RADIOTHERAPY FOR HEMATOLOGICAL MALIGNANCIES

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RADIOTHERAPY
RADIOTHERAPY FACTS

• Used to eradicate or control tumors (malignant or benign)
• Local therapy
• Can be used in combination with surgery, chemotherapy, endocrine therapy
• Indications
  • Curative
  • Adjuvant or neo-adjuvant
  • Palliative
  • For definitive treatment of recurrent disease
• Ultimate goal is tumour eradication and cure
• Palliative goal is to alleviate symptoms - > 80% effective
RADIOThERAPY SOURCES

- Photons
  - Most common source
- Electrons
- Beta particles
- Heavy particles (protons, neutrons)

Linac = high frequency (alternating) electric field is used to accelerate electrons and produce high energy x-rays (photons) and electrons
TYPES OF RADIOTHERAPY

• **External beam** (from Linac or 60Co)
  - Most commonly used for lymphoma
    - 3D CONFORMAL
    - IMRT
    - Stereotactic Radiotherapy/Radiosurgery

• **Brachytherapy**
  - Sealed radioactive source put into the body
  - For prostate, and gynecologic applications

• **Radionuclide therapy** (radioimmunotherapy)
  - 131Iodine or 90Yttrium tagged with antibody
RADIOBIOLOGY

5 Rs of radiobiology

- Repair
- Reoxygenation
- Reassortment
- Intrinsic Radiosensitivity
- Repopulation

Therapeutic ratio

![Graph showing Probability vs. Dose (Gy)]
Hematologic malignancies are very radiation sensitive. Doses used range:

- 12 Gy for the CNS phase in leukemia
- 20 Gy for low risk Hodgkin after chemo
- 30 Gy for most lymphomas
- 40 Gy for resistant tumors

Much lower than for other cancers:

- Breast cancer (50 Gy), prostate (78 Gy)

Local relapse within radiotherapy field is very rare.
RADIATION THERAPY: HOW?

• If decision is to have radiation
  • Diagnostic CT/PET (pre and post chemo)
  • Counseling
    • Fertility
    • Smoking
    • BC- underlying risk and future surveillance
    • CVD
  • Simulation session – half to 1 hour Scan (CT simulator)
    • Depending on area, may be a mask, vacuum fixation device, knee bolsters, testicular shield
    • Possibly tattoo marks
WHAT HAPPENS TO A PATIENT BEING CONSIDERED FOR RADIOTHERAPY

1. Consultation
2. Simulation
3. Dosimetry/planning
4. RT treatment

7 to 10 days
IMMOBILISATION

PT MUST BE ABLE TO LIE FLAT AND STILL
RADIATION THERAPY SET UP
EXPECTATIONS FOR PATIENTS

- Daily attendance Mon-Fri (2-3 weeks)
- Treatment takes 5-10 minutes
- Pain free
- Within 1 week-2 if tumour present it will shrink
- Side effects only local- depends on dose and volume treated
- RT does not interfere with chemo
  - Exception: Adriamycin
- Does not produce drop in blood counts
  - Exception: very large treatment fields (TBI)
- Can be repeated once for same area (time dependent)
POSSIBLE ACUTE SIDE EFFECTS

- **Eye**  
  Dye eye, cataracts

- **Neck**  
  Taste, dryness, swallowing

- **Chest**  
  Swallowing, lung reaction/scar

- **Abdomen**  
  Nausea, loose stools

- **Pelvis**  
  Bladder irritability, sterility

- **Extremities**  
  Nil

- **Any site**  
  Fatigue

- **Skin redness**  
  Mild

- **Late effect***  
  Second malignancy, infertility, CVD, thyroid function
High cure rates in young population
Aim of Rx to achieve cure and FFP with minimal long term toxicity
RT ALONE FOR EARLY STAGE FAVORABLE DISEASE

- Required RT fields wide (Mantle or total nodal) with relatively high doses
- EORTC H7, 1997: Mantle RT alone → OS 96% but RFS 73% suggesting that Mantle alone is not sufficient. Most relapses were in the abdomen.
- 25% of pt have subclinical infra-diaphragmatic disease → mantle a/w high risk of relapse below the diaphragm
- Specht metaanalysis 1998 JCO:
  - Mantle vs IFRT for early stage favourable HL
  - No diff in OS but IFRT a/w higher risk of relapse

**Only indication for RT alone**
- Early-stage lymphocyte-predominant HL
- When pt unable to have chemotherapy
COMBINED MODALITY THERAPY

STANDARD OF CARE

• Combination chemotherapy has evolved with increasing efficacy and plays a major role

• Early randomised trials proved the superiority of CMT over EFRT alone
  • EORTC H7 1997 and 2005, SWOG/Intergroup 2000, EORTC-GELA H8 2007, GHSG 8 and Specht Meta-analysis
    • CMT is superior to RT alone: Reduces 10 y recurrence rates and DFS by 50%. NO DIFFERENCE IN OS.

