Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Alessandro Gozzetti

Le Gammapatie Monoclonali a Significato Clinico Renale (MGRS)

Coordinatore Scientifico
Michele CAVO

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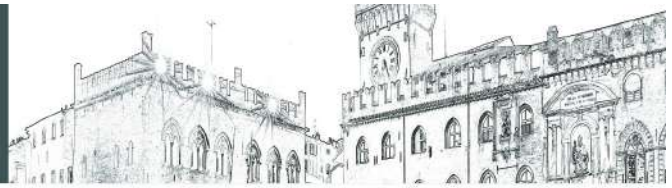


Box 2 | **Updated diagnostic criteria for MGUS, SMM, and MM**[40]

MGUS

- Monoclonal protein[a] levels in serum <3 g/dl
- 10% clonal bone marrow plasma cells (BMPCs)
- Monoclonal protein levels in urine <500 mg per 24 h
- Absence of MM-defining events or amyloidosis

SMM

- At least one of the following:
  - Immunoglobulin G (IgG) or IgA levels in serum ≥3 g/dl
  - Monoclonal protein levels in urine ≥500 mg per 24 h
  - Clonal BMPCs 10–60%
- Absence of MM-defining events or amyloidosis

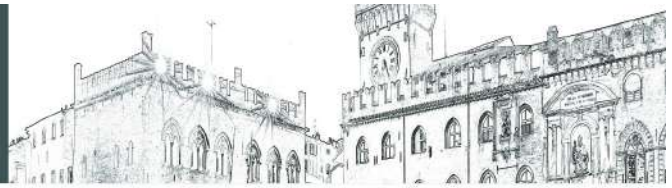
Newly diagnosed MM

- Clonal BMPCs ≥10% or biopsy-proven plasmacytoma in addition to one of the following:
- An MM-defining event:
  - Hypercalcaemia: calcium levels in serum >1 mg/dl over the upper limit of normal[b] or >11 mg/dl
  - Renal insufficiency: creatinine clearance <40 ml per min or creatinine levels in serum >2 mg/dl
  - Anaemia: haemoglobin levels in serum >20 g/l below the lower limit of normal or <100 g/l
  - Detection of osteolytic lesions on radiography, CT, or PET–CT
- A biomarker of early progression:
  - Clonal BMPC percentage ≥60%
  - Involved:uninvolved serum free light chain ratio ≥100
  - At least one focal lesion detected on MRI

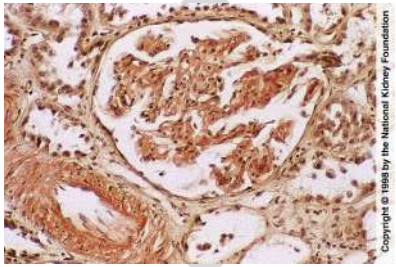
MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smouldering MM. [a]Monoclonal protein refers to the levels of monoclonal antibodies. [b]Within the expected physiological range.

Criteri diagnostici MGUS-SMM-MM

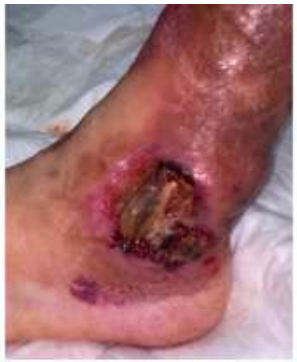
Rajkumar, Lancet Oncol 2014



Gammapatie Monoclonali a Significato Clinico (MGCS)

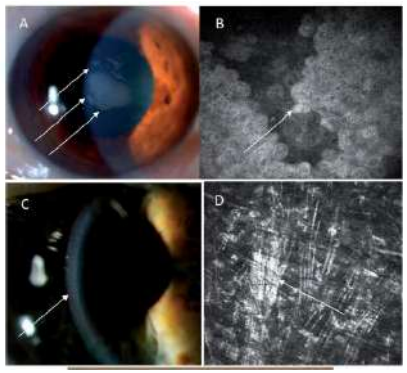


- MGRenalS



- MGDermatologicalS

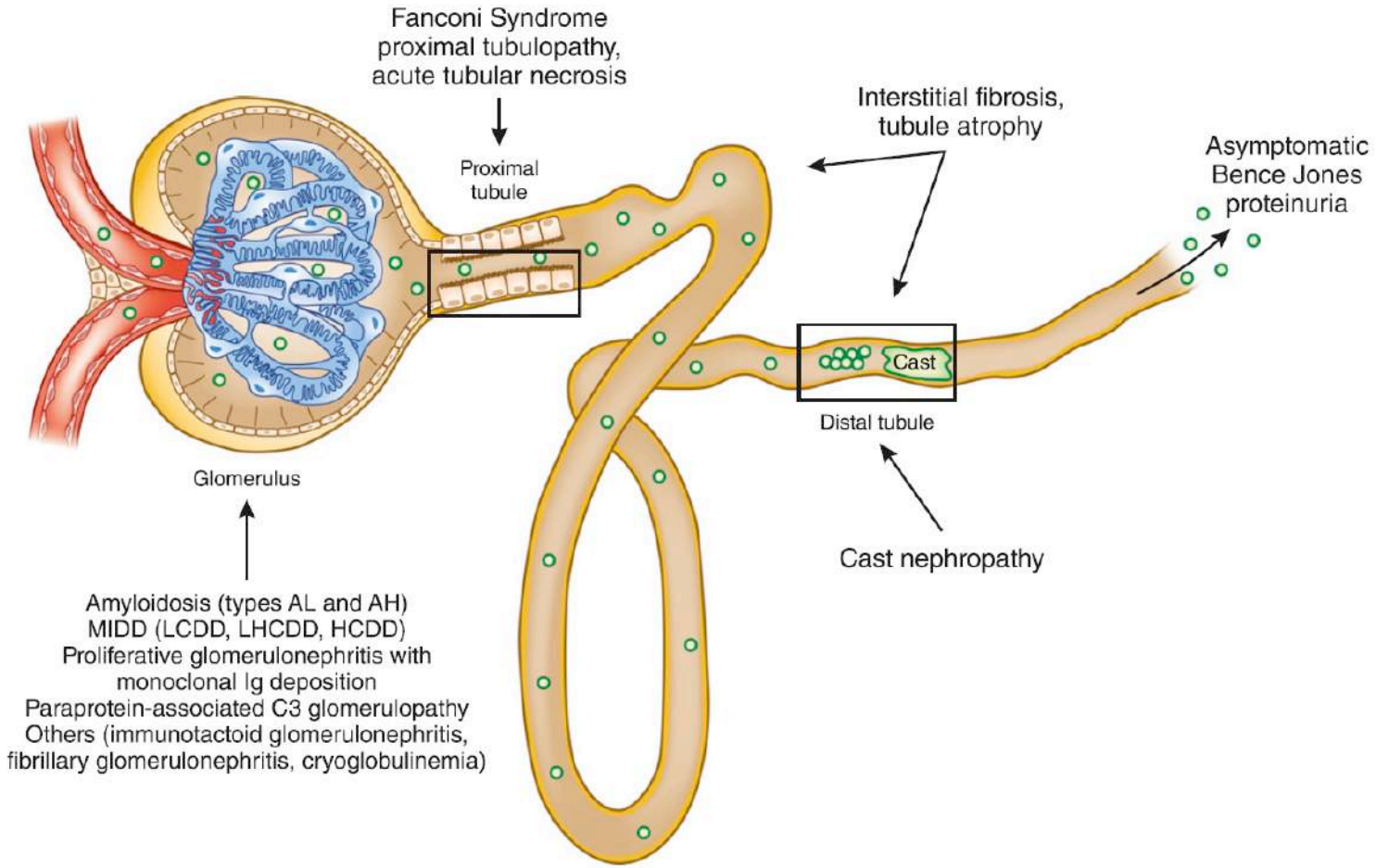
- MGOcularS

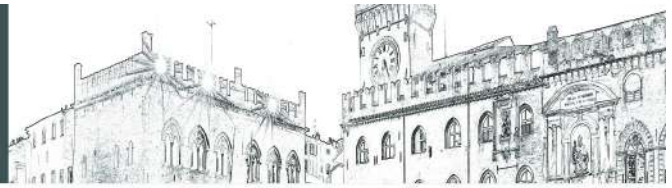


- MGNeurologicalS

Dispenzieri, Hematology 2020
Castillo AJH 2021
Garderet, Leuk Lymph 2021

INSUFFICIENZA RENALE E GAMMAPATIE MONOCLONALI





Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung,[1,2] Frank Bridoux,[3] Colin A. Hutchison,[4] Samih H. Nasr,[5] Paul Cockwell,[4] Jean-Paul Fermand,[6] Angela Dispenzieri,[2] Kevin W. Song,[7] and Robert A. Kyle,[2] on behalf of the International Kidney and Monoclonal Gammopathy Research Group

MGUS non richiede trattamento in assenza di MDE

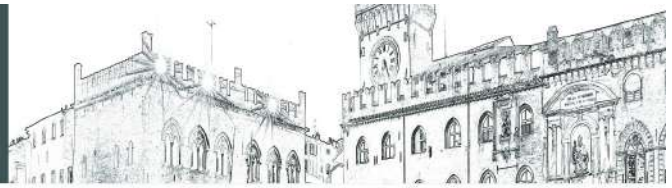
Solo 15% delle amiloidosi AL e 65% delle MIDD (malattia da deposito di immunoglobuline monoclonali) hanno mieloma

Molte MGUS con danno renale sotto-trattate o mai trattate

MGRS: comp M <3g/L nel siero; PC <10% alla BOM,

MGUS, LNH,CLL malattie indolenti ma con

danno renale correlato



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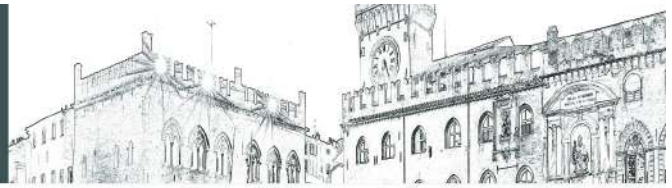
MGRS non rispondono a terapia immunosoppressiva come nelle nefropatie autoimmuni

Alta percentuale di ricaduta (90%) dopo trapianto di rene

Alta probabilità di evoluzione in malattia sintomatica (MM-CLL-MW)

BLOOD, 22 NOVEMBER 2012 • VOLUME 120, NUMBER 22

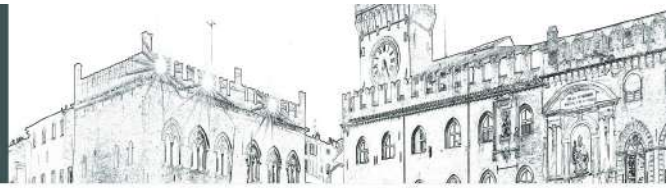


MGRS

- Il tipo di danno renale presente nelle gammopatie monoclonali è principalmente determinato dalle caratteristiche fisiochimiche dell'immunoglobulina patogenetica, in particolare della parte variabile.

