Update on Late Effects

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Disclosures: None

Disclosures: None (sadly)

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Late Effects After Childhood GU Cancers

- Really only comprehensively reported after WT
- High EFS/OS in WT and improving EFS/OS in other childhood cancers make an appreciation of late effects even more relevant
- 3 major groups of late effects
  - Effects of therapy (medical and surgical)
  - Secondary malignant neoplasms (including those related to predisposition syndromes)
  - Fertility considerations

A Quiz

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EXTRA **The Villager** EXTRA

VOLUME 1 — Richland, Washington, Monday, August 6, 1945 — NUMBER 32—A

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To nearly everyone the news of what Richland was helping to make came as a complete surprise. Even those who may have been in the know would not admit it. The old habit of secrecy was strong upon them.

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(Continued on Page 2)

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The bomb, made in the Hanford Engineer Works, in Oak Ridge, near Knoxville, Tennessee, and an unnamed installation near Santa Fe, New Mexico, produces more than 2,000 times the blast of the largest bomb ever used before.

The bombs blast even the landscape out of sight. Nothing is impossible. The first bomb was dropped on Hiroshima a few hours ago. Observers report that the explosion was thousands of times greater than an earthquake and may change the course of civilization.

Atomic power was released against the Japs in answer to their refusal to the ultimatum issued last week. Source of the power is said to be coal, oil and power produced by the great dams in the Northwest and Tennessee.

In making the announcement, President Truman said that the bomb has added new and revolutionary increase in destruction on the Japanese. Mr. Truman went on that "it is an Atomic bomb. A harnessing of the basic power of the universe, the force from which the sun draws its power."

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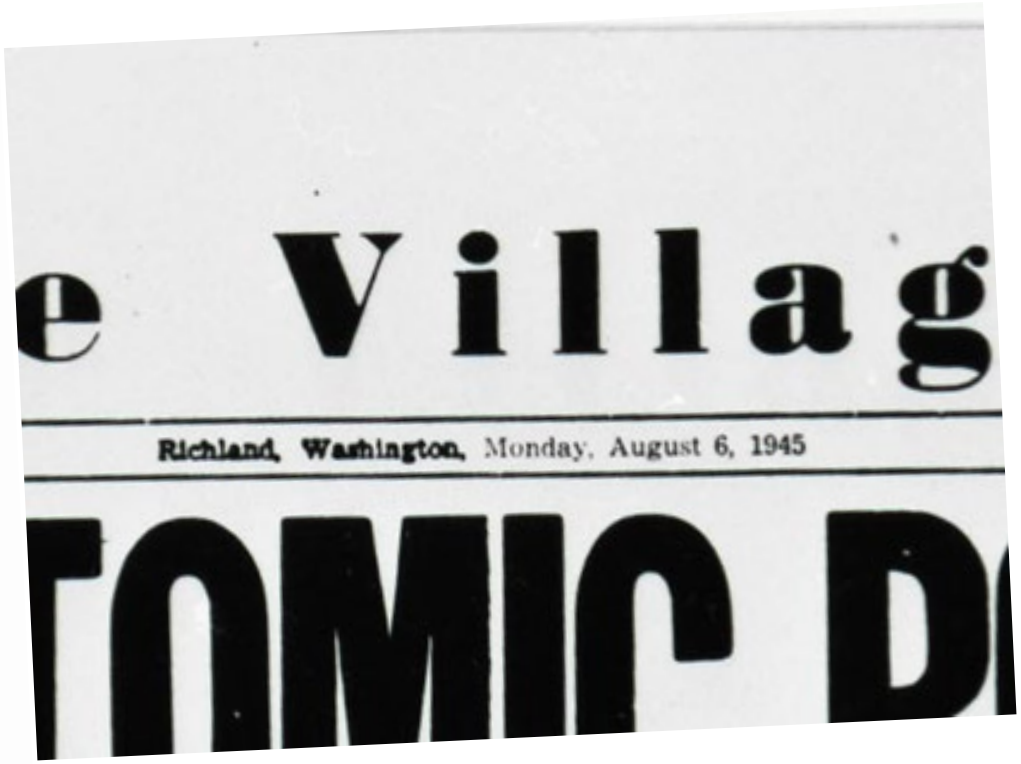

