Modern radiation therapy for lymphoma: Principles of ISRT
(involved site radiation therapy)

Lena Specht MD DMSc
Professor of Oncology, Chief Oncologist
Copenhagen University Hospital – Rigshospitalet
Denmark

Disclosures

Employers:

- Rigshospitalet, Dept. of Oncology, Capital Region, Denmark
- University of Copenhagen, Faculty of Health and Medical Sciences, Denmark

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- Speaker honoraria: Takeda
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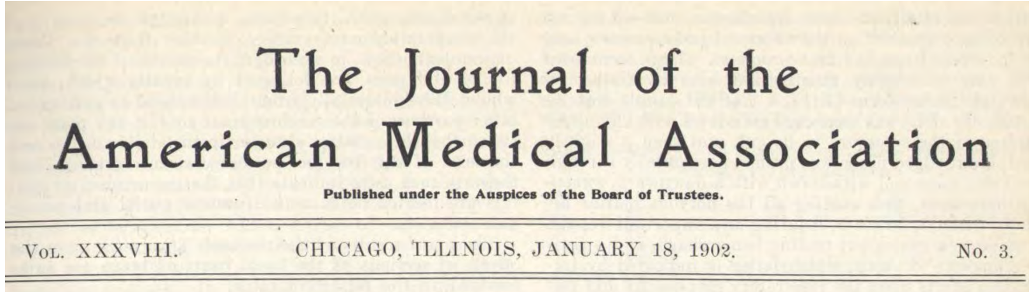
- Research Grants: Varian, ViewRay, Danish Cancer Society

”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage

Radiotherapy is the most powerful agent for achieving local lymphoma control



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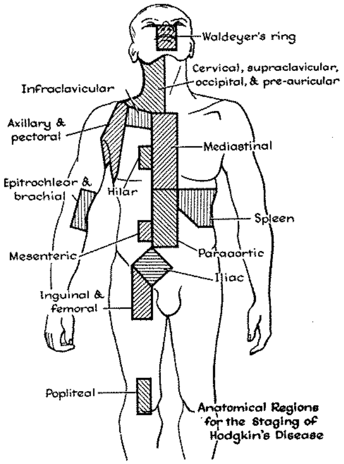
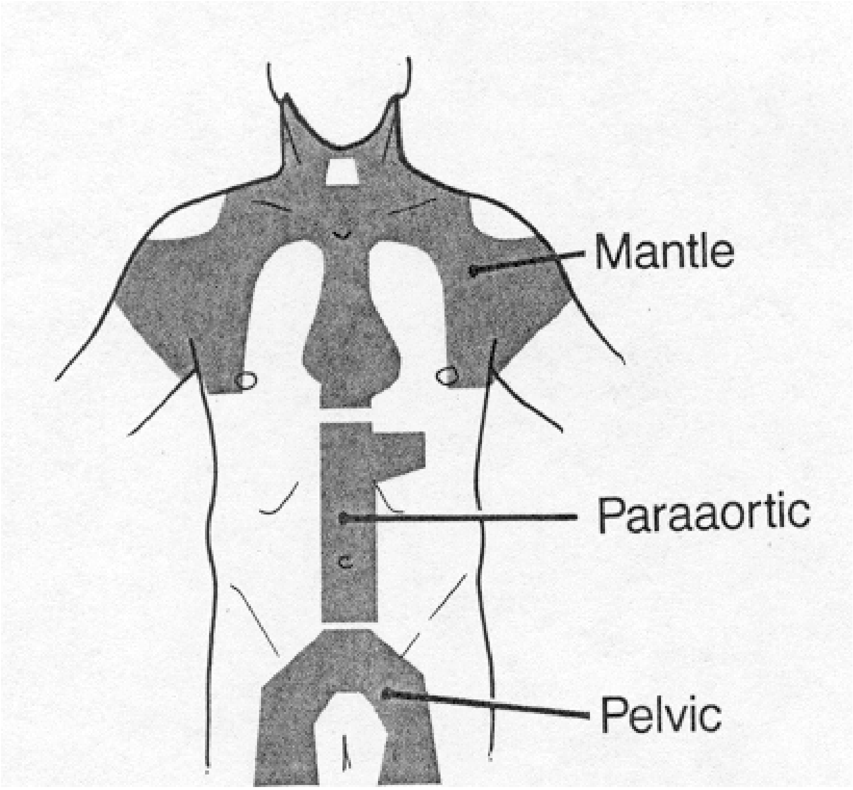
Radiotherapy, the first curative treatment of lymphoma

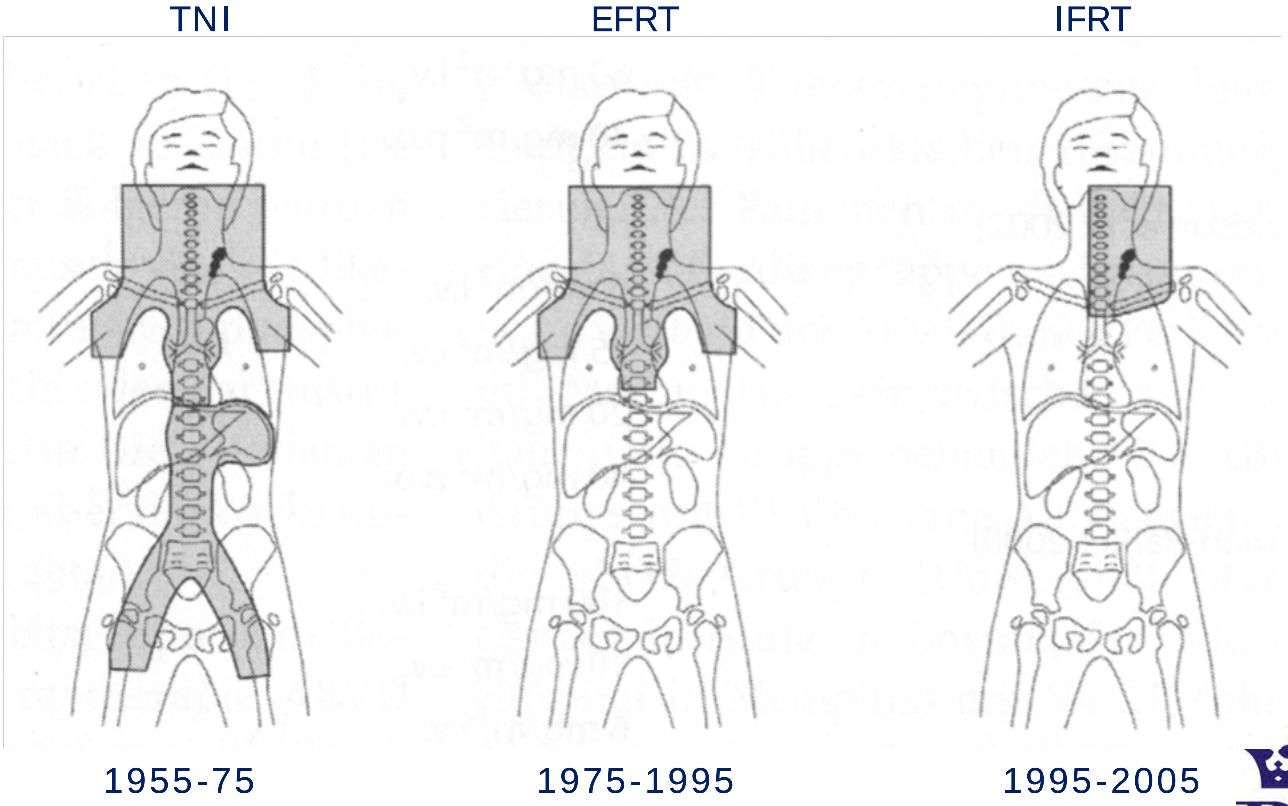
- Prophylactic irradiation of clinically uninvolved volumes
- Very large treatment fields, especially for Hodgkin lymphoma
- Regional irradiation, based on Ann Arbor region definition





