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30 YEARS EMPOWERING PATIENTS
BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Late Effects after a Transplant Using Your Own Cells (Autologous Transplant)

Celebrating a Second Chance at Life Survivorship Symposium

April 17-23, 2021

R. Greg Bociek MD
Nebraska Medicine

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Late Effects of Autologous Hematopoietic Stem Cell Transplantation

R. Gregory Bociek MD MSc.

University of Nebraska Medical Center
Nebraska Medicine

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Objectives

- Review concept of autologous hematopoietic stem cell transplantation (AHSCT)
- Review common illnesses for which we transplant
- Review long term complications:
  - Immunologic/Hematologic issues
  - Late infectious complications/immunizations
  - Pulmonary (BCNU pulmonary toxicity)
  - Endocrine (thyroid, bone health, fertility)
  - Cardiac complications
  - Psychosocial issues

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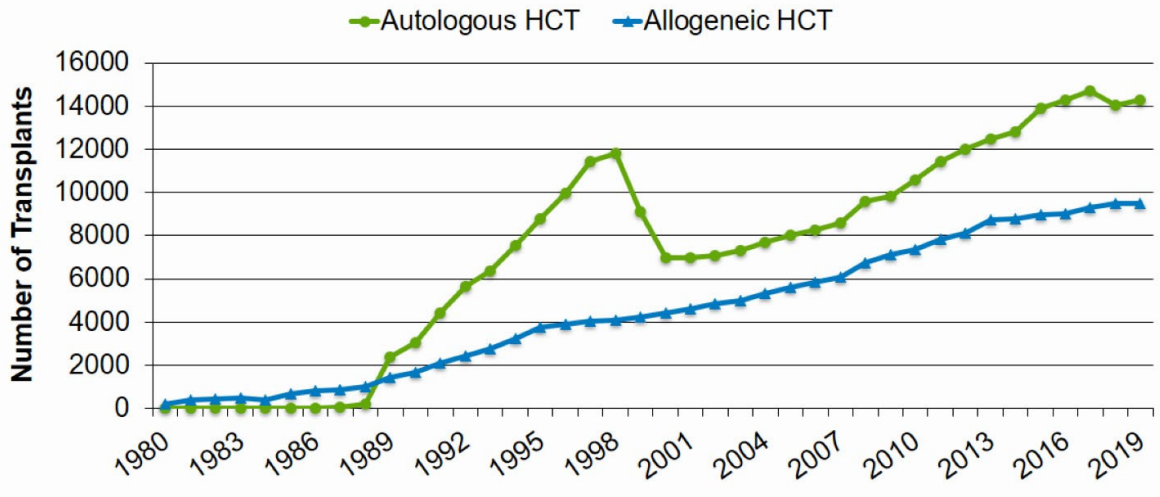
Estimated Annual Number of HCT Recipients in the US by Transplant Type