- Il danno renale non è solo la conseguenza della deposizione della proteina monoclonale ma possono essere implicati altri meccanismi quali la secrezione di vari fattori biologici (es. VEGF) o un'attività autoanticorpale della IM (es. IgG3 kappa monoclonale con attività autoanticorpale verso il recettore della PA2)

Leung NEJM, 2021



MGRS

- La diagnosi precoce è essenziale; nella maggior parte delle MGRS il GFR basale è il principale determinante della prognosi renale.
- Necessario sempre ricercare attentamente la correlazione tra danno renale e gammopatia: 10% di amiloidosi familiari diagnosticate inizialmente come amiloidosi AL per la contemporanea presenza di una IM.
- La proteina monoclonale può essere “intrappolata” nei depositi di amiloide di altro tipo.

MGRS possono essere suddivise in due gruppi principali:

MGRS a depositi organizzati

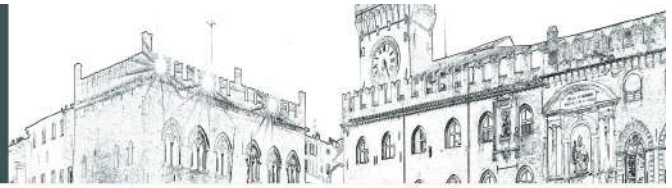
MGRS a depositi prevalentemente granulari

Table 1. Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig

Organized			Nonorganized (granular)	
Crystals	**Fibrillar**	**Microtubular**	**MIDD (Randall type)**	**Other**
Myeloma cast nephropathy	Light chain amyloidosis	Type I and type II cryoglobulinemic glomerulonephritis	LCDD	Proliferative GN with monoclonal Ig deposits
Light chain proximal tubulopathy (with or without Fanconi syndrome)	Nonamyloid	Immunotactoid GN	LHCDD	Waldenström
Crystal-storing histocytosis	Fibrillary GN*	GOMMID	HCDD	Macroglobulinemia

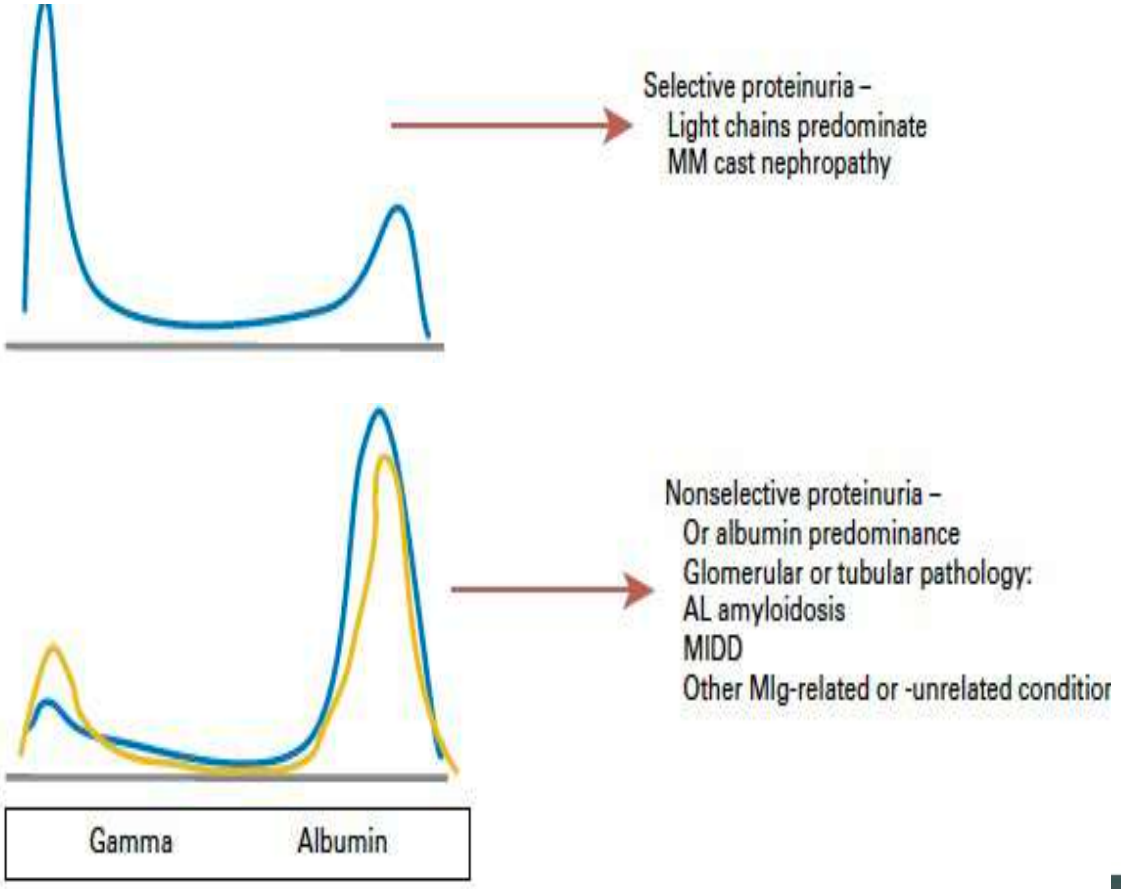
GN indicates glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal Ig deposits; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; and HCDD, heavy-chain deposition disease.
*Mostly associated with polyclonal IgG deposits.

Leung Nat REv Nephrol, 2019



Biopsia renale: quando?

Creatinina, FLC sieriche, proteinuria 24 ore, elettroforesi urine



FLC alte >500 mg/L
Probabile Cast nephropathy
No biopsia renale

FLC basse<500 mg/L
albuminuria
Si biopsia renale

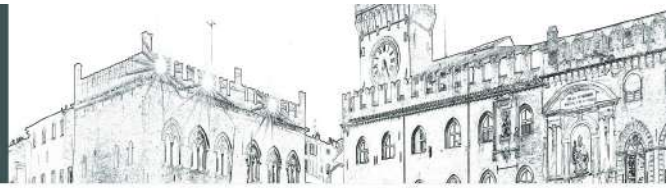
BIOPSIA RENALE

L'incidenza di MGUS a >80 anni è 8%

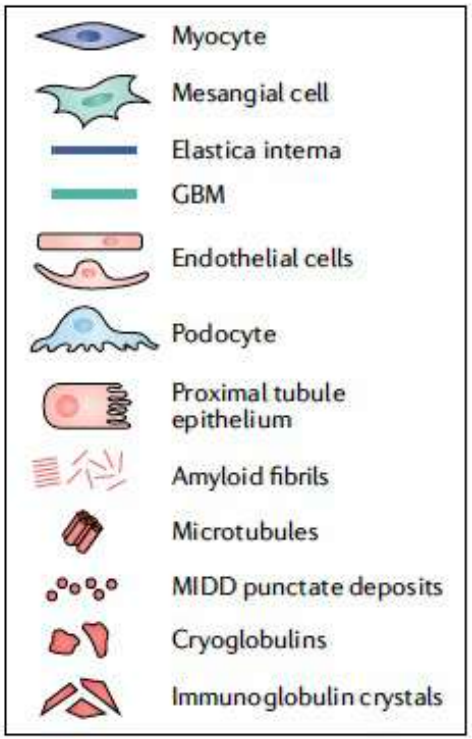
L'incidenza di malattia cronica renale aumenta con l'età

In uno studio su MGUS e biospia renale il 45% dei pazienti non aveva MGRS

1. Kyle RA et al. N Engl J Med. 2006;
2. 2. Delanaye P et al. Clin Biochem Rev. 2016;
3. Paueksakon P et al. Am. J. Kidney Dis. 2003.



