Second primary malignancy: Focus on Hodgkin lymphoma

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Roadmap: Second primary malignancy

- Principle of oncogenicity
- Scope of the problem (across tumor and treatment types)
- Case study: Hodgkin lymphoma
  - Impact of SPM
  - Types of secondary malignancies
  - Prevention for patients
  - Screening for survivors

Principle of oncogenicity

- All treatments have side effects: Either "off-target" (e.g., pneumonitis from bleomycin) or "friendly fire" (e.g., pneumonitis from mediastinal radiation)
- Any treatment that disrupts DNA can lead to mutagenesis and "friendly fire" oncogenesis

Principle of oncogenicity

Three criteria to determine oncogenic risk:

- Potentially oncogenic therapy
- Susceptible organs exposed to oncogenic agents
- Time
  - Latency can vary dramatically
  - (Survivors only need apply)

Whenever susceptible organs are exposed to potentially oncogenic therapy in patients who may expect to survive past the relevant latency period, ***consider the risk of second primary malignancy***

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SPM: Scope of the problem

- Overall, treatment-induced SPM accounts for a small fraction of new cancer diagnoses
- Survivors of specific cancers can have dramatically increased risks of SPM depending on features of treatment: Oncogenic potential, organs exposed, age & prognosis of patient

Irradiation of solid organs → in-field or near-field tumors, leukemia

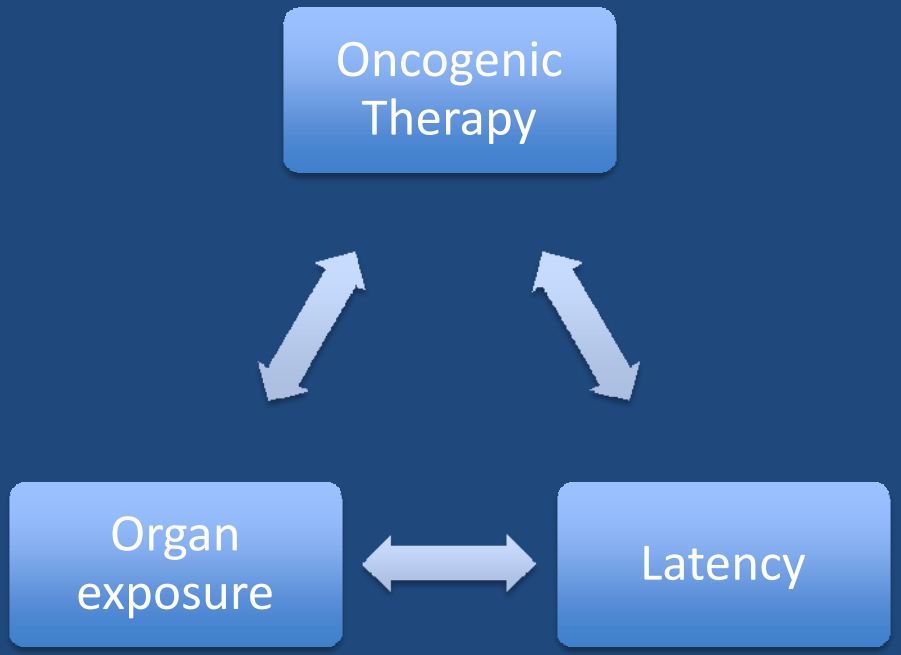
Total body irradiation [used in stem cell transplant] → (total body) solid tumors

Chemotherapy → hematologic neoplasia (leukemia, lymphoma), potentiation of RT-induced oncogenesis

