



Secondary Cancers

Celebrating a Second Chance at Life Survivorship Symposium

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Peter McSweeney MD, ChB

Colorado Blood Cancer Institute,
Presbyterian St. Luke's Hospital

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Secondary Cancers after Transplant: Overview

- What are secondary cancers?
- Who's at risk after transplant?
- How often do secondary cancers occur?
- Monitoring and Prevention
- Treatment Options

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Second Cancers after Transplant: Trying to Understand the Problem

- Study sizes and methods
 - Larger versus smaller
 - Length of follow-up
 - How good is the data?
- Concept of relative risk to population
 - Younger people have lower risk of cancer
- Potential to affect life expectancy
- Risk may be affected by many factors

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General Factors Promoting Cancer Development

- Immune deficiency
- Aging
- Exposure to carcinogens
 - Viruses
 - Smoking
 - Alcohol
 - Sun
- Genetic predisposition
 - Family history
 - Telomere shortening
- Treatment with cancer promoting therapies
 - Drugs
 - Radiation

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Factors That May Affect Cancer Risk after Transplant

- Underlying disease, prior therapies
- Donor versus own stem cells
- Drugs given to prevent GVHD
- Graft-versus-host disease
- Viral Infections – EBV, HPV
- Radiation use before or during transplant
- Higher-versus-lower dose transplant regimens
- Maintenance therapies after transplant

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Secondary Cancers after Allogeneic Transplants (transplants using donor cells)

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Patient Story

- 64 year-old gentleman from Colorado, indoor occupations
- DX with follicular NHL in 2004 at age 47, and myelodysplastic syndrome (MDS) in 2011 at age 54
- Had both cancers at time of transplant with matched sibling 2011
 - In remission of both diseases after transplant
 - Relapsed with myelodysplastic syndrome at 3 months
 - Treated with more chemo and tapering of immunosuppressants

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Patient Developed GVHD

- Severe GVHD: skin, mouth, eyes
- GVHD gradually better but persistent, still on low-dose immunosuppressants
- Frequent skin cancers and scaly patches on skin
 - Squamous cell mostly, also a melanoma
 - Carcinoma on the tongue led to partial tongue resection
- Hard to tell difference between GVHD and pre-cancerous changes

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Patient Now Disease-Free

- Check ups regularly
 - GVHD assessments
 - Dermatology visit every 3 months
 - Regular oral medicine visits
- No relapse of lymphoma or MDS

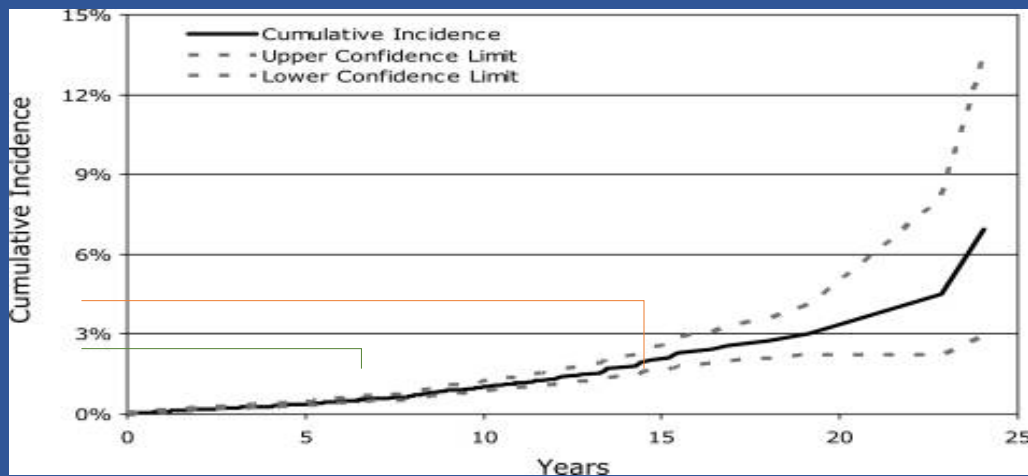
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Secondary Cancers after Allogeneic Transplant (CIBMTR – 28,874 cases)

- 2nd cancers occurred at more than 2x expected rate of general population
- Highest excess risk in lip, salivary gland, tongue, bone, soft tissue and liver
- The relative risk for most solid tumors increased over time
- Increased risk with GVHD and radiation exposure at younger ages

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Cumulative incidence of second solid malignancies after allogeneic HCT.



Demonstrates the need for long term health screening and monitoring

Rizzo et al. Blood, 2009 Jan 29; 113(5): 1175-1183.

