2014-2-18 字型：+ - 發言 列印 轉寄

骨髓移植失敗...40歲女成70歲嬤

〔記者王英傑、鄭淑婷／桃園報導〕桃園縣四十歲未婚陳姓美容師，原本皮膚白皙光滑且有雙水汪汪的大眼睛，前年她因「後天性再生不良性貧血症」，在林口長庚醫院接受造血幹細胞移植，術後卻發生排斥，全身皮膚潰爛，兩年內變成貌似七十歲老婦！


陳女幹細胞移植後產生排斥，從熟女變阿嬤。（記者王英傑攝）

陳女怨醫師沒說明後遺症

陳女說，她三年前被診斷出罹患後天性再生不良性貧血症，在林口長庚醫院血液科就診，主治醫生王博南在一年內為她進行兩次手術。第一次是免疫球蛋白及環孢靈聯合免疫抑制療法。術後半年，王博南表示手術失敗，得進行造血幹細胞移植手術，「不做就是等死！」一○一年七月與胞妹骨髓配對成功後，進行了移植手術。


陳女接受移植前，皮膚白皙。（記者王英傑翻攝）

陳女說，她曾詢問移植手術的後遺症如何？王博南「輕描淡寫」地說，四肢皮膚會變不好，指甲會亂長，未提及全身皮膚嚴重潰爛等可能狀況。

陳女昨天由桃園縣議員劉茂群陪同召開記者會哭訴：「出門還被叫阿嬤，希望有人可以救救我，變回原來的樣貌。」陳女說，連骨頭也因疼痛幾乎無法行走，沒辦法正常洗澡，實在很後悔聽信醫生的話做

Incidence, Risk factors, Outcomes of Sclerosis in patients with Chronic GVHD

Inamoto Y, Storer BE, Petersdorf EW, Nelson JL, Lee SJ, Carpenter PA, Sandmaier BM, Hansen JA, Martin PJ, Flowers MED,

《Blood 2013; 121:5098-5103》

Fred Hutchinson
Cancer research center **Seatlle, Washington**
1975

北榮內科部 血液腫瘤科
Supervisor: VS 楊慕華
Presenter: R4 王浩元

Sclerosis in chronic GVHD

- **Sclerotic skin manifestations of chronic GVHD**

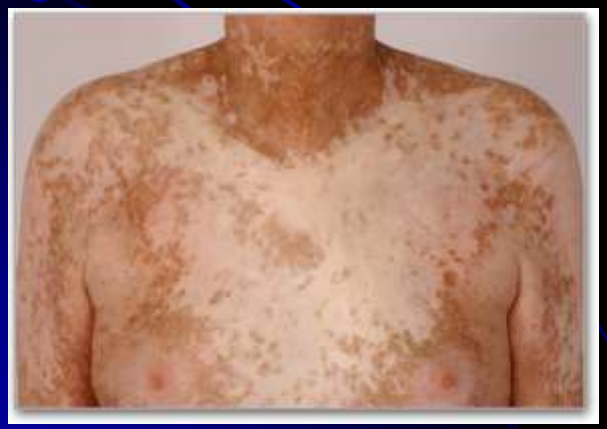
	Sclerotic cGVHD	Systemic sclerosis
Visceral organ involvement	Rare	Frequent
Vasculopathy	Rare	Frequent
Skin involvement	Superficial→deeper	Deeper→superficial

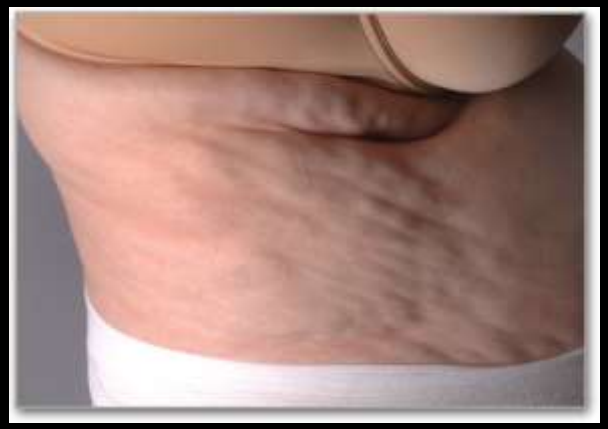
Sclerosis in chronic GVHD

- [Ann Intern Med. **1977**;87(6):703-706]
- NIH consensus for cGVHD: Diagnosis
  [Biol Blood Marrow Transplant. **2005**;11(12):945-956]

Sclerotic features

smooth, waxy, indurated skin (thickened or tight skin), caused by deep & diffuse sclerosis over a wide area





Sclerosis in chronic GVHD

- Sclerodermatous chronic GVHD.
  Analysis of **7** cases
  [J Am Acad Dermatol. **1992**;26(1):49-55]

- Sclerodermatous GVHD:
  clinical & pathological study of **17** patients
  [Arch Dermatol. **2002**;138(7):924-934]

- Sclerodermatous chronic GVHD after allogeneic hematopoietic stem cell transplantation (**14** cases): incidence, predictors and outcome
  [Haematologica. **2006**;91(2):258-261]

Sclerosis in chronic GVHD

- Incidence: **13%** in cGVHD
- A late manifestation of cGVHD,
  with a mean onset **> 1 year after transplantation**
- NOT an acute life-threatening manifestation,
  but lead to **functional disability & morbidity**
- Skin ulceration & poor wound healing → **infection**
- **Poor** response to topical interventions,
  often **recalcitrant** to systemic therapy

Sclerotic-type chronic GVHD of the skin: clinical risk factors, lab markers, burden of disease

Blood. 2011;118(15):4250-4257

- **NIH cGVHD Natural History cohort**
- **206** patients, mostly **severe** & **refractory**
  (63% "severe“) (median Tx = 4)
- **Single-visit**, cross-sectional design
- ScGVHD: **109 (52.9%)** of 206 patients
- ScGVHD associated with
  - **greater PLT** (P<0.001)
  - **greater C3** (P<0.001)
  - **decreased FVC** (P=0.013)
- Risk factors: **TBI (RIC)** **(14/15 patients, P < 0.0001)**
- Widespread BSA involvement:
  functional impairment & **poorer survival (P=0.015)**

Aim of study

cGVHD under systemic immunosuppression:

1. **O**verall **incidence** of sclerosis
2. **Risk factors** of sclerosis
3. **Transplant** outcomes [with vs without sclerosis]

Methods

Inclusion:

- After 1st allogeneic HCT
- Initiate systemic Tx for cGVHD

2000/05
|
2009/12

Exclusion:

- Double cord blood transplantation
- Recurrent malignancy before cGVHD

Sclerotic cGVHD:

- Medical record
  - Cutaneous sclerosis
  - Fasciitis
  - Joint contracture

Primary endpoint:

- Development of sclerosis in cGVHD

Secondary endpoint:

For chronic GVHD「with」vs「without」sclerosis

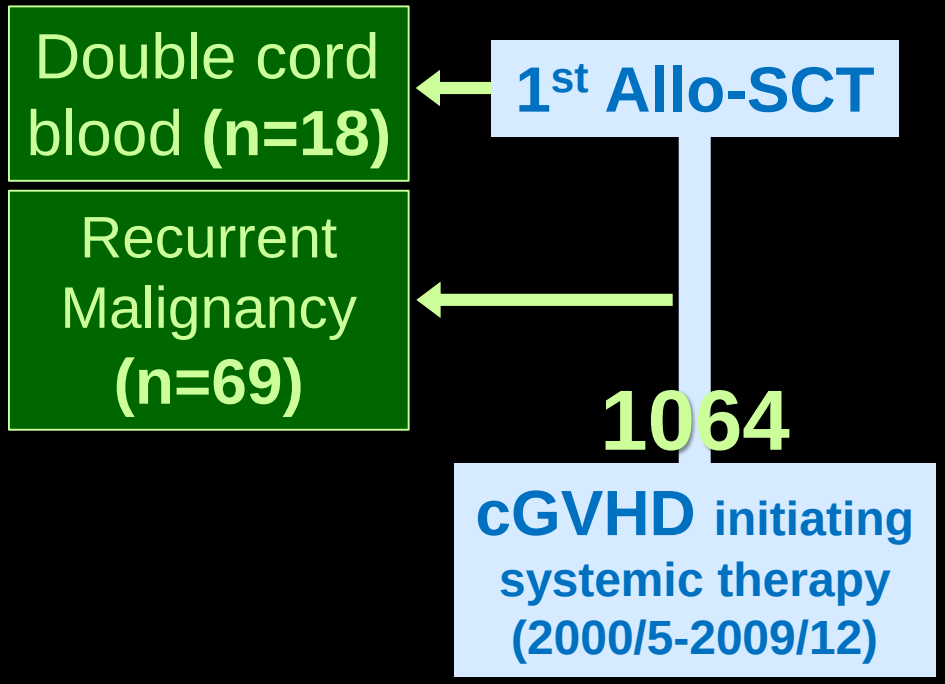
- Overall mortality
- Non-relapse mortality
- Recurrent malignancy
- End of systemic immunosuppressive Tx

