

IL MIELOMA **MULTIPLO**

Nuove prospettive ed aspettative di vita



RESPONSABILI SCIENTIFICI

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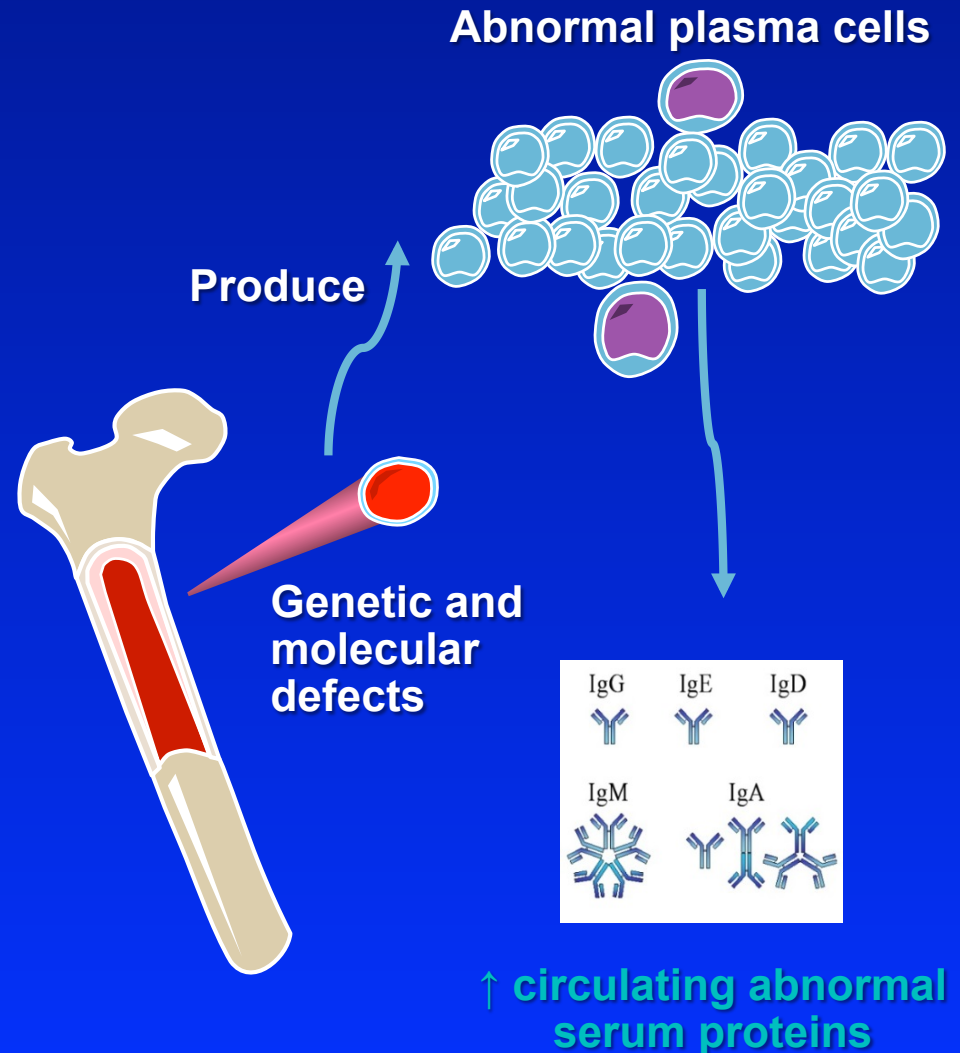
HOTEL ROYAL CONTINENTAL

Inquadramento e dati di epidemiologia nazionale

Fabrizio Pane

Multiple Myeloma

- Neoplastic transformation of the bone marrow plasma cells
- Presence of monoclonal component (Complete Immunoglobulins)
- Progressive and usually aggressive clinical course
- May be associated to chemical or environmental toxic exposure



DISCRASIE PLASMACELLULARI ASSOCIATE A COMPONENTE MONOCLONALE

Gammopatia monoclonale di significato indeterminato (MGUS)

- primitiva
- secondaria /transitoria

• Mieloma Multiplo

- Smoldering myeloma
- Plasma cell leukemia
- Mieloma micromolecolare
- Mieloma non-secernente
- Mieloma osteosclerotico
- (*POEMS: polineuropatia, organomegalia endocrinopatia, M protein, skin changes*)

• Plasmocitoma solitario

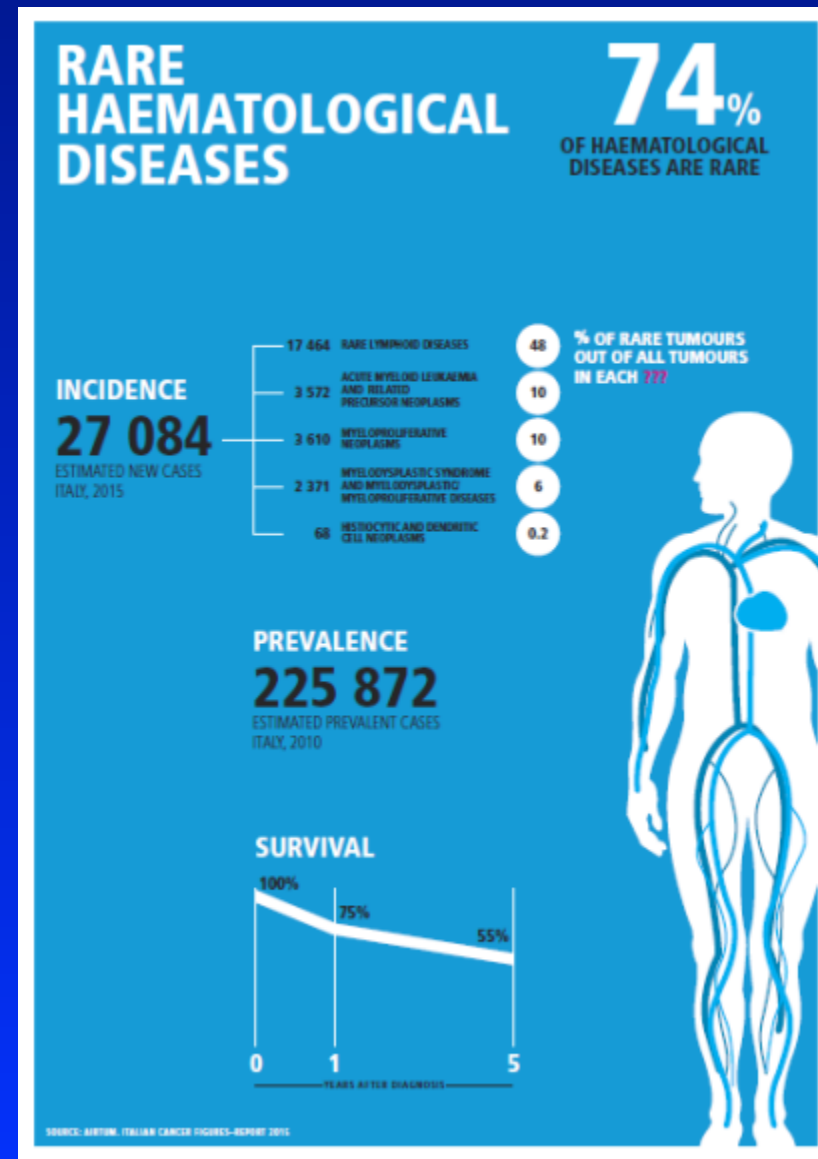
- osseo
- extraosseo o dei tessuti molli

DISCRASIE PLASMACELLULARI ASSOCIATE A COMPONENTE MONOCLONALE

- **Macroglobulinemia di Waldenström**
- **Amiloidosi**
 - primitiva (AL)
 - secondaria
- **Malattia da catene pesanti (HCD)**
 - γ HCD
 - α HCD
 - μ HCD
- **Crioglobulinemie**
- **Linfoma maligno**

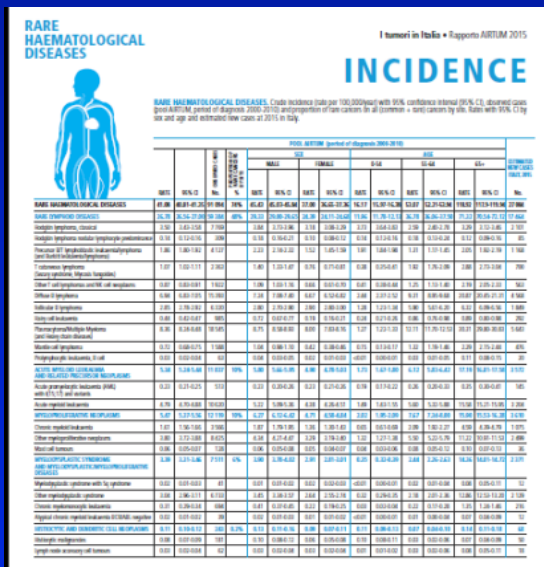
Epidemiology of Hematologic Tumors

Recent revision in the framework of a collaboration between the Italian Society of Hematology (SIE) and the Italian Association of Tumor Registries (AIRTUM)



Epidemiology of Multiple Myeloma in Italy

Incidence



POOL AIRTUM (period of diagnosis 2000-2010)														ESTIMATED NEW CASES ITALY, 2015
RATE	95% CI	OBSERVED CASES	PROPORTION OF RARE CANCERS BY SITE	SEX				AGE						
				MALE		FEMALE		0-54		55-64		65+		
				RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	
8.36	8.24-8.48	18 545		8.75	8.58-8.93	8.00	7.83-8.16	1.27	1.22-1.33	12.11	11.70-12.53	30.31	29.80-30.83	5 643

- Crude incidence (rate per 100,000/year) with 95% confidence interval (95% CI)
- Observed cases (pool AIRTUM, period of diagnosis 2000-2010)
- Rates with 95% CI by sex and age
- Estimated new cases at 2015 in Italy.

Epidemiology of Multiple Myeloma in Italy

Prevalence

RARE HAEMATOLOGICAL DISEASES

PREVALENCE

1 tumore in Italia • Rapporto AIRCUM 2015

RARE HAEMATOLOGICAL DISEASES. Observed prevalence (proportion per 100,000 and 95% confidence interval - 95% CI) by duration (2, 2-4, 15 years) prior to prevalence date (1st January 2007), complete prevalence and estimated prevalent cases at 2010 in Italy.

