

Low Dose Radiation in Medical Interventions (Radiation Oncology Experience)

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Basic assumption of radiation exposures for medical purposes

- “With regard to medical exposure of patients, it is not appropriate to apply dose limits or dose constraints, because such limits would often do more harm than good. Often, there are concurrent chronic, severe, or even life-threatening medical conditions that are more critical than the radiation exposure. ...”

(ICRP, 2007. Radiological Protection in Medicine. ICRP Publication 105. Ann. ICRP 37 (6).)

- It is important to understand that medical exposure is fundamentally different from exposure to the public.
- But, with that said, ...

Data on the Application of Radiation in Medicine

- In the month of September, 2011,

CT >2,000,000 patients*

PET, PET/CT >48,000 patients*

Radiotherapy >20,000 patients**

* Number of tests ** number of CT simulation

Population of Fukushima prefecture: $\approx 1,890,000$ (2017)

How much radiation are these people (patients) receiving?

Radiotherapy

- Radiation oncology professionals prescribes ionizing radiation to treat cancer in the form of external beam radiotherapy or brachytherapy.
- In curative treatment, it is our aim to cure the patients and expect long-term survival.
- In Japan, about 200,000 patients/year receive radiotherapy.
- The dose we prescribe is about 60 Gy to the malignant lesion.
- In most cases, radiotherapy is given in 2 Gy/fraction.

So, how much is the radiation used for radiotherapy?

- Natural radiation ≈ 2 mSv/year
 - CT (diagnosis) ≈ 5 -30 mSv/scan
 - Radiotherapy ≈ 2 Gy (Sv)/day (This is 2,000 mSv/day)
- This is about **1,000 years worth** of natural radiation, per day.
(Average natural radiation in Japan = 2.1 mSv/year)
“Millennium radiation/day”

In total, the dose is 60-70 Gy (Sv)/treatment.

(This is 30,000-35,000 years worth of natural radiation in total.)

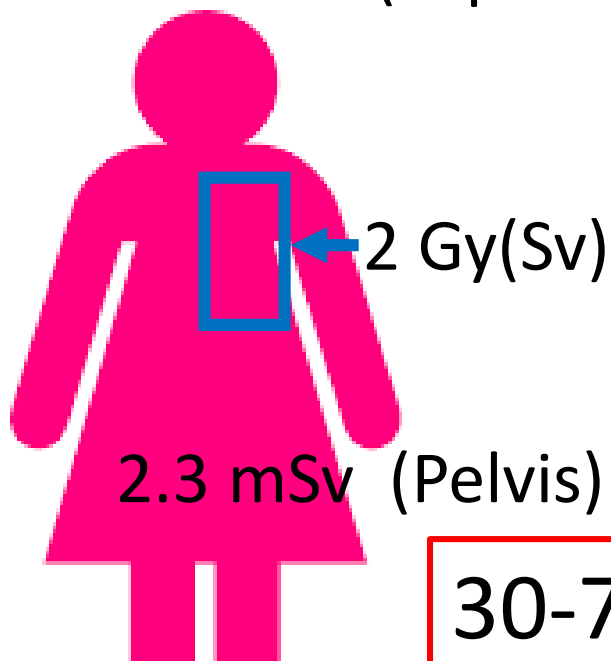
What is “low dose” in radiotherapy? – Certainly, NOT in RT field.
So, how about the dose outside of the radiation field?

How much is out-of-field radiation?