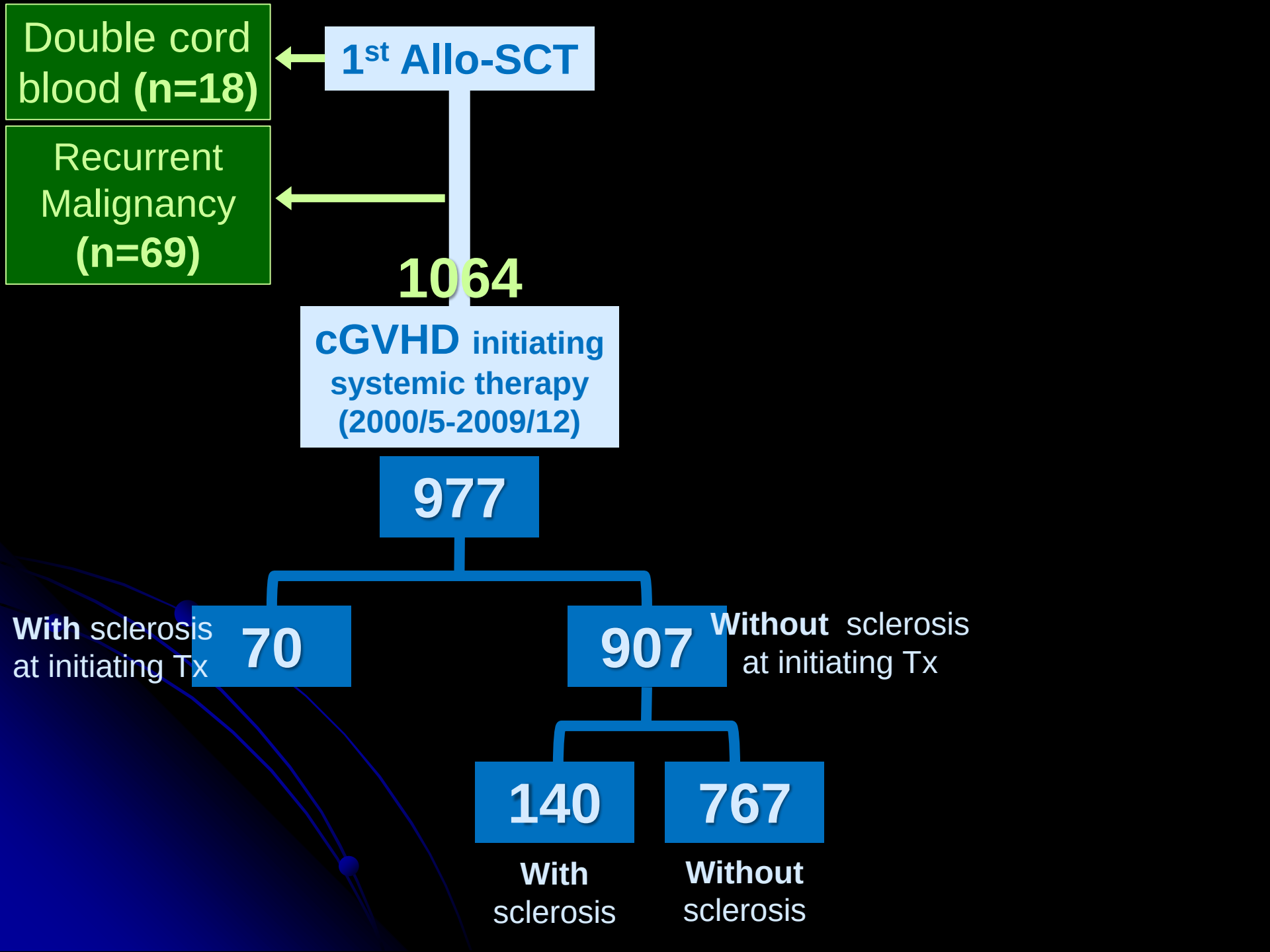
Results

1st Allo-SCT

1064

cGVHD initiating systemic therapy (2000/5-2009/12)


Double cord blood (n=18)
1st Allo-SCT
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)


