Late effects and long-term survivorship after HSCT

André Tichelli

What are late effects?

Why is it of importance?

How to proceed in daily routine?

59-year old male survivor
22 years after allogeneic HSCT

- Chronic myeloid leukemia in chronic phase
  - Allogeneic HSCT at 37-years of age
    - conditioning with TBI, cyclophosphamide and etoposide
    - Persisting complete molecular remission since 1991

- Long-term follow-up
  - 2 years, cataract, surgical repair
  - 3 years, infertility and gonadal insufficiency (remarried)
  - 6 years, osteopenia (osteodensitometry)
  - Over the years, cardiovascular risk factors
    - Overweight (BMI 27kg/m2)
    - Dyslipidemia, arterial hypertension
    - No physical activity,
  - 18 years, basal cell carcinoma, complete excision
  - 20 years, cardiovascular complications
    - Myocardial infarction

Last annual control (3 months ago)

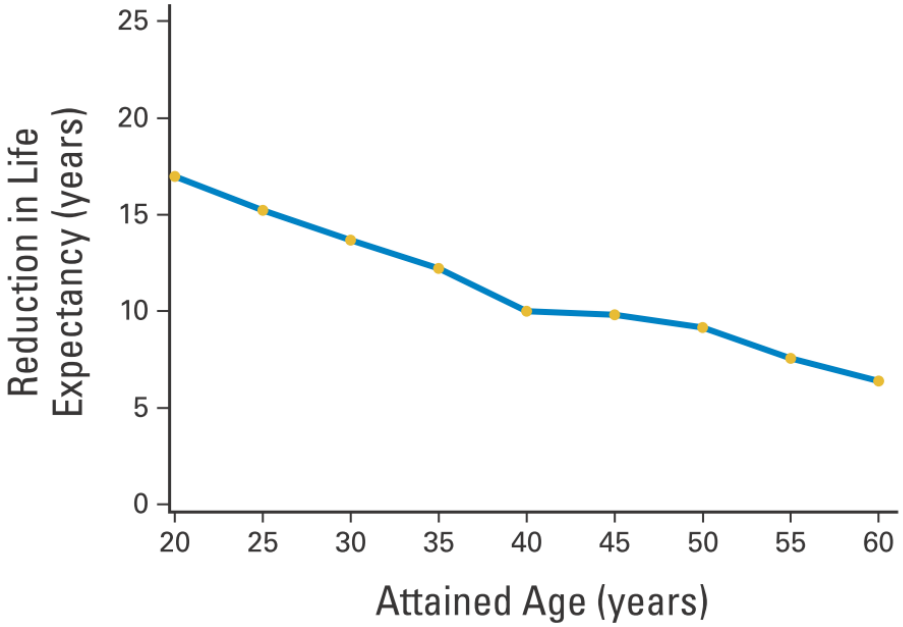
- Physically in good condition
- Subjective complains
  - Sicca syndrome
    - Xerophthalmia
    - Skin dryness
  - Fatigue , depression, loss of concentration
  - Works 50%; needs 50% social support; financial problems
  - Divorced, remarried, three children (conceived before HSCT)

What is the problem ?
The definitive aim of the HSCT

- Cure from the primary disease
- Complete recovery of the health status

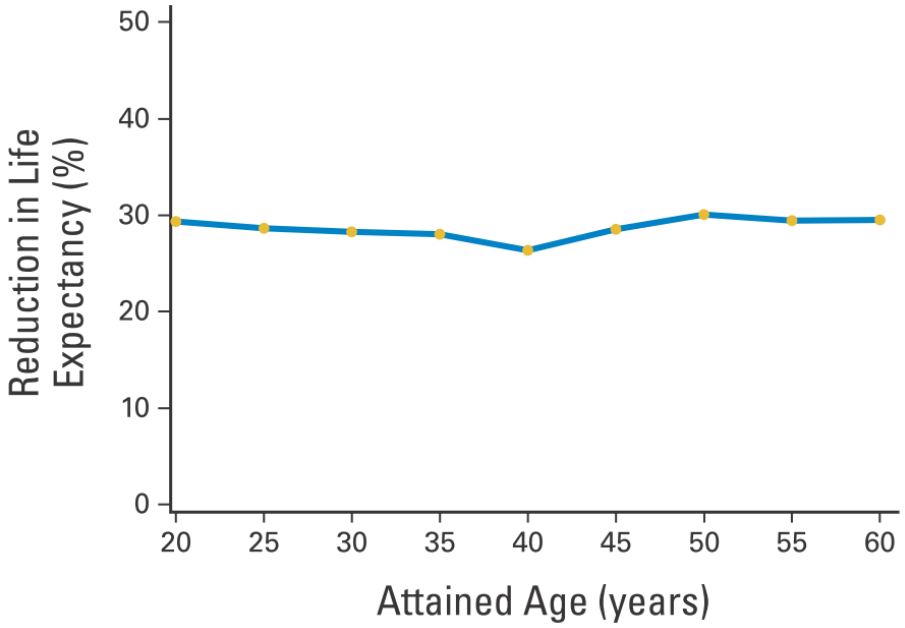
Estimated 30% lower life expectancy than that of the US population, regardless of current age

Projected reduction in life expectancy in patients surviving > 5 years after HSCT



Absolute reduction in years

Percentage reduction in years

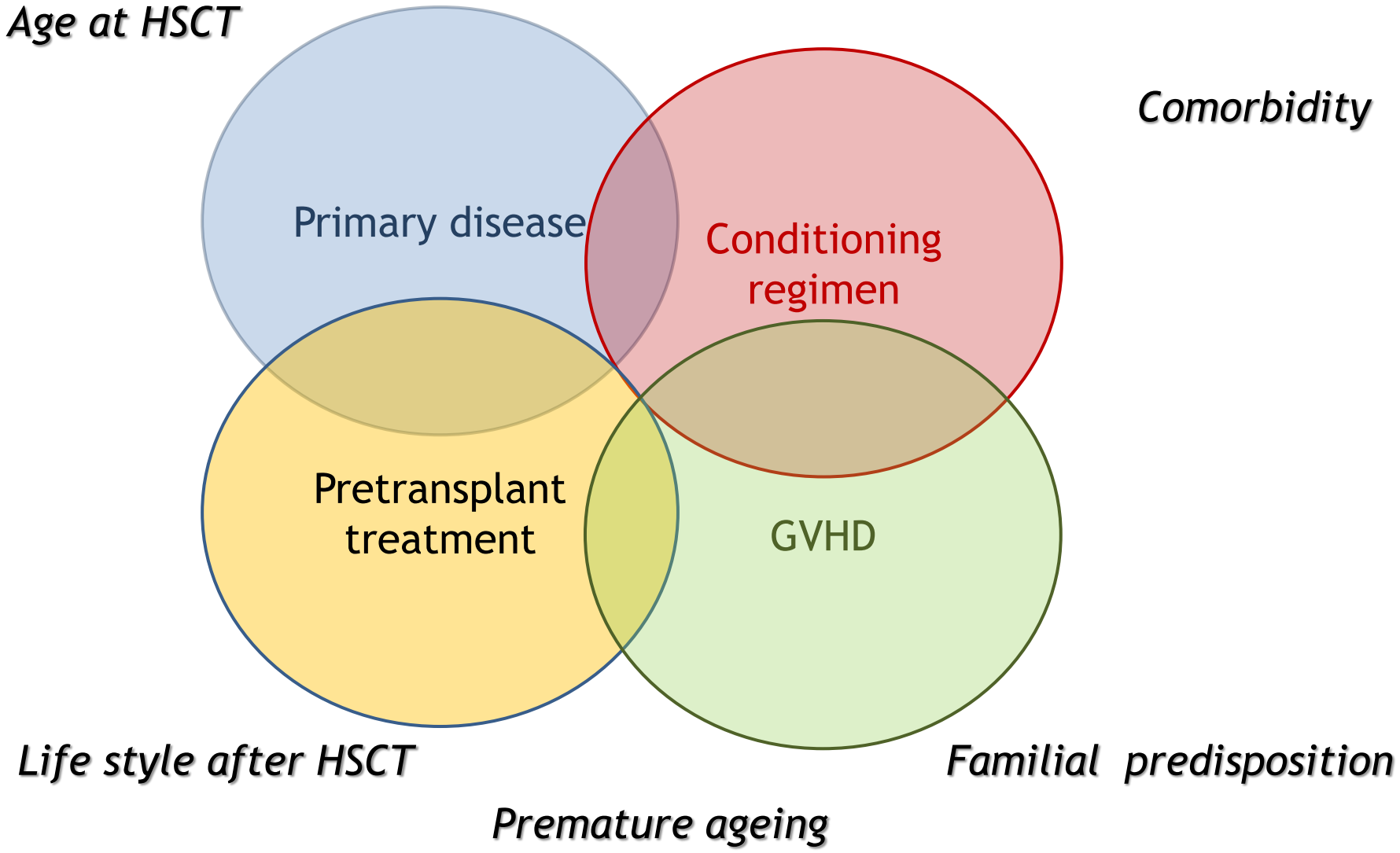


PJ Martin et al. JCO 2010;28:1011-1016

What does affect long-term survivorship after HSCT?

