



RAVENNA, 10 OTTOBRE 2020

AULA MAGNA – Casa Matha

**La terapia front-line del mieloma
multiplo è uguale per tutti i pazienti?
Introduzione**

Patrizia Tosi

UO Ematologia

Rimini

Terapia front-line paziente eleggibile al trapianto

- **VTD x 4-6**
- **MEL 200 + ASCT (1-2)**
- **VTD x 2**
- **Mantenimento (Talidomide o Lenalidomide)**

Terapia front-line paziente non eleggibile al trapianto

- **MPT**

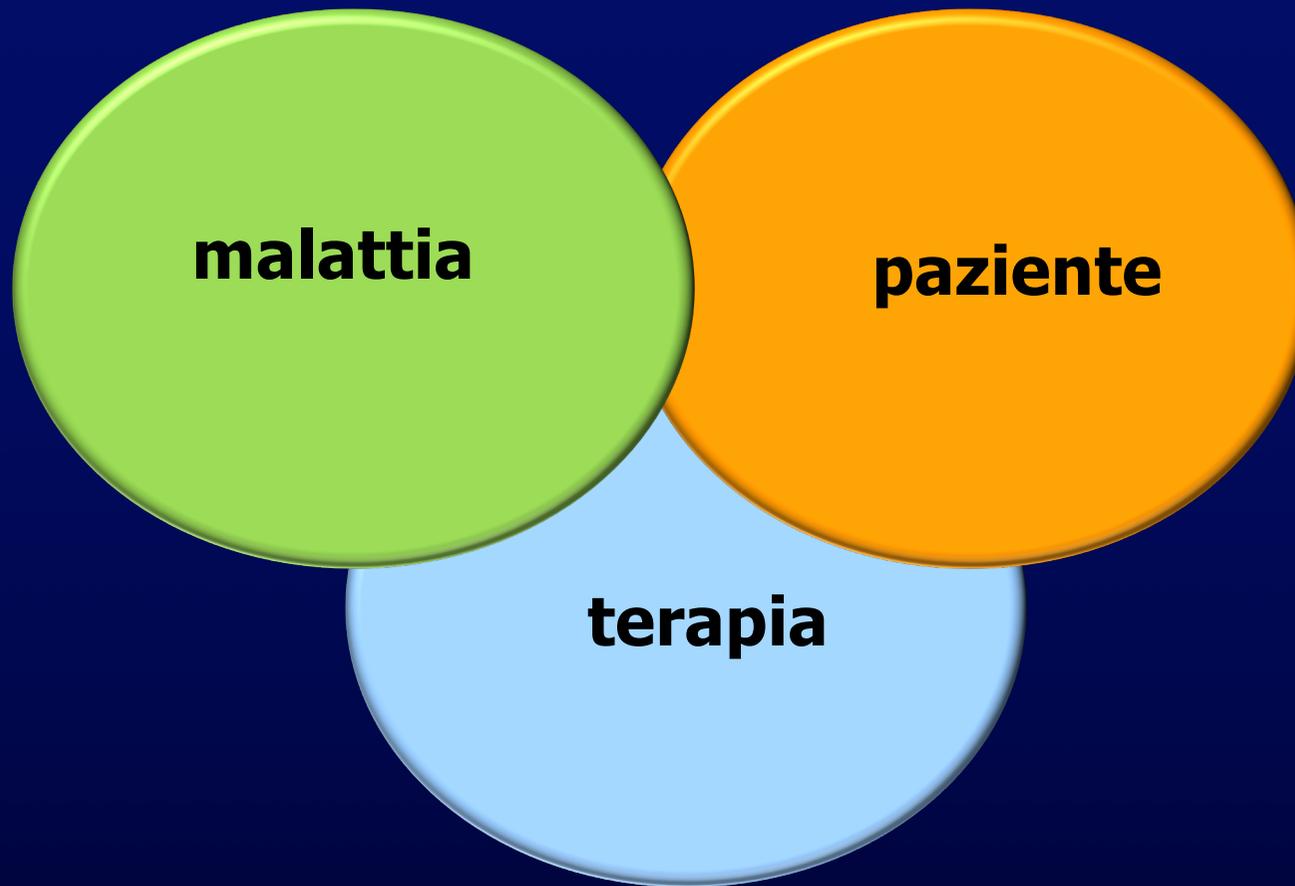
oppure

- **VMP**

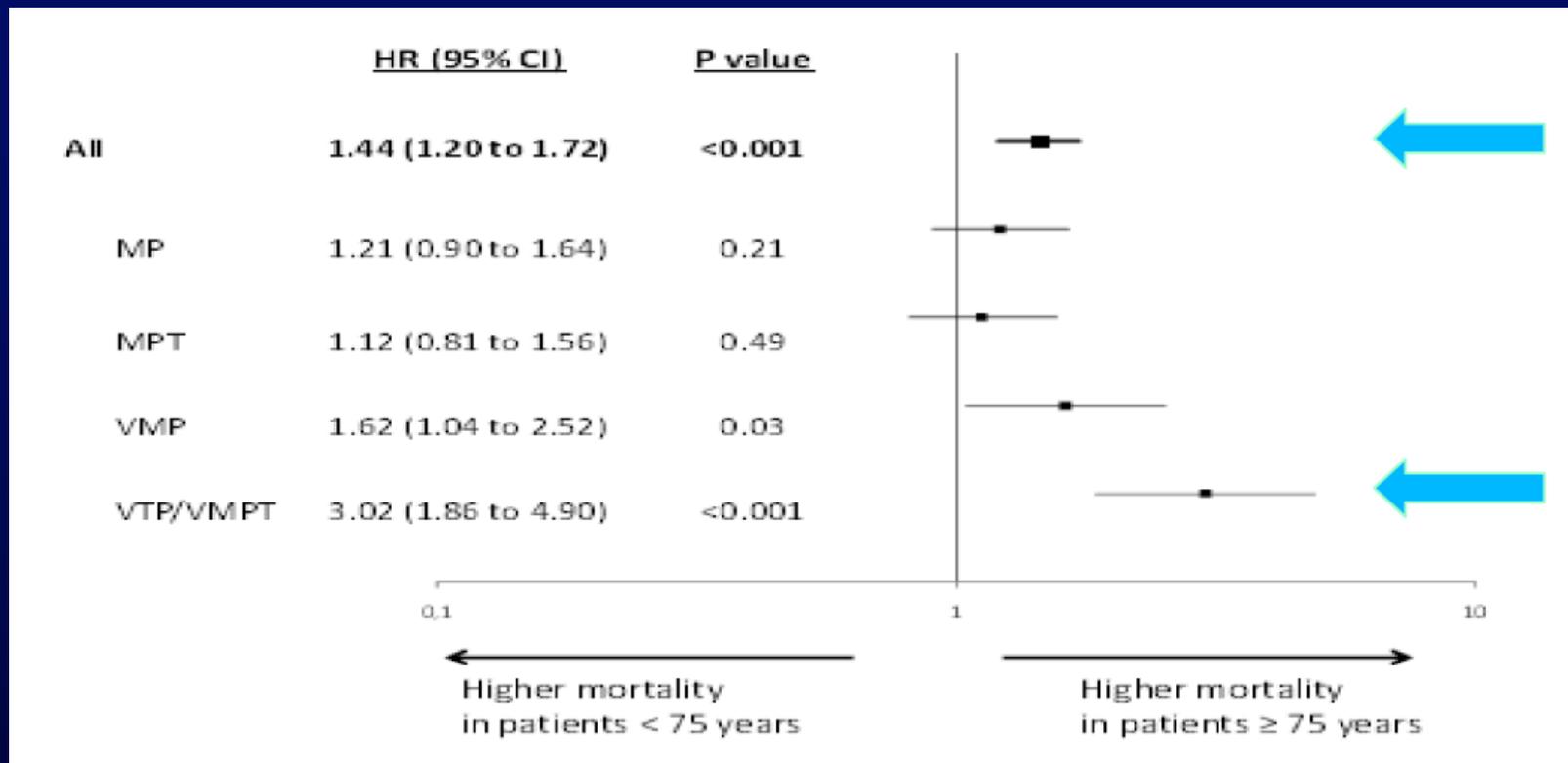
oppure

- **RD**

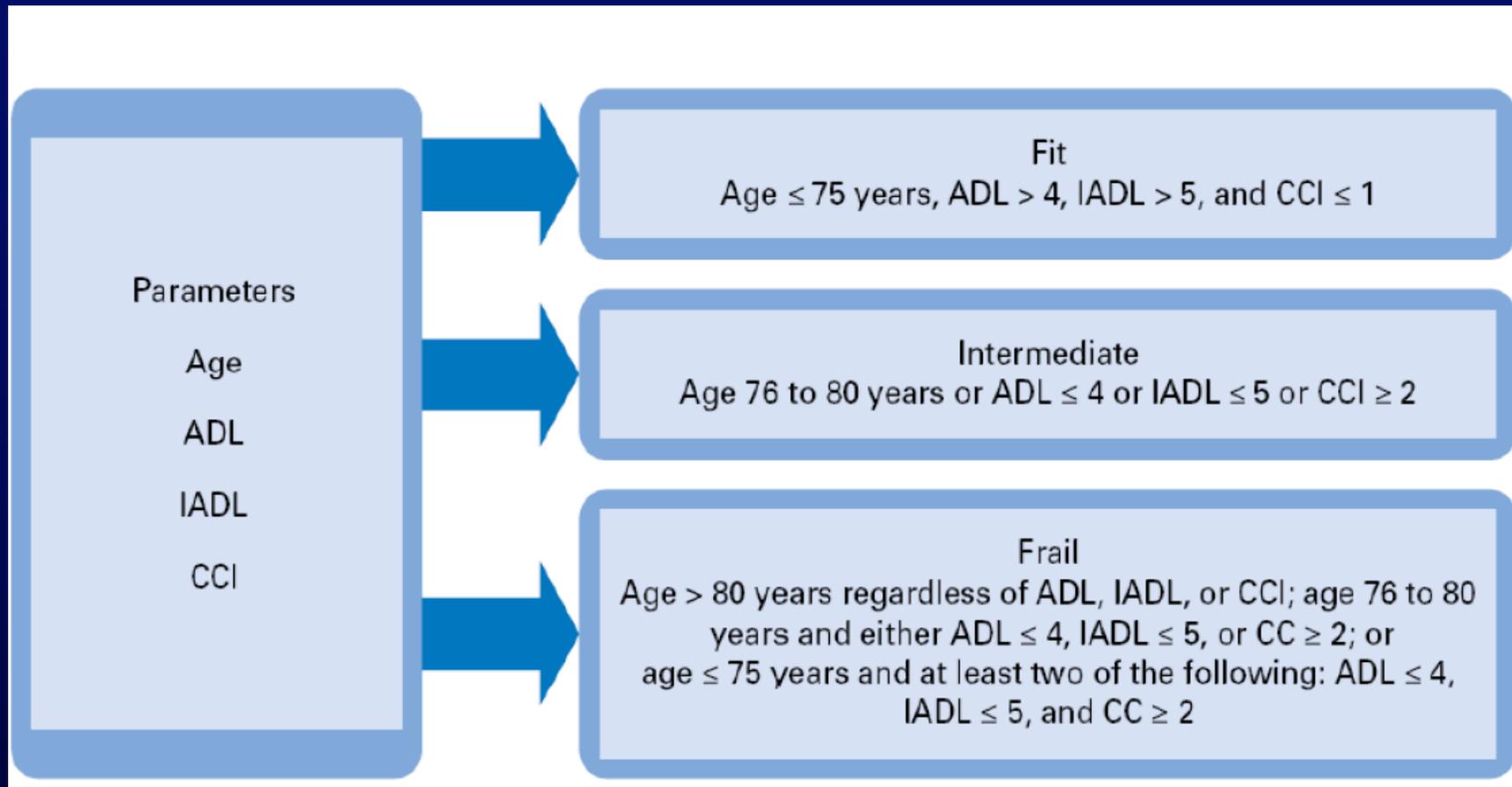
