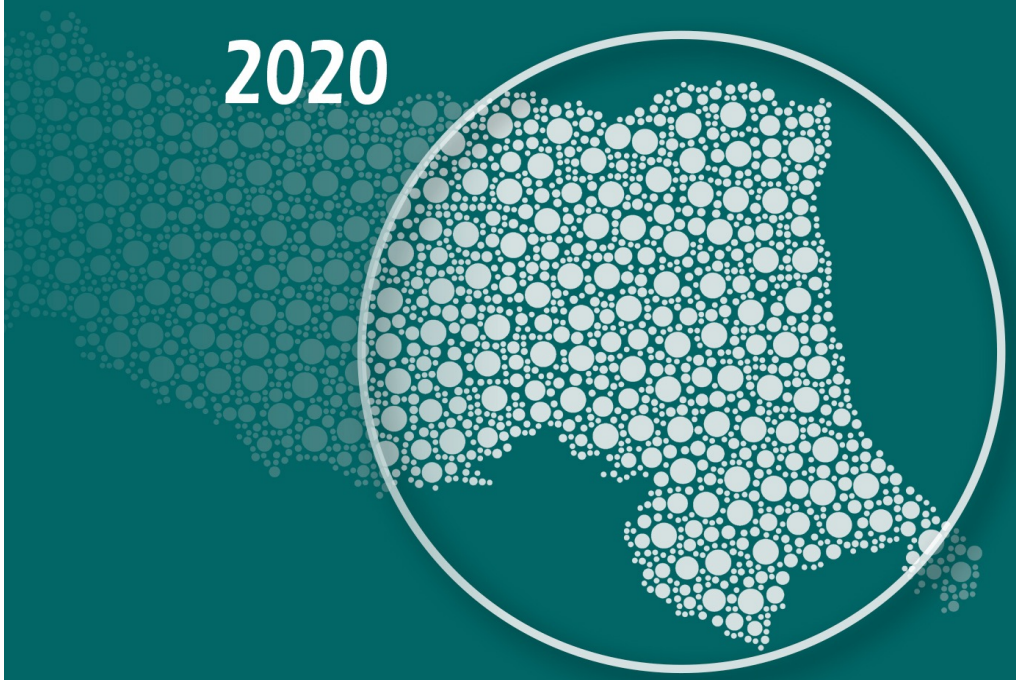

Progetto
Ematologia
Romagna

Il sarcoma mieloide: l' approccio terapeutico

Stefania Paolini

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- Nothing to disclosure

Myeloid sarcoma: therapeutic approach

Surgery

Systemic

Therapeutic dilemmas

Chemotherapy

Localized

Radiotherapy

- **Chloroma**

1893

CHLOROMA AND ITS RELATION TO LEUKÆMIA.

By George Dock, M.D.,

Professor of Theory and Practice of Medicine in the University of Michigan, Ann Arbor, Mich.

omy, in Head and Ne

nly J Med 17:17, 1853

- **Granulocytic sarcoma**
  - **Rappaport H.** «Tumor of the as
    III, Fascicle 8. Armed Forced ning
  - Laslo J and Grode H.E. «Gran ulur
    April 1967
- **FAB classification** (1970)
- **WHO classification 2001**: included ca
- **WHO classification 2008**: separate

MERCURIO

Epidemiology

- **De novo**
  - AML, myeloproliferative neoplasm, myelodysplastic syndrome
- **Secondary**
  - especially in patients following allogeneic hematopoietic stem cell transplant (5-12%)

- **2.5**-**9.1**% AML: **concomitant**, following, preceding (**isolated myeloid sarcoma: 1%**)
  - Retrospective data
  - Physical examination, autopsy series

- **Soft tissues**, **skin**, **bones** and **lymph nodes**
  - genitourinary system, gastrointestinal tract, heart, orbit and central nervous system

Diagnostic work up

- **Cytogenetic analysis**
  - **50%** multiple chromosomal alterations
  - **t(8;21)**(q22;q22), **inv(16)**, 11q23, t(9;11), t(8;16), t(8;17); t(1;11), trisomies 4,8,11, monosomy 7, deletions 5q, 16q, 20q;
  - **Complex karyotype**:
    - **17**% isolated myeloid sarcoma
    - **39**% myeloid sarcoma arising in AML setting
  - Correlation with **localization**:
    - inv(16) associated with involvement of **small intestine**
    - t(8;21) associated with **orbital sarcoma** in pediatric population
- Conventional cytogenetic studies on bone marrow, peripheral blasts and on **freshly obtained myeloid sarcoma cells**.

Treatment

- **No consensus on treatment of myeloid sarcoma**
  - Rarity of disease lack of randomized controlled studies

- Treatment with **AML protocols** is the most reasonable approach
  - All patients with myeloid sarcoma eventually develop AML

Treatment

Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet

12.3 Myeloid sarcoma

Myeloid sarcoma occurring de novo should be considered as AML and treated as such. Data on the prognostic impact of myeloid sarcoma are limited. Whereas some studies reported a negative impact in selected subgroups,[269,270] others suggest that outcome of patients with myeloid sarcoma after conventional chemotherapy or allogeneic HSCT may not be inferior.[271,272] Involved field radiation therapy may be considered to enhance local tumor control.

- **Site of the tumor** (skin, CNS, others)
- **Timing** of myeloid sarcoma (upfront, relapse after chemo, relapse after alloSCT)
- **Patient- related** characteristic (age, PS, comorbidities)

Treatment

MS is associated with superior EFS and OS

Tsimberidou A.M. et al Cancer 113 (2008): 1370-1378

- **Retrospective study** on **23** MS patients
  - From 1990 to 2004
  - MS localization:
    - **Skin** (n=10)
    - **Lymph-node** (n=5)
    - **Dura** (n=2)
    - Breast+ skin (n=1)
    - Bladder (n=1)
    - Gynecologic tract (n=1)
    - Pleura and chest wall (n=1)
  - **16**/23 treated with **araC plus ida/fluda**
  - 2/23 surgical only
  - 5/23 unknown

Treatment

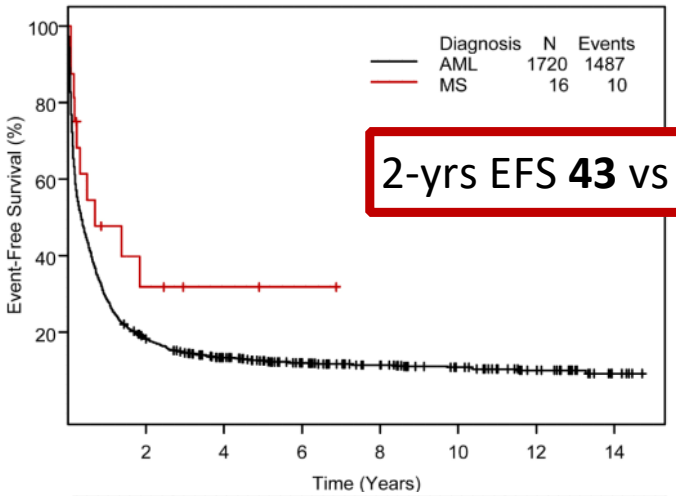
	MS n=23 (%)	AML n=1720 (%)
Age		
▪ Median	57	60
▪ Range	7-81	14-89
Cytogenetics		
• inv(16) or t(8;21)	2 (9)	138 (8)
• Normal	11(48)	640 (37)
• +8	6 (28)	127 (7)
• -5,-7	1 (4)	372 (22)
• Abn 11q23 or other	3 (11)	358 (21)
• na	0 (0)	85 (5)
CR after 1^ cycle	**69**	**57**

