New Developments in Hemithoracic Radiation for Mesothelioma

CANADIAN MESOTHELIOMA FOUNDATION CONFERENCE

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Disclosures

- SAB for Canadian Mesothelioma Foundation

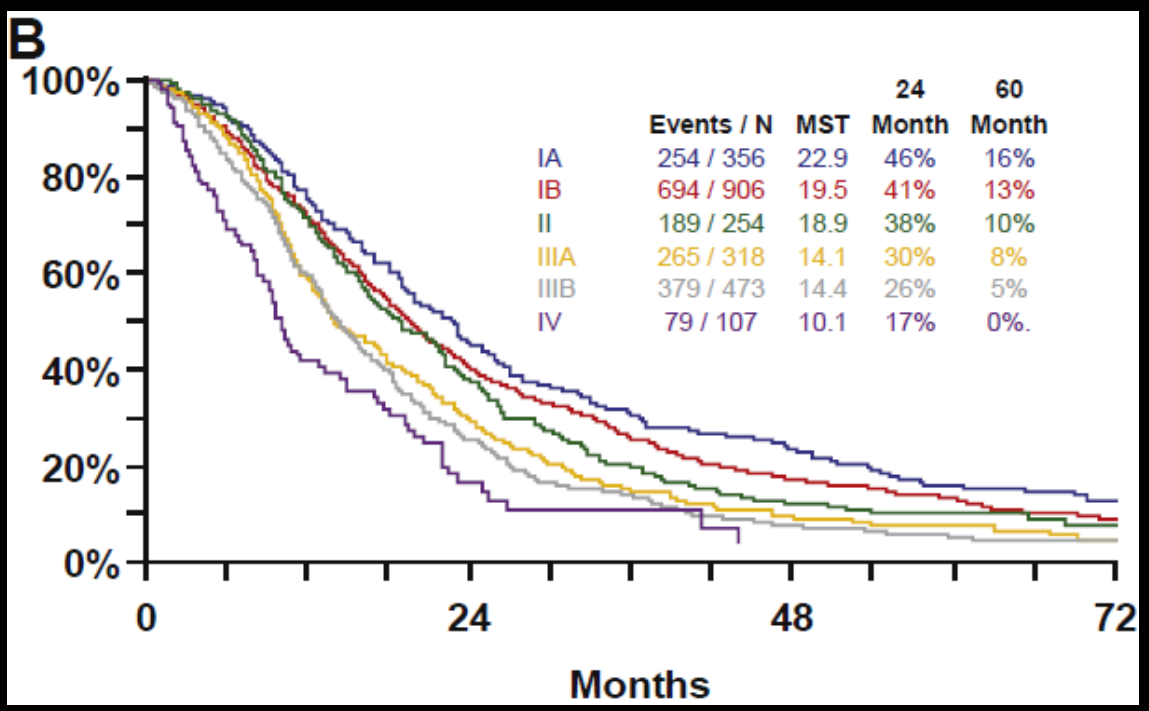
Overview

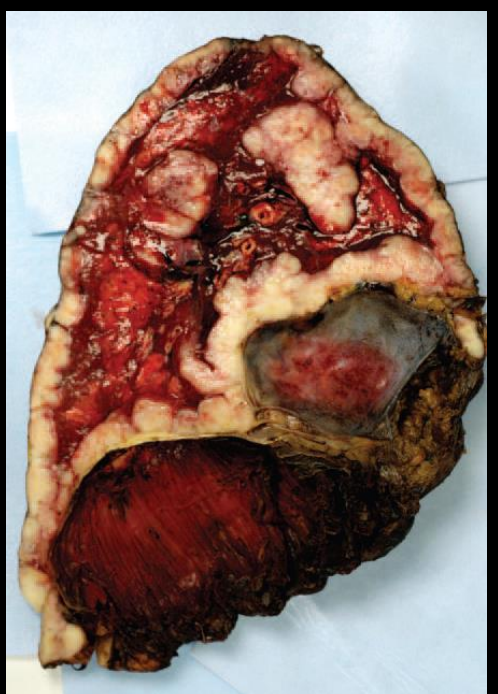
- Background
  - Mesothelioma
- Radiation
  - Rationale
  - SMART
  - SMARTER

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)

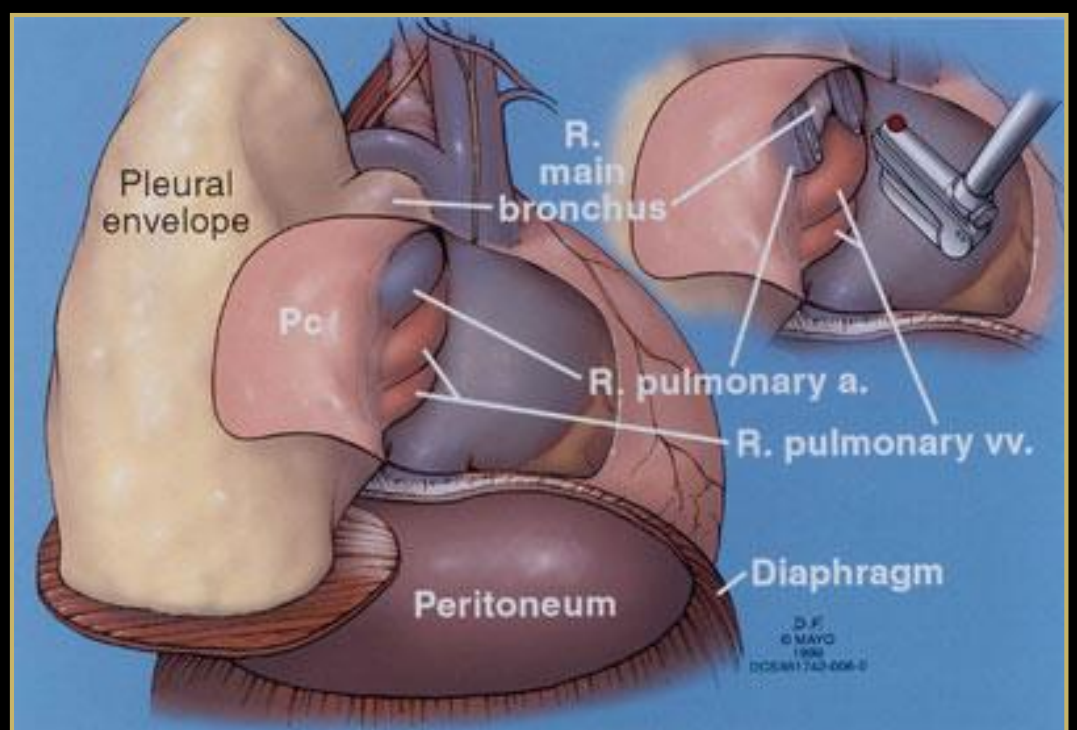




Rusch et al. *Journal of Thoracic Oncology*, 11(12), 2112-2119 (2016)


JIM CARREY
JEFF DANIELS
DUMB AND DUMBER
SMART AND SMARTER
FOR HARRY AND LLOYD
EVERYDAY IS A
NO BRAINER.