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Most Common Solid Cancers after Transplant (EBMT (Europe) – 4,065 cases)

- Lung
- Breast
- Colorectal
- Prostate
- Melanoma

Ticelle et al, Jama Oncology 2019;5(2):229-235

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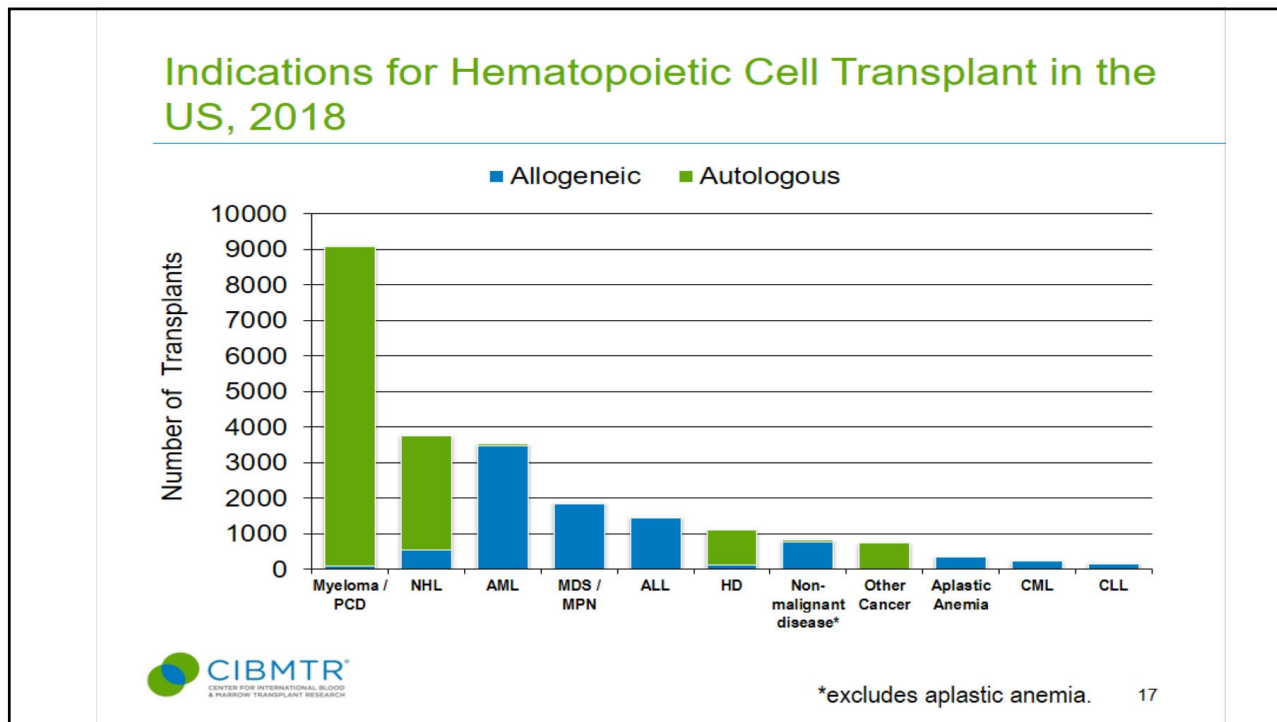
Post-Transplant Lymphoproliferative Disorder

- Presents as a lymphoma usually in first year or two after transplant
- Associated with Epstein-Barr Virus (mononucleosis virus)
- Associated with more immunosuppressed transplants
 - T cell depleted
 - severe GVHD
 - cord blood
- May be treatable with rituximab, chemo, cell infusions

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Secondary Cancers after Autologous Transplants (transplant using your own cells)

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Risk Factors for Secondary Cancer after Autologous Transplant

- Age
- Type of cancer
- Pre-transplant therapies
- Stem cell collection
- Post-transplant therapies
- Use of radiotherapy
 - for underlying disease
 - with transplant

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Secondary Cancers in California Myeloma Patients One Year Post-Transplant

3,202 transplant patients , 13,129 non-transplant patients

- Solid tumors
 - 3.6% at 5 years
 - 6.7% at 10 years
- Hematological tumors
 - 1.3% at 5 years
 - 2.7% at 10 years
- No overall increase in second cancers overall in transplant group vs. non-transplant group
- Slight increase in hematologic malignancy risk (1.5X)
- Very little effect on overall mortality
- Does not include effects of Revlimid maintenance

Rosenberg, A.S. et al. *Blood Cancer J.* 11, 5 (2021)

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Revlimid Maintenance Therapy and Cancer

- Revlimid prolongs progression-free and overall survival
Increases risk of new cancers
- “Lenalidomide increased the risk of a second primary cancer, but the survival benefits outweigh this risk.”
Syed, Drugs 2017.
- Safer maintenance needed

