Secondary cancer after radiotherapy review of the literature

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Summary

- Setting the scene: Epidemiological data
- Factors affecting secondary cancer risk
  1. the patient age at time of radiation treatment
  2. genetic risk factors
  3. the organ and tissue site receiving radiation
  4. the dose and volume of tissue being irradiated by a particular radiation technology.
- Conclusions

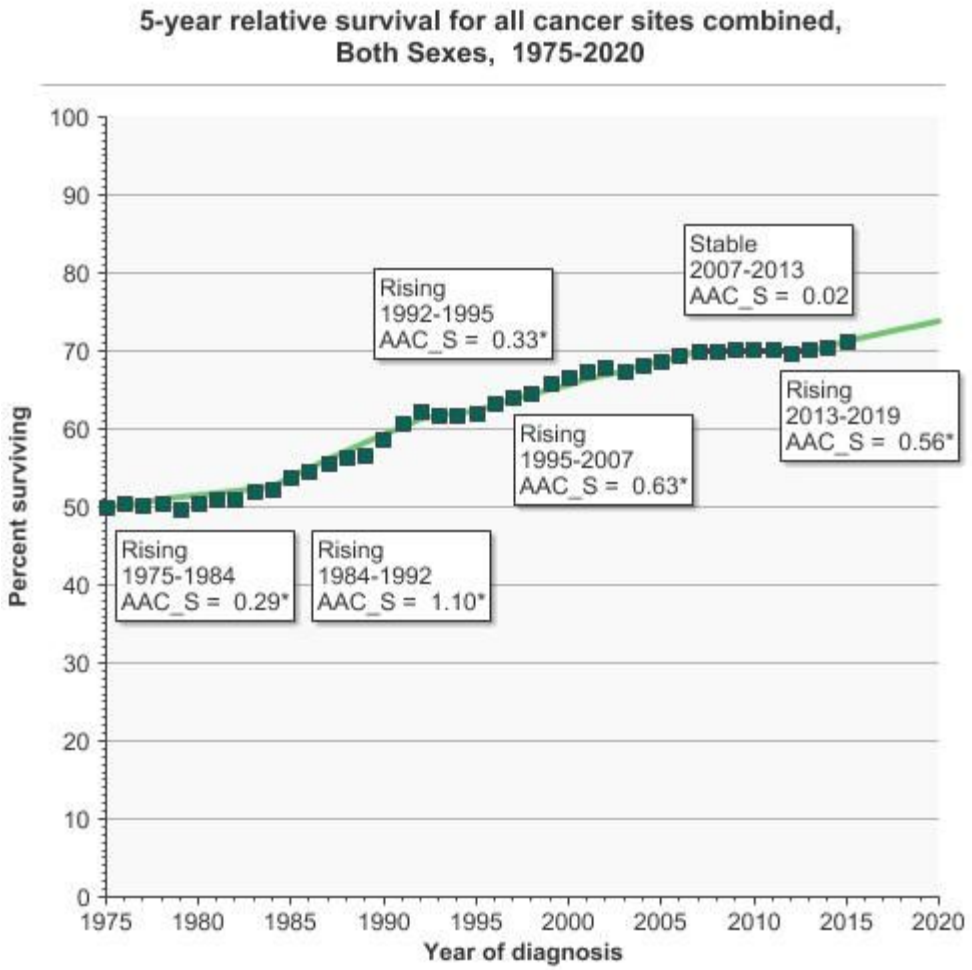
Setting the scene

- The prevalence of second malignancies after radiotherapy for pediatric and young adult populations is well established as one of the significant long-term sequelae of radiation treatment

- it is uncertain as to whether secondary malignancy estimates from studies on patients treated using older radiation techniques are reliable or directly applicable toward the broader populations of patients receiving radiotherapy today with contemporary modern radiation techniques.

- Despite this uncertainty, it is generally agreed that a major goal in modern radiotherapy is to minimize its late effects, which include secondary cancer risks.

Cancer Survival rates



The Healthy People 2030 Target for survival is pending revisions. This measure will be updated once the Healthy People 2030 target is finalized.
Source: SEER Program, National Cancer Institute. Underlying incidence data are from the SEER 8 areas (http://seer.cancer.gov/registries/terms.html).
Data are not age-adjusted.
Expected survival rates are derived from the U.S. Annual Life Tables.
Regression lines are calculated using the JPSurv software, National Cancer Institute.
The Average Absolute Change in Survival (AAC_S) represents the average percentage points difference of cancer survival for people diagnosed in one calendar year compared to the prior year.
* Denotes statistical significance.