Double cord blood (n=18)
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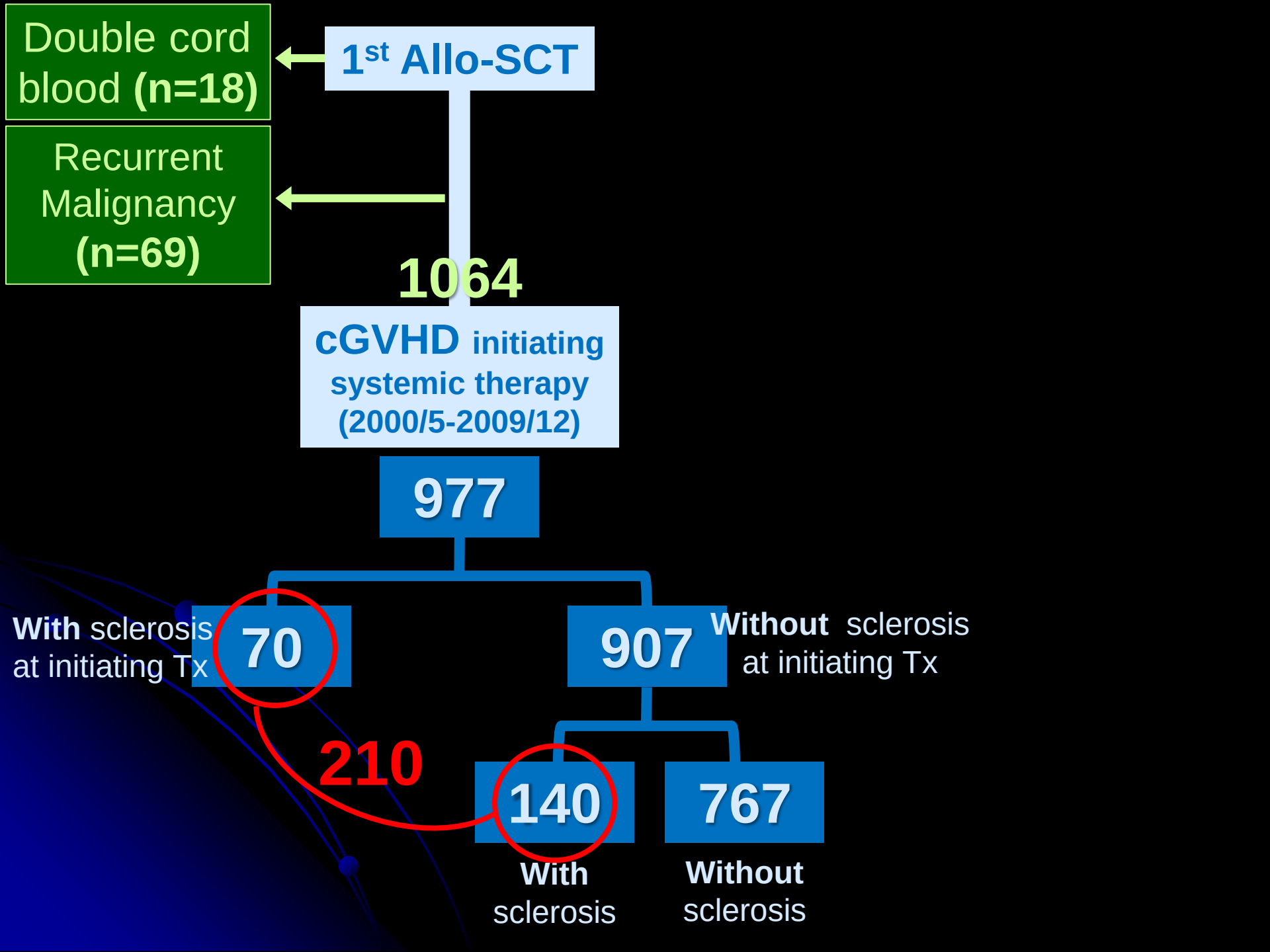
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
977
With sclerosis at initiating Tx
70
907
Without sclerosis at initiating Tx
140
767
With sclerosis
Without sclerosis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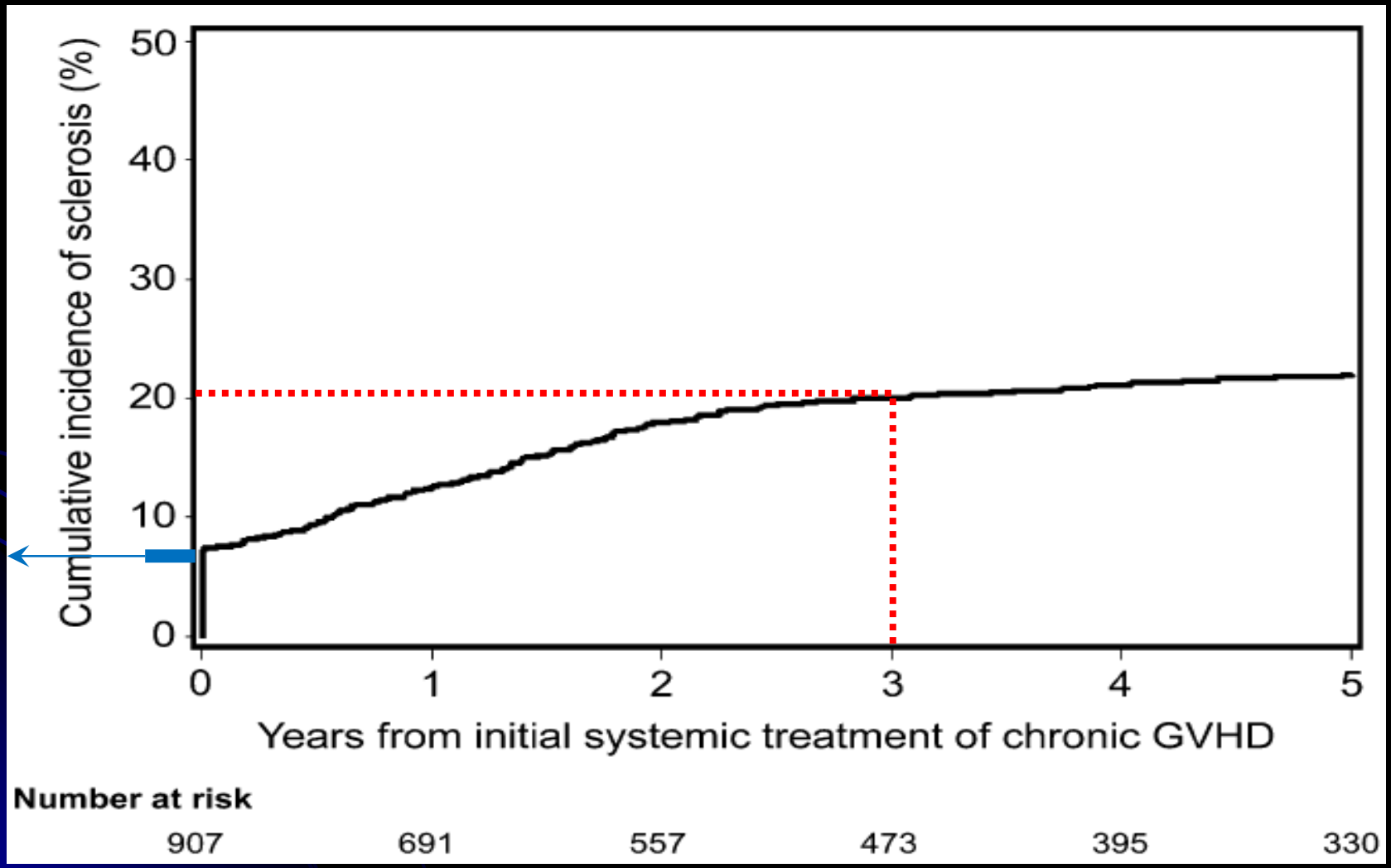
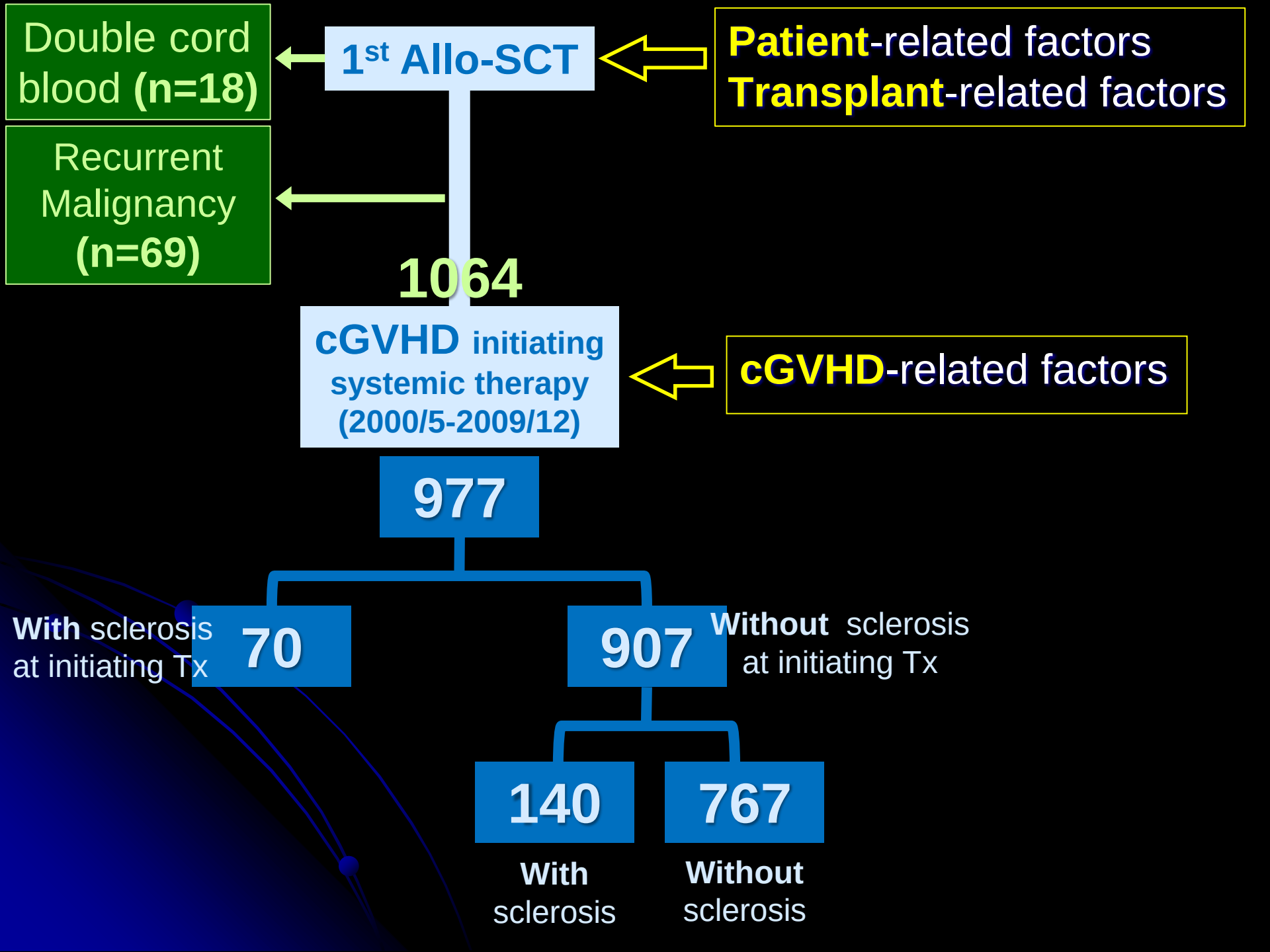
With sclerosis
Without sclerosis