Tumour Spillage Hypothesis



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+ → 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

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 3, pp. 640–645, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.03.012

RAPID COMMUNICATION

FATAL PNEUMONITIS ASSOCIATED WITH INTENSITY-MODULATED RADIATION THERAPY FOR MESOTHELIOMA

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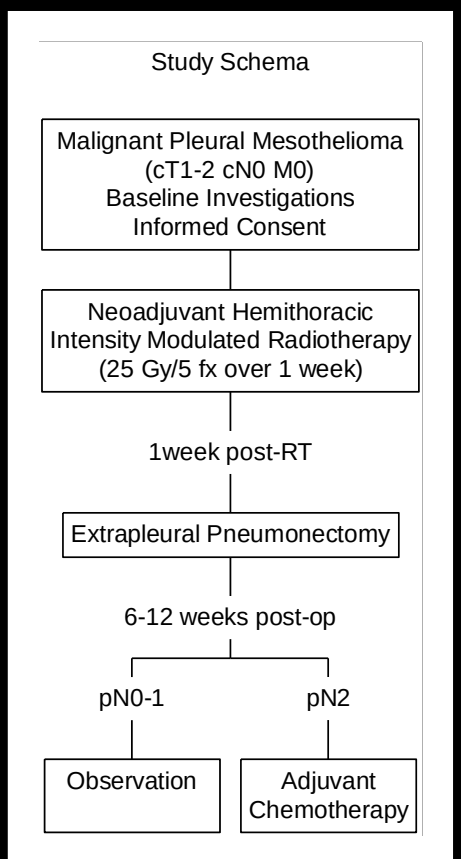
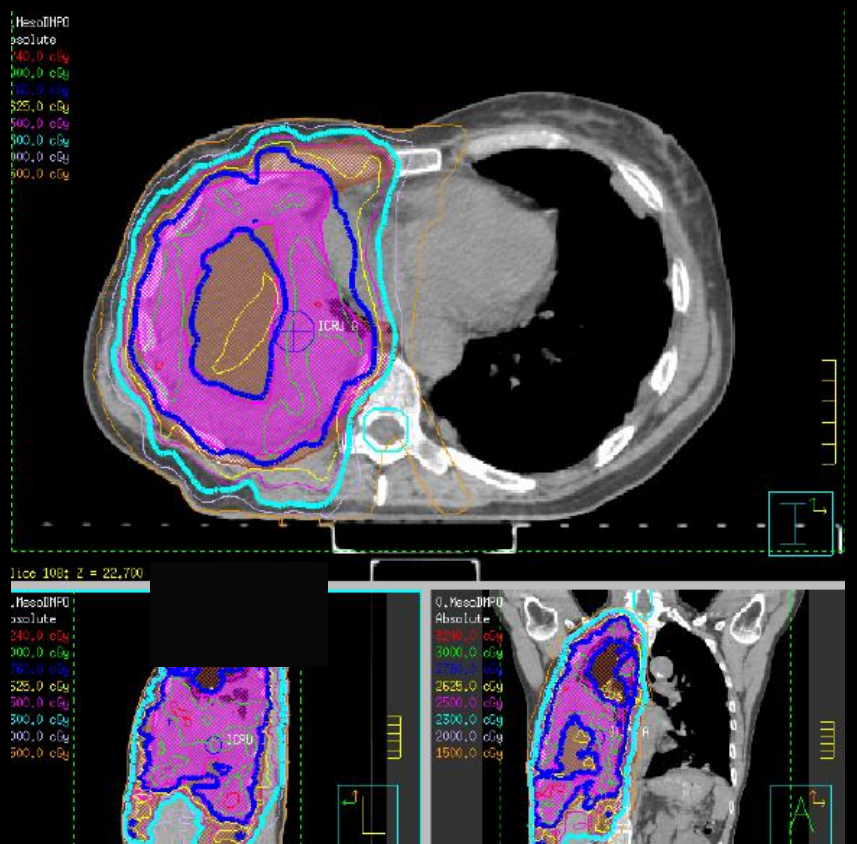
- Neoadjuvant RT to whole lung challenging