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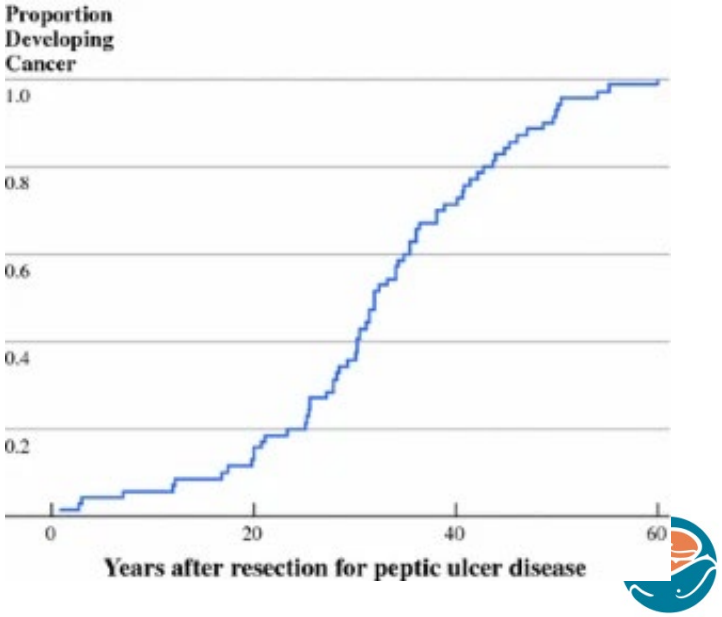
My Friend, Dr. James Mezhir (1973-2016)

Gastrointestinal Oncology | Published: 10 November 2010

Treatment and Outcome of Patients with Gastric Remnant Cancer After Resection for Peptic Ulcer Disease

James J. Mezhir MD, Mithat Gonen PhD, John B. Ammori MD, Vivian E. Strong MD, Murray F. Brennan MD & Daniel G. Coit MD

Annals of Surgical Oncology **18**, 670–676 (2011) | Cite this article



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Important Considerations

- Evolving best practices for management of childhood cancer means data on late effects need to be considered carefully

- Your values may not be your patient's values
  - Length of life =/= quality of life
  - Substituted judgment

- I would encourage you to think critically and partner with your patients

A Comment From My Husband

- “Kathleen, when you’ve had cancer and actually thought about planning your funeral, you can tell me how to live my life. I’m not going to OrangeTheory with you.”

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Late Effects of Medical and Surgical Therapies

- Renal insufficiency
- Hypertension
- Cardiac considerations
- Musculoskeletal considerations
- Dental considerations
- Bowel obstruction
- Mental health considerations
- Secondary malignant neoplasms
- Urinary considerations
- Fertility considerations

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- **Secondary malignant neoplasms**
- **Urinary considerations**
- **Fertility considerations**

Secondary Malignant Neoplasms

- Second leading cause of death in childhood cancer survivors
- At 20 years, become leading cause of death
- Many “sporadic” cases of childhood cancer are now being linked to predisposition syndromes
- Prevalence may not change with treatment era

Pinto 2016; Spunt 2005

Secondary Malignant Neoplasms

- CCSS: 10% of children surviving at least 5 years after cancer diagnosis developed a secondary neoplasm
  - 20.5% cumulative incidence of SMN in the three decades following cancer diagnosis
  - Median time to SMN diagnosis was over 17 years
  - Kidney cancer had the lowest cumulative incidence (4.0% over 30 years)

- Greater risk of SMN in women (RR=1.5) and after Hodgkin's lymphoma or who received radiation therapy

- Children < 4 years at diagnosis had the lowest risk

Friedman 2010

Secondary Malignant Neoplasms

- WT survivors: 3x risk compared with sibling controls
  - Liver, colon, soft tissue, thyroid cancers, AML (not breast cancer)
  - Solid organ SMN have delayed diagnoses compared with hematogenous malignancies
  - Time since treatment is important: increased risk about two decades after diagnosis and peaking at about 35 years after diagnosis
    - Children with early SMN tended to have a predisposition syndrome (Beckwith-Wiedemann syndrome; BWS).

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Lee 2015; Termuhlen 2011; Breslow 2010.

