

Understanding Radiation-related Late Effects: Epidemiologic Considerations

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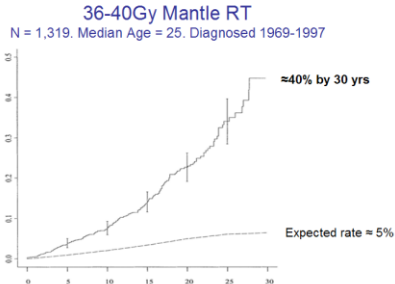


Introduction

- Limitations and advantages of epidemiologic evaluation of late effects and NTCP models
 - Outcome definitions
 - Host factors
 - Time-dependent exposures
 - Competing risks



Second Cancer Risk



Ng A K et al. Blood 2002;100:1989-1996

Epidmiologic Measures of Risk

- Cancer survivors followed for 10-30 years after completion of treatment.
 - Cases of SC ascertained.
 - Patients censored at death or loss to follow-up.
- Standardized Incidence Ratio (SIR)
 - The ratio of the observed to the expected new cases of cancer
 - The expected number is based on the sex- and age-specific rates published for the general population.
- Absolute Excess Risk
 - (O - E)/person-years at risk.



Limitations of Standard Cohort Studies

- Delay
 - Latency required to observe SC (or other late toxicity) means that results apply to outdated technology/techniques
- Lack of Individual Specificity
 - Patients receiving nominally the same form of RT may have dramatically different exposures
 - e.g. "involved-field RT"
- Difficult to Interpret Clinically
 - RT reduces risk of HL relapse by ~8% at 5-years after diagnosis
 - Also associated with SIR of breast cancer = 1.8
 - So is RT worth it?



NTCP Models: Lyman-Kutcher-Burman

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-\frac{x^2}{2}} dx$$

the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution

$$t = \frac{D_{eff} - TD_{50}}{\lambda mTD_{50}}$$

the uniform dose given to the entire organ that results in 50% complication risk

the slope of the sigmoid curve

$$D_{eff} = \left(\sum_i v_i D_i^{1/\alpha} \right)^{\alpha}$$

volume parameter

The potential advantages are to have an individualized estimate of risk and the possibility of modifying RT plan to limit this risk before treatment.



What Do Epidemiologic studies Tell Us about NTCP Models?

1. The variable values in the model will be highly dependent on how the adverse outcome is defined.
 - Consider "cardiac toxicity"
 - Self-reported incidence of heart disease among childhood cancer survivors receiving mediastinal RT is <5%
 - In contrast, echocardiographic abnormalities can be found in >50% of survivors.
 - The D_{eff} etc, of these two outcomes will be very different.

Int J Radiat Oncol Biol Phys. 2010; 76(30): S10-S19
 J Clin Oncol 22:3139-3148, 2004



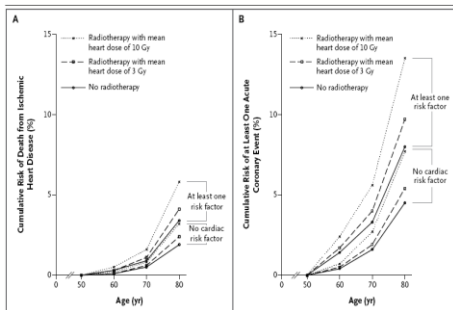
2. The Effects of RT Interact with Host Biology

- Several studies indicate that late cardiac toxicity following mediastinal RT occurs largely in patients with other cardiac risk factors.
- Conventional risk factors may have greater risk in patients who have had RT than in the general population.

	Adverse Cardiac Events (O/E)
All patients	1.90
With cardiac risk factors	2.36
Without Cardiac risk factors	0.96

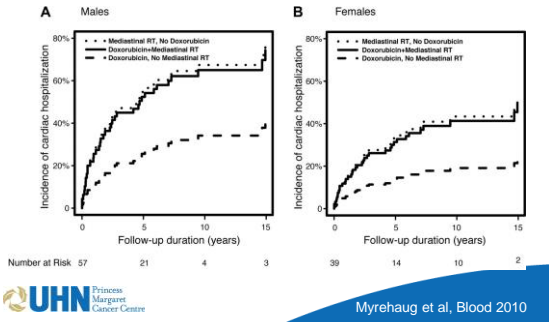


Glanzmann et al, Radiother Oncol 1998



Darby et al NEJM 2013

2. The Effects of RT Interact with Host Biology Cardiotoxicity in Adults with Pre-Existing Heart Disease.



RT Effects Interact with Host Biology

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_0^t e^{-\frac{x^2}{2}} dx$$

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}}$$

$$D_{eff} = \left(\sum_i v_i D_i^{m_i} \right)^{\frac{1}{m}}$$

- The implication is that the slope of the dose response curve will differ among different patients.
 - In this case those with and without cardiac risk factors.