Surgery for Mesothelioma After Radiation Therapy





De Perrot. *J Thorac Cardiovasc Surg* 2016;151:468-75

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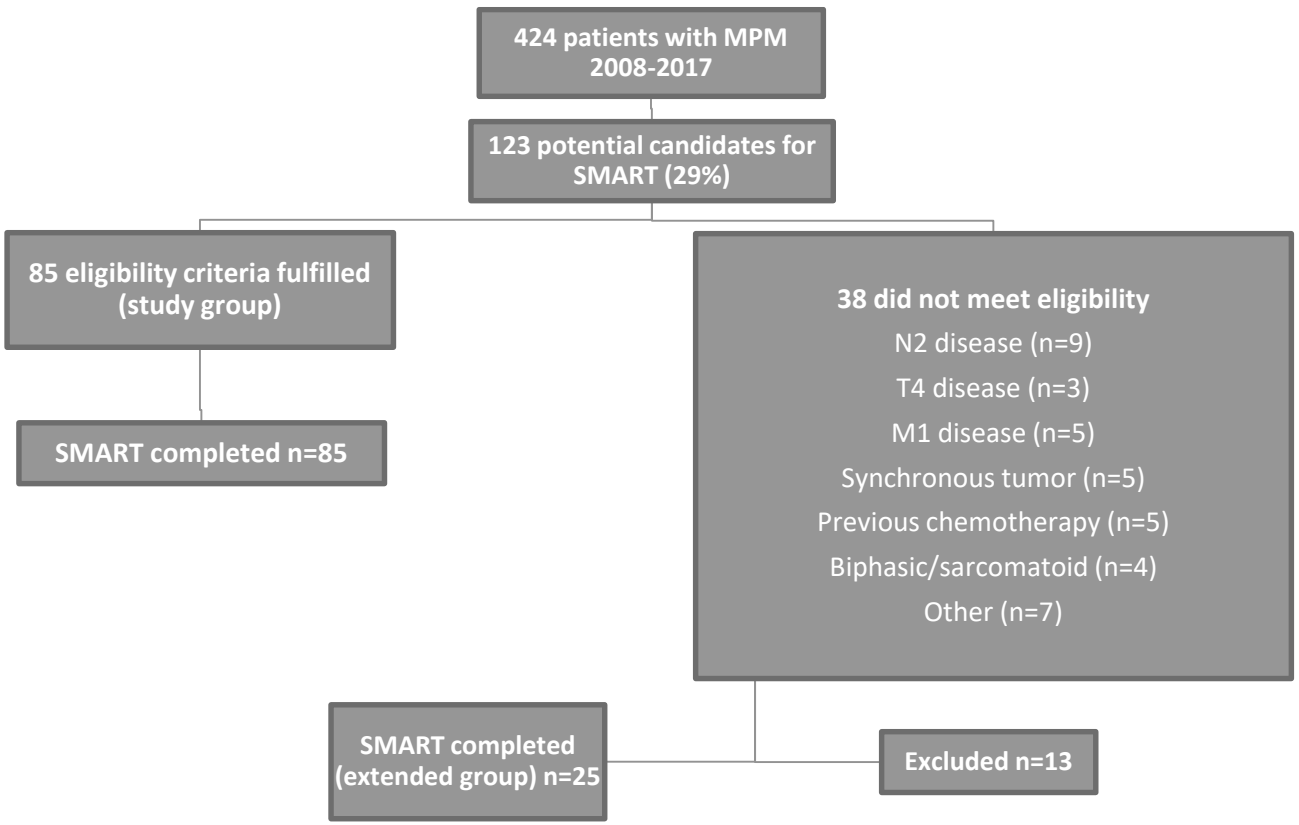
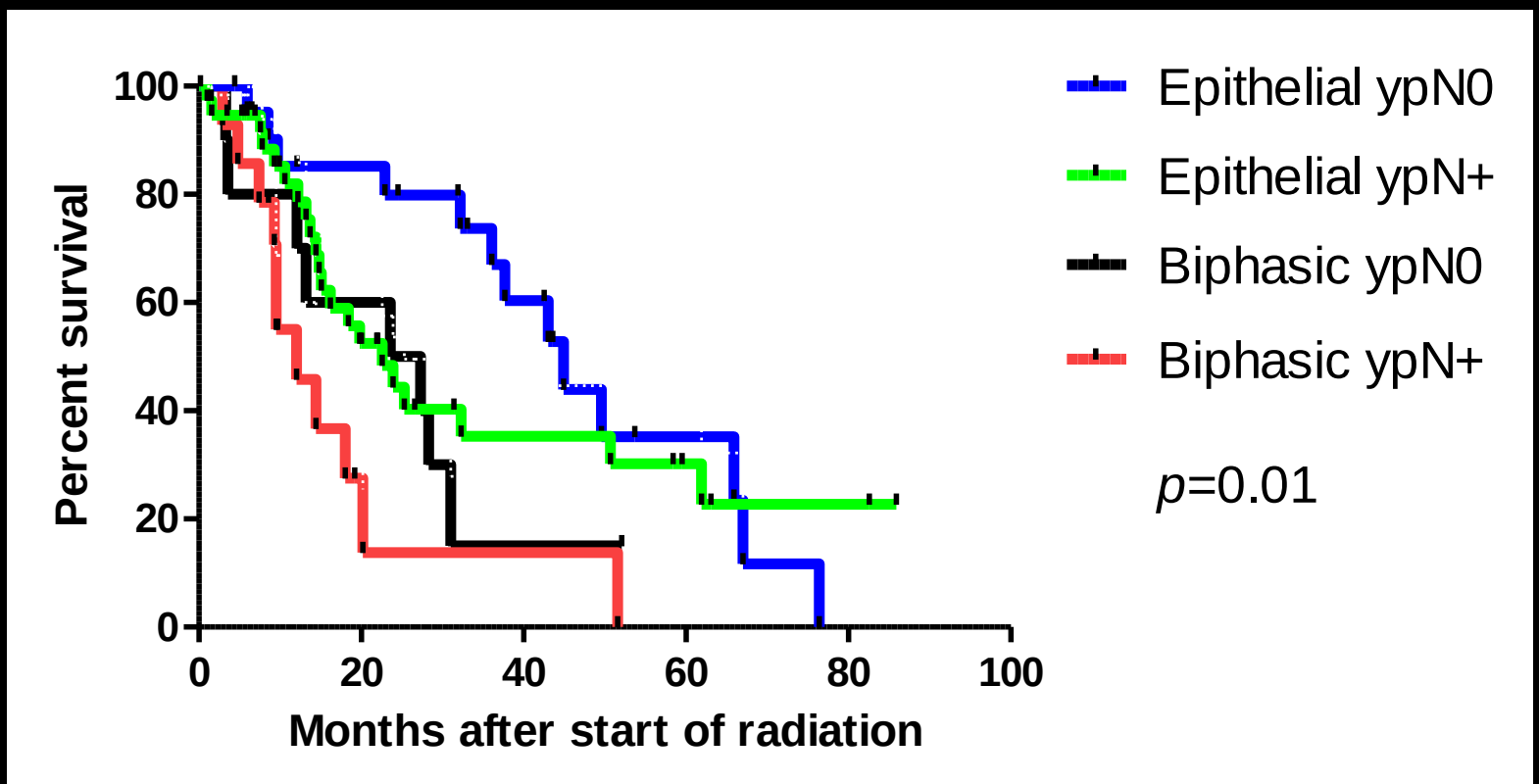
CONSORT Diagram