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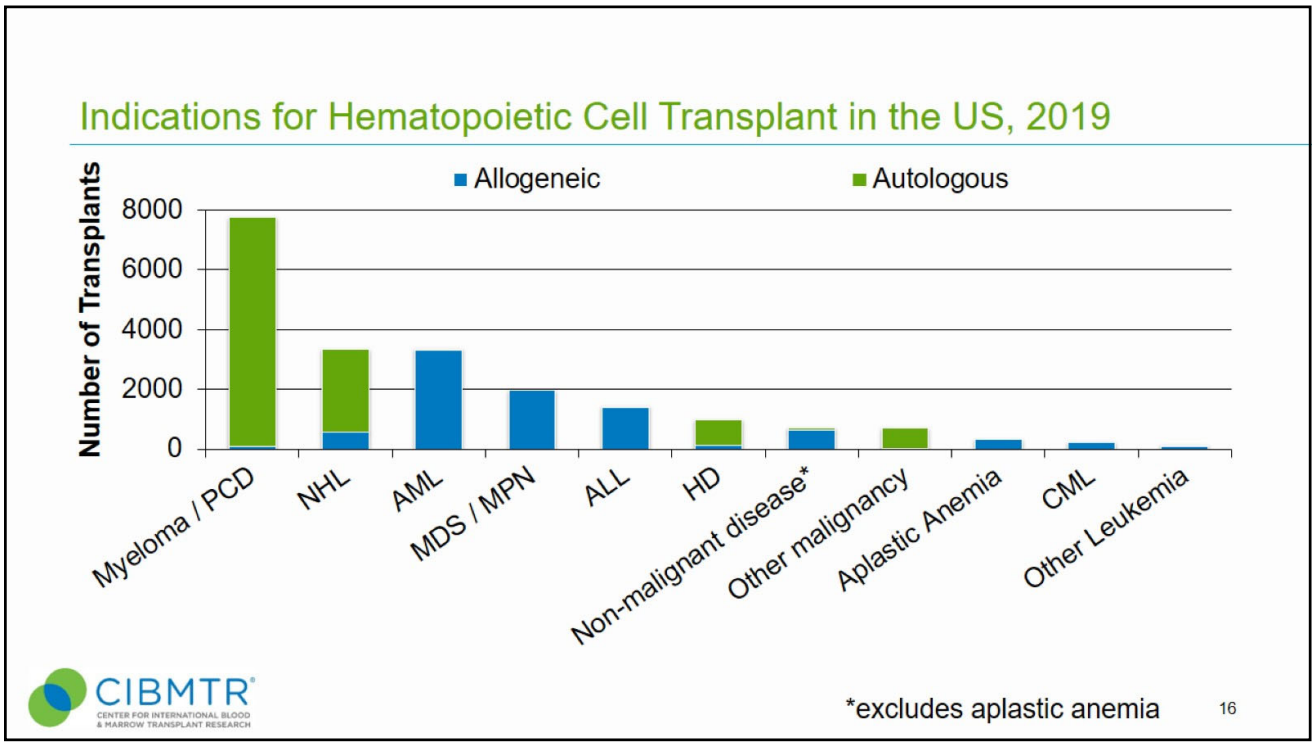
Indications for Hematopoietic Cell Transplant in the US, 2019
Allogeneic
Autologous
Number of Transplants
8000
6000
4000
2000
0
Myeloma / PCD
NHL
AML
MDS / MPN
ALL
HD
Non-malignant disease*
Other malignancy
Aplastic Anemia
CML
Other Leukemia
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*excludes aplastic anemia
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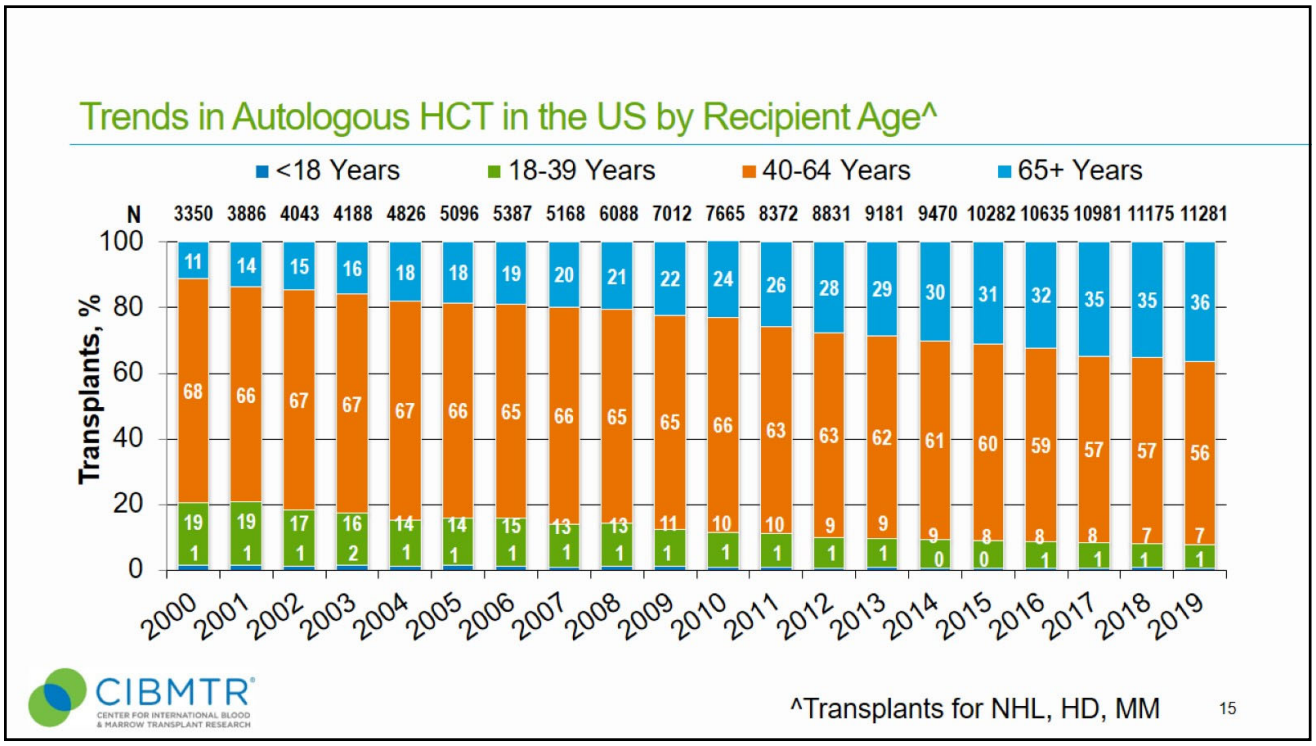
Trends in Autologous HCT in the US by Recipient Age^
<18 Years
18-39 Years
40-64 Years
65+ Years
N
3350 3886 4043 4188 4826 5096 5387 5168 6088 7012 7665 8372 8831 9181 9470 10282 10635 10981 11175 11281
Transplants, %
100
80
60
40
20
0
11 14 15 16 18 18 19 20 21 22 24 26 28 29 30 31 32 35 35 36
68 66 67 67 67 66 65 66 65 65 66 63 63 62 61 60 59 57 57 56
19 19 17 16 14 14 15 13 13 11 10 10 9 9 9 8 8 8 7 7
1 1 1 2 1 1 1 1 1 1 1 1 1 1 0 0 1 1 1 1
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
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^Transplants for NHL, HD, MM
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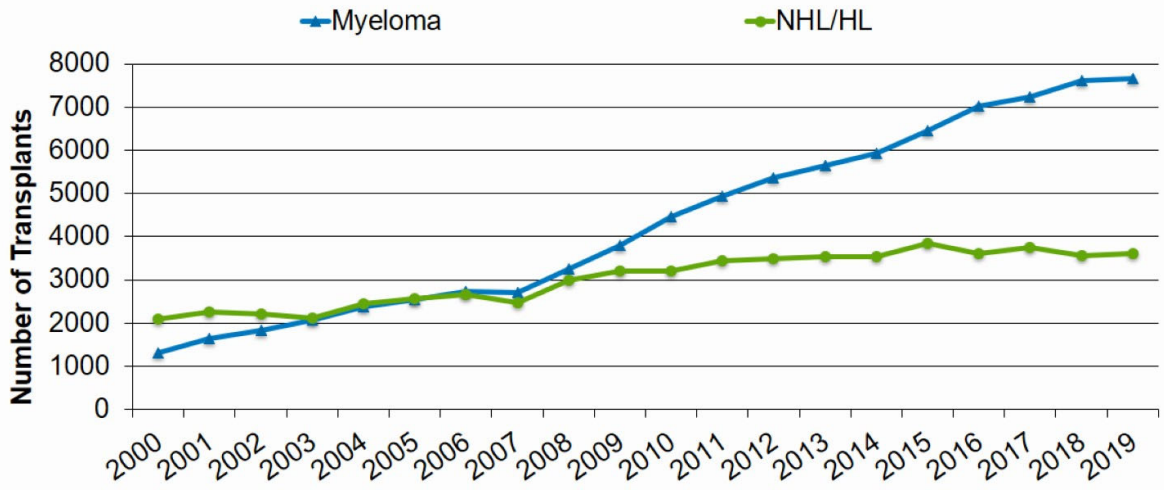
Selected Disease Trends for Autologous HCT in the US