Breast Cancer

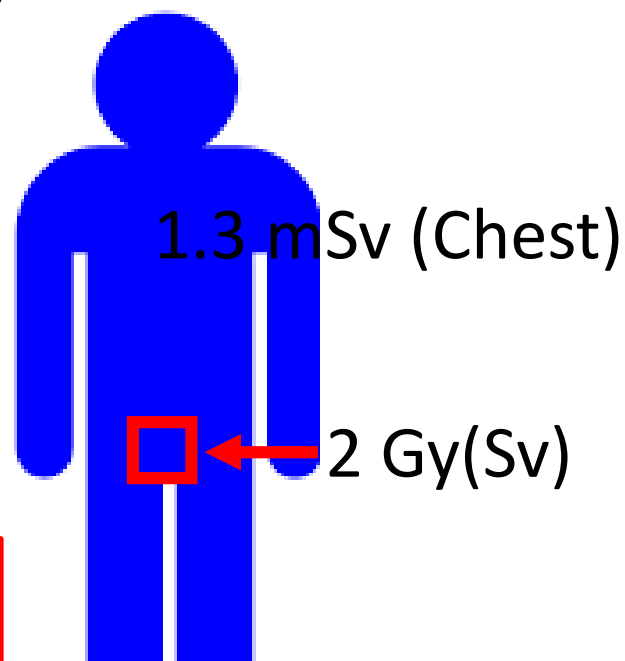
Whole breast irradiation

2.2 mSv (Top of the head) 0.8 mSv



Prostate Cancer

Prostate irradiation



In this presentation, "low dose" is defined as the dose outside of the radiation field.

What is the effect of low dose? (out-of-field dose)

- There are no acute symptoms which raise concerns for radiation oncologists in a regular clinic.
- The only concern may be the risk of second cancers.
- HOWEVER, for clinicians, the risk of second cancers in high-dose regions within the radiation fields tend to be a much bigger concern (for logical reasons).
- How much is the risk of second cancers from the “low dose”?

Issues in the analysis of second primary cancer (SPC)

- The incidence of SPC is influenced by many factors
 - Radiation (in-field and out-of-field)
 - Other factors: age, genetic factors, environmental factors, etc.
- Often, “radiation induced” SPC is defined by the following characteristics:
 - Diagnosed after a latency period (often ≥ 5 years)
 - Within the radiation field
 - Different histology from the original cancer
 - Not present at the time of radiotherapy

Issues in the analysis of second primary cancer (SPC)

- Who to compare with...
 - General population vs. non-irradiated patients
 - The presence of bias (difference in surveillance, background risk factors, observed duration) requires attention
- Study Designs
 - Population-based study
 - Higher statistical power: large cohort
 - Limited information of possible risk factors (other than radiation)
 - Institutional study
 - Lower statistical power: limited size
 - Possible bias (selection, etc)
 - Ability to analyze the effect of risk factors

Radiotherapy for breast cancer

- For early stage breast cancer, the patients receive breast conserving surgery and post-surgery whole breast irradiation.
- The post-surgery radiotherapy reduces the risk of recurrence in breast to about 1/3.
- Recent development in surgery, radiotherapy, and chemo/hormonal therapy is improving the clinical outcomes of breast cancer treatment including loco-regional control.

Radiotherapy for breast cancer

Risk of second primary cancer (meta-analysis)

Systematic review

Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients

Trine Grantzau*, Jens Overgaard

Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

22 studies

245,575 irradiated pts.

277,164 non-irradiated pts.

- Incidence of SPC in close proximity to radiation field (lung, esophagus, soft tissues and the thyroid regions) were analyzed.
- "... irradiated patients overall had a 23% higher risk of second non-breast cancer compared with the general female population. ..." (non-irradiated had a 8% higher risk)
- "The above findings do not upset the benefit of radiation in the loco-regional treatment of breast cancer, but it certainly calls for awareness."