LOCALIZZAZIONE MGRS



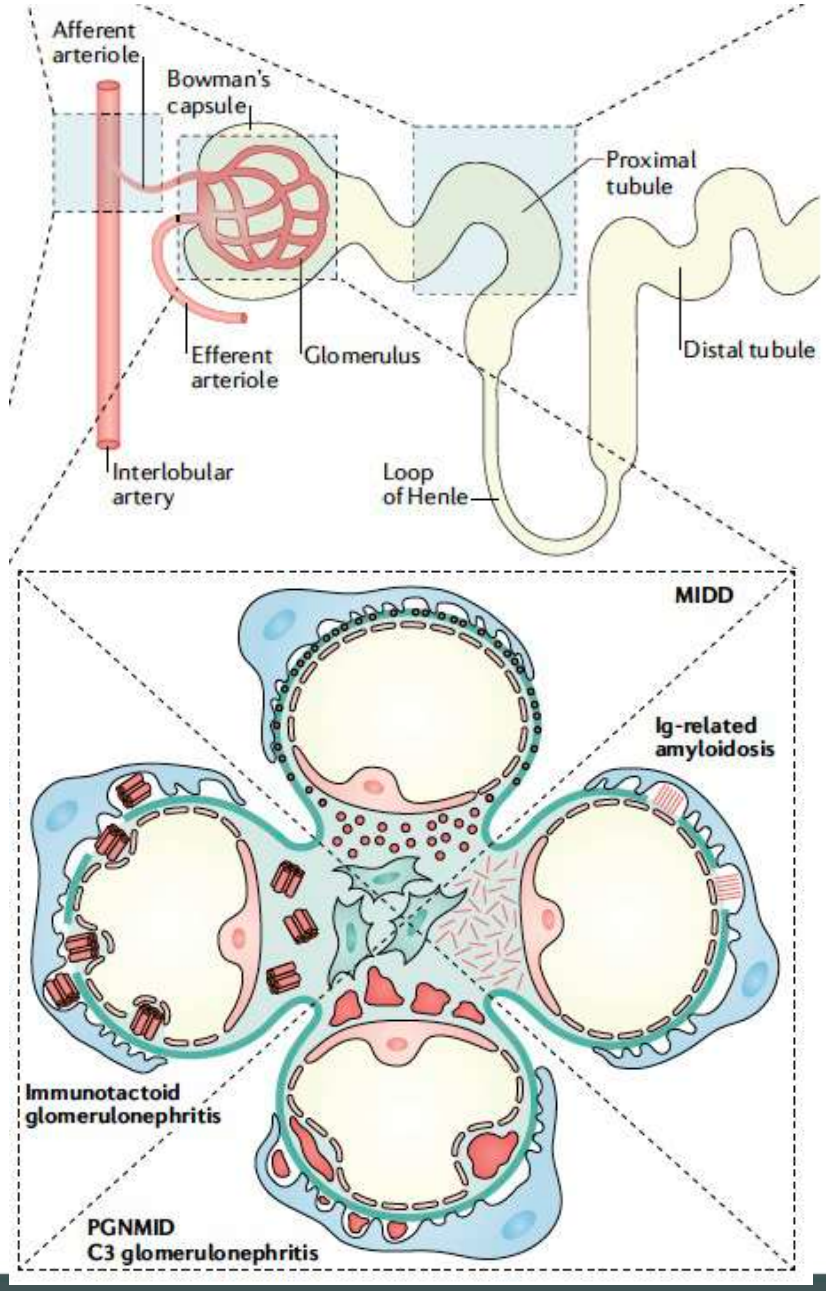
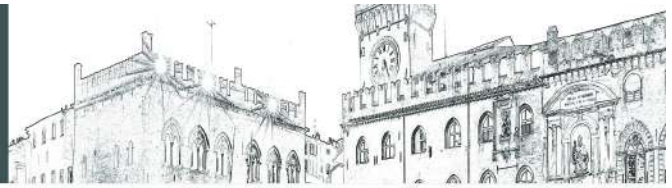


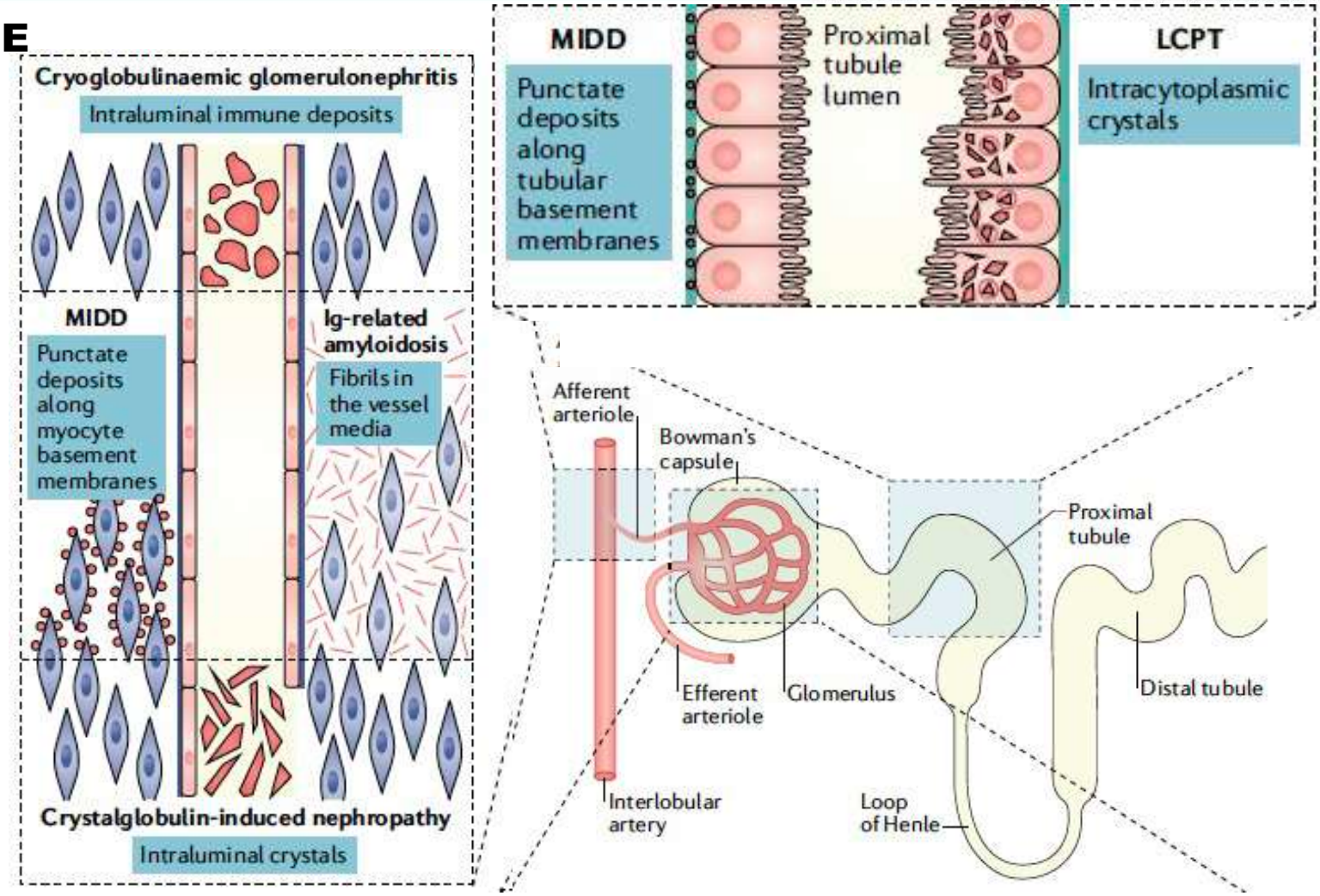
Fig. 1 | **Localization of MGRS-associated renal lesions.** Monoclonal gammopathy of renal significance (MGRS)-associated lesions can involve one or more renal compartments. In immunotactoid glomerulonephritis, C3 glomerulopathy and proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), MGRS-associated lesions involve only the glomeruli, whereas in light-chain proximal tubulopathy (LCPT), MGRS-associated lesions involve only the proximal tubules. MGRS-associated lesions in cryoglobulinaemic glomerulonephritis mainly involve the glomeruli but can occasionally affect blood vessels in the form of intravascular cryoglobulin thrombi or endovasculitis. Immunoglobulin-related amyloidosis and monoclonal immunoglobulin deposition disease (MIDD) usually affect all renal compartments, including glomeruli, vessels and the tubulointerstitium. GBM, glomerular basement membrane.

