

Survivorship

Deborah Toppmeyer, MD

Associate Professor of Medicine

UMDNJ / Robert Wood Johnson School of Medicine

The Cancer Institute of New Jersey

Overview

Issues to be addressed:

- ◆ Risk of late sequelae associated with treatment
- ◆ Risk of disease recurrence
- ◆ Risk of associated malignancies
- ◆ Impact on family members
- ◆ Psychiatric / psychosocial issues of survivorship

Challenges to Medical System

- Evolving information about issues
 - ◆ Risks, Screening, Prevention strategies
- Who follows young survivors & their level of knowledge
 - ◆ Oncology team – overwhelmed, too focused
 - ◆ Primary care team – lack of information
 - ◆ Survivors Clinics

Late Effects of Therapy

- Risks of late effects vary by tissue and age of patient at time of exposure
- Dose, modality & time specific
- Additive effect of combined modality Rx.
- Important for future management
 - ◆ Screening
 - ◆ Risk reduction strategies
 - ◆ Lifestyle changes
 - ◆ exposures

Late Effects of Treatment

- Fatigue
- Pain
- Menopausal symptoms
- Reproductive & fertility concerns
- Growth / development effects
- End-organ dysfunction
 - pulmonary toxicity
 - cardiac toxicity
 - neurotoxicity
 - nephrotoxicity
 - vascular toxicity

Late Effects of Surgery

- Limb Amputation
- Abdominal Surgery
- Lymphadenectomy (Breast, Melanoma)
- Splenectomy (HD)
- Pelvic Surgery (male & female effects)

Late Effects of Chemotherapy

- Cardiac (Anthracyclines, High dose C, Herceptin)
- Pulmonary (Bleomycin)
- CNS (Mtx)
- Peripheral Nervous System (Cisplatin, Vincas, Taxol)
- Renal (Cisplatin, Mtx)
- Hematologic (AML, MDS, Neutropenia)
- Gonadal

Late Effects of Radiotherapy

- Bone & soft tissue -- growth effects
- Dental / oral
- Eye
- Cardiovascular (HD)
- Pulmonary
- CNS
- Hematologic
- GI / GU

Fertility Effects of Therapy

- Planning for this issue needs to begin at time of diagnosis and treatment – when possible!!!
- Preservation of Fertility, hormone levels & sexual function
 - ◆ Choice of regimens
 - ◆ Gonadal shielding
 - ◆ Sperm/egg cryopreservation
 - ◆ Pharmacologic attempts to preserve fertility – lupron
 - ◆ Assisted reproductive techniques
- Outcomes of Pregnancy
 - ◆ No increased birth defects or genetic diseases in offspring conceived after cytotoxic therapy (baseline population level 4%)