Cumulative incidence of sclerosis after initiating systemic Tx for cGVHD



7%
(n=70)


Double cord blood (n=18)
1st Allo-SCT
Patient-related factors
Transplant-related factors
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
cGVHD-related factors
977
With sclerosis at initiating Tx
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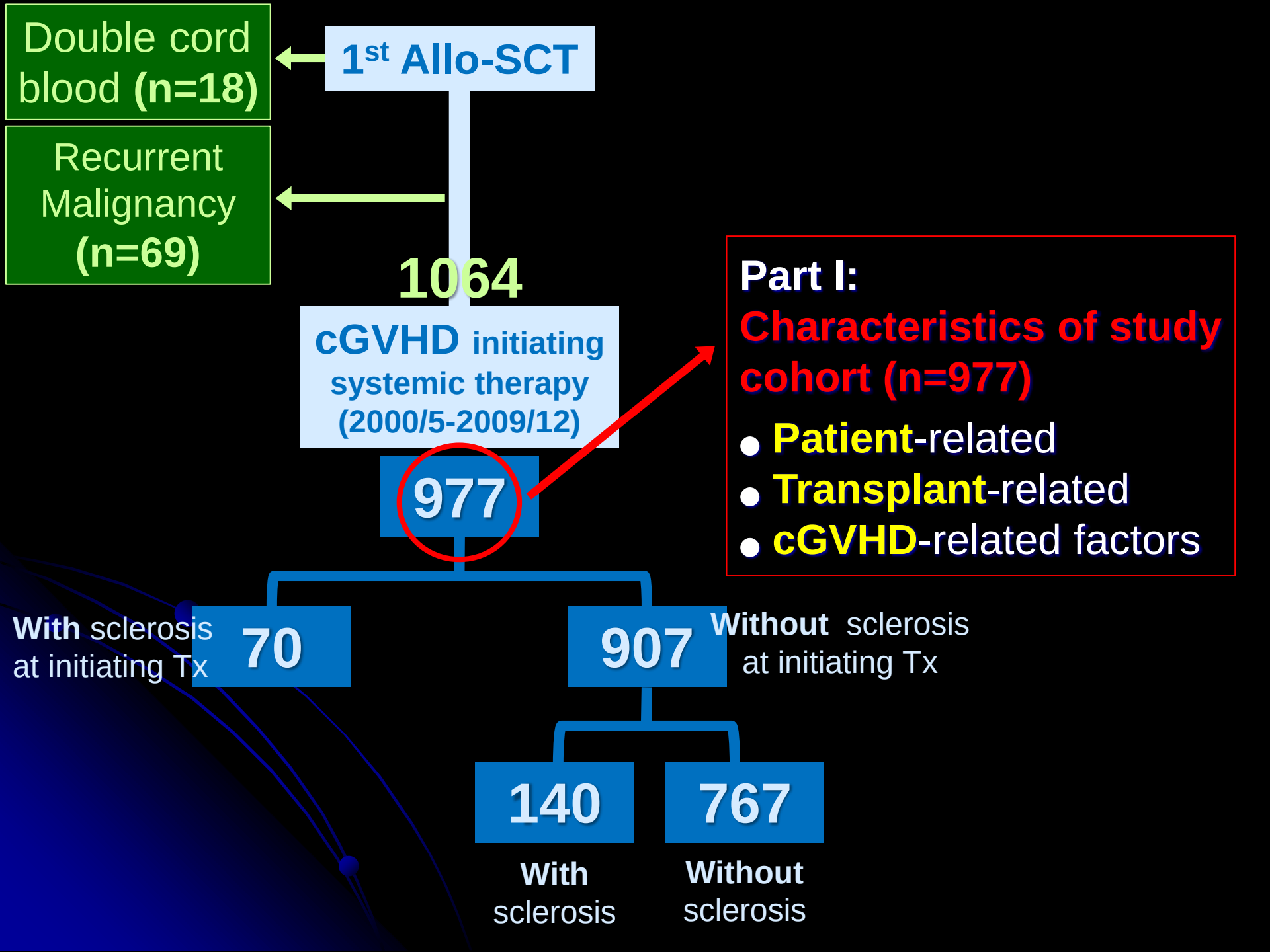

Double cord blood (n=18)
1st Allo-SCT
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
977
Part I:
Characteristics of study cohort (n=977)
Patient-related
Transplant-related
cGVHD-related factors
With sclerosis at initiating Tx
70
907
Without sclerosis at initiating Tx
140
767
With sclerosis
Without sclerosis

Patient Transplant related factors

Table 1. Characteristics of the study cohort

Characteristic	Cohort, N = 977
Median time from transplantation to initial systemic treatment for chronic GVHD, mo (range)	5.3 (2.5–33.5)
Median patient age at transplantation, y (range)	48 (0–78)
Median donor age at transplantation, y (range)	39 (0–78)
Patient gender, no. (%)	
Male	565 (58)
Female	412 (42)
Donor–recipient gender combination, no. (%)	
Male to male	297 (30)
Female to male	268 (27)
Male to female	179 (18)
Female to female	233 (24)
Patient race, no. (%)	
Caucasian	766 (78)
African American	16 (2)
Other	166 (17)
Missing data	29 (3)
Diagnosis, no. (%)	
Acute myeloid leukemia	301 (31)
Acute lymphoid leukemia	105 (11)
Chronic myeloid leukemia	108 (11)
Myelodysplastic syndromes or myeloproliferative neoplasms	212 (22)
Chronic lymphocytic leukemia	40 (4)
Malignant lymphoma	105 (11)
Multiple myeloma	59 (6)
Aplastic anemia	14 (1)
Other	33 (3)