Course of the primary disease	➡ Late relapse of the primary disease
Late complications	➡ Malignant and non-malignant
Chronic health condition	➡ Burden of active late complications
Quality of life	➡ The way that the life is perceived
Social integration	➡ Family, partnership, school, job, financial aspects, assurances

Main players and confounders for late complications



Late complications after HSCT

Malignant complications

- Secondary MDS/AML after autologous HSCT
- Donor type leukemia
- Solid tumors
- Post-transplant lymphoproliferative disorders (PTLD)

Non-malignant complications

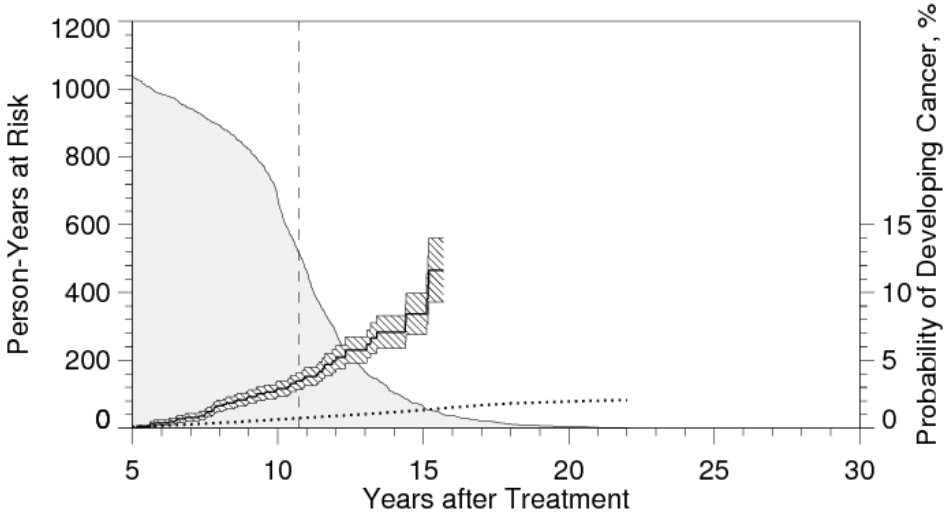
- Endocrine dysfunction
- Skeletal disorders
- Ocular problems, skin, mucosa
- Respiratory tract problems
- Liver complication
- Chronic kidney disorder
- Neurological complications
- Cardiac and vascular complications
- Others…..

Socié G. et al. Blood. 2003; 101: 3373-3385 (review)
Tichelli A et al. Expert Rev Hematol. 2009. 2: 583-601

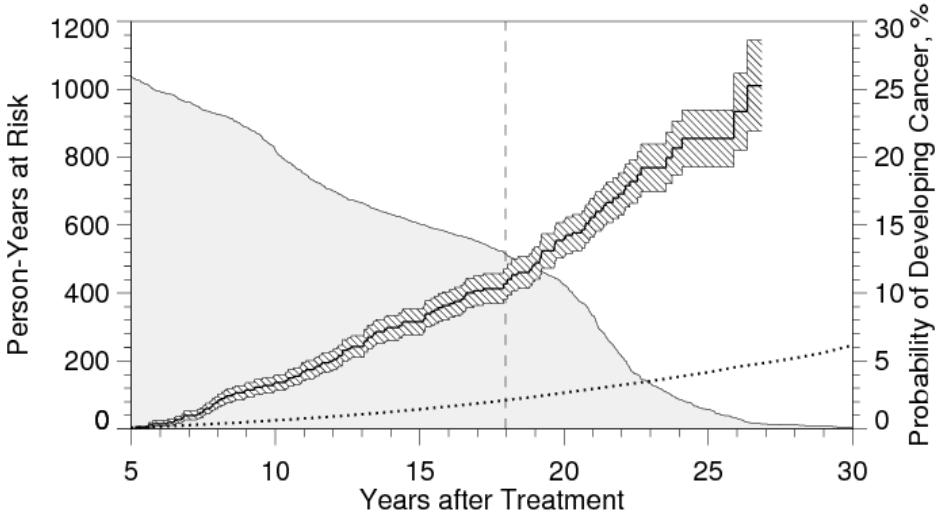
Bhatia S. Expert Rev Hematol. 2011. 4: 437-454 (review)
Tichelli A, Rovó A and G. Socié. Curr Probl Dermatol. 2012; 43:132-149

Secondary malignancy after allogeneic HSCT

Update	Patients with secondary malignancy
1999	54/1117 patients
2008	134/959 patients



1999



2008

Secondary solid tumor increase with longer follow-up time since HSCT

Kolb HJ. Ann Intern Med. 1999;131:738-744
Heilmeier B. BMT. Abstract 2010

Risk factors of secondary cancers after HSCT

>28’000 allo transplants; 189 tumors

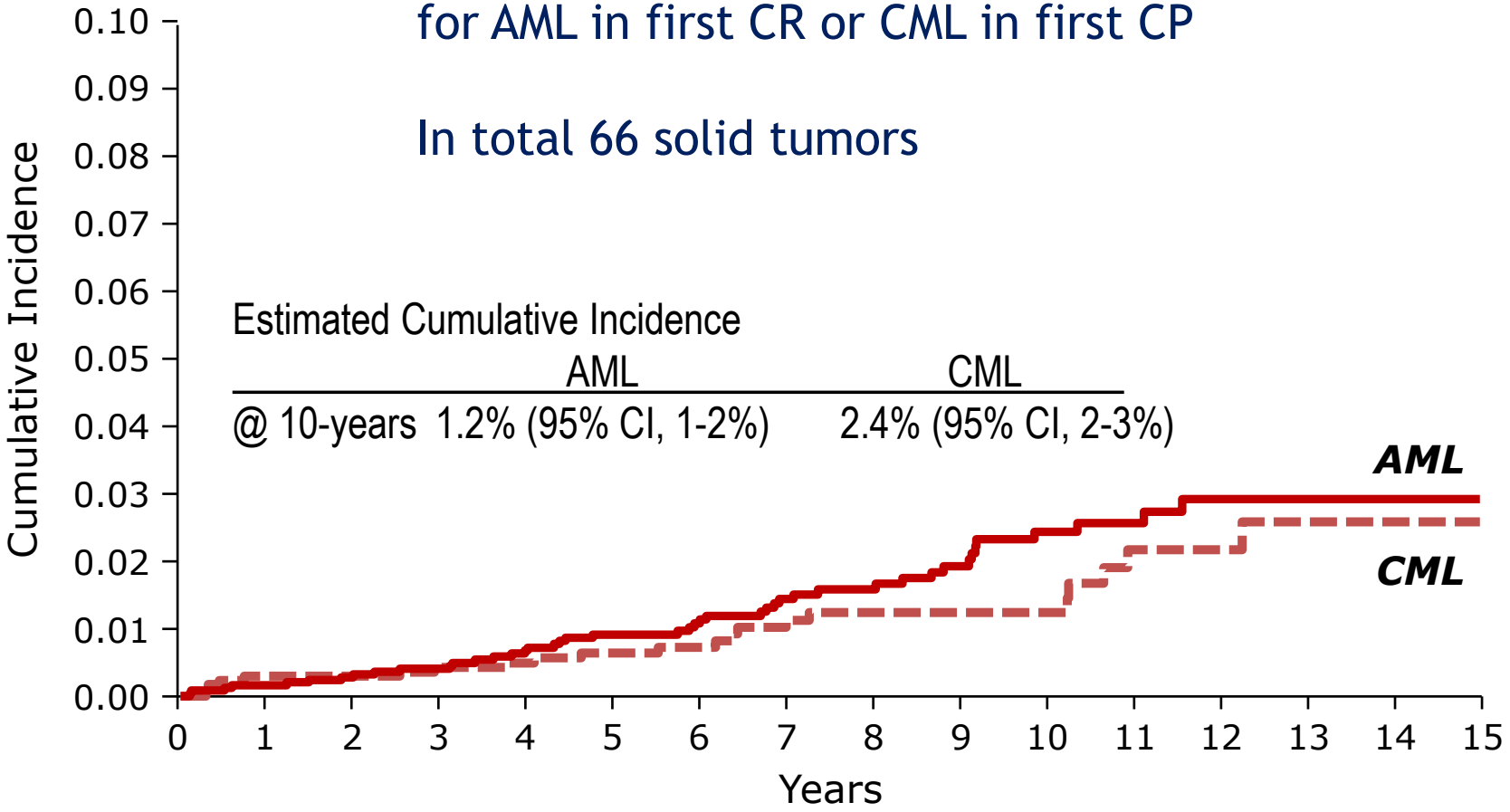
Type	Risk factor	Carcinoma
Non-squamous cell carcinoma	Radiation Younger age at radiation (<30) Increasing with longer follow-up	Breast cancer Thyroid Brain Bone and connective tissue Melanoma
Squamous cell carcinoma	Chronic GVHD Male sex No relation with TBI and with time since follow-up	Oral cavity
Others	Cirrhosis, HCV infection T-cell depletion	Liver Melanoma

Rizzo D. et al. Blood. 2009; 113:1175-1183

Also recipients of allogeneic HSCT using Bu-Cy conditioning are at risk for secondary solid tumors

