Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

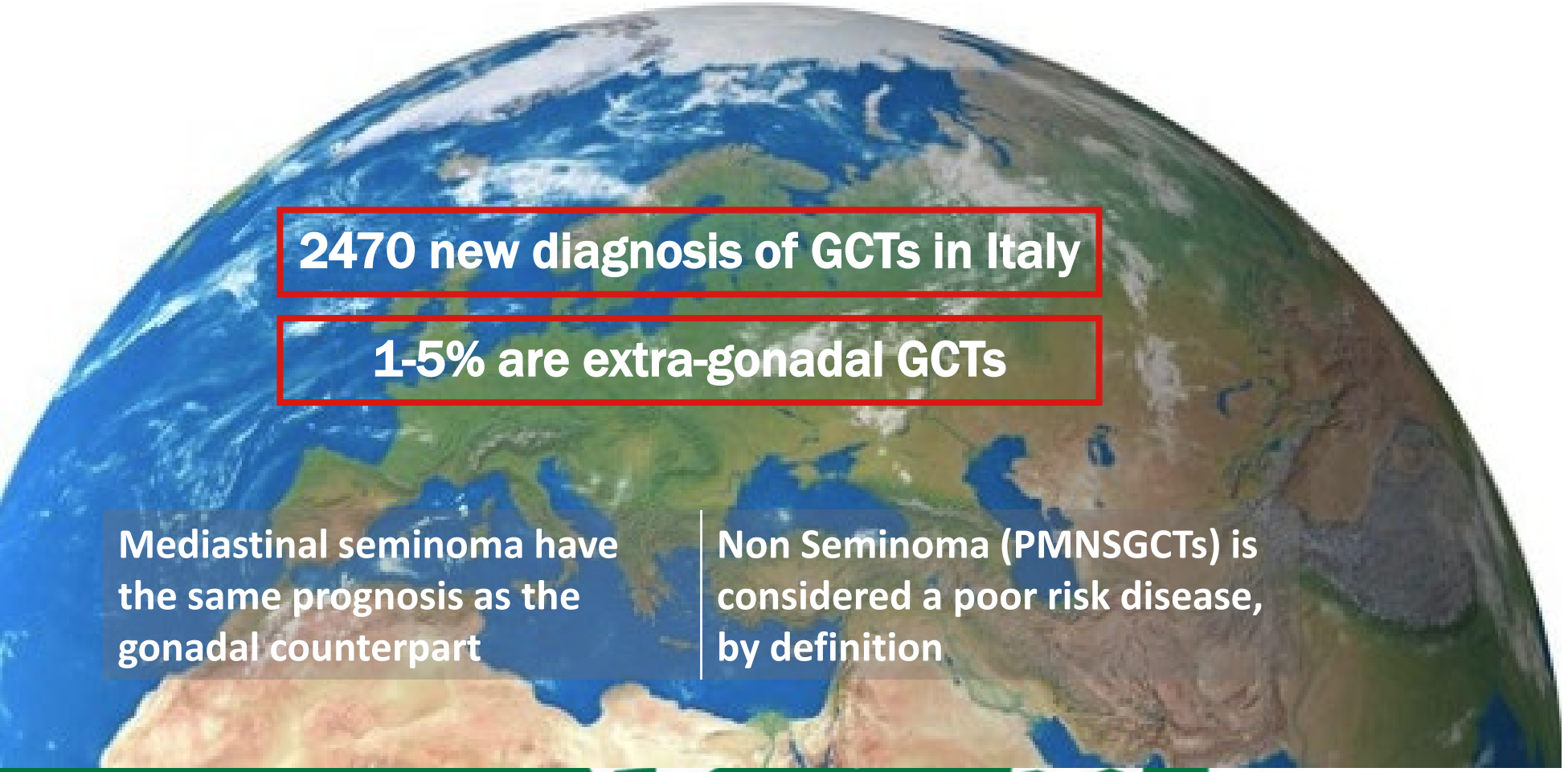
20/11/2024

Simona Secondino

I tumori extragonadici

Germ cell tumors (GCTs)

2022



2470 new diagnosis of GCTs in Italy

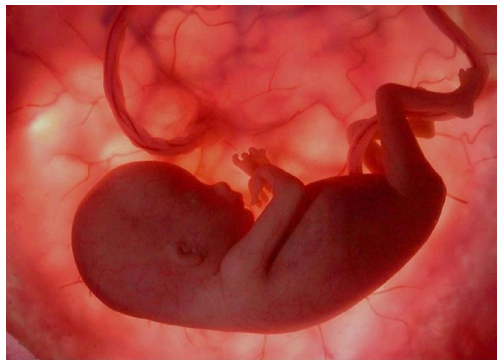
1-5% are extra-gonadal GCTs

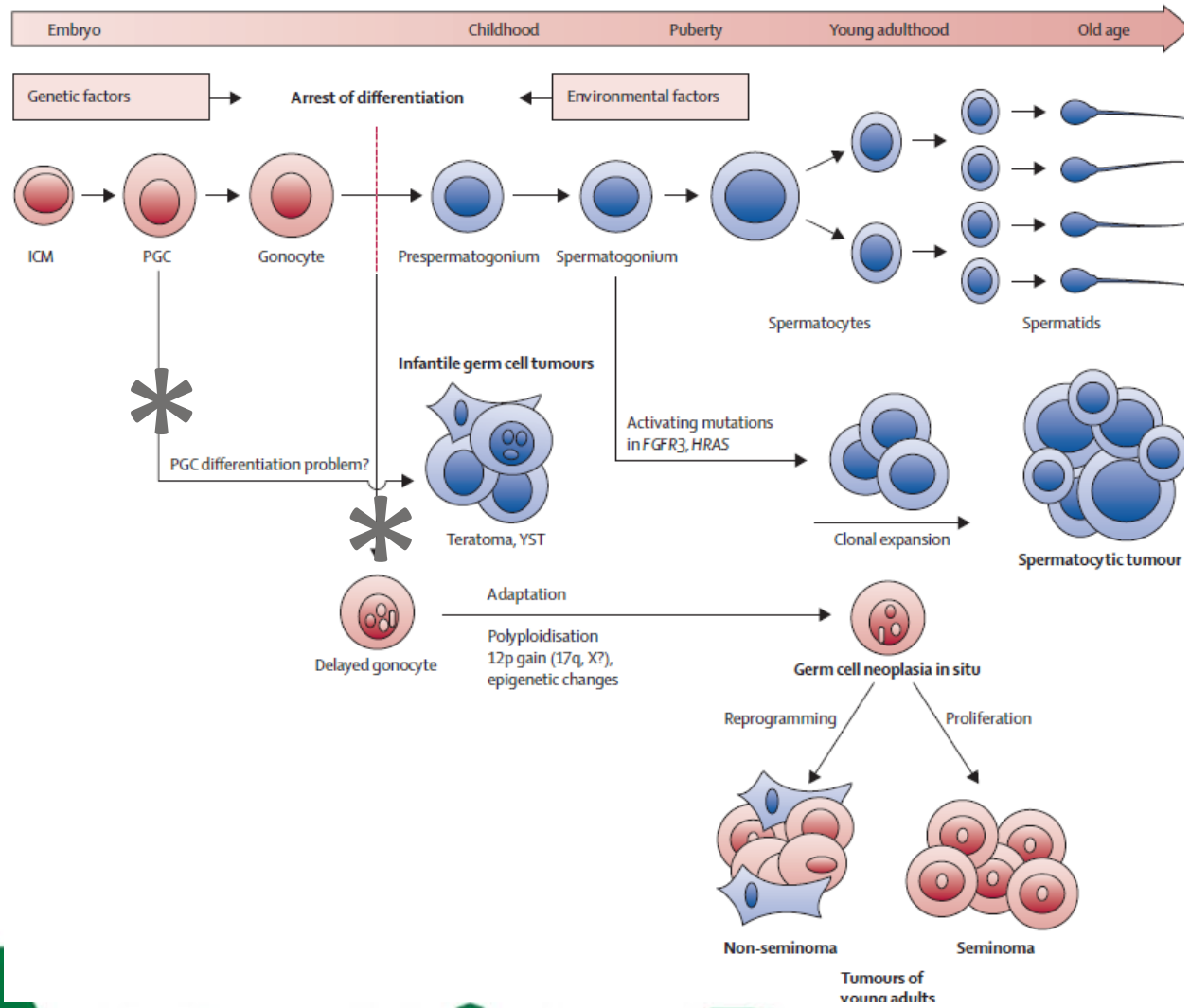
Mediastinal seminoma have the same prognosis as the gonadal counterpart

