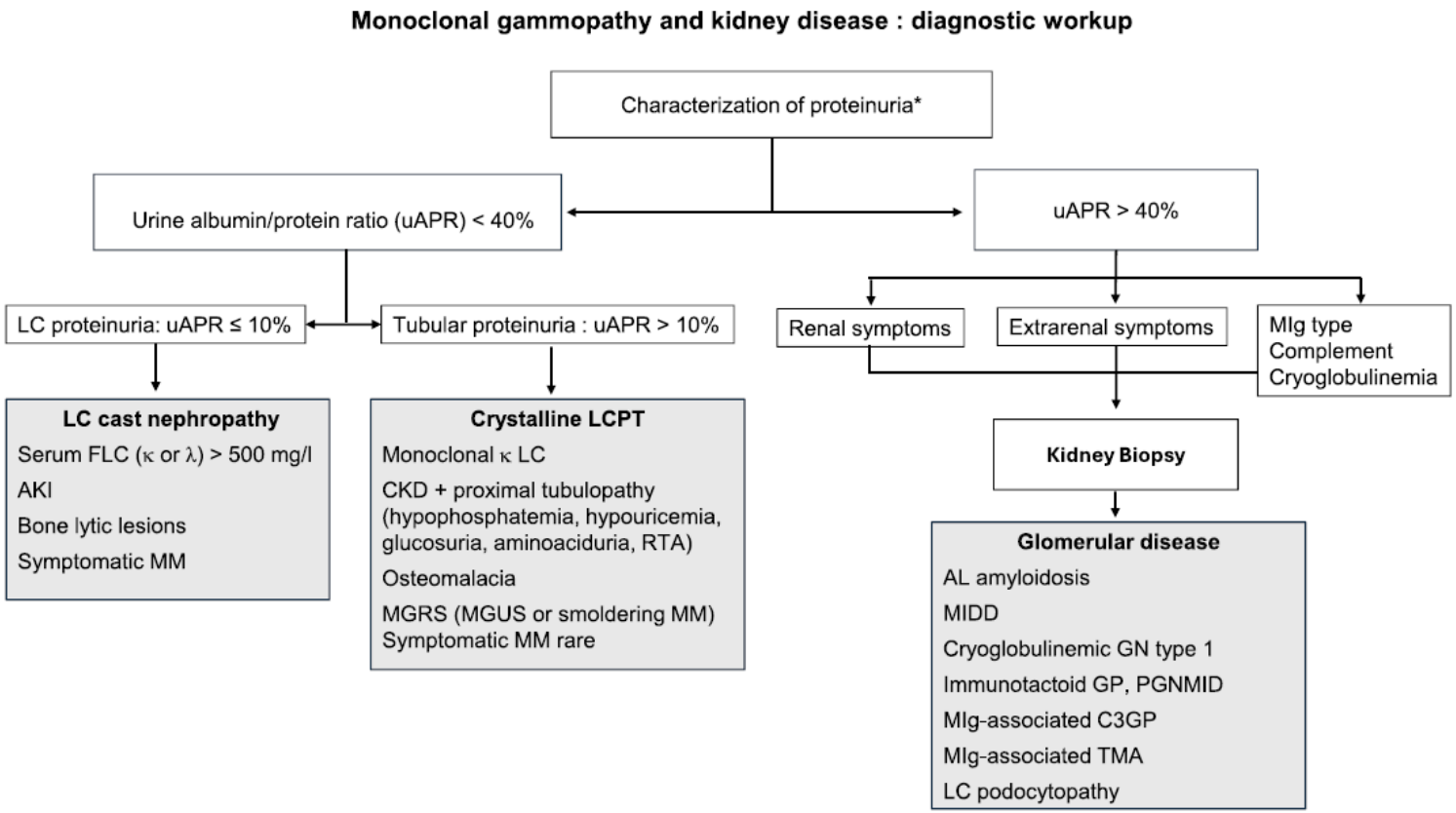
Prävalenz von Nierenerkrankungen bei Monoklonaler Gammopathie

- Prävalenz Monoklonale Gammopathie von 5% im Alter >50 Jahre
- renale Beteiligung ~ 5-6 %
- stärkste Prädiktoren für eine Nierenbeteiligung:
  - erhöhte Leichtkettenratio
  - Proteinurie ≥ 1,5 g/d
  - Hämaturie



1. Klomjit N, Leung N, Fervenza F, Sethi S, Zand L. Rate and Predictors of Finding Monoclonal Gammopathy of Renal Significance (MGRS) Lesions on Kidney Biopsy in Patients with Monoclonal Gammopathy. J Am Soc Nephrol. 2020
2. Yong ZH, et. al. Kidney Histopathologic Spectrum and Clinical Indicators Associated with MGRS. Clin J Am Soc Nephrol. 2022

Diagnostik



Bridoux F, et al.; International Kidney and Monoclonal Gammopathy Research Group. Kidney disease in multiple myeloma. Presse Med. 2025

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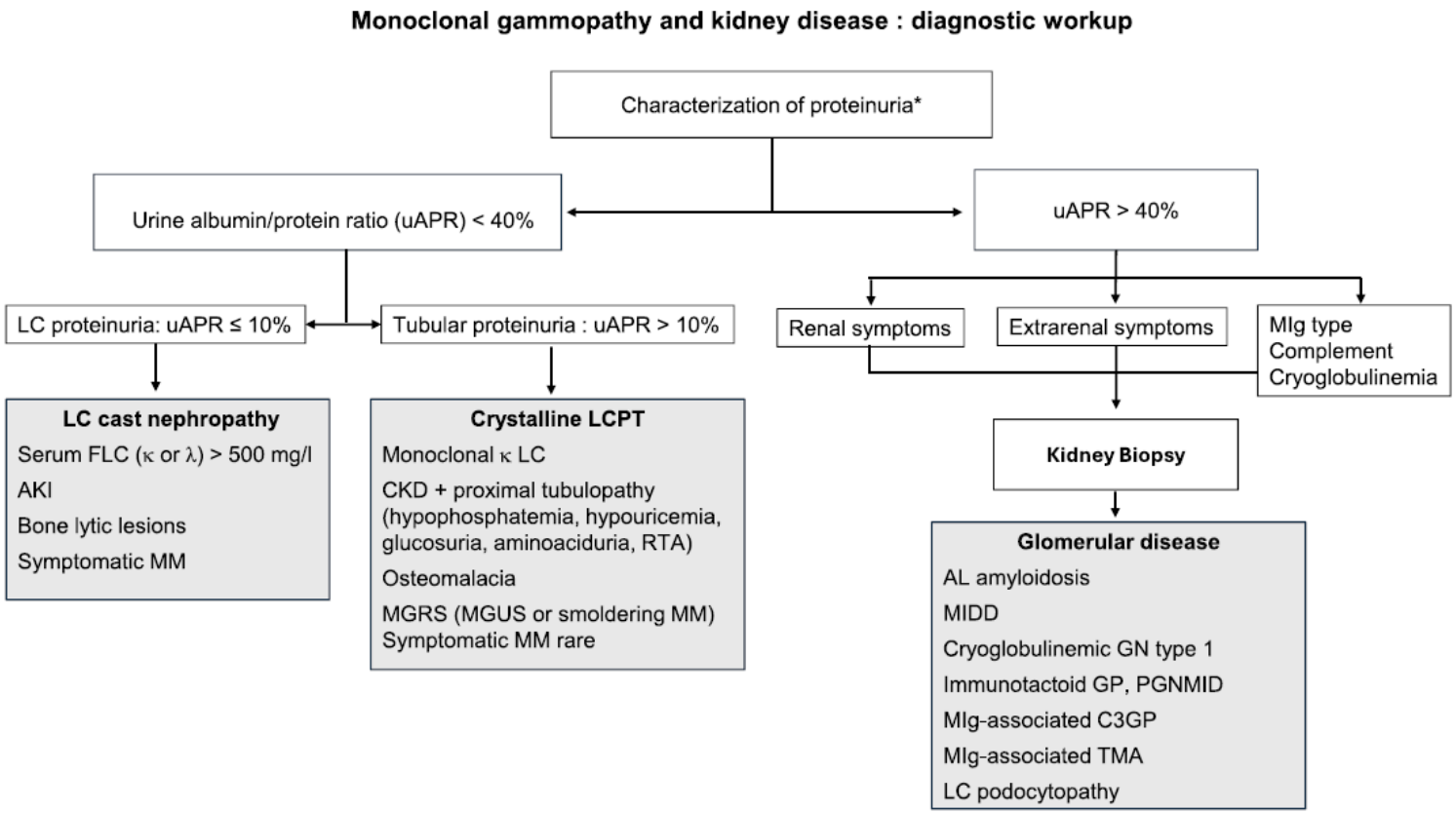