Patient Transplant related factors

Table 1. Characteristics of the study cohort

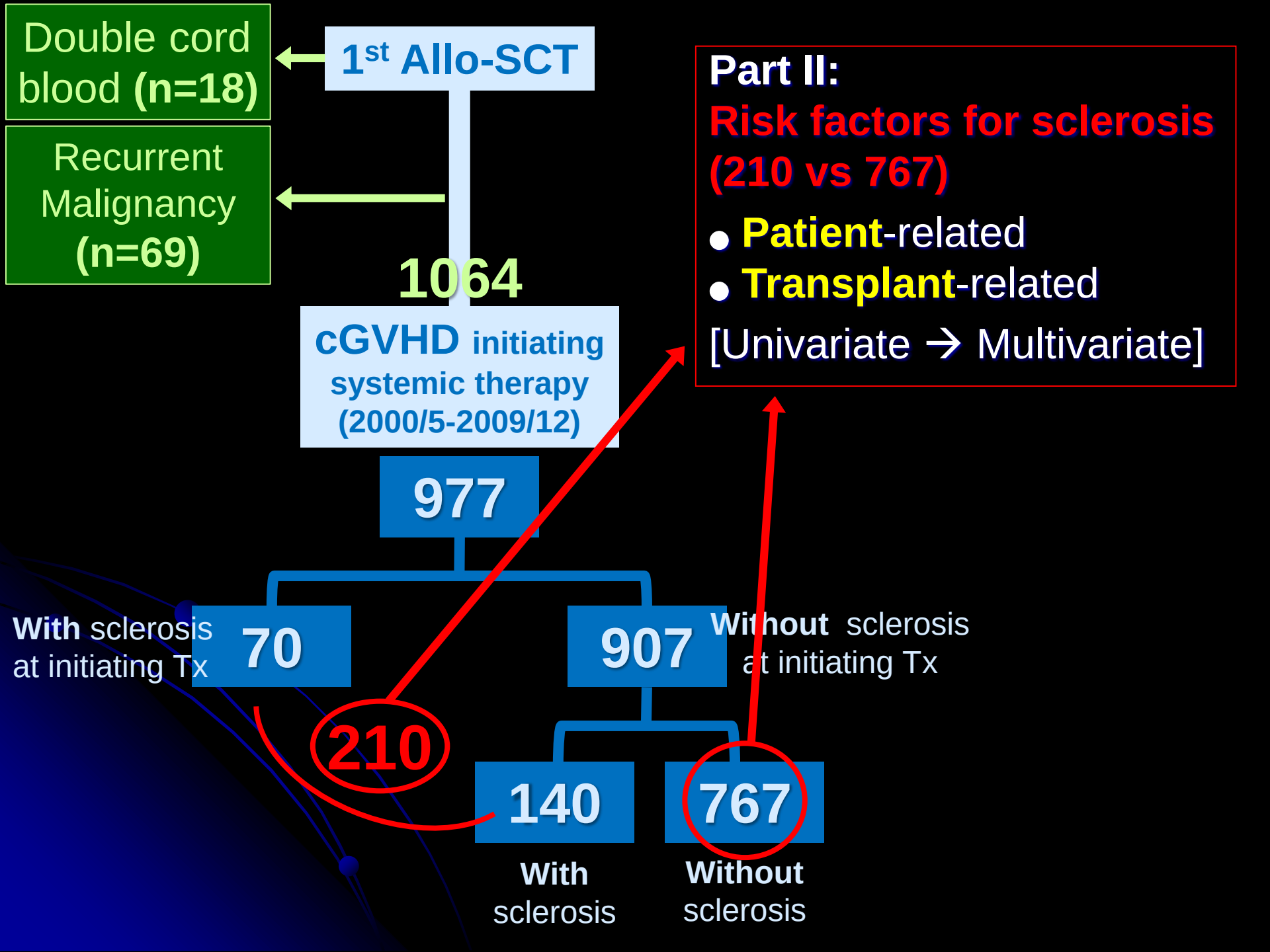
Characteristic	Cohort, N = 977
Disease risk,* no. (%)	
Low	337 (34)
High	640 (66)
Stem cell graft source, no. (%)	
Bone marrow	143 (15)
Mobilized blood cells	820 (84)
Umbilical cord blood	14 (1)
HLA and donor type, no. (%)	
HLA matched related	406 (42)
HLA matched unrelated	373 (38)
HLA mismatched related	36 (4)
HLA mismatched unrelated	162 (17)
ABO compatibility, no. (%)	
Match	533 (55)
Minor mismatch	197 (20)
Major mismatch	247 (25)
Intensity of conditioning regimen, no. (%)	
High	693 (71)
Reduced	284 (29)
TBI dose in conditioning regimen, no. (%)	
None	385 (39)
≤450 cGy	360 (37)
>450 cGy	232 (24)
ATG in conditioning regimen, no. (%)	54 (6)

Patient Transplant related factors

cGVHD related factors

Table 1. Characteristics of the study cohort

Characteristic	Cohort, N = 977
GVHD prophylaxis, no. (%)	
Cyclosporine + MTX/MMF	593 (61)
Tacrolimus + MTX/MMF	350 (36)
Other	34 (3)
Prior grade II–IV acute GVHD, no. (%)	725 (74)
Prior stage 3–4 skin acute GVHD, no. (%)	359 (37)
Sites involved with chronic GVHD at initial systemic treatment, no. (%)	
Skin	674 (69)
Eye	267 (27)
Mouth	740 (76)
Gastrointestinal tract	374 (38)
Liver	254 (26)
Lung (bronchiolitis obliterans)	16 (2)
Joint or fascia	63 (6)
Genital tract	45 (5)
Eosinophilia >400/μL at initial systemic treatment, no. (%)	156 (16)
Thrombocytopenia <100 000/μL at initial systemic treatment, no. (%)	318 (33)
Progressive onset,† no. (%)	339 (35)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cGVHD initiating systemic therapy (2000/5-2009/12)
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With sclerosis at initiating Tx
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907
Without sclerosis at initiating Tx
210
140
767
With sclerosis
Without sclerosis
Part II:
Risk factors for sclerosis (210 vs 767)
Patient-related
Transplant-related
[Univariate → Multivariate]

Table 2. Risk factors for sclerosis

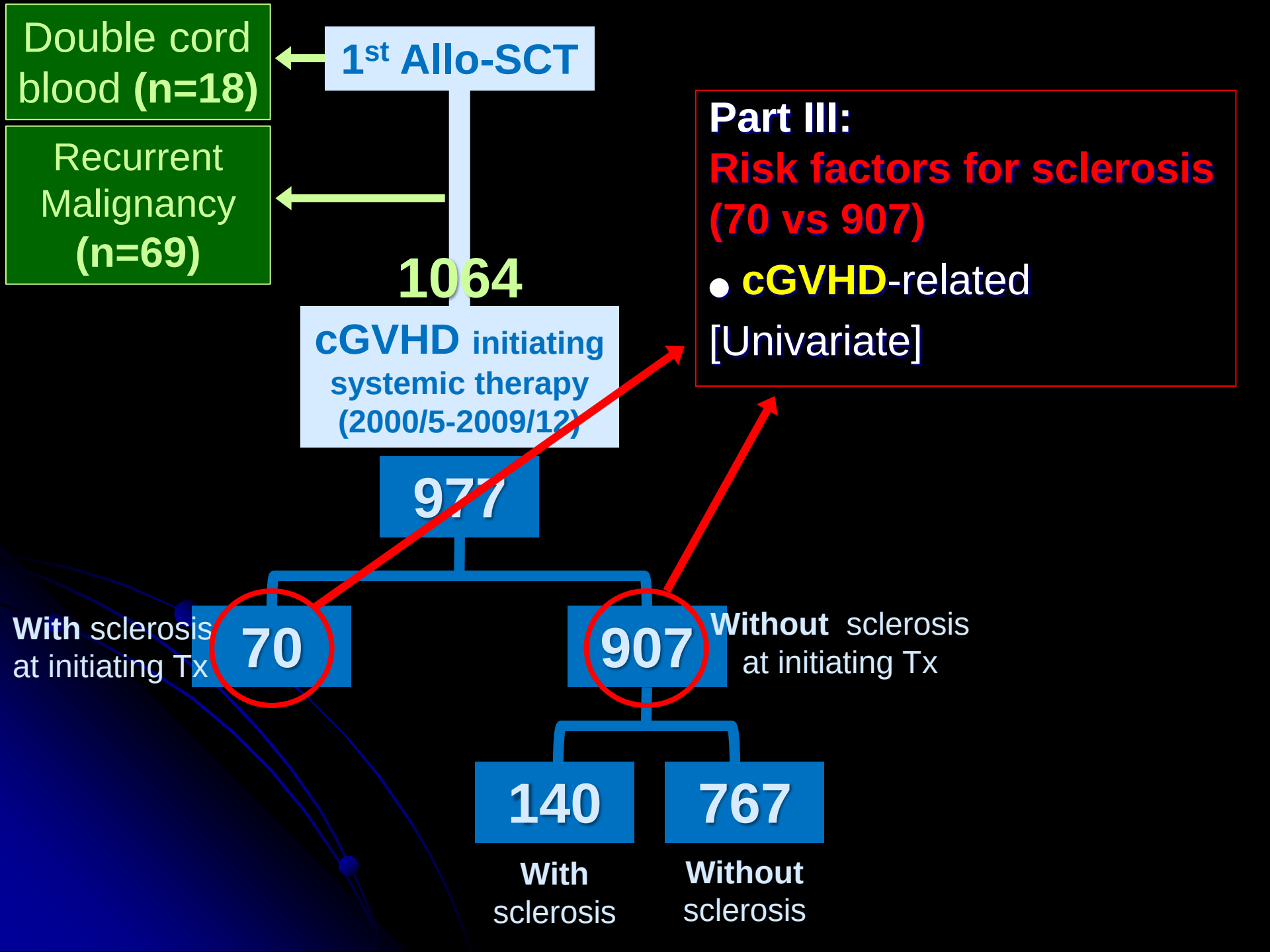
Risk factor	Univariate HR (95% CI)	*P*
Patient age Per 10 y	1.10 (1.01–1.20)	.04
Donor age Per 10 y	1.07 (0.96–1.18)	.24
Patient gender		
Male	1.00 (reference)	
Female	1.25 (0.95–1.63)	.11
Donor–recipient gender combination		
Male to male	1.00 (reference)	
Female to male	0.70 (0.48–1.02)	.07
Male to female	0.87 (0.58–1.31)	.50
Female to female	1.22 (0.86–1.72)	.26
Disease risk at transplantation		
Low	1.00 (reference)	
High	1.11 (0.84–1.48)	.46
Stem cell graft source		
Bone marrow	1.00 (reference)	
Mobilized blood cells	2.15 (1.31–3.53)	.003
Umbilical cord blood	0.57 (0.08–4.29)	.59
Donor relation		
Related	1.00 (reference)	
Unrelated	0.98 (0.75–1.29)	.89
HLA matching		
Matched	1.00 (reference)	
Mismatched	0.51 (0.33–0.78)	.002