p=0.45

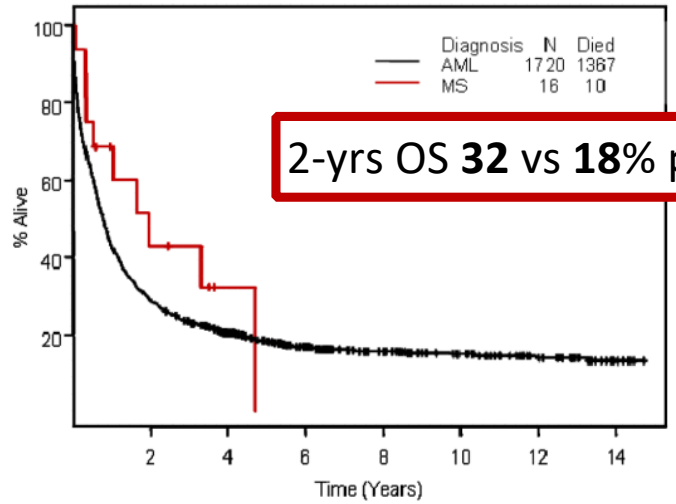
4/23 SM cytogenetic: 12p- (n=1); complex (n=2); 8q-(n=1)
19/23 BM cytogenetic: normal (n=11); +8 (n=5); -7 (n=1)
inv(16) (n=2)

MS is associated with superior EFS and OS

Tsimberidou A.M. et al Cancer 113 (2008): 1370-1378



2-yrs EFS **43** vs **29**% p=**0.08**



2-yrs OS **32** vs **18**% p=**0.11**

Treatment

	MS n=23 (%)	AML n=1720 (%)
Post remission therapy		
▪ Chemotherapy	64	58
▪ alloSCT	0	1
▪ None	24	0
▪ other	8	10
1^ relapse therapy		
• Chemotherapy	75	68
• alloSCT	0	9
• Other	25	32

Multivariated analysis EFS and OS:

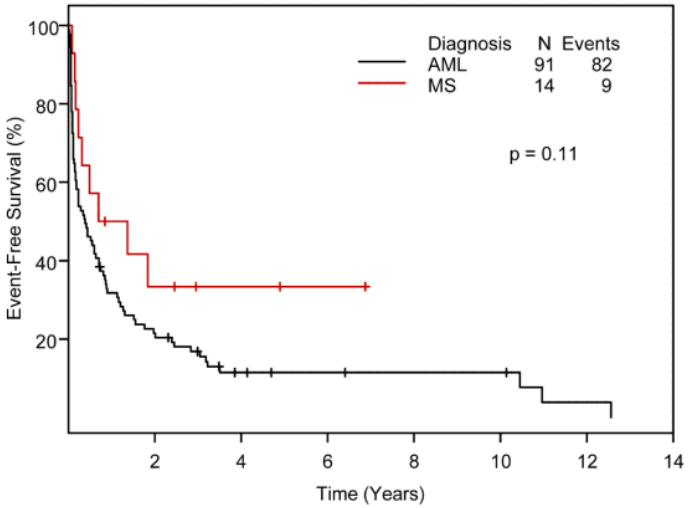
- ✓ High risk cytogenetics
- ✓ Poor PS
- ✓ AHD
- ✓ Higher leukocyte

MS vs AML was not a significant factor

MS is associated with superior EFS and OS

Tsimberidou A.M. et al Cancer 113 (2008): 1370-1378

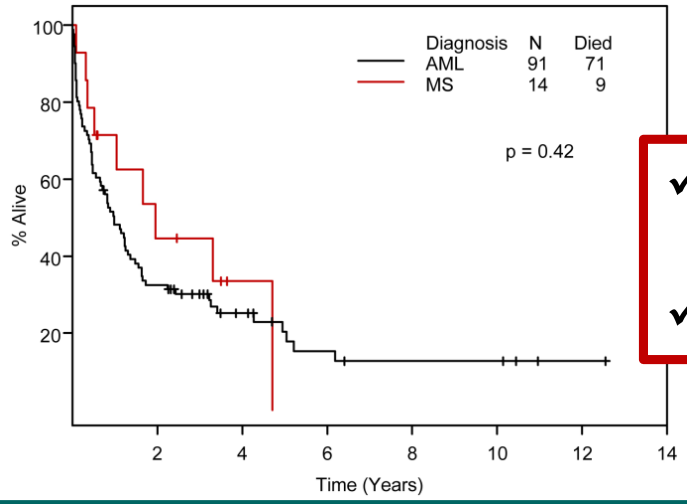
Treatment



Pair matches analisys:

- Cytogenetic
- Age
- PS
- Time of treatment (1990-1997 and 1998-2007)

✓ **91 AML patients** identify to produce 94 matches



✓ EFS longer in **56** MS pair-mates, shorter in **26** and similar in **11** patients

✓ OS similar results

Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

- **Retrospective study** on **48** MS patients
  - From 2005 to 2015
  - MS localization
    - Lymph nodes (**46**%)
    - Skin (**27**%)
    - Soft tissue (**21**%)

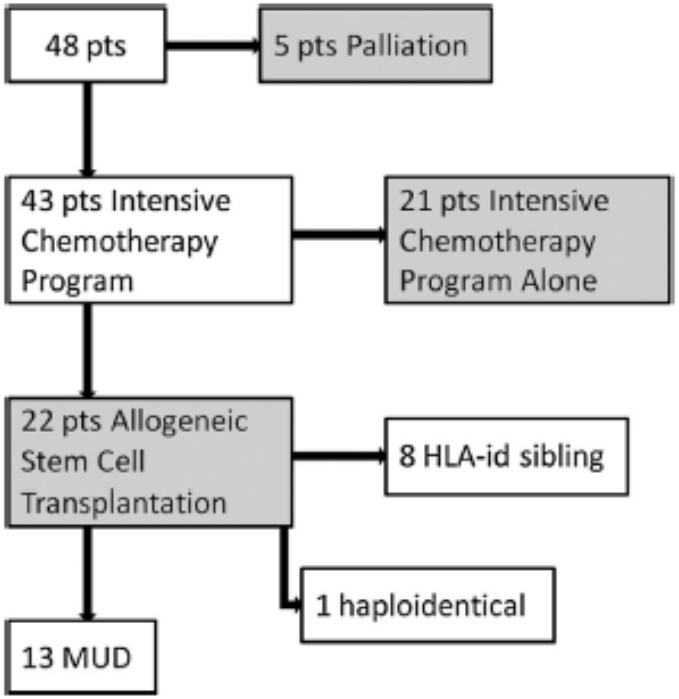
Patients' Characteristics (48 pts)		
Sex M/F	26/22	
Median Age (range)	46	(15–82)
MS SUBTYPE	**N°**	**%**
de novo extramedullary MS	9	19%
de novo AML-related MS	24	50%
secondary AML-related MS	15	31%
KARYOTYPE (available in 32/48)	**N°**	**%**
normal	14	44%
complex	7	22%
t(8;21), inv(16) or t(16;16)	5	15%
trisomy 8, other	6	19%
MOLECULAR BIOLOGY (available in 32/48)[a]	**N°**	**%**
no alterations	13	41%
NPM1	8	25%
FLT3-ITD or D835	10	31%
AML1-ETO or CBFbeta-MYH11	7	22%
CEBPA, ETV6-MLL or JAK2	1	3%

Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

- **43/48 (90%) intensive chemotherapy**
  - FLAI, MEC, ICE, IDA/HDAC, HyperCVAD
  - 3/43 death (2 induction, 1 consolidation)
  - 13/43 (**30**%) plus **radiation therapy**
- Median of **2.5** cycles (range 1-5)
- **18/40 (45%) CR**
  - 22/40 no CR → **2/22 (9%) CR** from EM involved site
- **22/43 (51%) alloSCT**
  - 13 CR, 9 active disease
- **9 *de novo* MS**
  - 7 (78%) intensive treatment with CR rate **71**%
  - 3 (43%) alloSCT

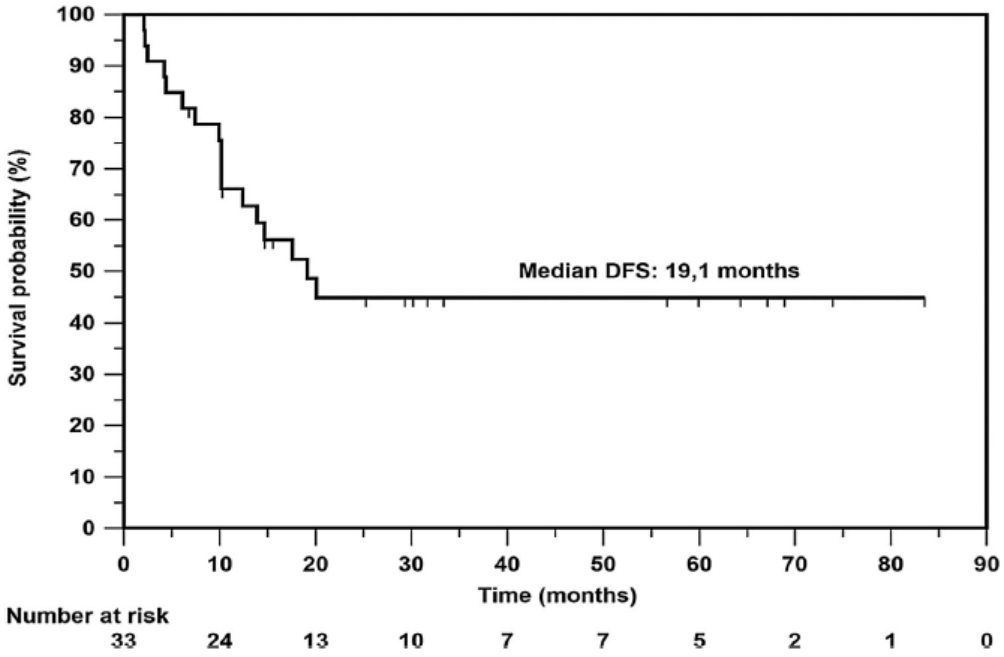


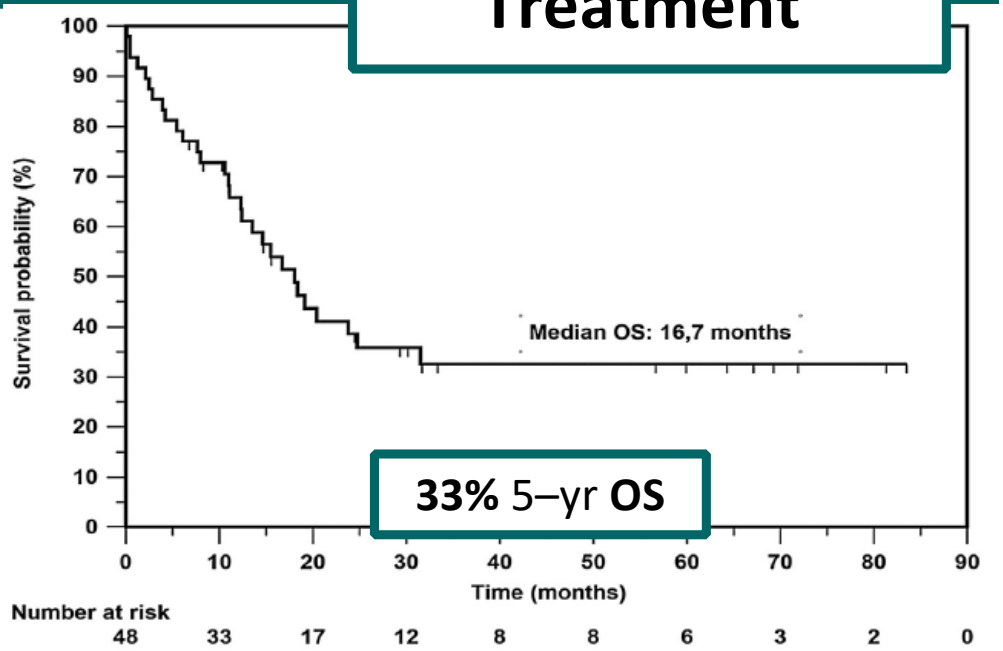
Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

- **Median follow-up: 15 months (1-83.5)**
  - 19/48 (40%) alive (75% CR)
  - 29/48 (60%) died (69% disease; 31% other)