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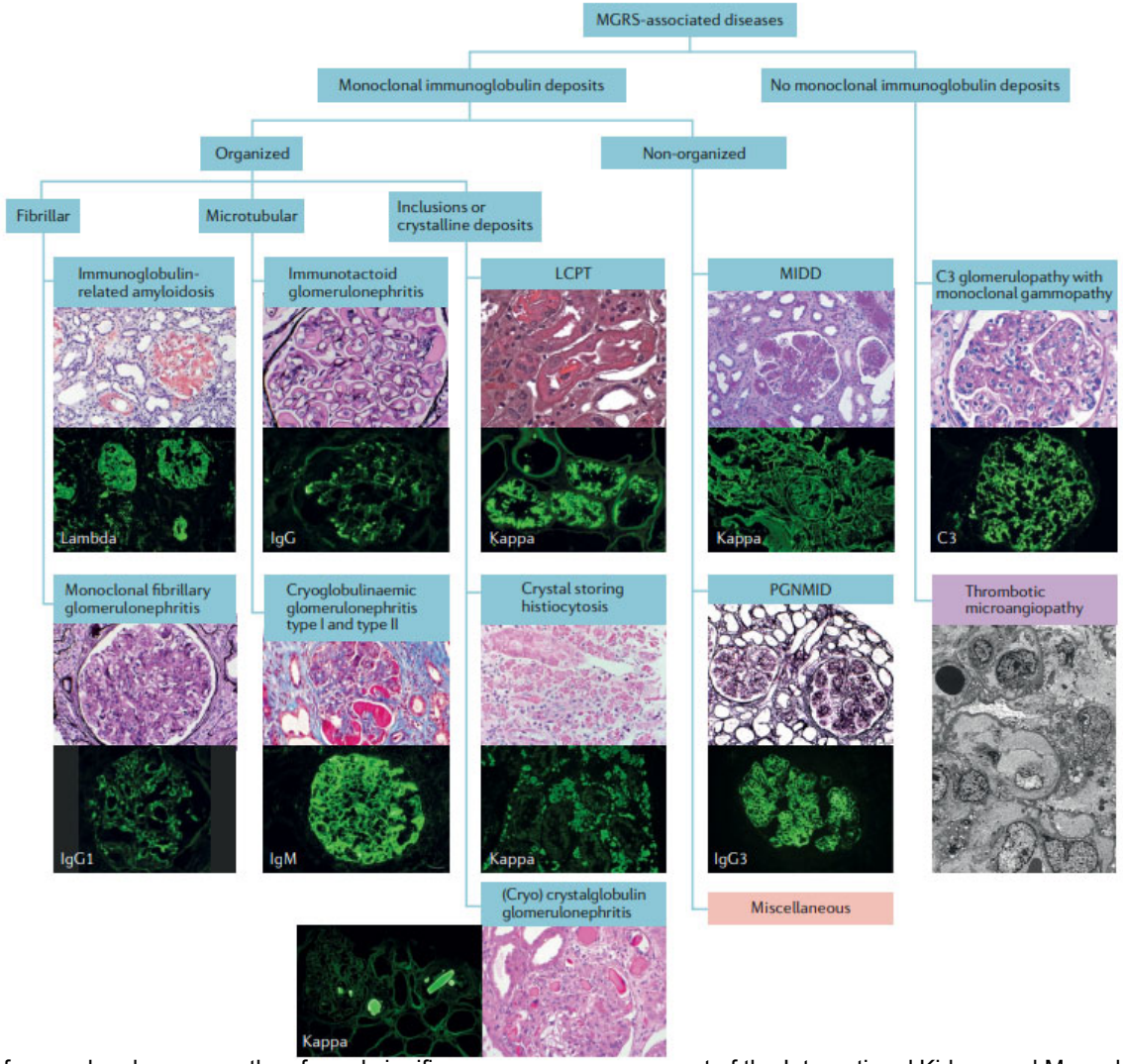
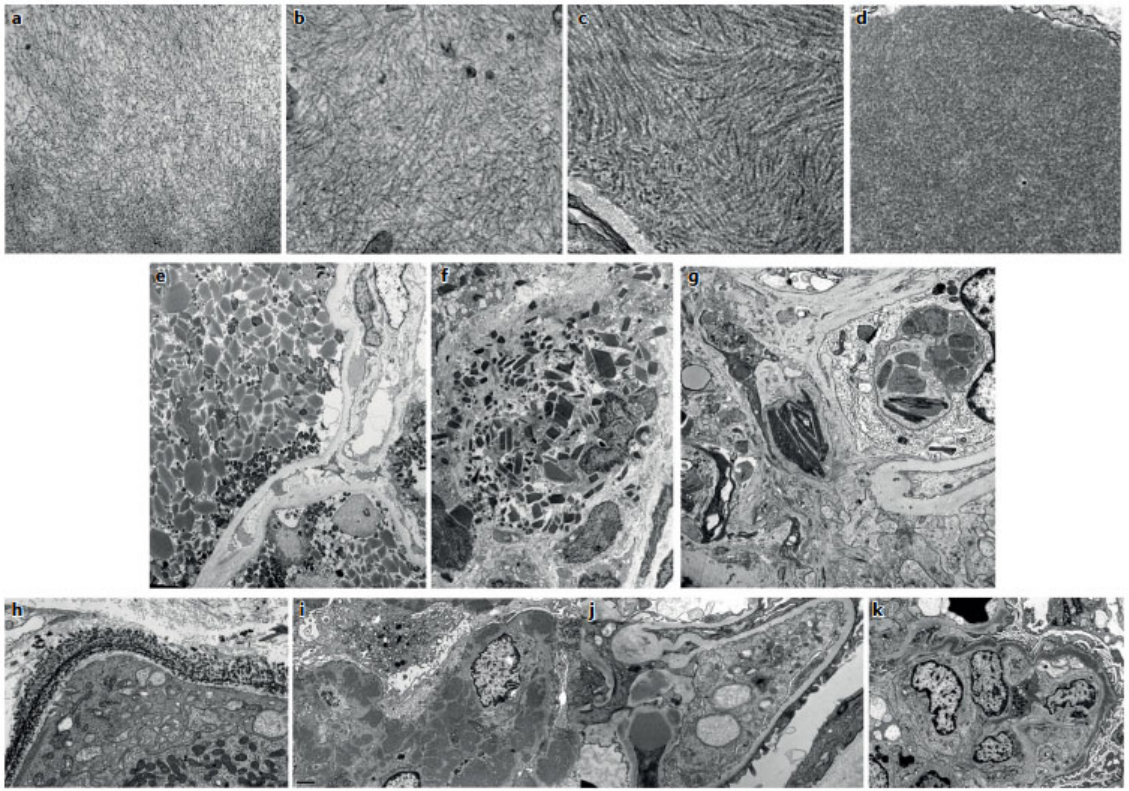
Histologie



