



# Implementing Advanced Radiation Therapy Modalities in Lung Cancer

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CANCER CENTER

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# Disclosures

- No disclosures.

# The Scope of the problem

- As of 2017, 222,500 new cases of lung cancer and over 155,000 deaths.
- Vast majority are non-small cell lung cancer.
- Overall survival for all lung cancer patients is just 17.4%.
- Approximately 57% of patients present with distant metastatic disease.
  - 16% have disease at the primary site in the lung only.
  - 22% have disease which has spread to lymph nodes.

Seigel et al. CA Cancer J Clin 2017

# Reasons for optimism

- Screening has now demonstrated ability to detect cancers earlier. With early intervention, survival improves.
- Early stage cancers have increasing and improving options.
  - Video assisted or robotic assisted thoracoscopic surgery.
  - Stereotactic body radiation therapy (SBRT) for inoperable or borderline surgical candidates.
- For patients with local regional disease:
  - Minimally invasive surgery
  - Investigating the role of emerging induction systemic therapy options.
  - Improving radiation therapy planning and delivery.
  - Proton therapy.

# Reasons for optimism

- Advanced disease
  - Improving outcomes for aggressively managed patients with limited metastatic disease by incorporating local therapy.
  - Improving progression free survival and time to change of therapy in patients with limited metastatic progression by introducing locally ablative therapies.
  - Exciting options for mutation directed targeted therapy and immunotherapy.

# Proton therapy

- >99% of all radiation therapy is delivered with x-rays or electrons.



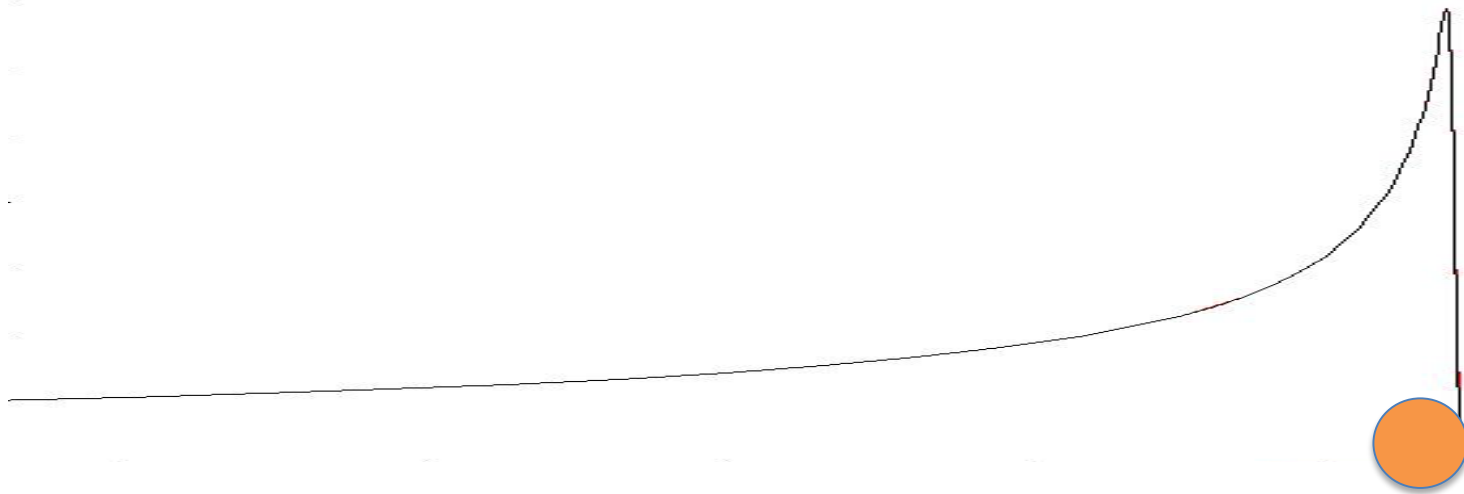
- State of the art equipment delivers extremely high doses with exceptional precision.

# PROTON Therapy

- High energy x-rays have a fundamental limitation.
- As William Conrad Roentgen discovered in 1895, x-rays pass through matter and can be detected on the other side.
- Allows treatment to deep tumors but at the expense of adjacent tissues in the path of the beam.
- For lung cancer, these tissues are the spinal cord, the esophagus, normal lung tissue and the heart.