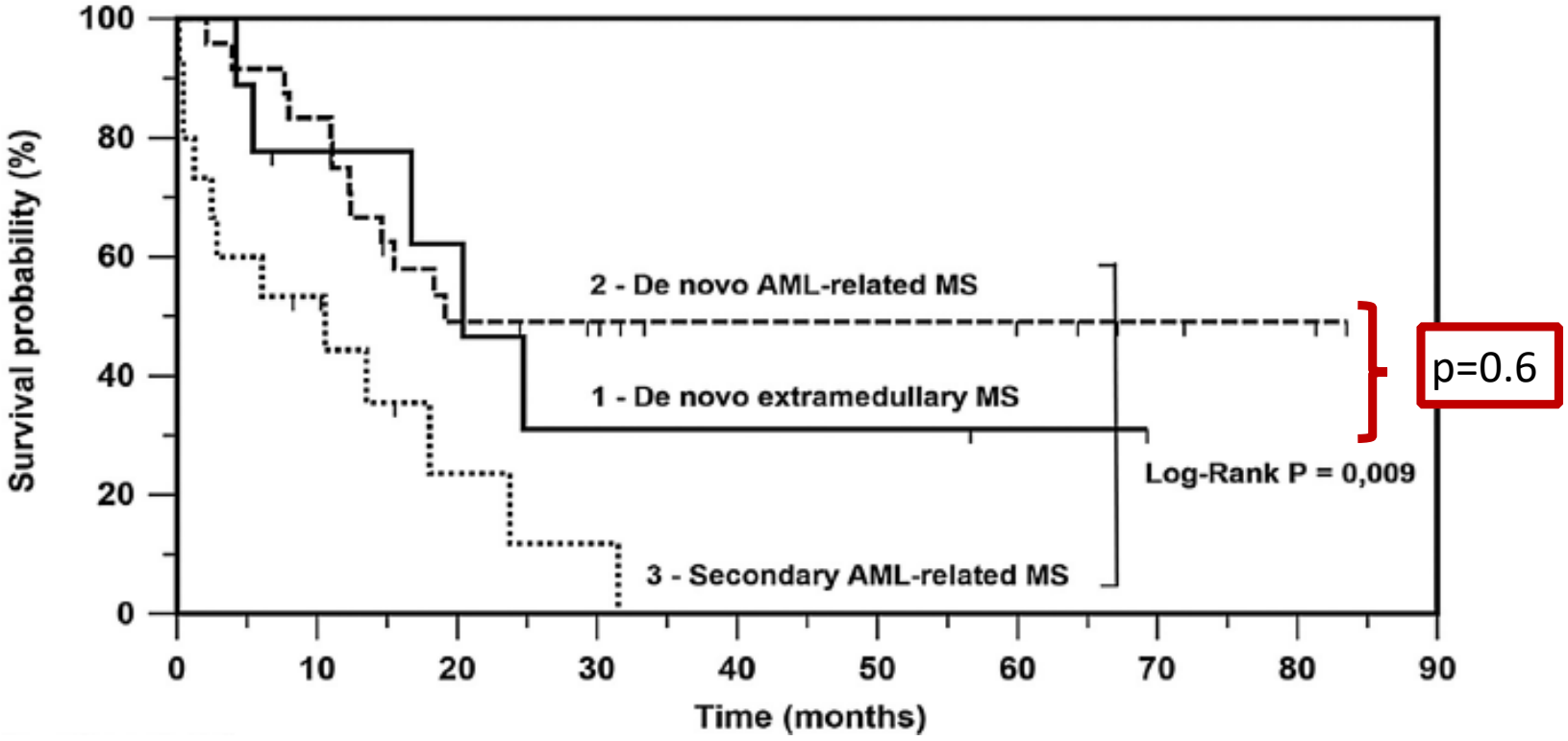


Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

- No significant differences in OS between de novo AML-related MS and de novo extramedullary MS

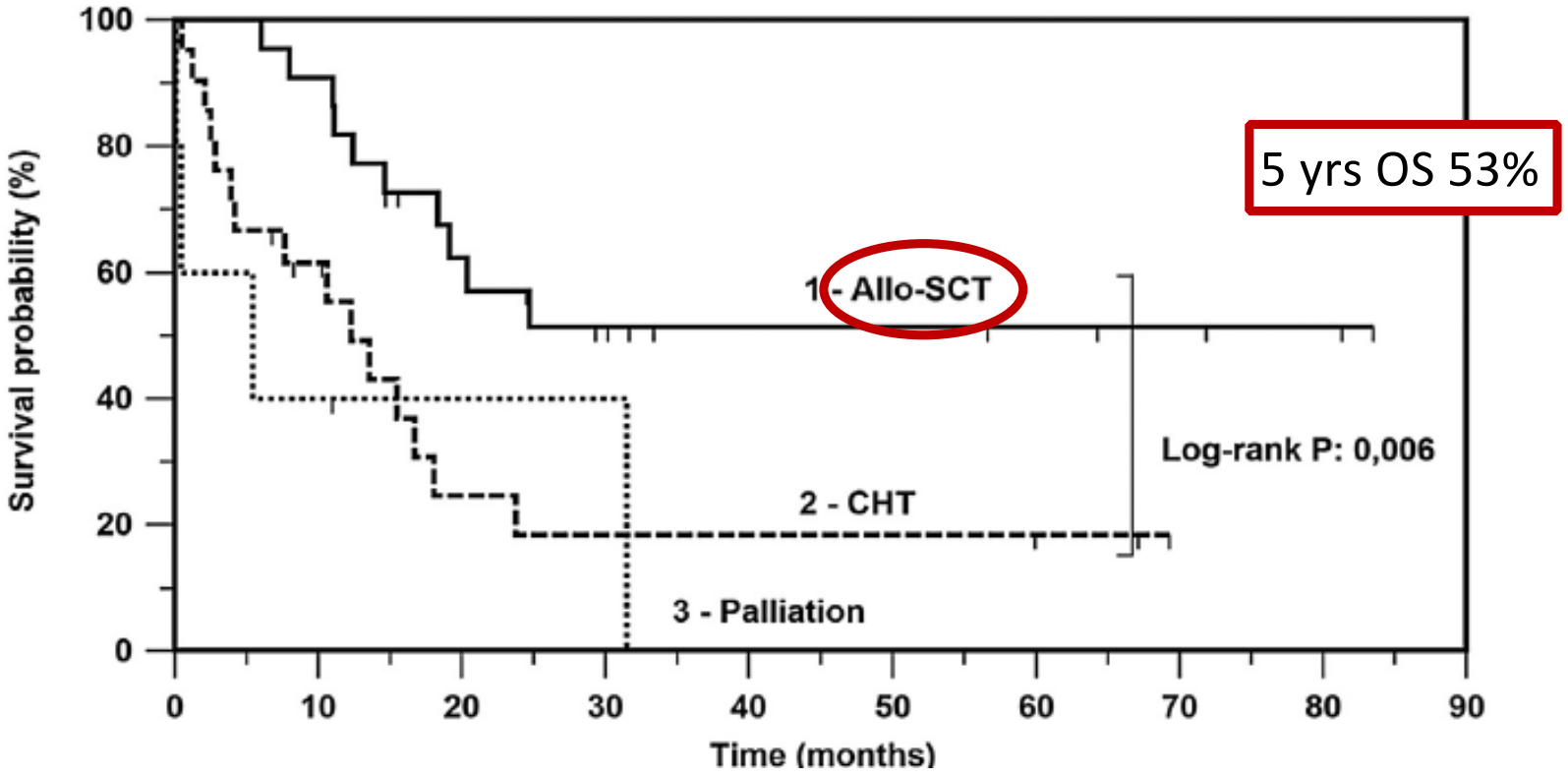


Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

- Intensively treated patients with or without allo SCT had a better OS (18 vs 5 months).