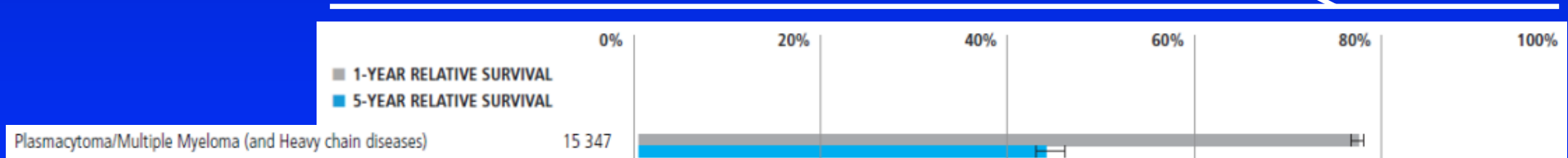
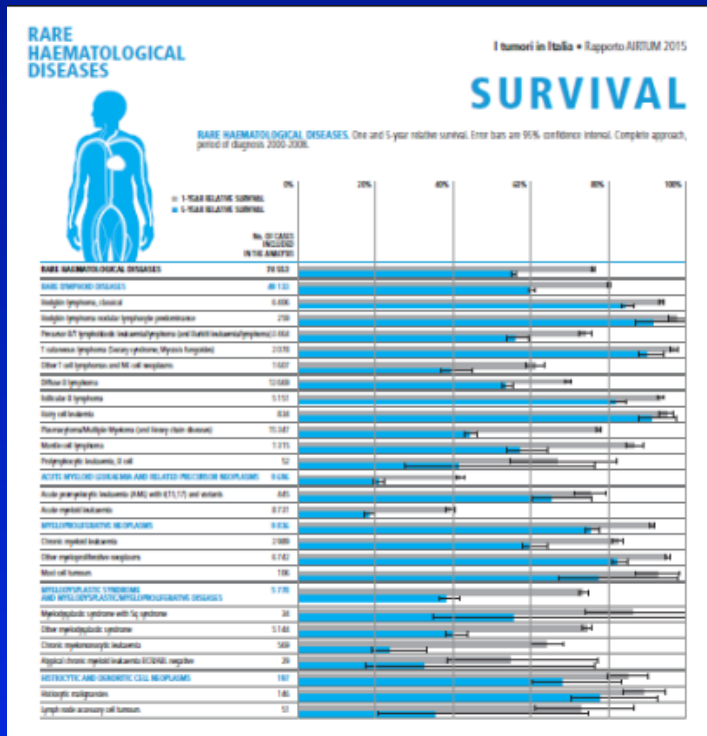
	POOL REGION								ESTIMATED PREVALENT CASES AT 2010 IN ITALY
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE		
	<2 YEARS		2-4 YEARS		>15 YEARS		PROPORTION	95% CI	
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	
RARE HAEMATOLOGICAL DISEASES	75.79	70.02-72.19	48.29	46.32-49.84	252.26	239.92-254.62	277.86	271.99-282.59	225 872
RARE LYMPHOID DISEASES	47.76	46.71-49.23	48.29	47.73-50.69	107.40	104.30-108.34	206.64	200.05-207.84	178 217
Hodgkin lymphoma, classical	0.82	0.29-1.80	0.86	0.27-0.82	17.95	16.61-19.26	19.56	17.58-21.34	41 296
Hodgkin lymphoma, nodular lymphocyte predominant	0.26	0.17-0.40	0.21	0.22-0.40	1.25	1.03-1.32	1.22	1.25-1.30	1 894
Provisional T lymphoblastic leukaemia/lymphoma (and B-cell leukaemia/lymphoma)	1.06	1.13-1.03	1.71	1.38-1.08	12.19	11.85-12.98	16.49	16.71-16.26	31 881
T-cell leukaemia/lymphoma (T-cell lymphoma, Mycosis fungoides)	2.62	2.29-2.98	2.84	2.98-2.86	12.25	12.6-14.75	18.57	17.45-19.70	11 173
Other T cell lymphomas and NK cell lymphomas	1.01	0.81-1.25	1.02	0.82-1.25	1.64	1.25-4.07	4.63	4.19-5.12	2 817
Diffuse B lymphoma	10.67	9.98-11.22	10.79	10.73-11.49	47.36	45.02-47.73	68.29	66.71-69.88	29 153
Mantle cell lymphoma	0.58	0.42-1.10	0.41	1.11-0.10	10.47	11.6-14.03	17.28	16.96-18.11	16 875
Aggressive B-cell leukaemia	0.88	0.76-1.27	1.21	1.10-1.40	1.05	4.19-1.54	7.58	6.73-8.86	4 627
Plasmacytoma/Multiple Myeloma (and heavy chain disease)	16.70	13.91-15.12	19.20	12.49-19.88	49.70	42.11-45.17	47.76	46.23-49.30	38 228
Multiple myeloma	1.51	1.26-1.79	1.36	1.12-1.42	5.86	4.88-5.97	6.25	5.68-6.87	2 721
Plasmacytoma, B-cell	0.05	0.07-0.12	0.08	0.03-0.17	0.16	0.09-0.27	0.16	0.08-0.28	112
ACUTE MYELOID LEUKAEMIA AND RELATED PROGENITOR NEOPLASMS	4.47	4.01-4.83	2.73	2.48-3.19	12.69	11.76-13.25	18.84	17.76-20.08	11 146
Acute promyelocytic leukaemia (PML) with t(15;17) and variants	0.27	0.25-0.52	0.43	0.28-0.59	1.42	1.36-1.80	1.79	1.69-2.08	1 039
Acute myeloid leukaemia	3.82	3.42-4.26	2.10	1.85-2.48	10.05	9.39-10.74	16.53	15.45-17.67	10 481
MYELODYSPLASTIC NEOPLASMS	12.27	11.89-12.87	10.86	11.28-12.23	38.77	37.07-40.28	45.20	42.64-46.76	24 263
Chronic myeloid leukaemia	2.42	2.19-2.77	1.88	2.02-2.39	9.88	9.33-10.67	10.76	10.08-11.48	4 221
Other myelodysplastic neoplasms	9.85	9.69-10.25	8.98	8.26-9.84	28.89	27.74-29.61	34.44	32.56-35.28	19 429
Miscellaneous	0.11	0.08-0.21	0.21	0.12-0.22	0.88	0.25-0.65	0.97	0.68-1.29	179
MYELOIDIC ACUTE LYMPHOBLASTIC AND MYELOIDIC/PLASMA MYELOIDIC/PLASMA DISEASES	3.17	3.43-3.76	4.11	3.76-4.42	10.86	11.12-14.76	15.87	14.86-16.78	9 213
Myeloid acute lymphoblastic leukaemia with Tg leukaemia	0.09	0.04-0.10	0.05	0.07-0.12	0.15	0.09-0.26	0.17	0.08-0.27	102
Other myeloid acute lymphoblastic leukaemia	0.12	0.09-1.08	0.87	0.41-0.26	10.67	11.83-11.88	15.52	12.75-14.12	7 865
Chronic myelomonocytic leukaemia	0.94	0.48-0.71	0.36	0.20-0.46	1.05	0.82-1.27	1.27	1.07-1.57	803
Myeloid chronic myeloid leukaemia (CML) negative	0.02	0.01-0.08	0.08	0.01-0.04	0.05	0.07-0.12	0.05	0.01-0.10	28
MYELOIDIC AND BLENDED CLL NEOPLASMS	0.22	0.12-0.30	0.12	0.06-0.23	0.77	0.40-0.88	1.48	1.19-2.17	1 823
Marginal cell neoplasms	0.11	0.08-0.21	0.11	0.08-0.21	0.64	0.49-0.88	1.45	0.99-1.92	895
Lymph node anaplastic cell tumour	0.10	0.05-0.20	0.01	0.01-0.06	0.13	0.05-0.22	0.23	0.09-0.37	128

COMPLETE PREVALENCE		ESTIMATED PREVALENT CASES AT 2010 IN ITALY
PROPORTION	95% CI	
48.29	46.71-49.88	29 550

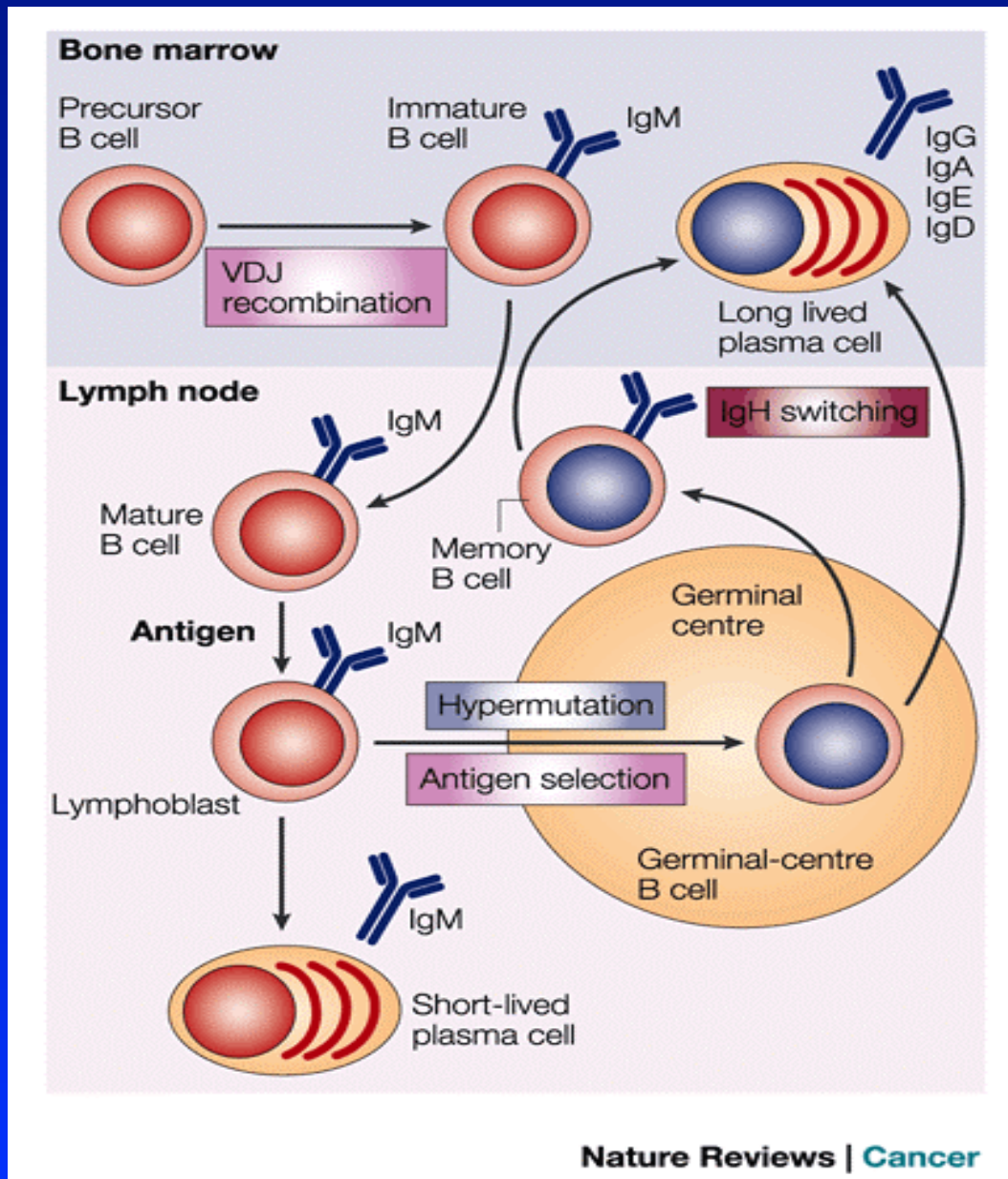
Complete prevalence and Estimated prevalent cases at 2010 in Italy

Epidemiology of Multiple Myeloma in Italy

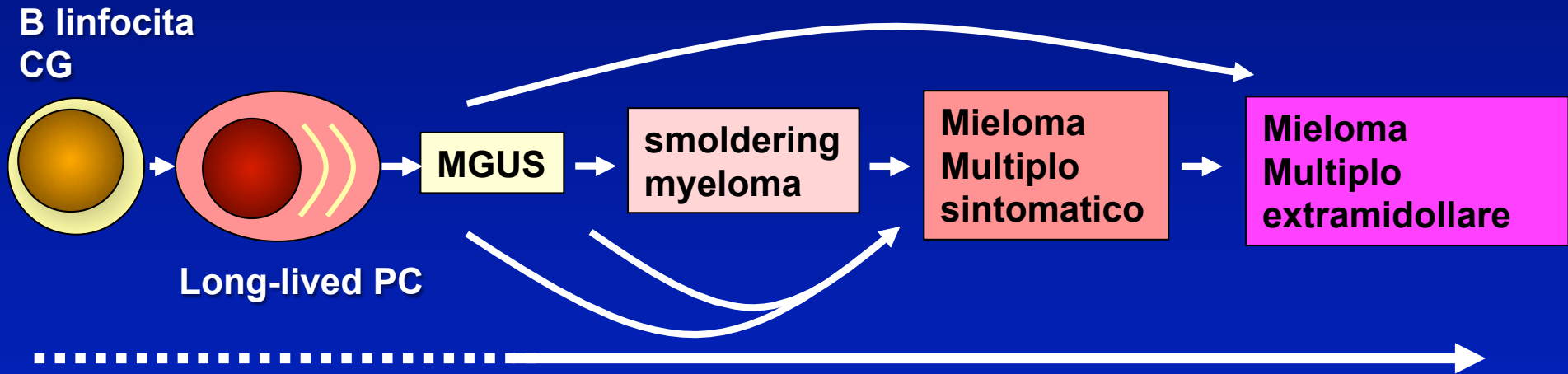
Survival



PATOGENESI (1)



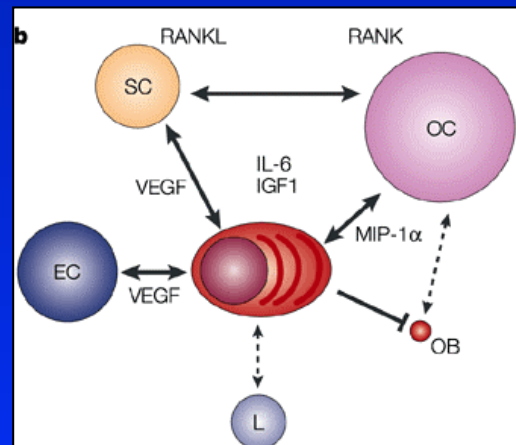
EVENTI PATOGENETICI (2)



instabilita' genetica

alterazioni genetiche

microambiente



- homing delle PC nel midollo
- paracrinia

sopravvivenza
differenziazione
proliferazione

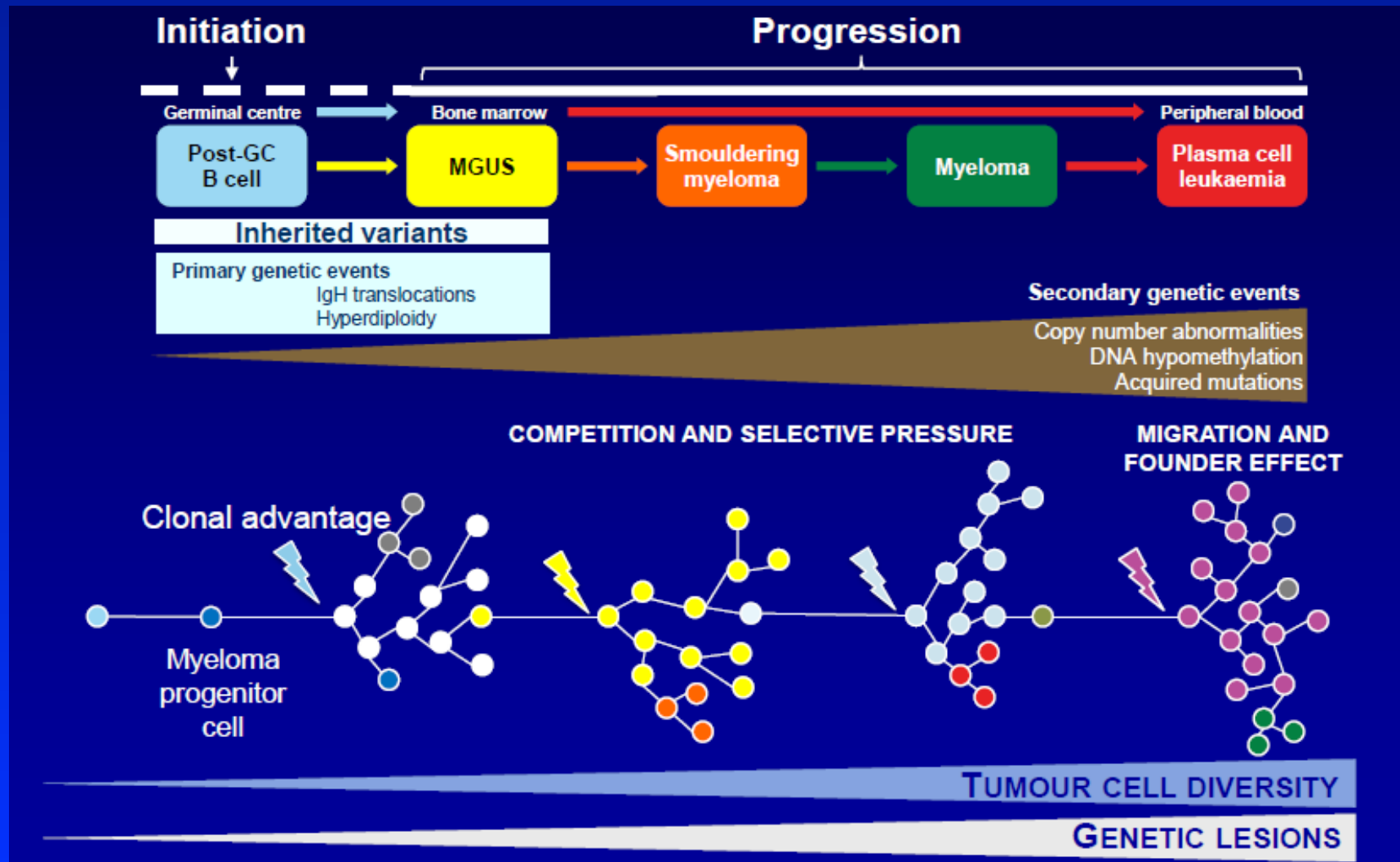
- angiogenesi
- osteoclastogenesi
- inibizione osteogenesi