Table 2. Risk factors for sclerosis

Risk factor	Univariate HR (95% CI)	*P*
ABO compatibility		
Match	1.00 (reference)	
Minor mismatch	1.08 (0.78–1.49)	.66
Major mismatch	0.62 (0.43–0.90)	.01
Intensity of conditioning regimen		
High	1.00 (reference)	
Reduced	1.26 (0.94–1.68)	.12
TBI dose in conditioning regimen		
None	1.00 (reference)	
≤450 cGy	1.38 (1.01–1.89)	.05
>450 cGy	1.40 (0.99–1.99)	.06
ATG in conditioning regimen		
No	1.00 (reference)	
Yes	0.55 (0.26–1.17)	.12
GVHD prophylaxis		
Cyclosporine + MTX/MMF	1.00 (reference)	
Tacrolimus + MTX/MMF	1.14 (0.86–1.52)	.35
Other	0.71 (0.29–1.73)	.45
Prior grade II–IV acute GVHD		
No	1.00 (reference)	
Yes	0.87 (0.65–1.17)	.37
Prior stage 3–4 skin acute GVHD		
No	1.00 (reference)	
Yes	1.02 (0.77–1.35)	.88

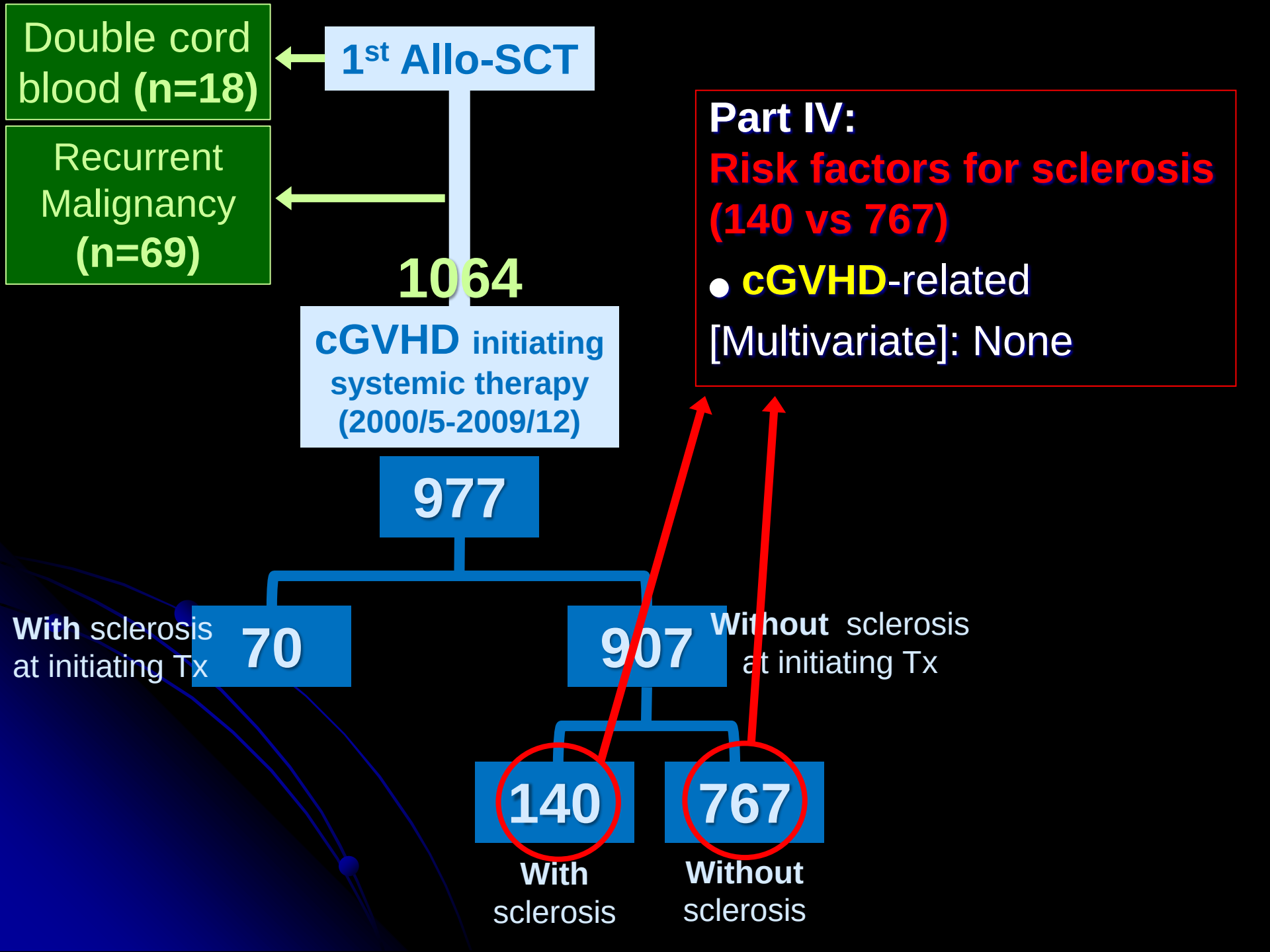
Table 2. Risk factors for sclerosis

Risk factor	Univariate HR (95% CI)	*P*	Multivariate* HR (95% CI)	*P*
Stem cell graft source				
Bone marrow	1.00 (reference)		1.00 (reference)	
Mobilized blood cells	2.15 (1.31–3.53)	.003	1.99 (1.20–3.31)	.008
Umbilical cord blood	0.57 (0.08–4.29)	.59	0.74 (0.10–5.63)	.77
TBI dose in conditioning regimen				
None	1.00 (reference)		1.00 (reference)	
≤450 cGy	1.38 (1.01–1.89)	.05	1.27 (0.93–1.75)	.14
>450 cGy	1.40 (0.99–1.99)	.06	1.62 (1.14–2.31)	.008
HLA matching				
Matched	1.00 (reference)		1.00 (reference)	
Mismatched	0.51 (0.33–0.78)	.002	0.57 (0.37–0.89)	.01
ABO compatibility				
Match	1.00 (reference)		1.00 (reference)	
Minor mismatch	1.08 (0.78–1.49)	.66	1.13 (0.81–1.57)	.46
Major mismatch	0.62 (0.43–0.90)	.01	0.65 (0.45–0.94)	.02