- The 5-year survival for all cancer types in US has reached 67.7 % whereas 40% of these patients survive 10 years or more after primary diagnosis
- For patients diagnosed with cancer in 2015, 71.3% survived the cancer for at least five years.

Data Source

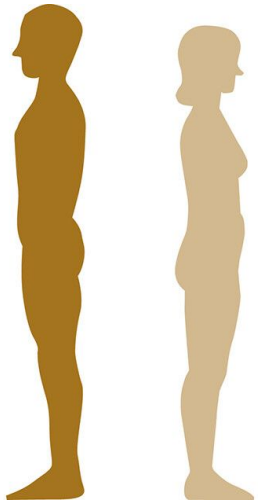
SEER Program, National Cancer Institute, 1975–2014 with follow-up through 2019

https://progressreport.cancer.gov/after/survival

Overall Cancer Prevalence

- The 3 most prevalent cancers in 2022 are prostate (3,523,230), melanoma of the skin (760,640), and colon and rectum (726,450) among males and breast (4,055,770), uterine corpus (891,560), and thyroid (823,800) among females (Fig. 1). The distribution of prevalent cancers differs from that of incident cancers because prevalent cancers reflect survival and median age at diagnosis as well as cancer occurrence.

Male	
Prostate	3,523,230
Melanoma of the skin	760,640
Colon & rectum	726,450
Urinary bladder	597,880
Non-Hodgkin lymphoma	451,370
Kidney & renal pelvis	376,280
Oral cavity & pharynx	311,200
Testis	303,040
Leukemia	300,250
Lung & bronchus	287,050
All sites	**8,321,200**



Female	
Breast	4,055,770
Uterine corpus	891,560
Thyroid	823,800
Melanoma of the skin	713,790
Colon & rectum	710,670
Non-Hodgkin lymphoma	394,180
Lung & bronchus	367,570
Uterine cervix	300,240
Ovary	246,940
Kidney & renal pelvis	230,960
All sites	**9,738,900**

Estimated Number of US Cancer Survivors by Site as of January 1, 2022. Estimates do not include in situ carcinoma of any site except urinary bladder and do not include basal cell or squamous cell skin cancers.

Miller KD, et al Cancer treatment and survivorship statistics, 2022.

RT treatment by cancer type

Breast

Stage	% receiving Chemo and/or RT
I-II	50%
III	9%
IV	60%

Rectum

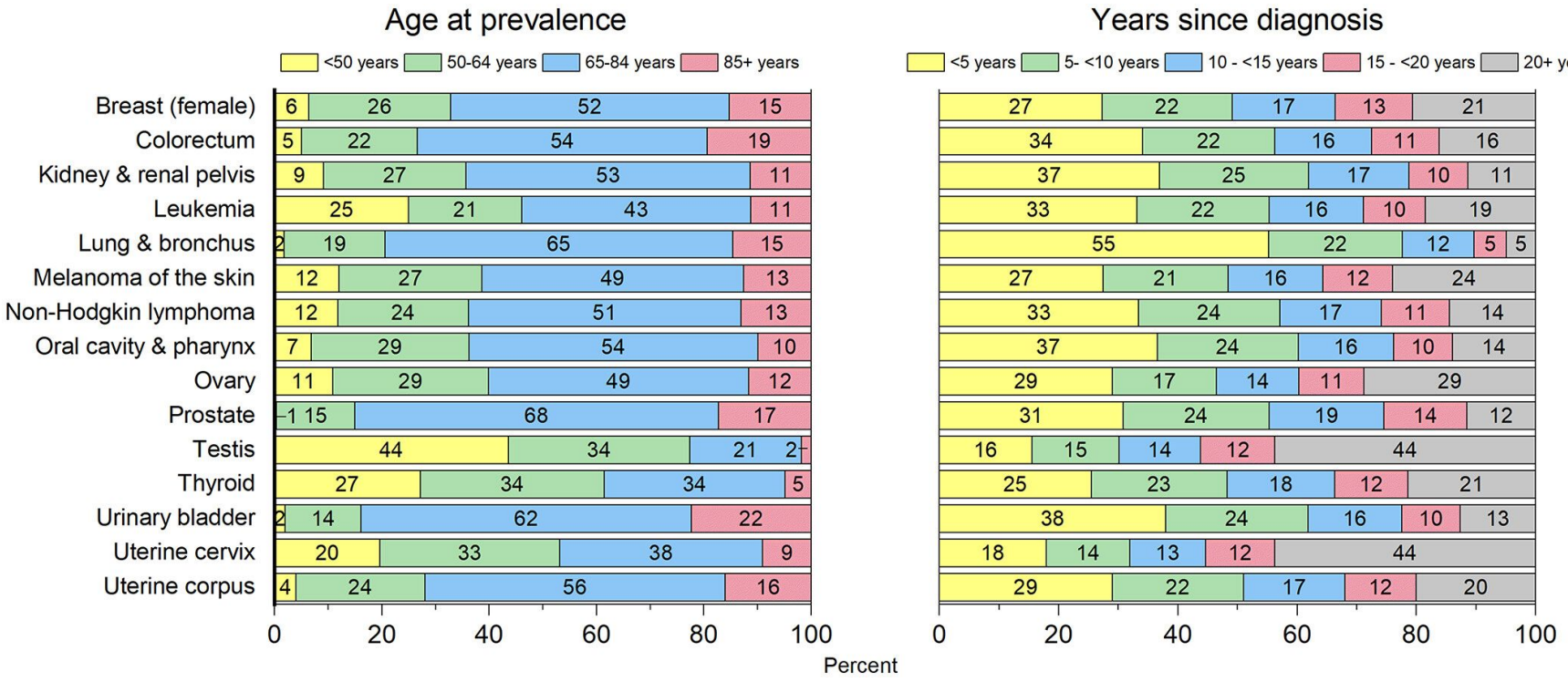
Stage	% receiving Chemo and/or RT
I	36%
II-III	83%
IV	80%