Development of lymphoma radiation volumes in the 2D era, based on:

2 D planning, regions, bony landmarks defining fields, and ”fixed” margins



Modern, highly conformal radiation therapy developed rapidly in the early 2000s

Based on

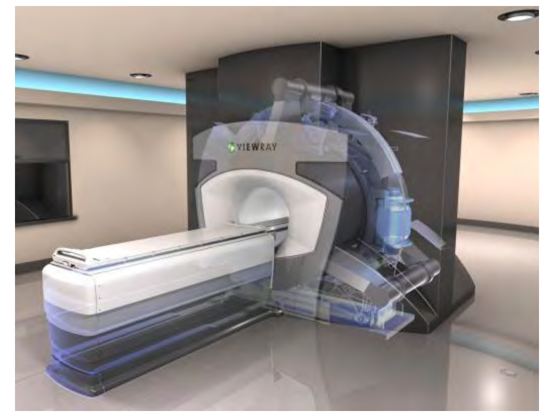
- Advanced imaging with
  - multi-slice CT-techniques generating 3D views of any anatomical regions with superb spatial resolution
  - Combined with 3D FDG-PET yielding time-dependent metabolic information with mm resolution
- Advances in radiation therapy planning with
  - Direct use of the 3D data on radiation energy deposition from CT-scans
  - Sophisticated treatment–planning optimization algorithms
- Advances in radiation therapy machinery allowing accurate delivery

High precision radiotherapy techniques

Linear accelerator, intensity modulated RT, volumetric arc therapy

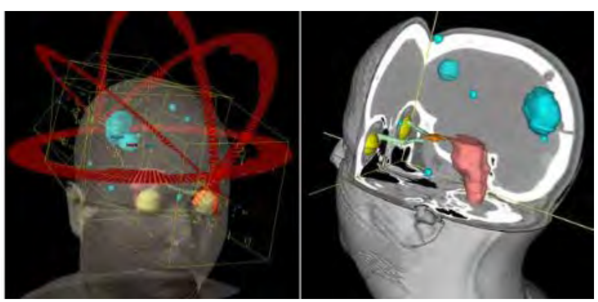
Online adaptive treatments, AI and deformable image registration

MR accelerator, tracking adaptive planning



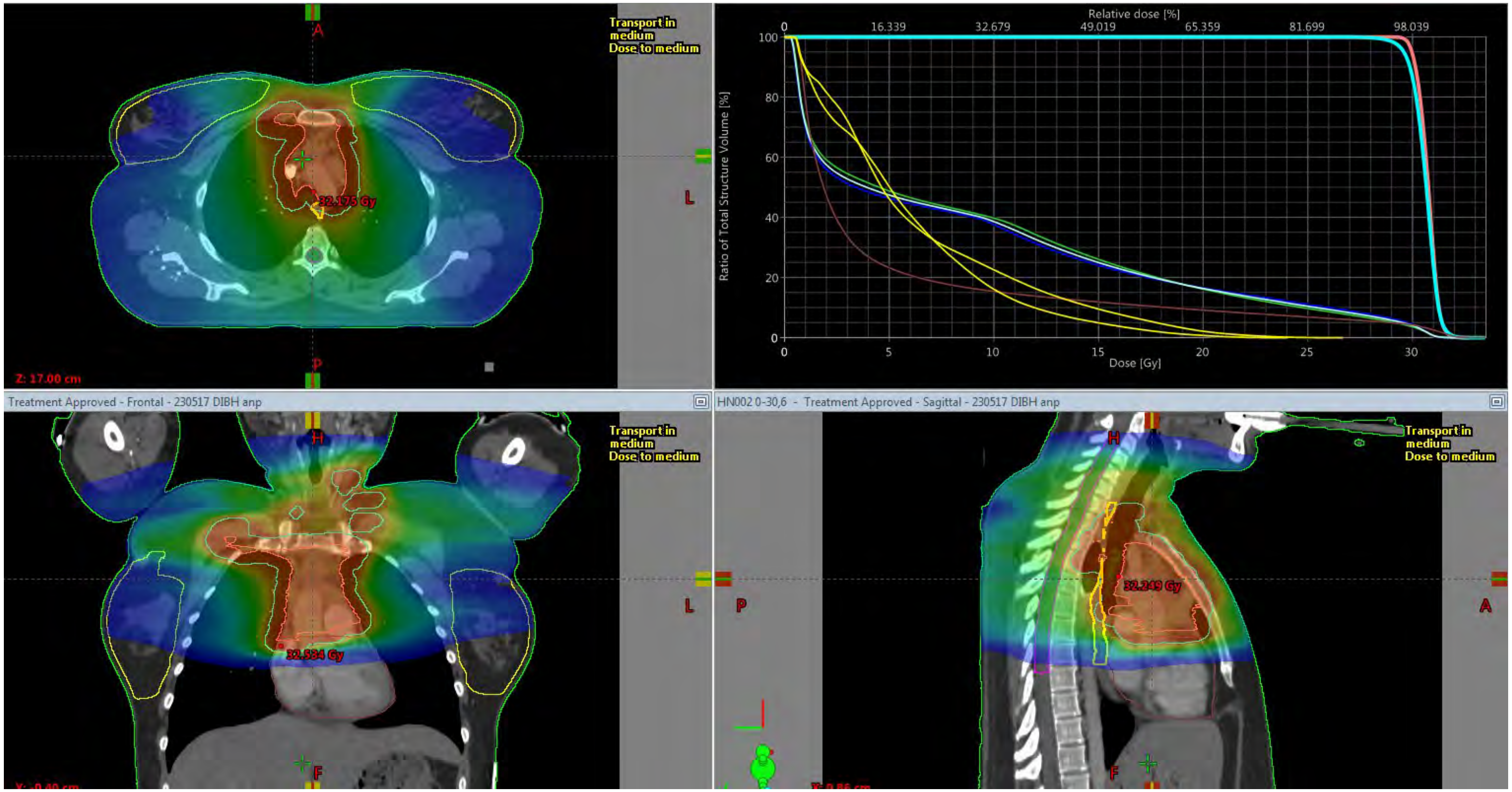
Proton therapy

Stereotactic radiotherapy



Surface recognition motion management

For the first time in the history of radiation therapy we are able to shape the high dose volume in the patient so that it fits (conforms) almost exactly to the tumour we wish to irradiate



Modern, highly conformal radiation therapy

Allows:

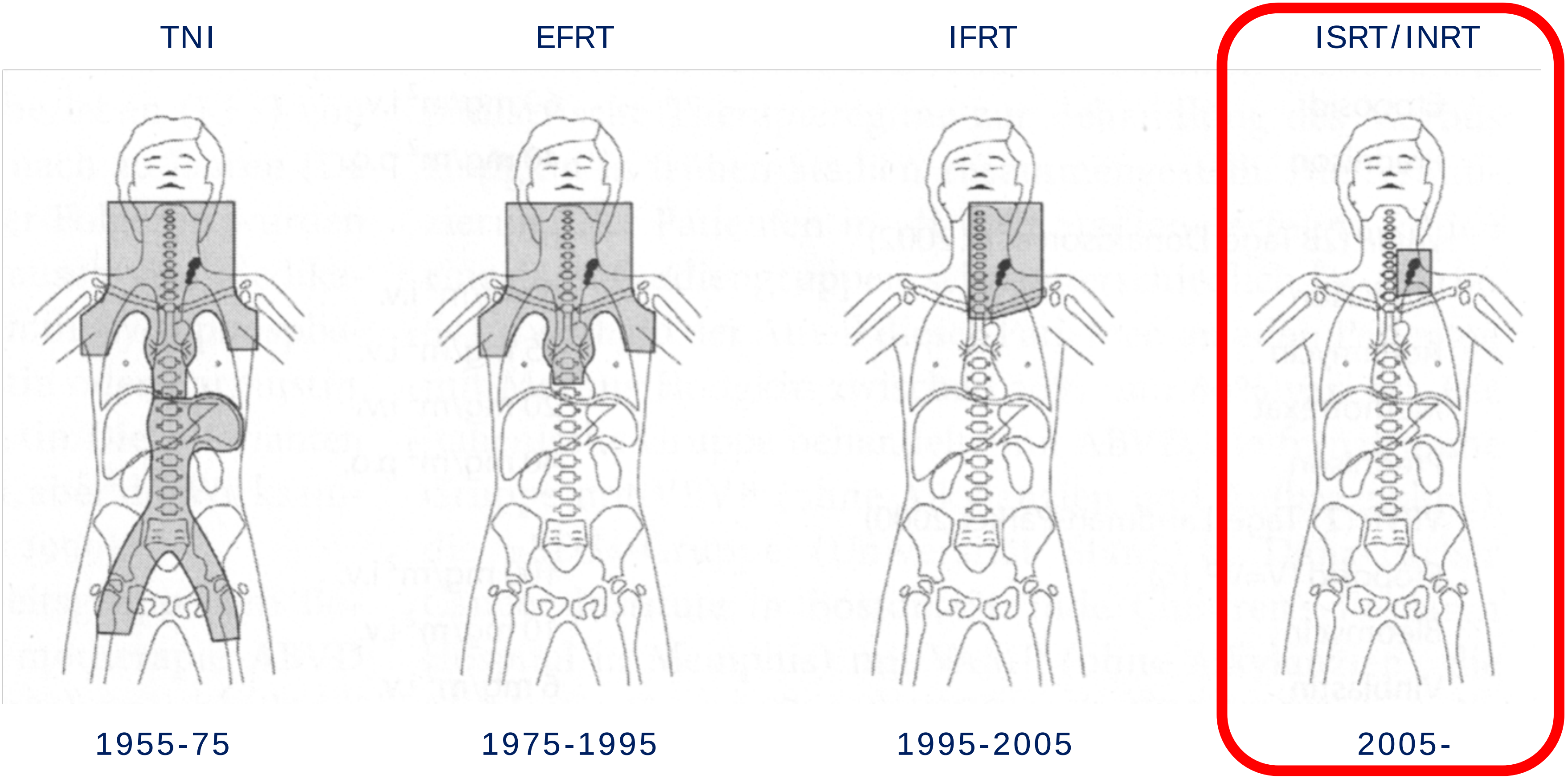
Escalation of the absorbed dose to malignant tissues for same normal tissue response

- very important for many solid tumours
- not necessary for lymphomas

Less radiation to normal tissues for same radiation to tumour

- Very important for lymphomas, since the very large treated volumes in the past caused
  - acute toxicity which could be difficult to tolerate for older patients, a large and increasing group of lymphoma patients
  - serious long-term consequences

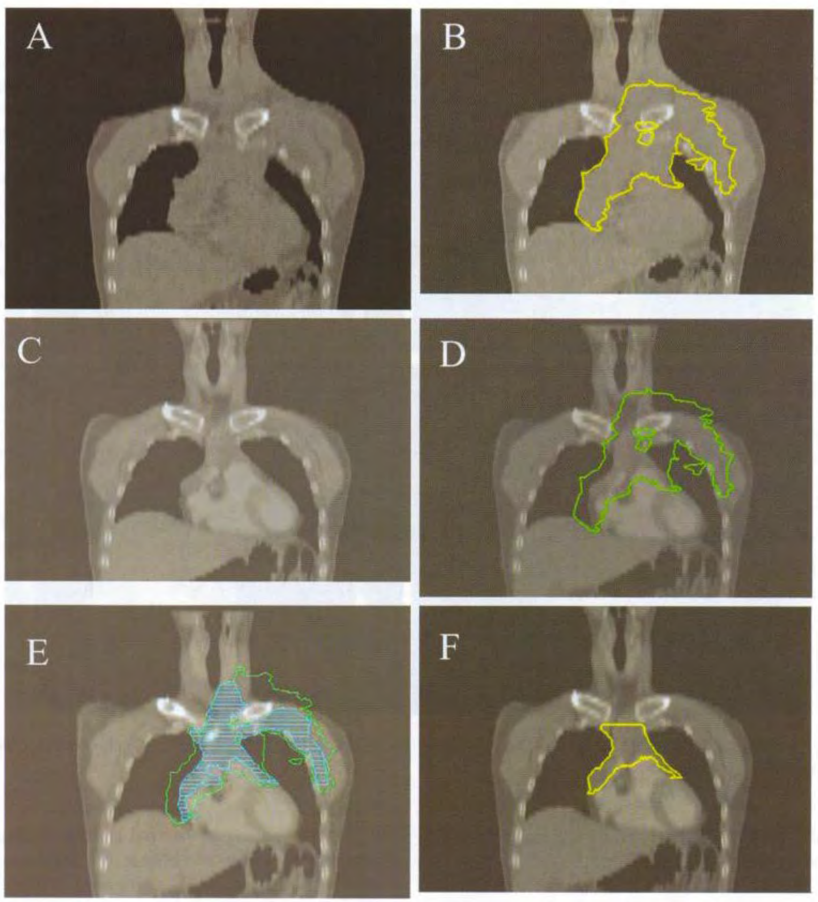
Development of lymphoma radiation volumes