Non tutti i mielomi sono uguali



L'età è un fattore prognostico negativo per la sopravvivenza dei pazienti con MM di nuova diagnosi



Definizione di fragilità nel paziente anziano

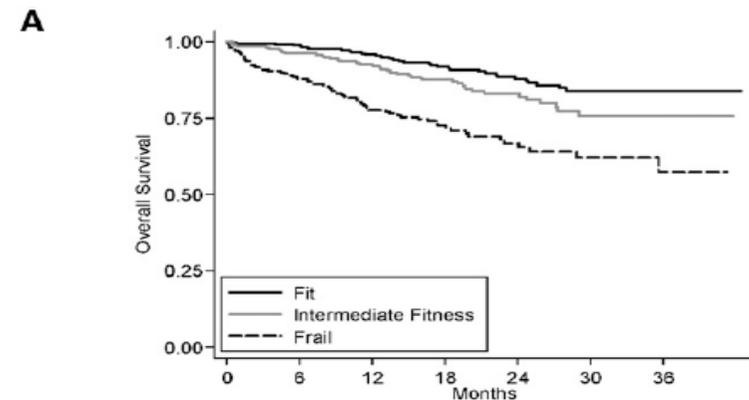


Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report

Antonio Palumbo,¹ Sara Brinchen,¹ Maria-Victoria Mateos,² Alessandra Larocca,¹ Thierry Facon,³ Shaji K. Kumar,⁴ Massimo Offidani,⁵ Philip McCarthy,⁶ Andrea Evangelista,⁷ Sagar Lonial,⁸ Sonja Zweegman,⁹ Pellegrino Musto,¹⁰ Evangelos Terpos,¹¹ Andrew Belch,¹² Roman Hajek,¹³ Heinz Ludwig,¹⁴ A. Keith