Non Seminoma (PMNSGCTs) is considered a poor risk disease, by definition

AIOM guidelines, 2024

The origin…





Ruipert-De Meyts, Lancet 2015

How they look like…

Extra-gonadal GCTs:
1-5% of all GCTs

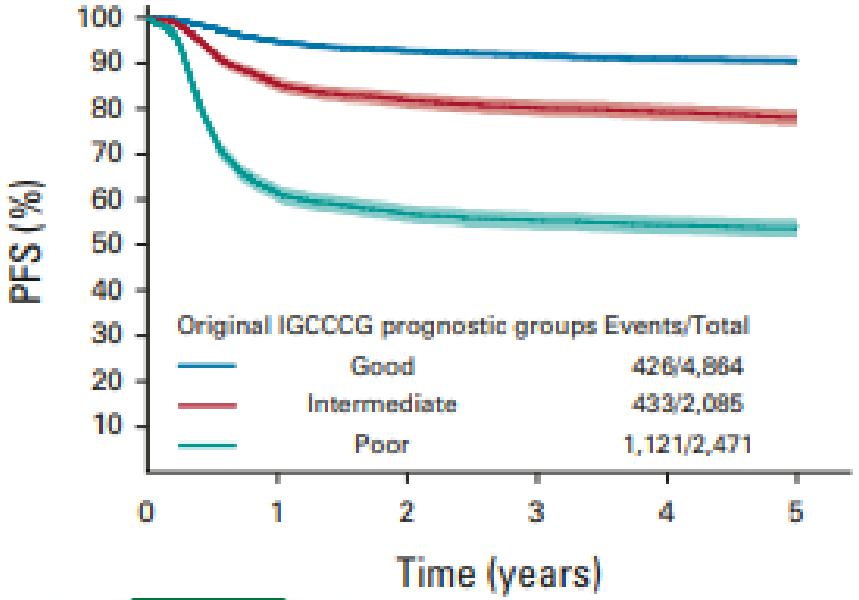
Among extra-gonadal GCTs:

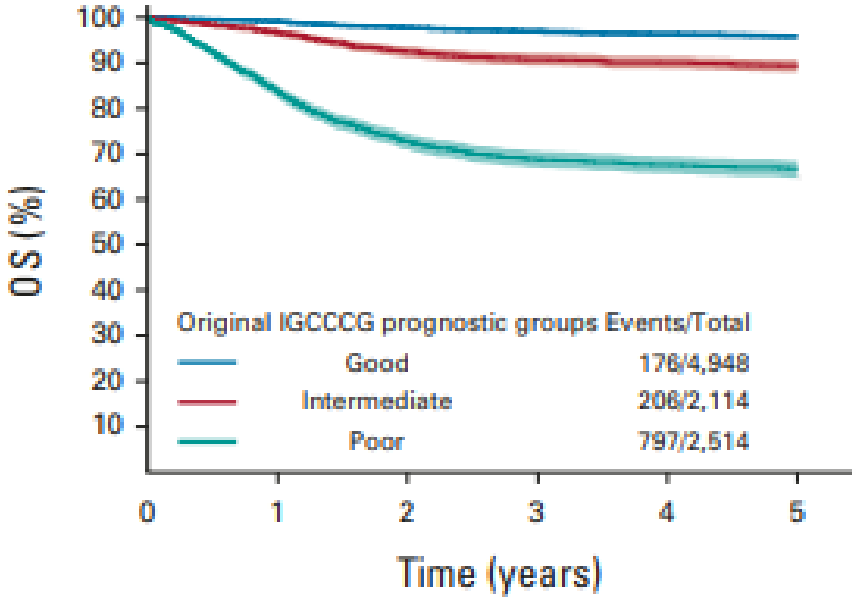
- **60-70%** are PMGCT
- **30%** are RP (if any…)
- **5%** are pineal GCT

Rosti G, Sem Oncol 2019

...same origin same story?