4,318 recipients of first allogeneic HCT for AML in first CR or CML in first CP

In total 66 solid tumors



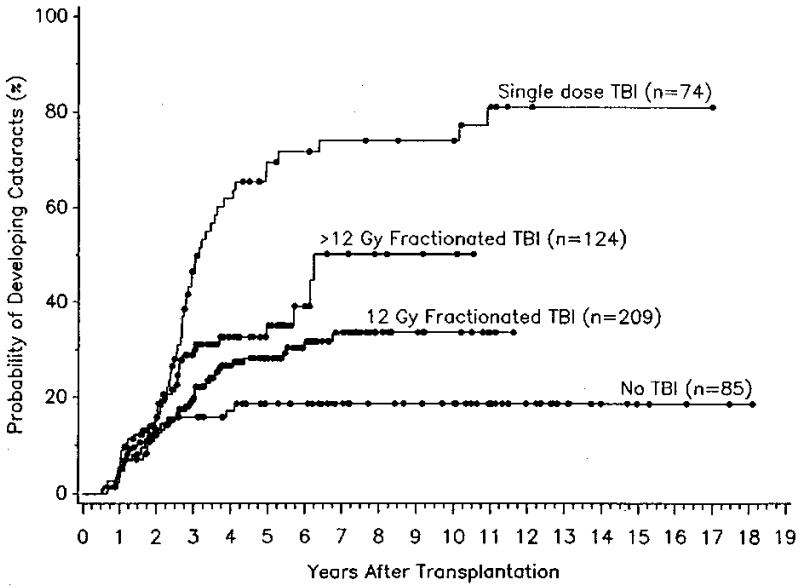
Majhail NS. et al. Blood. 2011; 117: 316-322

However, the type of solid cancers can be different

Risk-factor	*No. of Events*	*Relative risk (95% CI)*	*P-value*
Trachea, bronchus and lung	10		
Age at transplantation			
<35 years	1	1.0	0.01
35-50 years	5	5.0 (0.6-43.2)	0.14
>50 years	4	17.4 (1.9-159.3)	0.01
Smoking prior to HCT			
No	1	1.0	0.006
Yes	8	13.3 (1.6-108.5)	0.02
Missing	1	3.8 (0.2-61.7)	0.34
Lip, tongue and mouth	11		
Chronic GVHD			
No	1	1.0	0.02
Yes	10	12.4 (1.6-96.9)	

Majhail NS. et al. Blood. 2011; 117: 316-322

Reduced use of TBI changes the pattern of late effects



- In a cohort of 620 patients transplanted between 1997-2007
  - 8 patients presented steroid-induced cataract

Tabbara KF. et al. Ophtalmology. 2009; 116: 1624 - 1629.

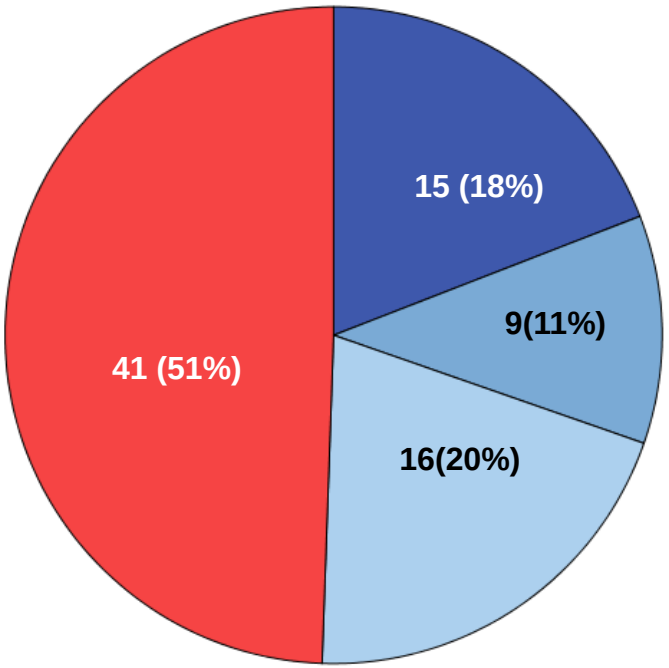
Main risk factors of cataracts

- TBI
- Dose, fractionation and dose rate
- Steroids

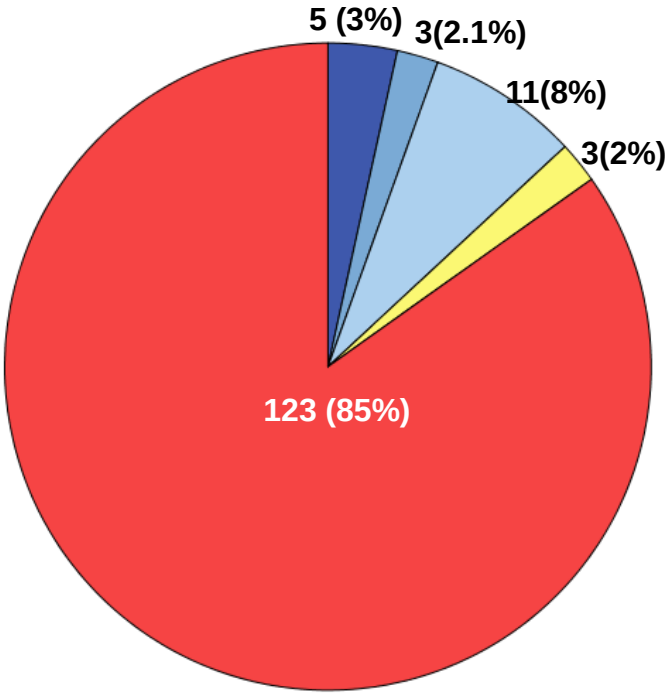
Belkacemi Y. et al. Int J Radiat Oncol Biol Phys. 1998; 41, 659-668
Tichelli et al. Ann Int Med 1993. 119; 1175-1180.

“Asymptomatic” late effects with significant effects on long-term survivorship

without TBI n = 81



with TBI n= 145



p<0.0001

Normozoospermic (≥20x10x6/ml)
Oligozoosoermic (5 to 20x10x6/ml)
Severely Oligospermic (<5x10x6/ml)
Cryptospermic (only in microscopic observation)
Azoospermia

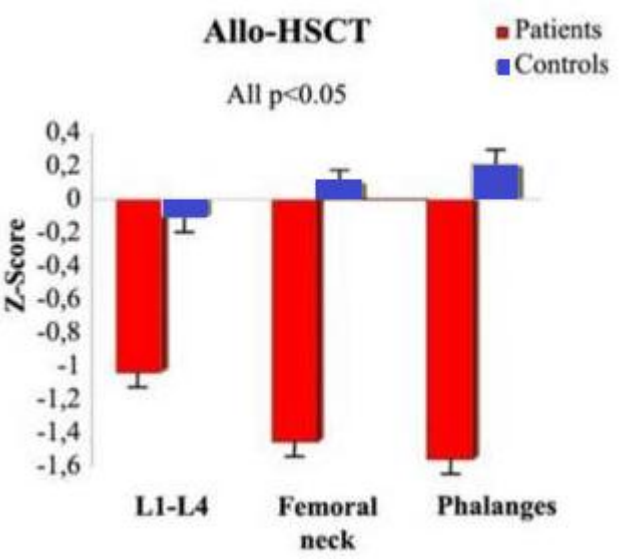
Rovó A. et al. BMT. 2010; 45 (Suppl 2): S4, 92.

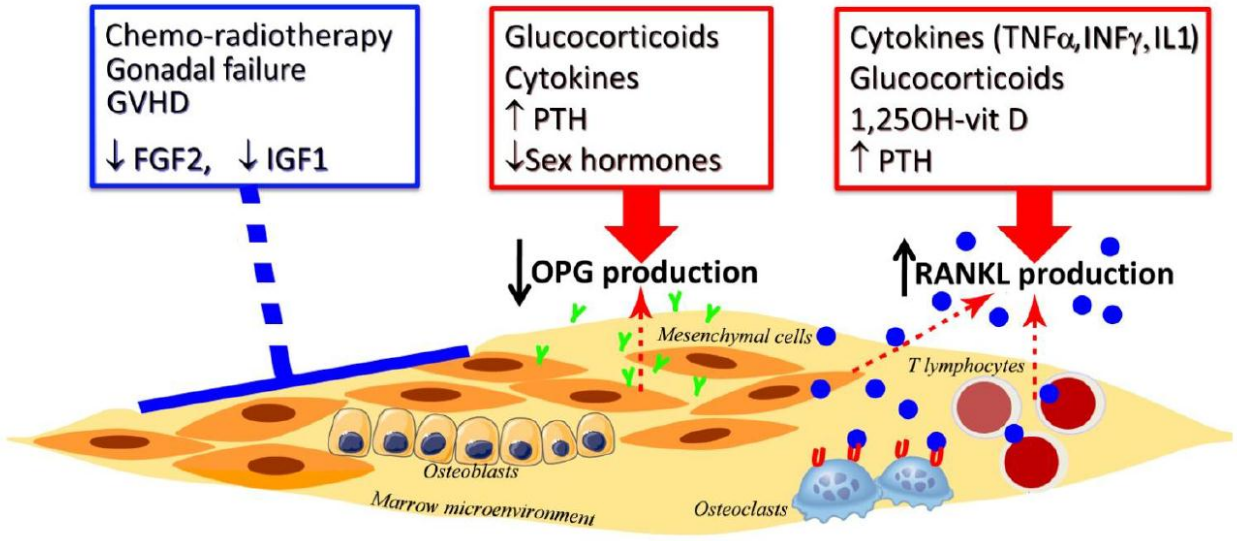
Accelerated bone mineral loss and micro-architectural deterioration

