Role of radiotherapy in the treatment of lymphoma in 2016

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

James O. Armitage

• Its role has changed
• Now part of combined modality treatment in most situations
• Often as consolidary treatment after primary chemotherapy
Most lymphoma types are highly radiosensitive

**Mechanism of action**

- Microarray gene expression profiles before and after 2 Gy x 2 showed major and consistent activation of p53 target genes involved in cell-cycle arrest and apoptosis

- Immunohistochemistry showed increased P53 protein levels and decreased MK167 (down regulation of cell cycle related genes)

Imaging of apoptosis after 2 Gy x 2
Haas et al, IJROBP 2004; 59: 782-7

Annexin V SPECT

Cytologic Giemsa-stained smear before and 24 hours after radiotherapy. A: Viable lymphoma cells. B: Massive nuclear chromatin condensation and apoptotic body formation
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
Irradiating these very large volumes caused serious long-term sequelae in patients surviving many decades.
Meta-analysis of randomized trials of more vs. less extensive radiotherapy
Time to failure and overall survival

- Total comparison events: 309/1005 = 30.7% (95% CI: 14-42)
- Time to failure:
  - More RT events: 36.8 (25/69)
  - Less RT events: 14.4 (18/127)
  - Ratio: 2.57 (95% CI: 1.63-4.03)
  - Reduction: 13% (95% CI: 3.2-23.5)

- Overall survival:
  - More RT events: 79.6 (78/98)
  - Less RT events: 74.7 (72/97)
  - Ratio: 1.06 (95% CI: 0.8-1.4)
  - Reduction: 0.6% (95% CI: 0-8.5)

Heterogeneity between trials: \( x^2_{df} = 18.8; p = 0.02 \)
Modern lymphoma treatment

- In Hodgkin lymphoma and aggressive non-Hodgkin lymphomas effective chemotherapy exists which eradicates microscopic disease.

- Recurrences after chemotherapy alone usually occur in initial macroscopic involvement.

- In the combined modality setting, we only need to irradiate the volume which contained macroscopic disease from the outset before chemotherapy.

- The extended fields of the past are no longer necessary.

- Modern imaging and treatment planning and delivery have enabled dramatic reductions in the irradiated volume.
Paradigm shift in lymphoma radiotherapy

Mantle field (EFRT) or involved field (IFRT)

Based on:
- 2 D planning
- Regions
- Bony landmarks defining fields
- “Fixed” margins

Involved site (ISRT) or involved node (INRT)

Based on:
- 3 D planning
- Actual lymphoma involvement
- Contouring of volumes (GTV, CTV, PTV), ICRU Guidelines
- Margins (GTV → CTV) based on clinical judgement and (CTV → PTV) based on internal and setup uncertainties
Highly conformal radiotherapy
(3D conformal, intensity modulated radiotherapy IMRT, volumetric arc therapy VMAT, intensity modulated proton therapy IMPT)

- High dose volume conforms almost precisely to the target we contour
- Very steep dose gradients around the target
- Precise target definition is crucial
- If we contour (CTV, PTV) too small we will miss lymphoma and jeopardize the patient’s chance of cure
- If we contour (CTV, PTV) too large unnecessary radiation will be given to normal structures
Radiation therapy is a local treatment

- The prescribed dose is only given to the defined target volume (e.g., 30 Gy = 30 J/kg)
- Normal tissues near the target volume get some, but much lower, doses
- Other parts of the body do not get any dose (except for scattered radiation, in the order of magnitude of what you get from diagnostic scans)
- Recurrences occurring outside previously irradiated sites are not radioresistant, they have never been treated with radiation
Radiotherapy induces DNA damage that can be modulated in space and time which makes it an attractive component of multi-modality treatment.
Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV
Post-chemo planning CT scan

Pre-chemo gross tumour volume  Post-chemo clinical target volume
Margins and corresponding tissue volumes

M = 5 mm  V = 50%

Breathing adapted RT

Petersen PM et al. Acta Oncol 2015; 54: 60-6
Using breath hold PET for radiotherapy planning
Only parts of the lymphoma volume are FDG avid
Role of radiation therapy in 2016

- **Primary treatment for early stage indolent lymphomas**
- **Consolidation therapy for early stage aggressive lymphomas (inc. HL)**
- **Treatment of bulky or residual mass in advanced aggressive lymphoma**
- **Treatment of recurrent disease +/- systemic treatment**
- **Part of conditioning for autologous transplant for recurrent/refractory disease**
- **Palliative treatment in advanced indolent lymphoma**
Role of radiation (and medical) oncology

- Close collaboration from the outset between systemic treatment (medical oncologist/ hematologist/clinical oncologist) and local treatment (radiation oncologist/clinical oncologist)

- The entire treatment strategy must be planned from the outset to allow optimal treatment

- Treatment modifications during treatment must be decided with due regard to both local and systemic treatment options

- Treatment interactions must be considered
Guidelines for radiotherapy of lymphomas implemented by NCCN and most cooperative groups

Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group
Tim Illidge, MD, PhD, Lena Specht, MD, Joachim Yahalom, MD, Berthe Aleman, MD, PhD, Anne Kil Berthelsen, MD, Louis Constine, MD, Bouthaina Babaja, MD, Kavita Dharmarajan, MD, Andrea Ng, MD, Umberto Ricardi, MD, and Andrew Wirth, MD, on behalf of the International Lymphoma Radiation Oncology Group  IJROBP 2014; 89: 49-58

Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group
Lena Specht, MD, PhD, Bouthaina Babaja, MD, Tim Illidge, MD, PhD, Lynn D. Wilson, MD, and Richard T. Hoppe, MD, on behalf of the International Lymphoma Radiation Oncology Group  IJROBP 2015; 92: 32-39

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)
Lena Specht, MD, PhD, Joachim Yahalom, MD, Tim Illidge, MD, PhD, Anne Kil Berthelsen, MD, Louis S. Constine, MD, Hans Theodor Eich, MD, PhD, Theodore Girinsky, MD, Richard T. Hoppe, MD, Peter Mauch, MD, N. George Mikhaeil, MD, and Andrea Ng, MD, MPH, on behalf of ILROG  IJROBP 2014; 89: 854-62

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group
Joachim Yahalom, MD, Tim Illidge, MD, PhD, Lena Specht, MD, PhD, Richard T. Hoppe, MD, Ye-Xiong Li, MD, Richard Tsang, MD, and Andrew Wirth, MD, on behalf of the International Lymphoma Radiation Oncology Group  IJROBP 2015; 92: 11-31
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