SPM: Scope of the problem

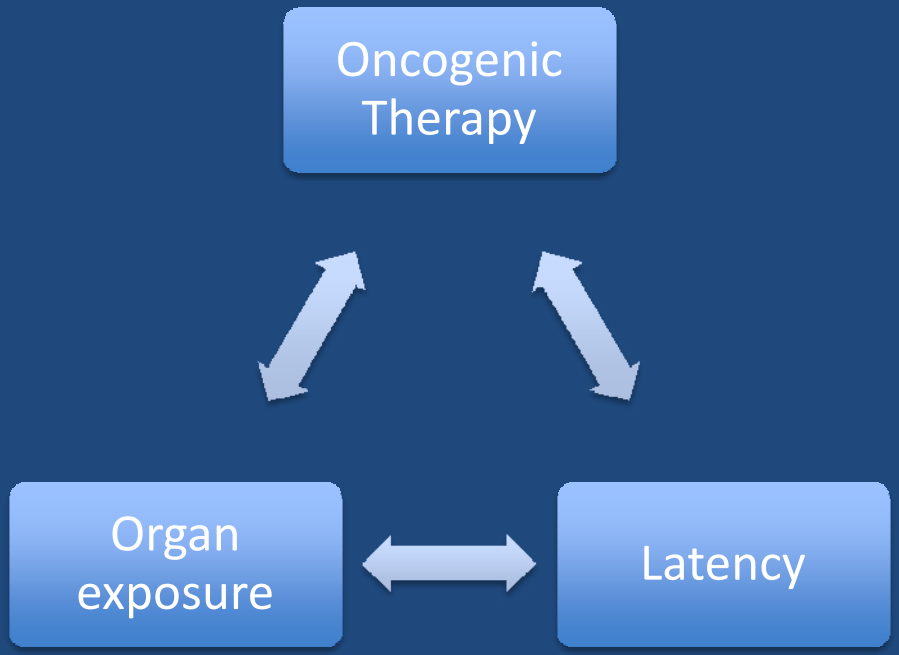
- Survivors of many individual types of malignancies may have increased risks of SPM depending on treatment
  - Risks associated with treatment
  - Interaction with risk factors for the first cancer
- Risks of SPM vary by cancer type and treatment modality

Breast cancer



- Leukemia
  - Alkylator chemotherapy
  - Radiation (breast, axilla, chest wall)
  - Latency begins 2y after Rx
- Lung cancer
  - Post-mastectomy RT
  - Synergy with tobacco