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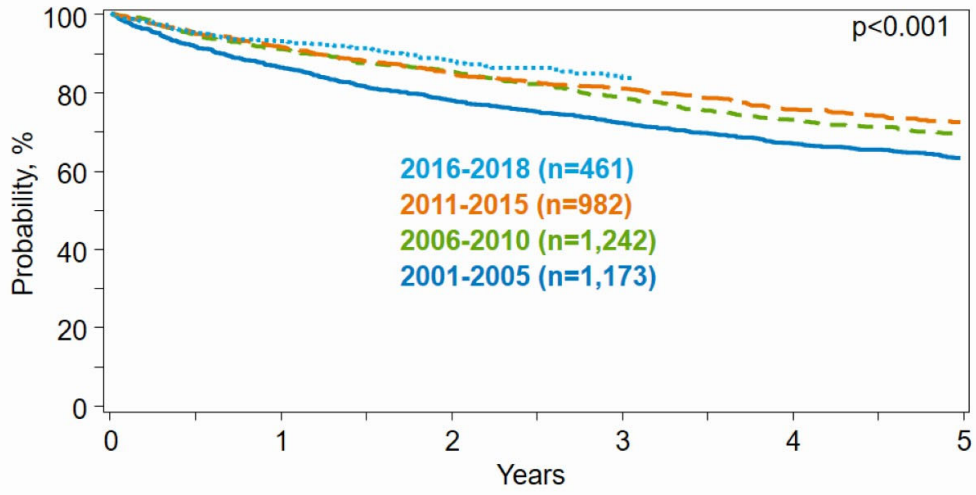
Trends in Survival after Autologous HCT for Follicular Lymphoma (FL), in the US, 2001-2018



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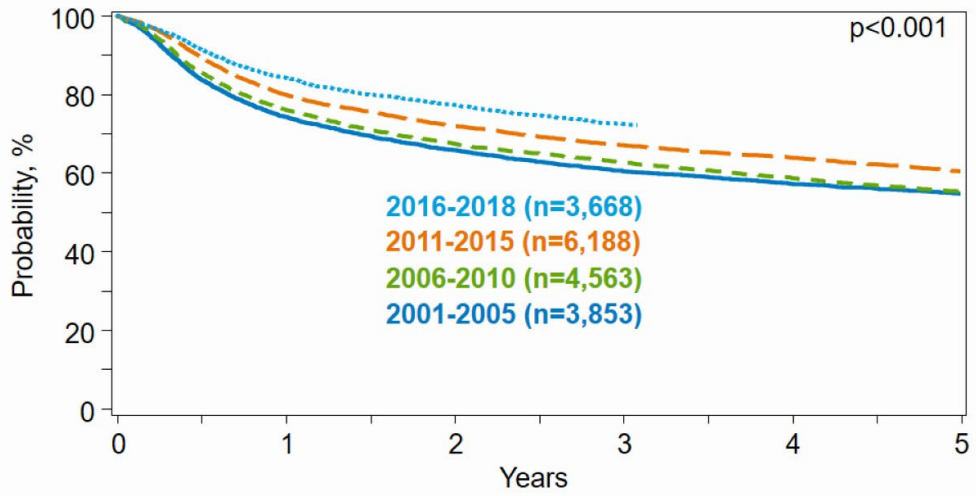
Trends in Survival after Autologous HCT for Diffuse Large B-Cell Lymphoma (DLBCL), in the US, 2001-2018



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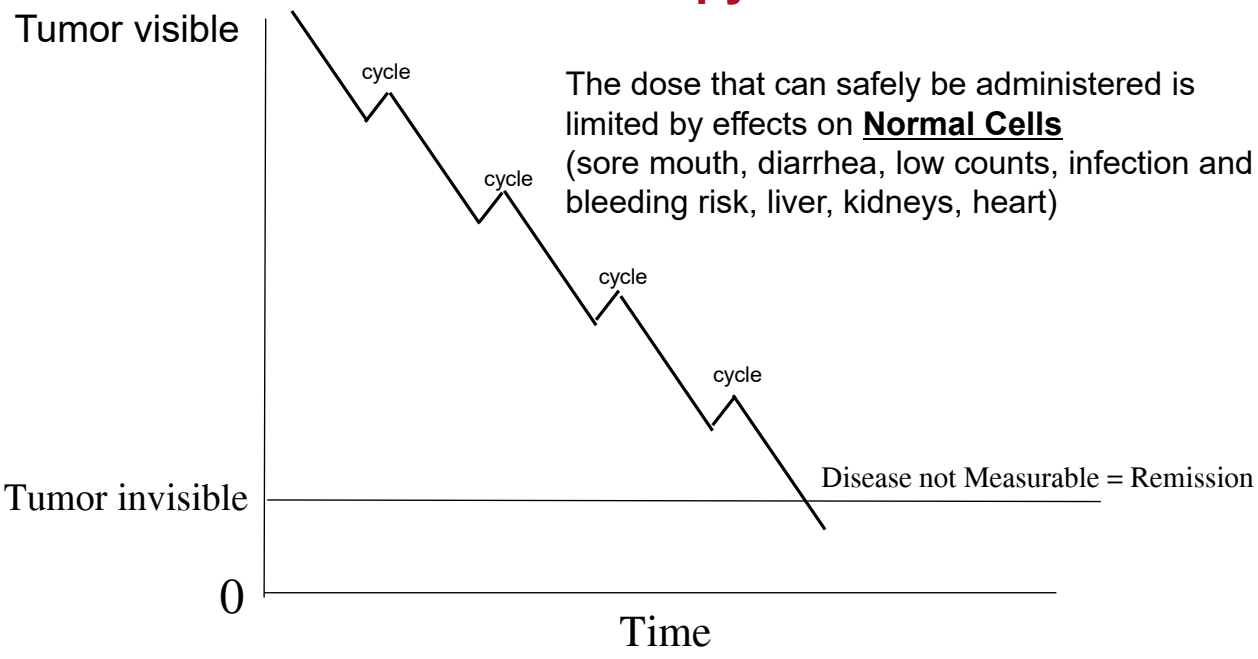
Effect of Chemotherapy on Tumor Burden