Stewart,¹⁵ Philippe Moreau,¹⁶ Kenneth Anderson,¹⁷ Hermann Einsele,¹⁸ Brian G. M. Durie,¹⁹ Meletios A. Dimopoulos,¹¹ Ola Landgren,²⁰ Jesus F. San Miguel,²¹ Paul Richardson,²² Pieter Sonneveld,²³ and S. Vincent Rajkumar⁴

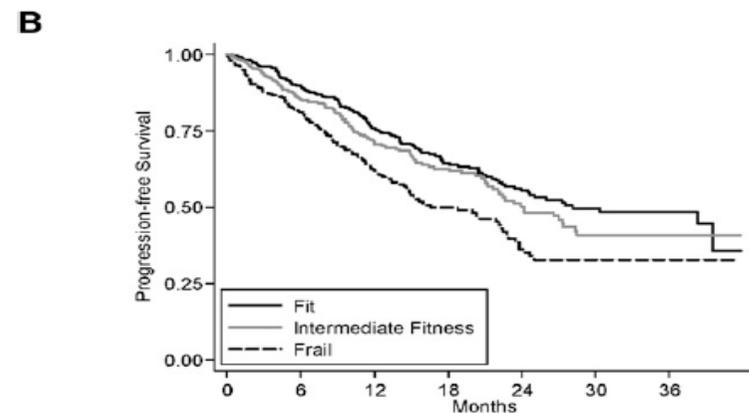
final stratification of variables was defined according to the following cutoff: ADL (>4, ≤4), IADL (>5, ≤5), and CCI (<2, ≥2).

Additive total score	Patient status
0	Fit
1	Intermediate-fitness
≥2	Frail



At risk:

Fit	340	323	248	182	133	84	43
Intermediate Fitness	269	242	183	123	83	47	15
Frail	260	209	151	91	52	27	12