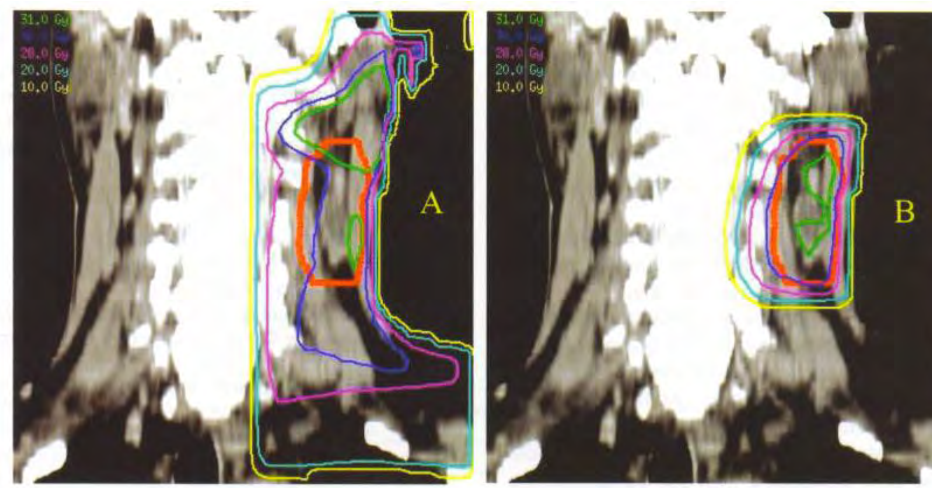


Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines

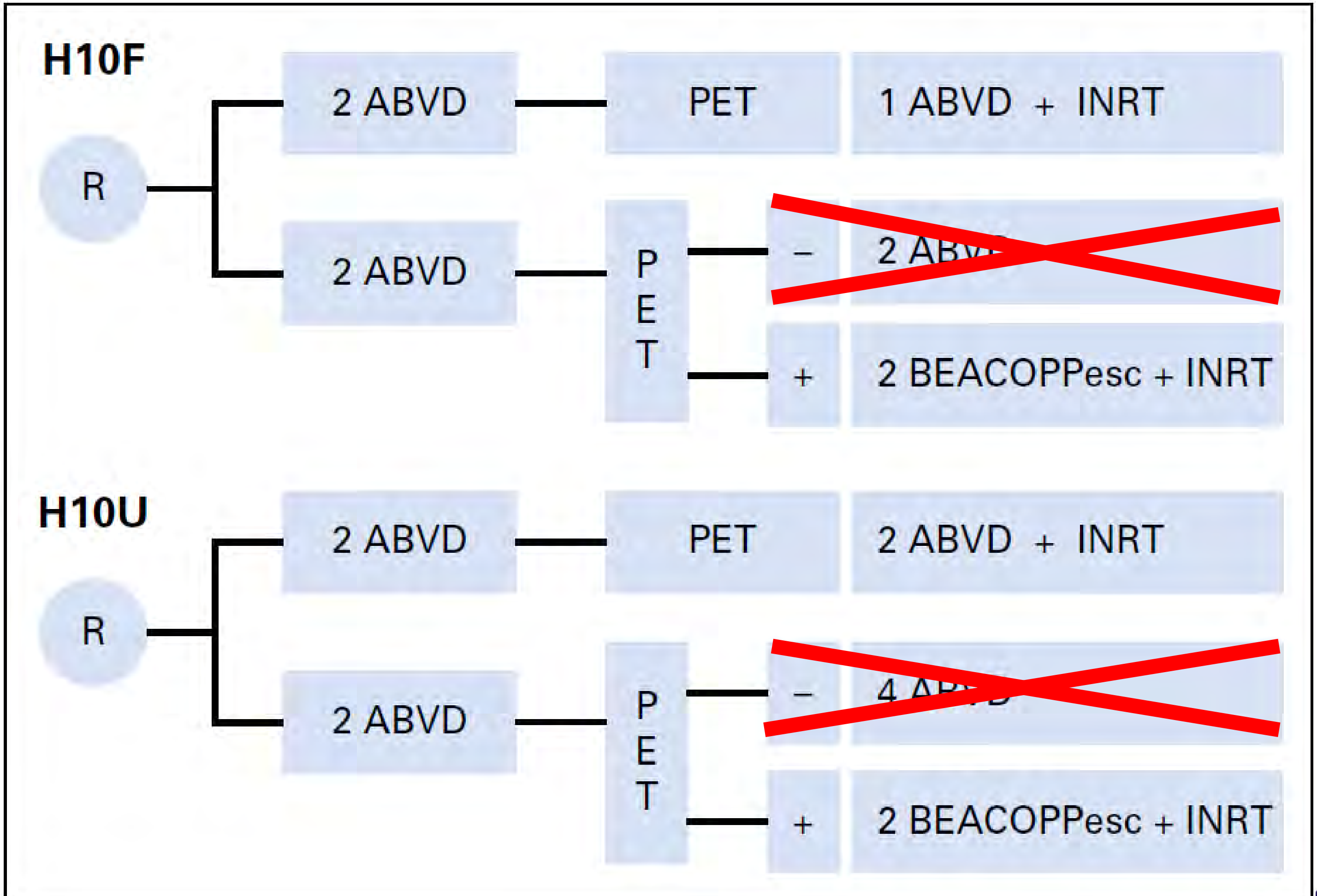
Theodore Girinsky[a,*], Richard van der Maazen[b], Lena Specht[c], Berthe Aleman[d], Philip Poortmans[e], Yolande Lievens[f], Paul Meijnders[g], Mithra Ghalibafian[a], Jacobus Meerwaldt[h], Evert Noordijk[i], on behalf of the EORTC-GELA Lymphoma Group

Radiother Oncol 2006; 79: 270-7





INRT tested first in EORTC/LYSA/FIL H10 trial



André M et al. JCO 2017; 35: 1786-94

ILROG 1st Steering Committee Meeting
Rigshospitalet, Copenhagen, 2011

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Decision: We need to make guidelines

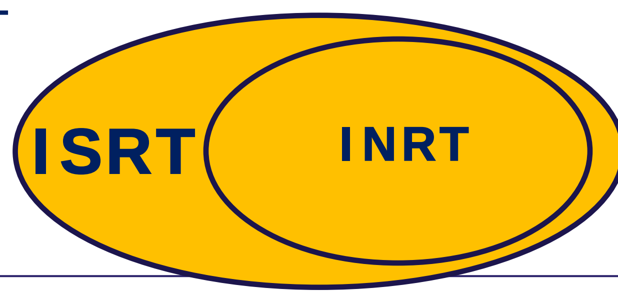
Involved Site Radiotherapy (ISRT)

Detailed pre-chemotherapy information and imaging is not always optimal in standard clinical practice

- Image fusion may not be possible
- Pre-chemotherapy staging PET/CT will have to be used as visual guidance

Compared to INRT slightly larger volumes needed to ensure irradiation of all initially involved tissue volumes, but the same principles apply

In most situations, ISRT will include significantly smaller volumes than IFRT



ISRT scenarios

- Optimal pre-chemo imaging of all the initially involved lymphomas is available and image fusion with the planning CT-scan is possible:
  - INRT
- Pre-chemo imaging (CT, PET, or MR) of the initially involved lymphomas is available, but image fusion with the planning CT-scan is not possible:
  - Contour with pre-chemo images as a visual aid, allowing for uncertainties of the contouring and differences in positioning

ILROG Principles of ISRT

Only irradiate to the prescribed dose the volume that is necessary, determined by:

- Lymphoma type
- Lymphoma anatomy
- Lymphoma biology
- Any additional treatment
- Efficacy of the additional treatment

Doses to normal structures should be kept as low as possible

Use all the tools available to achieve this

Follow the principles of the ICRU 83 guidelines

- Modern lymphoma radiotherapy follows the same principles as radiotherapy for other tumour types (solid tumours)
- Modern lymphoma radiotherapy is ”mainstream”, it was the lymphoma radiotherapy of the past that was ”special”

Gross tumor volume (GTV) (ICRU 83)

Gross demonstrable extent and location of the tumor (lymphoma)

Original (before any treatment) lymphoma:
pre-chemo GTV

Residual (after systemic treatment) lymphoma:
post-chemo GTV

Clinical target volume (CTV) (ICRU 83)

Volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy i.e. is likely to contain lymphoma cells

Encompasses the pre-chemo GTV

If treated with chemotherapy up front:

pre-chemo GTV is modified to account for anatomic changes

post-chemo GTV is always part of the CTV

Normal structures (e.g., lungs, kidneys, muscles) that were clearly uninvolved should be excluded

What volume is relevant for therapy in lymphomas – how do we define the CTV?

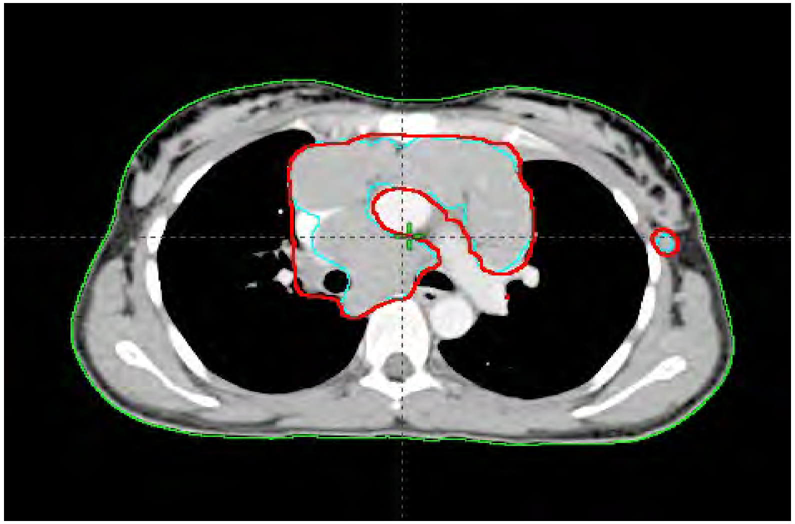
Depends on

- Lymphoma type
- Stage
- Localization
- Whether or not effective systemic therapy is administered up front