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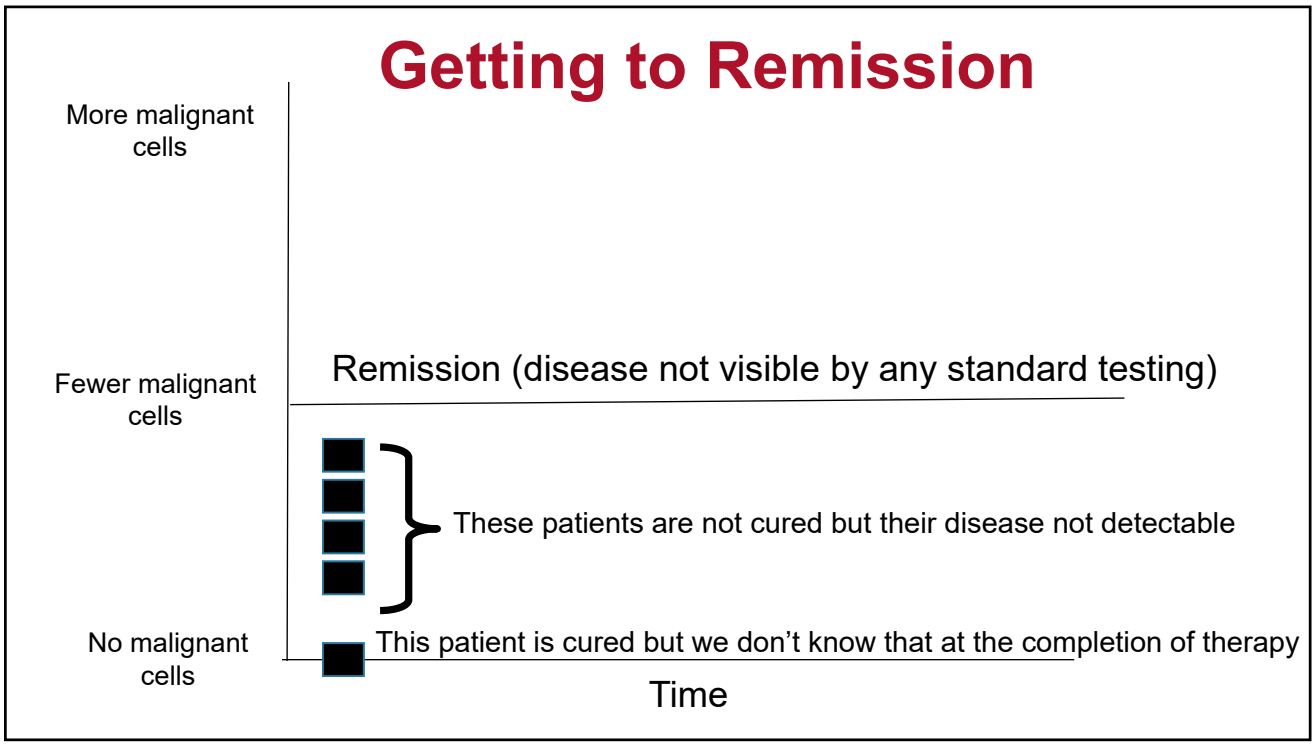
Getting to Remission
More malignant cells
Fewer malignant cells
No malignant cells
Remission (disease not visible by any standard testing)
These patients are not cured but their disease not detectable
This patient is cured but we don't know that at the completion of therapy
Time

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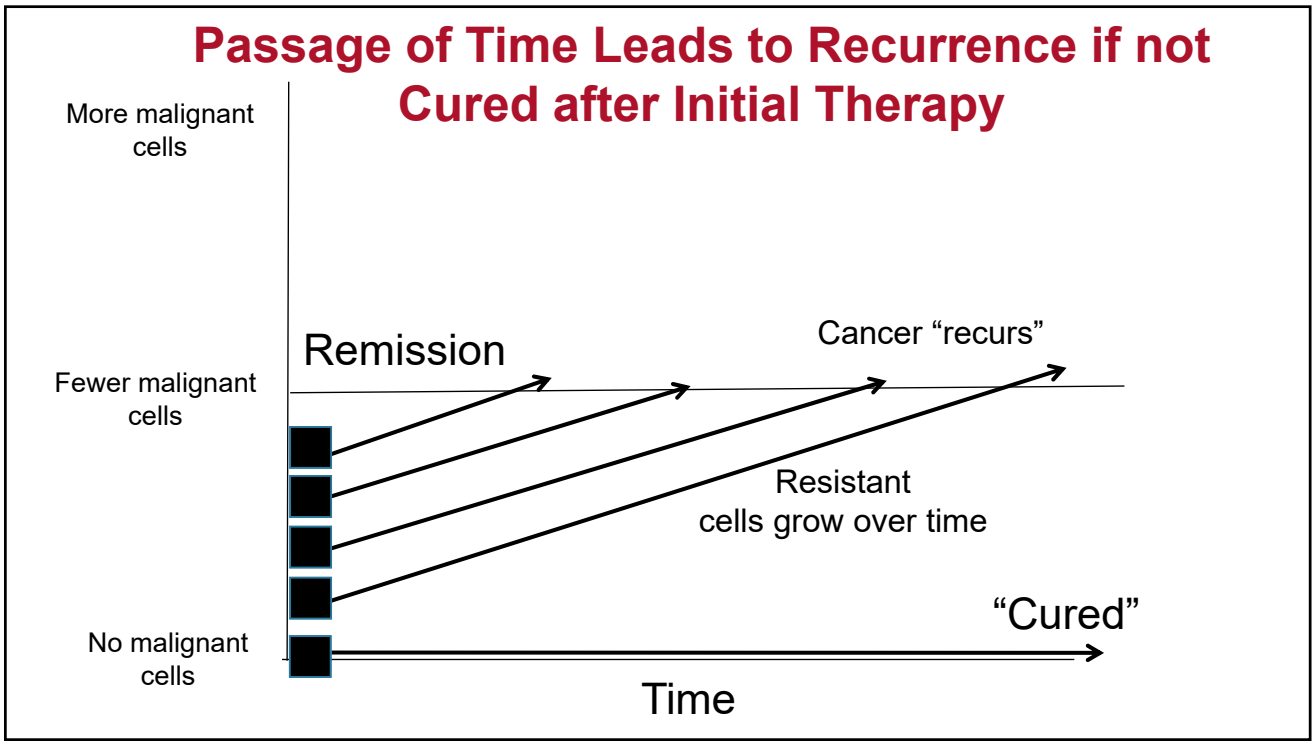
Passage of Time Leads to Recurrence if not Cured after Initial Therapy
More malignant cells
Fewer malignant cells
No malignant cells
Remission
Cancer "recurs"
Resistant cells grow over time
"Cured"
Time