• RT has an important place in ensuring LRC and improving PFS
Early PET used to adapt treatment for stage I and II F and U HD

? Can INRT be omitted in early PET – patients after 2 x ABVD

To test the non-inferiority of No RT arm

Interim analysis
• 1137 pts
• RT associated with superior 1 y PFS H10 F 5.1% and 2.5% H10U
• Independent data monitoring committee stopped the randomisation of the PET-patient as they concluded it was unlikely for the trial to show non-inferiority
EVOLUTION OF RT DOSE FIELD AND TECHNIQUE

1. Lower dose
   • Efficacy of radiation doses below 36-40Gy in combination with chemotherapy demonstrated in multiple controlled randomised trials (EORTC H8F, EORTC H8 U, German HD10, German HD 11)

2. Smaller Filed size
   • Same CRTs investigating the role of reduced dose investigated the efficacy of smaller field IFRT as opposed to wide field STNI and demonstrated equal outcomes in terms of PFS
   • Site of failure is usually at initially involved site when pt have chemo alone (Shahidi et al)

REDUCED TOXICITY
1370 patients with newly diagnosed early-stage Hodgkin’s lymphoma with a favorable prognosis to one of four treatment groups (German HD10 trial) **German HD10**

<table>
<thead>
<tr>
<th>CHEMO</th>
<th>IFRT</th>
<th>8-Y Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD X 4</td>
<td>30 GY</td>
<td>94.4%</td>
</tr>
<tr>
<td>ABVD X 4</td>
<td>20 GY</td>
<td>94.7%</td>
</tr>
<tr>
<td>ABVD X 2</td>
<td>30 GY</td>
<td>93.6%</td>
</tr>
<tr>
<td>ABVD X 2</td>
<td>20 GY</td>
<td>95.1%</td>
</tr>
</tbody>
</table>

STAGE I-II GOOD PROGNOSIS HD

- Present SOC for low risk disease
  - ABVD X 2 CYCLES
  - INRT/IFRT 20GY

REDUCES ACUTE TOXICITY BY ALMOST 50%
PRESENTLY RESULTS AVAILABLE FOR 10 Y
**EARLY STAGE POOR PROGNOSIS HD**

- **German HD 11 trial**
  - 2 x 2 factorial design 1395 pts

<table>
<thead>
<tr>
<th>CHEMO</th>
<th>IFRT</th>
<th>5 Year FFTF</th>
<th>5 Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD X 4</td>
<td>30 GY</td>
<td>85.3%</td>
<td>94.3%</td>
</tr>
<tr>
<td>ABVD X 4</td>
<td>20 GY</td>
<td><strong>81.0%</strong></td>
<td>94.6%</td>
</tr>
<tr>
<td>BEACOPP X 4</td>
<td>30 GY</td>
<td>87.1%</td>
<td>95.1%</td>
</tr>
<tr>
<td>BEACOPP X 4</td>
<td>20 GY</td>
<td>86.8%</td>
<td>93.8%</td>
</tr>
</tbody>
</table>
EARLY STAGE POOR PROGNOSIS HD

- German HD 11 conclusion:
  - OS similar in all 4 schedules
  - Freedom from treatment failure inferior in ABVD x 4 + 20Gy
  - BEACOPP resulted in 70% acut etoxicity as opposed to AB+VD 50%
  - **ABVD x 4 + IFRT/INRT 30 Gy** standard of care
- Other supportive CRT: EORTC /GELA H9 U
  - ABVD x 4 + IFRT 30 Gy
  - ABVD x 6 + IFRT 30Gy
  - BEACOPPP x 4 + IFRT 30 Gy
  - Cancer related outcomes similar in all 3 arms but BEACOPP more toxic
EVOLUTION OF THE RT VOLUME DEFINITIONS