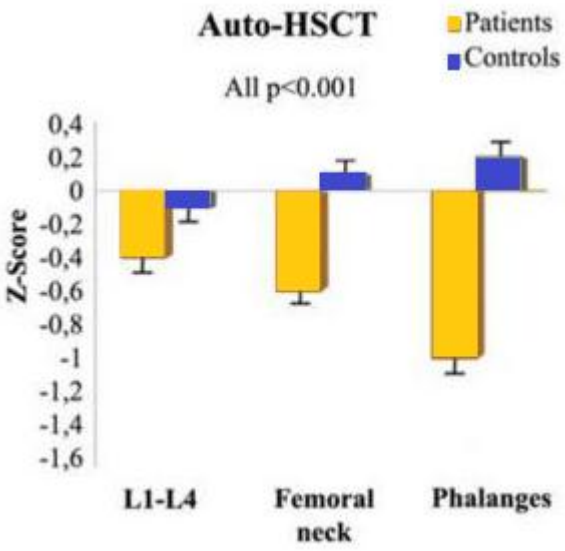
- Allo > auto HSCT
- Allo-HSCT with GVHD at higher risk for bone loss

Osteoprotegrin (OPG) ↘ ➡ osteoblast progenitors ↘

RANKL ↗ ➡ osteoclastic production ↗

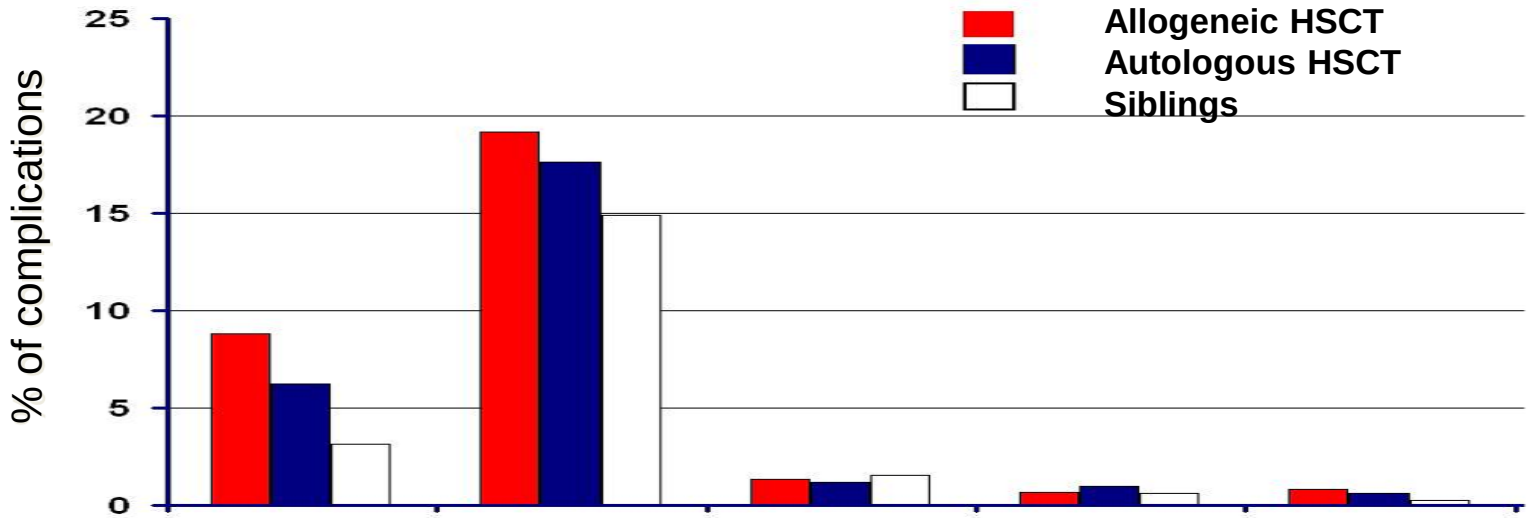






Pezzullo SB. Translational Medicine. 2013; 5:7-13

Diabetes, Hypertension and CV Events in long-term HSCT-Survivors



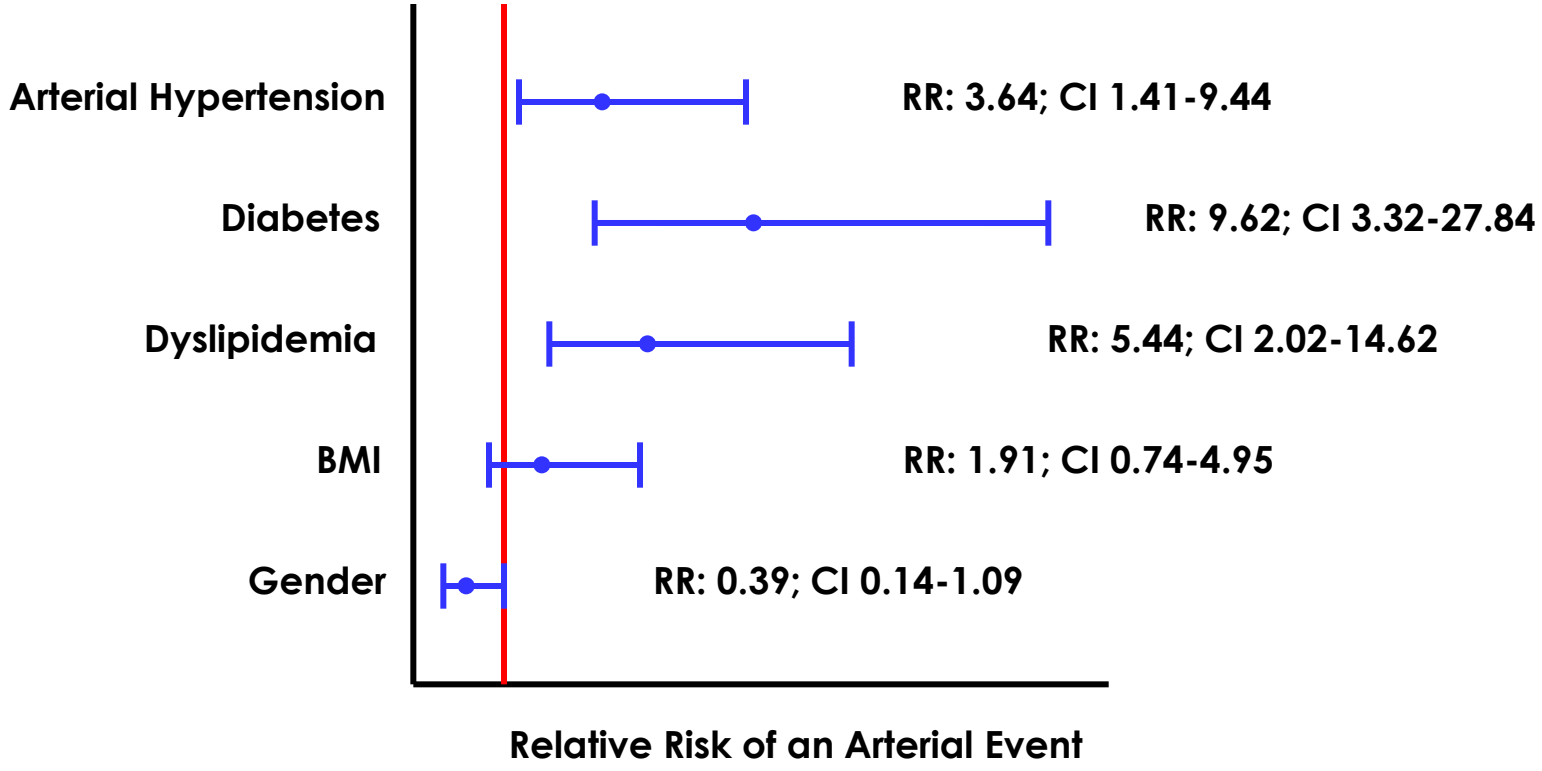
OR (95%CI)

	Diabetes	Hypertension	Arterial Disease	MI	Stroke
Allo	3.6 (1.8-7.3)	2.1 (1.4-3.0)	1.2 (0.3-4.0)	1.2 (0.2-6.0)	3.5 (0.4-30.6)
Auto	2.0 (0.8-4.2)	0.9 (0.6-1.4)	0.4 (0.1-1.5)	0.4 (0.1-1.5)	2.6 (0.3-26.8)
Sibling	1	1	1	1	1