5 yrs OS 53%

Clinical outcome of MS in adult patient

Lazzarotto et al Leuk Res 53 (2017): 74-81

Treatment

Young age

Response to intensive chemo

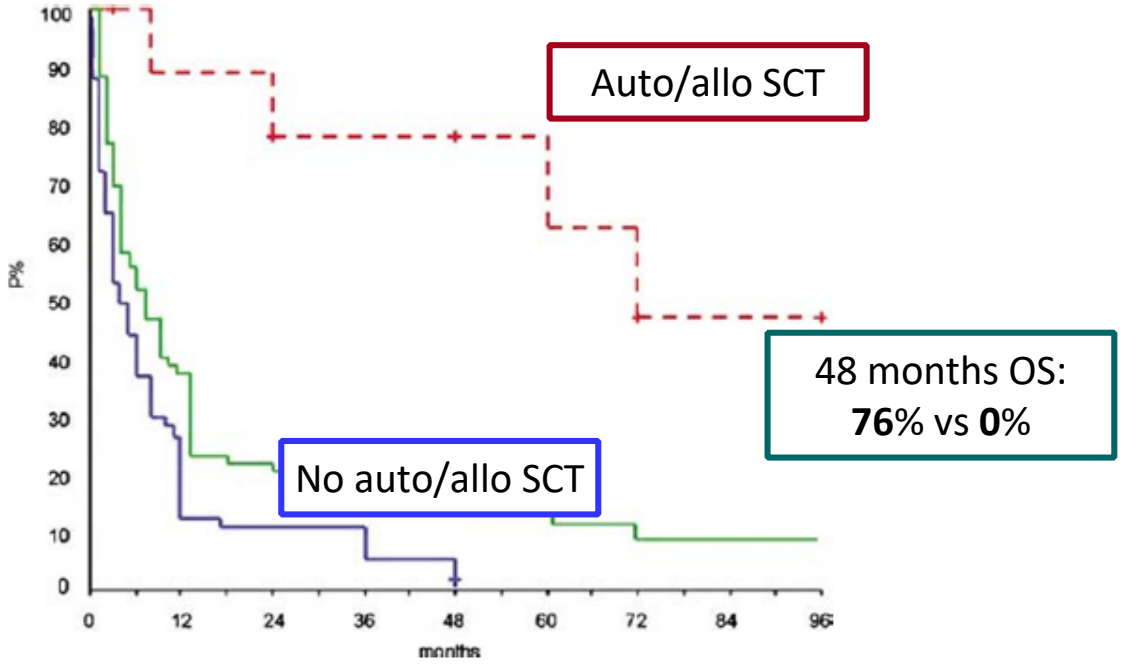
Multivariable analysis

Secondary AML-related MS

alloSCT

MS: clinico-pathologic, phenotypic and cytogenetics analysis of 92 adult patients Pileri S. et al. Leukemia 2007;21:340-350.

Treatment



	n=92
M/F	1.42/1
Median age (range)	55.8 (16-87)
Isolated MS (%)	**25** (27)
Sincronous MS (%)	**32** (35)
• AML	26
• MPD	1
• MDS	5
Antecedent hematological disease (%)	**35** (38)
• AML	12
• MPD	13
• MDS	1
• MS	9

67 patients with complete follow-up data. Median FU 150 months:

- **60** (89.5%) died for the disease (8/60 CR after 1^ line treatment)
- **7** (10.5%) alive in **CR** (100% CR after 1^ line treatment)
- 6/7 **alloSCT**

AlloSCT for isolated and leukemic MS

Chevallier P et al Haematologica 2011;96(9).

Treatment

- **Retrospective** study on **99** MS patients reported on EBMT registry between 01/1991 and 06/2009

	Isolated MS n=30 (%)	**Leukemic MS** n=69 (%)	
Median age	40 (18-69)	39 (18-69)	p=0.65
Median year of transplant	2005 (1991-2009)	2003 (1991-2009)	p=0.03
Cytogenetic			
Favorable	3 (21%)	13 (22%)	
Intermediate	9 (64%)	39 (65%)	p=0.36
High risk	2 (14%)	8 (13%)	
Missing data	16	9	
Status at transplant			
1^ CR	14 (47%)	38 (55%)	
2^ CR or beyond	7 (23%)	21 (30%)	
Advance disease	9 (30%)	10 (15%)	p=0.99
Primary refractory	5	5	
1^ relapse	4	5	

AlloSCT for isolated and leukemic MS

Chevallier P et al Haematologica 2011;96(9).

Treatment

Outcomes	Overall cohort n=99	Isolated myeloid sarcoma n=30	Leukemic myeloid sarcoma n=69	P*
5-year OS	48±6% Median: 39 months	33±13%	51%±7%	0.63
5-year LFS Overall	36±5% Median: 17 months	30±9%	37±6%	0.45
5-year CI of relapse	40±4%	45±10%	38±6%	0.64
5-year CI of NRM	19±4%	17±5%	19±7%	0.76

Similar outcome comparing isolated and leukemic myeloid sarcoma

Multivariate analysis:

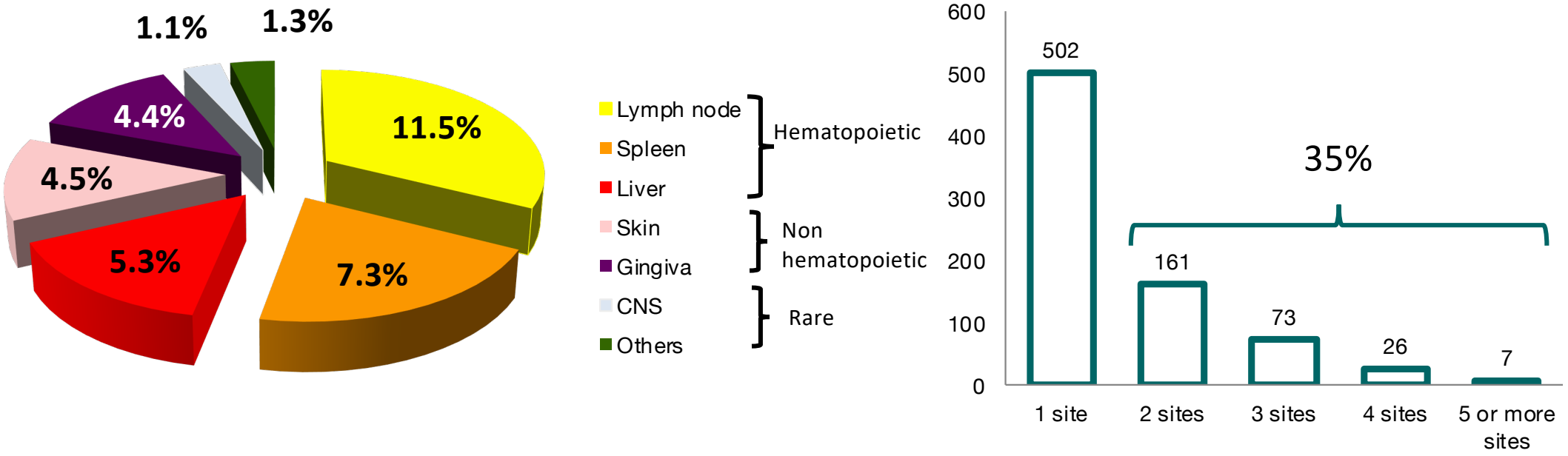
- **CR** status at transplant associated with **improved LFS**
- **High risk cytogenetics** associated with **reduced LFS**

Extramedullary disease in AML is common BUT lacks independent significance

Ganzel C. et al J Clin Oncol 2016;34(29):3544-3553

Treatment

- **Retrospective** study on **3522 newly diagnosed AML** patients (age > 15 yrs) evaluated from 1980 to 2008 in **11** ECOG-ACRIN clinical trials
- **Extramedullary** incidence **23.7**% (769/3240 enrolled patients)



Extramedullary disease in AML is common BUT lacks independent significance

Ganzel C. et al J Clin Oncol 2016;34(29):3544-3553

Treatment

	AML with EMD n=769 (%)	**AML without EMD** n=2472 (%)	
Median age (years)	**45.7**	**52.9**	p<0.001
Male Sex	445 (**57.9**)	1284 (**52**)	p=0.006
PS ECOG 0-1	585 (**76.4**)	2108 (**86**)	P<0.001
WBC count (median/µL)	**41.6**/µL	**10.2**/µL	P<0.001
FAB M4/M5 (%)	**39/15.9**	**26/6.8**	P<0.001
CR rate (%)	**59**	**60**	p=ns
alloSCT	93 (**14.7**)	353 (**18**)	p=0.07