Leung Nat Rev Nephrol, 2019

NATURE REVIEWS | NEPHROLOGY



LOCALIZZAZIONE MGRS



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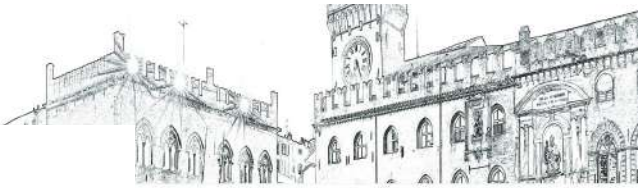
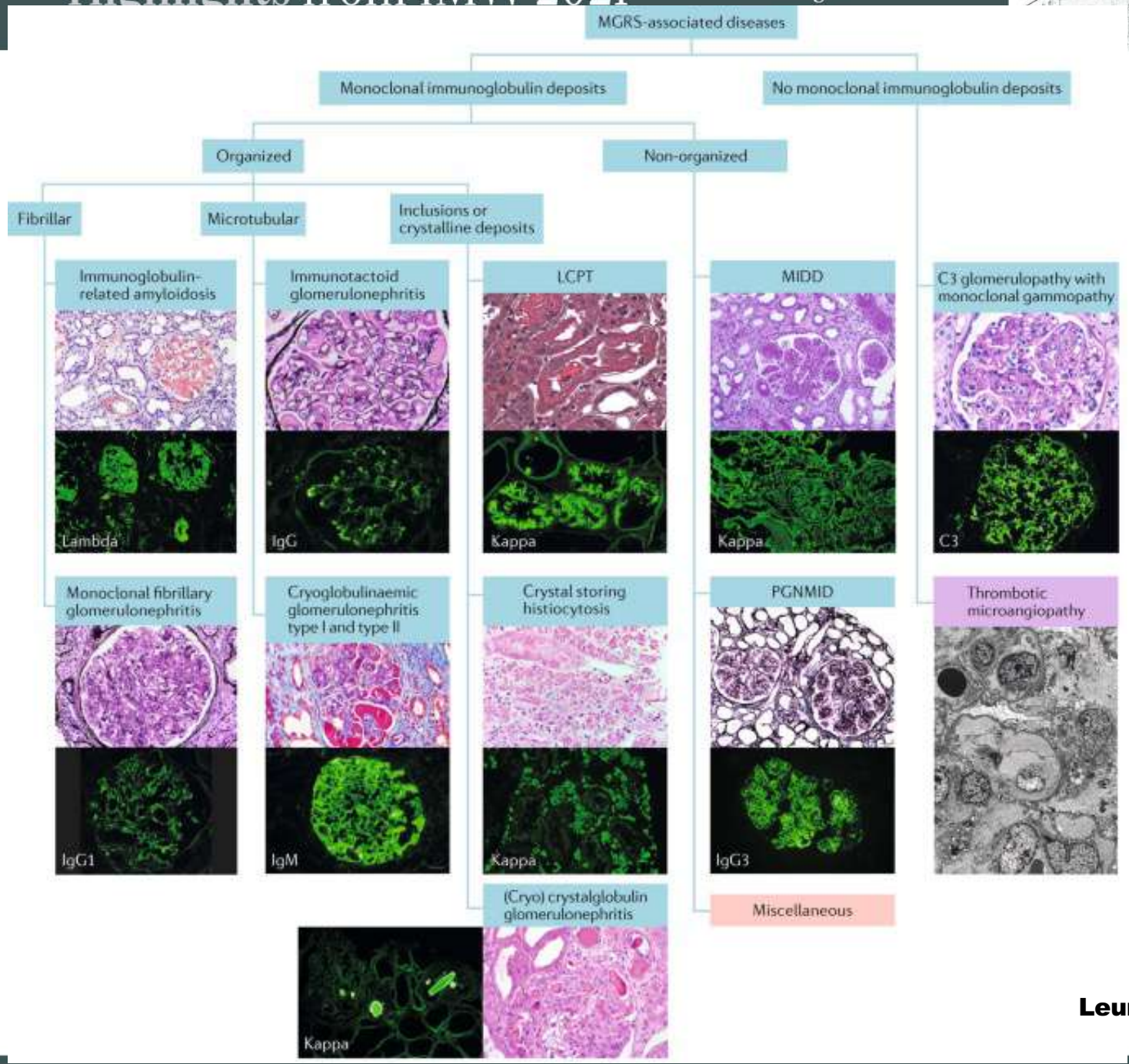
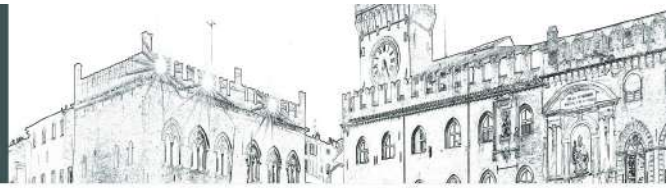
Leung Nat REv Nephrol, 2019





Leung Nat REv Nephrol, 2019



Danno renale

- Le proprietà fisiochimiche e le dimensioni della Immunoglobulina Monoclonale (IM) sono probabilmente responsabili del tipo di lesione renale riscontrabile alla biopsia.

- IM di peso molecolare maggiore, formate da catene leggere e pesanti, difficilmente potranno attraversare la barriera del capillare glomerulare formando pertanto depositi glomerulari con attivazione di processi infiammatori (Glomerulonefriti con depositi monoclonali, GN immunotattoide)

- IM di peso molecolare minore, formate solo da catene leggere, potranno più facilmente attraversare la barriera del capillare glomerulare con conseguente danno prevalentemente tubulare (LCDD).

- IM formate da catene leggere e pesanti ma legate ad altre proteine potranno formare depositi sia glomerulari sia tubulari (Amiloidosi)

Leung Nat REv Nephrol, 2019

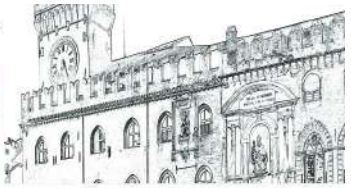
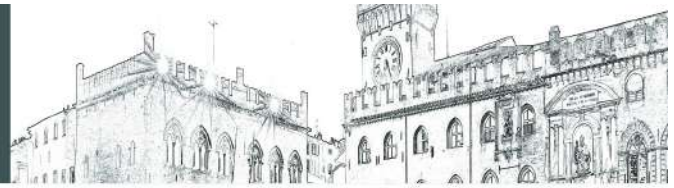


Table 2 | **Consensus recommendations for the evaluation of MGRS-associated disorders**

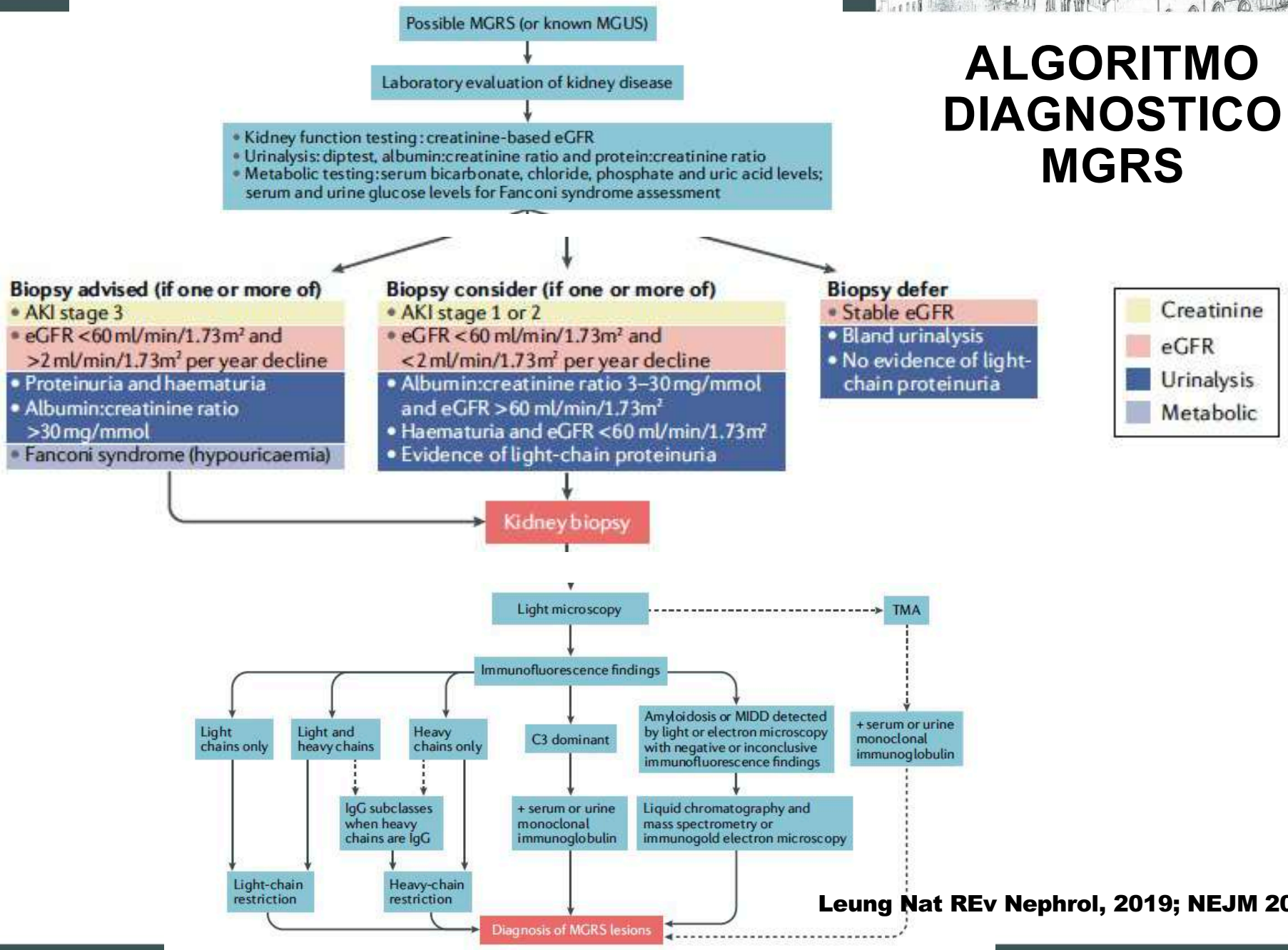
Modality	Recommendations	Refs
Kidney biopsy	Recommended in the following patients: • Those with monoclonal gammopathy and unexplained kidney disease • Those with known risk factors for chronic kidney disease but an atypical clinical course • Patients with kidney disease and monoclonal gammopathy aged <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

MGUS,
SMM,
LNH
CLL

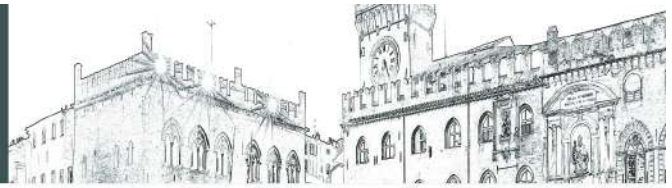
Leung Nat REv Nephrol, 2019



ALGORITMO DIAGNOSTICO MGRS



Leung Nat REv Nephrol, 2019; NEJM 2021



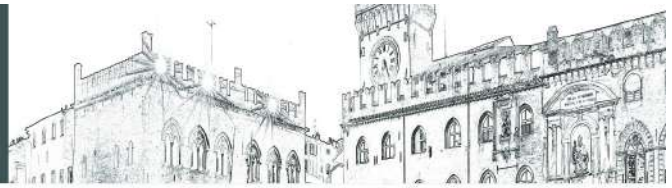
MGRS e terapia: Quando possibile eliminare il clone

Table 1. Kidney outcomes in the largest monoclonal gammopathies of renal significance case series

MGRS Disorder	*N*	Average Follow-Up (mo)	Kidney Outcomes
LCDD (3)	63	28	57% ESRD
PGNMID (4)	37	30	38% complete/partial recovery 38% persistent renal dysfunction 22% ESRD
ITGN (5)	16	48	50% remission 33% persistent renal dysfunction 17% ESRD
MIDD (6)	64	25	39% ESRD 57% stable/improved renal function
LCDD (7)	53	74	53% ESRD (10% ESRD at presentation)

MGRS, monoclonal gammopathies of renal significance; LCDD, light chain deposition disease; PGNMID, proliferative GN with monoclonal Ig deposits; ITGN, immunotactoid glomerulopathy; MIDD, monoclonal Ig deposition disease.