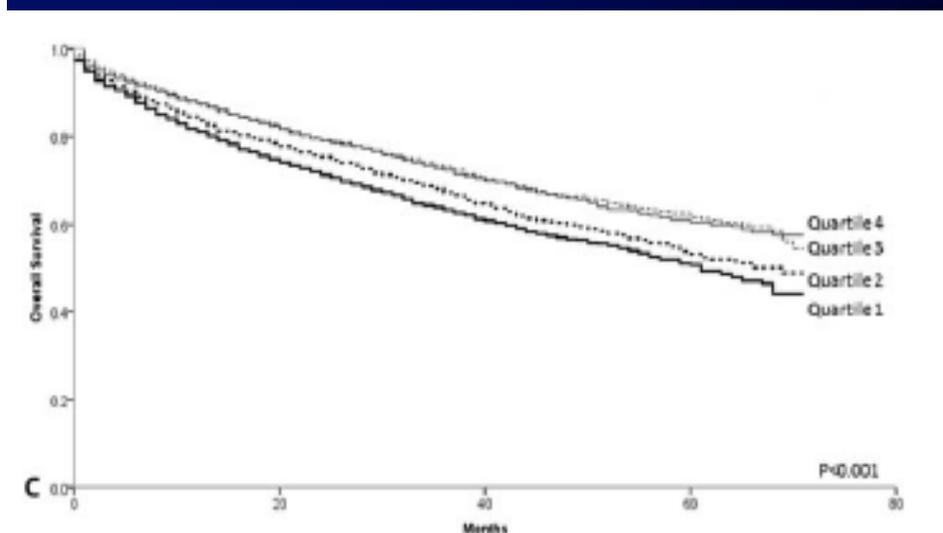
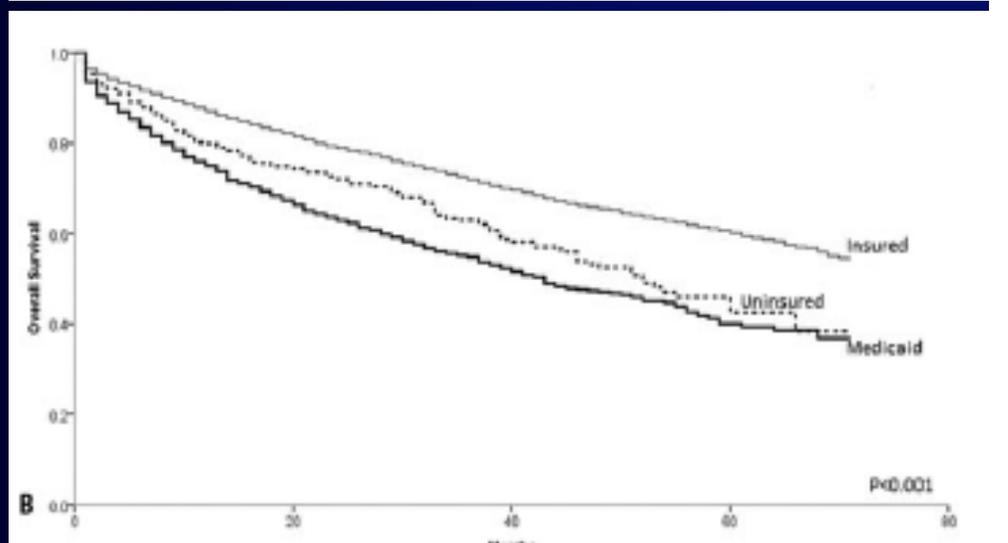
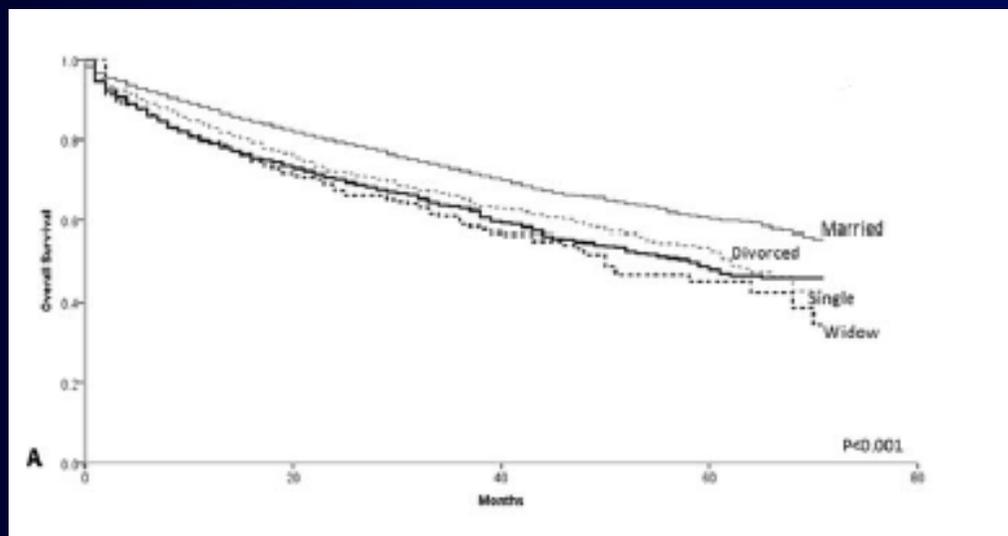


At risk:

Fit	340	292	196	127	78	45	19
Intermediate Fitness	269	216	138	88	50	28	8
Frail	260	193	120	63	31	17	8

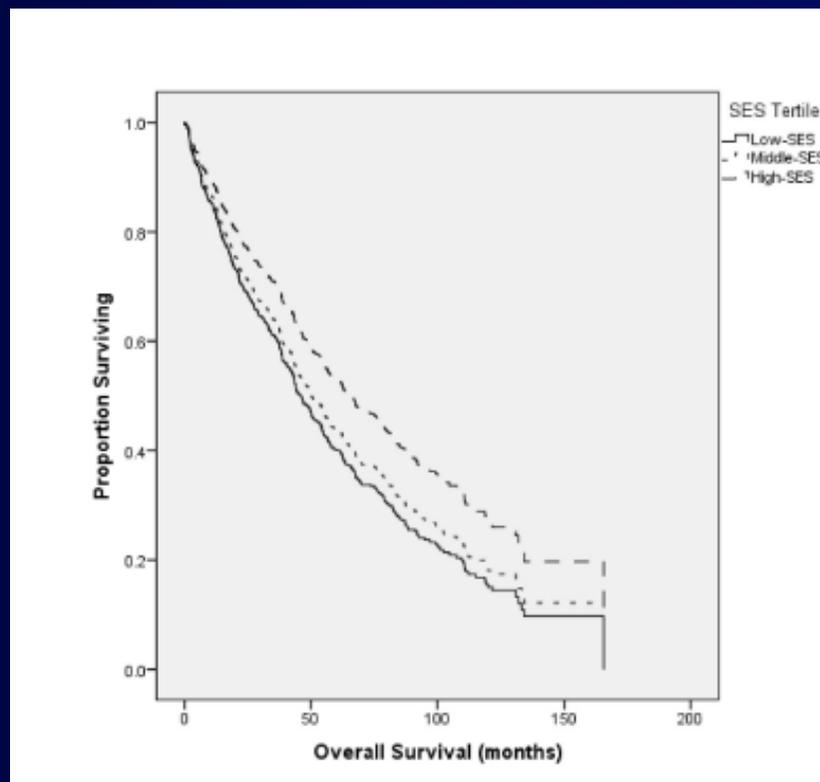
Impact of Marital Status, Insurance Status, Income, and Race/Ethnicity on the Survival of Younger Patients Diagnosed With Multiple Myeloma in the United States