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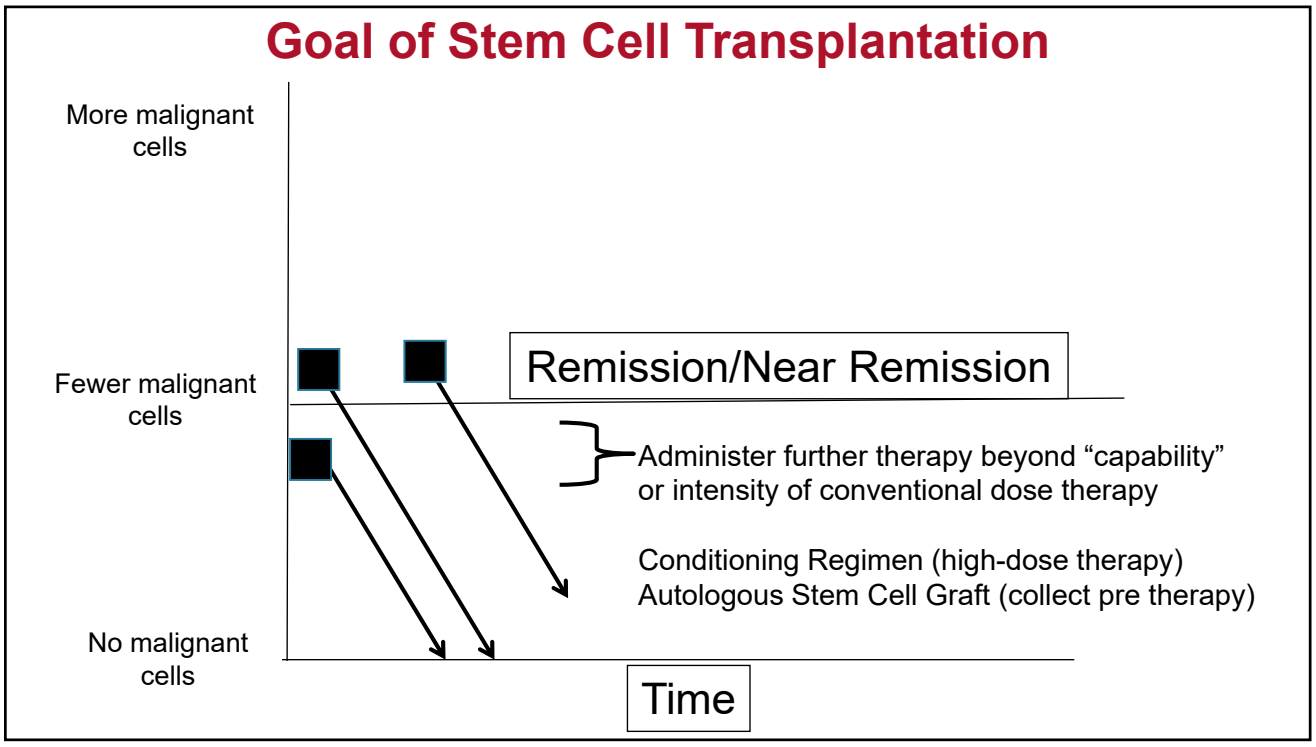
Goal of Stem Cell Transplantation
More malignant cells
Fewer malignant cells
No malignant cells
Remission/Near Remission
Administer further therapy beyond "capability" or intensity of conventional dose therapy
Conditioning Regimen (high-dose therapy)
Autologous Stem Cell Graft (collect pre therapy)
Time

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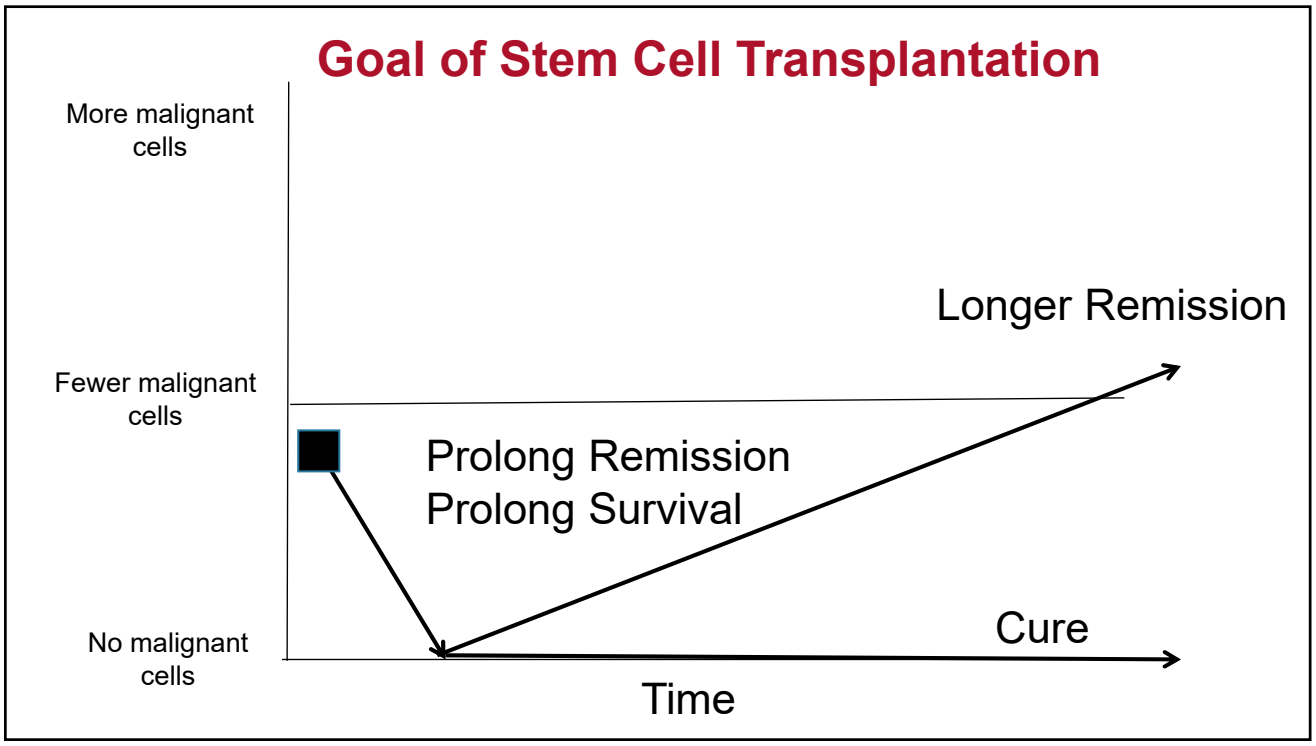
Goal of Stem Cell Transplantation
More malignant cells
Fewer malignant cells
No malignant cells
Longer Remission
Prolong Remission
Prolong Survival
Cure
Time