(Grantzau T, Overgaard J. *Radiother Oncol* 121:402-423, 2016)

Radiotherapy for breast cancer

Risk of second primary cancer (national population based study)

Radiotherapy-associated site vs. non-RT associated sites
(high-dose region) (low-dose region)

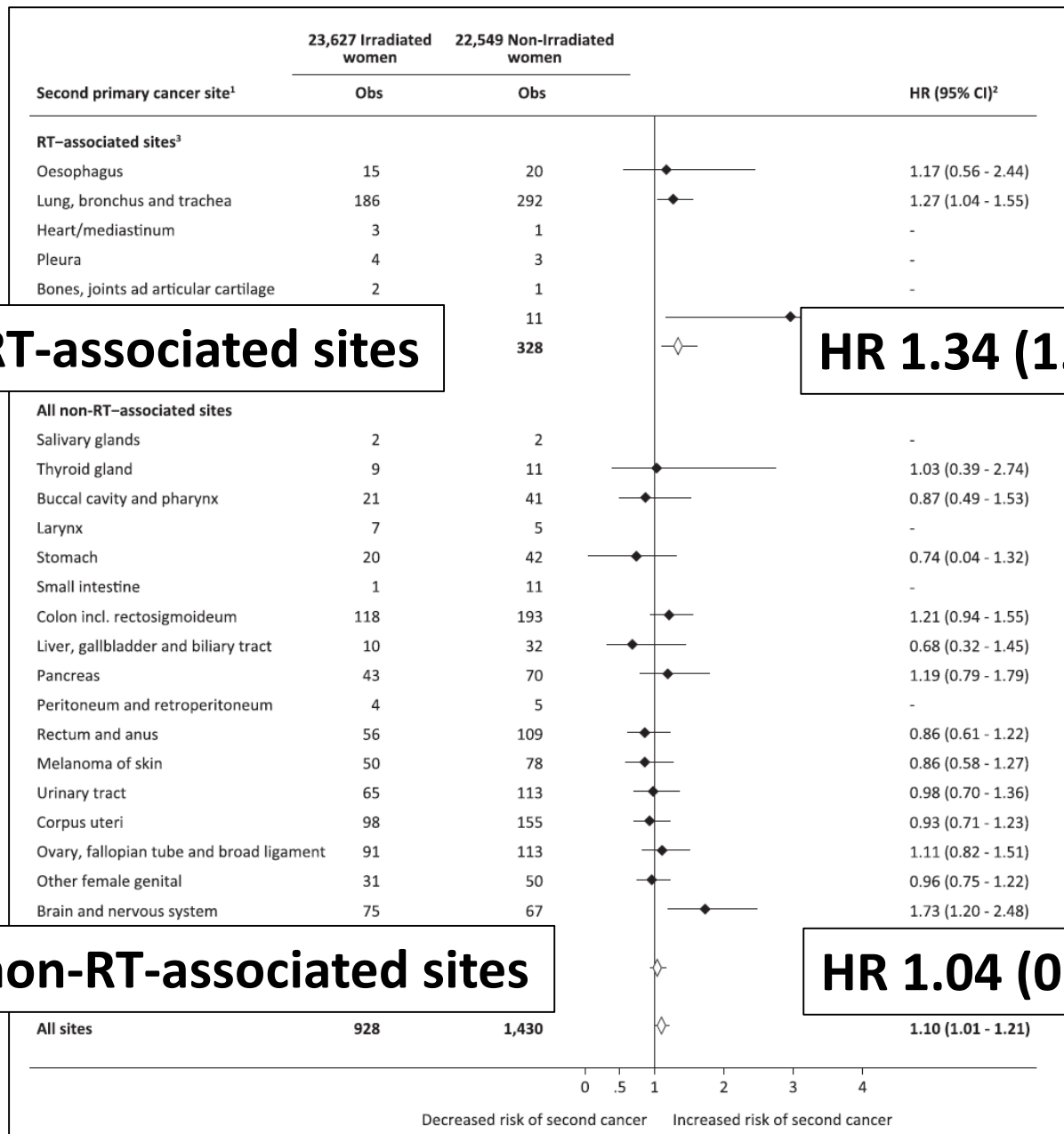
Second primary cancers after adjuvant radiotherapy in early breast cancer patients: A national population based study under the Danish Breast Cancer Cooperative Group (DBCG) [☆]

Trine Grantzau ^{a,*}, Lene Mellempkjær ^b, Jens Overgaard

23,627 irradiated pts.