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Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) after Autologous Transplant

- Marrow damage from prior cancer therapy can lead to bone marrow cancer
- Risk increased after autologous transplant
 - *Infrequently seen after allogeneic transplants*
- Have high-risk genetic features and greater resistance to therapy
- Tend to occur in first 5 years after transplant

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Risk of Myelodysplastic Syndromes (MDS) or Acute Myeloid Leukemia (AML) after Autologous Transplant

	Hodgkin Lymphoma (n = 916)	Non-Hodgkin Lymphoma (n = 3546)	Multiple Myeloma (n = 4566)
Years post-transplant	%	%	%
3	1	2	1
5	3	4	1
10	4	6	3

Risk 5-10 x background risk of normals

[Radivoyevich et al, Leuk Res. 2018 Nov; 74: 130–136.](#)

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Treatment for Therapy–Related MDS and AML

Options depend on general health and prior therapies and include:

- Supportive care
- Drug therapy - generally not curative
 - Newer venetoclax-based therapies may extend survival
- Allogeneic transplant may cure or extend survival
 - Best outcomes when blast counts low

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Other Maintenance Therapies and Cancer Risk

- Increasingly used after transplants to prevent or delay relapse
 - Rituxan after auto transplant for Mantle cell lymphoma
 - Brentuximab for Hodgkin disease
 - Vidaza after allo transplant for AML
 - Midostaurin after treatment for Flt-3 positive AML
- Weakens blood counts
- May suppress immunity
- May promote new cancers??

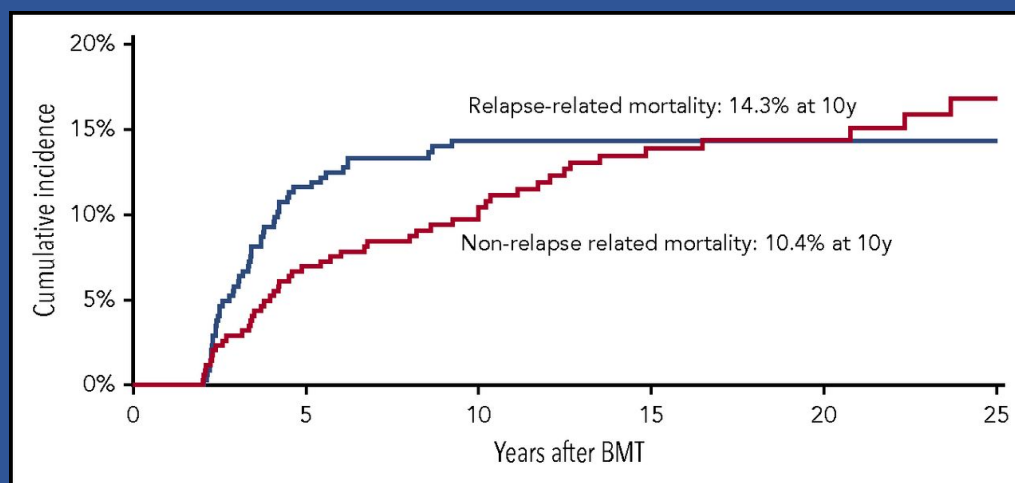
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Pediatric Transplant Recipients

- Different diseases and treatment protocols
 - Autologous: Neuroblastoma, CNS tumors, lymphoma, other
 - Allogeneic: Immune deficiencies, enzyme deficiencies, acute leukemia, sickle cell, thalassemia
- Exposures to toxic therapies early in life while still growing
- Fertility/hormonal effects
- Genetic pre-disposition to cancer, e.g. Fanconi syndrome
- Solid tumors can occur > 20 years after transplant
- Different cancer screening protocols, beginning at an earlier age than recommended for general population

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Late mortality after autologous transplant in childhood



21.4 % of late deaths from new cancers

Holmqvist et al, Blood, 2018, Figure 2

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Outcomes after Secondary Cancers

Depends on:

- Type of cancer
- Age
- Stage at diagnosis
- Localized or not
- Surgery or radiotherapy cure?
- Effectiveness of drug therapy
- Comorbidities
 - Infections
 - GVHD
 - General health

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Outcomes

Best (med survival > 10 years)	Intermediate (med survival 6-10 years)	Worst (med survival < 1 year)
Breast	Colorectal	Pancreas
Melanoma	Endometrial	Lung
Cervix	Sarcomas	Liver
Thyroid	Ovarian	Esophagus
Prostate	Oropharyngeal	Brain
	Bladder/Kidney	Stomach

A study from Japan showed:

- age of cancers developing was younger than of general populations
- poorer outcome of treatment than general population for allogeneic transplant recipients.