sistema immunitario

interazione diretta
interazione indiretta

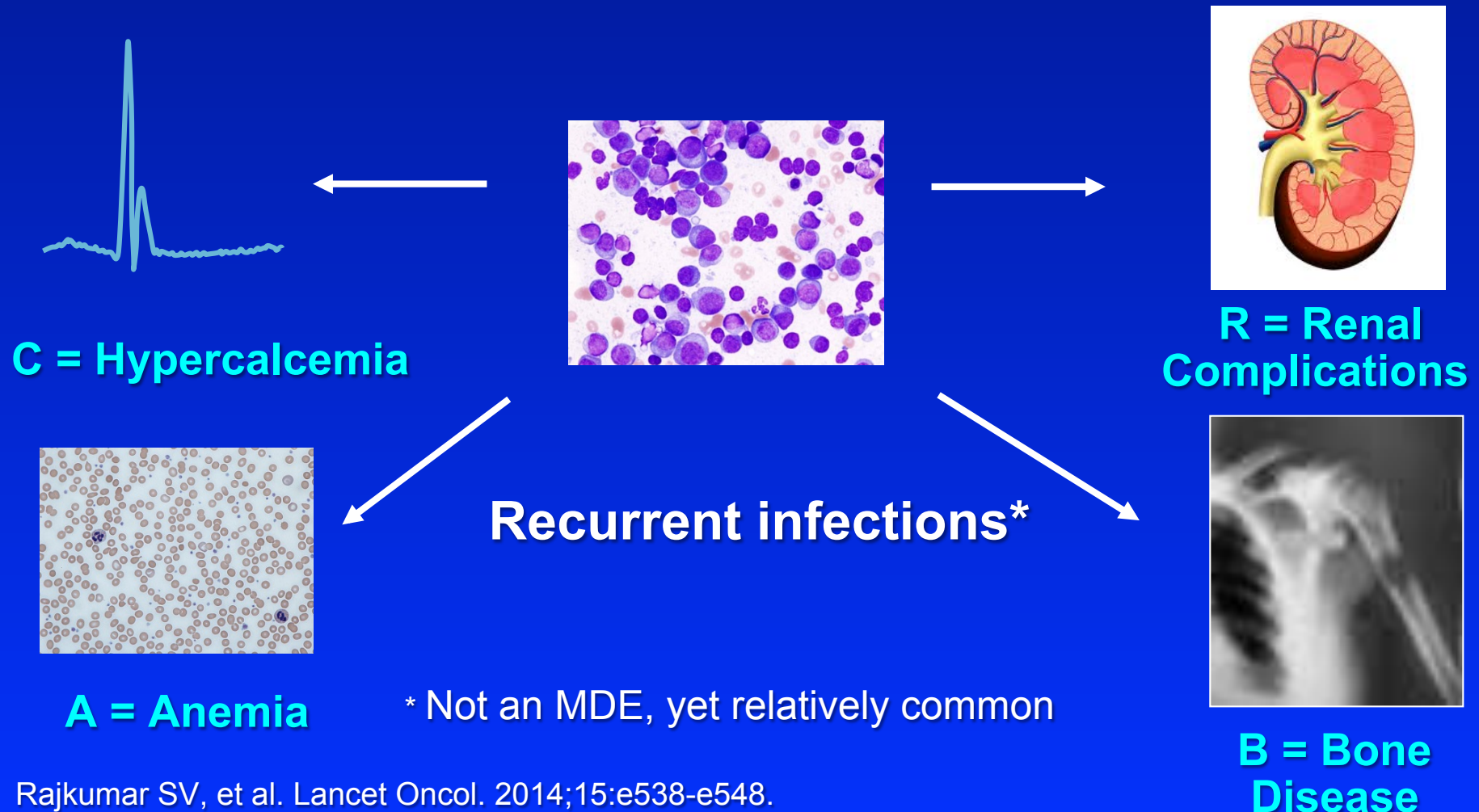
PROGRESSIONE DELLA MALATTIA

Modello basato sulla acquisizione random di alterazioni genetiche in subcloni neoplastici con selezione Darwiniana

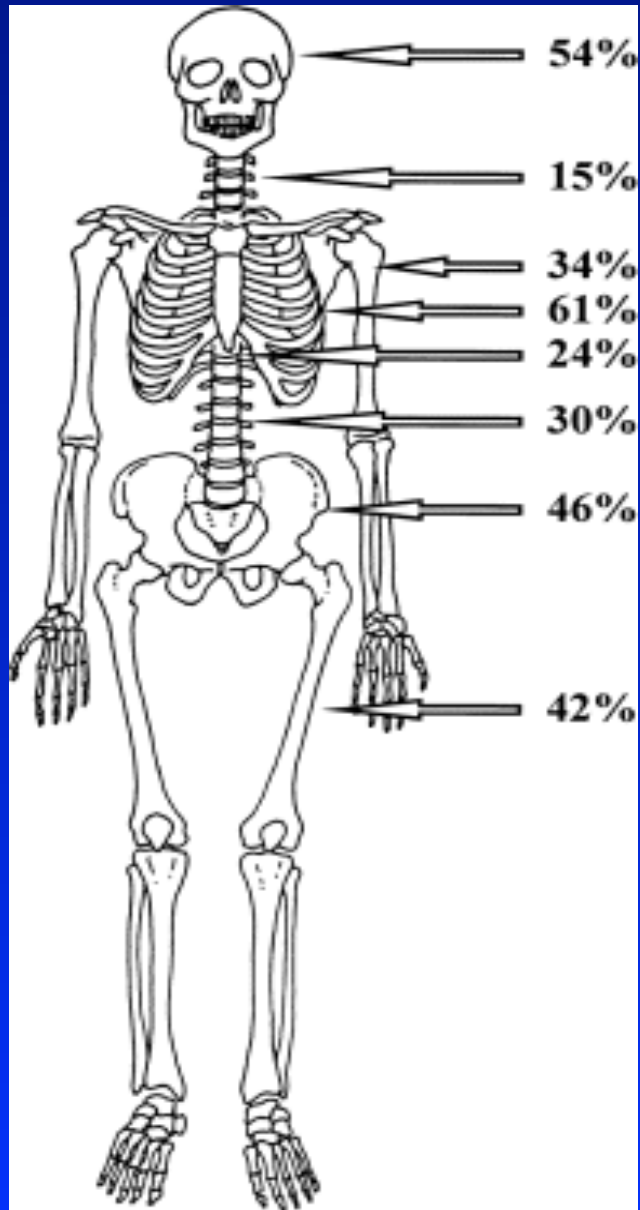


Multiple Myeloma: Clinical Manifestations

Series of genetic mutations, translocations, normal cell turns malignant
Hallmarks of myeloma: CRAB (also known as myeloma defining events)

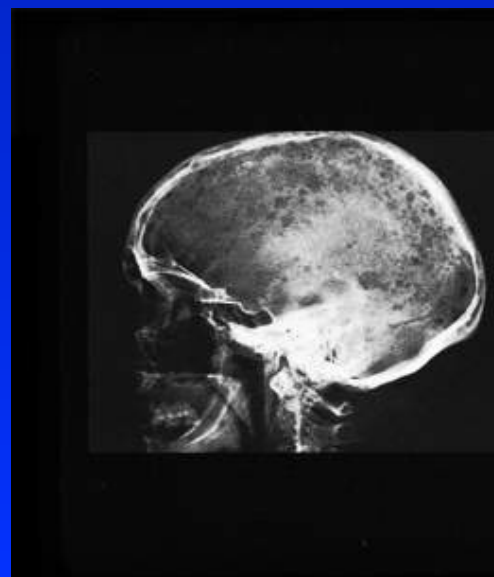
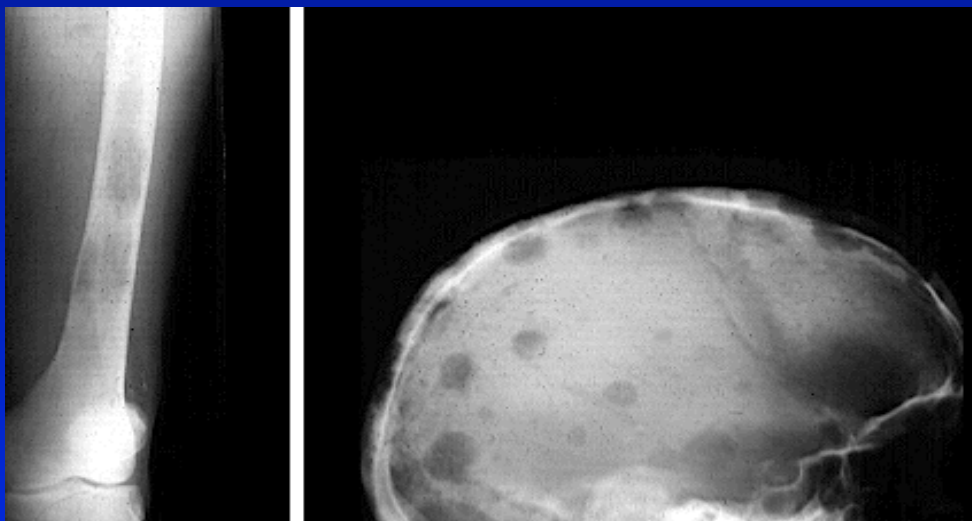


Lesioni Ossee

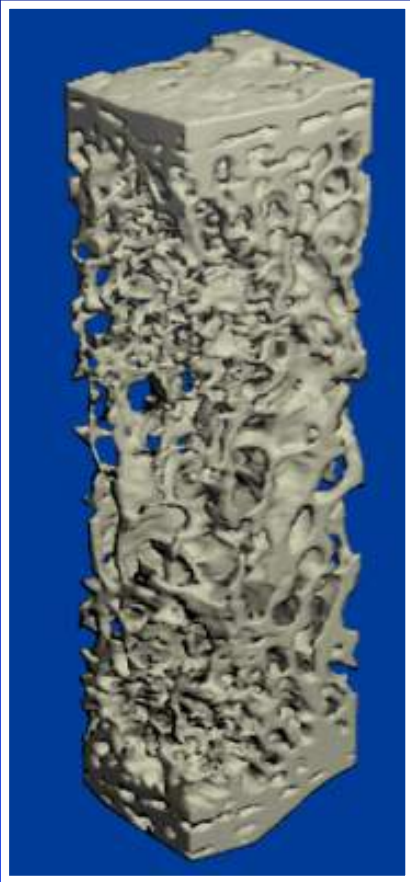


- Presente in circa 70% pazienti alla diagnosi, nella quasi totalità in ricaduta
- Può interessare tutte le ossa, per lo più colonna vertebrale e ossa piatte, sedi di mielopoiesi
- Lesioni osteolitiche, osteoporosi e quadri misti
- Condiziona fortemente la qualità di vita dei pazienti (dolore, rischio di complicanze quali fratture patologiche, crolli vertebrali, compressione midollare)
- Possibilità di sviluppo extra-osseo

PATOLOGIA SCHELETRICA

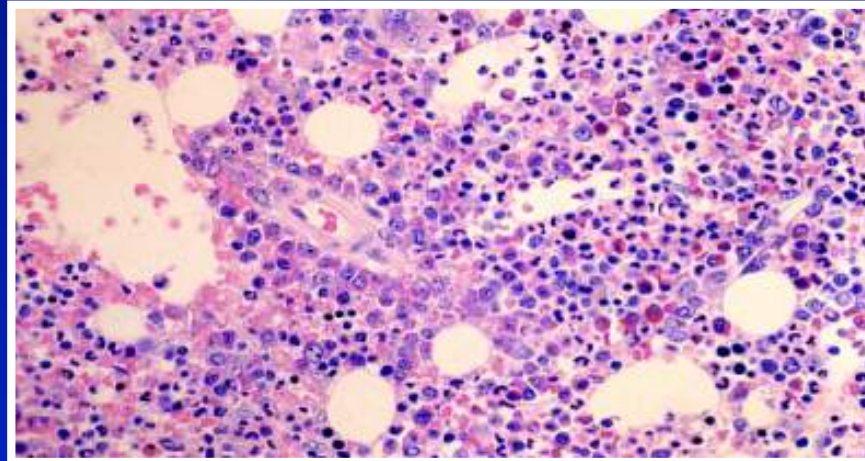


PATOGENESI DELLA MALATTIA SCHELETRICA



OSSO:

- matrice ossea (trabecole)
- osteoclasti
- osteoblasti

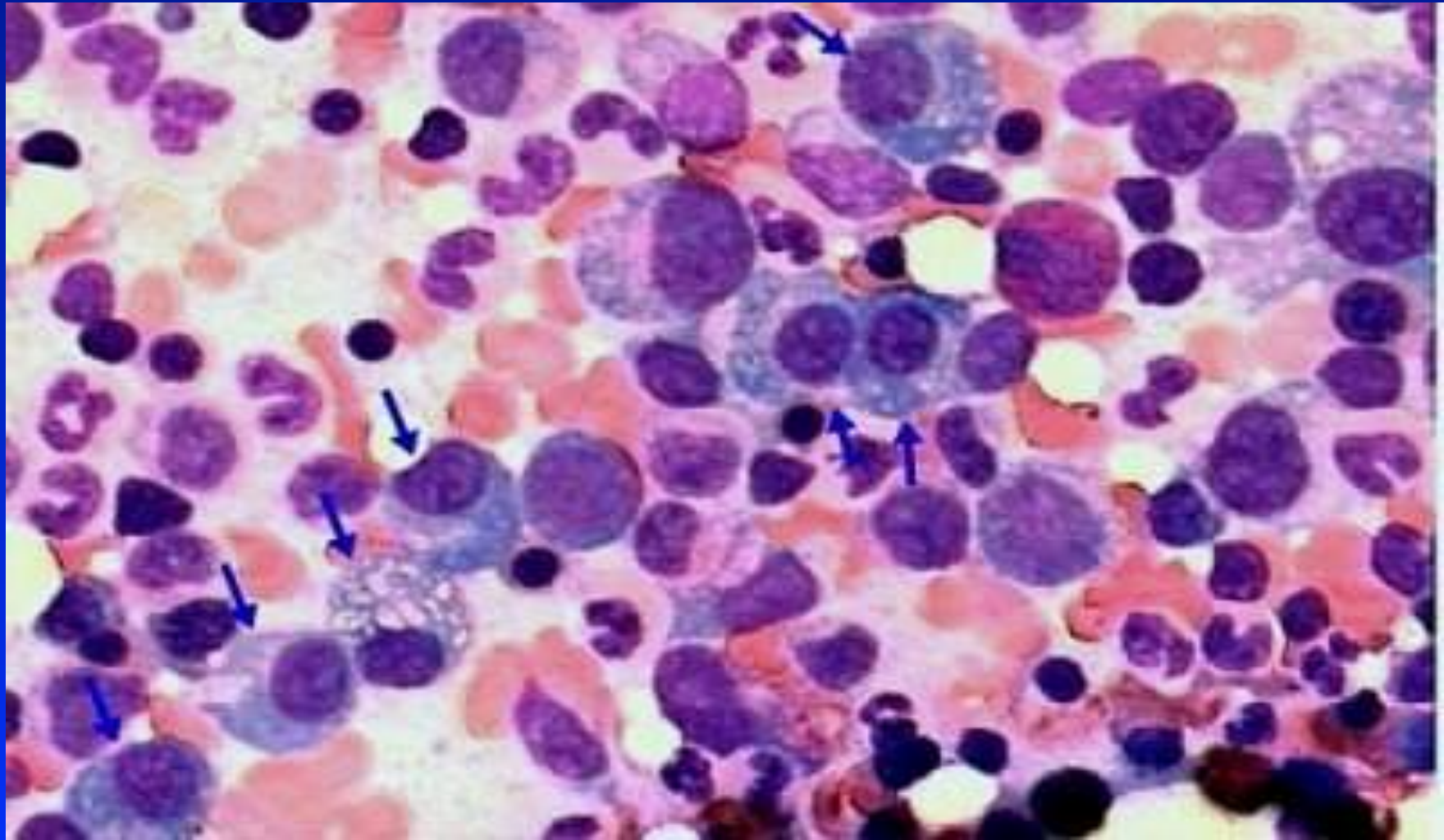


MIDOLLO OSSEO

- cellule emopoietiche
- vasi
- cellule stromali
 - adipociti
 - fibroblasti
 - macrofagi
 - mastociti
- matrice extracellulare

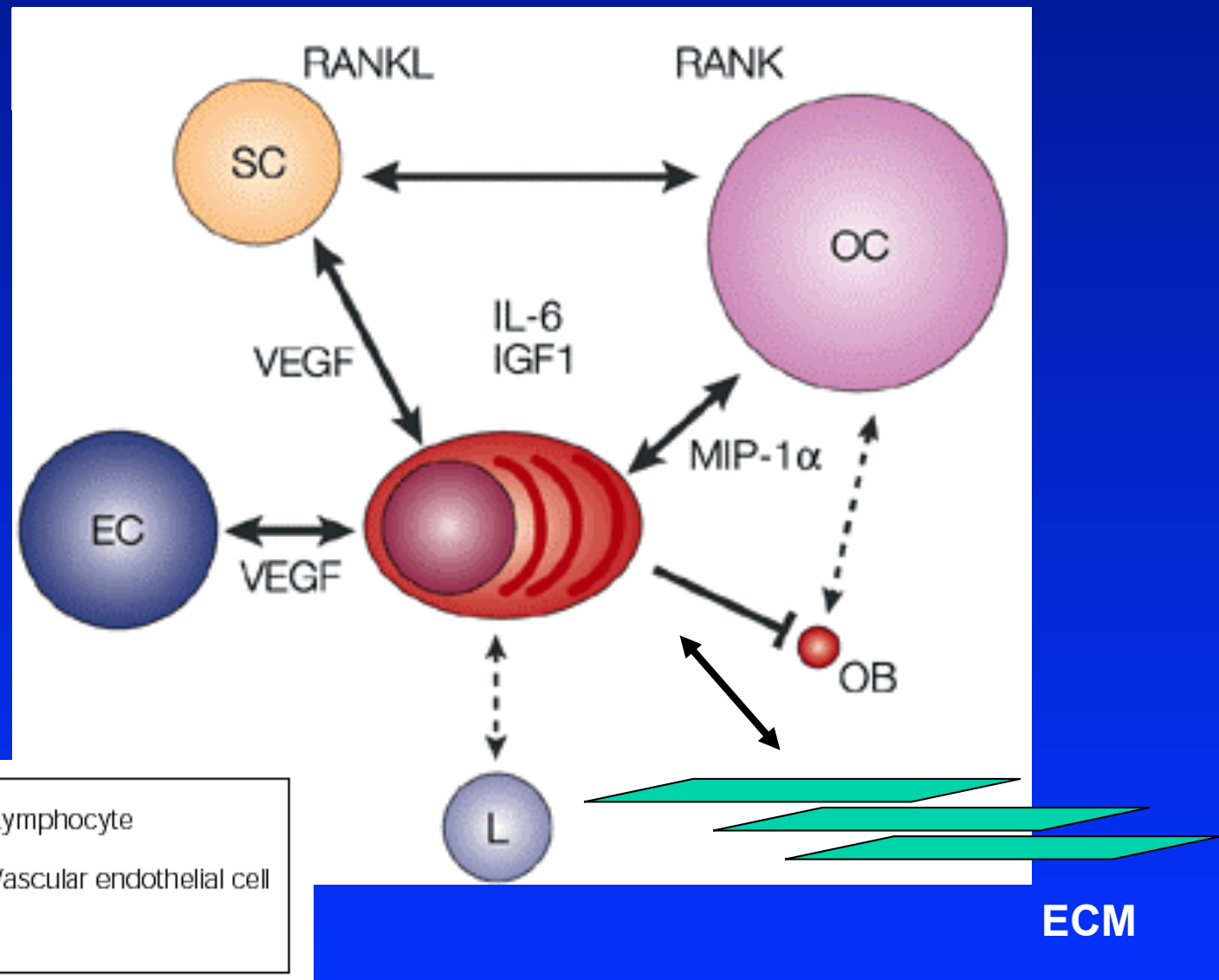
PATOGENESI DELLA MALATTIA SCHELETRICA

L'ESPANSIONE DEL CLONE PLASMACELLULARE



Patogenesi della Malattia Scheletrica

Interazione Clone Plasmacellulare con il Microambiente Midollare

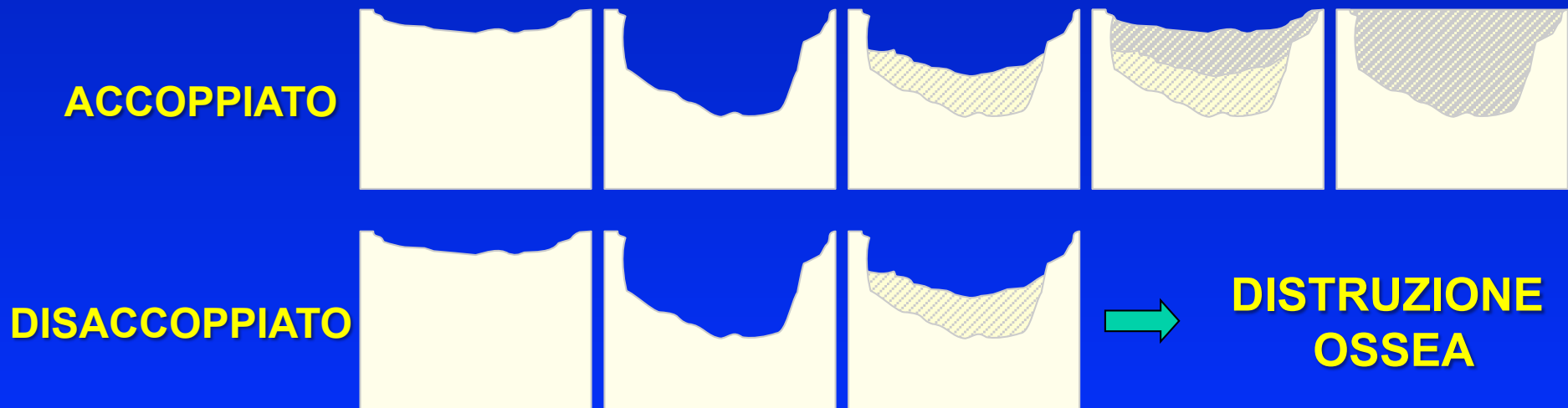


Patogenesi della malattia ossea nel MM

Le lesioni osteolitiche del MM sono causate da un disaccoppiamento tra osteosintesi e riassorbimento osseo:

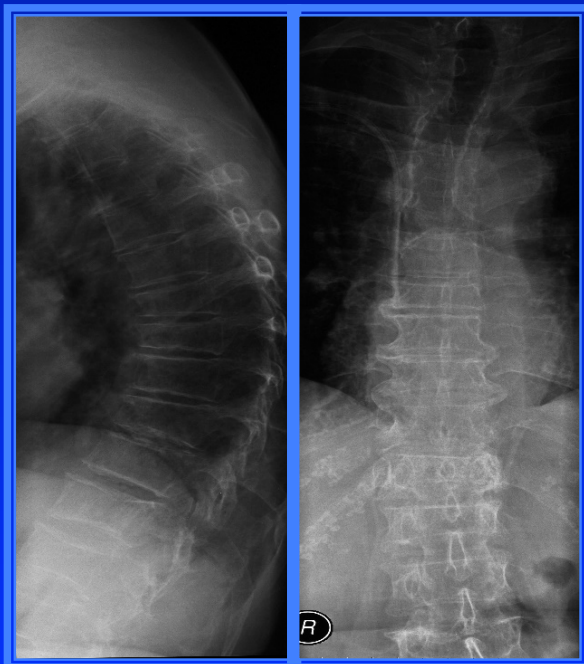
- Aumentato riassorbimento osseo per aumentata attività osteoclastica
- Ridotta neoformazione ossea per ridotta attività osteoblastica

Rimodellamento osseo

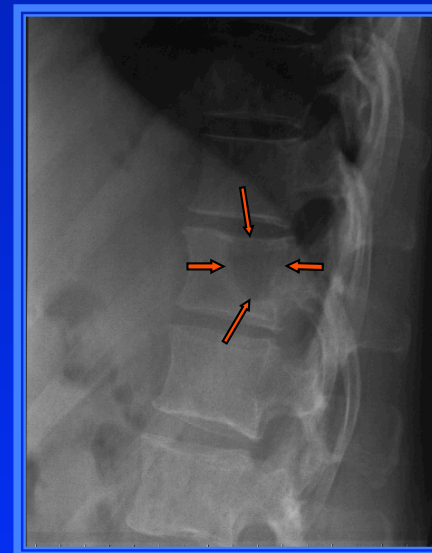


Identificazione della patologia scheletrica nel MM

- Quadro radiografico alterato nel 60-70% circa dei pazienti
- Osteolisi circoscritte senza sclerosi periostale, osteopenia, quadri misti
- Evidenza delle lesioni solo quando la massa ossea è ridotta di almeno il 50%
- Possibile sottostima delle lesioni per incapacità di identificare lesioni piccole e basso potere risolutivo nella colonna vertebrale



Pattern osteoporotico



Pattern osteolitico

RISONANZA MAGNETICA NUCLEARE

- Possibilità di valutazione qualitativa del midollo osseo: lesioni tipicamente **ipointense in T1, iperintense in T2, fortemente captanti il mdc (gadolinio)**
- Patterns di alterazione: focale, variegato, diffuso
- Alto potere risolutivo nella colonna vertebrale, dove distingue malattia/osteoporosi e identifica le eventuali complicanze neurologiche
- Valutazione di masse extraossee



Pattern normale



Pattern focale



Pattern diffuso

INSUFFICIENZA RENALE

- E' presente in circa il 50% dei pazienti
- Nel 10-20% dei casi è sintomo d'esordio, nei restanti compare in fase di progressione
- Patogenesi multifattoriale:
 - Proteinuria di Bence Jones
 - Ipercalcemia
 - Sostanze nefrotossiche: FANS, antibiotici, mezzi di contrasto iodati
 - Infezioni/disidratazione
- Diversi quadri isto-patologici

Insufficienza Renale

Quadri istopatologici e funzionali

	RENE DA MIELOMA	MALATTIA DA DEPOSITO DI CATENE LEGGERE	AMILOIDOSI AL
SEDE DEL DANNO	<ul style="list-style-type: none">•Tubulo prossimale•Tubulo distale	<ul style="list-style-type: none">•Tubulo•Glomerulo	<ul style="list-style-type: none">•Glomerulo
MECCANISMO	<ul style="list-style-type: none">•Danno e atrofia•Precipitazione di catene leggere (CL)	<ul style="list-style-type: none">•Deposizione di catene leggere	<ul style="list-style-type: none">•Deposizione di amiloide
QUADRO ISTOLOGICO	<ul style="list-style-type: none">•Cilindri ostruttivi tubulari distali (CL e prot. Tamm Horsfall)•Atrofia dei tubuli prossimali	<ul style="list-style-type: none">•CL a livello del mesangio e della membrana basale dei glomeruli e dei tubuli•Glomerulosclerosi nodulare	<ul style="list-style-type: none">•Fibrille di amiloide a livello mesangiale e vascolare
DANNO FUNZIONALE	<ul style="list-style-type: none">•Tubulopatia	<ul style="list-style-type: none">•Tubulopatia•Albuminuria	<ul style="list-style-type: none">•Sindrome nefrosica

SINDROME DA IPERCALCEMIA

- E' rilevata in circa il 30-40% dei pazienti con MM, nella metà di questi circa all'esordio, in un'altra metà durante il decorso della malattia
- Riconducibile patogeneticamente all'aumentato riassorbimento osseo, con rilascio di calcio nel sangue
- Manifestazioni cliniche: poliuria, polidipsia, anoressia, nausea, vomito, astenia. Se il quadro persiste: disidratazione, confusione, delirio fino al coma (encefalopatia ipercalcemica)

Insufficienza midollare: anemia “secondaria” da cause multiple

- Sostituzione midollare
- Deficit di eritropoietina
 - IRC
 - Inadeguata produzione
- Mielosoppressione post terapia
- Produzione di citochine infiammatorie
- Emodiluizione!!