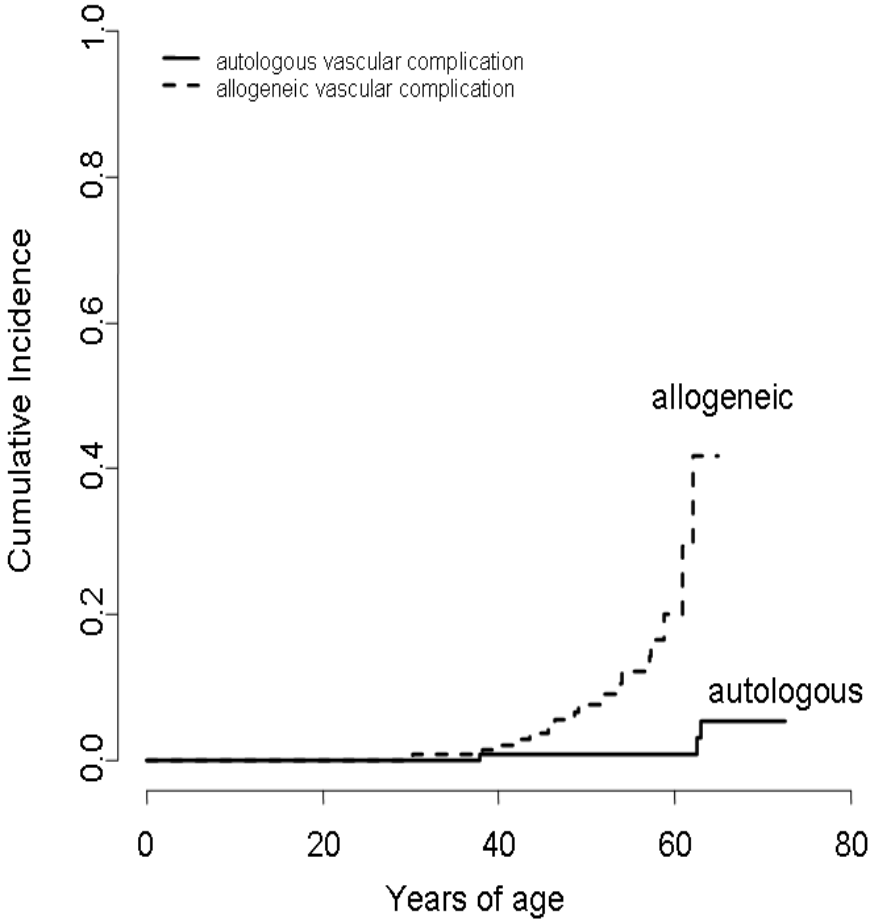
Adjusted for age, age at transplant, and sex

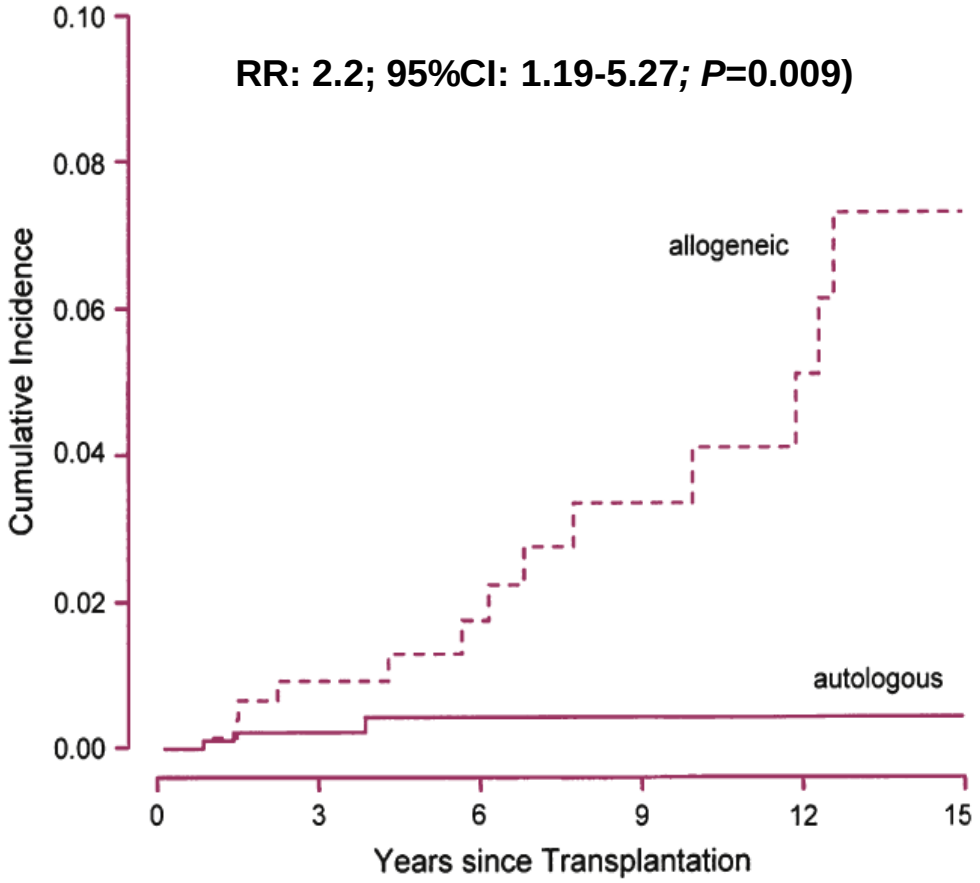
Baker S. et al. Blood, 2007; 109: 1765 - 1772.

Risk factors for late vascular complications after allogeneic HSCT



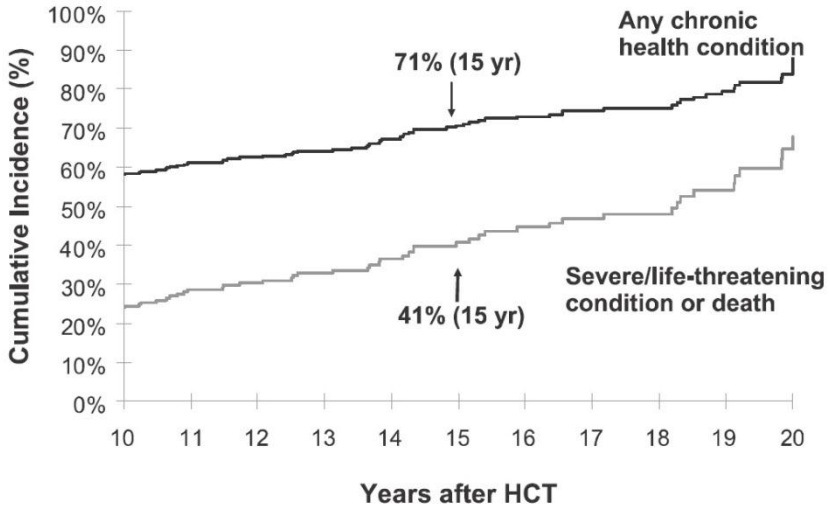
Cardiovascular events after HSCT: Premature vascular aging?





Tichelli A. et al. Blood. 2007; 110:3463-347.

Burden of morbidity with active late complications even beyond 10 years post HSCT



- No difference between autologous and allogeneic HSCT
- Significant higher among allo HSCT survivors with active chronic GVHD

Chronic health conditions in HSCT recipients with chronic GVHD

- Diabetes
- Coronary artery disease
- Stroke
- Ocular complications resulting in significant visual impairment
- Osteonecrosis that necessitated joint replacement

- Nearly all patients maintained some medical contact
- Only 27% returned to transplantation centers

Sun, C.-L. et al. Blood 2010;116:3129-3139
Sun, C.-L. et al. BBMT 2013;19:1073-1080

Will we observe late effects after RIC?

Late effects due to toxicity of conditioning will be reduced

- Cataract
- Endocrine dysfunction
- Infertility
- Radiation associated cancers

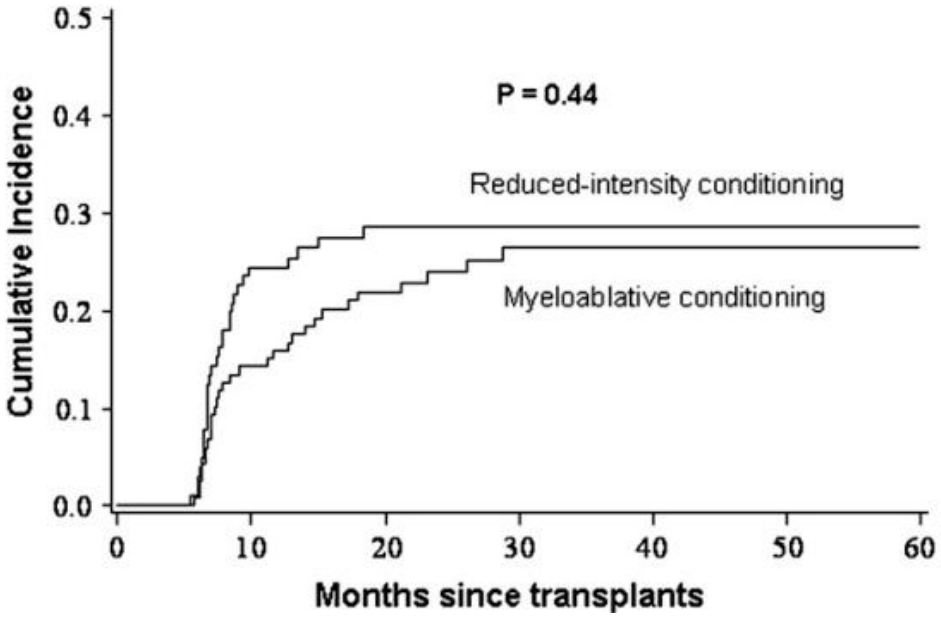
Late effects due to GVHD/IS will not be reduced

- Avascular osteonecrosis
- Squamous cell carcinoma
- Chronic kidney disease

But new confounders

- Older age
- More comorbidity
- New drugs (Fludarabine)

Cumulative incidence of chronic kidney disease after allogeneic HSCT



The question with RIC is not so much more or less, but which type of late effects

Al-Hazzouri A. et al. BBMT. 2008:;14: 658-663

Why does it matter to know about late complications?