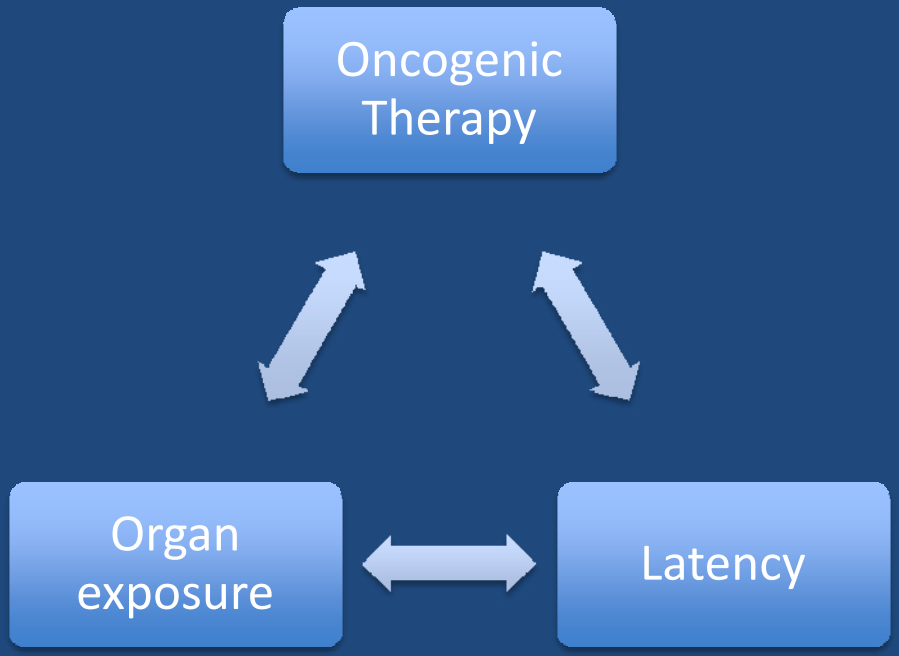
Small cell lung cancer



- Upper aerodigestive cancers
- Leukemia

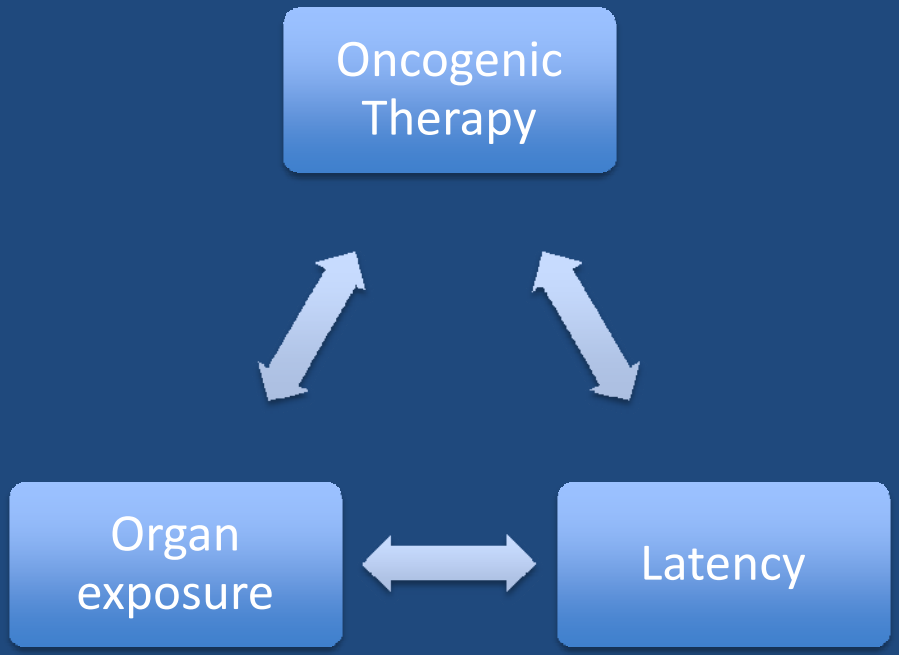
- Total risk as high as 10% per year, lifetime risk of 50%, among SCLC survivors

Prostate cancer



- Bladder cancer
  - Radiation
- Breast cancer
  - Anti-androgen
- ???
  - Chemotherapy

Testis cancer



- Bladder
- Rectum
- Pancreas
- Soft tissue sarcoma
- NHL
  - All due to radiation
- Leukemia
  - Chemotherapy & combined modality

Other adult cancers

- Uterine cancer
  - Colon, vulva, bladder
  - Leukemia
- Ovarian cancer
  - Leukemia? (chemo)
- GI cancers
  - No clear risk of increased SPM
- Non-Hodgkin lymphoma
  - Chemotherapy
  - Radiation
  - High-dose therapy
  - Immune suppression (or immunodeficiency)

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Case study: Hodgkin lymphoma

- Hodgkin lymphoma (HL) is rare: 8,200 cases/yr in US (compared to 66,000 non-Hodgkin lymphoma, 108,000 colon cancer, 215,000 lung cancer)
- Bimodal age distribution, peaks in the 20s and 70s.
- Increasing success over the last 3 decades – a true success story of modern oncology

Hodgkin Lymphoma	1975-77	1981-83	1990-92	1996-2004
All races	74%	76%	83%	86%
Whites	74%	76%	84%	87%
African-Americans	71%	73%	74%	80%

Case study: Hodgkin lymphoma

- Treatments of HL have evolved over this time, and have come to rely either upon chemotherapy alone or combination of chemotherapy and involved field radiation therapy

- Chemotherapy agents used to treat HL
- Common:
  - Doxorubicin
  - Bleomycin
  - Vinblastine
  - Dacarbazine
- Less common:
  - Mechlorethamine
  - Etoposide
  - Prednisone
  - Vincristine
  - Cyclophosphamide
  - Procarbazine