Aumento della suscettibilità alle infezioni

- Deficit di immunità umorale
- Aumentata incidenza di episodi infettivi (per lo più batterici)
- Poco frequente all'esordio di malattia, progressivamente più rilevante durante il decorso clinico (ricaduta di malattia e immunodepressione post terapia)

Le infezioni sono una delle principali cause di morte nel paziente con MM

Diagnostic Workup

Lab tests:

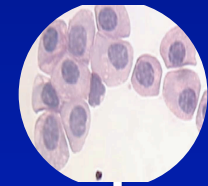
- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Complete metabolic panel (CMP)
- CBC + differential
- Plasma ratio of free kappa/lamba light chains
- Monoclonal protein analysis (MPA)

Bone marrow biopsy:

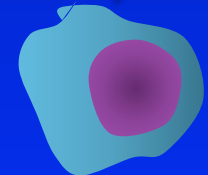
- FISH, cytogenetics, and gene expression profiling (GEP)

Imaging:

- Skeletal survey
- MRI, CT
- PET scan ± MRI, CT



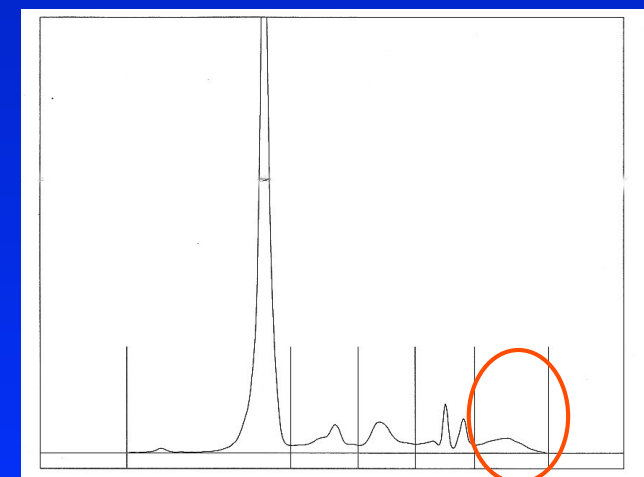
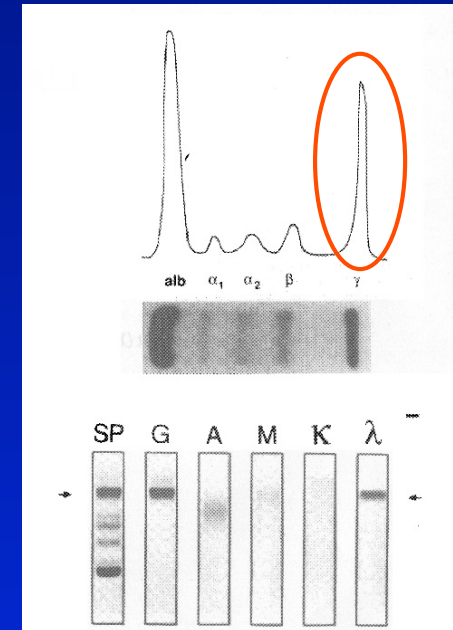
Genetic changes occur



ITER DIAGNOSTICO AL PAZIENTE CON SOSPETTO MIELOMA

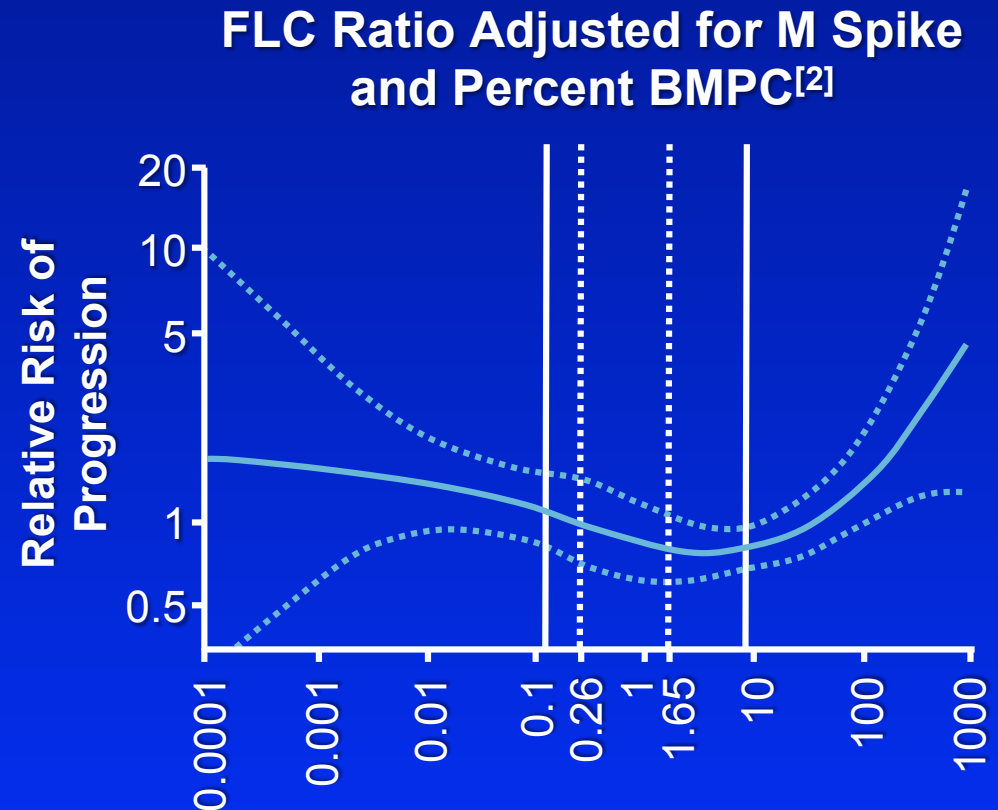
Indagini di laboratorio (i)

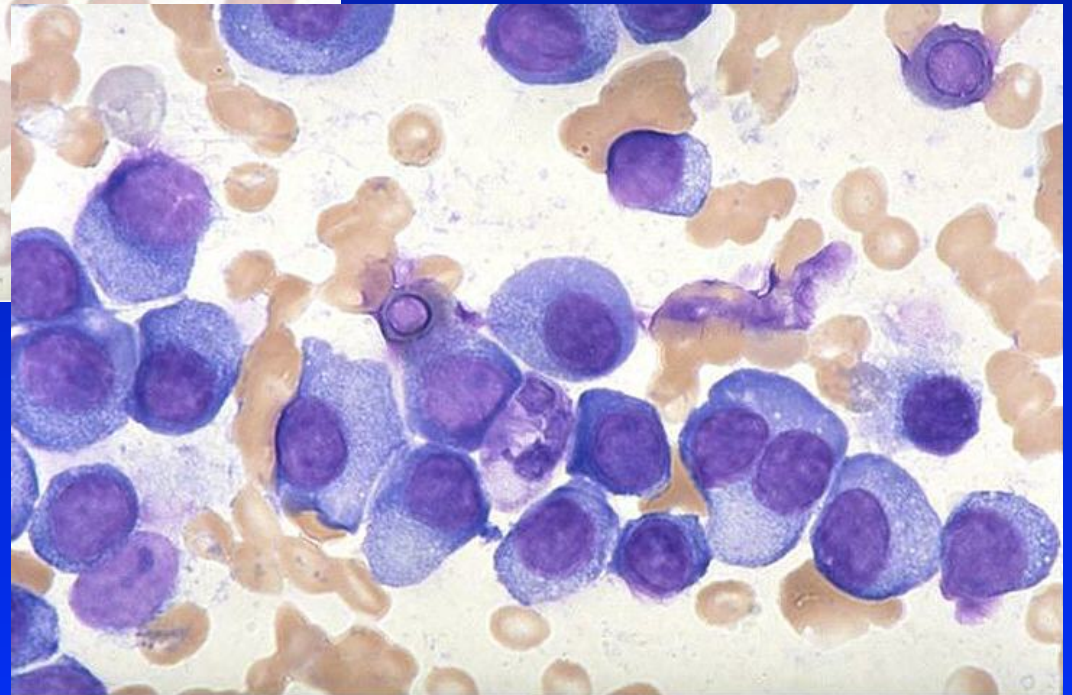
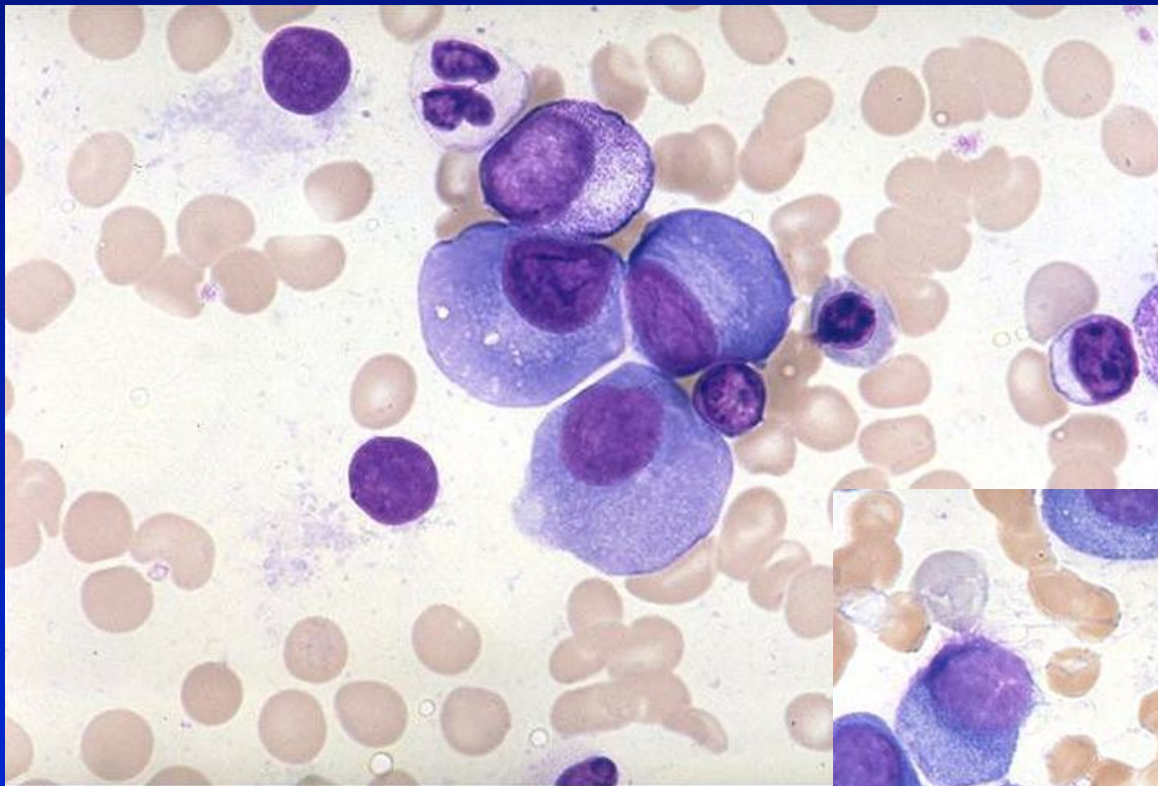
- Protidemia totale + elettroforesi (iper o ipogammaglobulinemia)
- Dosaggio Ig
- Proteinuria delle 24 ore con dosaggio quantitativo della escrezione delle catene leggere libere monoclonali
- Caratterizzazione della CM (Immunofissazione sierica e urinaria)
- Dosaggio delle catene leggere libere nel siero



Biomarkers of Malignancy: Involved-to-Uninvolved Serum FLC Ratio ≥ 100 ^[1-4]

- Automated nephelometric assay measuring κ and λ circulating serum light chains
- Abnormal FLC ratio and degree of abnormality predict risk of progression in MGUS, smoldering MM, AL amyloidosis, and solitary plasmacytoma





Aspirato midollare di MM

Biomarkers of Malignancy: $\geq 60\%$ Clonal Plasma Cells in Bone Marrow^[1]

- Based on conventional bone marrow aspirate or biopsy (use higher of 2 values)^[2]
- Estimation of bone marrow plasma cells should not be based on proportion reported by flow cytometry; studies ongoing to determine feasibility of flow-based enumeration^[3]
- Clonality established via:
 - κ/λ light-chain restriction on immunohistochemistry or immunofluorescence
 - Evidence on flow cytometry of phenotypic clonality
 - Assay demonstrating rearrangement of immunoglobulin-coding genes

STADIAZIONE DEL MM

- Classificazione ormai storica di Durie-Salmon (1975) che stimava la massa mielomatosa (**tre stadi clinici**) mediante i seguenti parametri:
 - Emoglobina
 - Calcemia
 - Concentrazione di componente monoclonale
 - Numero di lesioni osseee la funzionalità renale (**varietà A o B**)
- I nuovi sistemi classificativi prendono in considerazione **l'albumina e la β 2 microglobulina**
- Le **alterazioni genetico-molecolari** non sono ancora entrate a formare una precisa stadiazione anche se possono fornire un importante elemento prognostico

PROGNOSTIC FACTORS

Risk Factors	Standard Risk (80%) (Expected OS: 6-7 Yrs)	High Risk (20%) (Expected OS: 2-3 Yrs)
FISH	t(11;14), t(6;14)	del(17p), t(4;14)* t(14;16), +1q21
Cytogenetics	Hyperdiploidy	Hypodiploidy del(13q)
β_2 -microglobulin*	Low (< 3.5 mg/L)	High (\geq 5.5 mg/L)
PCLI	< 3%	High (\geq 3%)
Isotype	--	IgA
Gene expression profile	Good risk	High risk

*Pts with t(4;14), β_2 -microglobulin < 4 mg/L, and Hb \geq 10 g/dL may have intermediate-risk disease.