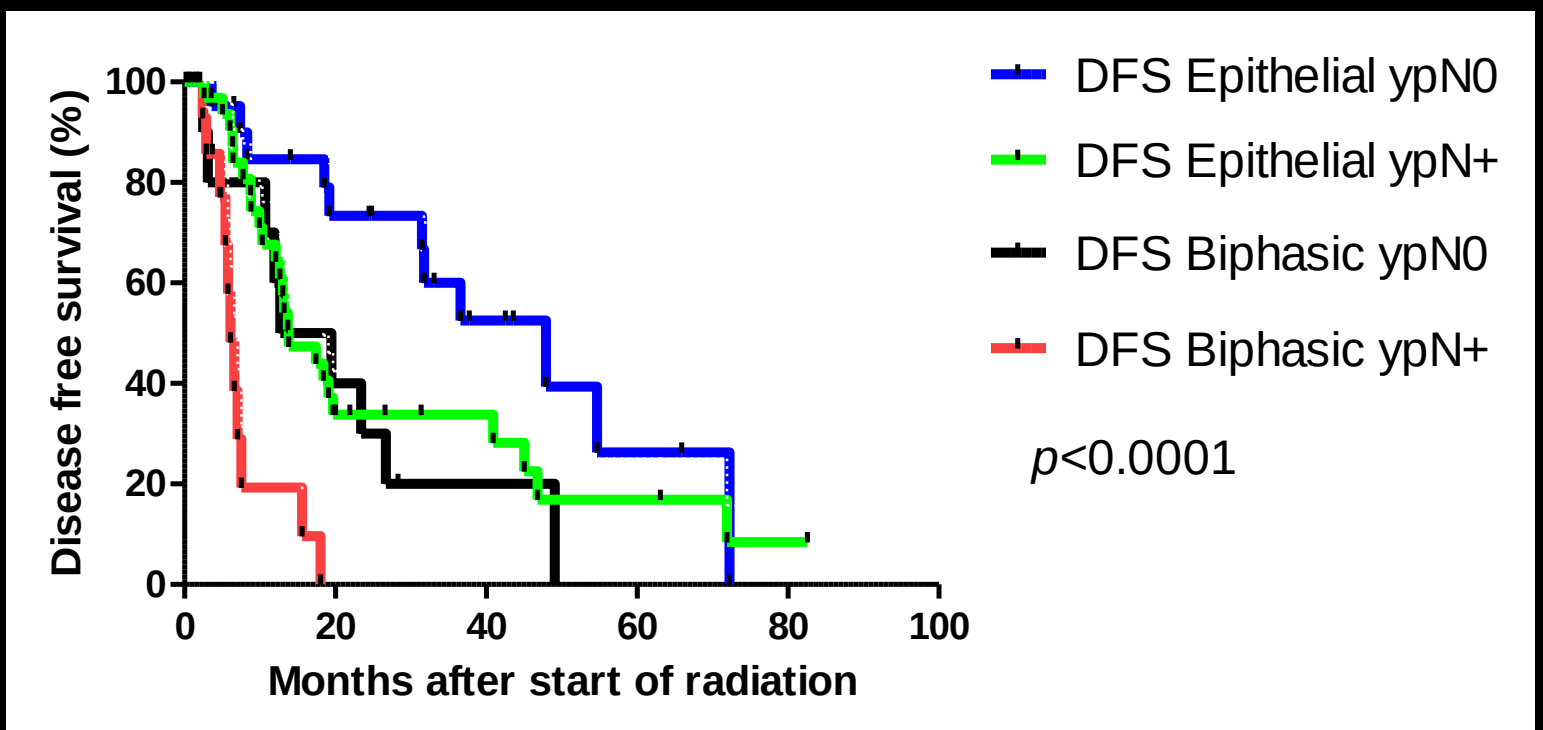
Overall Survival

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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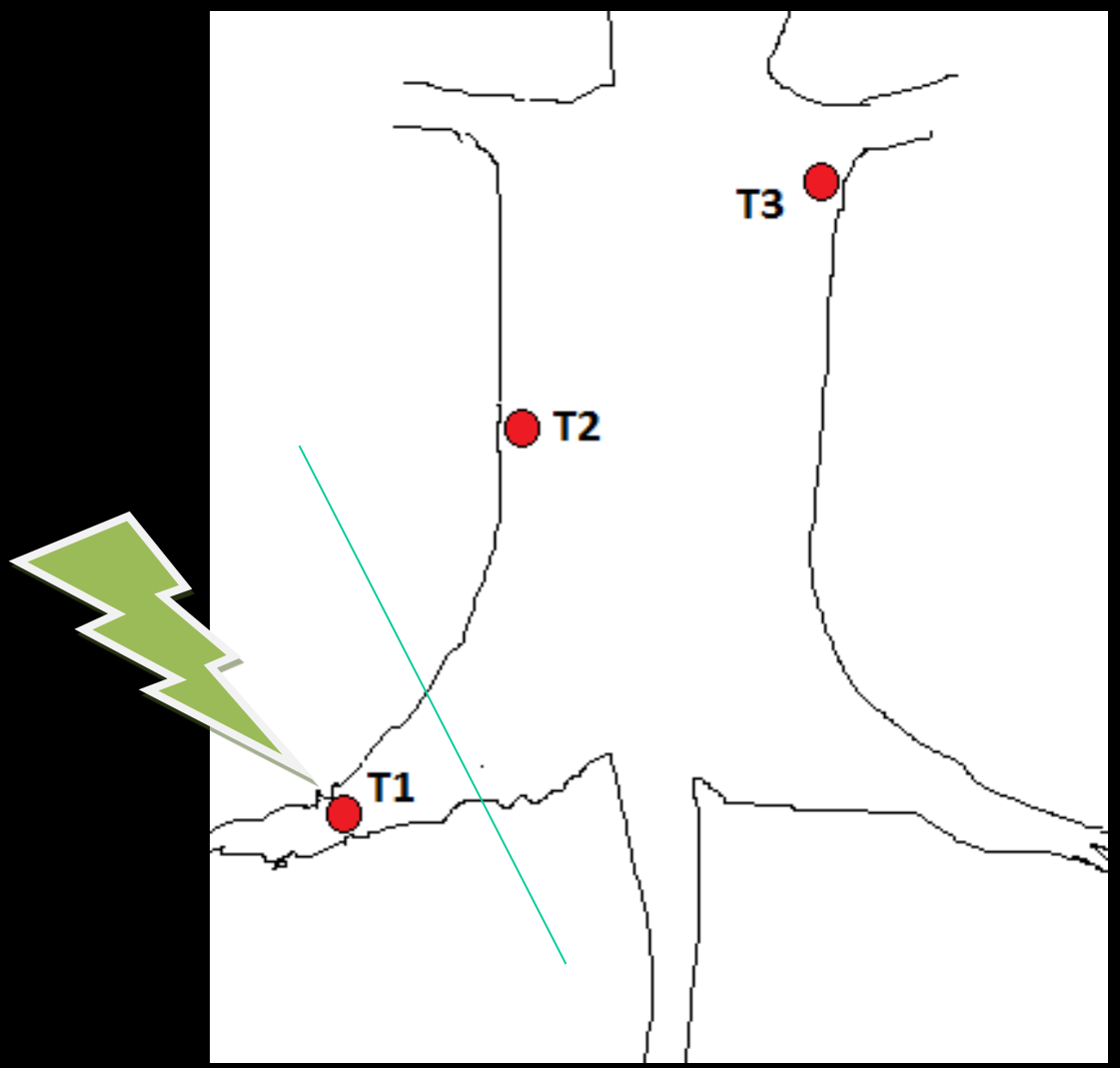
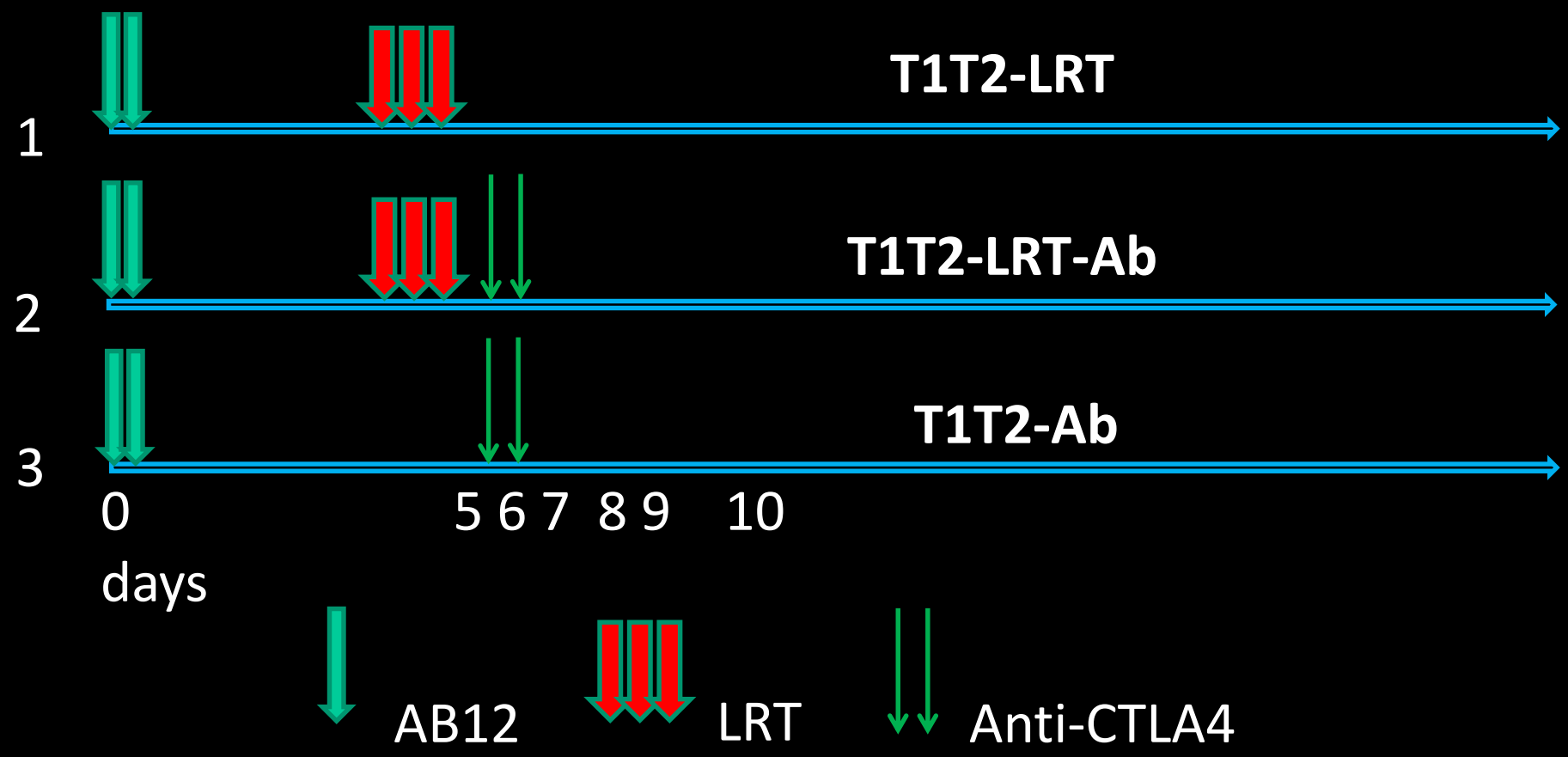
Abscopal Effect?