Ticelle et al, Jama Oncology 2019;5(2):229-235
Inamoto et al. Blood Advances 2018.

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What Can You Do to Reduce the Risk of New Cancers after Transplant?

Reduce risk factors for cancer

- Think of cancer developing as a multistep process
- May be able to prevent or delay

Screening

- Follow guidelines
- Increased or early surveillance in some instances

Early Detection

- Better chance of catching more treatable disease

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Seven Steps to Prevent Cancer



- 1 Don't use tobacco.
- 2 Protect your skin from the sun.
- 3 Eat a healthy diet.
- 4 Maintain a healthy weight and be physically active.
- 5 Practice safer sex and avoid risky behaviors.
- 6 Get immunized (HPV & hepatitis vaccines).
- 7 Know your family medical history and get regular cancer screenings.

To learn more, please visit www.preventcancer.org

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Cancer Screening for Transplant Survivors

Y. Inamoto et al, 2015

- www.ncbi.nlm.nih.gov/pmc/articles/PMC4989866
- A lot of detail on screening
- Reviews and compares
 - American Cancer Society
 - National Comprehensive Cancer Network
 - Consensus recommendations from CIMBTR and EBMT
- Ask your transplant team for guidance

Inamoto Y, et al, Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant. 2015 Aug; 50(8): 1013–1023

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Symptoms That Could Indicate Cancer

- New lumps or bumps
- Unusual fatigue, fevers, sweats
- Urination difficult, painful
- Cough, hoarseness, chest pain
- Bleeding anywhere, easy bruising
- Abdominal pain, bowel changes, loss appetite, trouble swallowing
- New blood clots
- Sores, new skin moles or lumps
- Headaches, vision changes, seizures, paralysis, numbness

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Skin Cancers

- Probably commonest post-transplant cancer
- High level of vigilance post-transplant
- Prevent with sunscreen and sun avoidance
- Regular dermatology visits
- Early intervention is important
- Can be more aggressive than in people with normal immunity
- Can be hard to tell benign from more aggressive disease

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Common forms of skin cancer

HUTTON KLEIN
HK
DERMATOLOGY



Actinic
keratoses (AK)



Basal Cell
Carcinoma (BCC)



Squamous Cell
Carcinoma (SCC)



Malignant
Melanoma

Images sourced from DermNet NZ

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Oral Cancer

- Regular dental visits
- Consult oral medicine specialist if you have concerns
 - discuss with your physician



Figure 2. cGVHD of the buccal mucosa with extensive multifocal areas of

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Breast Cancer

- **Average Risk**
 - age 20–40 years: Clinical breast exam every 1–3 years
 - age > 40 years: Annual clinical breast exam, Annual mammogram
- **Prior chest radiation therapy or TBI:**
 - Annual exam at age 25 years or 8 years after radiation therapy/TBI, whichever comes first, no later than age 40 years:
 - clinical breast exam
 - mammogram-
 - breast MRI

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Cervical Cancer

- Human Papilloma Virus (HPV) important
- Pelvic exams, cervix smears
- HPV Vaccine prevention in younger patients
- Annual Pap test and HPV DNA test

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Liver Cancer – Risk Factors

- Cirrhosis
- Alcohol
- Hepatitis B – vaccinate/treat
- Hepatitis C - treat
- Iron overload (?)
 - Phlebotomy
 - Iron chelating drugs

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Colorectal Cancer

- Treated by surgery, curable at early stage
- Tests
 - Coloscopy
 - Sigmoidoscopy
 - Stool blood and DNA testing
- First coloscopy recommended aged 45-50, screen up to 75 years
- Sigmoidoscopy every 5 years + FIT or high-sensitivity FOB
- More frequent if higher risk

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Lung Cancer

- Smoking main risk factor
- Many patients will have had a chest CT done during treatment course
- Screening with low-dose CT of chest recommended for two high-risk groups:
 - 55 years and ≥ 30 pack-year smoking history
 - ≥ 50 and have ≥ 20 pack-year smoking history with one additional risk factor

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Survivorship Planning

Written plan for recommended follow-up and self care

- Disease follow-up
- Healthcare maintenance and monitoring
- Vaccines
- Cancer screening
 - Delineate responsibility for cancer screening
 - Define plan based on risk factors
 - PCP important
 - Gynecologist
 - Oncologist/BMT physician

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Summary

- Secondary cancers are an uncommon but important problem after transplants
- Autologous transplants - more marrow disorders
- Allogeneic transplants - more solid tumors
- Risk increases over time especially for solid tumors
- Long-term follow-up with screening and early detection may help avoid severe illness

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Questions?



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