Original IGCCCG Prognostic Groups	Original IGCCCG Survival Estimates (1997)		Updated Estimates Based on Patients With Nonseminoma With Prechemotherapy IGCCCG Prognostic Groups Available	
	5-Year PFS (95% CI)	5-Year OS (95% CI)	5-Year PFS (95% CI)	5-Year OS (95% CI)
Good	89 (87 to 91)	92 (90 to 94)	90 (89 to 91)	96 (95 to 96)
Intermediate	75 (71 to 79)	80 (76 to 84)	78 (76 to 80)	89 (88 to 91)
Poor	41 (35 to 47)	48 (42 to 54)	54 (52 to 56)	67 (65 to 69)

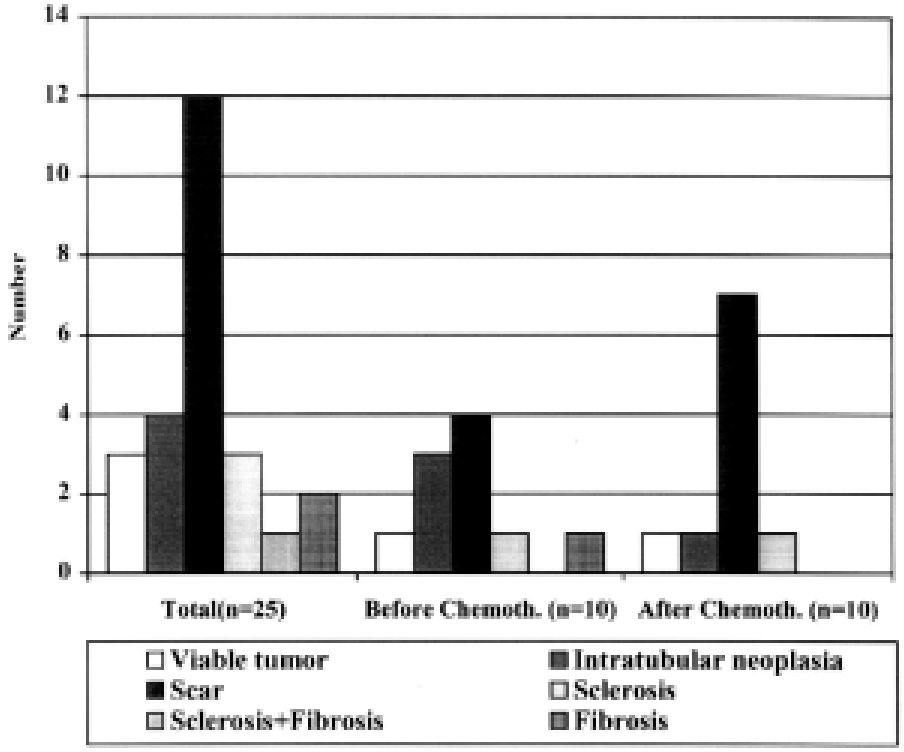




Gillessen, J Clin Oncol 2021

Retroperitoneum...=testis?

N=26



Hystopathological findings	N (%)
Scar tissue	12 (46,1%)
Sclerosis	3 (11,5%)
Fibrosis	2 (7,6%)
Fibrosis + scleroris	1 (3,8%)
GIN	4 (15,3%)
Viable cells	3 (11,5%)
Tot	25 (96%)

Scholz, Ann Oncol 2002

PMNSGCTs versus testis

Main GA subgroups	Genes altered	PMNSGCT[a]	Sem	NS	*p* value[b]
Total no.		44	22	86	
TP53 pathway	*TP53, MDM2*	36 (81.8%)	1 (4.5%)	17 (19.8%)	<.0001
RAS-RAF pathway	*KRAS, NRAS, HRAS, BRAF*	20 (45.4%)	13 (59.1%)	44 (51.2%)	.581
Cell-cycle pathway	*CCND1/2/3, CDK4/6, CDKN2A/B, RB1*	10 (22.7%)	12 (54.5%)	48 (55.8%)	.0004
RTK pathway	*ERBB2, PDGFRA, KIT, MET, FGFR1/2/3*	3 (6.8%)	6 (27.3%)	6 (6.9%)	>.99
PI3K pathway	*PIK3CA, MTOR, PTEN, AKT1/2*	19 (43.2%)	6 (27.3%)	6 (6.9%)	<.0001
DDR pathway	*BRCA1/2, ATM, CHEK2, MUTYH*	1 (2.3%)	3 (13.6%)	12 (13.9%)	.060
GA per tumor, mean (SD)		4.0 (2.5)	2.9 (2.6)	4.0 (2.7)	>.99
MSI-high		0	0	1 (1.2)	>.99
Median TMB, mut/Mb (range)		2.4 (0–55.7)	1.8 (0–6.3)	2.7 (0–23.4)	>.99
TMB ≥10–20 mut/Mb		3 (6.8)	0	3 (3.5)	>.99
TMB ≥20 mut/Mb		2 (4.5)	0	1 (1.2)	>.99

Necchi, Oncologist 2019

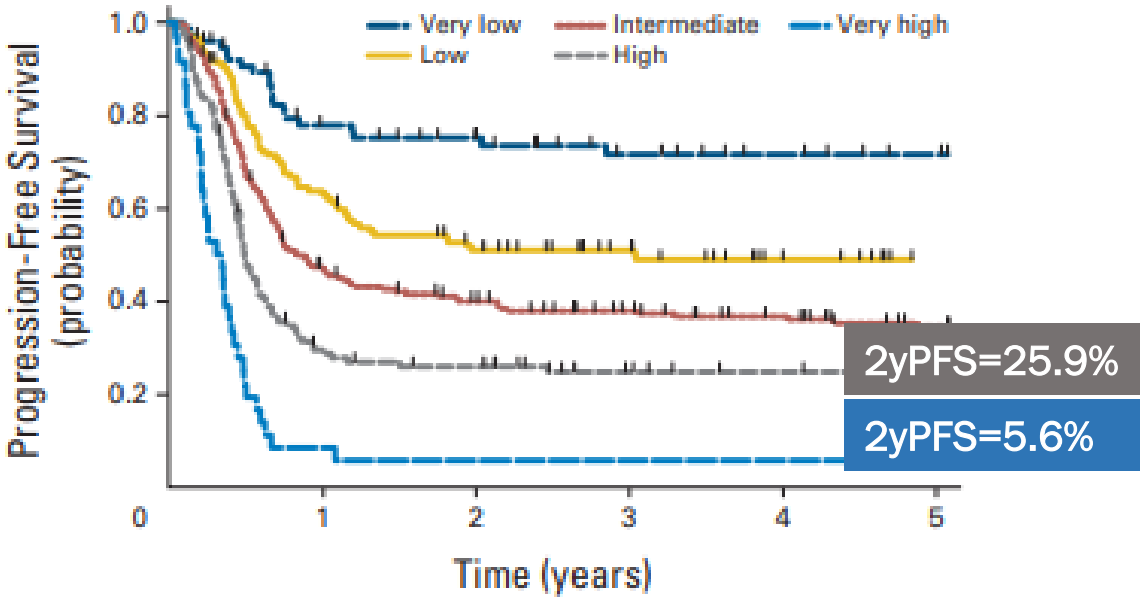
IPFSG Risk Classification

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

Parameter	Score Points 0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm−	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
HCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3					
Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

Abbreviations: CR, complete remission; PRm−, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