- **TNI** = Total Nodal Radiation
- **STNI** = Subtotal Nodal Radiation
- **EFRT** = Extended Field Radiation
- **IFRT** = Involved Filed Radiation
- **INRT** = Involved Nodal Radiation
EVOLUTION OF RT FIELD-EXTENDED FIELD RADIOTHERAPY

- Not only involved nodes but also adjacent uninvolved sites
  1. MANTLE (cervical, SCF, mediastinum, hilar, axillary)
  2. INVERTED Y
  3. TOTAL LYMPHOID IRRADIATION (1+2)
  4. SUBTOTAL LYMPHOID IRRADIATION (1+ PARAORTIC AND PELVIS)
The site of the clinically nodal group

Lymph node grouping not clearly identified

RT field determined based on bony anatomical landmarks
EXAMPLES - CERVICAL AND AXILLARY CHAINS
EVOLUTION OF RT FIELD-INVOLVED NODAL RADIOTHERAPY

- Concept developed in Europe in 2008
- Based on the finding that site of relapse is the initial node
- Aim to reduce radiotherapy fields and toxicity
- Target volume is the pre-chemotherapy volume on PET with a margin excluding normal structures such as heart, lung, kidneys and muscles
- Requires CT planning, Pre- chemo PET in planning position and preferably 3 D planning
INRT- ROLE OF IMAGING IN RADIATION PLANNING AND DELIVERY METHOD

• 3D-CT simulation a must
• Staging and response assessment CT and PET → Used in volume definition and preferably done in radiotherapy position
• The diagnostic images are fused with the simulation CT in planning computer software
• If moving target such as abdomen or mediastinum → 4D CT used as simulation CT. Acquires the position of the target in full range of motion
• INRT should start within 4 w of chemo
• Modern RT delivery techniques should be used to reduce normal tissue toxicity
A LITTLE ABOUT DELIVERY TECHNIQUE
IMRT: INTENSITY MODULATED RADIOTHERAPY

- Multiple beams from different angles used to shape the radiation field to the target
- Each beam delivers a different shape and intensity of radiation to the target
- In general, each beam treats a portion of the target
- Needs vigorous QA
- Advantages
  - Reduces dose to the OAR- Sharp dose fall off
  - Improves homogeneity within target volume
A LITTLE ABOUT DELIVERY TECHNIQUE
DEEP INSPIRATION BREATH HOLD

Target often within mediastinum

Respiratory movement affects dose received by target as well as OAR

Several studies have demonstrated that treatment in inspiration allows significant sparing of the lung and heart

LONG TERM RISKS

Tissue damage (esp the lungs, heart or thyroid or bone marrow) and causing new cancers (esp breast or leukemia)
Cumulative absolute risk of breast ca in HL pt < 30 yo

- Age, calendar year of diagnosis, population breast cancer incidence rates, and competing causes of death.
- Calculated relative risk based on dose of RT to the chest and use of alkylating agents
- January 1, 1965, through December 31, 1994
- 3817 females
- Used modified standardised incidence ratios
- CA risk increased with age at end of F/U, time since HL dx and RT dose

<table>
<thead>
<tr>
<th>Age at Dx</th>
<th>Dose to chest</th>
<th>CA risk at age 35</th>
<th>CA risk at age 45</th>
<th>CA risk at age 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>40</td>
<td>1.4%</td>
<td>11.1%</td>
<td>29%</td>
</tr>
<tr>
<td>25</td>
<td>20- &lt;40</td>
<td>0.6%</td>
<td>4.4%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Journal of the National Cancer Institute, Vol. 97, No. 19, October 5, 2005
LONG TERM CSM OF PTS TREATED WITH HD

JCO SEP 15, 2003: 3431-3439

• To analyze long term cause specific mortality of HD pts
• 1965-1987, 1261 pt, < 40, stage IA-IIB HL
• CS mortality was compared with general population to assess RR and AR
• Median F/U 17.8y
• RR of death from all other causes than HD 6.8 x general population
• RR from solid new tumours and CVD increased overall (6.6 and 6.3)
• Main cause of death was lymphoma but after 20 y HD mortality was negligible
• The RR and AR of death from secondary ca and CVD continued to rise after 10 and 20 y
Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study