Extramedullary disease in AML is common BUT lacks independent significance

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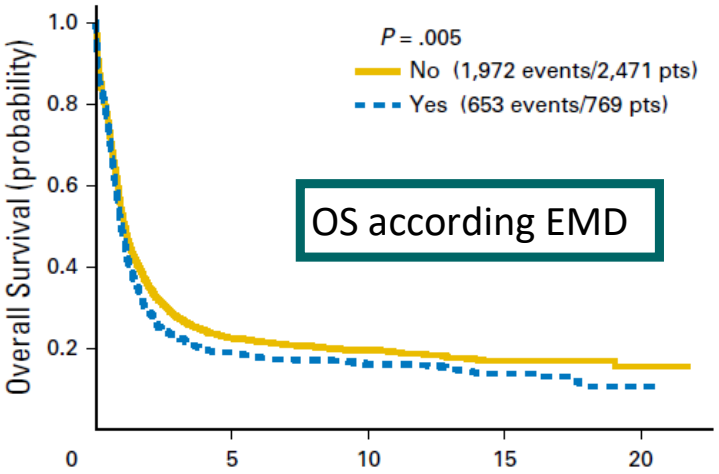
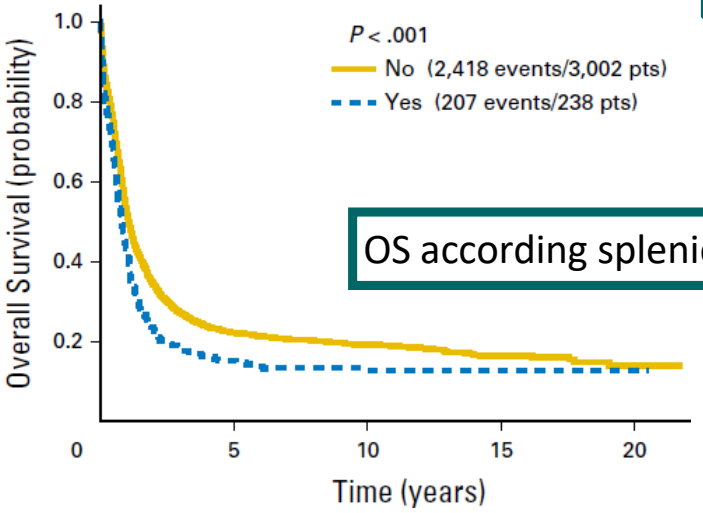
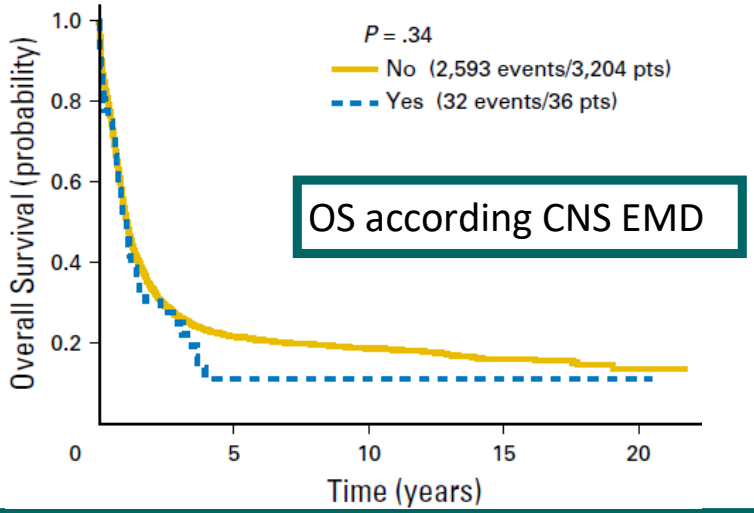
Treatment



OS according EMD



OS according splenic EMD



OS according CNS EMD

Univariable analysis:

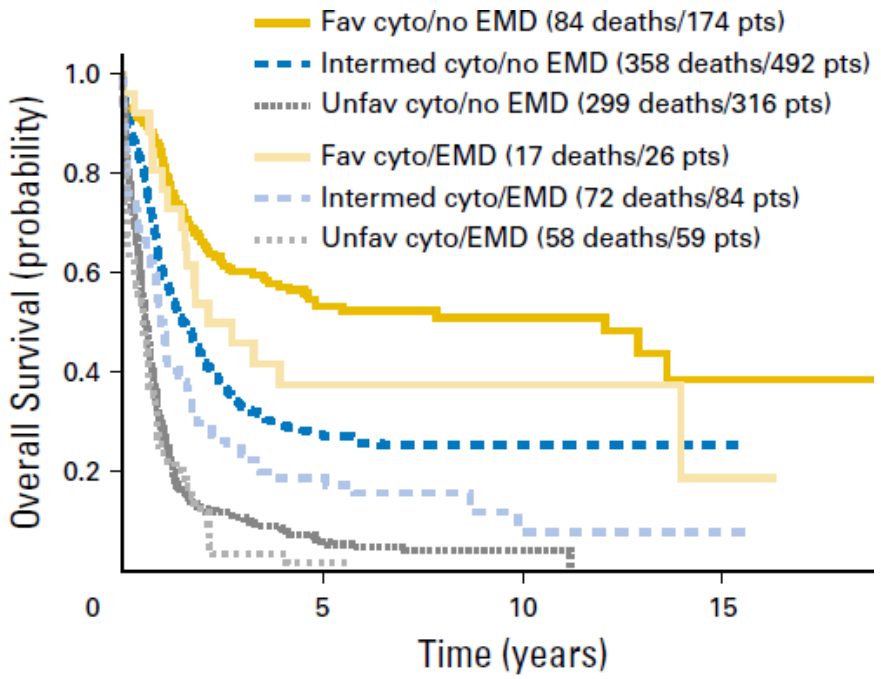
- **EMD** associated with a shorter OS
- **Skin** (p=0.002), **spleen** (p<0.001) and **liver** (p<0.001) BUT NOT CNS (p=0.34), nodal and gingival involvement associated with **shorter OS**

Extramedullary disease in AML is common BUT lacks independent significance

Ganzel C. et al J Clin Oncol 2016;34(29):3544-3553

Treatment

- **Multivariable analysis**: factors associated with **shorter OS**
  - Earlier year of registration
  - Older age
  - High WBC count
  - Low PLTs count
  - Worse PS
  - High risk cytogenetic status
  - No CR



- **Favorable cytogenetic risk**: median OS **32.9** (with EMD) versus **94.2** months (without EMD)