Case study: Hodgkin lymphoma

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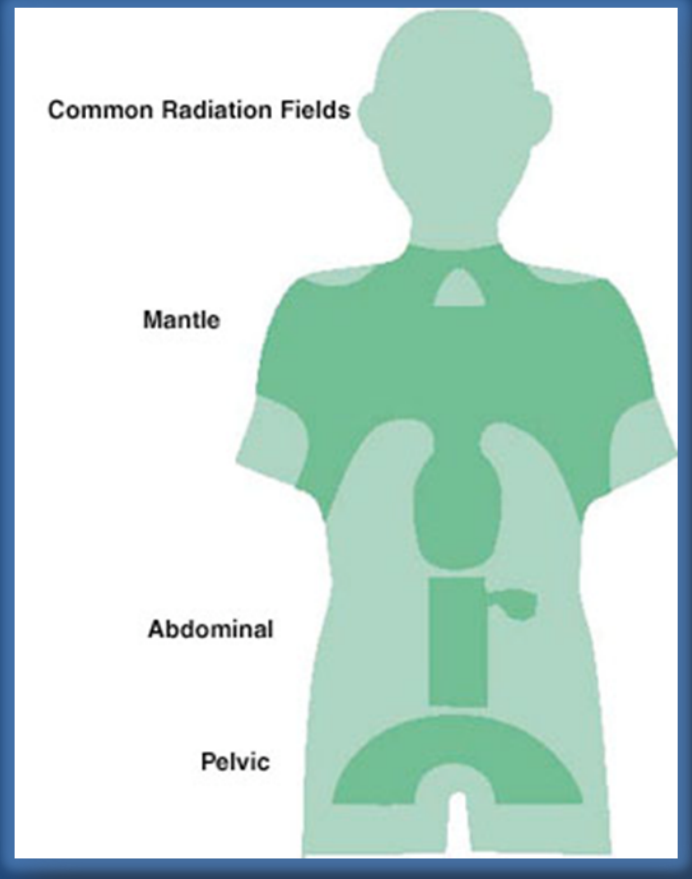
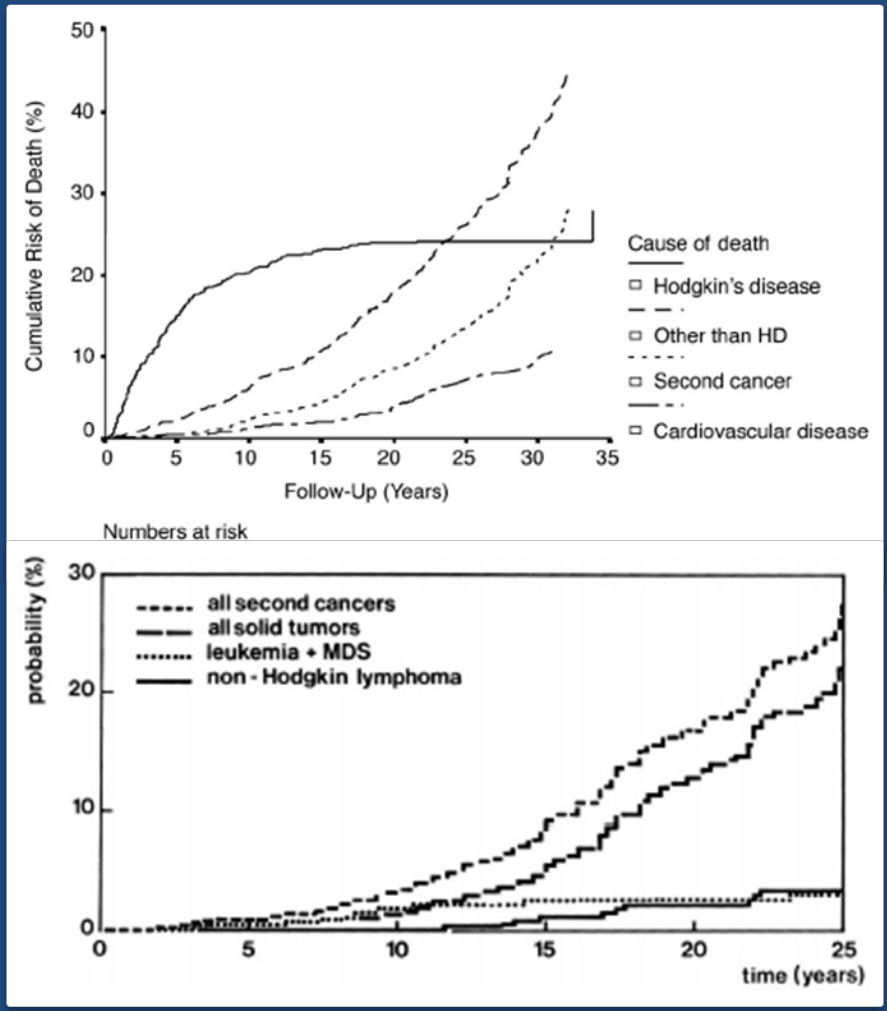