Pianificazione della Terapia

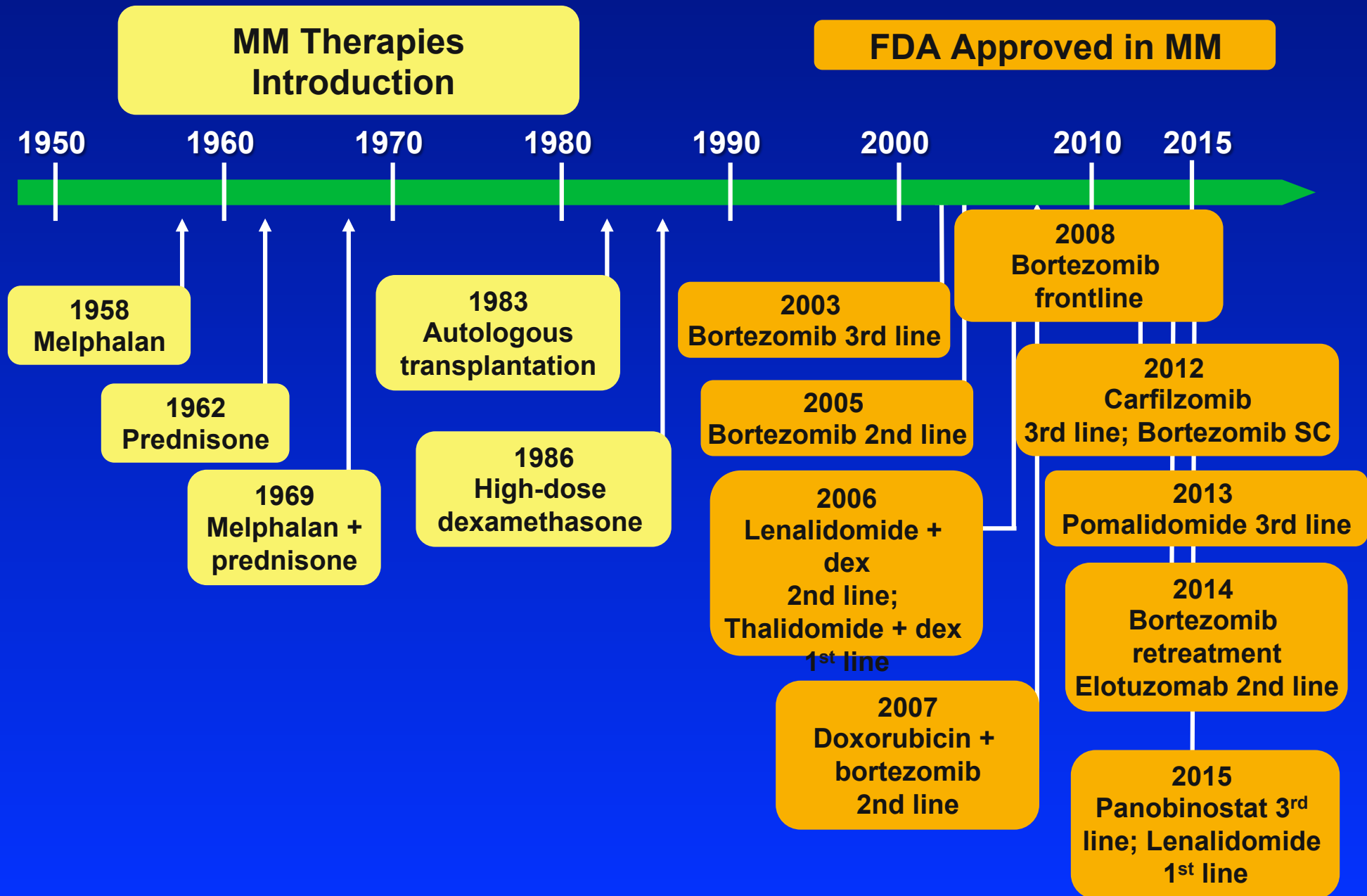
- La terapia va iniziata in presenza di MM sintomatico, cioè in presenza di danno d'organo (CRAB):
 - Calcemia > 10.5 mg/L
 - Insufficienza renale (creat. > 2 mg/dl)
 - Anemia (Hb < 10 g/dL o 2 g $<$ normale)
 - Lesioni ossee (osteolitiche o osteoporosi)

Strategie Terapeutiche

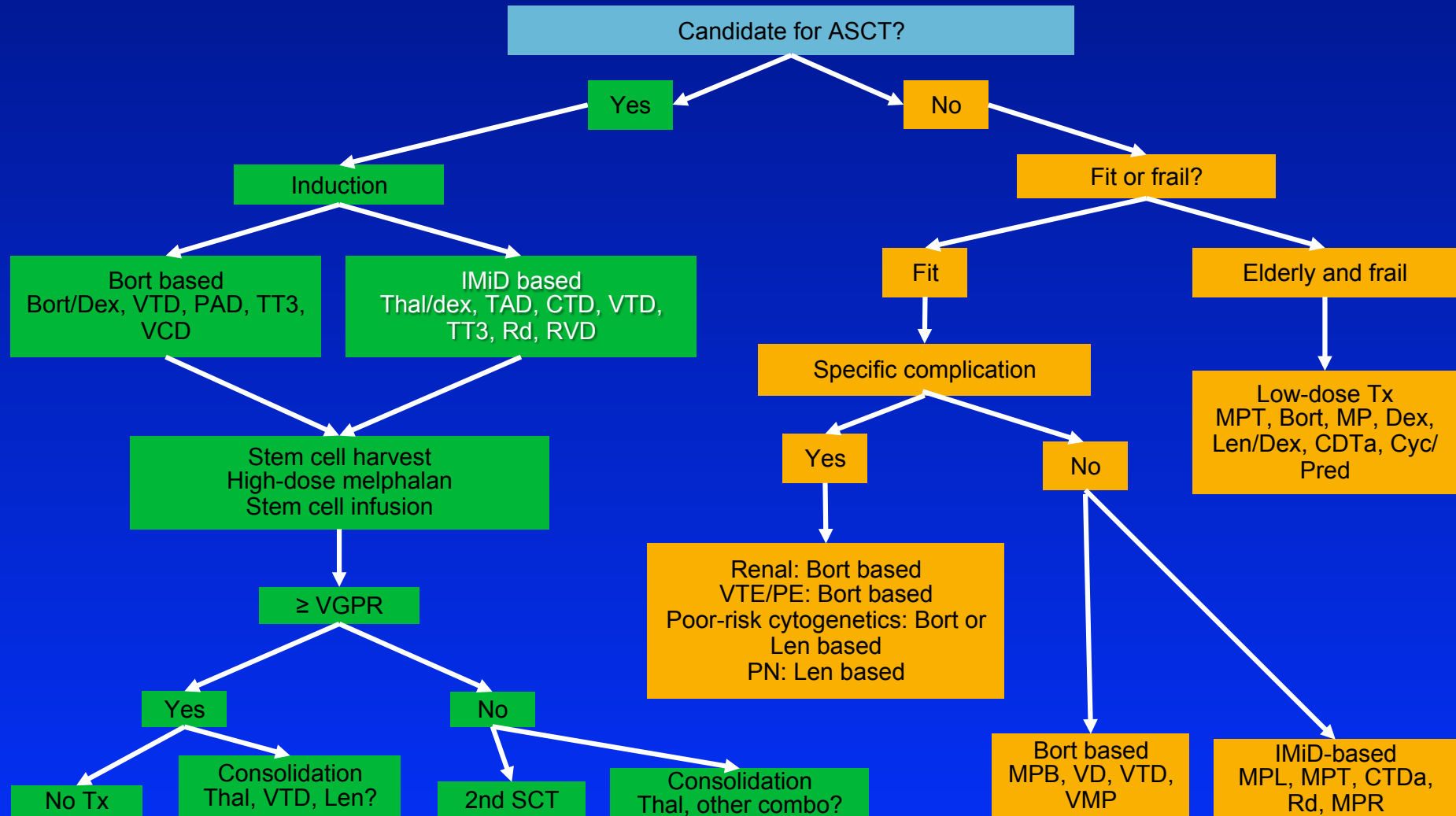
La strategia terapeutica è adattata all'età (e fitness) del paziente

- **Pazienti anziani (> 65 - 70 anni):** chemioterapia a dosi convenzionali insieme a steroidi con l'aggiunta dei nuovi farmaci biologici
- **Pazienti giovani (< 65 70 anni):**
 - **Induzione** con steroide associato ad una combinazione di due farmaci biologici di cui uno è un IMiD (trattamento del microambiente midollare)
 - **Consolidamento** mediante chemioterapia con un agente alchilante ad alte dosi seguito da un trapianto di progenitori emopoietici (autologhi)