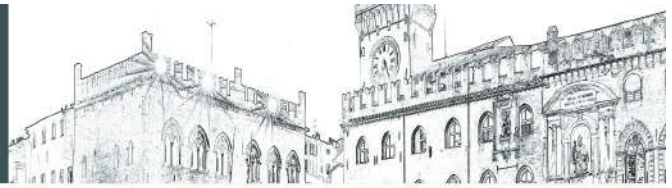
Clin J Am Soc Nephrol 11: 1681–1691, September, 2016



MGRS e terapia

Table 2. Therapeutic options for monoclonal gammopathies of renal significance

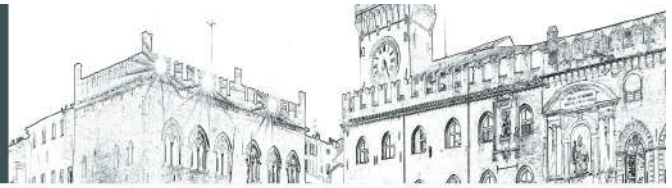
Agent (Dosage Form)	Clone Sensitivity		Dose Adjustment for eGFR?	Described Kidney-Associated Toxicities	Common Adverse Events
	B Cell	Plasma Cell			
Proteasome inhibitors					
Bortezomib (IV, SC)	X	X	No	None	Thrombocytopenia Peripheral neuropathy Varicella zoster reactivation
Carfilzomib (IV)	X	X	Yes	AKI, thrombotic microangiopathy	Thrombocytopenia Dyspnea Hypersensitivity reaction Varicella zoster reactivation
Monoclonal antibodies					
Rituximab (anti-CD20) (IV)	X		No	None	Infusion reactions Hepatitis B reactivation
Daratumumab (anti-CD38) (IV)		X	No	None	Infusion reactions
Cytotoxic agents					
Cyclophosphamide (IV, PO)	X	X	No	None	Nausea Cytopenias
Melphalan (IV, PO)	X	X	Yes	None	Nausea Cytopenias
Bendamustine (IV)	X	X	Yes	None	Cytopenias
Immunomodulatory agents					
Thalidomide (IV, PO)	X	X	No	Hyperkalemia observed in renal insufficiency	Constipation Fatigue, somnolence Peripheral neuropathy Venous thrombosis Rash Teratogenicity
Lenalidomide (IV)	X	X	Yes	Increased myelosuppression in renal insufficiency, AKI observed in AL amyloidosis	Cytopenias Venous thrombosis Diarrhea Constipation Rash Teratogenicity
Pomalidomide (IV)		X	Unknown	No	Cytopenias Venous thrombosis Diarrhea; Constipation Teratogenicity



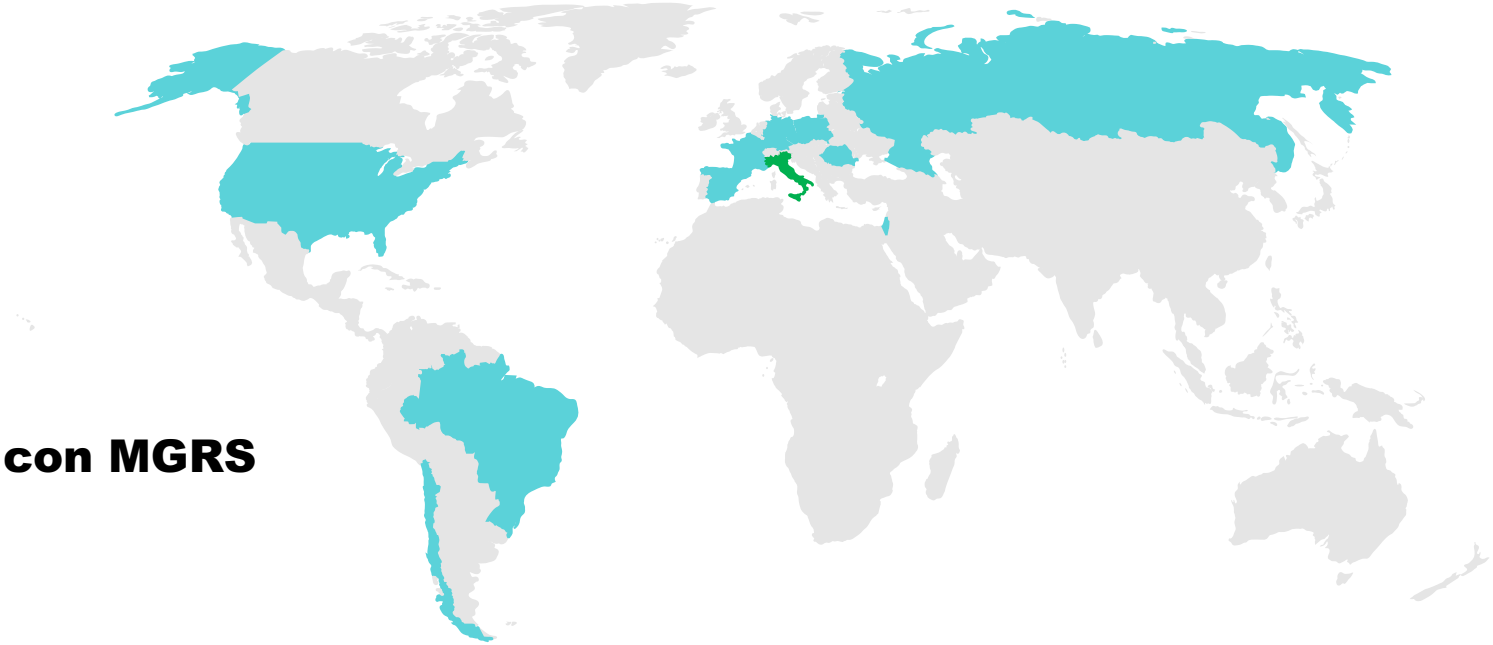
MGRS e terapia

- Valutare e definire la risposta può essere difficoltoso
- Benché non ci siano studi validati nelle MGRS è ragionevole seguire il livello della IM quando possibile
- Considerando che in una percentuale significativa di casi non si rilevano IM su siero e urine, i soli markers utilizzabili possono essere creatinina e proteinuria
- La remissione della proteinuria è comunque un end-point non validato nelle MGRS
- Inoltre non è noto se sia necessario ottenere una risposta ematologica completa per avere una risposta sulla progressione della nefropatia

STUDI NECESSARI!!



REAL WORLD DATA AND PROGNOSTIC FACTORS IN MGRS



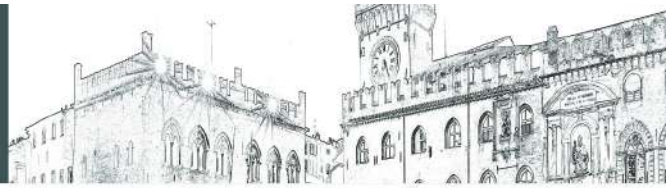
280 pazienti con MGRS

12 paesi

19 centri ematologici

Diagnosi: 2003-2020

Gozzetti et al. submitted



CARATTERISTICHE DEI PAZIENTI

	Median or %
Median age, years (range)	61 (25 – 87)
Male sex	50,5%
Monoclonal component	
IgA	5%
IgG	38%
IgM	7%
Free Light chains	50%

	Median	RANGE
Bone marrow involvement (PC%)	6%	0-55 %
MGUS/SMM/LNH	214/55/9	-
Quantity of monoclonal component (mg/dl)	11	0-3000
FLC kappa (mg(dl)	36	0.01-6680
FLC lambda (mg/dl)	41	0-4260
FLC kappa/lambda	1	0.003-1040
Albumin (mg/dl)	27	2-76
B2microglobulin	5	1,5-114
LDH	249	77-1040
Creatinine (mg/dl)	133	42.24-1149.2
GFR (ml/min/m2)	44	3-121
24 hours urine protein [g]	6	0-14850
Quantity of BJ protein [mg/24 hours]	10	0-2700
Dyalisis	61	22%

Type of MGRS

	%
Amyloidosis	**64%**
MIDD	**19%**
PGNMID	**5%**
LC proximal tubulopathy	**4%**
Monoclonal fibrillary GN	**1%**
Immunotactoid GN	**1%**
C3 glomerulopathy	**3%**
Other	**2%**
Cryoglobulinemic GN	**1%**