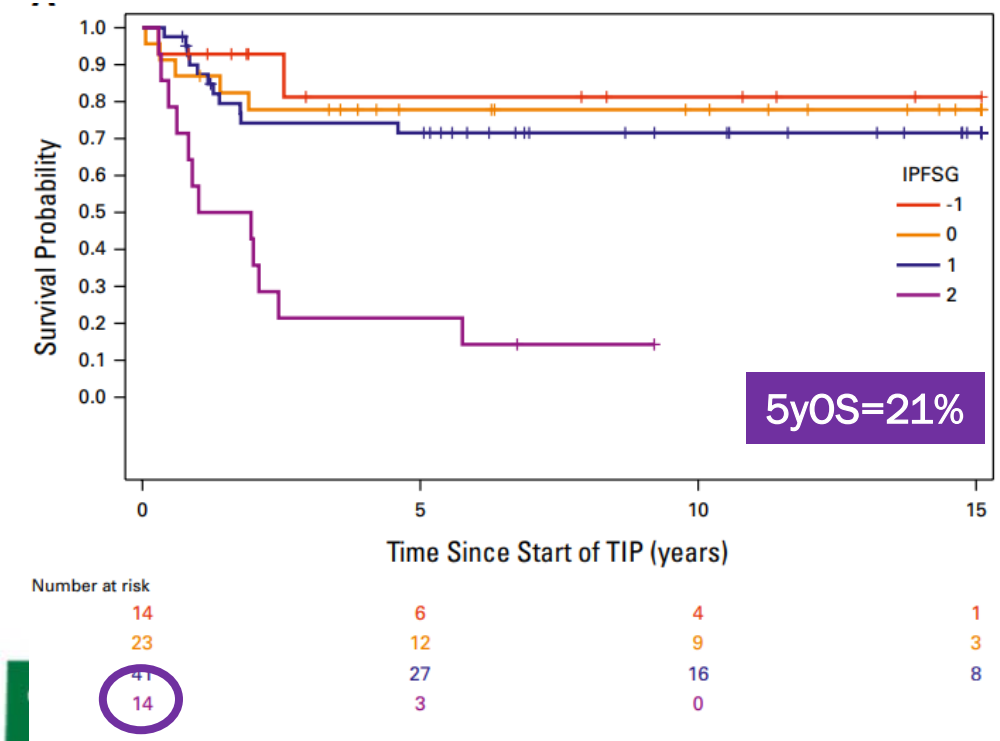
N=1980



The International Prognostic Factors Study Group, J Clin Oncol 2010

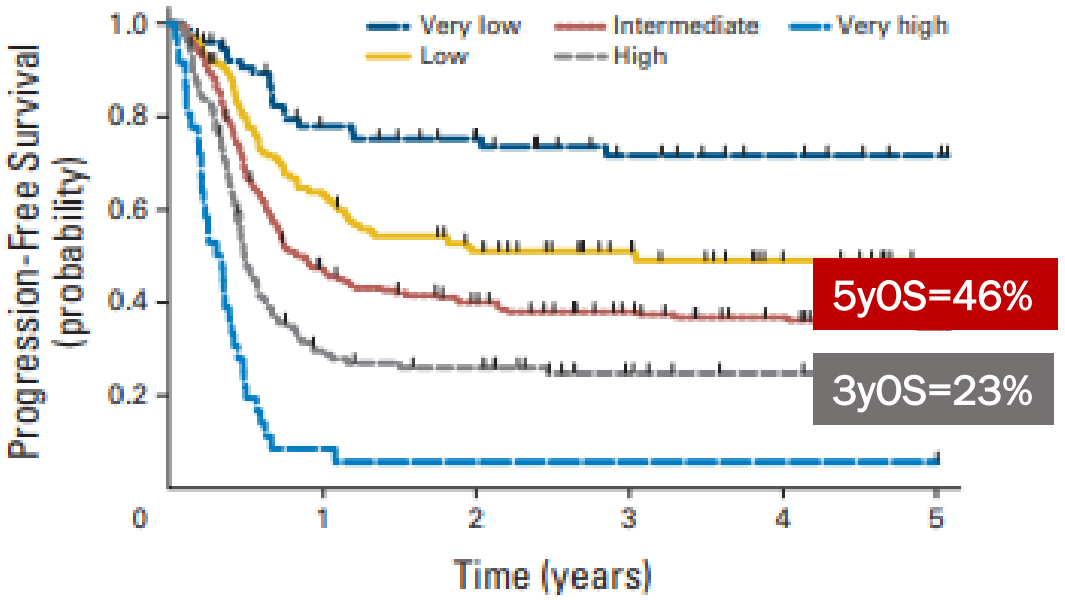
Have we ameliorate our results?

N=104 2^line TIP Series 1994-2019



5y0S=73,3%

5y0S=21%



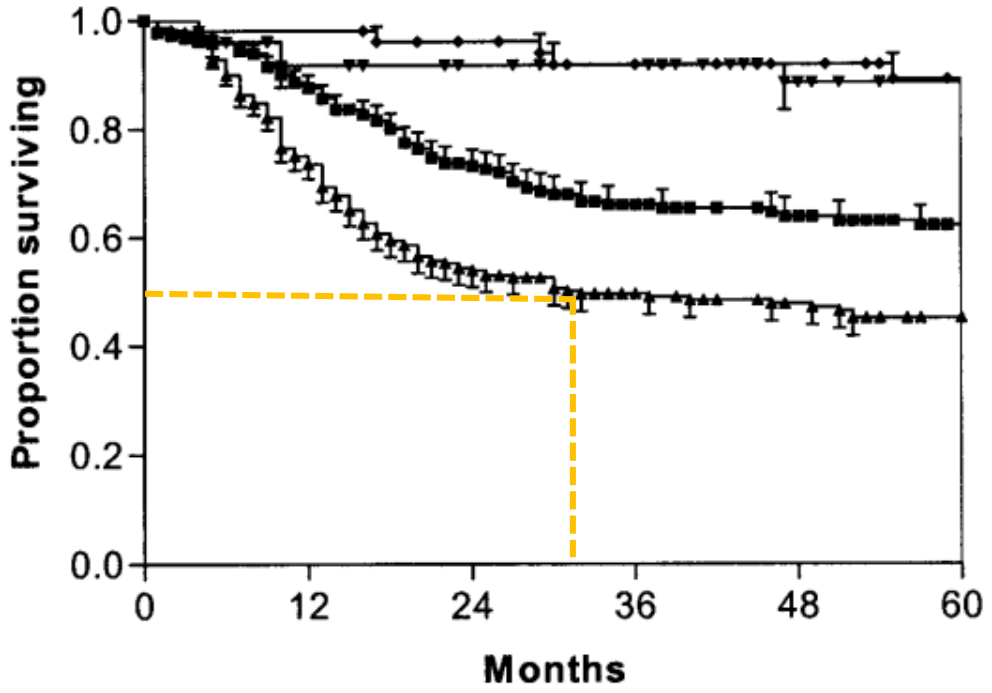
5y0S=46%

3y0S=23%

Gleeson, J Clin Oncol 2024

… and PMGCTs?