Increased Treatment Options in MM

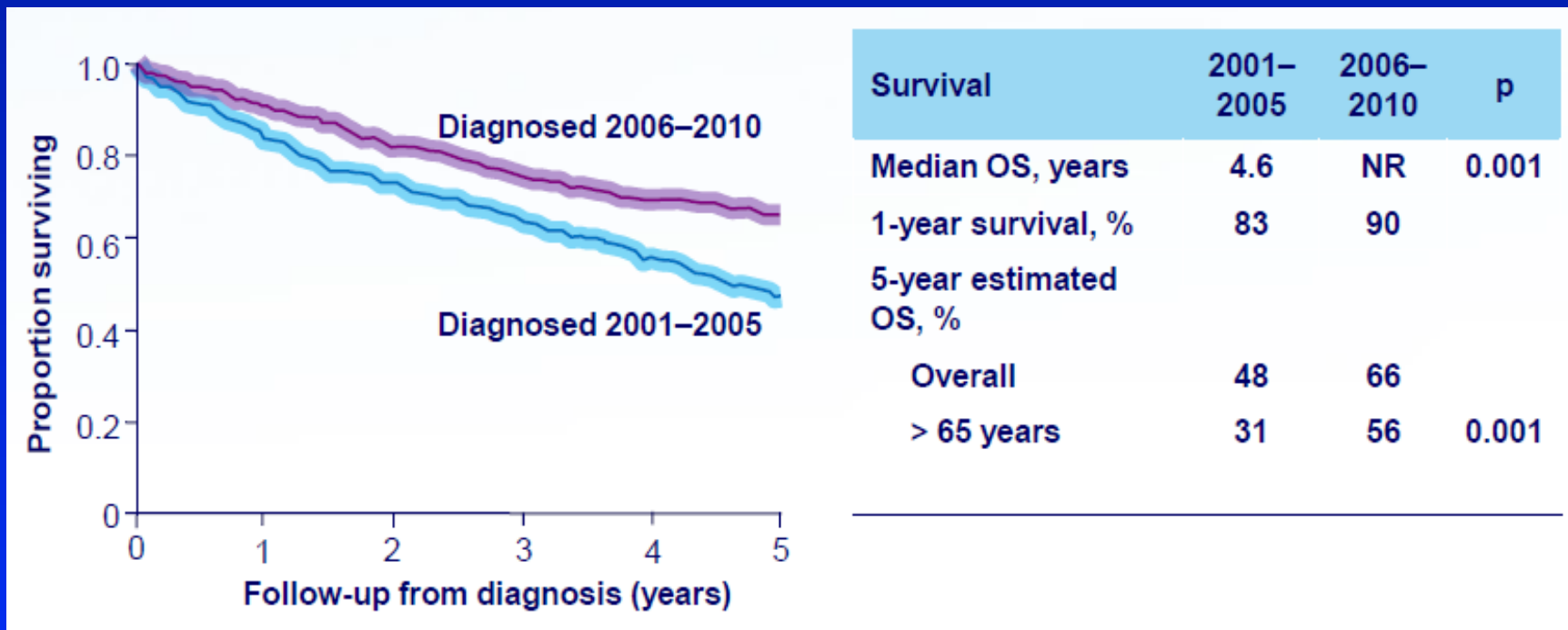


Frontline Treatment

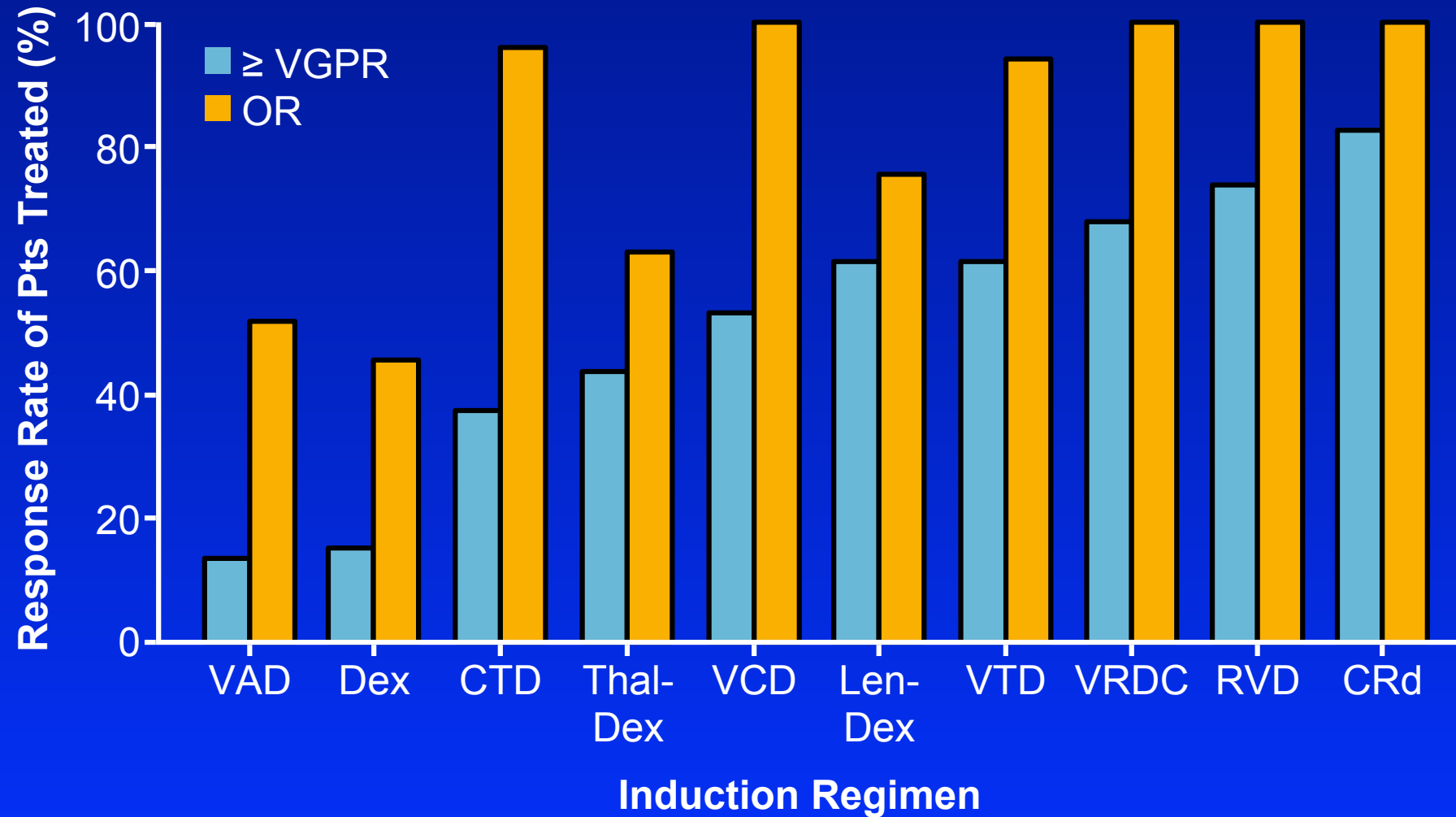


Continued Improvement in Survival Since the Introduction of Novel Agents

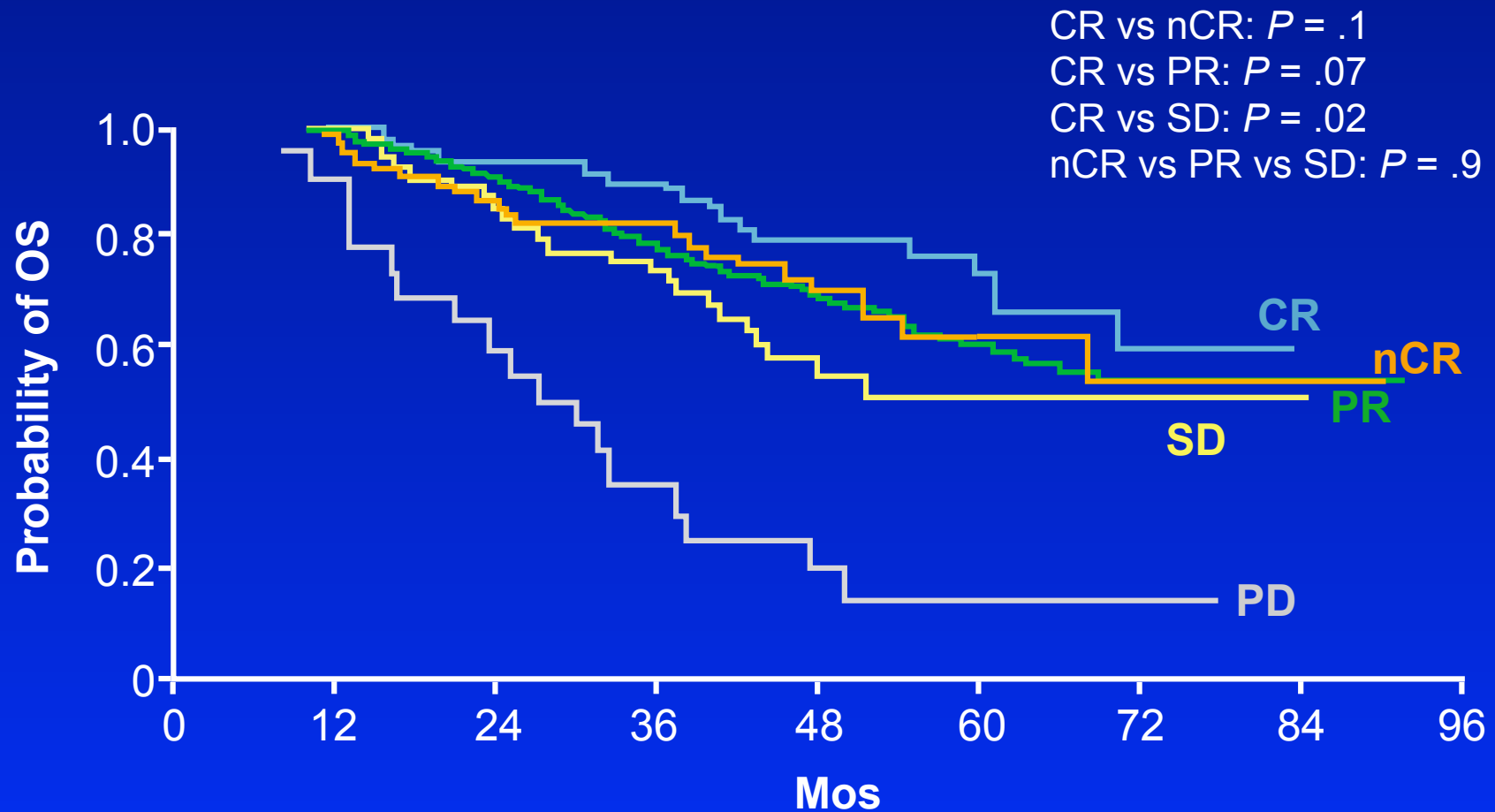
- 1,056 patients grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in patients aged > 65 years (p = 0.001)



Newer Myeloma Drugs Are Associated With Better Clinical Response

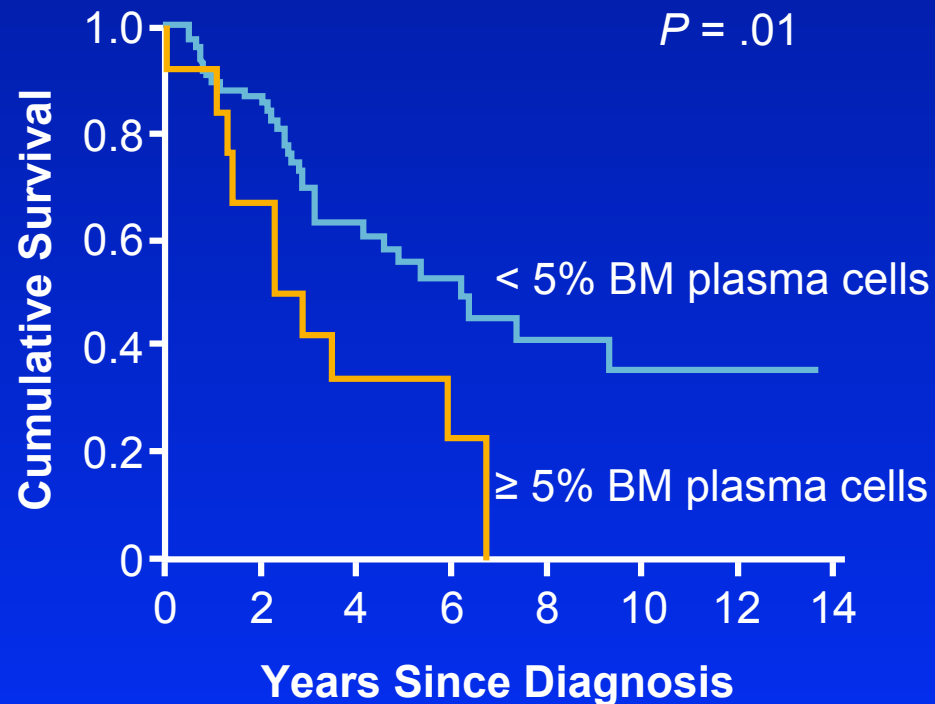


Clinical Response to MM Therapy Affects OS

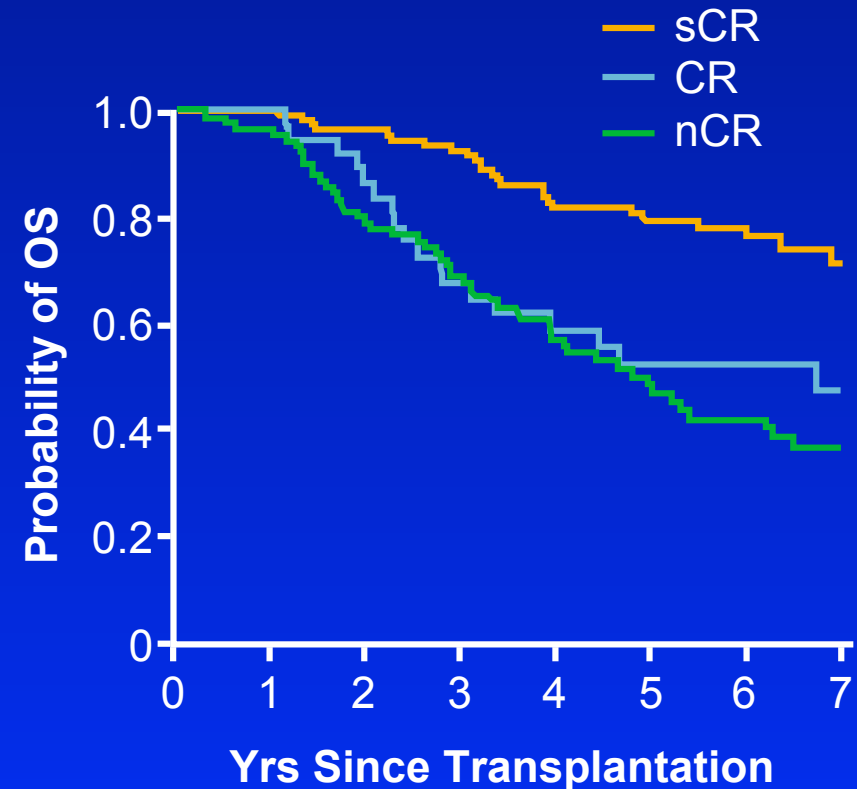


Improved Response Needs Improved Measurements

Conventional microscopy (CR)^[1]



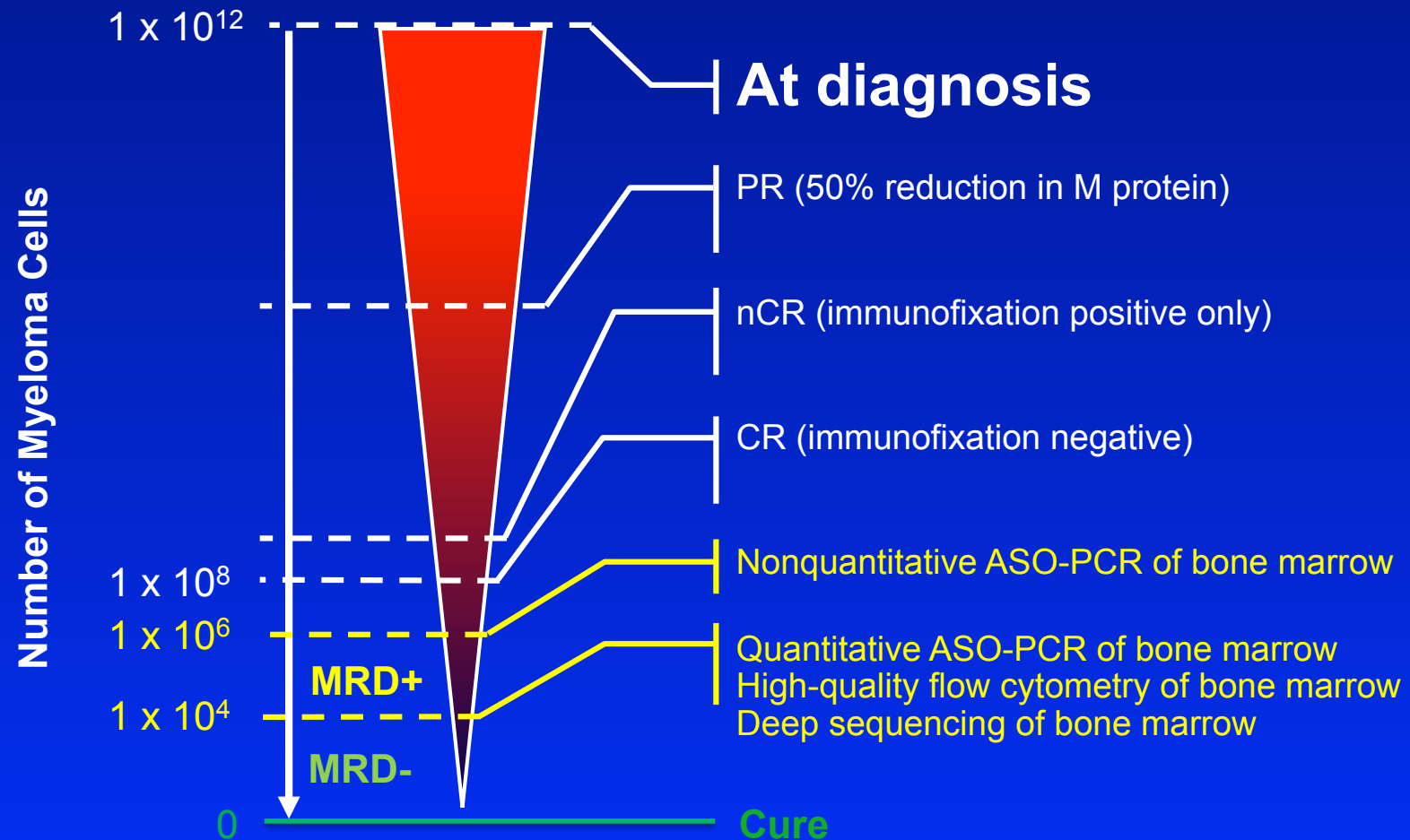
Immunohistochemistry (sCR)^[2]