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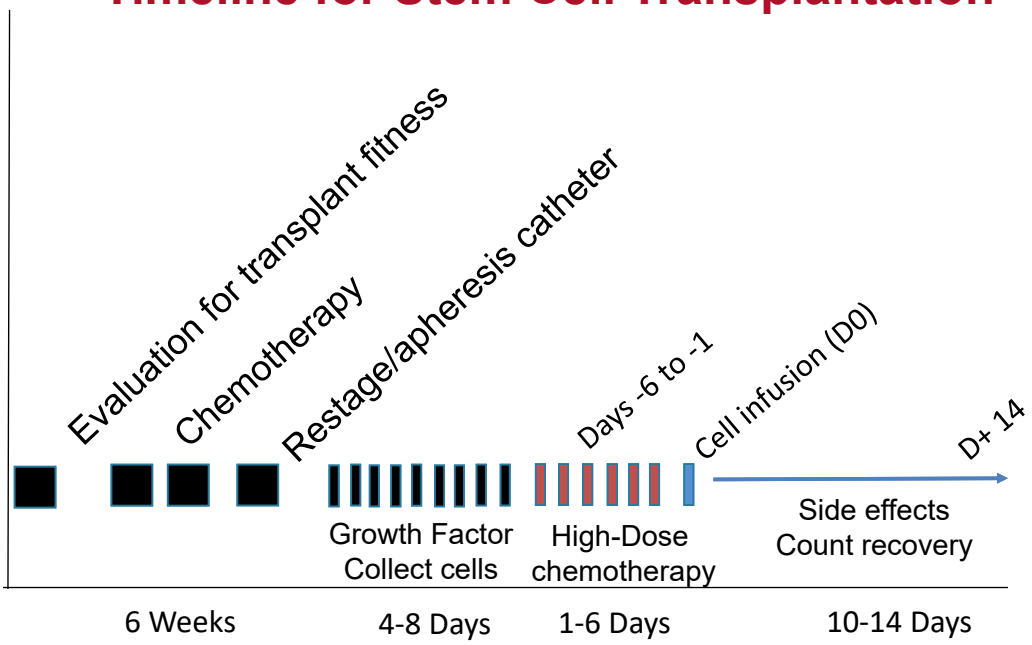
Timeline for Stem Cell Transplantation



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Components of Autologous Hematopoietic Stem Cell Transplant

Preparative Regimen
- Chemotherapy
- Possibly radiation
- Variable intensities

Graft Source (autologous or syngeneic)
- Peripheral blood (stimulated by growth factor)
- Bone marrow (rarely used or required today)

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Rationale for AHSCT

- Temporary Substantial bone marrow suppression
- Modest Degree of Immunosuppression
- Regimen-Related Side-effects Significant
- High-Dose Regimen is the Therapy; cells are support

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Preventing Recurrence after Transplant

- Maintenance Treatments:
  - Rituximab (mantle cell lymphoma)
  - Lenalidomide (multiple myeloma)
  - Brentuximab (Hodgkin lymphoma)
- Consolidative Radiation
  - To one or two sites of disease that were “largest” pre transplant

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Survey: Knowledge of Diagnosis and Post-Transplant Complications (3-25 years post transplant)

- 81% knew their diagnosis
- 99% knew the "components" of the transplant
- 90% were aware of most possible late effects
- 35% felt they had received follow-up surveillance/discussion of late effects
- Greater knowledge of late effects in the following patients:
  - Younger age at diagnosis
  - Mediastinal radiation
  - Those receiving follow-up care for late adverse effects

ACTA ONCOLOGICA 2019;58:1315

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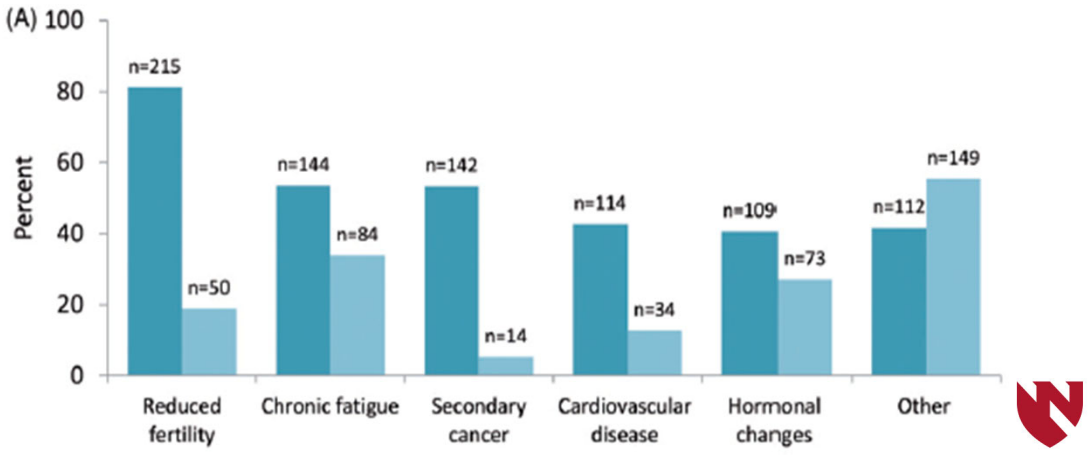
Survey: Knowledge of Post-Transplant Complications



ACTA ONCOLOGICA 2019;58:1315

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"Early" Post-Hospital Recovery Period

- Recover blood counts (days to weeks)
- Recover any other organ toxicity (e.g., kidneys)
- Remove apheresis catheter (days)
- Preventative antibiotics (acyclovir- months)
- Nutritional recovery (weeks to months)
- Muscle mass recovery (weeks to months)
- Begin re-vaccination series

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Early to Middle Post-Hospital Recovery Period: Vaccination

	3 mo	6 mo	9 mo	12 mo	2 yr
Prevnar	x	x	x		
Pneumovax				x	
Inact Polio	x	x	x		
HIB	x	x	x		
TDaP		x	x	x	
Hep B		x	x	x	
Influenza	In season				
Zoster		x		x	
** MMR					x x