22,549 non-irradiated pts.

- The estimated attributable risk related to radiotherapy:
 - Radiotherapy-associated sites (high-dose region):
 - 1 second cancer in every 200 women treated.
 - Non-radiotherapy-associated sites (“low-dose” region):
 - No increased risk.



Subtotal RT-associated sites

HR 1.34 (1.11 – 1.61)

Subtotal non-RT-associated sites

HR 1.04 (0.94 – 1.16)

Prostate Cancer

- Good clinical outcomes compared to other cancers
10-year relative survival rate – Overall 94.5%
(Report from National Cancer Center Japan)
 - Stage I: 100%
 - Stage II: 100%
 - Stage III: 100%
 - Stage IV: 40.5%
- Multiple treatment options: Active surveillance, hormonal therapy, surgery, and radiotherapy.
- Common radiotherapy today: Total of 70—80 Gy in 2 Gy/fraction using IMRT technique.

Radiotherapy for prostate cancer

Risk of second primary cancer (meta-analysis)

Systematic review

Second primary cancers after radiation for prostate cancer: A systematic review of the clinical data and impact of treatment technique



Louise Murray^a, Anne ... Peter Hoskin^b, Frank ... Jack Vensele ... of the

PROBATE ... ESTRO

^aSt. ... oncology, Leeds; ^bMount Vernon Cancer C ... ood, UK; ^cKlinik für Strahlentherapie, Kiel, Germany; ^dInstitute Verbeeten, Tilburg, Netherlands

19 registry publications

21 institutional studies

7 other series

- “Given the multiple factors involved, and heterogeneity among studies, it is very difficult to tease out definitive answers regarding irradiation and the risk of SPCs.”
- “Putting all the potential cofounders and biases aside, however, it must be acknowledged that a small increased risk of SPC and RISPC (radiation-induced SPC) in irradiated prostate patients has been observed in several studies.”
- The risk of RISPC appears small: in the range of 1 in 220 to 1 in 290 over all durations of follow-up, based on older radiation techniques.

(Murray L, et al. *Radiother Oncol* 110:213-228, 2014)

Radiotherapy for prostate cancer

Risk of second primary cancer (institutional study)

Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention

Michael J. Zelefsky, Xin Pei, Tatiana Teslova, Deborah Kuk,
Juan Martin Magsanoc, Marisa Kollmeier, Brett Cox and Zhigang Zhang
Departments of Radiation Oncology, Biostatistics and Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- 2658 patients
 - Surgery (n=1348)
 - IMRT (n=897)
 - Brachy (n=413)

- The 10-year SPC-free survival:
 - Surgery 89%, IMRT 83%, Brachy 87%
(Surgery vs. IMRT, $p = 0.002$)
- Overall, the incidence of SPC after IMRT or BT, both pelvic (high-dose) and extrapelvic (low-dose), was not significantly different from that after surgery when adjusted for age and smoking history.

(Zelefsky MJ, et al. *BJU International*, 110:1696-1701, 2012)

List of priorities...

- Local Control (curability of treated region)
- Acute toxicities (high dose region)
- Disease control (recurrence)
- Late toxicities (high dose region)
- ...
- Second primary cancer (high dose region)
 - RT-independent >> RT-related
- Second primary cancer (low dose region)
 - RT-independent >> RT-related

Summary

- In the field of radiotherapy (radiation oncology), the magnitude of out-of-field radiation dose can be in the range of 10-100 mSv.
- The effect of low dose radiation (\approx mSv) do not usually receive much attention compared to the high dose radiation (\approx Sv(Gy)) in radiotherapy.
- A small increase in second primary cancer related to high dose irradiation (often within irradiation fields) has been reported in cancer patients receiving radiotherapy. Such an increase is not significantly observed in low-dose region outside of the irradiation field, even in many of the population-based studies.
- The effect of radiation on the incidence of SPC should be carefully analyzed in the view of other significant risk factors, including age, smoking history, and etc.