Approximately 50% of all cancer patients will receive radiation therapy during their course of illness with an estimation that radiation therapy contributes to around 40% towards curative treatment.

Miller KD, et al Cancer treatment and survivorship statistics, 2022.

Prevalence by cancer type

More than one-half (53%) of survivors were diagnosed within the past 10 years; 18% were diagnosed ≥20 years ago (Table 1). About two-thirds (67%) are aged 65 years or older, although age distributions vary by cancer type For example, the majority of prostate cancer survivors (85%) are aged 65 years or older compared with slightly less than one-half (47%) of cervical cancer survivors



Prevalence by Cancer Type, Years Since Diagnosis, and Age at Prevalence as of January 1, 2022, United States.

Miller KD, et al Cancer treatment and survivorship statistics, 2022.

Secondary Cancer

Def. (Cahan et al 1948)

- The secondary cancer is located in a region exposed to a therapeutic beam
- The tumor has a different histology than the original tumor, which means it is not a metastasis.
- Several years of time pass between treatment and occurrence of the new tumor
- The tumor was not present during the treatment
- No cancer-prone syndrome is known in the patient

Epidemiological data

The cancer survivors have a 14 % more enhanced probability for developing a malignant disease than that of the general population .

Fraumeni JF et al , 2006

About 8% of the secondary malignancies in cancer survivors may be associated with the use of radiation therapy

Berrington de Gonzalez A, et al. Lancet Oncol 2011;

Radiation therapy for cervical carcinoma led to a 10% increase ERR in the risks for cancer for heavily and moderately irradiated sites in the first ten years after RT to a 100% increase 30 or more years later

Kleinerman et al Cancer. 1995

Brenner et al. found a statistically significant elevated relative risk (RR) for lung cancer induction in prostate cancer survivors subjected to radiation therapy. For a latency period of>10 years, the lung cancer risk was increased by 42 % in irradiated patients versus those subjected to surgery.

Brenner DJ, et al Cancer 2000;

Epidemiological data

Table 1
Distribution of the second tumors in accordance to the radiation dose received by the site of origin.

Study	Organ dose (Gy)	Incidence of second tumors (%)
Diallo et al. [11]	>2.5	69
	0.1–2.5	25
	<0.1	6
Harbron et al. [78]	>1	64
	0.1–1	27
	<0.1	9
Gonzalez et al. [79]	>5	54
	1–5	17
	<1	29

Proportion

Table 2
Distribution of the second tumors in accordance with the tumor location in respect to the treatment volume.