3. Late Toxicity is Dependent on other Chronic Exposures Long after RT is Delivered

- Endogenous estrogens and RT-related breast cancer risk.

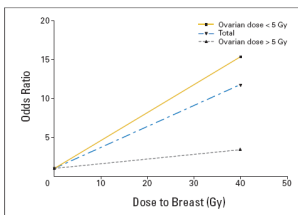


Fig 2 Fitted breast cancer risk by radiation dose to the breast and ovary.



Inskip et al, JCO 2009



Post-treatment Modifiers of Breast Cancer Risk

Longer Duration of Endogenous Estrogen Exposure = Greater Risk

Duration of Intact Ovarian Func'n	Age at Exposure		
	<21 years	21-30 years	31-40 years
<10 years	0.1	0.1	1.2
10-20 years	1 (ref)	1 (ref)	1 (ref)
>20 years	11.9	6.0	3.2



DeBruin et al JCO 2009

Chronic Risk Exposures Following RT

- The implication is that an NTCP model calculated at the time of treatment cannot account for subsequent exposures that may have a significant impact on risk.
- Further, the impact of time-dependent covariates are challenging to model as part of NTCP modeling.



4. The Cumulative Incidence of Late Effects are Highly Dependent on Competing Risks of Death.

- Kaplan-Meier method was developed to estimate overall survival, where the event (death) is inevitable.
- It assumes that censored patients are as likely to develop the event as those who remain in the analysis.
- aka “non-informative censoring”.

Leisenring, et al JCO, 2009 vol. 27 no. 14 2319-2327
Gooley TA et al. Stat Med 18:695-706, 1999



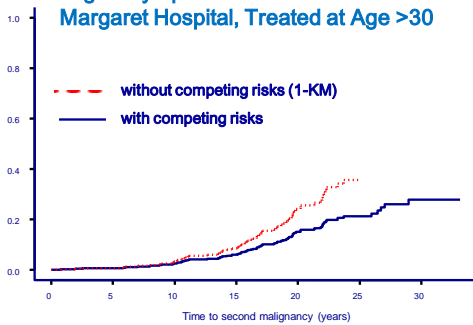
Implication for Estimates of Late Toxicity

- In many analyses, patients are censored at the time of relapse, death from primary cancer or any death occurring before the late effect of interest.
- The assumption of non-informative censoring implies that these dead patients are as likely to develop the late effect as the surviving patients(!)
- The result is an overestimation of the cumulative incidence of the late effect.
- Also true for SIR and AER and Cox models which censor at time of death.

Leisenring, et al JCO, 2009 vol. 27 no. 14 2319-2327
 Gooley TA et al. Stat Med 18:695-706, 1999



Cumulative Incidence of Second Cancer in Hodgkin Lymphoma Survivors at Princess Margaret Hospital, Treated at Age >30



Implications for Second Cancer Modeling

Comparison of passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors.

- Organ equivalent dose (OED) models used to estimate risks of RT-induced carcinoma and sarcoma in pediatric patients receiving RT for CNS tumors.

$$OED_C = \frac{1}{V} \sum_i V_i \frac{e^{-\alpha_i D_i}}{\alpha_i R} (1 - 2R + R^2 e^{\alpha_i D_i} - (1 - R)^2 e^{-\frac{\alpha_i R}{1-R} D_i})$$

$$OED_S = \frac{1}{V} \sum_i V_i \frac{e^{-\alpha_i D_i}}{\alpha_i R} (1 - 2R + R^2 e^{\alpha_i D_i} - \alpha_i' R D_i - (1 - R)^2 e^{-\frac{\alpha_i R}{1-R} D_i}).$$



Phys. Med. Biol. 59 (2014) 2883

Implications for Second Cancer Modeling

Comparison of passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors.