Luciano J. Costa, MD, PhD^{1,2}; Ilene K. Brill, MPH³; and Elizabeth E. Brown, PhD, MPH^{2,4}



Socioeconomic Status is Independently Associated with Overall Survival in Patients with Multiple Myeloma

Mark A. Fiala, BS, CCRP¹, Joseph D. Finney, BS¹, Jingxia Liu, PhD², Keith E. Stockerl-Goldstein, MD¹, Michael H. Tomasson, MD¹, Ravi Vij, MBBS, MD¹, and Tanya M. Wildes, MD, MSCI¹



Multivariate Survival Analysis (WUSM)

	HR [†]	95.0% CI for HR		p value
		Lower	Upper	
SES				0.022
High-SES	1 [‡]			
Middle-SES	1.25	0.95	1.65	0.114
Low-SES	1.54	1.13	2.09	0.006
Age (per year)	1.02	1.01	1.04	0.002
Year of Diagnosis (per year)	0.95	0.91	0.99	0.031
Race				<0.001
White	1 [‡]			
Black	0.57	0.42	0.76	0.001
Other	1.97	0.92	4.24	0.083
Comorbidity Score				0.002
None	1 [‡]			
Mild	1.12	0.85	1.47	0.433
Moderate	1.34	0.97	1.84	0.074
Severe	2.17	1.43	3.28	<0.001
SCT Utilization				<0.001
Yes	1 [‡]			
No	2.57	1.96	3.38	<0.001
Insurance Provider				0.058
Private	1 [‡]			
Medicare	0.74	0.53	1.03	.071
Medicaid	1.224	0.70	2.14	.478
No Insurance	1.59	0.94	2.70	.083

I fattori di prognosi legati alla malattia

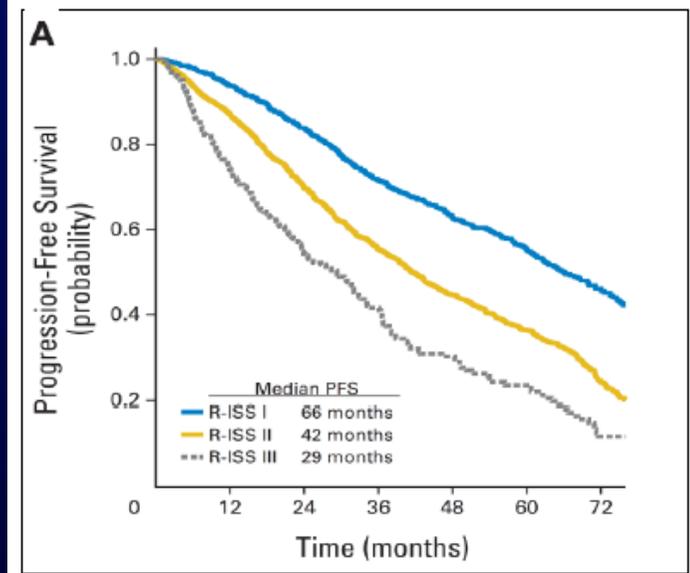
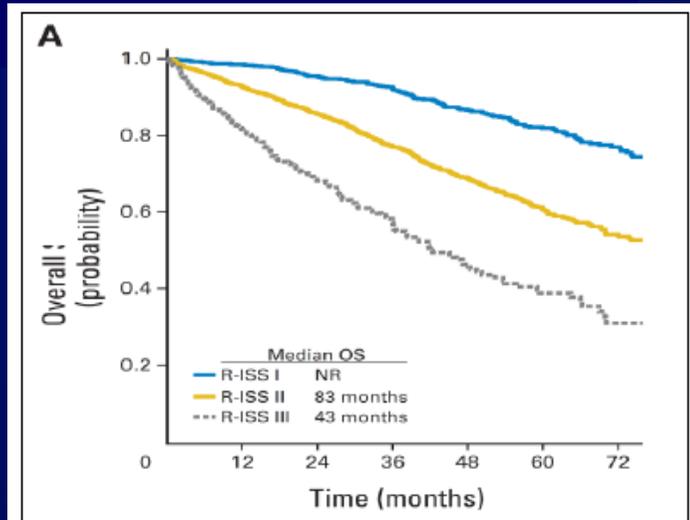
- **Biologia plasmacellulare**
 - Caratteristiche genetico-molecolari (ipodiploidia, del 17, t(4;14), t (14;16), amp 1q, del 1p, GEP.....)
 - Malattia extramidollare (PCL, SNC....)
 - Proliferazione PC (LI > 3%)
- **Tumor burden**
 - Stadio ISS
 - LDH, B2M....