Secondary Malignant Neoplasms and RMS

- RMS is most common pediatric soft tissue tumor
- 50% of patients are diagnosed at <10 years
- Predisposition syndromes
  - Li-Fraumeni: breast, soft tissue, blood, adrenal
  - Beckwith-Wiedemann
  - Neurofibromatosis type 1 (*NF1*)
  - Costello syndrome (*HRAS*)
  - Noonan syndrome (*PTPNI1*)

Secondary Malignant Neoplasms: RMS (SEER)

- One in five patients with SMN had primary STS
  - Predisposition syndromes?
  - Chemotherapeutic agents?
  - XRT?
- 2-5-fold risk compared with general population in SEER
- Greater for children with pleomorphic and embryonal histologies
- May not reflect XRT exposure

Archer 2015; Zhen 2021

Secondary Malignant Neoplasms: RMS (Again, SEER)

SMN Type	SIR	P value
Solid Tumors	1.95 95% CI: 1.54-2.44	p<0.05
Bone and Joint	35.25, 95% CI: 14.17 – 72.63	$p < 0.001$
Heart	22.5, 95% CI: 10.29 – 42.7	$p < 0.05$
Breasts	2.10, 95% CI: 1.05 – 3.75	$p < 0.05$)
Male GU System	118.14, 95% CI: 14.31 – 426.78	$p < 0.05$)
Urinary System	2.36, 95% CI: 1.02 – 4.66	$p < 0.05$)
Brain	9.21, 95% CI: 3.98 – 18.16	$p < 0.05$)
Nervous System	8.59, 95% CI: 3.71 – 16.93	$p < 0.05$)
Non-lymphocytic leukemia	5.24, 95% CI: 1.43 – 13.42	$p < 0.05$)
Myeloid and monocytic leukemia	5.90, 95% CI: 1.61 – 15.1	$p < 0.05$)

Archer 2015; Zhen 2021

Secondary Malignant Neoplasms: Counseling

- Routine preventive cancer screening
  - Can consider more frequent or earlier screening of patients at higher risk
  - Patient education
    - Risks for and timeline of secondary malignancy development
    - Lifestyle choices including good nutrition and tobacco avoidance
    - Signs and symptoms that should prompt earlier and more thorough evaluation

Van den Belt-Dusebout 2007; Li 2011; Nathan 2010; www.childrensoncologygroup.org/index.php/secondarycancer.

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A Word on Mental Health Considerations

- 90% of childhood cancer survivors have at least one emotional concern
- 14% of WT survivors have mental health complaints
  - 30% more likely than sibling controls to have mental health concerns
- Adult survivors of childhood cancer are 1.8 times as likely to have suicidal ideation compared with siblings
- <50% of childhood cancer survivors self-initiate therapy

Hudson 2003; Hayek 2020; Gil 2019; Brinkman 2014; Recklitis 2010.

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Musculoskeletal Considerations

- Most commonly a/w XRT (dose, duration dependent)
  - Vertebral body damage
  - Kyphosis
  - Iliac wing hypoplasia
  - Leg length discrepancy

- Cumulative incidence of musculoskeletal conditions declined from 5.8% (1970s) to 3.3% (1990s)--likely reflecting XRT regimen/delivery changes

- Musculoskeletal hypoplasia, connective tissue effects, scoliosis most common late effects in young women

Lucas 2017; Sasso 2010; Hoeben 2019; Spunt 2005

Voiding/Elimination Habits

- Chemo/radiation effects
- Surgical considerations
  - Urinary diversion
  - Change in lower tract dynamics

Voiding Habits: Post-Chemo

A prospective survey study of lower urinary tract dysfunction in childhood cancer survivors after vincristine and/or doxorubicin chemotherapy

Sarah L. Hecht[1] | Alan Quach[2] | Dexiang Gao[3] | Andrew Brazell[2] | Gemma Beltran[2] | Sheryl Holbrook[2] | Lia Gore[4] | Nao Iguchi[2] | Anna Malykhina[2] | Duncan Wilcox[2] | Nicholas G. Cost[2]

- 161 patients with chemotherapy (VCR +/- DOX) or without
- DVSS scores

TABLE 2 Dysfunctional voiding scoring system (DVSS) survey analysis

	Cancer	Control	*p*-Value	OR [95% CI]
DVSS sum score median [range]	6 [0–18]	4 [0–14]	.003[a]	
Male (%)	6 [0–18]	3 [0–14]	.04[a]	
Female (%)	6 [0–17]	4 [0–14]	.04[a]	
DVSS score above LUTD threshold[b] (%)	31 (39)	17 (21)	.014[b]	1.8 [1.1–3.1]
Male (%)	8 (20)	5 (12)	.339[b]	1.6 [0.6–4.6]
Female (%)	23 (57.5)	12 (30)	.013[b]	1.9 [1.1–3.3]

[a]Mann–Whitney *U* test.
[b]Pearson's chi-square test.
[c]DVSS gender-specific LUTD threshold: males ≥9; females ≥6.