Leung N, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019

Elektronenmikroskopische Befunde



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MGRS - Evaluation

Table 2 | **Consensus recommendations for the evaluation of MGRS-associated disorders**

Modality	Recommendations	Refs
Kidney biopsy	Recommended in the following patients: • Those with monoclonal gammopathy and unexplained kidney disease • Those with known risk factors for chronic kidney disease but an atypical clinical course • Patients with kidney disease and monoclonal gammopathy aged <50 years	NA
Protease immunofluorescence on kidney biopsy	Recommended in the following scenarios: • When glomeruli are lacking in frozen tissue samples • In patients with suspected LCPT and other forms of crystalline nephropathies, such as CSH and crystalglobulin-induced nephropathy • In patients with a monoclonal gammopathy in whom kidney biopsy samples show C3 glomerulonephritis or unclassified proliferative glomerulonephritis in the context of negative findings by immunofluorescence on frozen tissue samples (including in patients with features of cryoglobulinaemic glomerulonephritis on light or electron microscopy) • In patients with fibrillary glomerulonephritis who have apparent light-chain restriction detected by immunofluorescence on frozen tissue	NA
Renal amyloid typing by liquid chromatography and mass spectrometry	Recommended in the following situations: • When frozen tissue for immunofluorescence is not available • Negative immunofluorescence staining for κ and λ light chains, with negative immunoperoxidase staining for SAA and LECT2 • Equal staining for κ and λ light chains by immunofluorescence • Bright staining for IgG and/or IgA by immunofluorescence • Equivocal Congo red staining • To enable distinction between AHL amyloidosis and congophilic fibrillary glomerulonephritis	108
Flow cytometry or other immunotyping	• Neoplastic plasma cells frequently show aberrant loss of CD45 and CD19, as well as aberrant expression of CD56 and CD117; therefore, these markers (in addition to κ and λ light chains and CD38) are useful in identifying small plasma cell clones • Including CD5 and CD20 in the immunophenotyping of B cells can frequently separate small clones from polytypic cells • The most sensitive assay available at a given institution should be used. Although there is no established gold standard, many laboratories have the capability to determine minimal residual disease in MGRS at a sensitivity of 10^{-4} to 10^{-6} monoclonal cells. The sensitivity of flow cytometry immunophenotyping depends on the total number of collected cells, the number of antibodies used to find an aberrant phenotype, the phenotype of the abnormal clone and sample quality	118
Immunohistochemistry	• Immunohistochemistry of bone marrow biopsy samples has a low sensitivity for detecting κ-expressing and λ-expressing plasma cells and could be useful only if there is a major plasma cell clone and a lack of polyclonal plasma cells • Immunohistochemistry might be useful in the evaluation of atypical lymphoid infiltrates, particularly if flow cytometry is not available or infiltrates are very focal • If an abnormal clone is detected, the light-chain isotype should be compared with that present in renal lesions and additional information should be obtained	NA
Mutational analysis	The MYD88 L265P mutation is found in over 90% of patients with lymphoplasmacytic lymphoma or Waldenström macroglobulinaemia but in only 40–60% of individuals with IgM MGUS	119–121
FISH	Cyclin D1 FISH with immunostaining for CD10, BCL2 and BCL6 to subclassify diffuse large cell lymphoma, and prognostic FISH panels for MM and CLL, can also be useful	119–121