Gozzetti et al. submitted

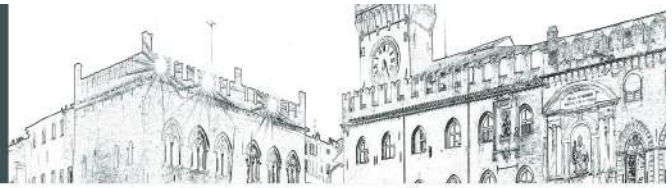
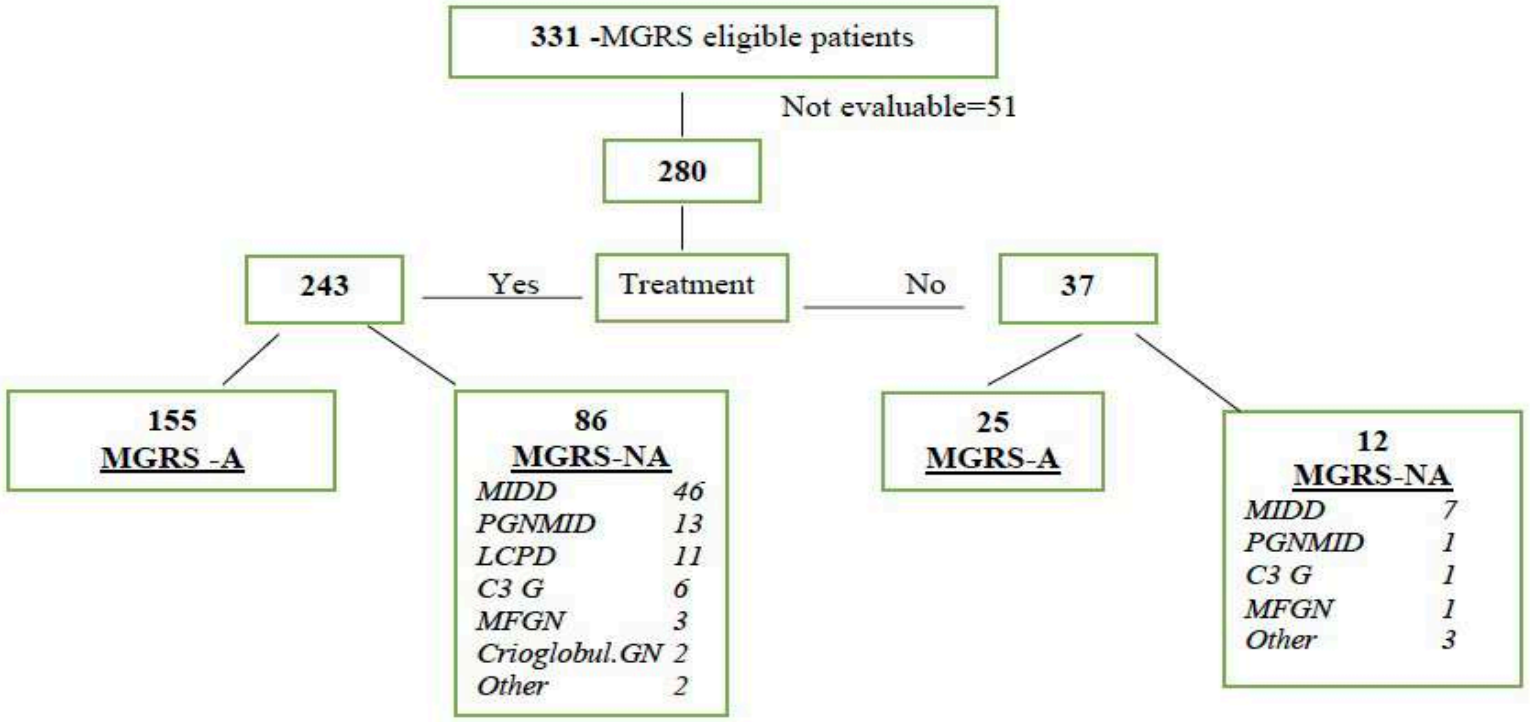


Table 1. MGRS patient's diagram.



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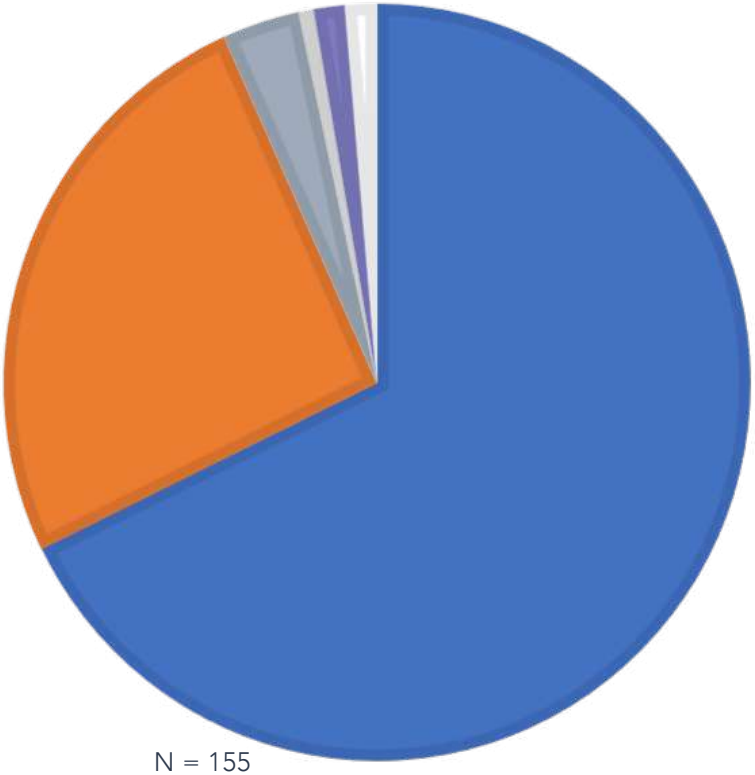
TERAPIA

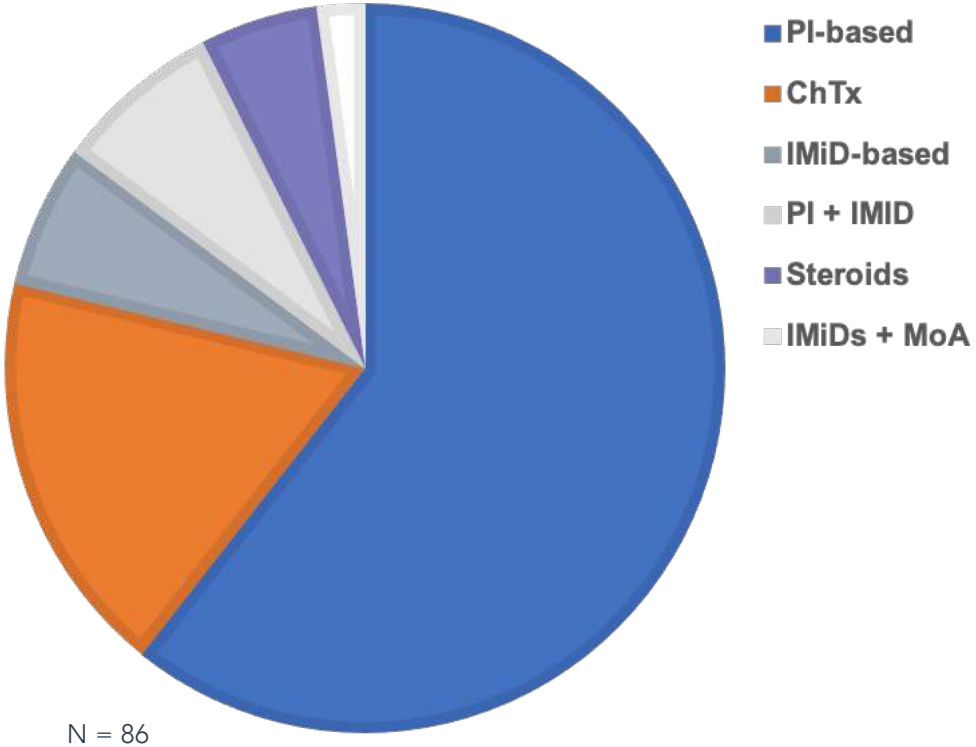
MGRS amyloidosis



N = 155

+ 11% ASCT

MGRS non-amyloidosis



N = 86

+ 28% ASCT

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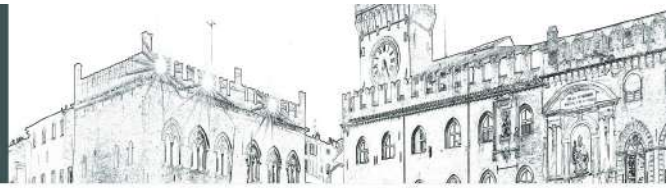

RISPOSTA EMATOLOGICA E RISPOSTA RENALE

MGRS-A

Hematologic response, N		Renal response, N (%)
CR	30	23 (76,5%)
PR/VGPR	38	18 (47%)
SD	37	2 (5,5%)
PD	15	3 (20%)

MGRS-NA

Hematologic response, N		Renal response, N (%)
CR	20	17 (85%)
PR/VGPR	25	17 (68%)
SD	16	2 (12.5%)
PD	2	0

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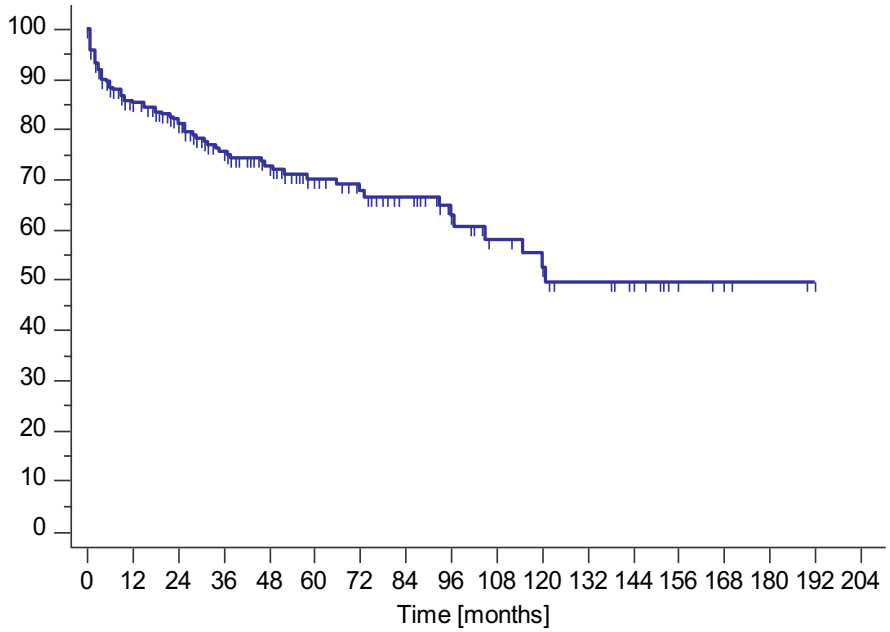
Overall survival

The median follow up was
72 mos. range 18 – 216 mos.