Study	Tumor location	Incidence of second tumors (%)
Diallo et al. [11]	<2.5 cm from F.E.	12
	2.5–5 cm from F.E.	66
	>5 cm from F.E.	22
Dorr et al. [12][1]	In-field	8
	<5 cm from F.E.	48
	5–20 from F.E.	14
	>20 cm from F.E.	30
Harbron et al. [78][1]	In-field	37
	<8 cm from F.E.	31
	>8 cm from F.E.	32
Gonazalez et al. [79]	<3 cm from F.E.	54
	3–10 cm from F.E.	17
	>10 cm from F.E.	29
Welte et al. [80]	In-field	46
	<5 cm from 95% I.L.	23
	>5 cm from 95% I.L.	31

Proportion

A considerable proportion of the radiotherapy-induced malignancies develop at sites excluded from the treatment volume as shown in Tables 1 and 2.

Mazonakis et al, Phys Med 2021

Factors affecting secondary cancer risk

Patient age at time of radiation treatment

Second cancers after radiotherapy have a latency of onset of 10 years or greater after the initial treatment.

The younger the patient is at the time of radiation treatment, the higher the risk is of a future second cancer.

Epidemiological evidences about impact of patient age at time of radiation treatment

Life Span Study

relative risk decreased by about 17% per decade increase in age at exposure.

The Childhood Cancer Survivors Study (more than 14,000 survivors of pediatric malignancies)

There was a cumulative incidence of 7.9% for invasive cancers at 30 years from primary cancer diagnosis, demonstrating the significant secondary malignancy risk for this population.

The highest cumulative incidence was for survivors of

1. Hodgkin's Lymphoma
2. Ewing's sarcoma
3. Soft tissue sarcomas

The Childhood Cancer Survivors Study

Hodgkin's Lymphoma (1380 Childrens)

- After primary disease relapse second cancers were the most common cause of mortality in these patients
- The estimated incidence of any second neoplasm was 7% at 15 years after diagnosis of Hodgkin's disease in this cohort
- The most common solid tumor in the Late Effects Study Group cohort was **breast cancer**, and it was recommended that greater systematic screening be implemented for this higher risk population, as their risk of developing future breast cancers was comparable to that of the BRCA population.
- For those patients receiving radiation treatment after the age of 30, the risk appeared to be small or not elevated
- The findings of the Late Effects Study Group were corroborated by the findings from the Stanford cohort characterizing their long-term survivors of Hodgkin's lymphoma.

Genetic risk factors

- The Women's Environment, Cancer, and Radiation Epidemiology cohort study (Bernstein et al 2010) follows over 52,000 female breast cancer survivors to study the interaction between radiation exposure and genetic predisposition toward breast cancer.
  - there was no clear evidence of increased contralateral breast cancer risk for patients treated with breast radiotherapy among carriers of BRCA1/BRCA2 deletion mutations
  - patients who carried rare ATM mutations appeared to be at an increased risk of contralateral breast cancer after radiation.
- In addition to the ATM and BRCA pathways, other potential markers of secondary cancer risks include p53, CHEK2, PALB2, and PTEN

- One particular pathway of interest involves the PRDM1 gene, which has been implicated in radiation-associated secondary malignancies after Hodgkin's lymphoma perhaps by serving as a radiation-responsive tumor suppressor.