Double cord blood (n=18)
1st Allo-SCT
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
977
With sclerosis at initiating Tx
70
907
Without sclerosis at initiating Tx
140
767
With sclerosis
Without sclerosis
Part III:
Risk factors for sclerosis (70 vs 907)
cGVHD-related
[Univariate]

	cGVHD **with** sclerosis when initiating systemic Tx (n=70)	cGVHD **without** sclerosis when initiating systemic Tx (n=907)	P value
Eosinophilia	**46%**	**14%**	P<0.0001
Thrombocytopenia	**11%**	**34%**	P<0.0001
Progressive onset	**11%**	**36%**	P<0.0001

- direct progression from acute to chronic GVHD
- onset of cGVHD during steroid treatment


Double cord blood (n=18)
1st Allo-SCT
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
977
With sclerosis at initiating Tx
70
907
Without sclerosis at initiating Tx
140
767
With sclerosis
Without sclerosis
Part IV:
Risk factors for sclerosis (140 vs 767)
• cGVHD-related
[Multivariate]: None

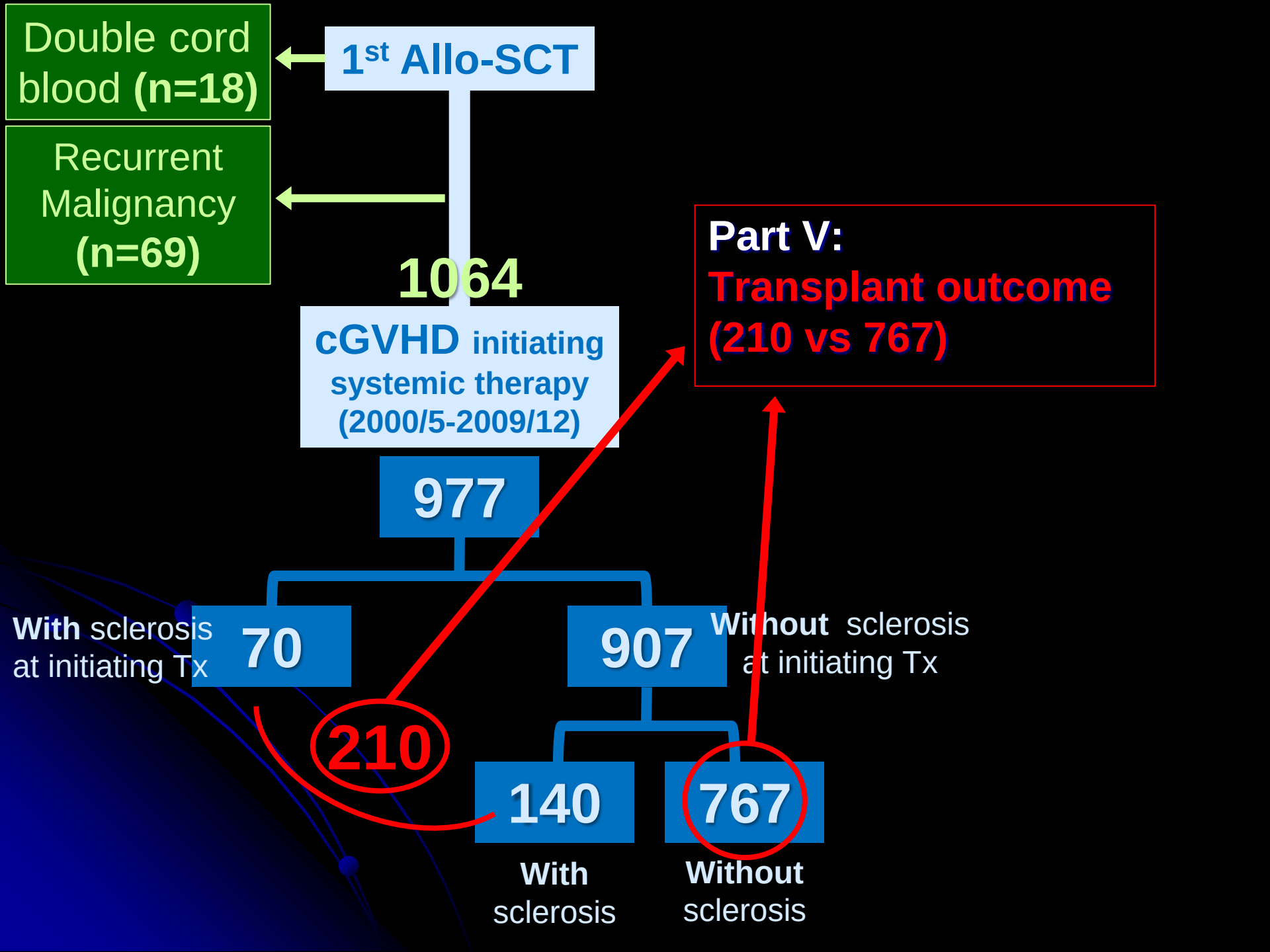

Double cord blood (n=18)
1st Allo-SCT
Recurrent Malignancy (n=69)
1064
cGVHD initiating systemic therapy (2000/5-2009/12)
Part V:
Transplant outcome
(210 vs 767)
977
With sclerosis at initiating Tx
70
907
Without sclerosis at initiating Tx
210
140
767
With sclerosis
Without sclerosis

Table 3. Association of sclerosis with transplant outcomes

Outcome	HR* (95% CI)	*P*
Overall mortality	0.87 (0.63–1.19)	.37
Nonrelapse mortality†	1.00 (0.67–1.49)	.99
Recurrent malignancy†	0.85 (0.53–1.34)	.48
Withdrawal of immunosuppressive treatment	0.65 (0.50–0.85)	.001

Sclerosis dose NOT affect mortality & recurrent malignancy in cGVHD

Discussion

Patient or Transplant - related factors

- **Risk factors**
  1. **TBI > 450cGy (vs None)**
  2. **PBSCT (vs BM)**

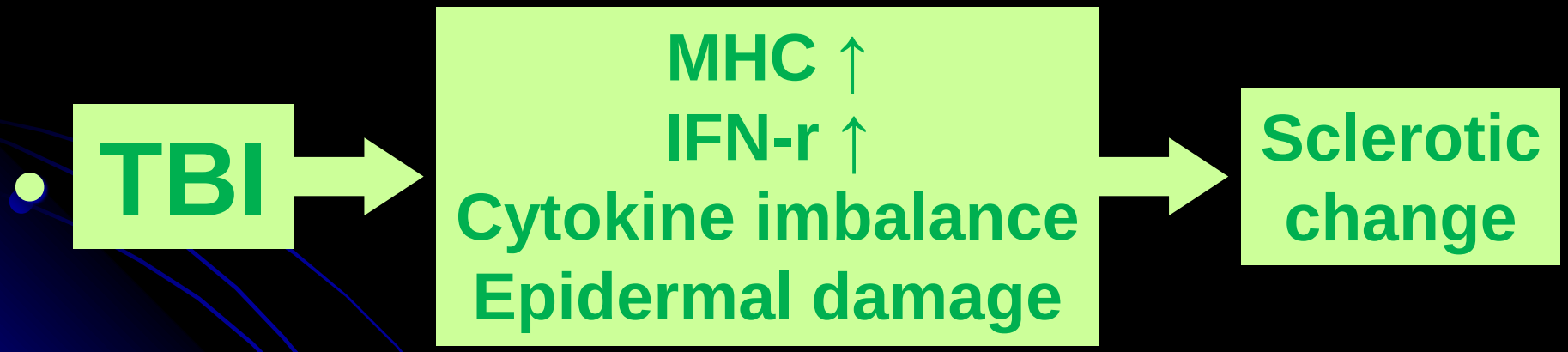
→ Compatible with risk factors of **cGVHD**

- **Protective factors**
  1. **HLA mismatch (vs match)** → **Counterintuitive**
  2. **ABO mismatch (vs match)** → **Hard to explain**

TBI > 450 cGy increase risk of sclerosis in cGVHD

- **Irradiated skin** predisposed to cutaneous GVHD

Lancet. 1980;1(8177):1081-1082.