Table 2. EAR and SMR for leading causes of death by time since diagnosis in 5-year survivors of Hodgkin lymphoma (n = 2633)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>5-9 y</th>
<th>10-19 y</th>
<th>≥ 20 y</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EAR/10 000 PY (95% CI)</td>
<td>SMR/1000 PY (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hodgkin lymphoma</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All other malignant neoplasms</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All other hematopoietic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal cavity/pharynx</td>
<td></td>
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<tr>
<td>Lung/trachea</td>
<td></td>
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<tr>
<td>Digestive organs/porionomus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All heart disease</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic endocardial, other myocardial insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmalignant respiratory disease</td>
<td></td>
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</tr>
</tbody>
</table>

- Substantial excess absolute risk of mortality per 10,000 P.Y
- Death due to HL 38.3
- Second malignant neoplasms 23
- Cardiovascular disease 13.1
- Risks for overall mortality: radiation dose > 30 Gy and anthracycline chemotherapy, non breast second malignancies and CV disease
- Excess risk of death from CVD and second malignancies persisted > 20y
• Most toxicity data based on old radiotherapy techniques and doses

• With advances in dose delivery, reduction in dose and RT volumes the likelihood of complications significantly reduced

**Individualized Estimates of Second Cancer Risks After Contemporary Radiation Therapy for Hodgkin Lymphoma**

• Used a validated radiobiological model to estimate risk of second malignancy according to RT dose and field

• Risk estimated in 37 pt having mediastinal IFRT

• Estimated RR for BC and LC after MFRT to 32 Gy confirmed historical data

• With IFRT 30Gy, 20 y excess RR reduced 63%

• With IFRT 20Gy, RR reduced by 77%
Involved-nodal radiation therapy leads to lower doses to critical organs-at-risk compared to involved-field radiation therapy

Table 2
Dosimetric comparison of IFRT and INRT for organs at risk.

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>IFRT</th>
<th>INRT</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung V50%</td>
<td>33.5%</td>
<td>19.4%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Heart V50%</td>
<td>41.3%</td>
<td>29.4%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Heart V10%</td>
<td>54.1%</td>
<td>40.1%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Breast V50%</td>
<td>31.2%</td>
<td>14.8%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>(B)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body V50% (cc)</td>
<td>9321 cc</td>
<td>4034 cc</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Total body V5% (cc)</td>
<td>16398 cc</td>
<td>9522 cc</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Lung mean dose (% of prescribed dose)</td>
<td>35.3%</td>
<td>21.9%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Heart mean dose (% of prescribed dose)</td>
<td>42.5%</td>
<td>30.8%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Thyroid mean dose (% of prescribed dose)</td>
<td>64.8%</td>
<td>23.8%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Kidneys mean dose (% of prescribed dose)</td>
<td>9.7%</td>
<td>5.6%</td>
<td>0.006</td>
</tr>
<tr>
<td>Parotids mean dose (% of prescribed dose)</td>
<td>39.0%</td>
<td>11.0%</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Radiotherapy and Oncology 112 (2014) 279–283
CURRENT GUIDELINES/RECOMMENDATIONS FOR ALL PT

- **Young women:**
  - Assess BC risk
  - BC screening at 35y or 8 y post treatment which ever earliest
  - Self examination and awareness

- **All**
  - Smoking cessation
  - Fertility advice
  - Late effects clinic if < 20 y
    - Clinical exam
    - TFT
    - FBE
RT INDICATIONS FOR NHL

- SLL localized
- Follicular Lymphoma early stage
- Gastric MALT (H. pylori negative)
- Nongastric MALT localized
- Mantle Cell, early stage
- Diffuse Large B Cell (esp bulky)
- Cutaneous B-Cell
- Peripheral T-Cell
- Mycosis Fungoides
- Extranodal NK-T
General Dose Guidelines:

- Localized CLL/SLL: 24-30 Gy
- Follicular lymphoma: 24-30 Gy
- Marginal zone lymphoma:
  - Stomach: 30 Gy
  - Other extranodal sites: 24-30 Gy
  - Nodal MZL: 24-30 Gy
- Early-stage mantle cell lymphoma: 30-36 Gy
- Mini-dose RT (2Gy X2 may be repeated) for palliation/local control of FL, MZL, SLL, MCL

- Diffuse large cell lymphoma or PTCL
  - Consolidation after chemotherapy CR: 30-36 Gy
  - Complimentary after PR: 40-50 Gy
  - RT as primary treatment for refractory or noncandidates for chemotherapy: 45-55 Gy
  - Salvage pre- or post-stem cell transplantation: 30-40 Gy
MULTIPLE MYELOMA