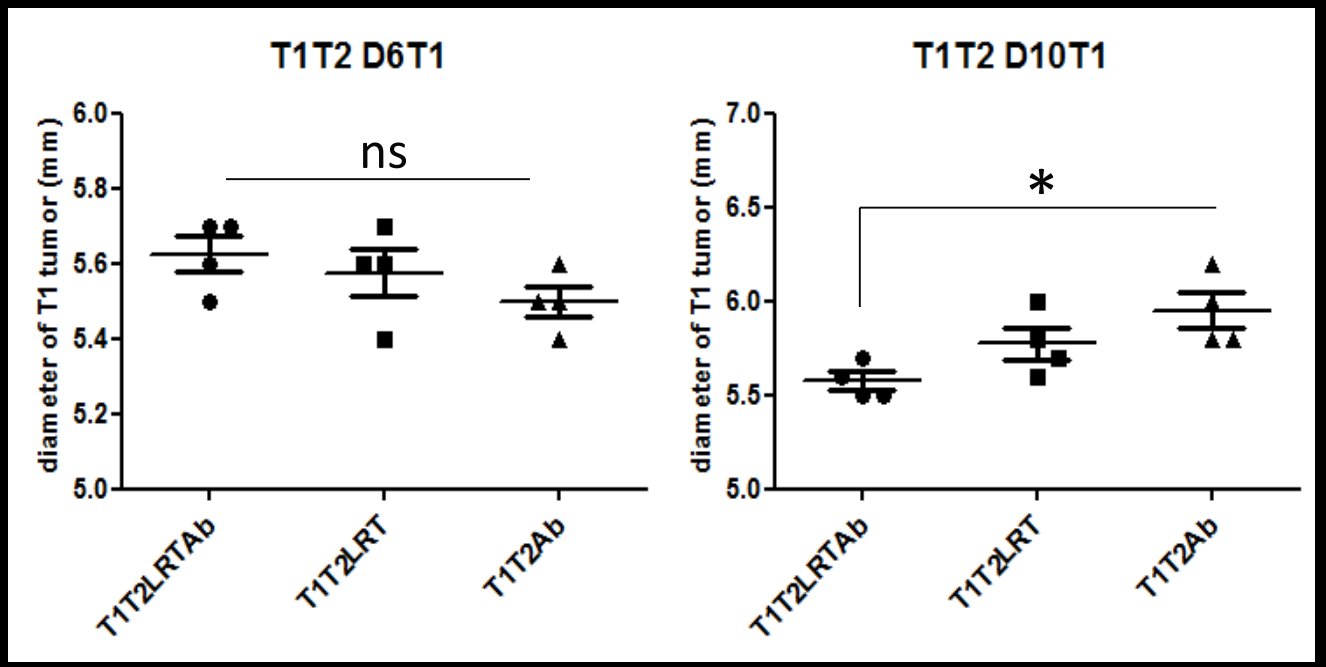


Experiment 2: Murine mesothelioma cells AB12 ($2x10^6$) were subcutaneously injected into the right hind leg (T1), right flank (T2) and left flank (T3). Local radiation (1Gyx3/LRT1 or 5Gyx3/LRT5) was given 5 days after tumor cell injection. 5 layers of lead sheet