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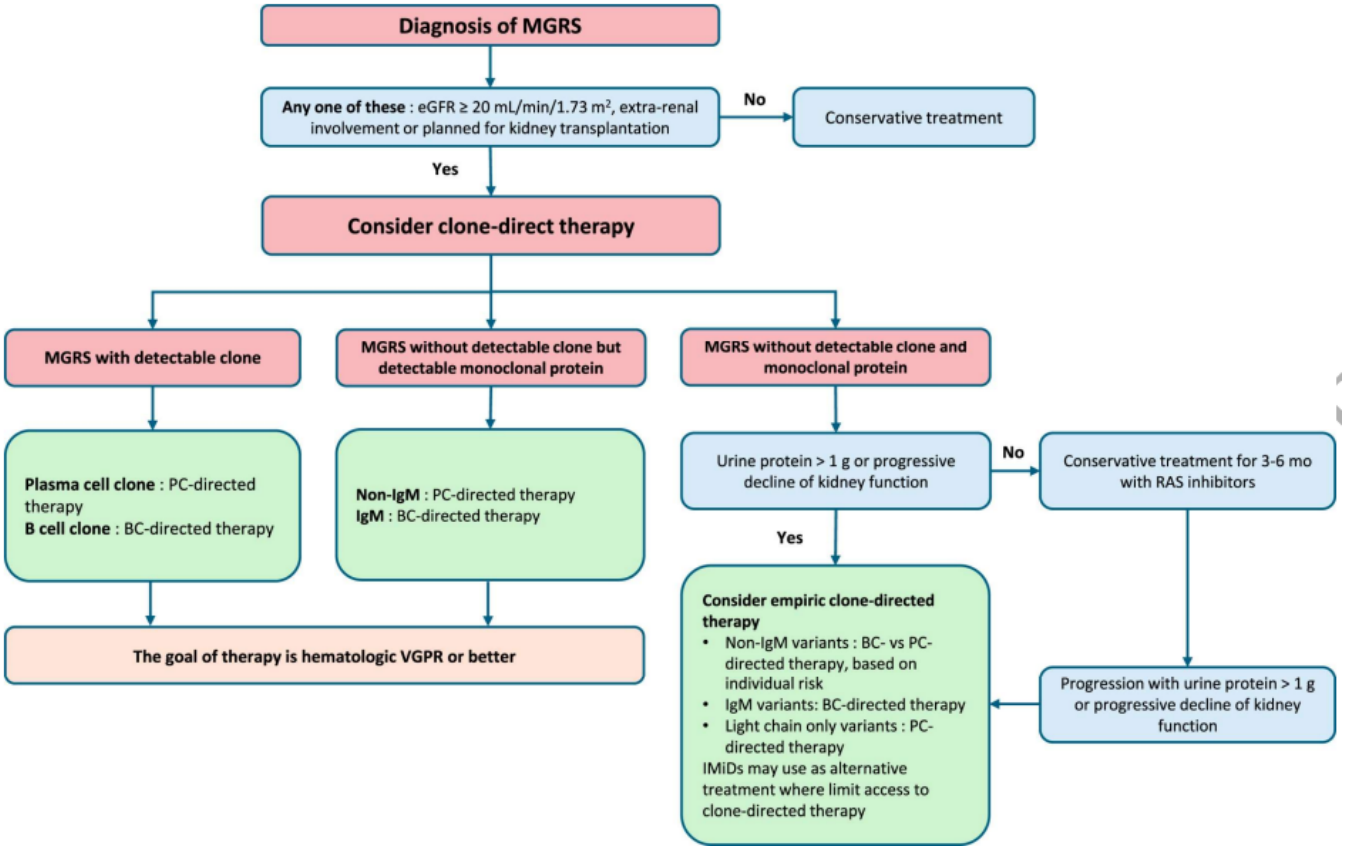
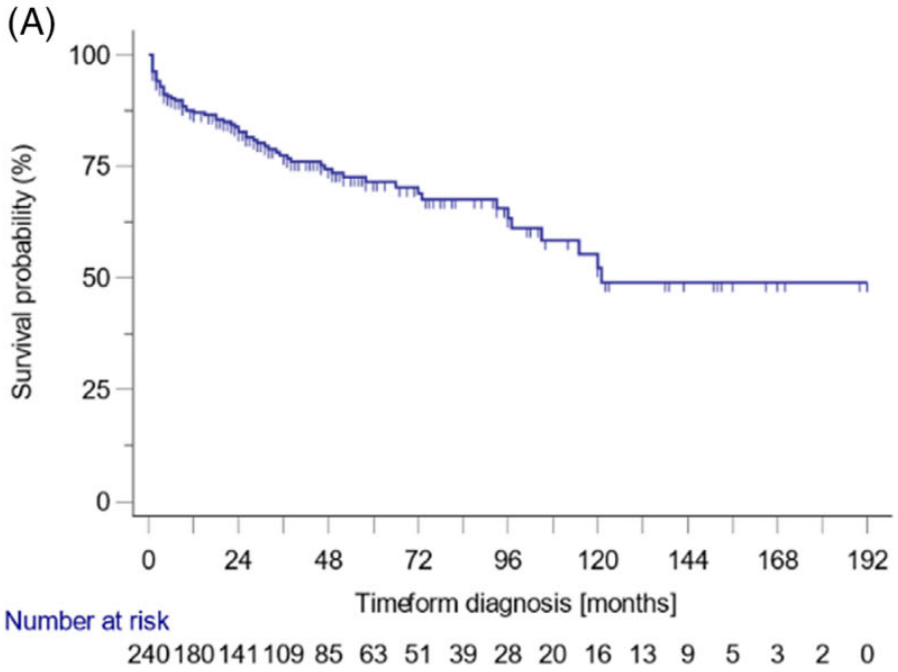
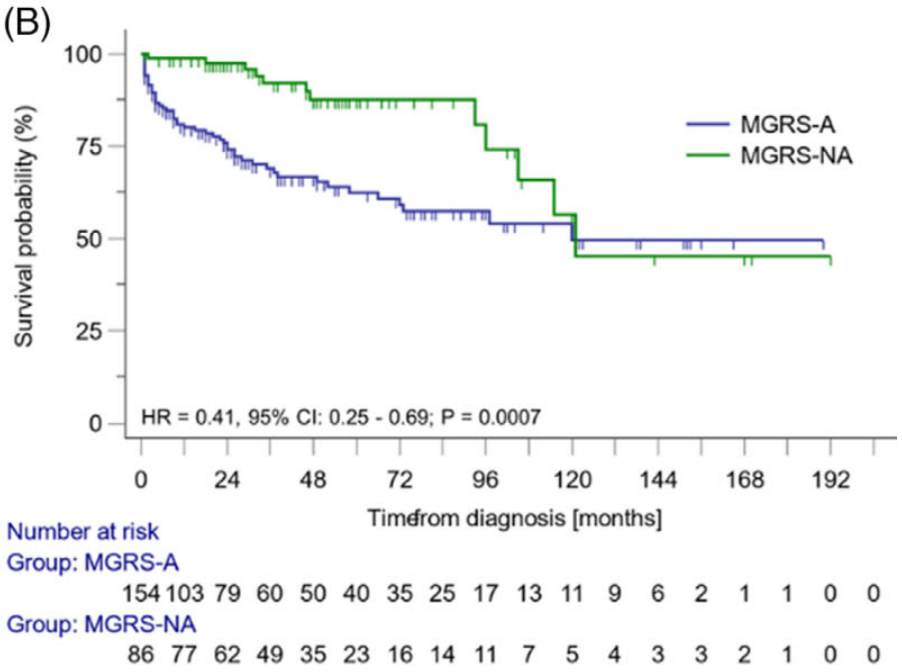
MGRS - Therapie



Jaturapisanukul S et al. Management of monoclonal gammopathy of renal significance: treatment standard. Nephrol Dial Transplant. 2025

Überleben bei MGRS





Gozzetti A, et al. Monoclonal gammopathy of renal significance (MGRS): Real-world data on outcomes and prognostic factors. Am J Hematol. 2022

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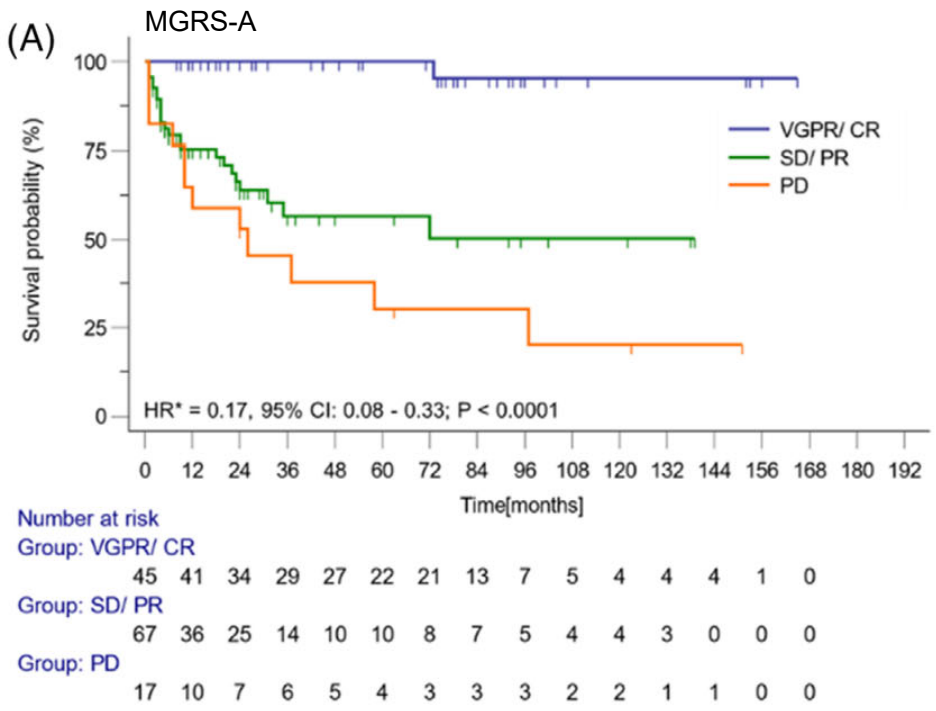