R-ISS

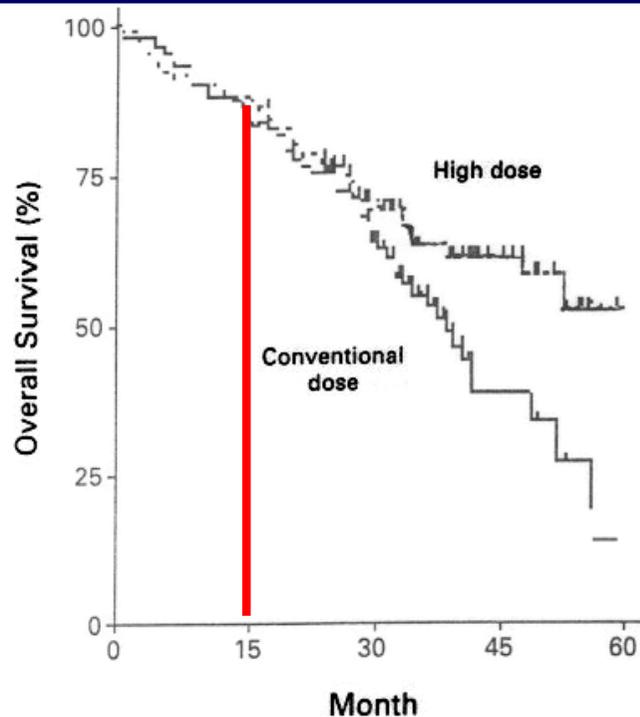
Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

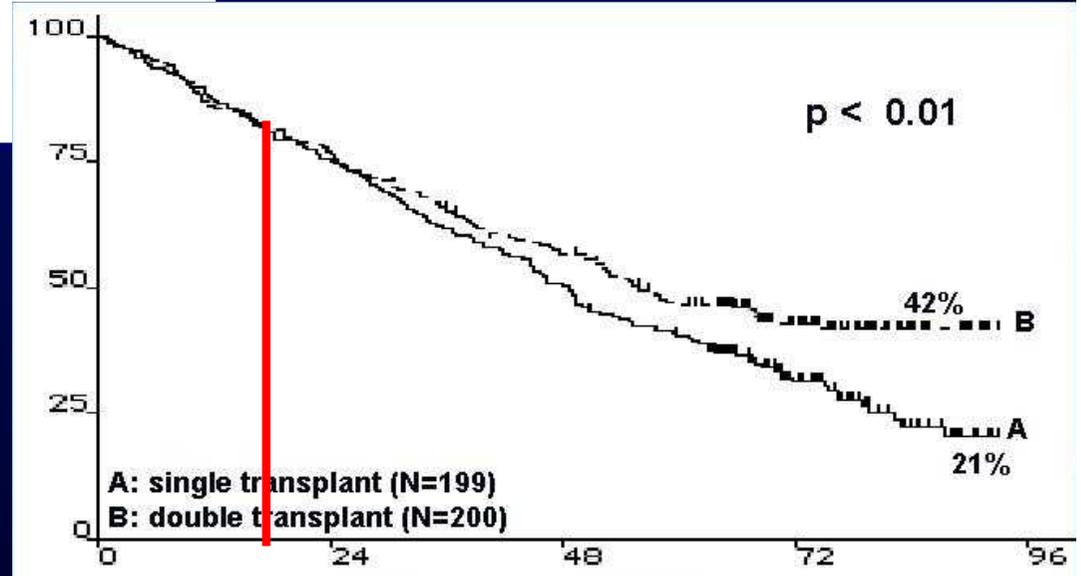


Esiste un gruppo a cattiva prognosi indipendentemente dalla terapia eseguita



Attal et al NEJM 1996

Attal et al NEJM 2005



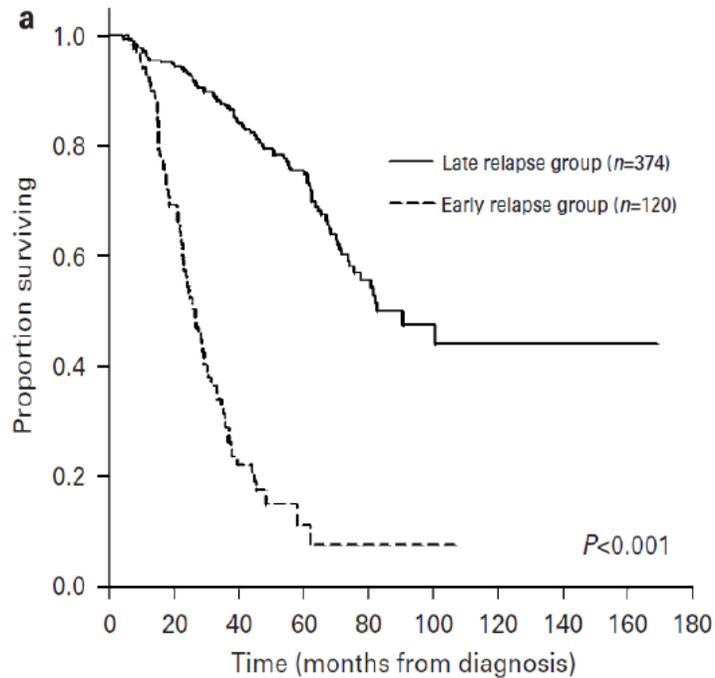
Il decorso **clinico** può rivelare una malattia ad alto rischio:

- **Malattia primariamente refrattaria**
- **Progressione durante brevi intervalli (es tra la raccolta PBSC ed il trapianto)**
- **Ricaduta precoce dopo trapianto (< 12mesi)**