- Not simply an enumeration of bad events

Early detection

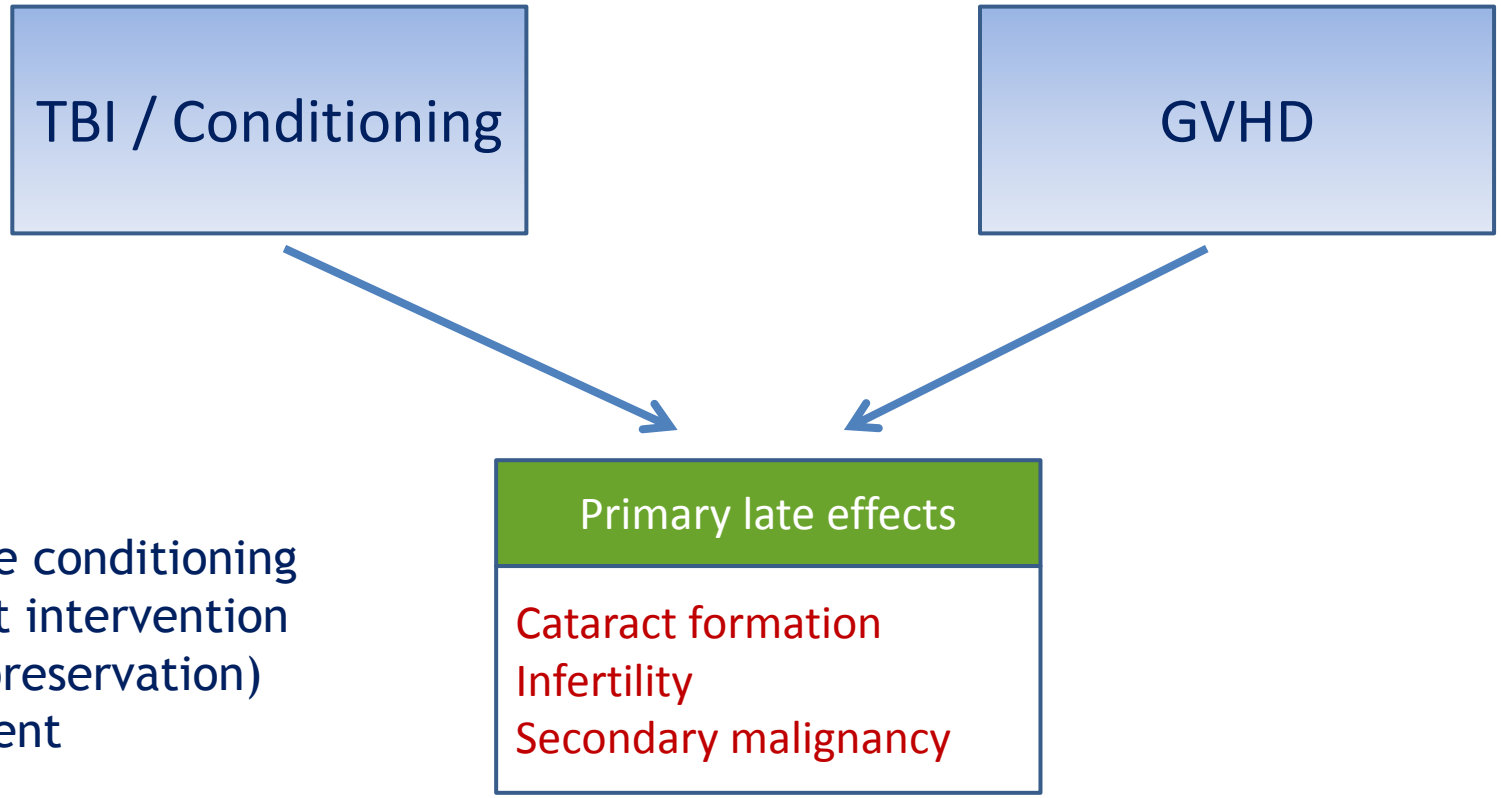
Prevention

Treatment

Change in the transplant procedure

Majhail NS. et al. BBMT. 2012; 18: 348-371
Majhail NS. et al. BMT. 2012; 47: 337-341
Majhail NS. et al. Hematol Oncol Stem Cell Ther 2012; 5:1-30
Majhail NS. et al. Rev Bras Hematol Hemoter. 2012; 34: 109-33

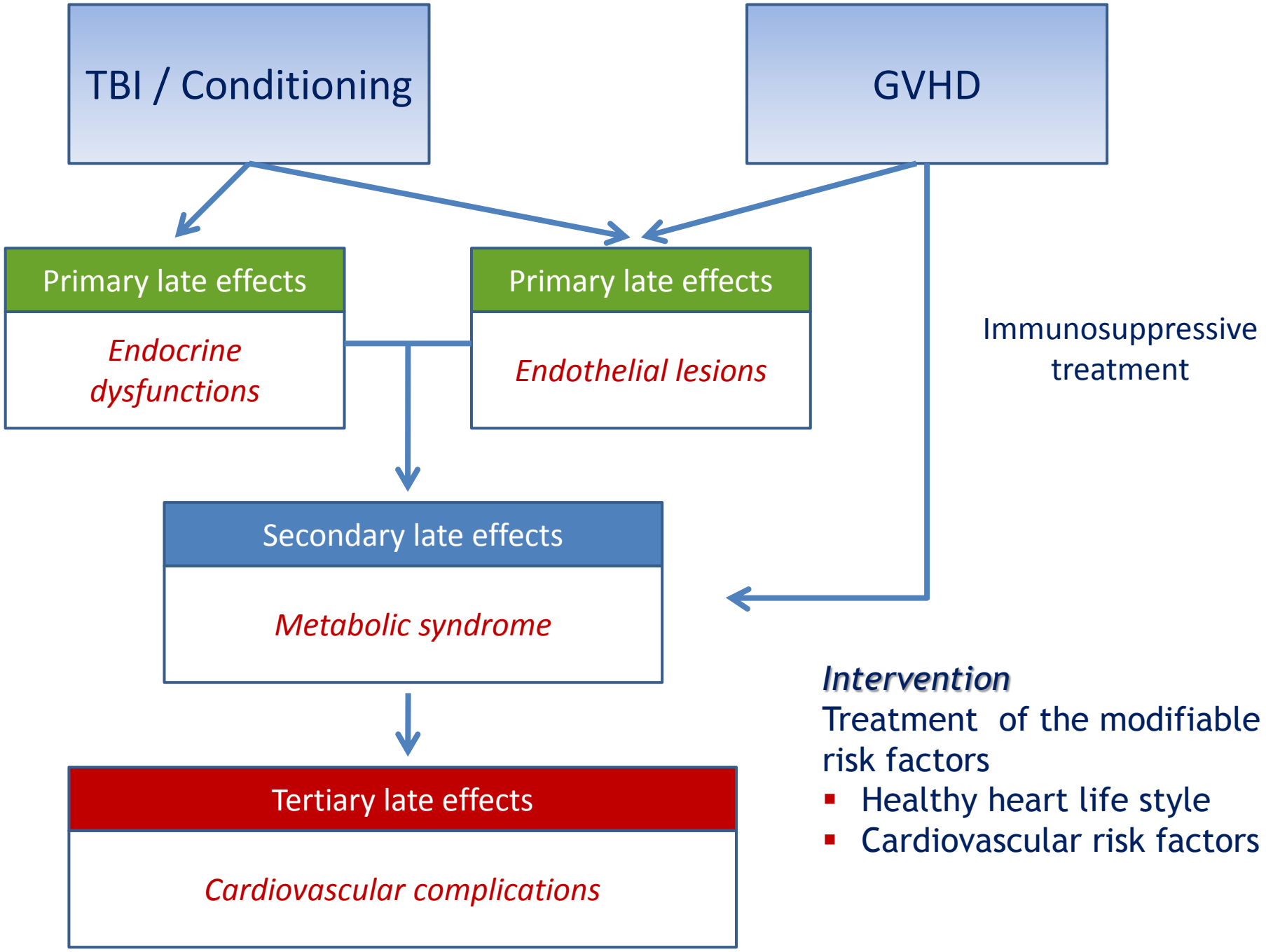
Late effects as a direct consequence of the transplant procedure



Intervention

- Change in the conditioning
- Pretransplant intervention (sperm cryopreservation)
- Early treatment