Disease Recurrence

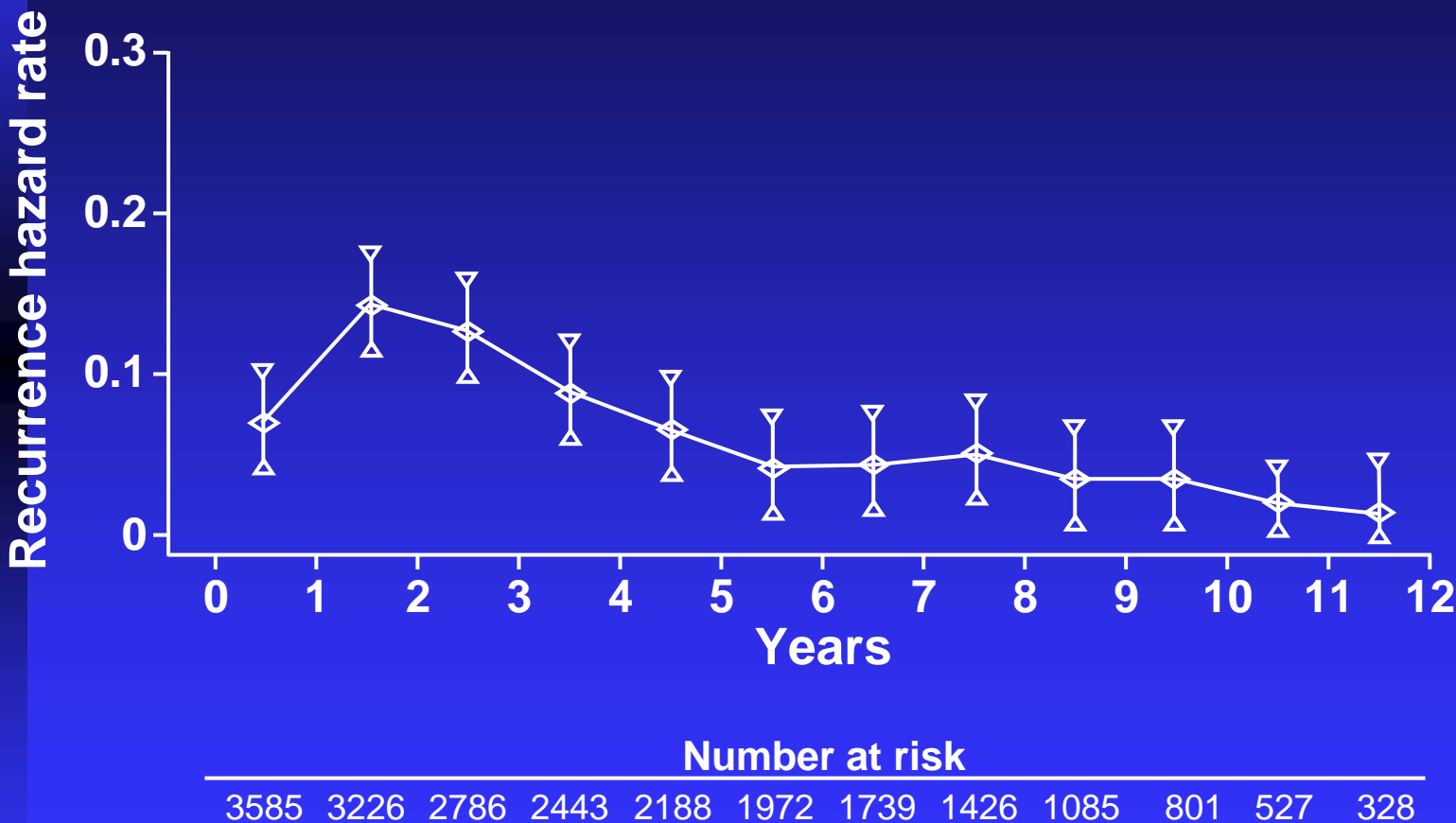
■ Risk

- ◆ dependent on stage and tumor pathologic factors
- ◆ Sites of recurrence depend on tumor type
 - ◆ Breast – bone, liver, lung
 - ◆ Colon- liver
- ◆ Newer tools to help assess recurrence risk and impact of treatment

Breast:

- ◆ Adjuvantonline!
- ◆ Oncotype dx

Recurrence Hazard Rates for Breast Cancer After Primary Therapy



Management of Recurrence Risk

Risk Modification

Adjuvant therapy – chemotherapy, hormone rx

Chemoprevention- Tamoxifen

Lifestyle modification - ????

Surveillance

Goal: Cure or Palliation

Cure – local recurrence, isolated metastasis

Palliation – diffuse metastasis

Guidelines: NCCN Guidelines

Examples:

Breast Cancer

Colon Cancer

Surveillance for Disease Recurrence

TESTS:

X-rays, CT's, MRI's, PET scan,

Nuclear studies – bone scans, CEA scans

Tumor markers:

Breast – CA27-29

Colon - CEA

Ovarian- CA125

Prostate – PSA

Others

Molecular genetic markers (p53, Kras)

Surveillance for Disease Recurrence

Breast Cancer - “Minimalism”

Surveillance for Disease Recurrence

Colon Cancer - “Intensivist”

Risk of Secondary Malignancies

Malignancies due to treatment

- ◆ Carcinogenicity of individual treatment modality varies

Associated Malignancies

- ◆ Shared environmental exposures

Hereditary Syndromes

Aging process

Secondary Malignancies - Impact

- # Cancers diagnosed 1998 1,200,000
 - # 2nd cancers / all cancers 6.6%
 - Estimated 2nd cancers 1998 80,000
- ∴ 5th most common “Cancer”

Fred Li, ASCO 1998

Secondary Malignancies - Effects of Treatment

- Combination Therapy
- SARCOMA – XRT
- Bladder Cancer – Cyclophosphamide
- Endometrial Cancer - Tamoxifen
- AML - CHEMOTHERAPY
 - ◆ Topo II Inhibitors (Etoposide, Adria)
 - ◆ Short Latency
 - ◆ Alkylating Agents
 - ◆ Latency > 5 years

Risk of Secondary Malignancies

- Varies with agent used
- Varies with total dose, duration of exposure, time of exposure in life cycle
- Endometrial Cancer & Tamoxifen use:
 - ◆ Ever use – RR 1.5
 - ◆ ≥ 5 years – RR 6.6