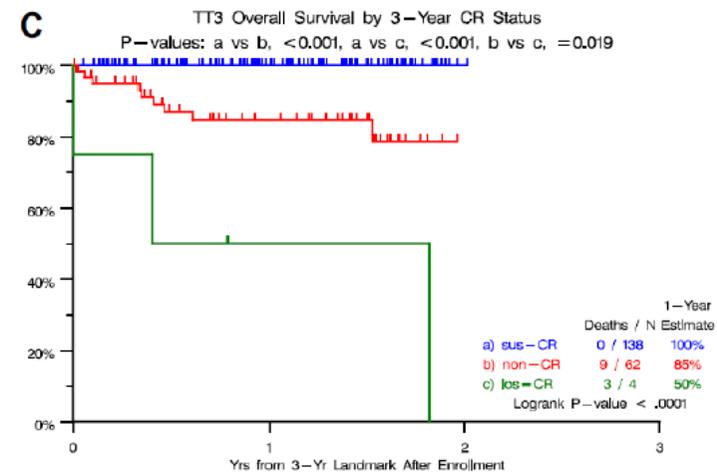
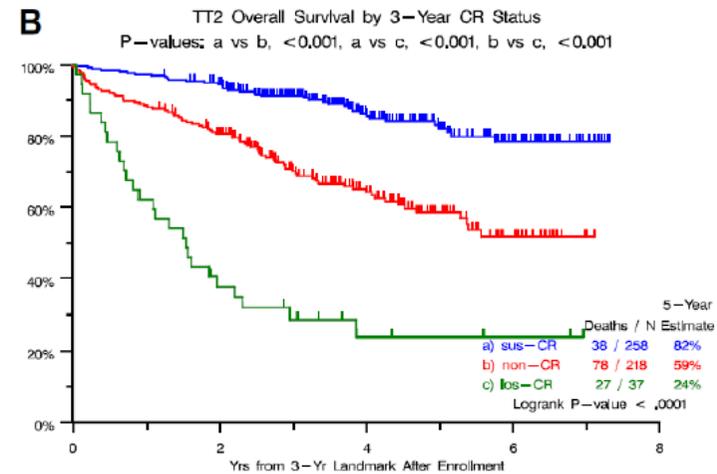