Tichelli A, Rovó A, and Socié G. Curr Probl Dermatol. 2012; 43: 132-149



Intervention

Treatment of the modifiable risk factors

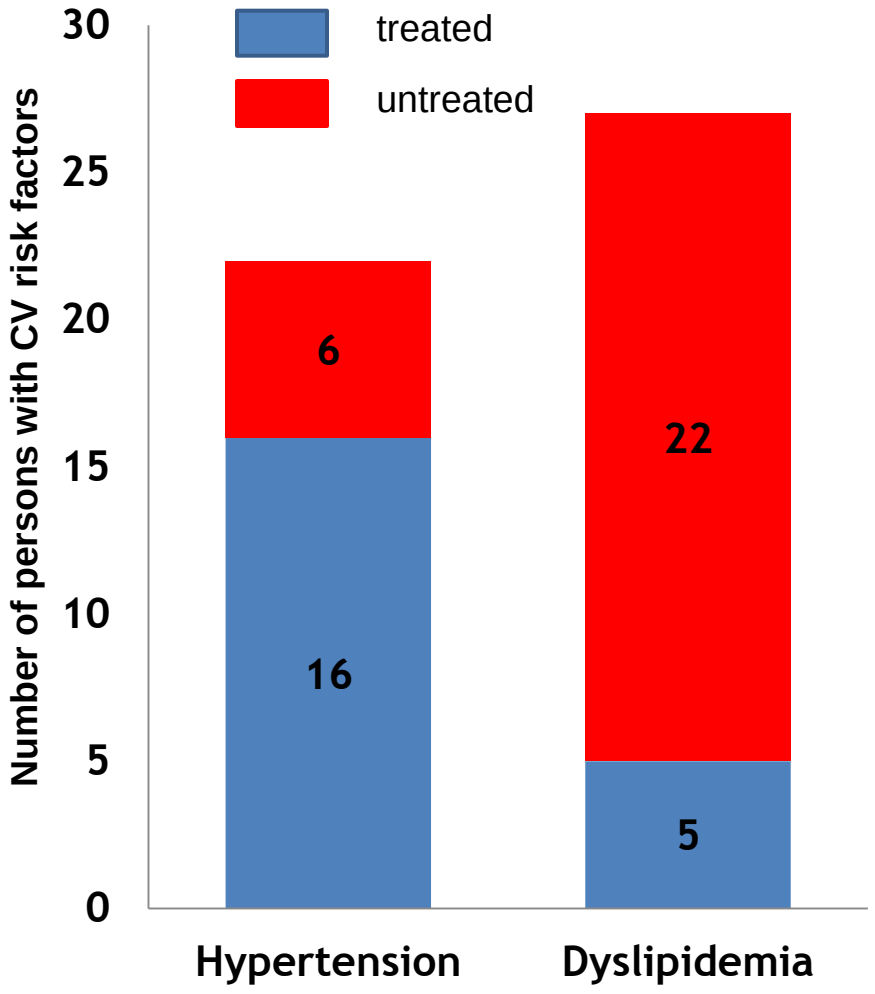
- Healthy heart life style
- Cardiovascular risk factors

Tichelli A, Rovó A, and Socié G. Curr Probl Dermatol. 2012; 43: 132-149

Centers' attitude in respect of cardiovascular risk factors after HSCT

- For long, cardiovascular risk factors have been underestimated and undertreated
- Argument evoked

  "CV risk-factors will disappear when immunosuppression is stopped"
- Since 2-3 years attitude in centers seem to improve



Rovó A. et al. BMT. 2009; 44 (Suppl 1):S69

Long-term follow-up (LTFU) transplant clinic setup

Why a transplant survivorship program

- Specialized follow-up care
- Increasing expectations
- Less disease oriented
- More on screening, prevention and counseling

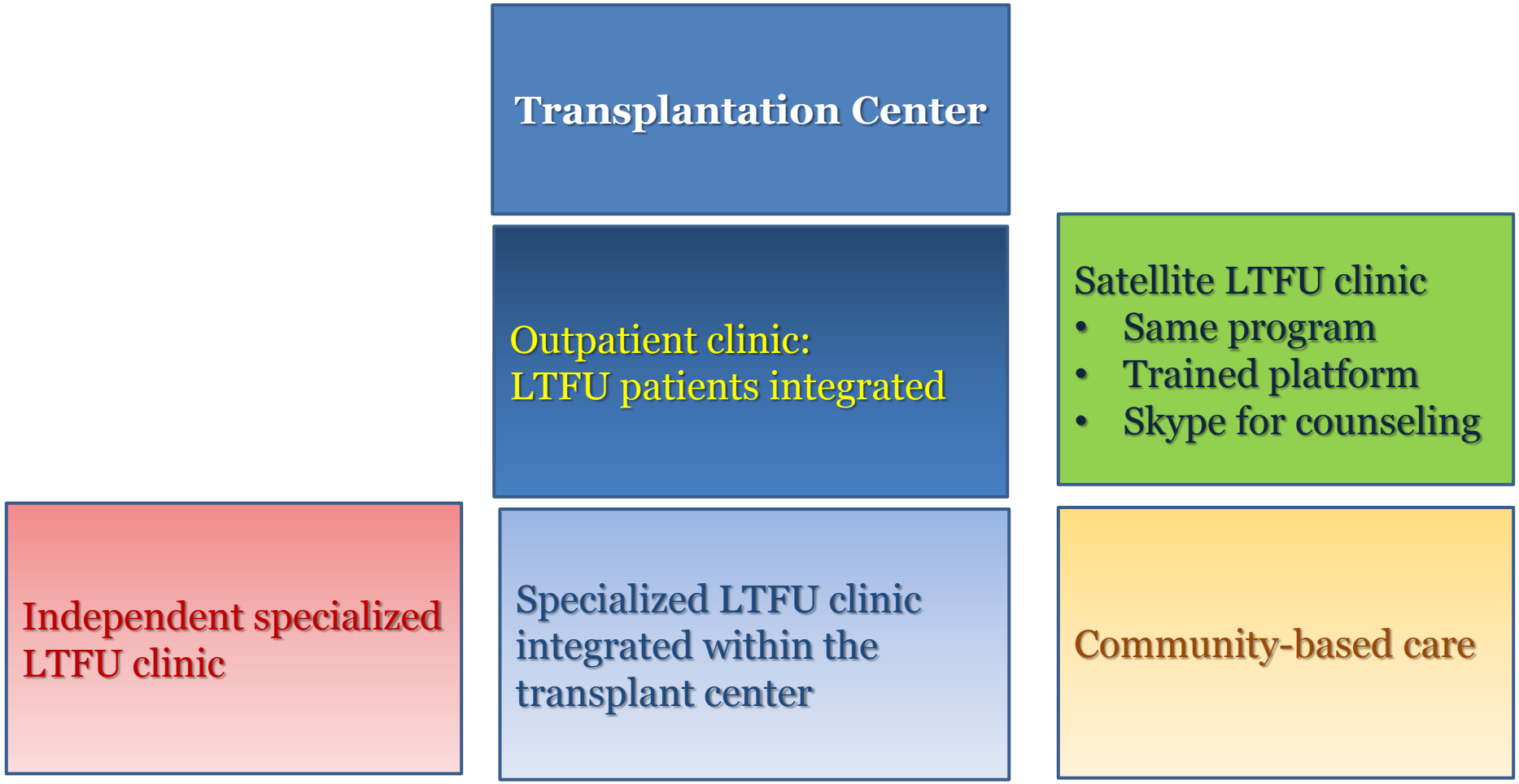
Main barriers for a LTFU transplant clinic

- lack of time, space, resources
- not enough support from the head of the transplant program
- deficits of knowledge
- not covered by health care insurance
- not perceived as a need
  - immediate complications and survival has priority
- ***Distance to the transplant center***

Tichelli A. et al. Book chapter in *Blood and Marrow Transplantation Long Term Management: Prevention and Complication* (in Press)

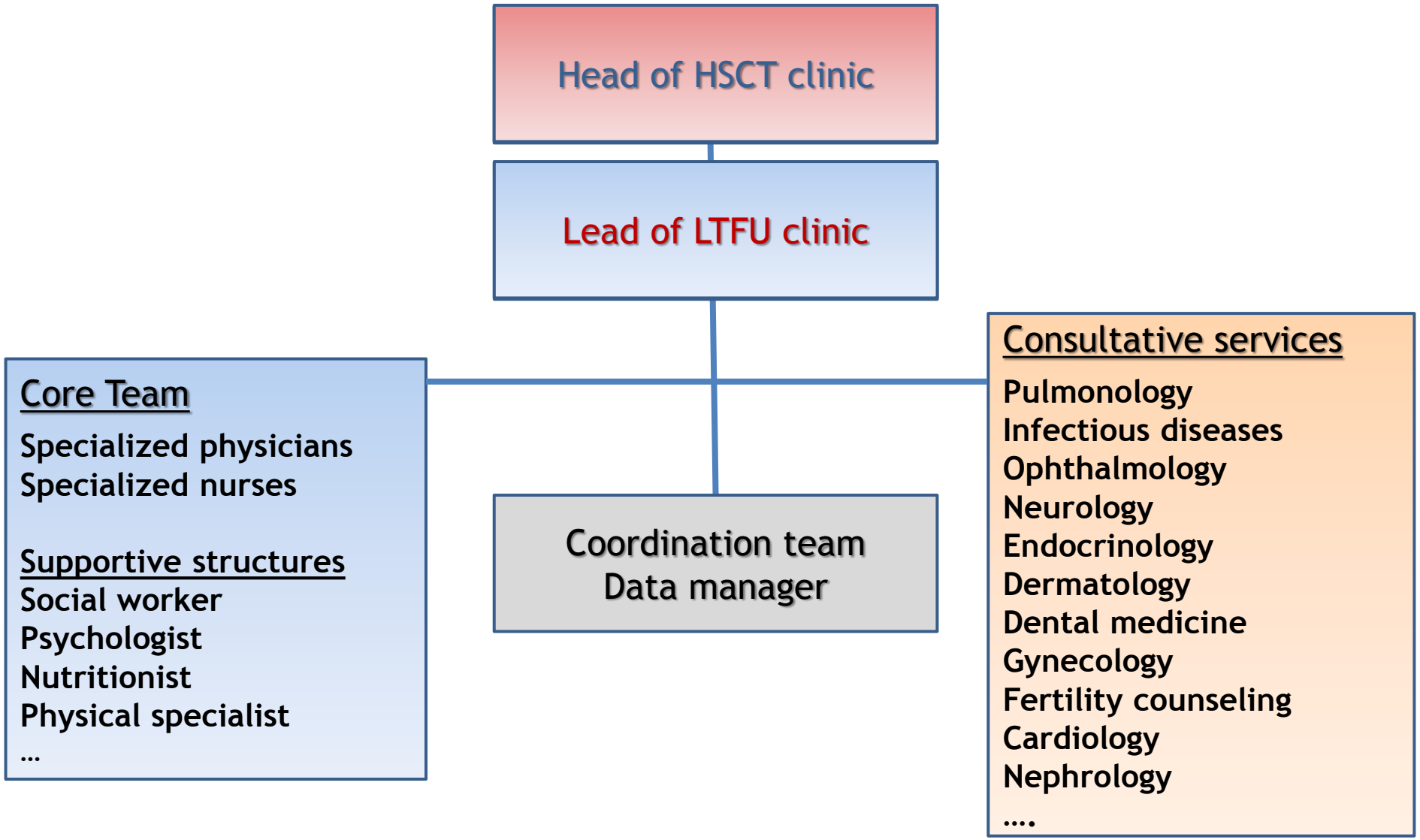
Eshelm-Kent J Cancer Surviv. 2011; 5; 345-357
Campbell. Cancer Surviv. 2011; 5:271-281