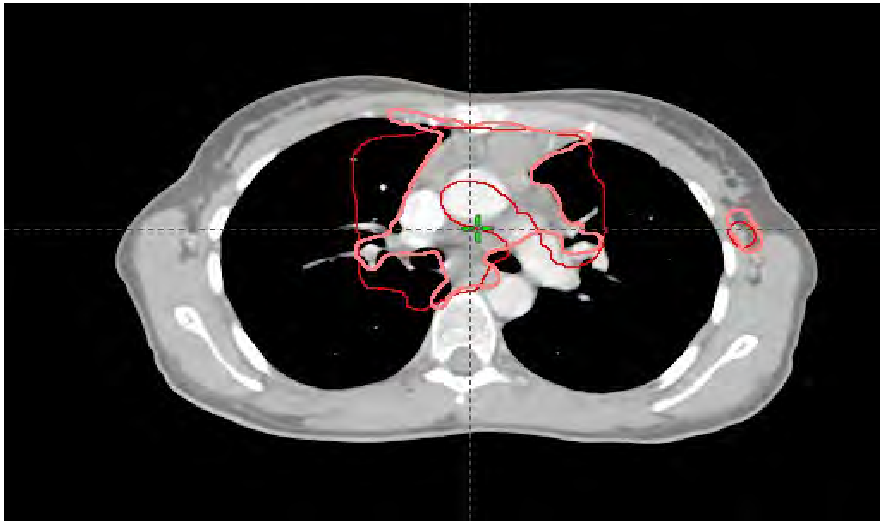
Effective systemic therapy is given (Classical HL, aggressive NHL)

- Effective chemotherapy deals with microscopic disease (true for B-cell lymphomas, less so for T-cell lymphomas)
- CTV in early stage disease is only the tissue volume which initially contained macroscopic lymphoma (pre-chemo GTV)
- CTV in advanced disease is only residual disease, or intially bulky or extranodal disease

Pre-chemo



Post-chemo



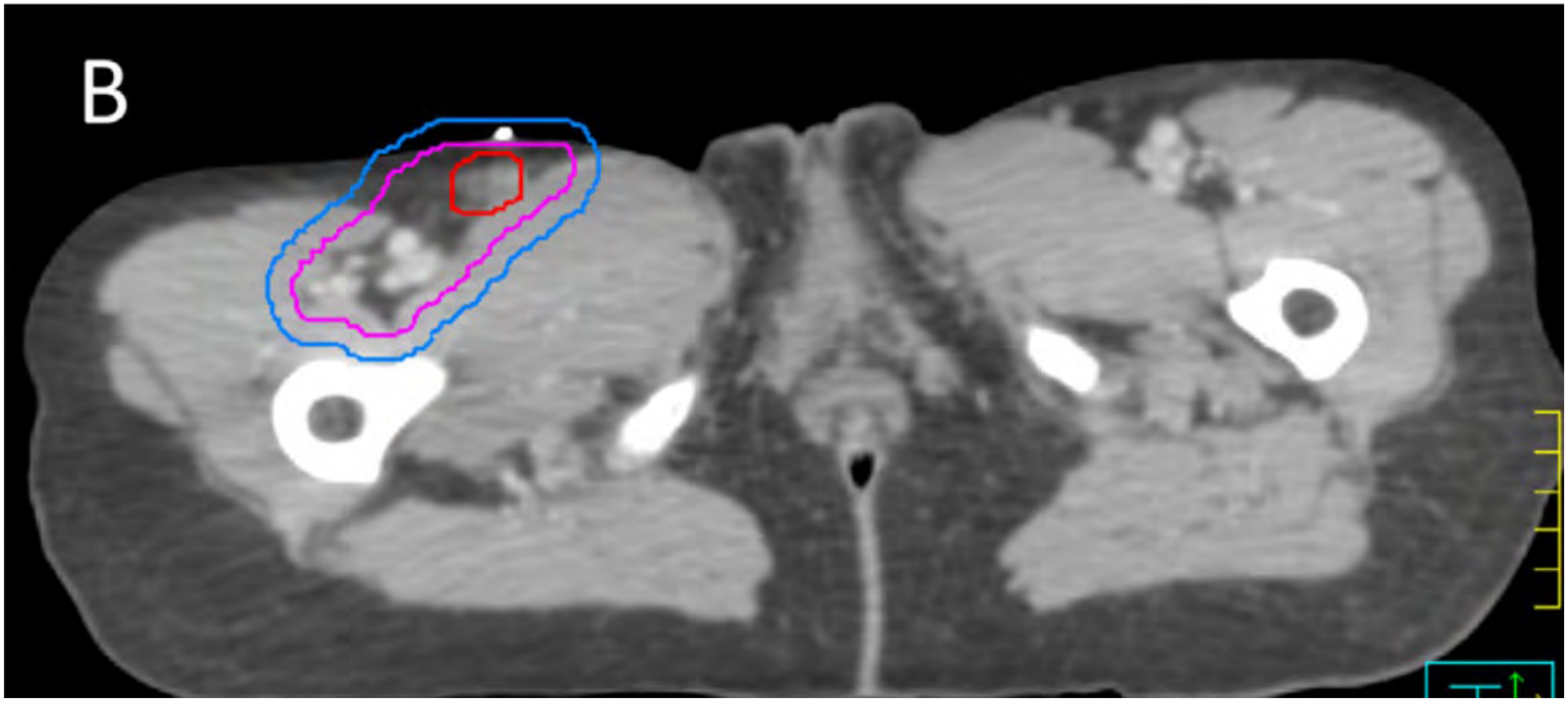
No systemic therapy is given (NLPHL, indolent NHL)

In early stage disease RT is the primary treatment.

- CTV is the macroscopic lymphoma (GTV) and adjacent nodes in that site with a generous margin

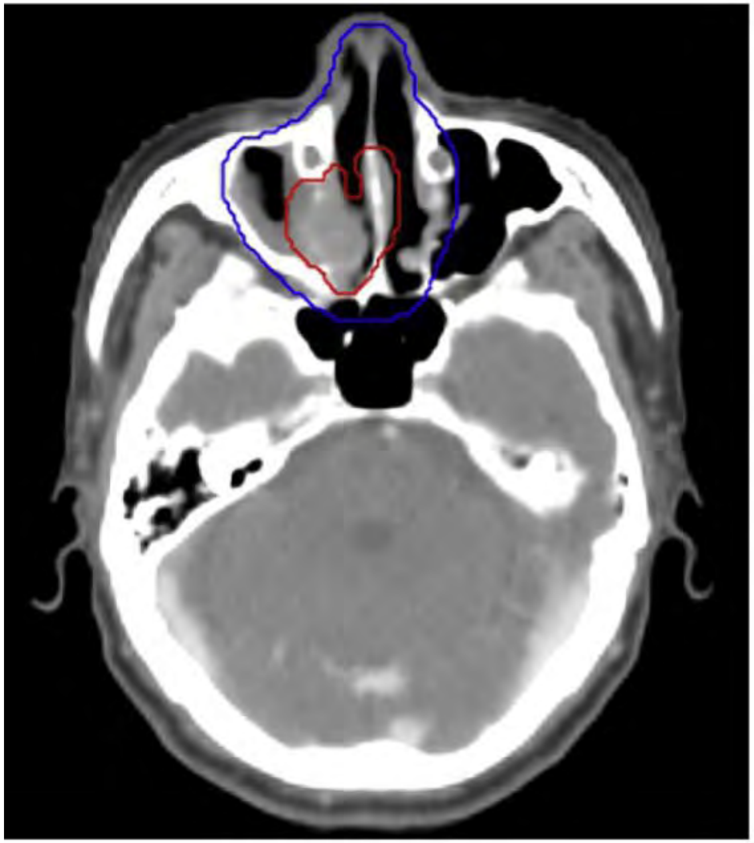
In advanced disease RT is palliative.