Indipendentemente da fattori di rischio noti

La durata della risposta

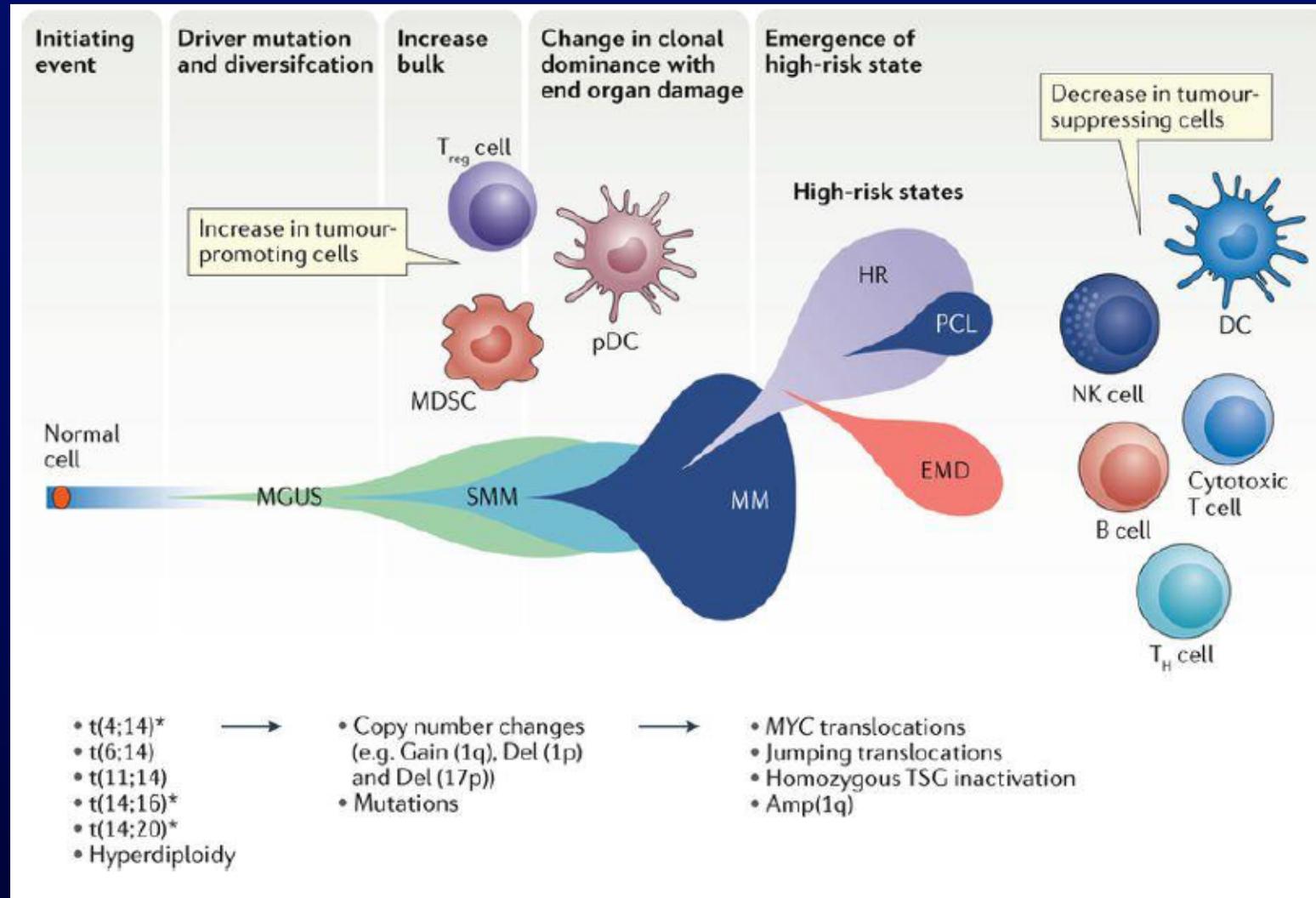


N Majithia et al. Leukemia 2016

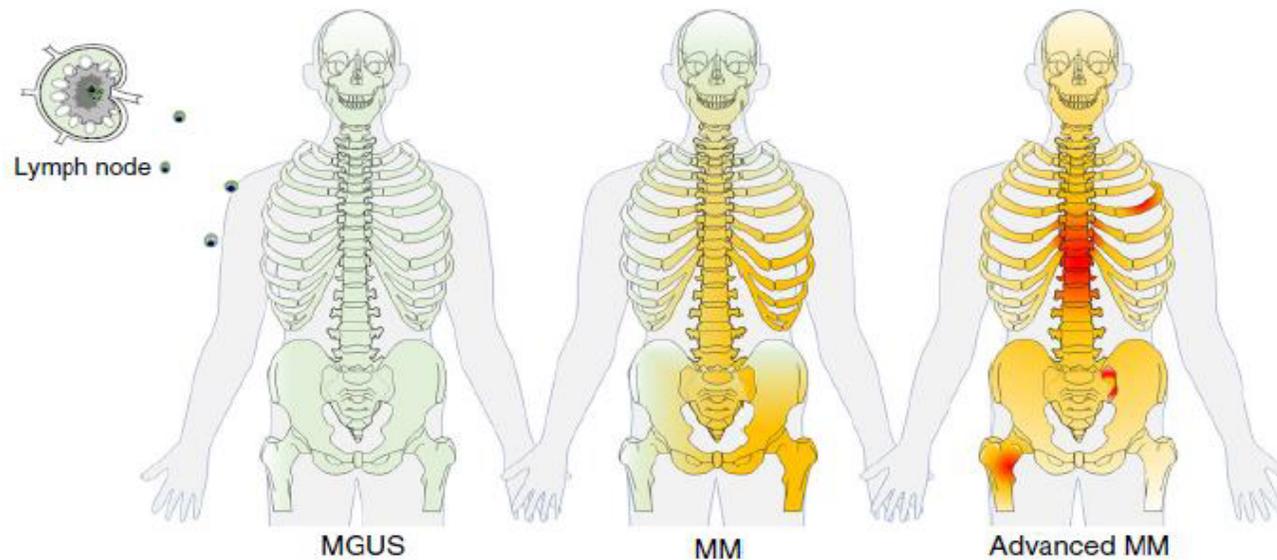


Barlogie B. et al Cancer 2008

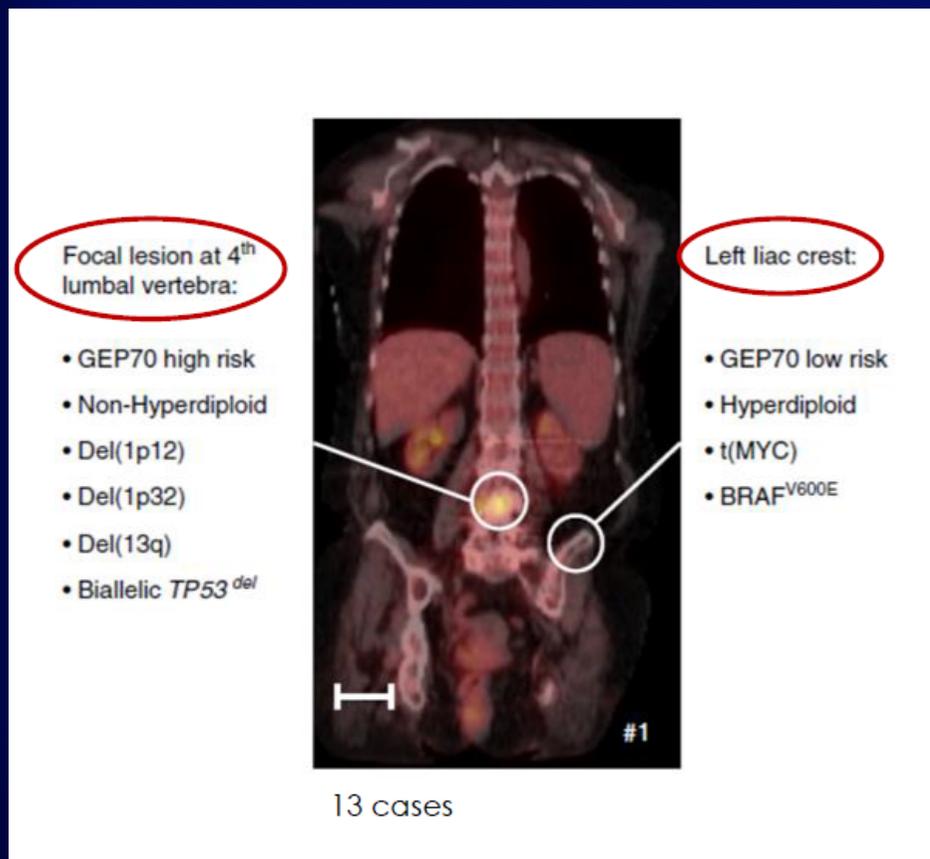
Il microambiente può favorire l'espansione di cloni ad alto rischio



Evoluzione regionale



Evoluzione regionale



• Con tecniche di imaging si identifica spesso una distribuzione "sbilanciata" del MM

• La mancata identificazione di cloni responsabili della ricaduta può essere spiegata dall'evoluzione regionale

• Valutazioni multi-regionali potrebbero essere utili per spiegare l'eterogeneità intra-paziente

I fattori prognostici sono dinamici

A priori

- **Clinici**
 - Età, comorbidità
- **Tumor burden**
 - ISS, LI, PCL
- **Biologici**
 - FISH, GEP

Durante il trattamento

- **Complicanze, intolleranza, sottodosaggio**
- **No CR**
- **No MRD (NGS, PET....)**
- **Evoluzione clonale**