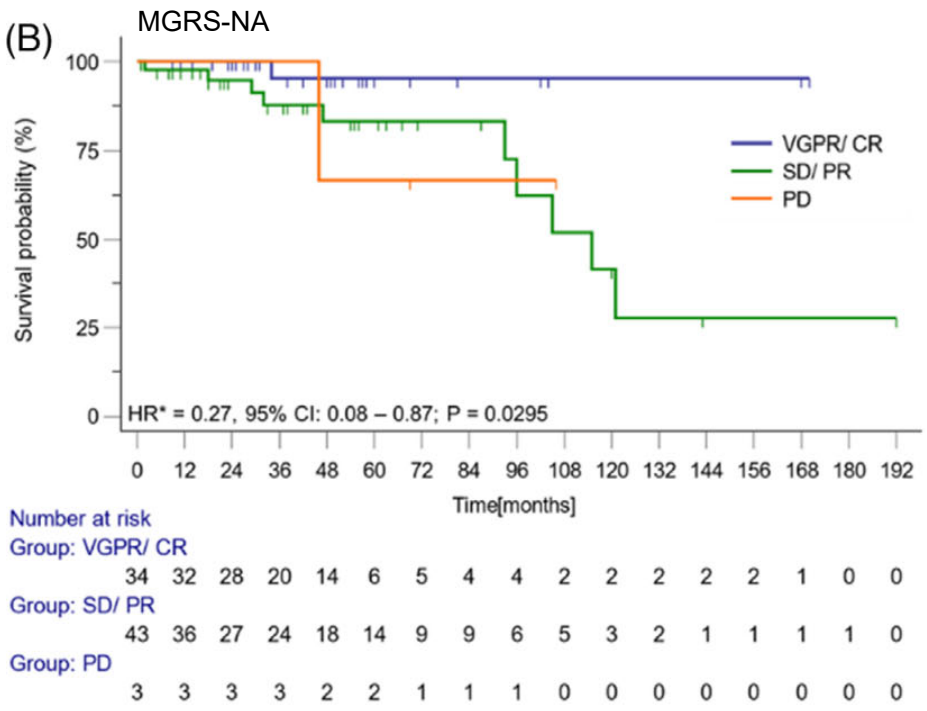

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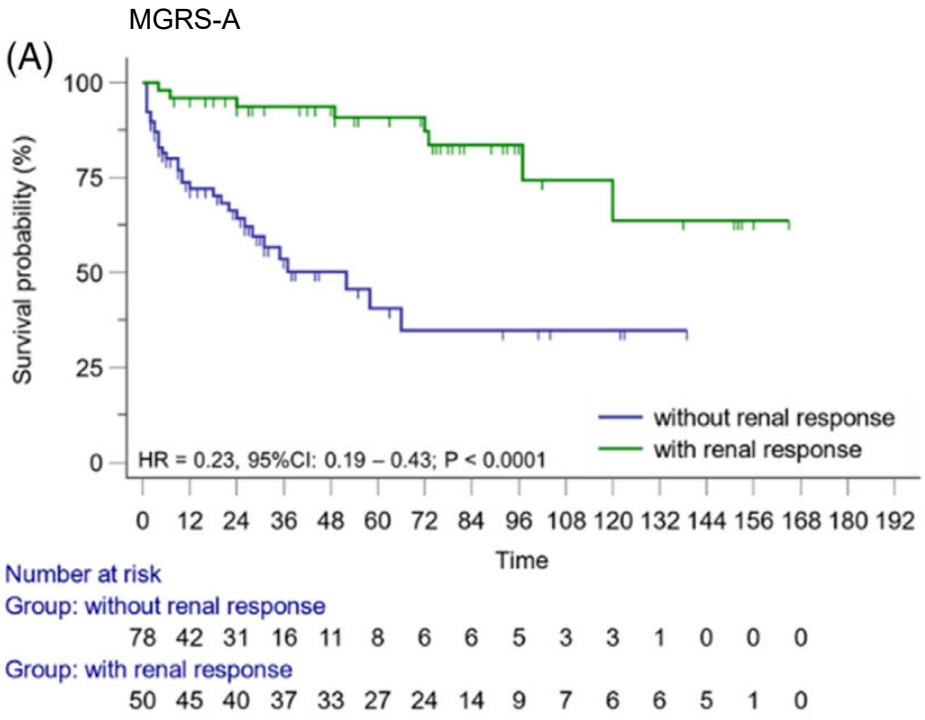