- CTV is localized symptomatic disease


B

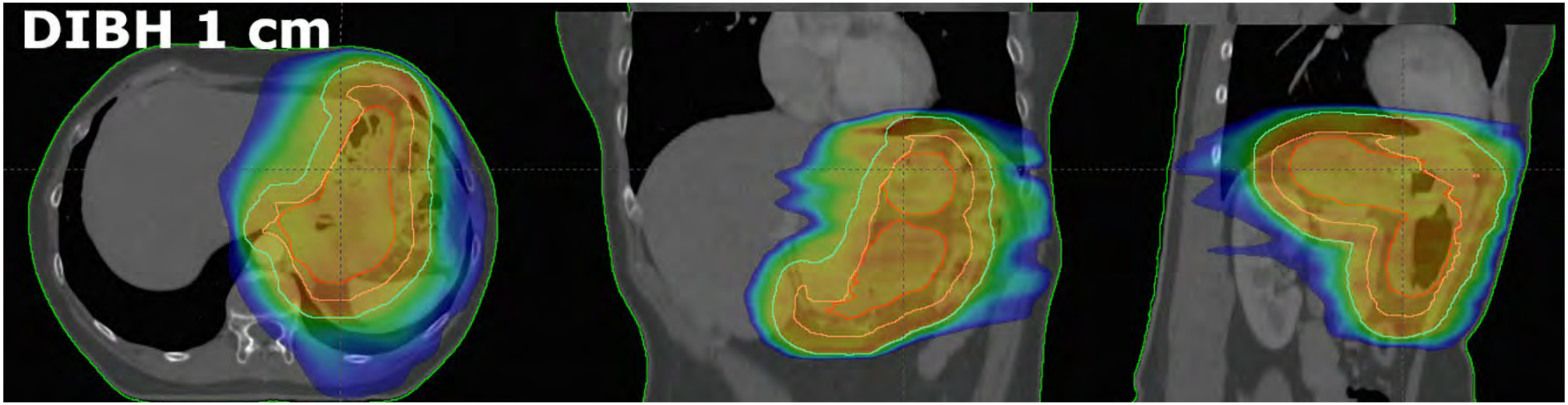
Systemic therapy is given, but efficacy is uncertain (NK/T-cell lymphoma)

- CTV in early stage disease is the tissue volume which initially contained macroscopic lymphoma (pre-chemo GTV) and adjacent areas in that site with a generous margin



Extranodal lymphomas

- Same principles as for nodal lymphomas
- Except that in many cases the whole organ is the CTV even if apparently only partially involved, because
  - In many organs (e.g., stomach, salivary glands, thyroid gland, CNS) lymphoma is multifocal
  - Even with modern imaging it may be difficult to accurately define the exact extent of disease in many extranodal sites


DIBH 1 cm

Internal target volume (ITV) (ICRU 83)

- CTV + margin for uncertainties in size, shape, and position of the CTV
- Defined in ICRU 62, optional in ICRU 83
- Mostly relevant when the target is moving (chest and upper abdomen)
- Margins may be obtained from 4-D CT, fluoroscopy or from expert clinician
- Margins should be added quadratically:

$$\sigma' = \sqrt{(\sigma^2{}_m + \sigma^2{}_s)}$$

Planning target volume (PTV) (ICRU 83)

- Accounts for set-up uncertainties in patient position and beam alignment during planning and through all treatment sessions
- Function of immobilization device, body site, image guidance, and patient cooperation
- Geometrical concept introduced to ensure that CTV and/or ITV are properly covered
- Applied by clinician or treatment planner

Modern radiation doses, > 10-fold variation significantly lower than doses for solid tumours

4 Gy Selected indolent lymphomas

(Hoskin et al. Lancet Oncol 2021; 22: 332-40)

20 Gy Early favourable classical Hodgkin lymphoma, combined modality

(Engert et al. N Engl J Med 2011; 363: 640-52)

24 Gy Standard indolent lymphomas

(Hoskin et al. Lancet Oncol 2021; 22: 332-40)

30 Gy Early aggressive NHL, combined modality

(Lowry et al. Radiother Oncol 2011; 100: 86-92)

Early unfavourable classical Hodgkin lymphoma, combined modality

(Eich et al. JCO 2010; 28: 4199-206)

36-40 Gy Advanced classical Hodgkin lymphoma and aggressive NHL, residual PET+ disease after systemic treatment

(Specht et al. IJROBP 2014; 89: 854-62. Illidge et al. IJROBP 2014; 89: 49-58. Yahalom et al. IJROBP 2015; 92: 11-31)

45-50 Gy Extranodal NK/T-cell lymphoma, nasal type

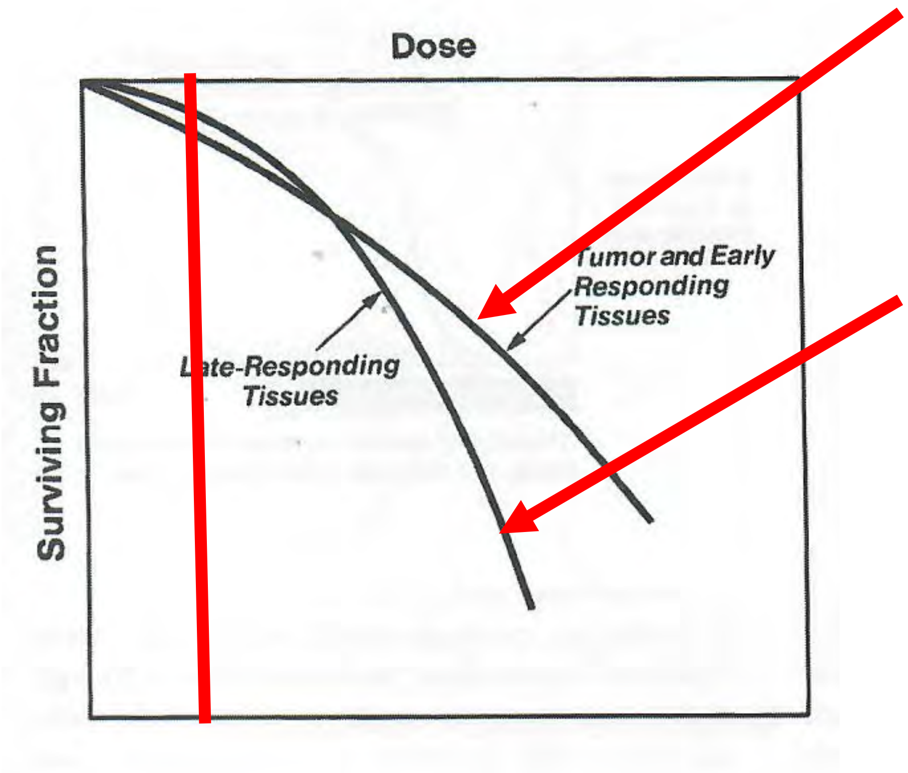
(Qi et al. IJROBP 2021; 110: 1064-81)

ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic

Joachim Yahalom,[1] Bouthaina Shbib Dabaja,[2] Umberto Ricardi,[3] Andrea Ng,[4] N. George Mikhaeel,[5] Ivan R. Vogelius,[6] Tim Illidge,[7] Shunan Qi,[8] Andrew Wirth,[9] and Lena Specht,[6] on behalf of the International Lymphoma Radiation Oncology Group (ILROG)

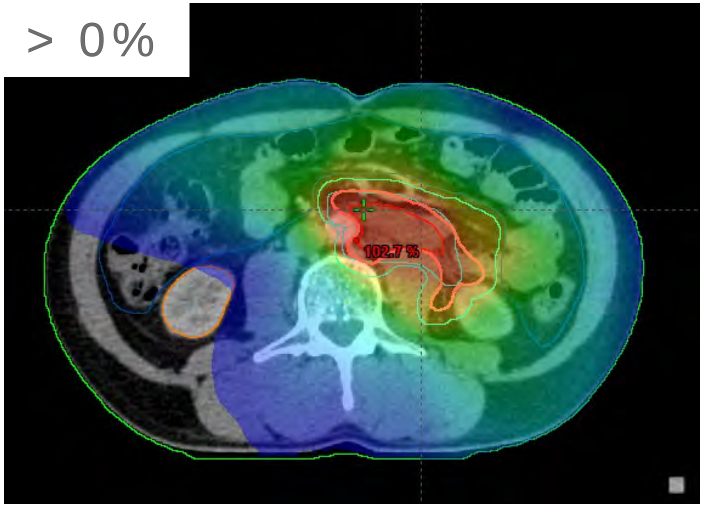
- Background
  - Anticipated reduction of treatment capacity
  - Desire for minimizing exposure of high-risk patients by limiting the number of visits
- Proposed solutions
  - Omitting radiotherapy in certain situations
  - Delaying radiotherapy in certain situations
  - Shortening the radiotherapy course - Hypofractionation