- MM is radiosensitive
- RT can offer very effective palliation for drug refractory bone pain
- RT can in some cases be used to control local disease
- Used for impending loss of function (SCC, fracture)
RT DOSE AND VOLUME FOR MM

- For bony lesions
  - 8Gy in 1 fraction sufficient and very effective 80% pain free
  - Can be repeated safely
  - Alternatively 20Gy/5 fractions more durable but not as convenient for pt
  - Volumes include bony abnormality and 1-2 cm margin
  - SCC from MM: single dose radiosurgery can achieve cord patency

- For chemo refractory mass
  - Up to 45Gy in 25 fractions

CAUTION IF RECENT VAD

Doxorubicin has a radiosensitising effect
Min 2 weeks between Doxorubicin and RT
Table III. Recommended diagnostic criteria for solitary bone plasmaoma (SBP) and extramedullary plasmaoma (SEP).

Solitary bone plasmaoma
- Single area of bone destruction due to clonal plasma cells
- Histologically normal marrow aspirate and trephine
- Normal results on skeletal survey, including radiology of long bones
- No anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia
- Absent or low serum or urinary level of monoclonal immunoglobulin
- No additional lesions on MRI scan of the spine

Solitary extramedullary plasmaoma
- Single extramedullary mass of clonal plasma cells
- Histologically normal marrow aspirate and trephine
- Normal results on skeletal survey, including radiology of long bones
- No anaemia, hypercalcaemia or renal impairment due to plasma cell dyscrasia
- Absent or low serum or urinary level of monoclonal immunoglobulin
# SOLITARY PLASMACYTOIDOMA (SBP AND SEP)

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>SEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>M:F</td>
<td>2:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Predominant site</td>
<td>Axial skeleton,</td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td>especially vertebrae</td>
<td></td>
</tr>
<tr>
<td>% with M protein</td>
<td>60</td>
<td>&lt;25</td>
</tr>
<tr>
<td>% developing MM</td>
<td>&gt;75</td>
<td>&lt;30</td>
</tr>
<tr>
<td>% survival at 10 years</td>
<td>40–50</td>
<td>70</td>
</tr>
</tbody>
</table>
SOLITARY PLASMOCYTOMA (SBP AND SEP)

• Radical radiotherapy primary treatment

• Indications for surgery
  • Tissue diagnosis (often EMP)
  • When fracture or impending fracture

• Local control with RT is favorable 83-100% (Mayr et al 1990, Holland et al 1992, Bolek et al 1996, Tsang et al 2001)

• RT dose (no clear dose response above 40Gy)
  • 40/20 # 4 weeks for lesions < 5cm
  • 50Gy/25 or 28# 5-5.5 weeks for lesions > 5cm

• RT field
  • Generous margin + 2cm, using MRI to guide field design to ensure full coverage
• Outcome
  • 1/3 of SBP are cured
  • ¾ of EMP are cured
  • M-protein disappearance is predictive of outcome
    • MD Anderson Cancer 2002
      • 60 pts
      • Mutivariate analysis prog factors
      • Presence of M-protein >12m after Rt only adverse prog factor
      • 90% pt with M protein after 12 m progressed to MM
Thank You
Involved Field Radiotherapy versus No Further Treatment in Patients with Clinical Stages IA/IIA Hodgkin Lymphoma and a “Negative” PET Scan After 3 Cycles ABVD: Results of the UK NCRI RAPID Trial

Radford J et al.
Proc ASH 2012;Abstract 547.
Phase III RAPID Study Design

Eligibility (n = 602)
- Histologically confirmed classic HL
- Stage IA/IIA by CT scan
- No mediastinal bulk or B symptoms
- No prior treatment

- PET +ve (n = 145) → 4th cycle ABVD then IFRT
- PET -ve (n = 420)* → IFRT 30 Gy (n = 209)†
- Response → PET scan (n = 571) → R
- No further treatment (NFT) (n = 211)

* 6 pts not randomized
† 25 pts did not receive treatment
EORTC H10 Author conclusion

- Demonstrated that the risk of early relapse in patients not undergoing irradiation was higher than that after combined-modality treatment in early PET-negative patients.

- Longer follow-up is required to establish the impact of a PET-directed approach on 10 and 20 year survival and cause of death.