IMWG Revised Uniform Response Criteria for MM

CR	Negative IFE of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% PCs in bone marrow (2 consecutive assessments)
Stringent CR	CR plus normal FLC ratio and absence of clonal PCs by immunohistochemistry or flow cytometry (2 consecutive assessments)
Immunophenotypic CR	Stringent CR plus absence of clonal BM PCs with minimum 1 million PCs analyzed by flow cytometry > 4 colors
Molecular CR	CR plus negative allele-specific oligonucleotide PCR (sensitivity 10^{-5})

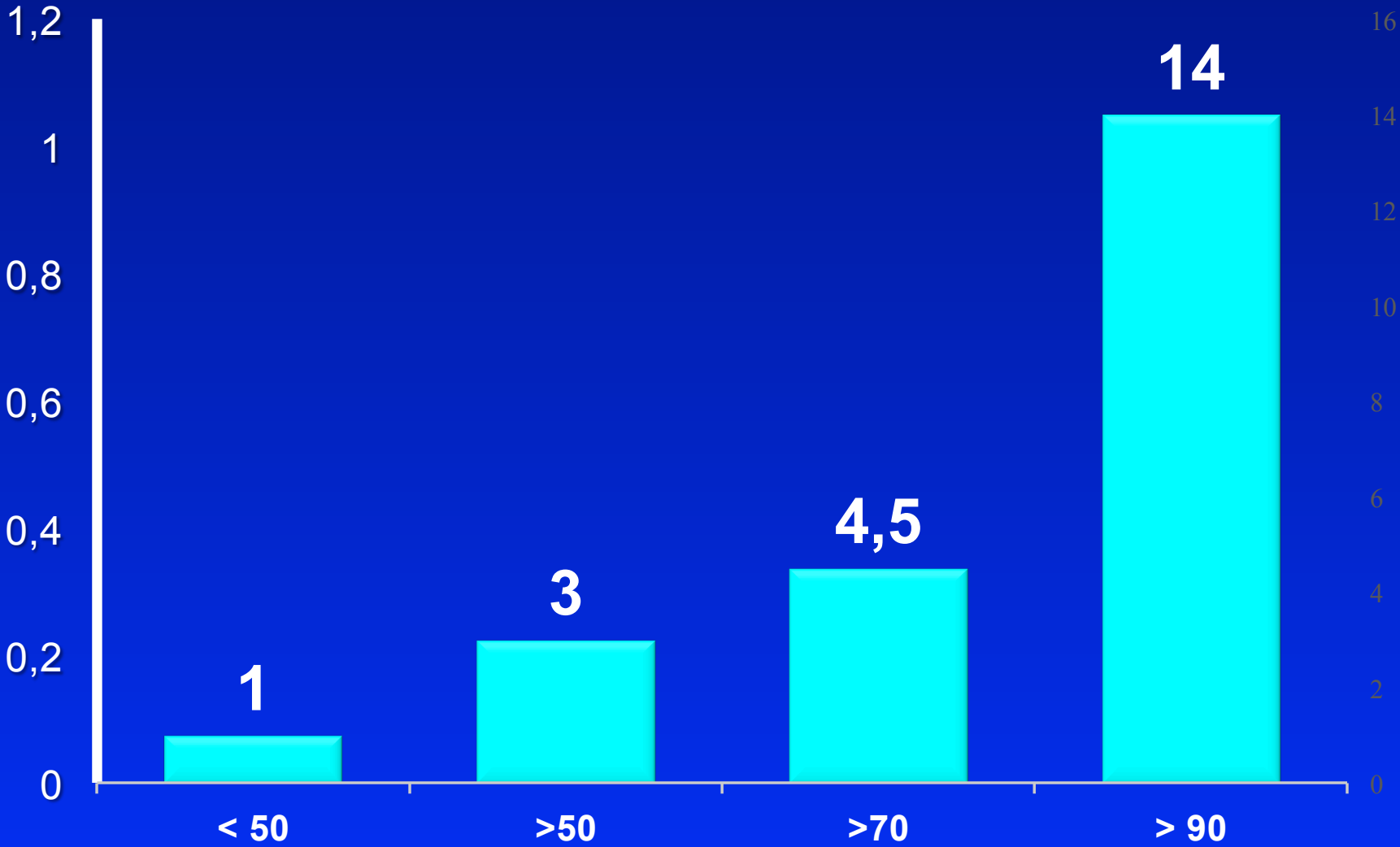
MRD Status Is a Relative Measure



La gammapatia monoclonale di significato non determinato (MGUS)

- Presenza di una componente monoclonale rilevata occasionalmente in corso di accertamenti di laboratorio
- Assenza di sintomi o danno d'organo
- Incidenza in aumento con l'età
- Terapia non necessaria

Incidenza della MGUS secondo l'età



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Revised IMWG Diagnostic Criteria for Multiple Myeloma*

MGUS

- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

Smoldering Myeloma

- M protein \geq 3 g/dL (serum) or \geq 500 mg/24 hrs (urine)
- Clonal plasma cells in BM 10% to 60%
- No myeloma-defining events

Multiple Myeloma

- Clonal BM plasma cells \geq 10% or \geq 1 biopsy-proven plasmacytoma AND 1 or more MM-defining events:
- \geq 1 CRAB[†] feature
- \geq 1 Biomarker of malignancy
 - Clonal plasma cells in BM \geq 60%
 - Serum FLC ratio \geq 100
 - > 1 MRI focal lesion \geq 5 mm on MRI

[†]**C**: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)

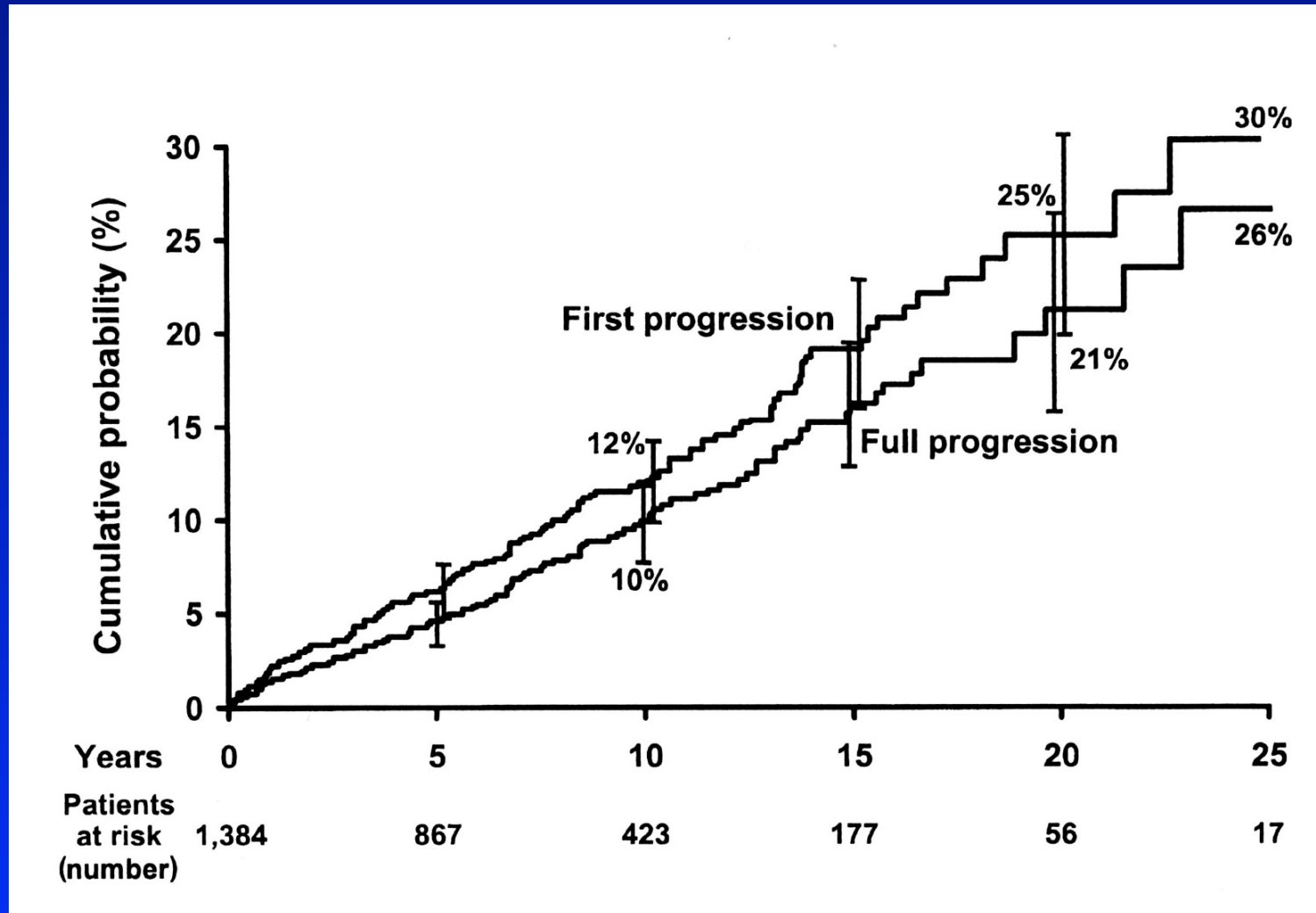
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)

A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)

B: Bone disease (\geq 1 lytic lesions on skeletal radiography, CT, or PET/CT)

*New criteria for SM associated with \geq 80% risk of progression to MM within 2 yrs.

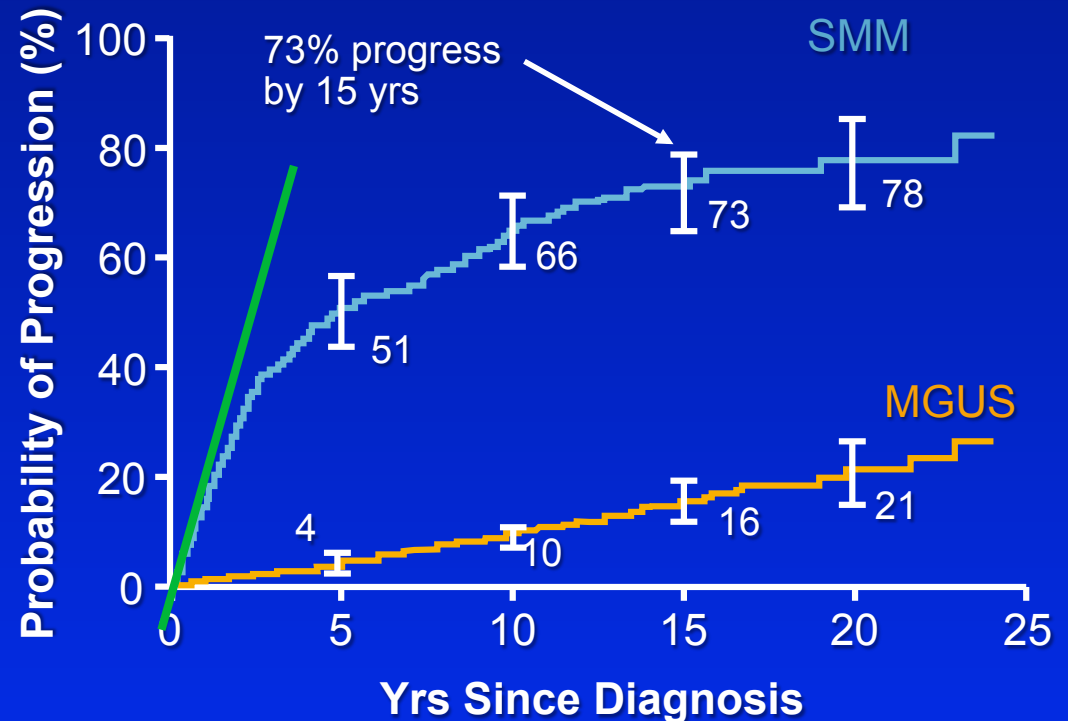
Cumulative Probability of Progression to Multiple Myeloma in 1384 subjects with MGUS



Kyle RA, NEJM 2002

Disease Progression in Patients with SMM and MGUS

- Spectrum of plasma cell disorders (MGUS): < 1% chance/yr
- SMM 10% per yr risk of progression: first 5 yrs
- **Strategy:** identify patients with high-risk of progression; suggest early treatment before organ damage occurs



SMM, Smoldering Multiple Myeloma; MGUS, Monoclonal Gammopathy of Undetermined Significance

Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Progress and Challenges in the Treatment of MM

■ Progress

- Better understanding of disease biology
- Substantial improvements in outcome due to availability of new effective therapies
- Therapeutic backbone of novel agents, specifically PIs and IMiDs, in addition to SCT and continued role of conventional cytotoxics
- Potential for MM to become a chronic disease in some pts
- Advances in the management of adverse events, comorbidities, administration of novel agents

■ Challenges

- MM remains incurable in most pts
- Increasing symptom burden due to disease and cumulative effects of treatments
- Managing balance of disease control and quality of life
- Novel mechanisms of action for next generation agents urgently needed