Models of long-term follow-up (LTFU) clinic



Tichelli A. et al. Book chapter in *Blood and Marrow Transplantation Long Term Management: Prevention and Complication* (in Press)

Multidisciplinary team for a long-term follow-up transplant clinic



Organization of the long-term follow-up visit

Survivorship care plan

- Patient's history and treatment summary
  - Exposure / radiation
- Co-morbidity
- Transplantation information
  - Type of HSCT
  - Conditioning
  - GVHD

➡ Risk profile for late complications

- Late complications
  - present
  - possible

Preparation

- Review of all documents
- Organization of the visit according risk profile
- Team meeting (who does what)

Follow-up visit

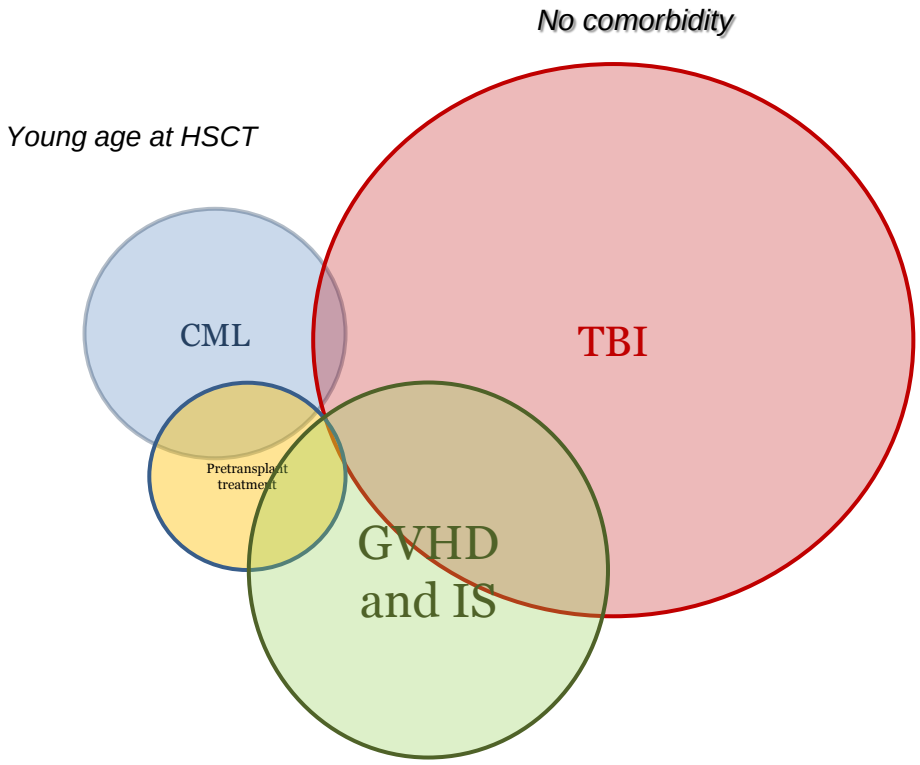
- Medical consultation
- Specialized investigations
- Consultative services
- Psychosocial assessment
- Counseling and answering special questions

Post-clinic follow-up

- Assemble and summarize all information
- Multidisciplinary discussion of the problems
- Recommendation plan for the next period

Tichelli A. et al. Book chapter in *Blood and Marrow Transplantation Long Term Management: Prevention and Complication* (in Press)

Back to our patient: Individualized risk profile
What we do during our follow-up control



Take home messages

- Late effects and their consequences are of major issue
- With change in the transplant procedure, late effects and long-term survivorship will continue to evolve
- Life-long controls, counseling and prevention/ treatment in a transplantation center are mandatory
- A model of long-term follow-up clinic should be available
- The “annual” follow-up control have to be planed
- We have to continue research on long-term survivorship “life-long”!


Thank you for your attention

Neglected long-term effects after HSCT

Genital chronic GVHD in men

- Single center cross-sectional analysis of 155 male patients
- genital skin changes in 31/155 (20%)
- 21 (13%) with inflammatory genital skin changes (genital GVHD)
- Significant higher coincidence of oral, ocular, cutaneous chronic GVHD
- Erectile dysfunction was significantly more frequent

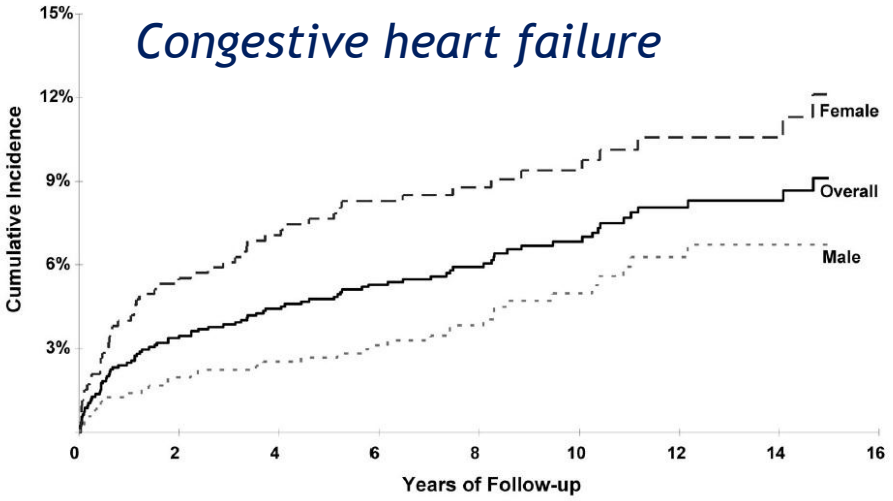
Increased death rate due to suicide and accident after HSCT

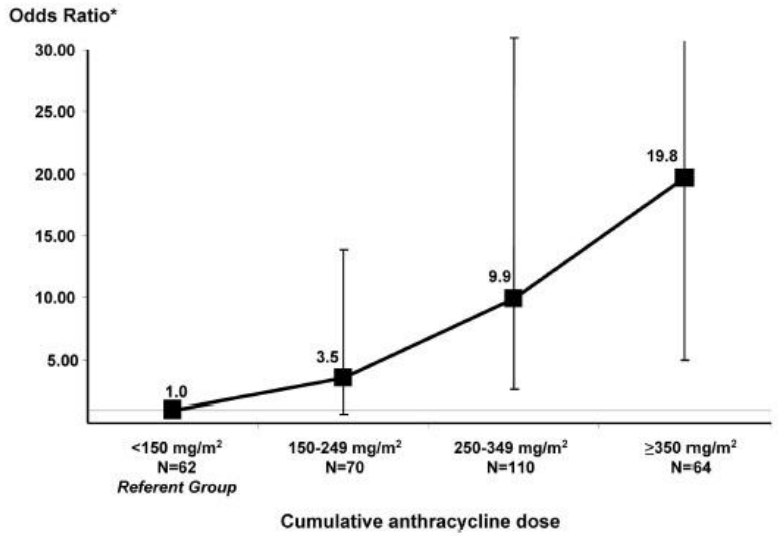
- Suicides (versus general population)
  - Standard mortality ratio 2.12
  - and absolute excess risk 10.91
- Accidents (versus general population)
  - Standard mortality ratio 2.12
  - and absolute excess risk 10.91
- Relapse associated with more suicide and accidents after autologous HSCT
- GVHD associated with more suicide after allogeneic HSCT

Mueller SM et al. BBMT Online 2013 (article in Press)

Tichelli A. et al. Cancer 2013; 119: 2012-2021

Late congestive heart failure mainly as the consequence of pretransplant treatments





- Dose dependent cardiotoxicity of anthracycline
  - 26% in non-HSCT population with doses ≥550mg/m^2
- Risk factors after autologous HSCT
  - Pretransplant exposure of anthracycline (≥250mg/m2)
  - Post-transplant cardiovascular risk factors in patients with pre-HSCT anthracycline therapy
- Genetic susceptibility to anthracycline-related cardiac failure after HSCT

Armenian S et al. Blood. 2011;118:6023-6029
Armenia S et al. BJH, Online 2013