N=524 (285 PNSMGCTs) Series 1975-1996 Outcome in patients with extra-gonadal CGTs



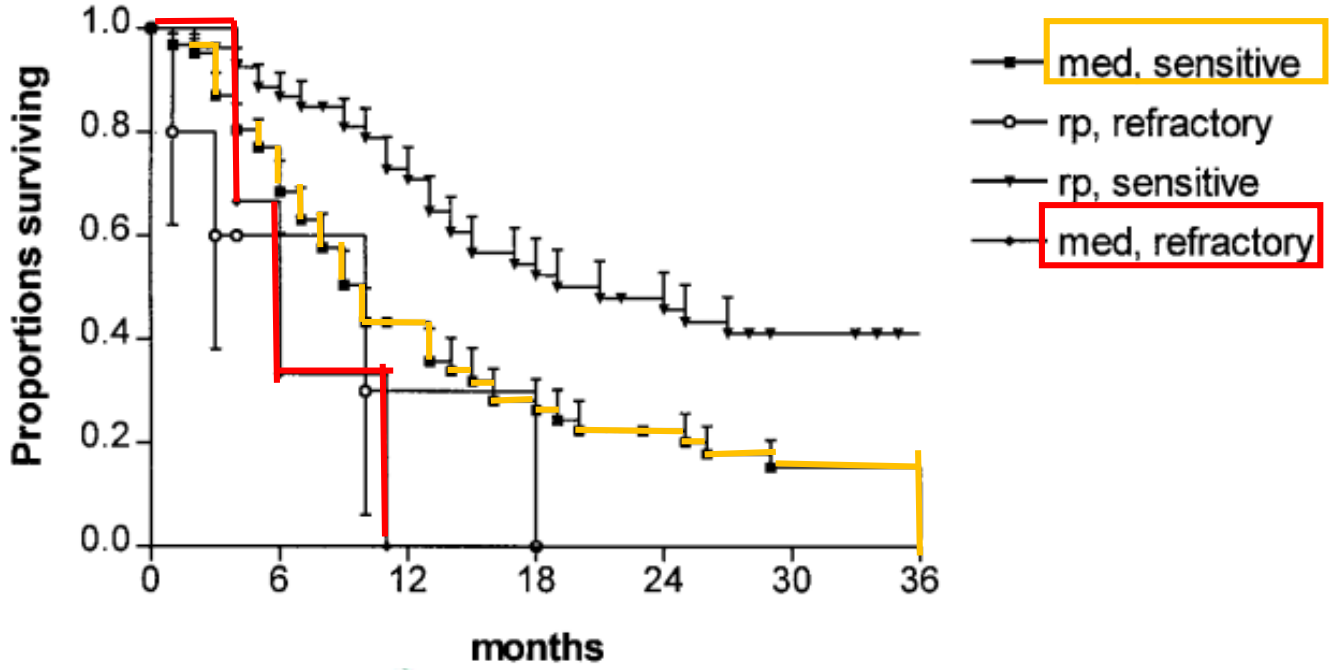
5y-PFS= 44%

5y-OS= 45%

Hartmann, Ann Oncol 2002

… and relapsed PMGCTs?

N=142 (79 PMGCTs) Series 1975-1996 Outcome in patients with relapsed extra-gonadal CGTs



Median survival (months):

10 months

6 months

Table 4. Type of Second-Line Chemotherapy and Outcome (N = 142)

	No. of Patients	%
Second-line chemotherapy regimen		
Cisplatin + ifosfamide ± other	43	30
Cisplatin + etoposide or vinblastine ± other	29	20
Cisplatin + paclitaxel ± other	3	2
High-dose carboplatin + etoposide ± ifosfamide or cyclophosphamide with ABMT	48	34
Other regimen	19	13
Current status		
No evidence of disease	27	19
Alive with disease	12	9
Dead of disease	92	65
Treatment-related death	8	6
Lost to follow up	3	2

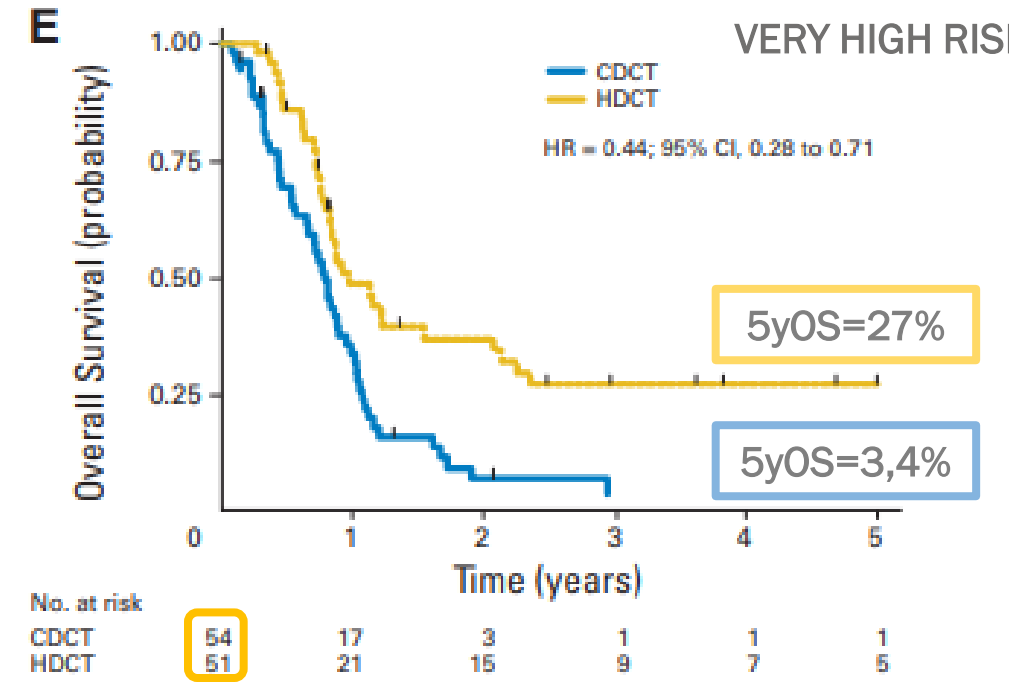
Abbreviation: ABMT, autologous bone marrow transplant.

Hartmann, J Clin Oncol 2001

… and relapsed PMGCTs in the alpha-gen?