OED then used to estimate Excess Absolute Risk (EAR) of second cancers

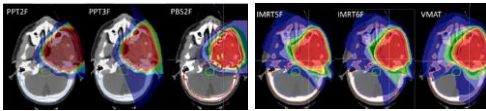
$$\text{EAR}(D, e, a, s) = \text{OED} \cdot \beta \cdot e^{(\gamma_e[e^{-30}] + \gamma_a \ln[a/70])} (1 \pm s).$$

- EAR then used to estimate Lifetime Attributable Risk of SC
 - the ratio $S(a)/S(e)$ defines the probability of surviving from age at exposure to the attained age

$$\text{LAR}(D, e, a) = \int_{a=e+L}^{75} \text{EAR}(D, e, a, s) \cdot \frac{S(a)}{S(e)} da.$$



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Absolute LAR (%) patient 3

Modalities	P2	P3	PBS2	IMRT5	IMRT6	VMAT
Skull sarcoma	0.04	0.05	0.05	0.19	0.16	0.19
Skull sarcoma (linear)	0.43	0.57	0.57	1.96	1.95	2.16
Soft tissue sarcoma	0.14	0.18	0.15	0.35	0.29	0.35
Soft tissue sarcoma (linear)	1.36	1.95	1.52	3.35	4.19	4.66
Soft tissue carcinoma	0.33	0.50	0.38	1.37	1.26	1.37
Soft tissue carcinoma (linear)	0.54	0.77	0.60	1.84	1.66	1.84



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Implications for Second Cancer Modeling

Comparison of passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors.

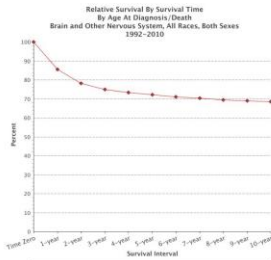
- EAR then used to estimate Lifetime Attributable Risk of SC
 - the ratio $S(a)/S(e)$ defines the probability of surviving from age at exposure to the attained age, **which was obtained from life tables for the US population.**

$$\text{LAR}(D, e, a) = \int_{a=e+L}^{75} \text{EAR}(D, e, a, s) \cdot \frac{S(a)}{S(e)} da.$$



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Competing Causes of Death in Pediatric Brain Tumor Patients



- 10 years after treatment, survival is 32% lower than the age- and sex-matched general population.
- Use of US general population statistics to estimate survival in models will overestimate survival and also the incidence of late effects (and the benefit of dose reductions).



Summary

- Epidemiologic studies reveal several challenges that may be overlooked in NTCP models:
 - The results will differ on how the outcome is defined.
 - The slope of the dose-response curve will differ depending on host biology
 - The risk of late toxicity may depend on time-dependent post-treatment exposures that are difficult to model.
 - Ignoring competing risks of death will produce erroneous overestimates of late toxicity (and overestimate the benefit of reducing RT dose).



Summary

- NTCP models could potentially be extremely valuable in developing personalized RT treatments to limit late effects.
 - Almost certainly superior to current practice in most cases.
- Could add meaningfully to discussions of therapeutic ratio, value of dose reductions or omitting RT, optimizing treatment plans to limit late toxicity.
- But this will require more sophisticated models than currently employed for acute toxicity.



SAM Question

Which of the following is false:

- 25% 1. The slope of the radiation dose-risk relationship for an adverse outcome will depend on how the outcome is defined.
- 50% 2. Radiation therapy to the heart over-rides the adverse effects of traditional cardiac risk factors on heart health, making them less important.
- 8% 3. Exposure to endogenous estrogens contributes to the risk of radiation-induced breast cancer.
- 17% 4. Most NTCP models do not fully account for the duration of exposure to other risk factors that contribute to the adverse outcome being modeled.



SAM Question

- Correct answer
- B. Radiation therapy to the heart over-rides the adverse effects of traditional cardiac risk factors on heart health, making them less important.
- Hull et al. JAMA. 2003 Dec 3;290(21):2831-7.
- Glanzmann et al. Radiother Oncol. 1998 Jan;46(1):51-62.



SAM Question

Which of the following is correct:

- 17% 1. Studies of late effects in children do not need to consider competing risks because of the lack of comorbid conditions in young people.
- 33% 2. The effect of competing risks of death is to increase the incidence of late-occurring toxicity.
- 27% 3. A study estimating proton therapy's potential to reduce late toxicity that neglects to consider competing risks will likely overestimate the benefit of the normal tissue sparing.
- 23% 4. Kaplan-Meier analysis is a good way of handling competing risks.



Correct Answer

C. A study estimating proton therapy's potential to reduce late toxicity that neglects to consider competing risks will likely overestimate the benefit of the normal tissue sparing.

(The risk of second cancer will be overestimated. Therefore, the benefit of reducing the risk will be overestimated).

Leisenring, et al JCO, 2009 vol. 27 no. 14 2319-2327
Gooley TA et al. Stat Med 18:695-706, 1999