The median OS was
121 mos. (95%CI: 105 – 121 mos)



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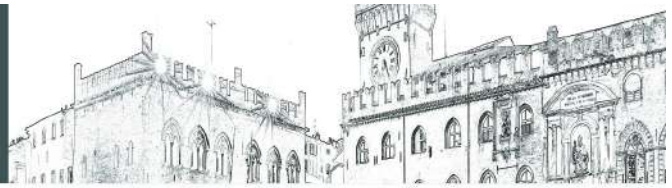
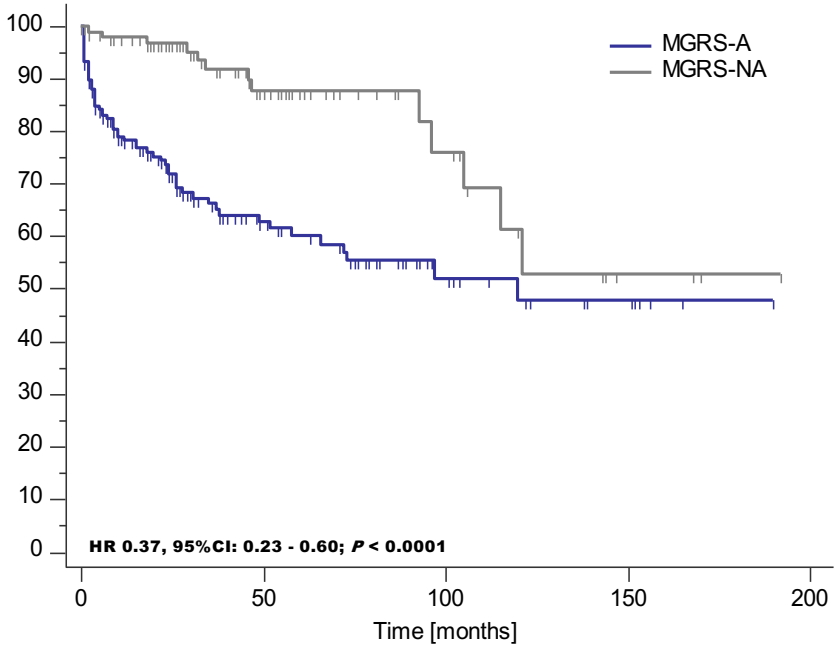


Overall Survival



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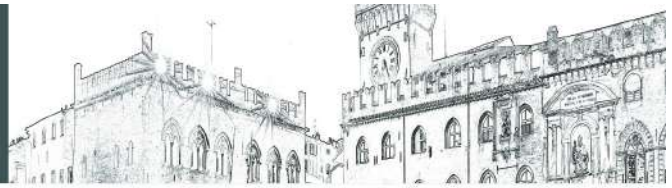
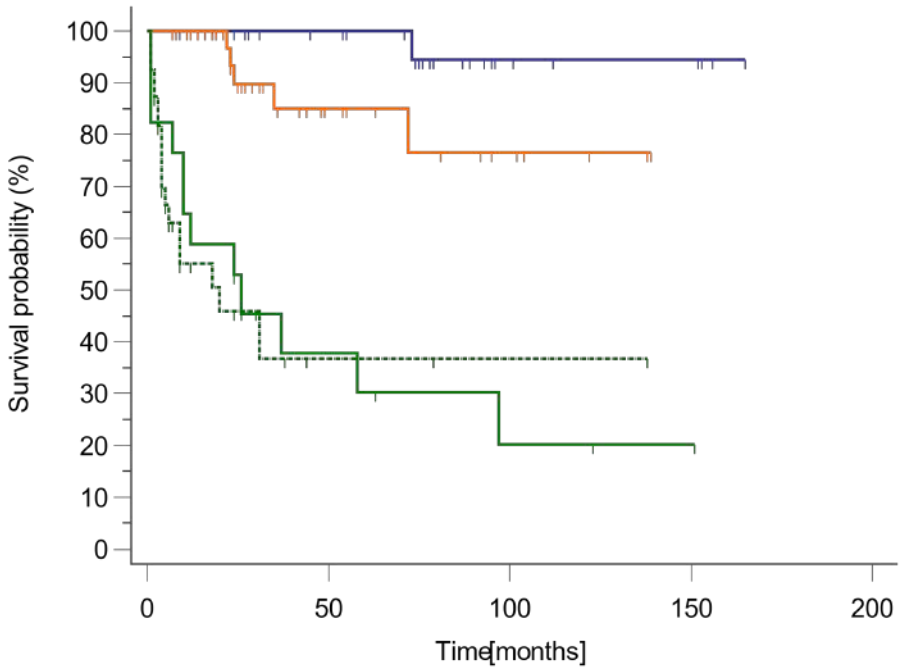
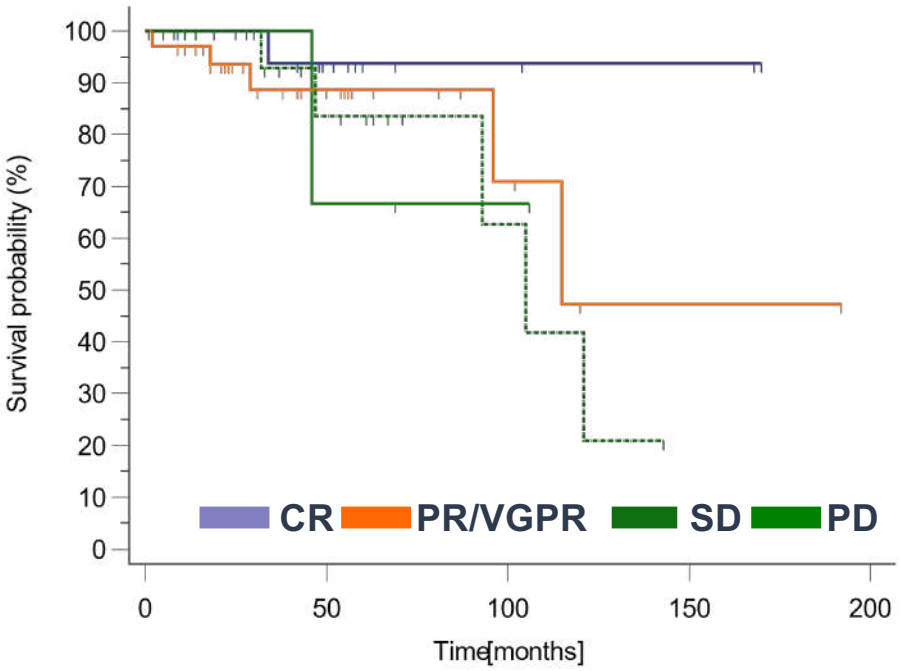


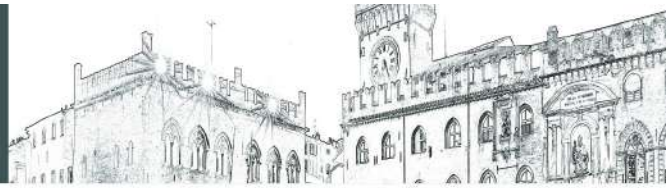
LA RISPOSTA AL PRIMO TRATTAMENTO SI CORRELA ALLA SOPRAVVIVENZA

MGRS-A



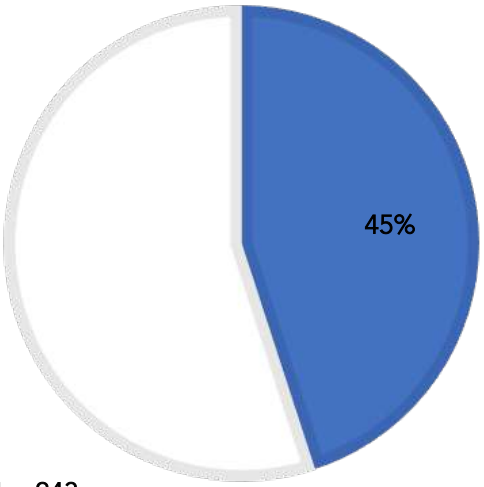
MGRS-NA





RISPOSTA

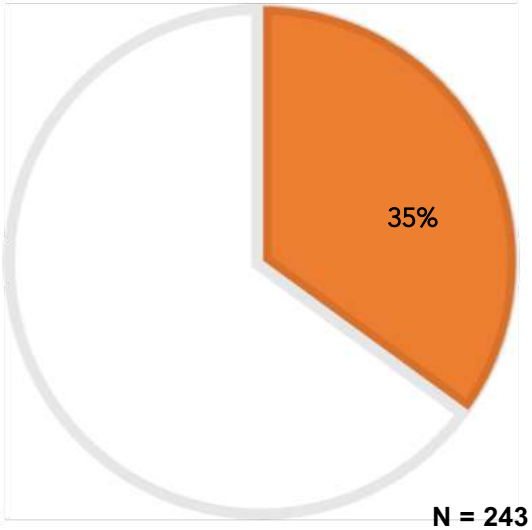
EMATOLOGICA



N = 243

Median time to response 120 days

RENALE



N = 243

Median time to response 180 days

Hematologic response: CR + VGPR/PR according to the IMWG criteria (BGM Durie et al. Leukemia (2006) 1-7.
Renal response: CR + PR + MR according to the IMWG criteria (Dimopoulos MA et al. J Clin Oncol. 2016;34(13):1544-57.)