Extramedullary disease in AML is common BUT lacks independent significance

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Treatment

- **Multivariable analysis**: factors associated with **shorter OS**
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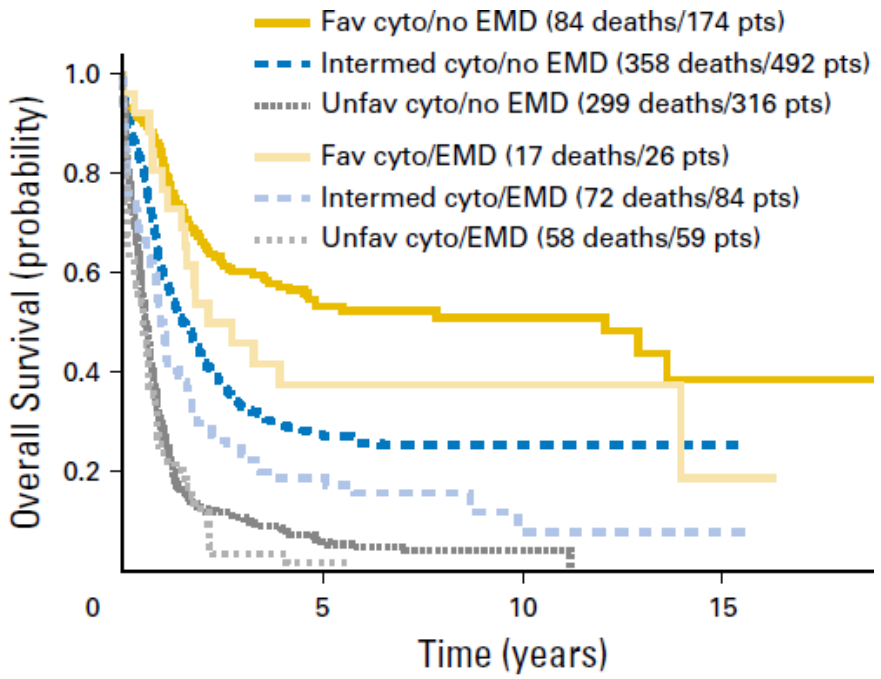


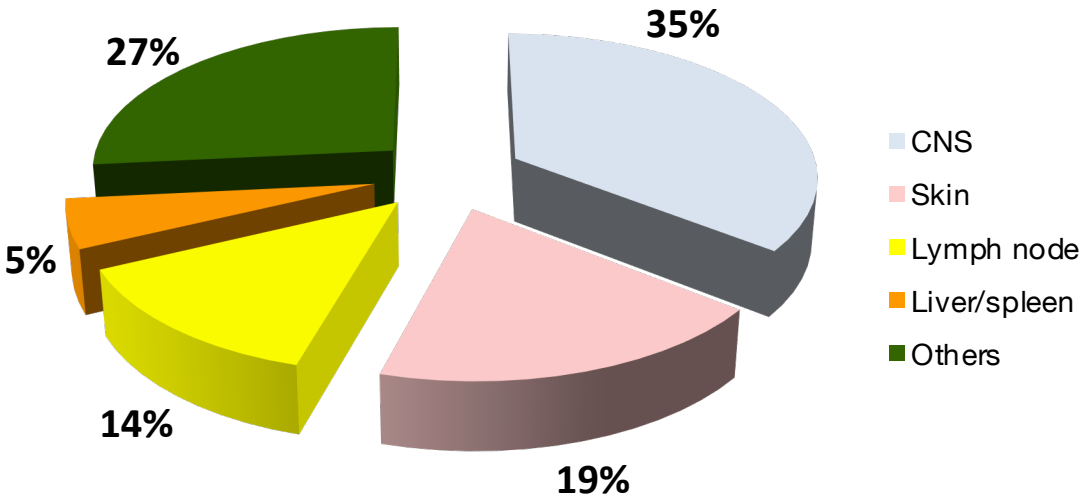
- **Favorable cytogenetic risk**: median OS **32.9** (with EMD) versus **94.2** months (without EMD)

Allo SCT for AML: no impact of pre-transplant extramedullary disease

Goyal S.D. et al . Bone Marrow Transplant. 2015;50(8):1057-1062

Treatment

- **Observational retrospective** study by CIBMTR on **9797 AML** patients (age 18-70 yrs) undergone alloSCT from 1995 to 2010 in 310 reporting center and 44 different countries
- **814** with EMD prior to SCT **(EMD group)**
- **8983** without EMD prior to SCT (no EMD group)



Allo SCT for AML: no impact of pre-transplant extramedullary disease

Goyal S.D. et al . Bone Marrow Transplant. 2015;50(8):1057-1062

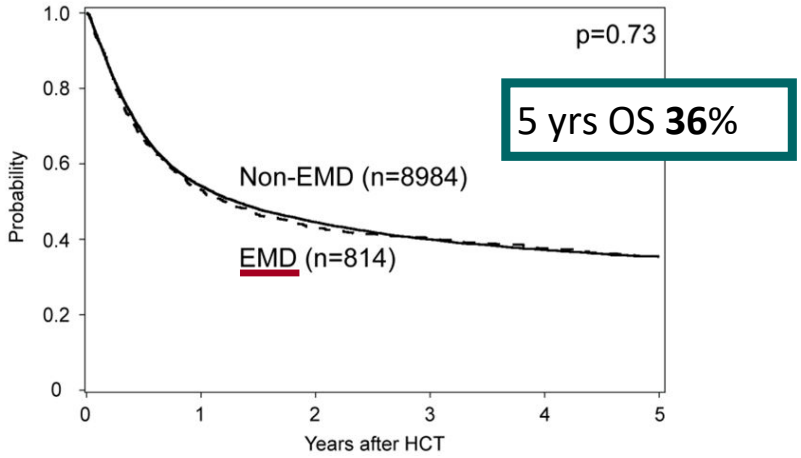
Treatment

	AML with EMD n=814 (%)	**AML without EMD** n=8983 (%)	
Median age (years)	**42**	**46**	p<0.001
WBC count (median/µL)	**22**/µL	**9**/µL	P<0.001
FAB M4/M5 (%)	**46**	**29**	P<0.001
Disease status at transplant			
Primary induction failure	**12**	**15**	
1^ CR	**37**	**49**	P<0.001
2^ CR or more	**26**	**20**	
Active relapse	**24**	**17**	
Duration of 1^CR in CR2 alloSCT	**9** months	**11** months	P<0.001
1^ CR < 6 months	32	19	
MAC/plus TBI	82/47	75/35	P<0.001

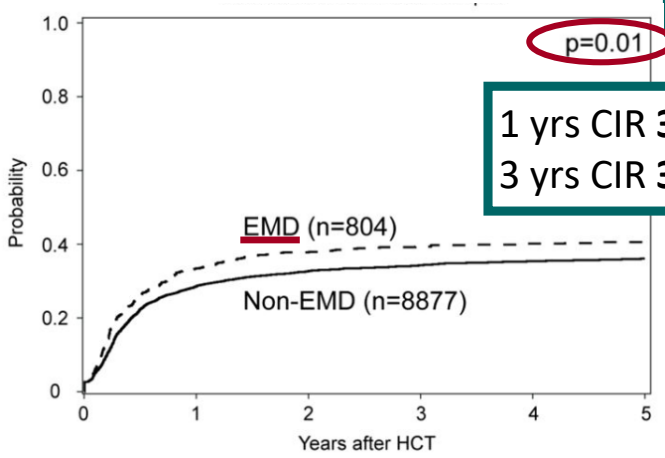
Allo SCT for AML: no impact of pre-transplant extramedullary disease