Hypofractionation in lymphoma radiotherapy

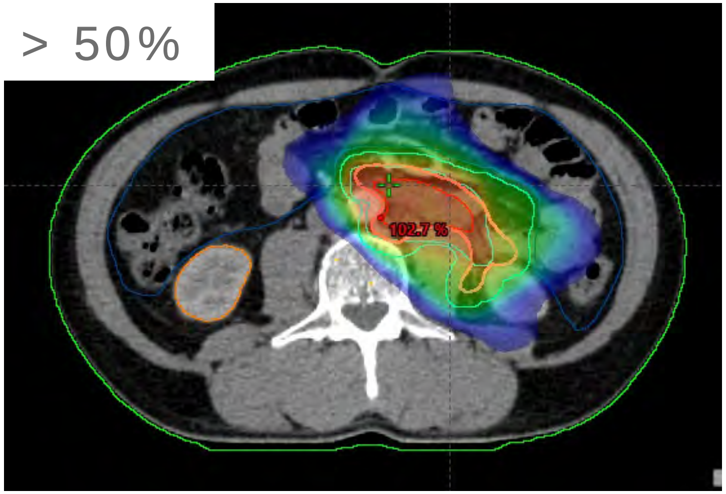


- Lymphoma: No difference between effect of large or small fractions
- Late effects in normal tissues: Large benefit of small vs. large fractions
- This is true if the doses to lymphoma and normal tissues are the same

> 0%



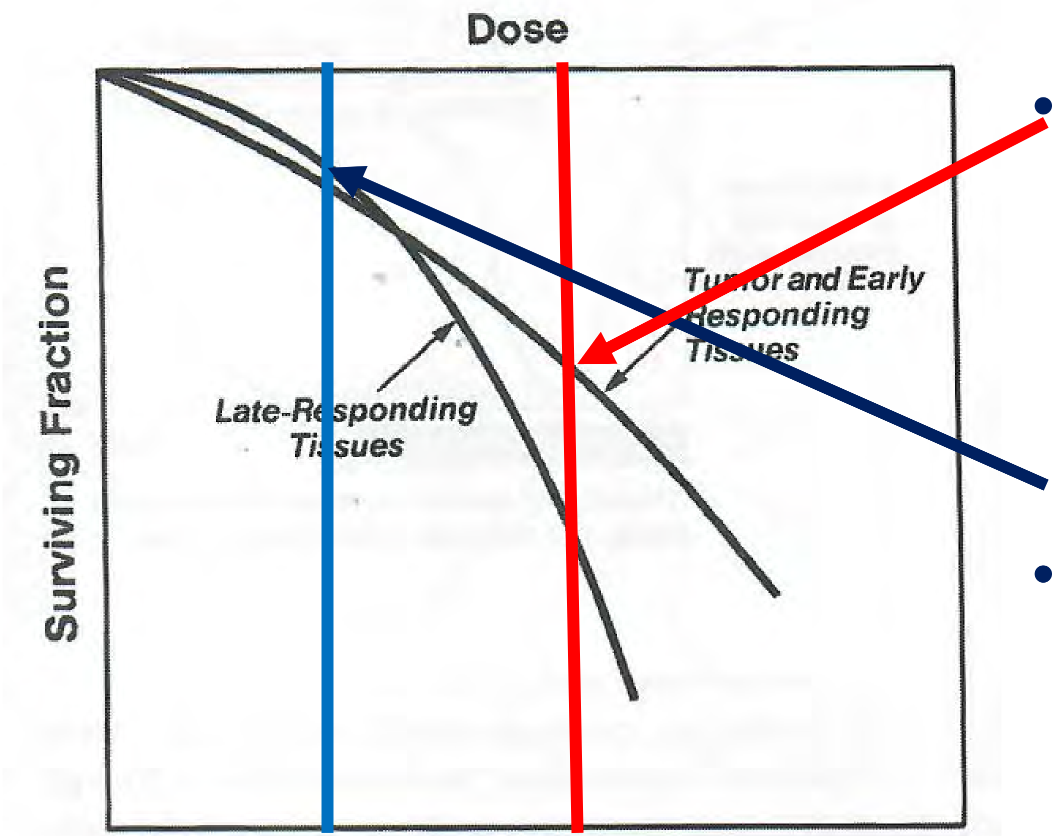
> 50%



No longer so!

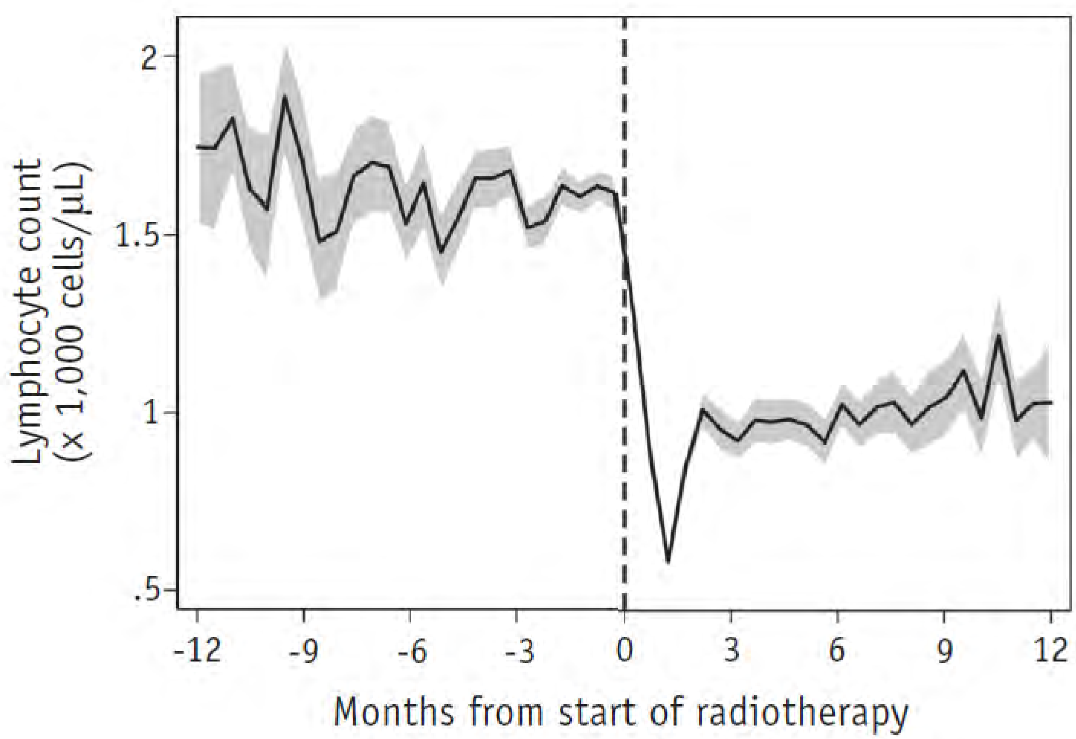
- With modern highly conformal techniques only the lymphoma and very close surrounding structures get the full dose
- Only very limited volumes of normal tissue get > 50 % of the dose
- With a prescribed fraction of e.g. 4 Gy only very limited volumes of normal tissue get > 2 Gy/fraction

Hypofractionation in modern highly conformal lymphoma radiotherapy



- Lymphoma: Gets a biological effect roughly proportional to the dose
- Normal tissues: Get not only a lower total dose, but also in small fractions