Case study: Hodgkin lymphoma

- Satisfying the principle of oncogenesis:
  - Potentially oncogenic therapy: Chemo, RT, both
  - Organs exposed: Breast, lung, thyroid; bone marrow and lymphatics
  - Time
- Victims of our own success: Over 140,000 in US living with a history of (treated) Hodgkin lymphoma

Case study: Hodgkin lymphoma

- By between 14 and 22 years after diagnosis, more patients will have died from other problems (#1: SPM) than from Hodgkin lymphoma itself
- For 100 patients receiving "older" therapy, by 20 years following diagnosis, 33 patients would have died of HL and 14 of second cancers
- Comparable numbers for more "modern" treatment (less alkylator therapy, lower doses of radiation) remain unknown



Excess risk of SPM in Hodgkin lymphoma

		Absolute increased risk, % per year	
Cancer type	Relative risk	Overall	10-yr survivors
All cancer	3.5	0.56	1.11
Acute leukemia	70.8	0.16	0.09
Non-Hodgkin lymphoma	18.6	0.11	0.28
Solid tumors	2.4	0.29	0.74
Lung cancer	4.2	0.14	0.34
Breast cancer	2.5	0.11	0.40
GI cancer	2.5	0.06	
Soft tissue sarcoma	7.0	0.01	
Thyroid cancer	4.7	0.005	
Melanoma	4.2	0.002	

High risk scenarios in HL

- Breast cancer & radiation therapy involving breast tissue (e.g., mantle field) in young women:
  - Age <20: 34% lifetime risk
  - Age 20-29: 22% lifetime risk
  - Age 30+: 3.5% lifetime risk
- Acute leukemia & intensive alkylator therapy:
  - MOPP: 1-2% lifetime risk
  - Escalated BEACOPP: 3-4% (+) lifetime risk
  - Auto-transplant: 7% (+) lifetime risk

High risk scenarios in HL

- Lung cancer & smokers: Relative risks compared to general population
  - RT → 3x risk
  - RT + chemotherapy → 4x risk
  - RT + chemotherapy + active smoker → 50x risk
- Risk of lung cancer in patients quitting smoking before treatment = that of never-smokers

SPM: Prevention

- Treatment selection: Avoid high-risk treatment selections when feasible
  - Avoid radiation to breasts in women < 30 yo
  - Avoid alkylator therapy in patients with low-risk dz
  - Avoid thoracic radiation in active smokers
- Risk modification
  - Smoking cessation!
  - Consideration of SERM prophylaxis for young women exposed to RT

SPM: Surveillance

- Screening offers possibility to decrease morbidity and mortality from second malignancy
- Effective screening must
  - Identify disease reliably at earlier stage in a
  - disease in which earlier diagnosis is desirable, resulting in
  - improved overall survival

SPM: Surveillance

- What *not* to screen for:
  - Secondary leukemia. Earlier diagnosis not advantageous, outcomes poor regardless of timeliness
  - Less common solid tumors (e.g., sarcoma)
- What (maybe) to screen for:
  - Lung cancer: Open debate as to whether early diagnosis via screening has an impact. For very-high-risk group, discuss risks/benefits
- What [almost definitely] to screen for:
  - Breast cancer in higher-risk patients. If irradiated at age <30, actuarial risk comparable to low-range estimates of BRCA 1/2 carriers. Intensive screening is a subject of research but has become the *de facto* standard of care

SPM: Surveillance

What NOT to screen *with:*

Whole body CT or PET/CT scans

- Appropriate (judicious) use of CT imaging during period of greatest risk of relapse: Every 6 months years 0-2, every year from year 2-5, every other years 6-7 (alternating with CXR), then discontinue

- 15 CT scans of the chest, abdomen, and pelvis give a cumulative dose greater than that of survivors at Hiroshima and Nagasaki
- 2% of all cancers estimated to be due to radiology
- Risk of false-positives with associated stress, expense, procedural risk

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