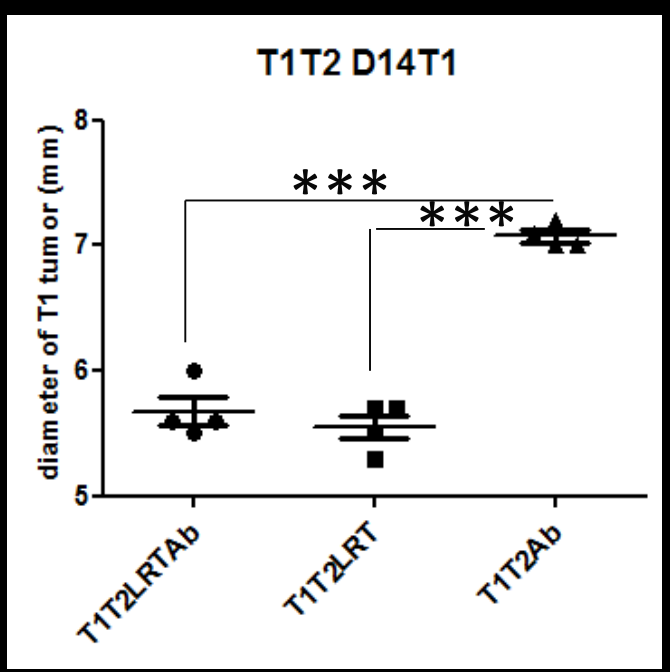
Schema of experimental design

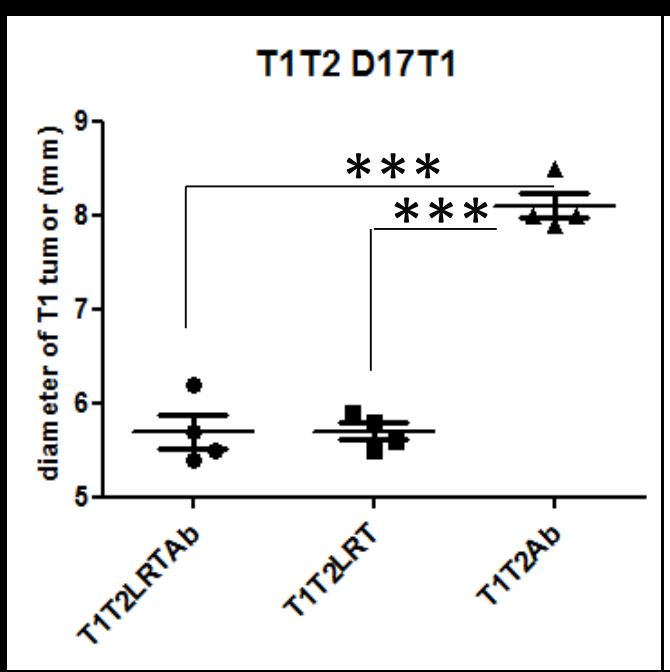


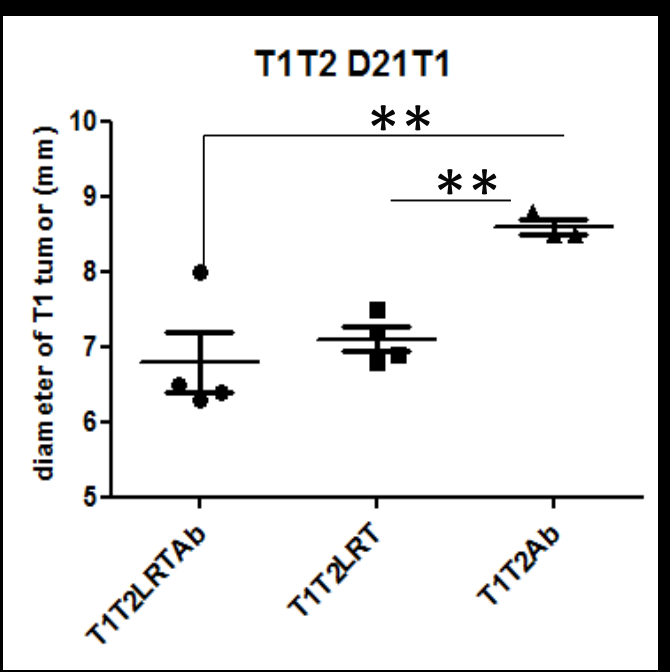
Local tumor (T1) growth after local RT +/- CTLA-4 blockade



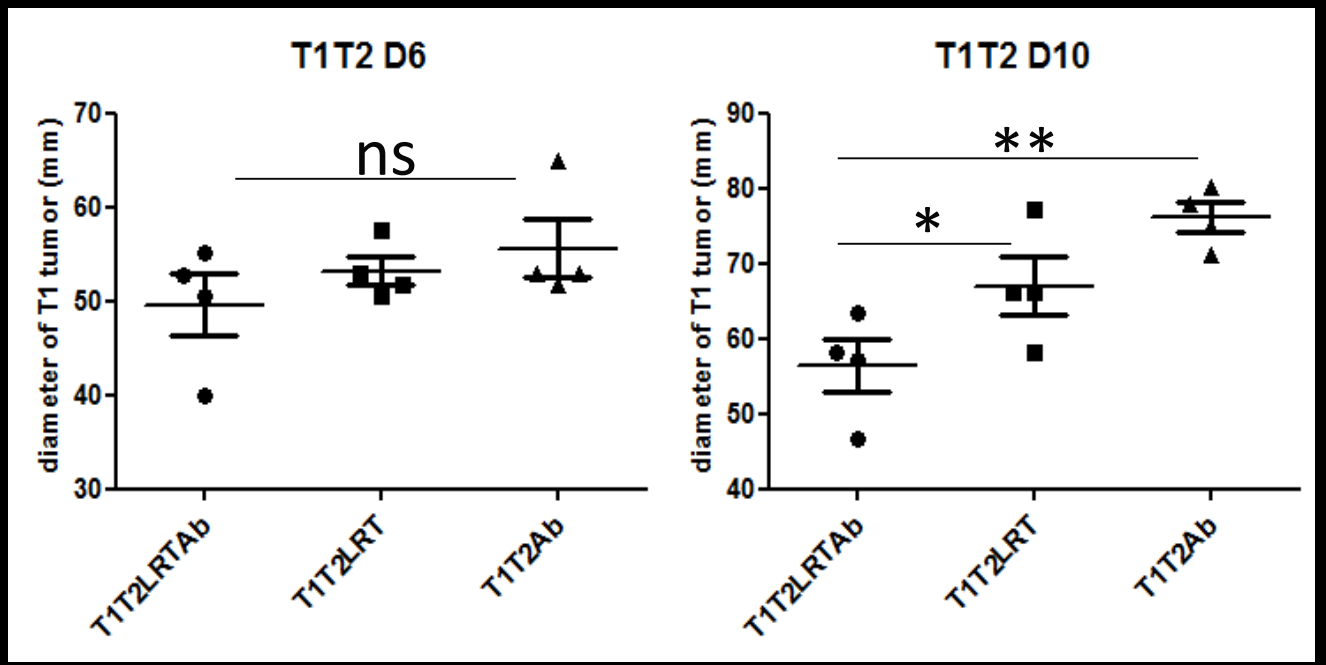
However, Ab had little effect on primary tumor (T1) either alone or in combination with LRT