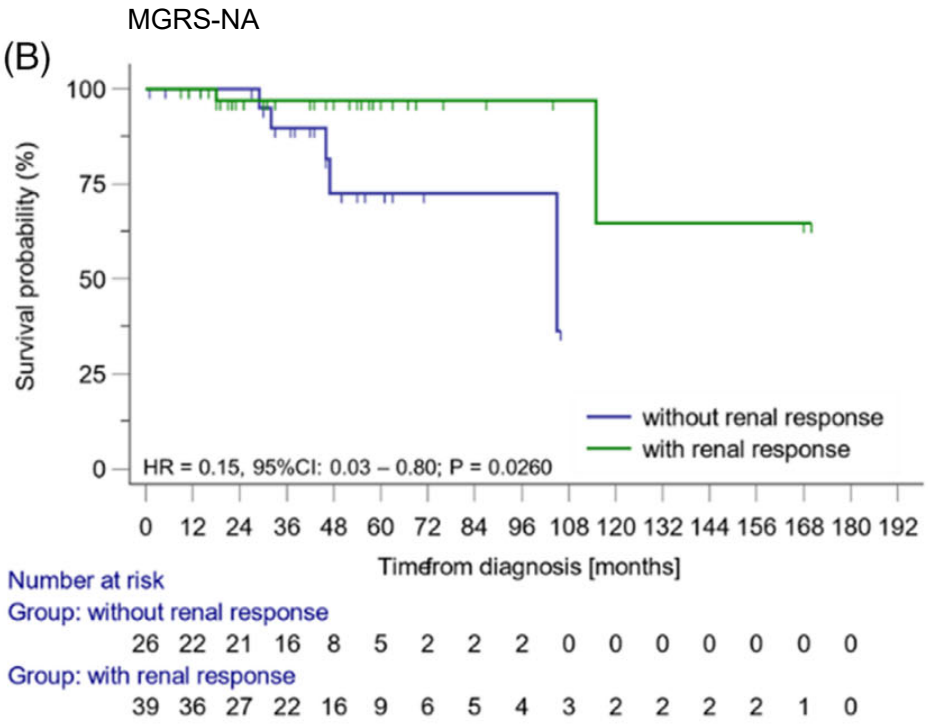

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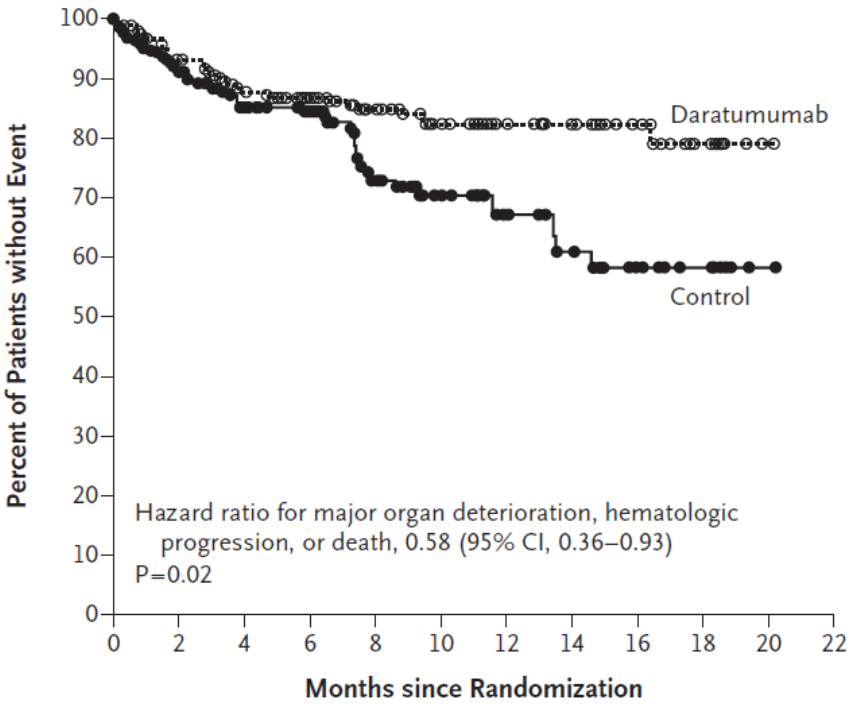
Daratumumab bei AL-Amyloidose

- Patienten mit AL-Amyloidose
- Ausschluss: symptomatisches Multiples Myelom
- Add-on zu Bortezomib, Cyclophosphamid und Dexamethason

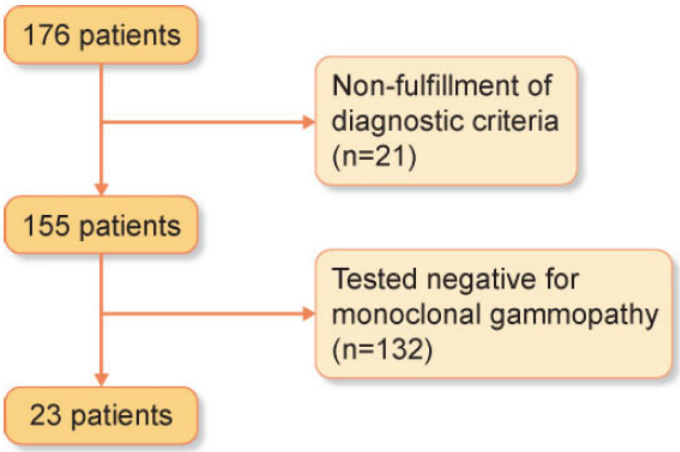


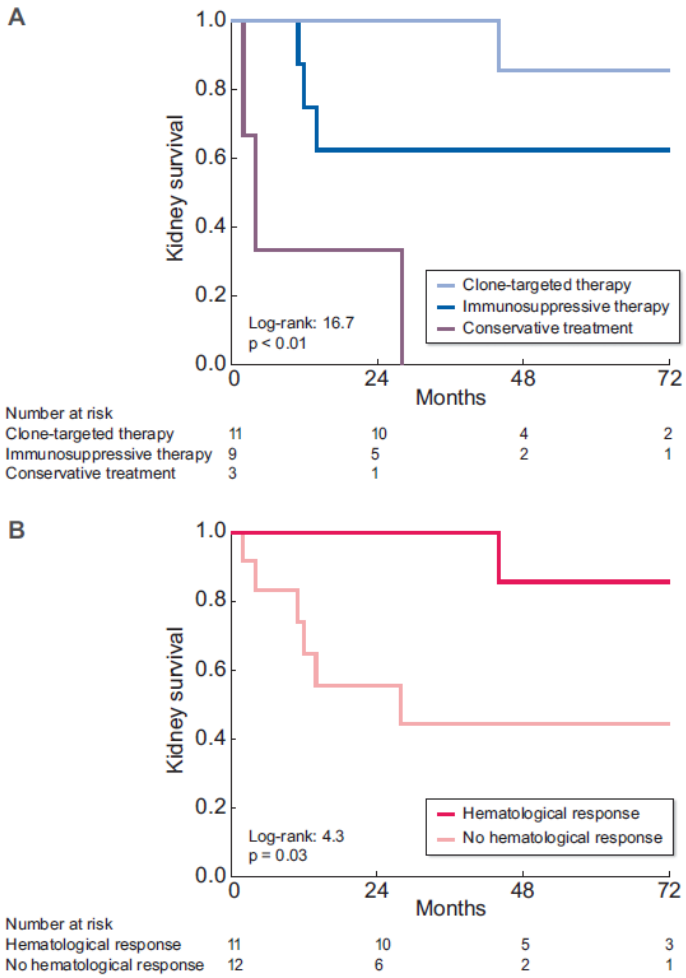
No. at Risk												
Daratumumab	195	178	166	147	114	86	60	44	27	10	1	0
Control	193	163	134	111	65	44	29	20	10	7	1	0

Figure 2. Kaplan–Meier Estimates of Survival Free from Major Organ Deterioration or Hematologic Progression.

Kastritis E, et al; ANDROMEDA Trial Investigators. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021

Klon-gerichtete Therapie bei Monoklonaler Gammopathie und C3G





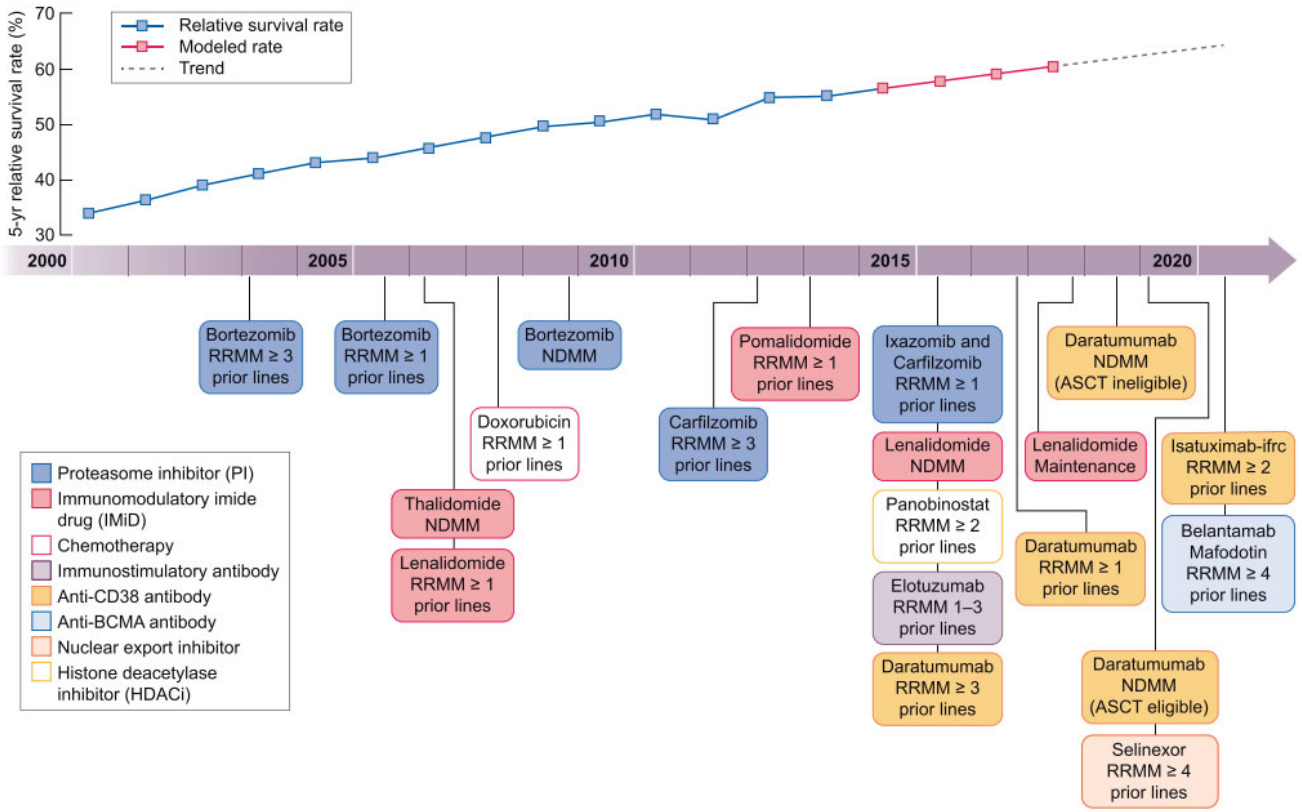
Caravaca-Fontán F, et al. C3 glomerulopathy associated with monoclonal gammopathy: impact of chronic histologic lesions and beneficial effects of clone-targeted therapies. Nephrol Dial Transplant. 2022