Risk of Secondary Malignancies

- Risk of Leukemia based on cumulative dose of platinum, duration of Rx, & specific agent

<u>Dose</u>	<u>RR</u>	<u>Duration</u>	<u>RR</u>
<500mg	1.9	<6 month	1.2
500-749	2.1	6-12month	4.3
750-999	4.1	>12 month	7.0
>1000	7.6		

<u>Specific Drug</u>	<u>RR</u>
Cisplatin	3.3
Carboplatin	6.5
Both	9.0

Travis et al. NEJM 1999;340:351

Risk of Secondary Malignancies

- Risk of secondary cancer in 1253 patients with Hodgkin's Disease according to age at start of treatment, type of 2nd cancer & age at dx of HD

<u>All Malignancies</u>	<u>observed cases</u>	<u>RR</u>
≤20	28	13.3
21-30	61	8.2
31-39	48	4.9
<u>Solid Tumors</u>		
≤20	25	13.9
21-30	43	6.5
31-39	38	4.2
<u>Breast Cancer</u>		
≤20	9	16.9
21-30	12	5.6
31-39	6	2.4
<u>Leukemia</u>		
≤20	2	27.6
21-30	14	7.3
31-39	2	9.3

Risk of Secondary Malignancies

- Risk of Bladder Cancer & cumulative dose & duration of cyclophosphamide

<u>Cumulative Dose</u>	<u>Cases</u>	<u>RR</u>
<20 grams	8	2.4
20-49	5	6.3
<u>≥50</u>	5	14.5
 <u>Duration of Therapy</u>		
<1 year	8	2.5
1-2 yrs	3	3.7
>2 yrs	7	11.8

Causes of Hereditary Susceptibility to Breast Cancer

Gene Contribution to Hereditary Breast Cancer

<u>BRCA1</u>	<u>20-40%</u>
<u>BRCA2</u>	<u>10-30%</u>
<u>TP53</u>	<u><1%</u>
<u>PTEN</u>	<u><1%</u>
<u>CHK2</u>	<u><1%</u>
<u>Undiscovered genes</u>	<u>30-70%</u>

Hereditary Syndromes

Breast Cancer

BRCA1/2 - 60% lifetime risk 2nd breast cancer

20-60% lifetime risk ovarian cancer

SPORATIC - 20% lifetime risk 2nd breast cancer

Retinoblastoma

HEREDITARY RB - 51% LR 2nd cancer by age 50

SPORATIC RB - 5% LR 2nd cancer

Risk of Colorectal Cancer (lifetime risk)

- General Population -----5%
- Personal Hx Colorectal Neoplasia-----15%
- Inflammatory Bowel Disease-----15-40%
- HNPCC Mutation-----70-80%
- FAP-----→95%

Management of Hereditary Risk

- Early detection
- Chemoprevention
- Prophylactic surgery
- ??Lifestyle change

Preventive Strategies

■ Modifiable Risk Factors

- Diet
- Obesity
- Tobacco
- Etoh

■ Chemopreventive Strategies

For disease recurrence & 2ndary malignancies

- Breast
- Prostate
- Colorectal
- Cervix

Risk to Family Members

- Spectrum of cancers
- Risk due to extent of family history
- Hereditary cancer syndromes
 - ◆ Breast / ovary syndrome
 - ◆ Colorectal cancer syndromes
 - ◆ Role of genetic testing

When to Suspect an Hereditary Syndrome

- Young age at onset
- Bilateral disease
- Multiple cancers in one organ
- Cluster of cancers in individual or family
 - ◆ Breast / Ovary – BRCA1
 - ◆ Breast/Ovary/melanoma/Pancreas – BRCA2
- Multiple generations affected
- Male breast cancer
- Precursor lesions
- Ashkenazi Jewish ancestry

Benefits and Limitations

■ Benefits

- ◆ Provides risk information for individuals and families
- ◆ Provides information useful in health care
- ◆ Results alleviate uncertainty and anxiety

■ Limitations

- ◆ A negative result is most definitive if there is a known mutation in the family
- ◆ Some genetic variants are of unknown clinical significance

Guidelines for Cancer Predisposition Testing

- *American Society of Clinical Oncology: “Cancer predisposition testing should be offered when...”*
 - ◆ The individual has personal *or* family history features suggestive of a genetic cancer susceptibility condition
 - ◆ The results will aid in the diagnosis or influence the medical/surgical management of the patient *or* family members at hereditary risk of cancer