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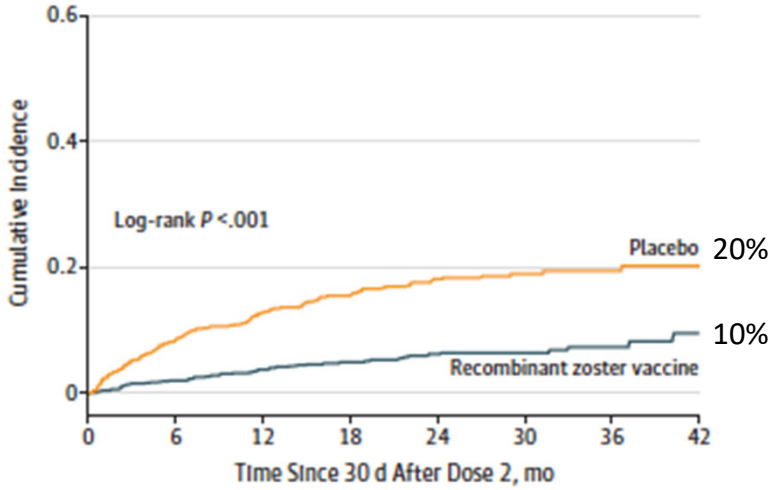
Risk of Zoster (Shingles) after AutoTransplant - Shingrix vaccine



JAMA 2019;322:123

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Early/Middle Post-Hospital Recovery Period - Lung Issues

"Idiopathic Pneumonia Syndrome"

- Older age at transplant
- Prior radiation or radiation as part of transplant preparative regimen
- Chemotherapy agents with risk:
  - BCNU (BEAM)
  - occasionally prior bleomycin
  - occasionally brentuximab

- Dry Cough, shortness of breath, reduced exercise tolerance
- Exam reveals "crepitations" or "crackles" (like squishing plastic wrap)
- Oxygen levels (saturation) may be normal or reduced
- Requires a high degree of suspicion and prompt evaluation

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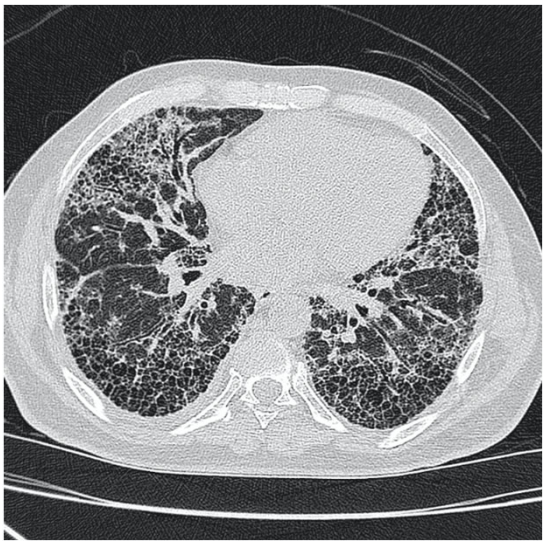
"Interstitial" Pattern of Injury



- ? Congestive heart failure
- Nasal washings for infectious causes
- Bronchoscopy for infectious causes
- Occasionally consider lung biopsy
- Treatment: Steroids (evidence is weak)
- Recovery can be complete

Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 27858

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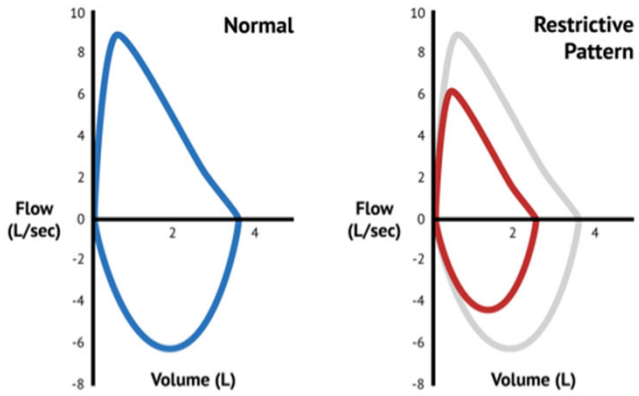
Lung Function Studies



- 6% of asymptomatic subjects after autologous transplant
- 37% impaired gas transfer
- More likely if current smoker

ACTA ONCOLOGICA 2018; 57:773

https://medschool.co/tests/lung-function/flow-volume-loops

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Immune Recovery after Transplant (30-365 days)

- WBC/neutrophils generally recover by 10-14 days (growth factor)
- Platelets slightly later; red cells generally last
- Lymphocytes (immune white cells) recover more slowly:
  - Cold sores (herpes simplex)
  - Shingles (herpes zoster)
  - Low immunoglobulin levels (bacterial infection) rarely a problem
  - Respiratory viruses may be more severe in this setting
- Infections relatively uncommon after recovery of cells except zoster (10-35% of patients)

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Late Neutropenia (30-365 days)

- Low bacteria-fighting blood cell count
- 10 weeks or later post-transplant
- Can last weeks
- Rarely leads to infection
- Associated with prior rituximab (transplant and non-transplant setting)
- Occasionally antibiotics or white blood cell growth factors might be used

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Late Bacterial Infections

- Uncommon
- Occasionally occur in setting of low immune proteins (immunoglobulins)
- Intravenous immune globulin (IVIG) may be used monthly to “fill” the body with the immune proteins it is not making
- Evidence for its benefit not strong in this setting

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Risks for Osteoporosis

- Advancing Age/mobility
- Gender (Female)
- Ethnicity (Caucasian, Asian)
- Smoking
- Alcohol
- Early Menopause/early testicular hormonal failure (young at BMT)
- Prolonged steroids-highly uncommon in auto-transplant setting
- Myeloma is a special category
- Allogeneic transplantation is a different situation
- Investigations depend on disease and age at transplant

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Bone Mineral Density after Autologous Transplant

- N=228 subjects Norway
- Bone Mineral Density post autologous transplant
- Age > 18
- Lunar Prodigy DEXA scan

Compared to population database

	Osteopenia	Osteoporosis	Population Osteoporosis
Male	35%	8%	8%
Female	41%	13%	11%

ACTA ONCOLOGICA, 2017;56;590

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Breast Health

Chest radiation between 10-30 years of age may increase risk of breast cancer

- Highly dependent on technique, dose, size of field (different in 2020 vs 2000), genetic risk

After age 25:

- Clinical exam starting 8 years after RT
- Annual mammogram 8 yrs after RT but not until age 30
- Annual breast MRI 8 yrs after RT not until age 25
- Breast awareness/education- low evidence no harm

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Female Sexual Health after Transplant