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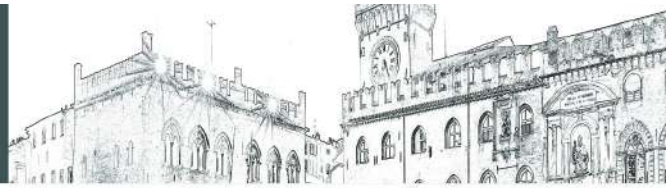
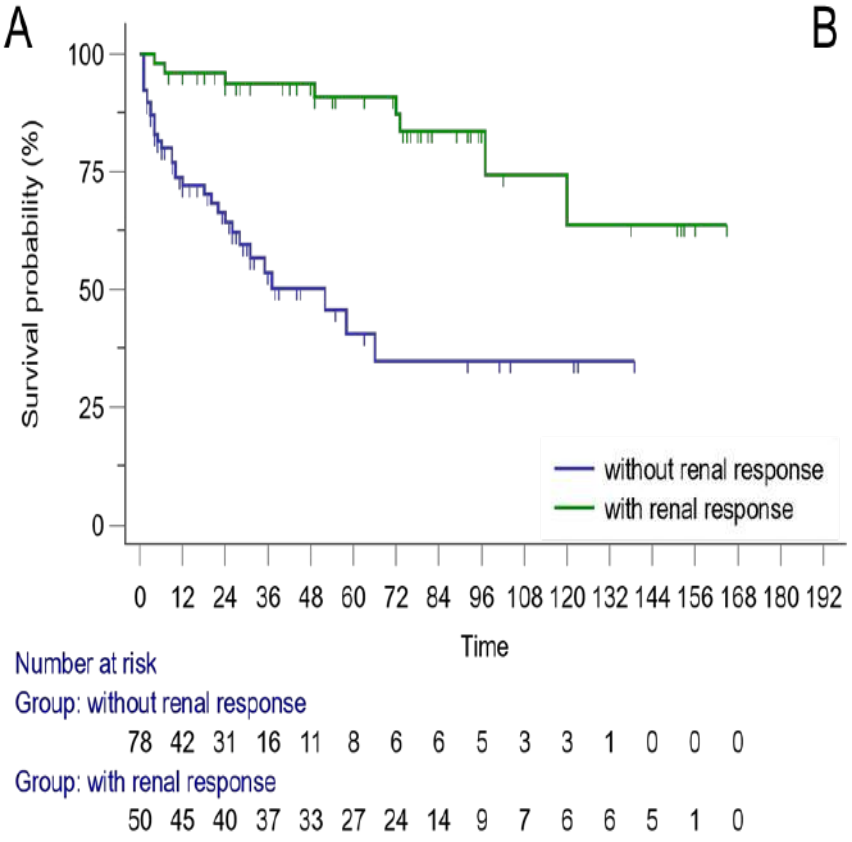
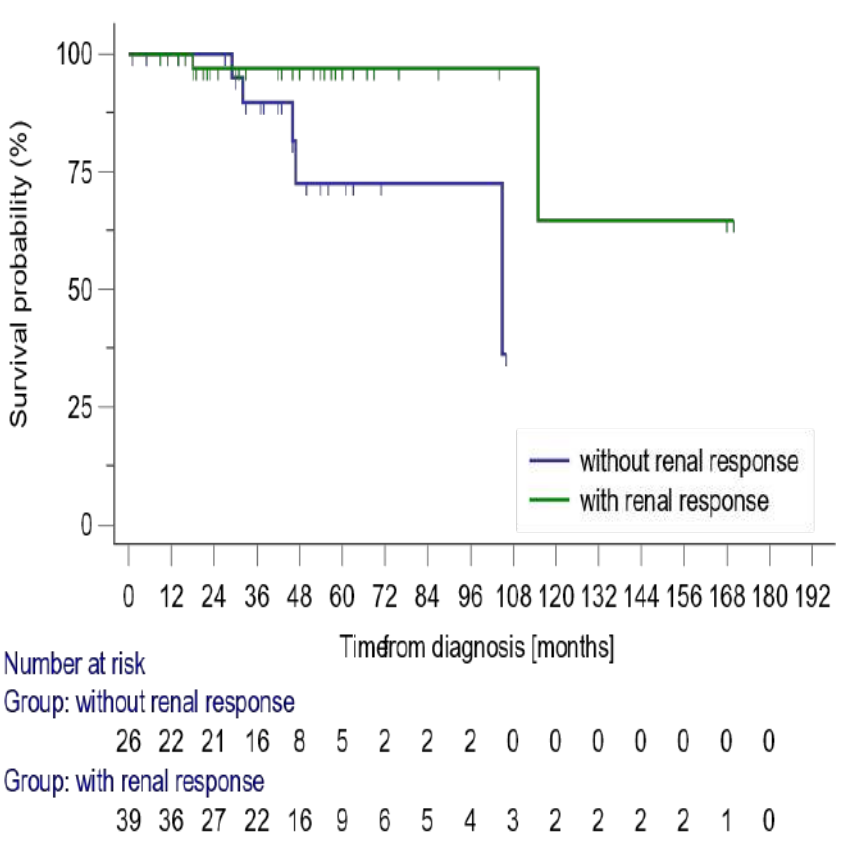


MGRS-A



MGRS-NA



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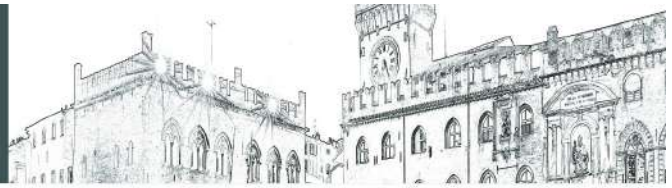
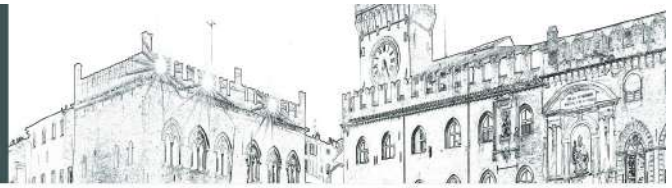


Fattori prognostici

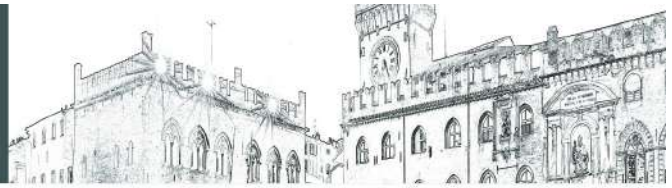
VARIABLE	MGRS-A HR (95%CI), P-value	MGRS-NA HR (95%CI), P-value
Age, ≤65 vs >65 years old	1.60 (0.91 - 2.79), P = 0.102	**3.85 (1.14 – 12.97), P = 0.0294**
Sex, male vs female	0.69 (0.39 - 1.20), P = 0.191	2.85 (0.79 - 10.25), P = 0.108
LDH, < 300 vs ≥ 300 U	1.41 (0.74 - 2.70), P = 0.299	1.35 (0.39 - 4.67), P = 0.638
FLC kappa/lambda, normal vs abnormal	1.34 (0.64 - 2.80), P = 0.435	1.53 (0.29 - 7.94), P = 0.615
Albumin, ≤3.5 vs > 3,5 g/ml	4.86 (0.66 - 35.58), P = 0.12	0.8376 (0.10 - 6.97), P = 0.87
Beta 2 m, ≤5.5 vs > 5.5 mg/l	**2.52 (1.08 - 5.87), P = 0.0315**	1.60 (0.30 - 8.44), P = 0.575
Creatinine, < 177 vs ≥ 177 umol/l	**2.35 (1.34 - 4.11), P = 0.00279**	0.98 (0.30 - 3.18), P > 0.9
Dialysis, Yes vs NO	**1.85 (1.02 - 3.35), P = 0.0408**	0.94 (0.28 – 3.13) P > 0.9

Gozzetti et al. submitted



MGRS
CONCLUSIONI

- La diagnosi è fondamentale: collaborazione con Nefrologo/**biopsia renale**
- Ricercare il clone ! SMM/CLL/LNH
- Terapia del MM :PI-based
- Terapia della CLL: R-based /BTKi
- Terapia NHL:R-Benda/BTKi
- Monitorare risposta non sempre facile

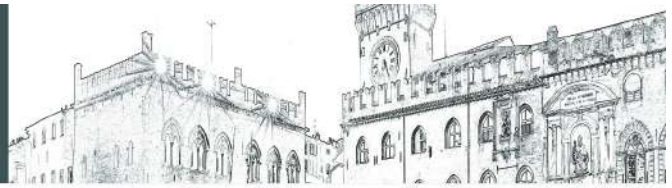


CONCLUSIONI
REAL WORLD MGRS:

- L'amiloidosi rappresenta la MGRS più frequente
- MIDD è la più frequente tra le MGRS-non da amiloidosi
- Terapie PI-based sono state le più utilizzate
- La percentuale di pazienti con una risposta renale si riduce se non si ottiene una risposta ematologica complete
- MGRS con amiloidosi hanno avuto una OS peggiore rispetto a MGRS-NA
- Fattori prognostici: età, B2m, creatinina e dialisi

Highlights from IMW 2021

1-2 Febbraio 2022
Bologna
Royal Hotel Carlton



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