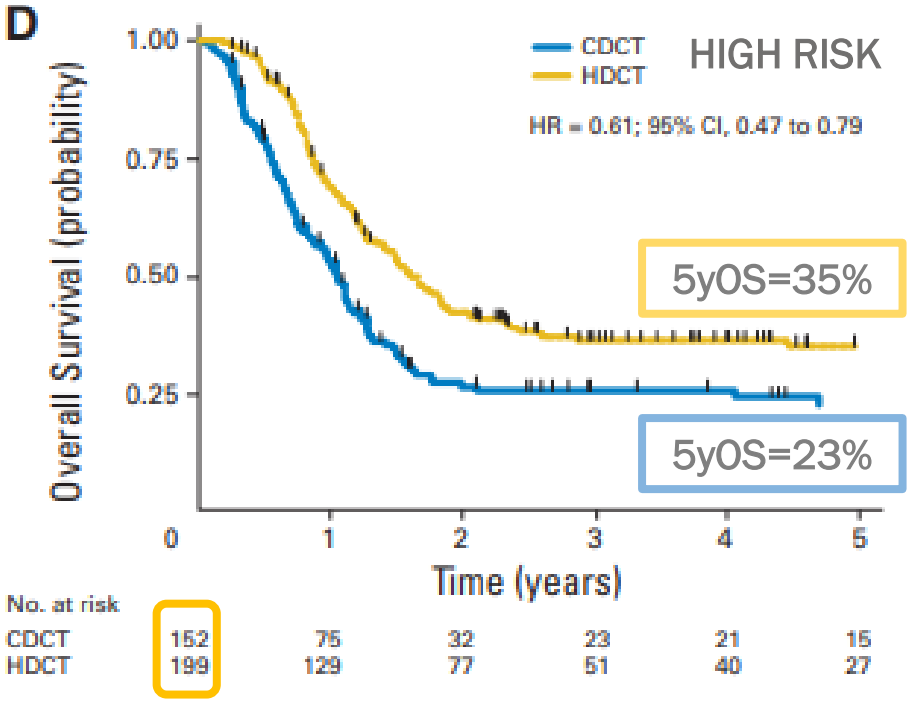
N=1435 (71 PMGCTs)

Outcome in patients with relapsed GCTs (CDCT versus HDCT)



N=105

N=351



Lorch, J Clin Oncol 2011

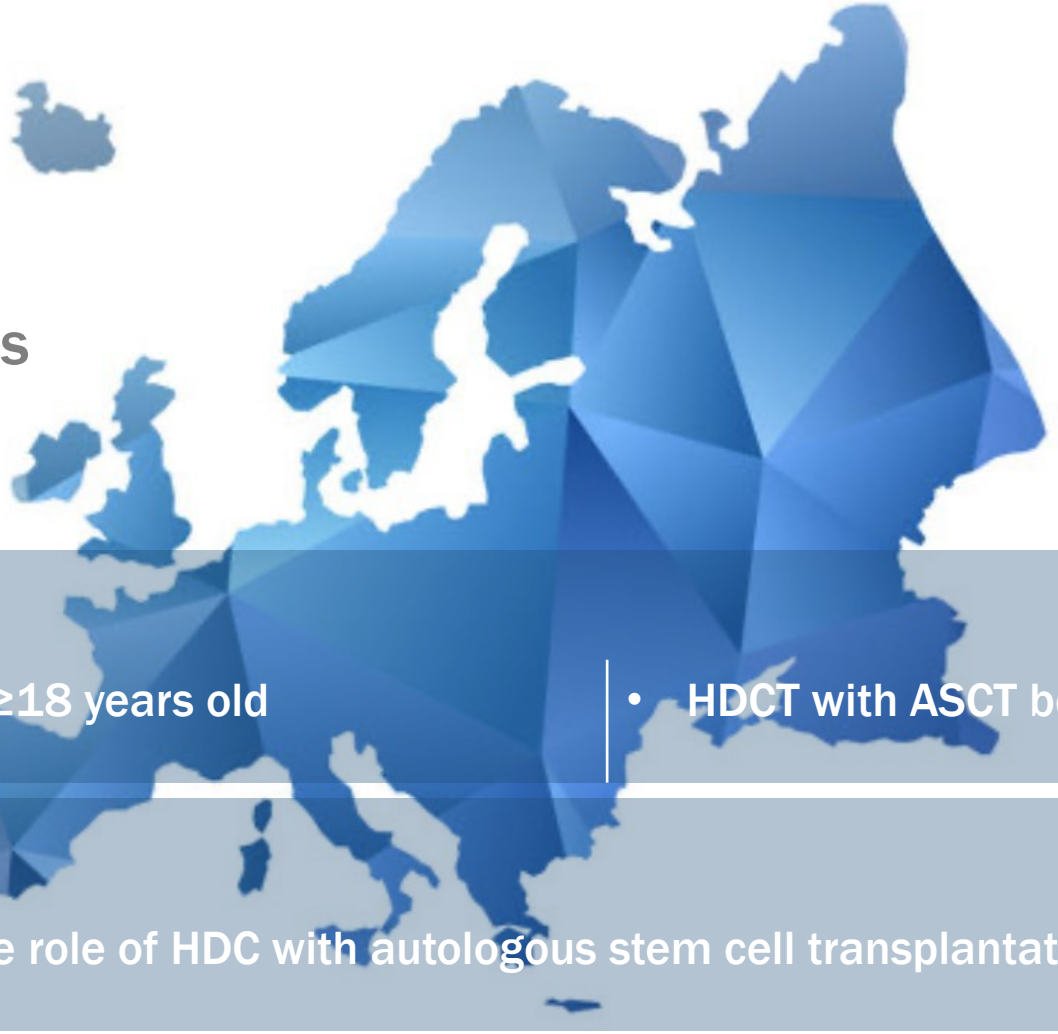
...considering only PMNSGCTs treated with HDCT

References	N	Trial	Treatment	Outcomes
Bokemeyer *(Br J Cancer 2003)*	28	P	Upfront-line sequential HD VIP vs CDCT	Absolute improvement of 15-20% of 2y-PFS and 2y-OS
Pico *(Ann Oncol 2005)*	25	P	Salvage therapy CDCT vs HDCT	No differences in OS
Hartmann *(J Clin Oncol 2001)*	79	R	Second-line CDCT vs HDCT	OS=12% No difference
De Giorgi *(Ann Oncol 2005)*	22	R	Second-line HDCT (one course)	3y-OS=14%
Adra (J Clin Oncol 2016)	20	R	Second, third-line or later HDCT (2 cycles)	2y-PFS=22%
Feldman *(J Clin Oncol 2010)*	21	P	First or subsequent line HDCT	Long-term DFS=24%
Richardson *(Cancer 2024)*	32	R	Second or third-line HDCT (2 cycles)	2y-PFS=31% 2y-OS=35%

Our experience…

PMNSGCTs=69

19 Centers
9 European Coutries



Inclusion criteria

- Male
- ≥18 years old
- HDCT with ASCT between 2000-2018

Aim of the study

- To better characterize the role of HDC with autologous stem cell transplantation in PMNSGCTs