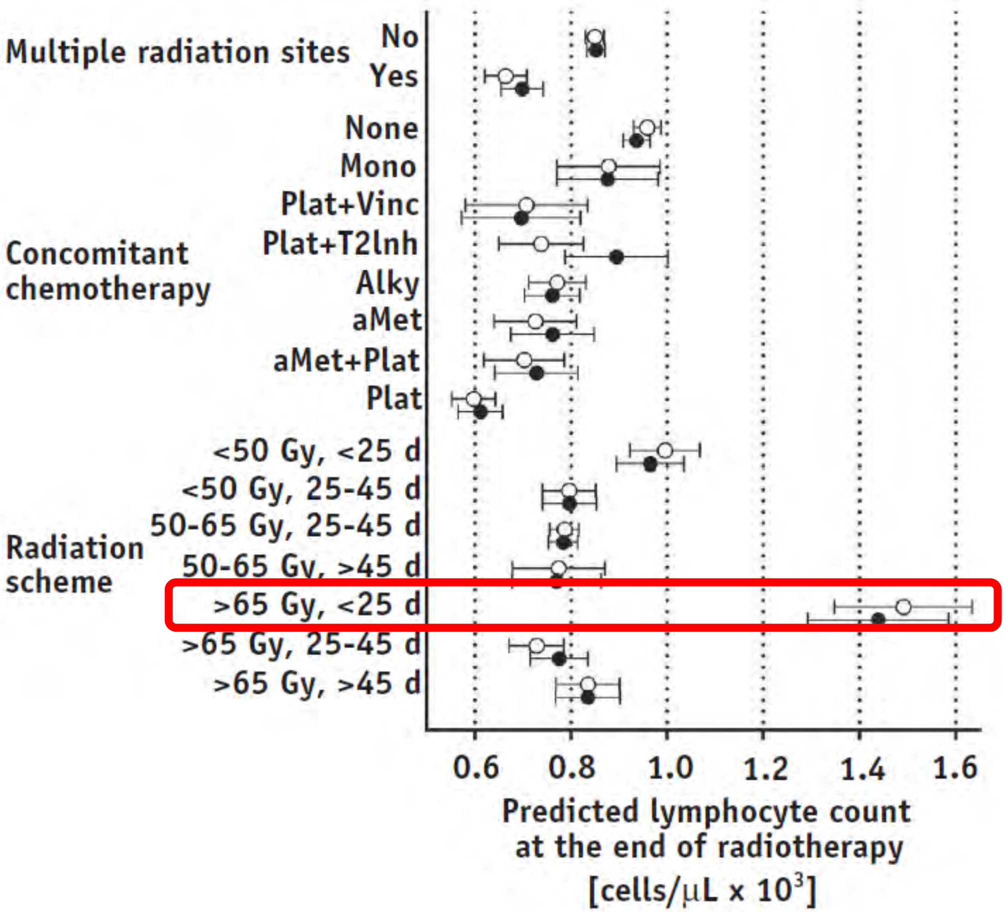
Lymphocyte counts decline during radiotherapy



- Lymphocytes are highly radiosensitive, 90% cell kill by just 0.5 Gy
- Lymphocyte counts decline during radiotherapy and remain low up to a year after

Terrones-Campos et al. IJROBP 2019; 105: 812-23

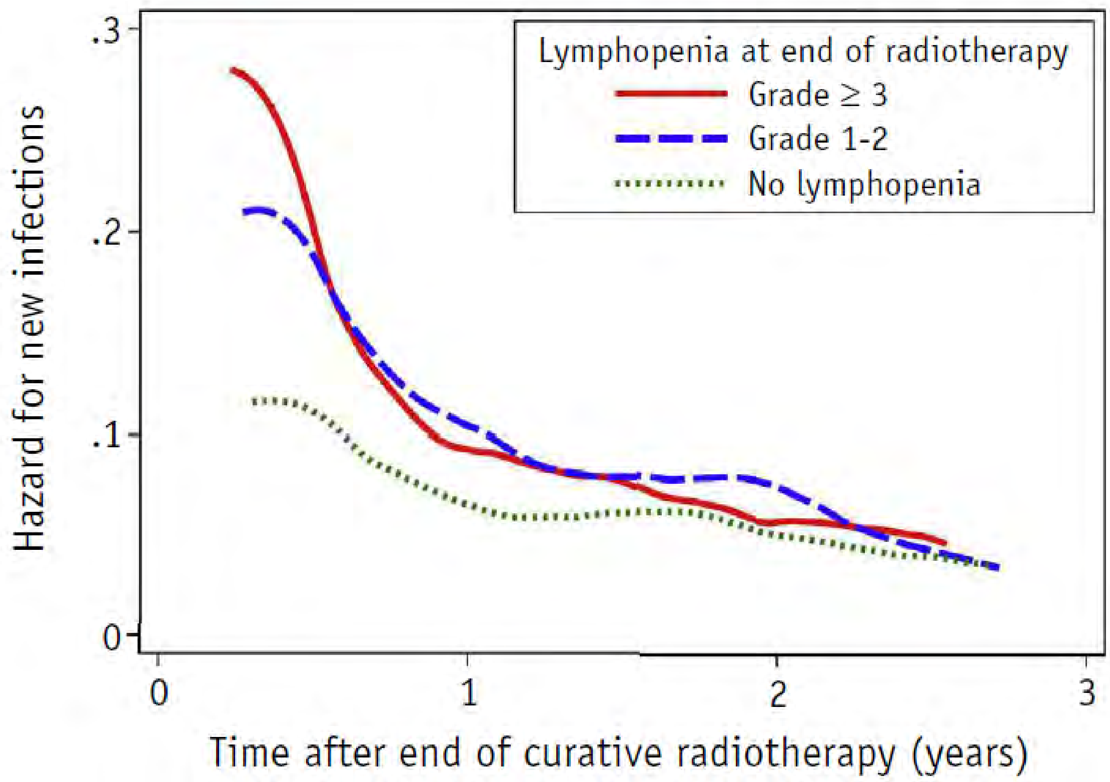
Many small fractions may have adverse effects



- Nearly all lymphocytes in the irradiated volume are killed with every fraction, regardless of fraction size
- The more fractions the higher the risk for a circulating lymphocyte to be killed
- Hypofractionation reduces the negative effect on the lymphocyte count

Terrones-Campos et al. IJROBP 2019; 105: 812-23

Clinical implications of lymphocytopenia



- Lymphocytopenia is a negative prognostic factor for survival
- Lymphocytopenia is associated with a higher risk of infection
- ? Effect on immune therapy?

Terrones-Campos et al. IJROBP 2019; 105: 812-23

Hypofractionation in haematological malignancies

- Normally always avoided as long-term side effects are crucial
- COVID made re-thinking necessary
- We used radiobiological considerations:
  - Little reduction of the total dose to achieve same tumour control (EQD2 using $\alpha/\beta = 10$ Gy)
  - Risks of late toxicity are higher (EQD2 using $\alpha/\beta = 3$ Gy), mitigated by
    - Steep dose gradients around the target by optimal conformality
    - Daily image guidance
    - Low doses used in haematological malignancies

Experience from the ILROG COVID-19 emergency fractionation

- Data from patients treated according to the guidelines are being gathered at MD Anderson Cancer Center (PIs Jillian Gunther and Joanna Yang)

- Preliminary analyses were presented at ASTRO and Lugano demonstrating low rates of acute toxicity and reasonable short-term efficacy

- Likely that at least some of the altered fractionation schemes will be useful as standard treatment

Conclusions regarding lymphoma radiotherapy

- **Radiation volumes**: dramatically reduced
- **Radiation doses**: reduced, even further reductions and refinements may come
- **Radiation fractionation**: up till now followed classical radiobiology, with many small fractions to protect normal tissues
- **Hypofractionation**:
  - May be possible with highly conformal radiotherapy without significant loss of protection of normal tissues
  - May offer further benefits by protecting the normal lymphocytes
  - Is more convenient, especially in older patients (a fast growing population)
  - Saves time (easier to integrate with other modalities)
  - Reduces cost (more affordable, also in low and middle income areas)

ESTRO

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Haematological malignancies

23 October 2023 - 26 October 2023

Lyon, France