Goyal S.D. et al . Bone Marrow Transplant. 2015;50(8):1057-1062

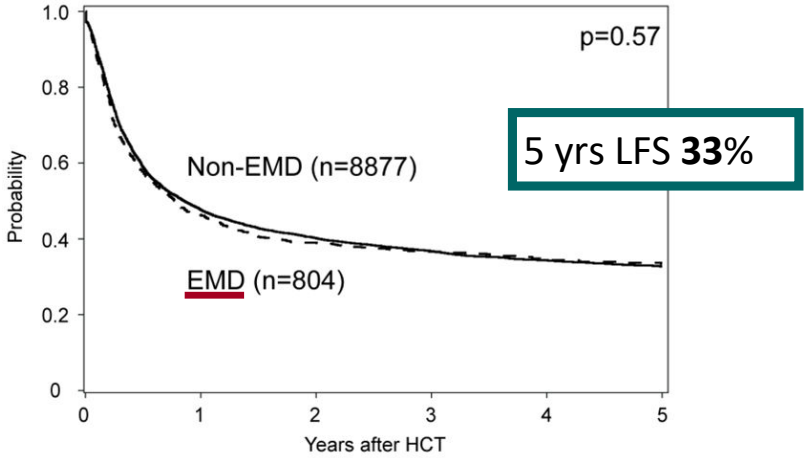
Treatment



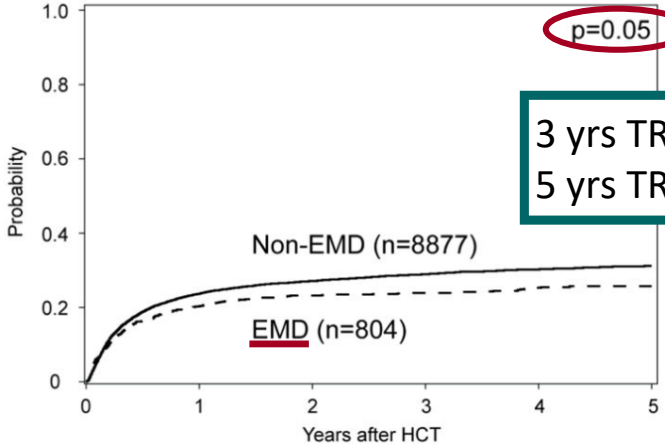
5 yrs OS **36**%



1 yrs CIR **33**% vs **29**%
3 yrs CIR **39**% vs **34**%



5 yrs LFS **33**%

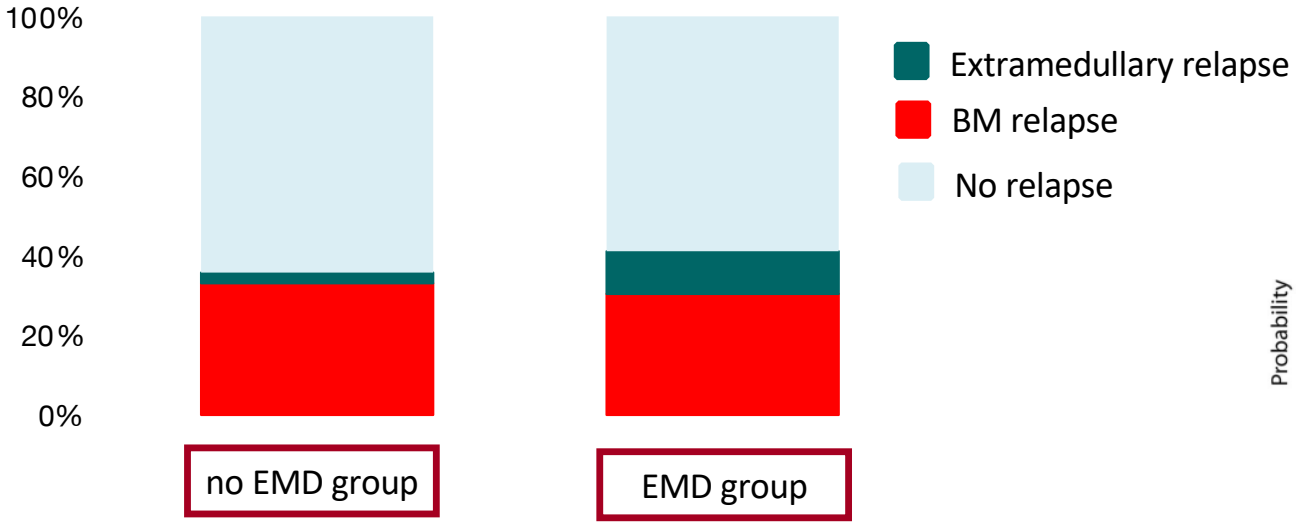


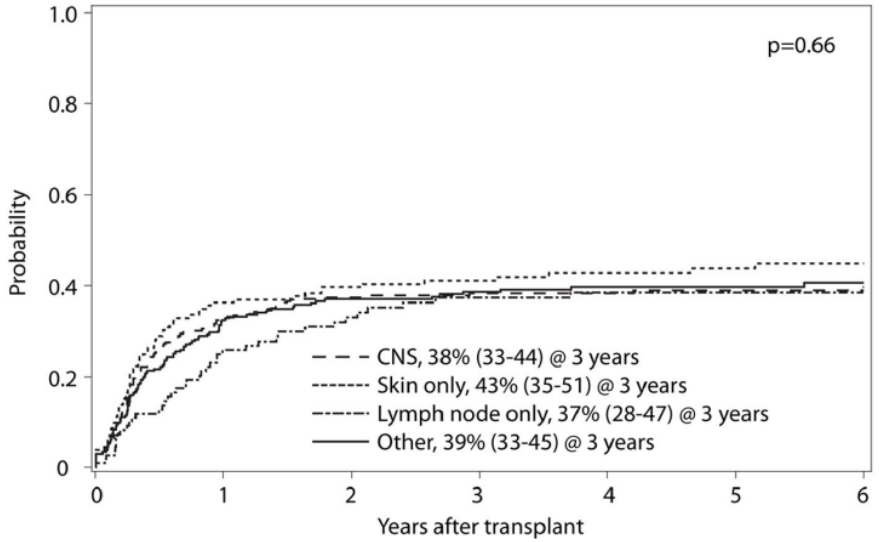
3 yrs TRM **24**% vs **29**%
5 yrs TRM **26**% vs **31**%

Allo SCT for AML: no impact of pre-transplant extramedullary disease

Goyal S.D. et al . Bone Marrow Transplant. 2015;50(8):1057-1062

Treatment





No significant differences in the rate of relapse or OS based on by site of EMD

Multivariate analysis:

- **EMD** did **not affect** neither **OS** nor **LFS**
- **TRM** and **RR failed** to retain their significance

Radiation in extramedullary leukemia: Guidelines from the ILROG

Bakst R. L. et al. Int J Radiation Oncol Biol Phys. 2018- 102(2):314-319.

Treatment

- Isolated MS with **inadeguate response** to chemotherapy
- **Isolated relapse** after allo-SCT
- **Palliation** of symptomatic vital structure compression
- Low-dose RT regimen (24 Gy in 12 fractions) not preclude TBI

Take home message

- Myeloid sarcoma is a **systemic disease** even if isolated
- **AML type chemotherapy** is the standard of care
- **Post remission** therapy **controversial** (alloSCT according to risk profile)
- Large **prospective trials** and better **biologic disease characterization** are needed to identify the **best therapeutic approach** hopefully with target therapy

Aknowledgement

Prof. Michele Cavo

Dr. Antonio Curti
Dr.ssa Cristina Papayannidis
Dr.ssa Sarah Parisi
Dr.ssa Chiara Sartor
Dr. Giovanni Marconi
Dr. Jacopo Nanni
Dr. Gianluca Cristiano

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