Our experience…

Characteristics of 69 patients

Characteristics	N=69
Age (years)	
Median	31
Range	19-71
Disease extension, *n* (%)	
Metastatic disease	42(63.6)
Locally advanced	24 (36.4)
Unknown	3
Prognosis risk, *n* (%)	
Poor	69 (100)
Time to relapse (months)	
Median	4.5
Range	<1-24.7

… continued	
Standard therapy before HDC, *n* (%)	
TIP	11 (47.8)
Gem-TIP	1 (4.3)
VIP	6 (26)
Other	5 (21.7)
Missing data	46
Status at tranplant, *n* (%)	
CR	9 (14.5)
PR	26 (37.6)
SD	4 (6.5)
PD	23 (33.3)
Missing data, *n*	7

56%

Secondino, ESMO Open 2024

Our experience…

Treatment Characteristics

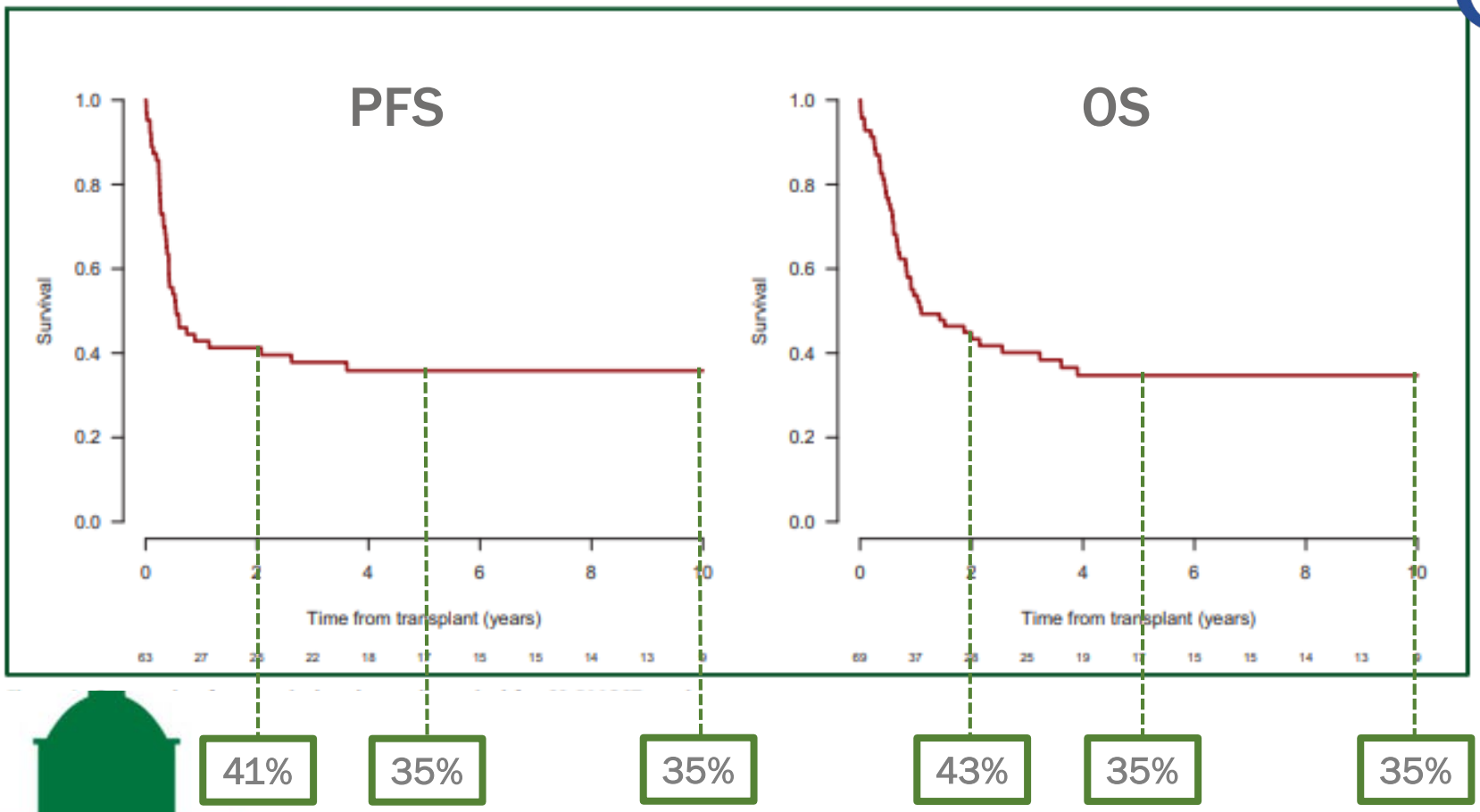
Characteristics	N=69
Mobilization regimen, *n* (%)	
Chemotherapy + G-CSF	63 (94)
G-CSF only	4 (6)
Missing	2
Preparative regimen, *n* (%)	
Carboplatin – Etoposide	37 (53.6)
Paclitaxel-containing	11 (15.9)
ICE	8 (11.6)
VIP	7 (10.2)
Other	6 (8.7)
HDC, *n* (%)	
Upfront	24 (34.8)
First relapse	23 (33.3)
Second relapse	15 (21.7)
Third relapse	6 (8.7)
Fourth relapse	1 (1.4)

… continued	
Number of tranplant, *n* (%)	
One	3 (4.4)
Two	37 (53.6)
Three	29 (42)
Outcomes after HDC, *n* (%)	
Complete remission	21 (35.6)
Partial remission	15 (25.4)
Never responsing	23 (39)
Missing	10
Surgery after HDC, *n* (%)	
Complete	17 (24.6)
Incomplete	3 (4.3)