Tissue and Organ dependence

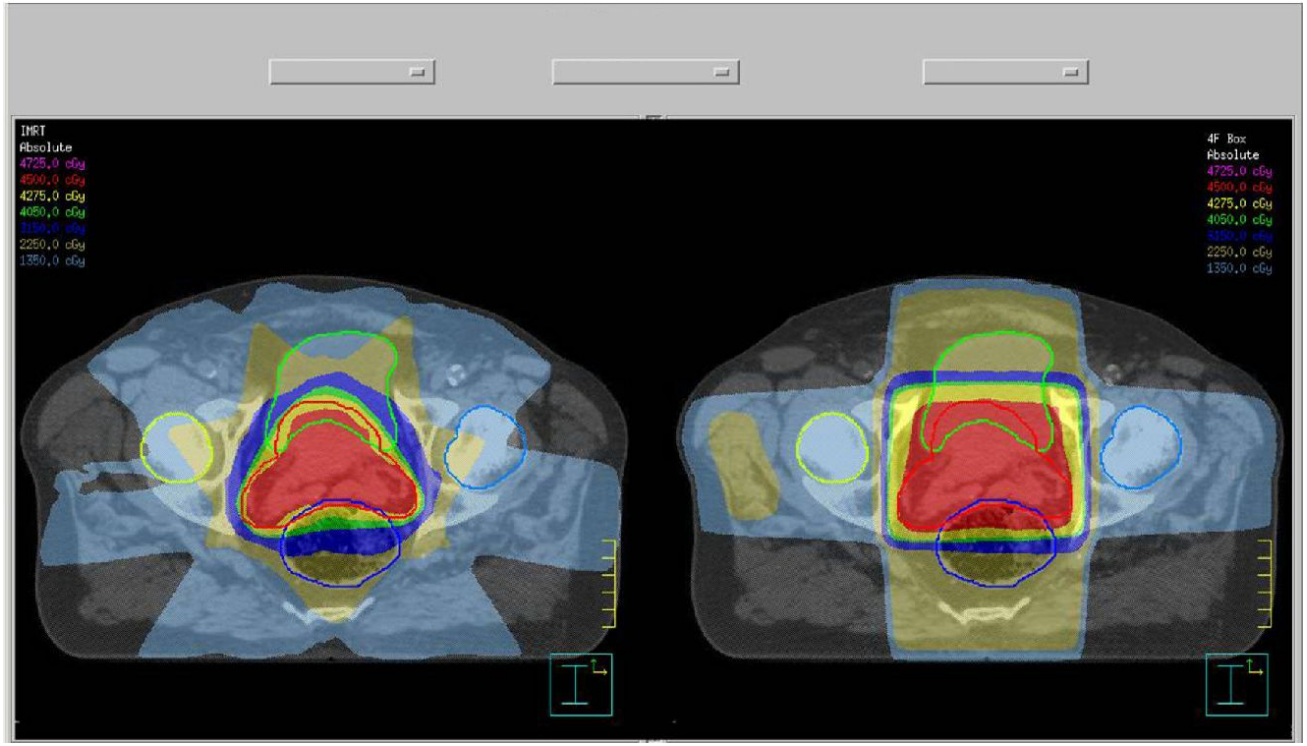
- In the survivors of Hodgkin's lymphoma who received chest irradiation as part of the treatment, after a latency of many years, breast cancers and sarcomas were the most common second invasive tumors noted.
- The Institute Curie group examined their >13,000 patients who had received breast radiotherapy and found a slightly increased risk of subsequent sarcomas and lung cancers, but not other types of cancers (Kyrova et al)
- Brenner et al performed a large-scale Surveillance, Epidemiology, and End Results Program analysis on patients treated with prostate radiotherapy and found a small, statistically significant increase in the risk of solid tumors of the bladder and rectum
- Other treated sites that have been investigated include cervical cancer radiation therapy, which did not find any increased risk of developing a second cancer after radiotherapy (Boice et al) again demonstrating that the impact of the tissue and organ irradiated is important.

Tissue and Organ dependence

The complex biologic processes that underlie the carcinogenic processes for the different tissue and organ sites will require future studies to unravel. While it is difficult to draw conclusive predictive estimates about the relationship between the irradiated tissue and radiation risk, its clinical importance highlights the importance of long-term patient follow-up and of improving carcinogenesis risk models.