Prävalenz von Nierenerkrankungen bei Multiplem Myelom

- bei Diagnosestellung haben bereits 25% eine Nierenfunktionseinschränkung
- Im Verlauf entwickeln 50% eine CKD
- ~10% haben CKD Stadium V mit Dialyseeinleitung bei Erstmanifestation
- Dialyse bei MM ist mit deutlich erhöhter Mortalität verbunden (medianes Überleben 16,8 Monate)

1. Chitty DW, et al. Kidney transplantation in patients with multiple myeloma: narrative analysis and review of the last two decades. Nephrol Dial Transplant. 2022
2. Martín Reyes G et al. Supervivencia de pacientes con mieloma tratados con diálisis [Survival of myeloma patients treated with dialysis]. Nefrologia. 2003

MM - Therapieoptionen und 5-Jahres-Überleben



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Nierentransplantation bei Plasmazelldyskrasien

- Unbehandelt hohes Rekurrenzrisiko
- Zeitpunkt hängt von der Grunderkrankung ab

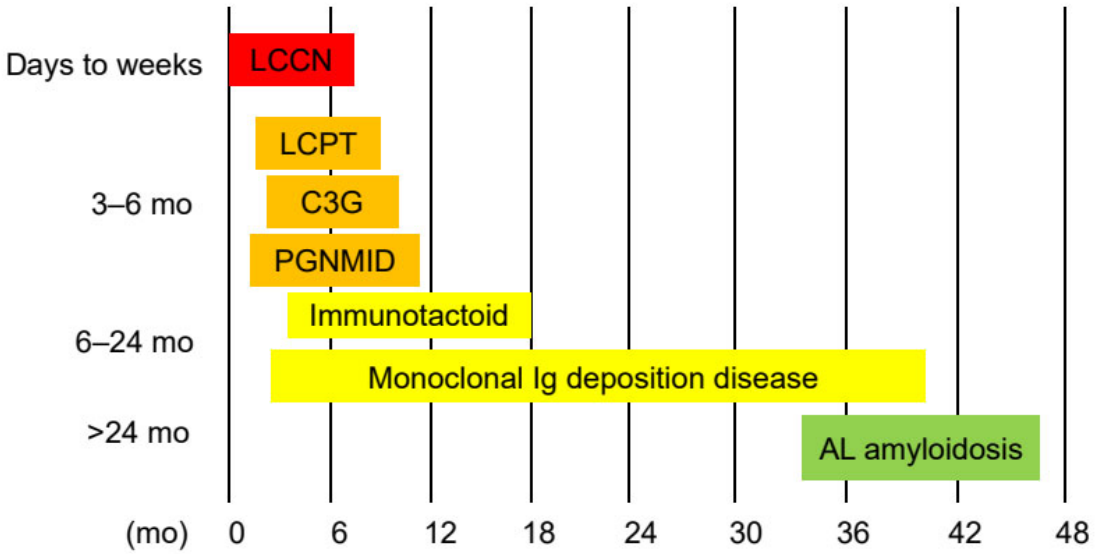

Figure 1 | Timing of recurrence of various plasma cell dyscrasias in kidney transplant allograft. C3G, C3 glomerulopathy; LCCN, light chain cast nephropathy; LCPT, light chain proximal tubulopathy; mo, month; PGNMID, proliferative glomerulitis with Ig deposit.

Murakami N, Blosser CD, Webber AB, Gupta G, Singh N, Boppana S, Master S, Parasuraman R, Campagnaro EL, Java A, Sprangers B, Bhasin-Chhabra B, Lum E, Khirfan D, Alexander MP, Molnar MZ, Benes B, Thakur AK, Bumma N, Karam S, Hultcrantz M, et al. Management recommendations for kidney transplantation in patients with plasma cell dyscrasia. Kidney Int. 2025

Nierentransplantatüberleben am Beispiel der Amyloidose

Table 2 | Summary of key cohort studies of AL amyloidosis and kidney transplantation

Studies	Study years	Cardiac involvement, %	HSCT, %	Living donor tx, %	mOS, yr	Allograft survival, yr	Recurrence, %, estimated time, yr	Prognosis factors
Mayo Clinic ($N = 60$)	1997–2018	47	60	80	10.3	NR	22, 10.2	CR/VGPR: longer mOS
BU Amyloidosis Center ($N = 49$)	1987–2017	33	80	65	10.5	8.3	29, 3.7	CR/VGPR: longer mOS and lower recurrence
Memorial Sloan Kettering ($N = 16$)	1999–2018	25	100	87	13.1	11.3	25, ND	ND
UK National Amyloidosis Centre ($N = 51$)	1989–2018	22	24	41	7.9	NR	14, 4.5	CR: improved mOS, IVSd >12 mm: worse mOS and higher recurrence
IKMG multicenter study ($N = 237$)	1987–2020	41	62	54	8.6	7.8	29, 6.6	CR/VGPR: longer mOS, lower recurrence, and longer allograft survival

BU, Boston University; CR, complete response; HSCT, hematopoietic stem cell transplant; IKMG, International Kidney and Monoclonal Gammopathy Research Group; IVSd, interventricular septal diameter; mOS, median overall survival; ND, not described; NR, not reached; tx, transplant; VGPR, very good partial response.