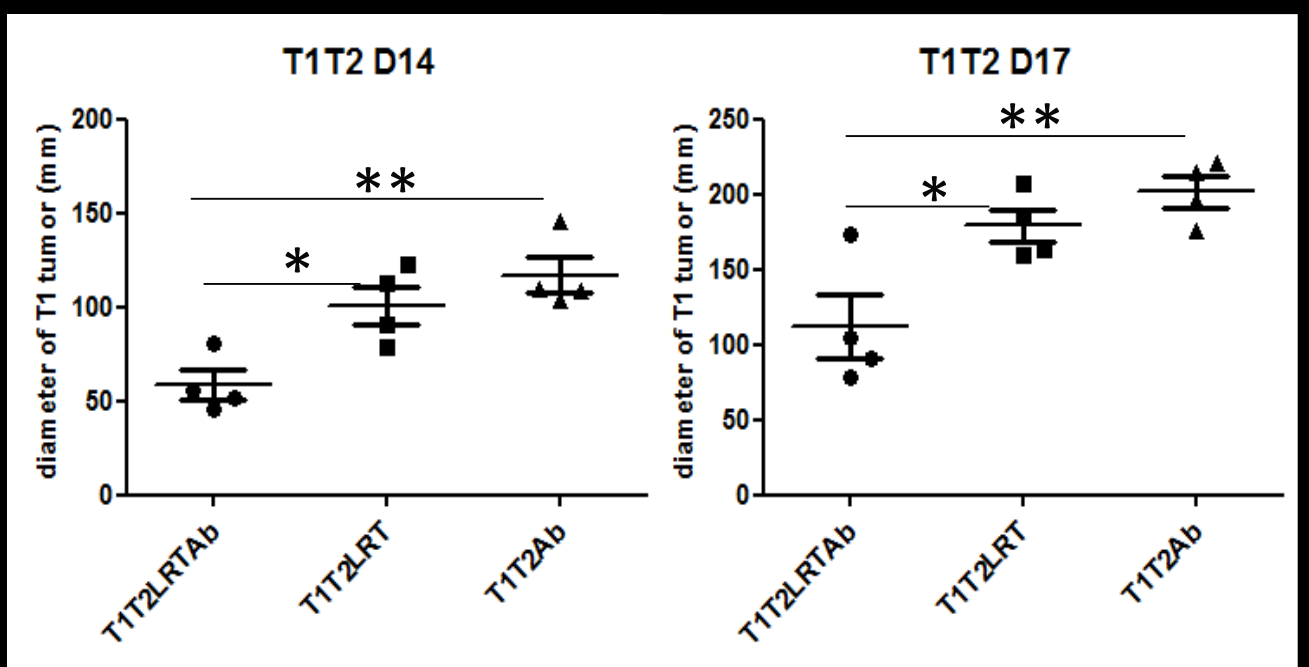


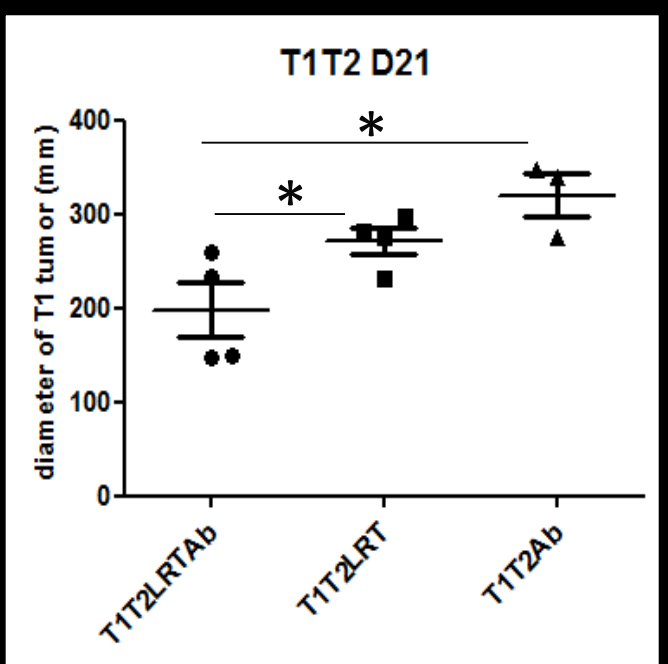


Distal tumor (T2) growth after local RT +/- CTLA-4 blockade



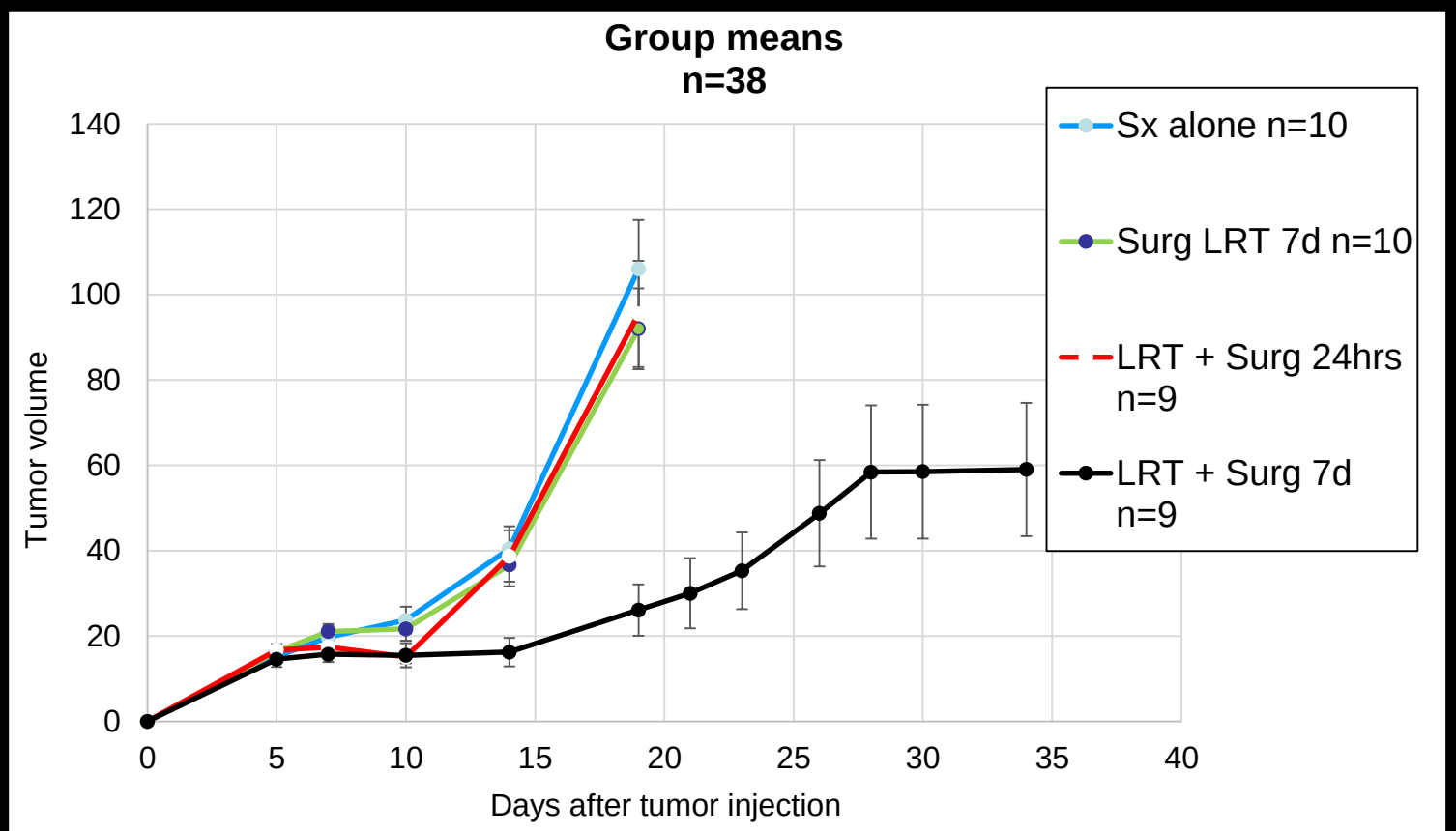
CTLA-4 blockade with its Ab can promote anti-tumor immunity, resulting in tumor growth delay of distal tumor (T2) when combined with LRT, compared with LRT alone.