Modern radiotherapy technologies and dose–volume dependence

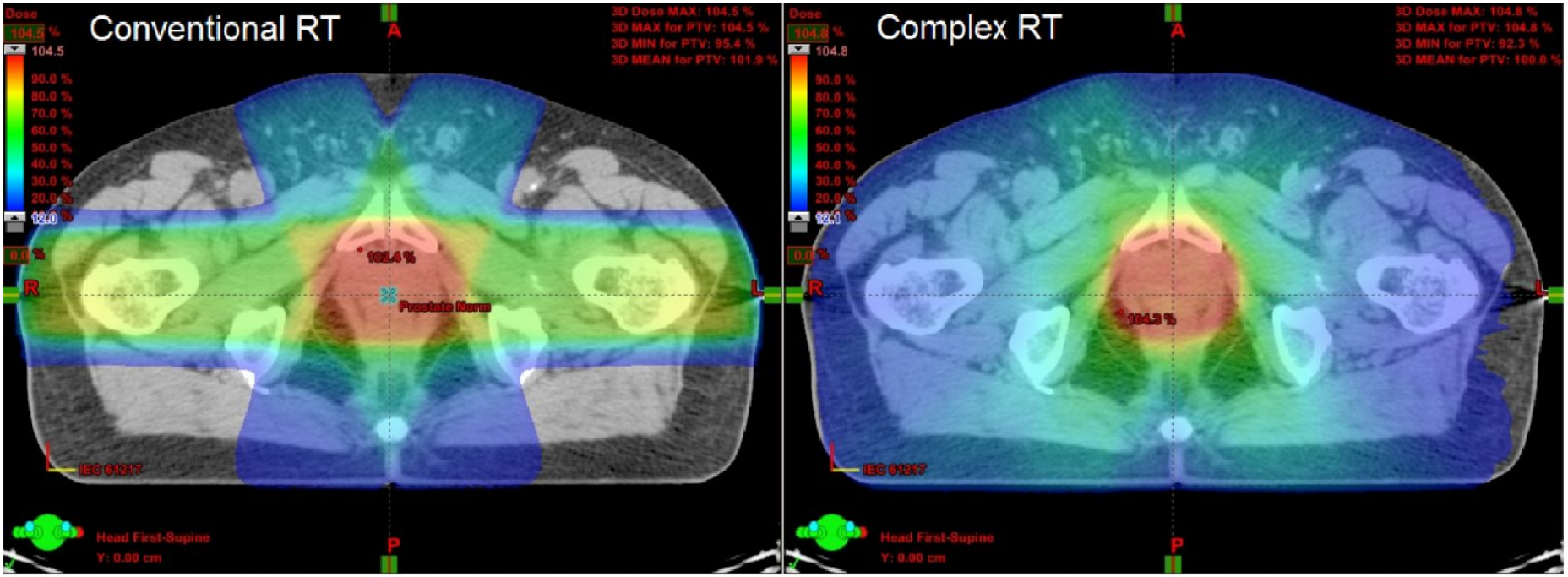
- The introduction of IMRT or VMAT and charged therapy has led to the ability to concentrate radiation dose to the target volume while sparing normal tissues
- The difference in conformality between the older 3-D conformal radiotherapy technique and the IMRT technique can be demonstrated by the side-by-side comparison of prostate radiotherapy plans



Courtesy of Brendan McClean

Modern radiotherapy technologies and dose–volume dependence

- With radiotherapy techniques dramatically changing the dose and volume of radiation for so many sites of radiotherapy, the applicability of the outcomes from the large epidemiologic studies of earlier decades utilizing outdated techniques to the modern context is unclear.



Courtesy of Brendan McClean

Newer radiotherapy technologies will necessarily reduce second cancer risks?

- IMRT delivers more conformal radiation doses to the treated target volume, but also involves using more radiation fields and exposes a larger volume of normal tissue to lower doses.
- There is often greater background leakage radiation from IMRT compared with 3-D conformal treatment planning. And indeed, in shielding calculations the IMRT factor (which is usually ranging 3-5) accounts for this phenomenon
- The expansion of large areas receiving low doses of radiation has led some to argue that the risk of secondary cancers will be substantially increased, as much as possibly doubling the incidence of second malignancies (Hall 2003) for patients surviving ten years
- The region of normal tissue receiving low dose exposure may be even greater with VMAT
- The increased scatter dose of neutrons led to large uncertainties regarding second cancer risks for patients treated with proton radiotherapy (Hall 2007).

Newer radiotherapy technologies will necessarily reduce second cancer risks?

- The unclear implications for second cancer risk of novel radiotherapy techniques despite their rapid adoption and utilization for treating patients emphasizes the critical value of dosimetric and modeling investigations.

- Many radiation oncologists point out that the large radiation fields used in the past to treat Hodgkin's lymphoma patients in the long-term epidemiologic studies such as the Late Effects Study Group are markedly different from the smaller, more conformal, and lower radiation dose fields used to treat lymphoma patients today.

- In breast cancer patients, the utilization of the prone technique for breast radiotherapy likely leads to lower doses of irradiated lung tissue (Griem 2003) possibly leading to a lower predicted risk of subsequent secondary lung cancers (Ng 2012)

- Until large epidemiologic studies with long-term follow-up report their results for these newer techniques, we will be dependent on dosimetric and modeling studies to provide important quantitative predictive information that may guide important clinical decisions.

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Conclusions

- Large epidemiologic studies done in the past have provided significant insights and much of the clinical evidence on the impact of radiotherapy for second cancer risks.
- The application of these findings toward optimizing risks in the modern clinical setting remains controversial and an evolving field of investigation.
- Genetic markers, molecular pathways, and evolving radiation techniques will likely profile these risks for subgroups of patients in the emerging era of personalized medicine
- Many unanswered questions remain in this field that await further advances in modern genetics and carcinogenesis modeling to address.

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