New Developments in Hemithoracic Radiation for Mesothelioma

CANADIAN MESOTHELIOMA FOUNDATION CONFERENCE
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Disclosures

- SAB for Canadian Mesothelioma Foundation
Overview

• Background
  – Mesothelioma

• Radiation
  – Rationale
  – SMART
  – SMARTER
Background

- At present, no consensus as to best treatment for malignant pleural mesothelioma (MPM)
  - Rare tumour with more complex anatomy than average (e.g. pleural space, fissures)
  - Poor outcomes (e.g. no curative treatment)
  - Paucity of high quality evidence from clinical trials (e.g. RCT challenging to accrue if control arm is BSC)
  - Difficult to acquire experience and expertise
Overall Survival (Best Stage 8th edition)

During EPP, diaphragm and pericardium resected so different anatomical compartments potentially exposed to each other → Potential route of spread → Source of distant relapse to peritoneum and contralateral lung? → Change sequence of treatment?
Neoadjuvant Therapy

- To reduce local failure by down-staging tumour to improve resectability (e.g. lung)
  - R+ $\rightarrow$ R0
- To reduce local failure (e.g. colorectal)
  - Sterilize “high risk” margins
- To reduce distant failure?
  - By preventing implantation/recurrence
  - Neoadjuvant RT to whole lung challenging
To reduce local failure by downsizing tumour to improve resectability (e.g. lung)

• R+ → R0

• To reduce local failure (e.g. colorectal)

• Sterilize “high risk” margins

• To reduce distant failure?

• By preventing implantation/recurrence

• Neoadjuvant RT to whole lung challenging
**Surgery for Mesothelioma After Radiation Therapy**

**Study Schema**

- Malignant Pleural Mesothelioma (cT1-2 cN0 M0)
- Baseline Investigations
- Informed Consent

- Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx over 1 week)
- 1 week post-RT
- Extrapleural Pneumonectomy
- 6-12 weeks post-op
- pN0-1
- pN2
- Observation
- Adjuvant Chemotherapy

424 patients with MPM 2008-2017

123 potential candidates for SMART (29%)

38 did not meet eligibility
- N2 disease (n=9)
- T4 disease (n=3)
- M1 disease (n=5)
- Synchronous tumor (n=5)
- Previous chemotherapy (n=5)
- Biphasic/sarcomatoid (n=4)
- Other (n=7)

85 eligibility criteria fulfilled (study group)

SMART completed n=85

Excluded n=13

SMART completed (extended group) n=25

85 eligibility criteria fulfilled (study group)
Overall Survival

MS epithelial ypN0 44.9 mo, epithelial ypN+ 22.6 mo
MS biphasic ypN0 25.5 mo, biphasic ypN+ 12.0 mo
Disease-free Survival

Median DFS epithelial ypN0 47.9 mo, epithelial ypN+ 13.8 mo,
Median DFS biphasic ypN0 16.1 mo, biphasic ypN+ 6.1 mo
Limitations and Challenges

- Neoadj hemithoracic RT cannot be given without EPP
  - Risk of G5 radiation pneumonitis with intact lung
- Thoracic surgeons reluctant to commit to EPP upfront
- Required EPP limits eligible pts
  - 20% MPM resectable at presentation
- Significant coordination required between Surgery and Rad Onc
- Extended recuperative period
  - Typically 3-6 months
Benefits

- Excellent survival outcomes
- Accelerated overall treatment time with total duration within 10 days
- 100% completion rates (by design)
- RT well tolerated with acceptable overall treatment morbidity
- Immune effect?
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- **Immune effect?**
**Experiment 2:** Murine mesothelioma cells AB12 (2x10^6) were subcutaneously injected into the right hind leg (T1), right flank (T2) and left flank (T3). Local radiation (1Gy x 3/LRT1 or 5Gy x 3/LRT5) was given 5 days after tumor cell injection. 5 layers of lead sheet
Local tumor (T1) growth after local RT +/- CTLA-4 blockade

However, Ab had little effect on primary tumor (T1) either alone or in combination with LRT.
Distal tumor (T2) growth after local RT +/- CTLA-4 blockade

CTLA-4 blockade with its Ab can promote anti-tumor immunity, resulting in tumor growth delay of distal tumor (T2) when combined with LRT, compared with LRT alone.
Vaccinal Effect?

- Local RT and Surgery Re-challenge with AE17-OVA after 60 days
Radiotherapy

• Can we give RT more optimally?
• RT traditionally concerned with
  – Tumour
  – Normal tissue
Radiotherapy

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\text{Therapeutic Index}
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• Ablative paradigm \( \rightarrow \) SBRT
Radiotherapy

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Ablative paradigm → SBRT

Therapeutic Index
Radiotherapy

• Can we give RT more optimally?
• RT traditionally concerned with
  – Tumour
  – Normal tissue
  – Immune system

• Vaccinal paradigm
Immunoradiotherapy Hypothesis

- RT, given appropriately, can stimulate a durable immune response against the tumour
- By leveraging body’s own immune system, significantly improve cytotoxic selectivity
  - Increase tumour control
  - Decrease normal tissue complications
Immunoradiotherapy

- Optimization complex system very (NP) hard
  - enormous solution space that must be searched
- Multidimensional
  - unique optima may not exist (Pareto optimal)
  - Trade-offs
- Context dependence
  - Same input cause different outputs, depending on situation
  - Radiation can be immunosuppressive or immunogenic
Immunoradiotherapy

- Immune system is complex system
  - Non-linearity (no simple dose-effect relationship)
  - Non-stationary (dynamic, adaptive)
- More degrees of freedom (larger solution space) allow for more optimal solutions
  - Hammer vs. scapel vs. swiss army knife
- Optimal doses different for different volumes
  - Tumour: high dose
  - Normal tissue: no dose
  - Immune system: ???
Optimal ImmunoRT

- To optimize immune system, differential doses needed
  - If too “cold”, then not immunogenic enough
    - Neoantigen formation, Coley toxin
  - If too “hot”, then too immunosuppressive
    - Total body irradiation for transplant
  - Looking for dosimetric “sweet spot”
Optimal ImmunoRT

- Traditionally, optimized only along dimension of dose
  - Because volume was fixed (GTV+margin)
- Can also optimize along dimension of time
  - Extreme hypofractionation with ablative doses (SBRT)
  - Assumed benefit is due to cytotoxic effect from high BED and accelerated RT
  - Sequencing and timing of intervention can have dramatic effects (immediate vs delayed surgery)
Optimal ImmunoRT

- Can also optimize along dimension of space/volume
  - Complete uniform coverage of tumour may not be needed
  - Dose to other functional structures
    - Draining lymph nodes rich in memory T-cells
    - Hypoxic/necrotic tumour cores may benefit from higher dose
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SMARTER Study Schema

- Obtain tissue pre-RT (biopsy), post-RT (surgery), blood
- Correlative studies for deep look into immune response
  - T-cell repertoire
  - ctDNA
  - Gene sequencing
SMARTER Boost Dose
Thank you for your attention