Female lymphoma subjects - average age 53 compared to control group

- More sexual problems compared to similar aged subjects without transplant
- More sexual discomfort
- Reduced frequency of sexual activity
- Had more sex-related fatigue
- Sexual activity associated with older age, being in a relationship
- Sex-related fatigue was related to being younger, having chronic fatigue, and having ongoing emotional distress

Bone Marrow Transplant 2019

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Male Sexual Health after Transplant

Male lymphoma subjects - average age 55 compared to control group

- 39% reported sexual satisfaction
- 30% sexual drive only a few days per month
- 41% erections firm enough for sexual activity only a few times per month
- All BFSI (brief sexual function inventory) measures lower
- Presence of cardiovascular disease associated with worse erectile function
- Age > 55, chronic fatigue, physical inactivity associated with lower sexual functioning

Bone Marrow Transplant 2020

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Fertility after Transplant

- Difficult to know "incidence" of infertility
  - survey
  - pre-existing conditions
  - unknown spousal fertility issues
- General Observations:
  - Can occur after regimens containing radiation
  - Fertility can return in both males and females, generally younger individuals
- Consider a safe waiting period (2 years)
  - Lack of menses does not mean infertility
  - always counsel and assume fertility!

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Pregnancy Risks after Transplant

- Miscarriages similar to population expected (10%)
- Requirement for Cesarian section may be higher (30%)
- Requirement for assisted fertility techniques (20%)
- Risk of pregnancy-related complications appears similar
- Incidence of pre-term delivery appears similar

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Working after Transplant

- Generally, recommendation is not to work first 3 months but depends on intensity of job
- Study: N= 274, mean age 52 years
  - 77% working pre-transplant
  - 69% working at time of survey
  - Employment pre transplant predicted for working post-transplant
  - Work hours did drop significantly post transplant
- We advocate short term disability if required and gradual return to full time hours with our input
- Our recommendations based on age, intensity of work, need to work

BMC Cancer 2021; 21:143

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Secondary Cancers: Risk Factors

- Pre-existing risks (e.g., smoking, alcohol intake)
- Post-transplant maintenance therapy (lenalidomide-multiple myeloma)
- Males may be at more risk
- Early age may be greater risk
- Earlier era of transplant

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Secondary Cancers: Types

- Second cancer risk varies by study and type of cancer
- Secondary MDS/AML likely the most common issue:
  - Extent of prior therapy
  - Age at transplant
  - Use of total body radiation (3% vs 10% at 10 years)
  - Prior alkylating agents
  - 5-10 fold increase
- Melanoma may have two-fold increase
- Non-Hodgkin Lymphomas up to three-fold increase

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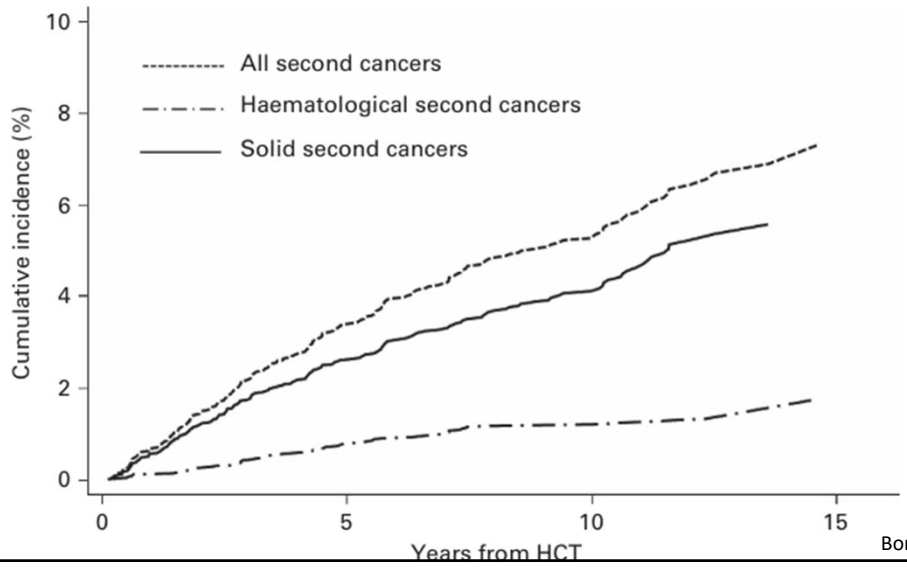
Secondary Cancers after AutoTransplant (n=7765)



Bone Marrow Transplant 2014

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Heart Health after AutoTransplant

- 10-year cumulative incidence:
  - Ischemic Heart Disease: 3.8%
  - Cardiomyopathy 6% (prior Adriamycin and dose may matter)
  - Stroke 3.5%
- Risks:
  - Pre-transplant smoking, BP, lipids, DM increased risk 1.5 fold
  - Persistence of abnormal BP and lipids at 1 year after transplant associated with increased risk

Biol Blood Marrow Transplant 2014;20:794

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Summary of Long-Term Follow-Up

Organ/System	What we Measure	What we Do
Thyroid gland function	Thyroid levels (blood)	Treat-Thyroxine
Cataracts	Symptoms/periodic eye exam	Surgically remove- low risk
Bone Health	Fracture Risk/DEXA Testosterone	Calcium, Vitamin D/ Osteoporosis Rx
Breast Health	Mammography/MRI in some	Refer as appropriate
Oral	Dental Evaluations/x-rays	Dental Care

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Summary of Long-Term Follow-Up

Organ/System	What we Measure	What we Do
Heart Health (heart failure, coronary disease)	Blood Pressure, Lipid levels	Refer/treat as appropriate Stress tests/echo as required Stop smoking
Skin Health	Annual Skin Exam/sun health	Refer as appropriate
Secondary Cancers	Blood Counts, exams	Stop smoking, Investigate as needed
Fertility	Hormone levels Semen Analysis	Pregnancy counseling/birth control
Immune System	Immune globulin levels if repeated infections	Infection prophylaxis Vaccines IVIG occasionally

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Summary of Life after AHSCT

- Many feel they get back to near 100% of pre-transplant health
- Few are left with major life-altering medical issues
- Fertility can return in younger individuals
- Normal work life can resume
- Psychological health is important
- Age-appropriate health screening/vaccines
- Sun safety
- Appropriate follow-up for transplant-related medical issues

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Questions?

Celebrating a Second Chance at Life Survivorship Symposium 2021

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