65%

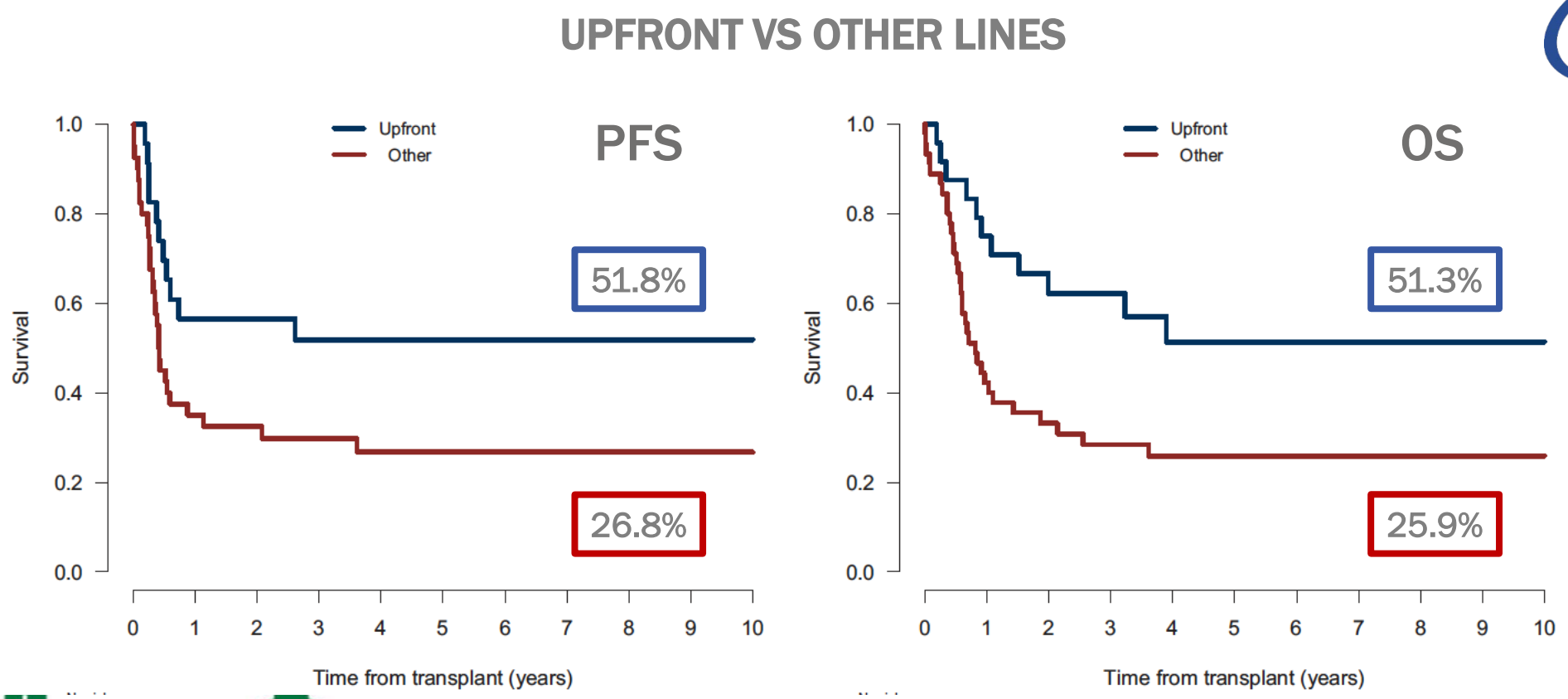
Secondino, ESMO Open 2024

Our experience: results



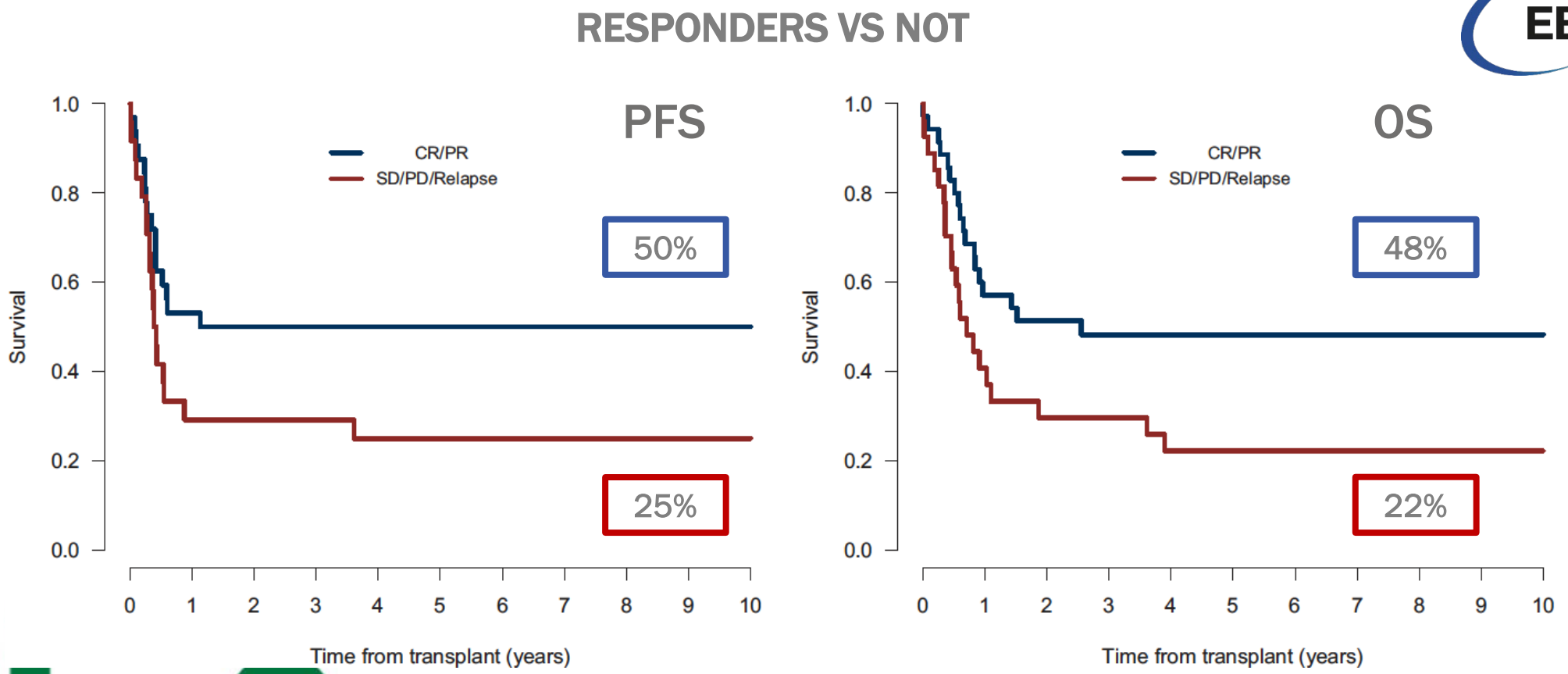
Secondino, ESMO Open 2024

Our experience: results



Secondino, ESMO Open 2024

Our experience: results



Secondino, ESMO Open 2024

Conclusions (1)

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Secondino *(Esmo Open 2024)*	69	R	Up-front and subsquent-line HDCT (2-3 cycles)	TRM in 3 patients (4.3%) No secondary malignancies

PMNSGCTs in the future…

Largest series in this setting

Long term follow-up capable to identify cure rates

Our results suggest that HDC with ASCT may well represent a **therapeutic option** in PMNSGCTs

PMNSGCTs are a **different disease**, with **different biological** pattern and different behaviour

Patients with advanced disease (preferably at first diagnosis) should be referred for treatment decisions wherever possible to **experienced centers**

Much effort to better know this disease, is warrant