PBSCT increase risk of sclerosis in cGVHD

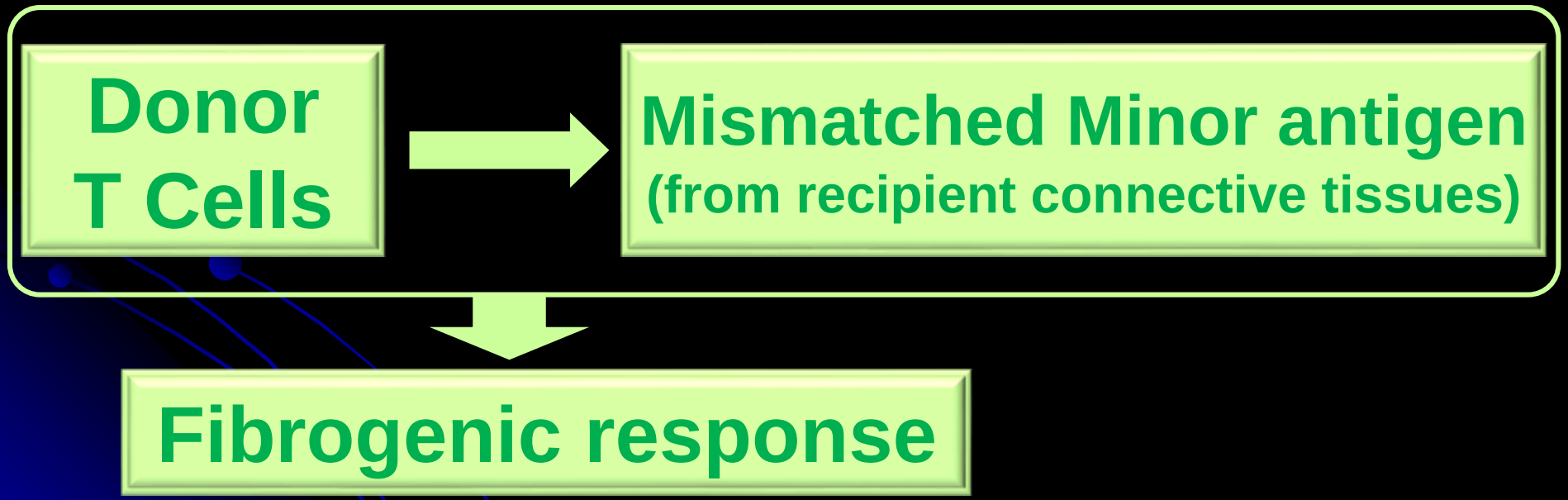
- In mouse model:

Blood. 2010;116(5):819-828

- [IL-17] associated with [disease severity of systemic sclerosis]

J Dermatol Sci. 2008;50(3):240-242

HLA mismatching



J Immunol. 2002;168(6):3088-3098

Blood. 2011;118(26):6733-6742

HLA mismatching

Major histocompatibility antigen

HLA mismatch

(Immunodominant effect)

Donor T Cells

Mismatched Minor antigen

(from recipient connective tissues)

Fibrogenic response

J Immunol. 2002;168(6):3088-3098

Blood. 2011;118(26):6733-6742

HLA mismatching

Major histocompatibility antigen

HLA mismatch

(Immunodominant effect)

Donor T Cells

Mismatched Minor antigen

(from recipient connective tissues)

~~**Fibrogenic response**~~

J Immunol. 2002;168(6):3088-3098

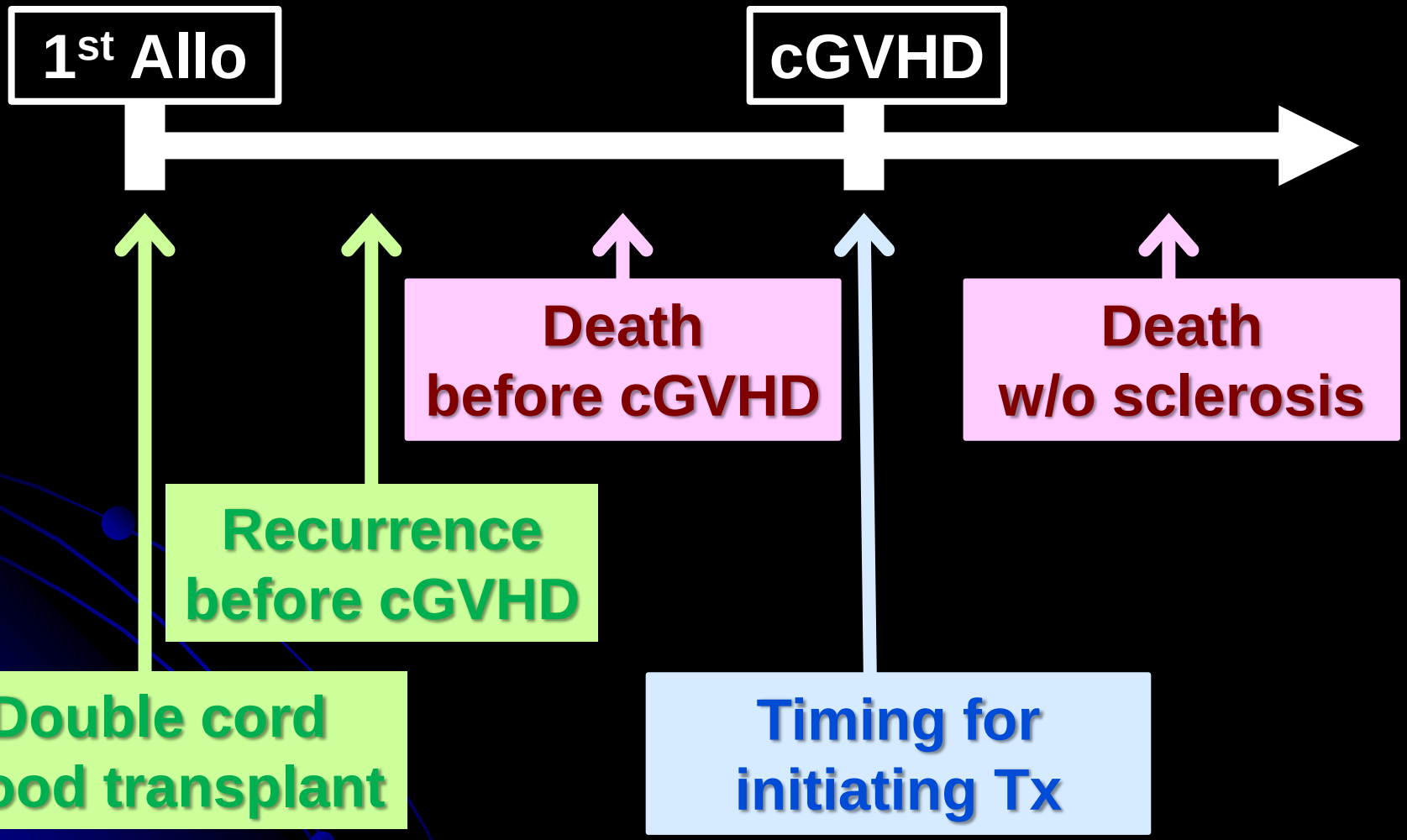
Blood. 2011;118(26):6733-6742

Limitation

- Doctors **NOT** familiar with sclerotic phenotype → **underestimate** incidence

- Unavailable data:
  - **Severity & extent of sclerosis**
  - **Disability level**
  - **Quality of life**
  - **Social recovery parameters**
  - **Treatment response**

Limitation


1st Allo
cGVHD
Death before cGVHD
Death w/o sclerosis
Recurrence before cGVHD
Double cord blood transplant
Timing for initiating Tx

Conclusion

- **Incidence** of sclerosis: **20%** at **3Y** after initiating systemic treatment for cGVHD

- **PBSCT** & **TBI**:
  risk factors for sclerosis in cGVHD

- Sclerosis dose **NOT** affect mortality & recurrent malignancy in cGVHD

Thanks for your attention