Hecht 2021

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Voiding Habits: Post-XRT

Pelvic radiation therapy: Between delight and disaster

- Radiation proctitis, radiation cystitis, radiation enteritis
- 90% of adult patients experience changes in bowel habits after XRT

Olopade 2005

Voiding Habits: Post-XRT

Pelvic radiation therapy: Between delight and disaster

- Radiation proctitis, radiation cystitis, radiation enteritis
- 90% of adult patients experience changes in bowel habits after XRT
- What is “normal” elimination in a child who has not yet undergone toilet training?

Olopade 2005

Dental Considerations

- Greatest risk with head and neck XRT or chemotherapy prior to the eruption of the permanent teeth
  - Tooth loss
  - Discoloration
  - Abnormal tooth enamel
  - Cavity development
  - Malocclusions
  - Abnormal tooth and root size and morphology
- Dry mouth usually only with high (>40 Gray) H&N XRT

Cubukçu 2008; Valéra 2015; Snider 2020.

Dental Considerations

- *Current recommendations from the American Academy of Pediatric Dentistry and COG*
  - Dental examination for all children prior to beginning cancer treatment and regularly thereafter
  - Consistent oral care (brushing with fluoridated toothpaste and—for dexterous children—flossing)
  - Minimizing cariogenic foods and oral trauma (e.g. using a soft toothbrush)
  - Orthodontic treatment is not recommended until the child has been disease-free for two years
    - May need to be modified to account for the structural differences in teeth following exposure to radiation and chemotherapeutic agent

www.childrensoncologygroup.org/index.php/sensory/dentalhealth.

Fertility Considerations: Lessons from WT

- May be related to treatment (surgical intervention, chemotherapy, or radiotherapy) or underlying risk factors (including syndromes associated with WT development

- Abdominal radiotherapy for WT and other childhood cancers has been consistently associated with poorer reproductive outcomes
  - Premature ovarian failure
  - Increased risk of miscarriage
  - Low (<2500 g) birth weight
  - Females receiving radiation to the pelvis often have small ovarian and uterine volume

Fertility Considerations

- One large-scale study did not find an association between chemotherapy and adverse pregnancy outcomes in childhood cancer survivors

- Chemotherapy has been associated with alterations in the HPG axis and on fertility parameters
  - FSH/LH alterations in 25-33% of men treated for cancer
  - Gonadal toxicity, particularly to the germinal epithelium has been well described for alkylating agents,
  - Differential methylation of spermatozoal DNA occurs after exposure to antineoplastic drugs

Shnorhavorian 2017; Hammoud 2010; Marques 2008.

Fertility Considerations

- Over half (57.7%) of females with pelvic RMS had gynecologic late effects
  - TAH +/- BSO
  - VVF/RVF (increased risk with XRT)
  - Vaginal stenosis
  - Infertility (42.3% surgical, 46.2% ovarian failure)

- Vaginal reconstruction can be associated with pelvic floor dysfunction, cellulitis, local tissue damage

- Secondary malignancies: cervical, endometrial

Spunt 2005

Fertility Considerations: Predisposition Syndromes

- Children with DDS may have fertility challenges
  - Patients with differences in sex development may be at increased risk for hypogonadism
  - Males with undescended testes may have lower testicular volume and decreased numbers of dark (Type Ad) spermatogonia
  - Females may have a bicornuate uterus or other uterine abnormalities

- WT1 gene has been linked to male and female factor fertility concerns even in the absence of a clear syndrome

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Lipska-Ziętkiewicz 2020; Nicholson; Byrne 2002; Nathan 2017; Xu 2017.

In Conclusion….

- Ongoing research and improved survivorship means that our knowledge of late effects is outpaced by treatment advances
- Be proactive: even as subspecialists, promote patient education
- Think about fertility preservation: it's the late effect that requires you to do something early!

Thank You! Questions?

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