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

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} Therapeutic Index

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- Ablative paradigm → SBRT

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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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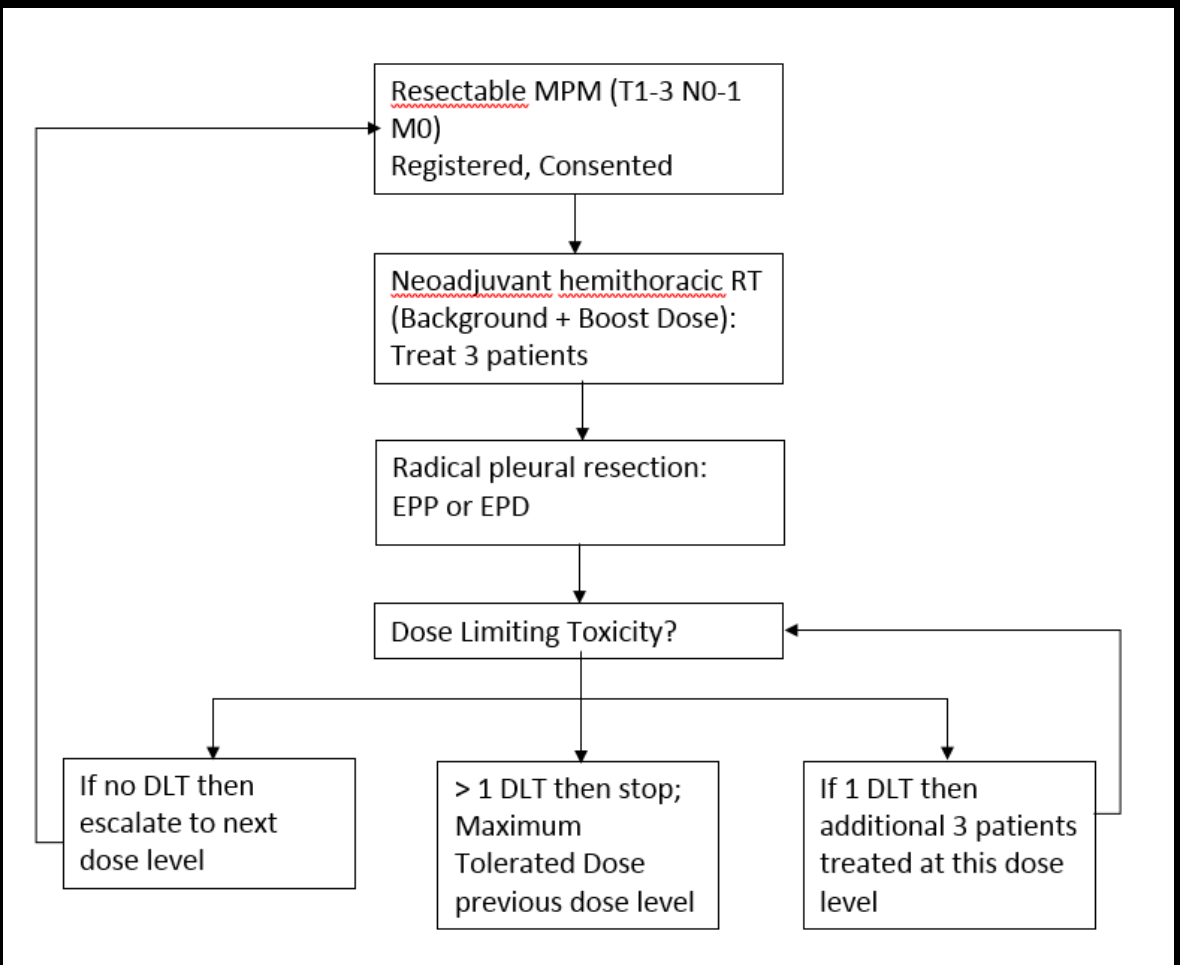
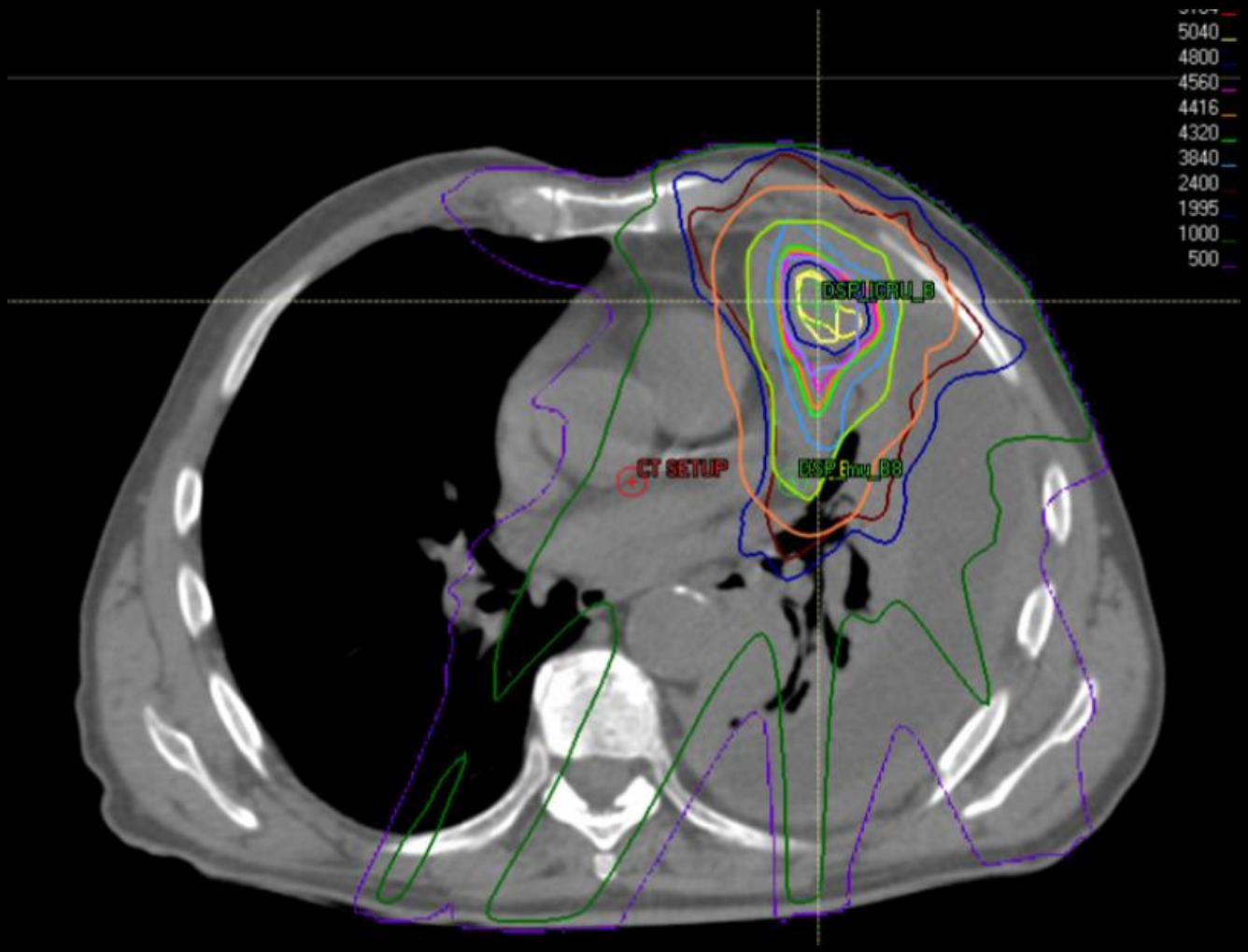
SMARTER Study Schema



- 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
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