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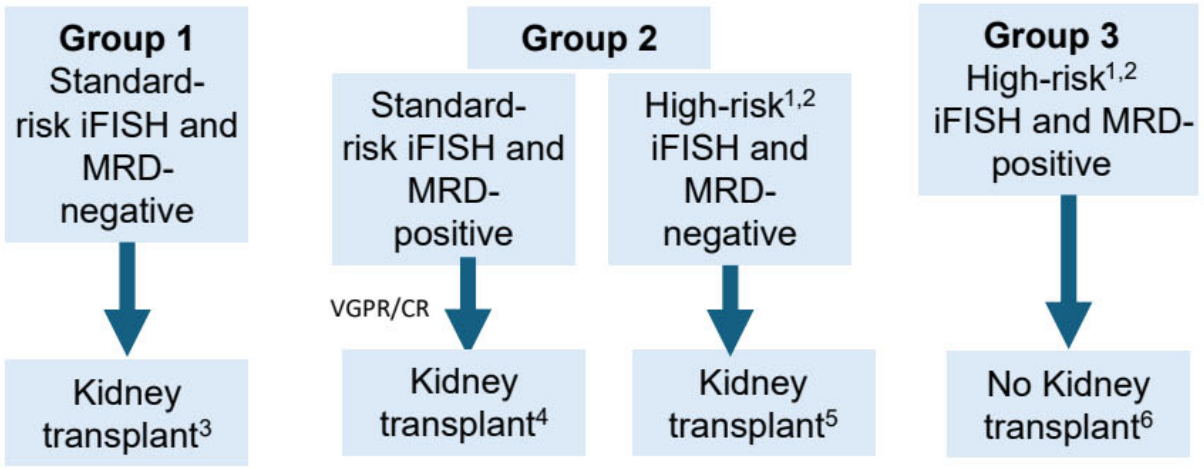
Nierentransplantation bei Multiplem Myelom



1. High-risk category is defined as 1 of the following: Having high-risk cytogenetics (below), high β_2-microglobulin (>5.5 mg/dl) with a normal creatinine (<1.2 mg/dl), extramedullary disease, or plasma cells clones in circulation at diagnosis.
2. High-risk cytogenetics (iFISH or NGS): Deletion (del) (17p) in >20% CD38+ plasma cells and/or TP53 mutation, monoallelic del (1p32), along with +1q, or biallelic del (1p32). One of the translocations: t(4;14), t(14;16), or t(14;20), which must co-occur with +1q or del(1p32).
3. In standard-risk, MRD-negative (10e-5 or 10e-6, depending on availability) MM patient, kidney transplant can be considered within 6 mo of achieving a hematologic response.*
4. In standard-risk, MRD-positive MM patient, kidney transplant can be considered 12 mo after achieving a VGPR/CR, but consider continuing/maintenance therapy.*
5. In high-risk, MRD-negative MM patient, kidney transplant can be considered 12–24 mo of achieving a hematologic response, but recommend continuing/maintenance therapy.*
6. High-risk patients who remain MRD-positive are not considered optimal kidney transplant candidates but could be considered in selected circumstances

*Contingent on overall transplant candidacy and availability of a living donor.

Figure 2 | Decision tree for patients with multiple myeloma (MM) and end-stage kidney disease based on risk category and response to therapy. CR, complete response; iFISH, interphase fluorescence *in situ* hybridization; MRD, minimal residual disease; NGS, next generation sequence; VGPR, very good partial response.

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Nierentransplantation bei C3G oder PGNMID

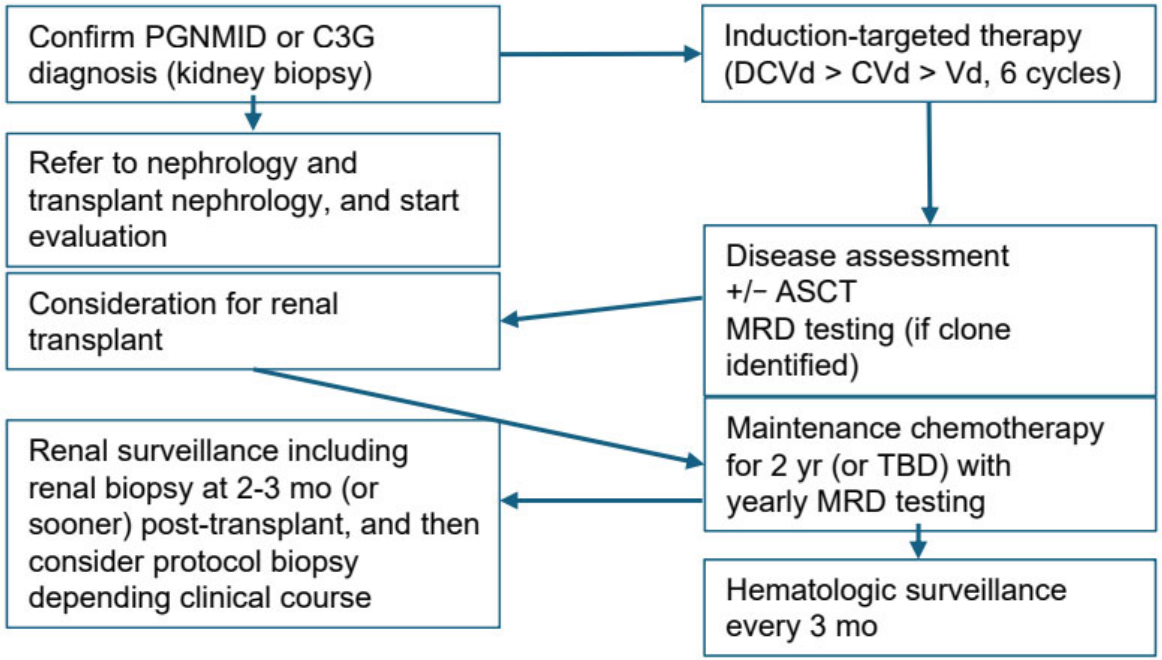

Figure 3 | Algorithm for proliferative glomerulitis with Ig deposits (PGNMIDs) and monoclonal gammopathy–associated C3 glomerulopathy (C3G). ASCT, autologous stem cell transplant; CVd, cyclophosphamide, bortezomib, and dexamethasone; DCVd, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; MRD, minimal residual disease; TBD, to be determined; Vd, bortezomib and dexamethasone.

Murakami N, Blosser CD, Webber AB, Gupta G, Singh N, Boppana S, Master S, Parasuraman R, Campagnaro EL, Java A, Sprangers B, Bhasin-Chhabra B, Lum E, Khirfan D, Alexander MP, Molnar MZ, Benes B, Thakur AK, Bumma N, Karam S, Hultcrantz M, et al. Management recommendations for kidney transplantation in patients with plasma cell dyscrasia. Kidney Int. 2025

Zusammenfassung

- Leichtketten können sowohl tubuläre als auch glomeruläre Nierenerkrankungen auslösen
- durch organisierte / nicht organisierte renale Ablagerungen aber auch indirekt durch Komplement-(Über)aktivierung
- variable Klinik
- die CAST-Nephropathie muss nicht zwingend histologisch gesichert werden
- glomeruläre Erkrankungen erfordern in der Regel eine Biopsie
- Beim MM aber auch beim MGRS besteht die Indikation zur Klon-gerichteten Therapie
- Prognose ist abhängig von Erkrankung, hämatologischem und renalem Ansprechen
- die Amyloidose hat eine schlechtere Prognose
- neue Therapien (insbesondere CD38-Antikörper) haben die Prognose von Myelom und Amyloidose deutlich verbessert
- dies eröffnet auch die Möglichkeit von Nierentransplantation bei Plasmazelldyskrasien

Vielen Dank für Ihre Aufmerksamkeit!

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