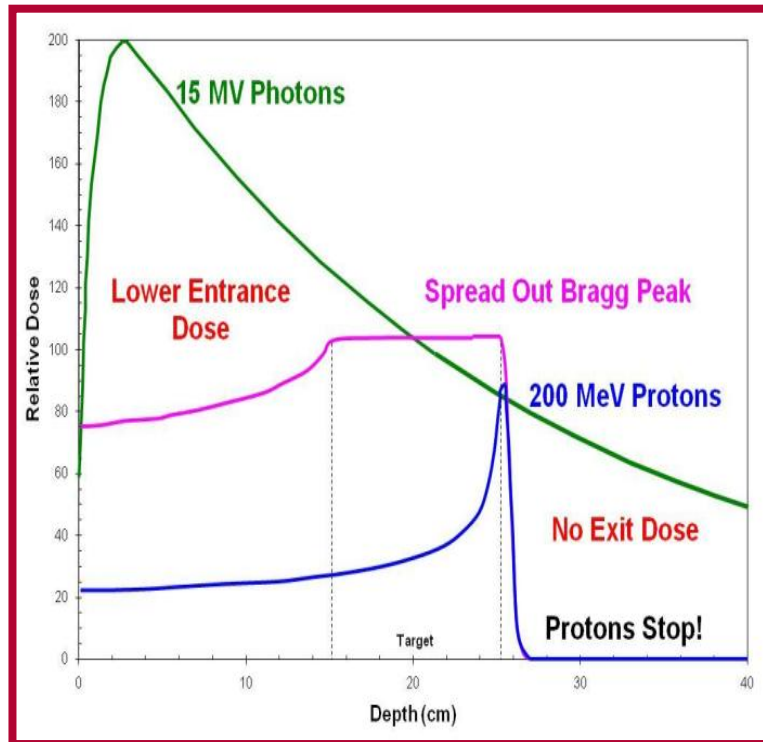
# What makes protons different?



- **THE BRAGG PEAK.**
  - The protons stop.



# Protons and the Bragg peak



- X-rays deposit high radiation dose at entrance into the patient and continue to deliver radiation until exiting.
  - Sophisticated planning and delivery techniques can decrease but not eliminate this phenomenon.
- Protons deliver less radiation at entrance.
- Protons deliver ZERO radiation beyond the defined target.

# PROTONS – HOW ARE THEY DELIVERED?

- Traditionally, protons are generated by a cyclotron or synchrocyclotron.
- Passed along a beam line



# Protons – ho

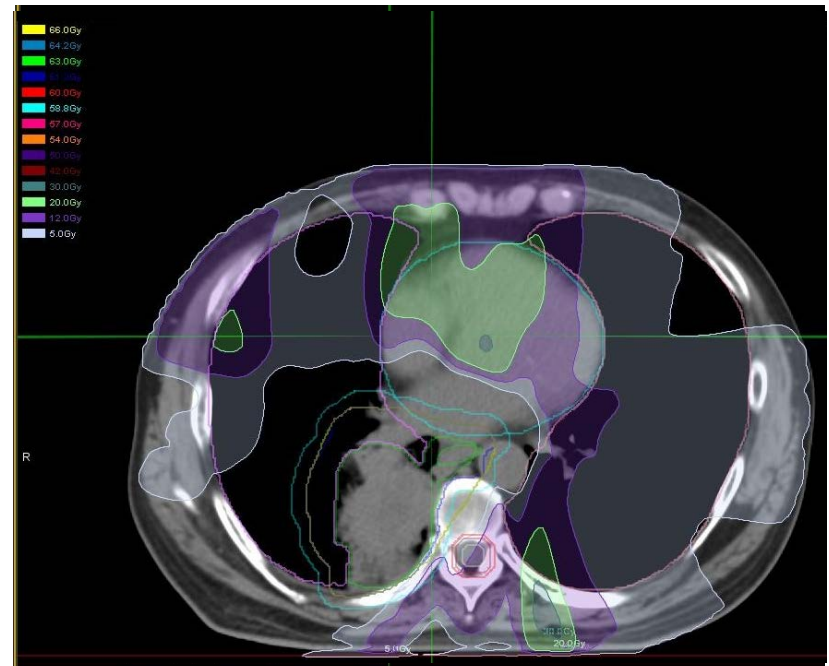
- Miniaturized system for proton therapy.
- High magnetic field in a reduced cyclotron just 6 feet.
- The cyclotron is mounted on a gantry and a robotic couch for beam delivery from all angles.
- Able to fit the entire system in a single vault.
- Still, just as powerful as traditional larger systems.



# PROTON therapy and lung cancer sample cases

- 64 year old male with O2 dependent COPD and stage IIIA non-small cell lung cancer.
- Not a candidate for surgery.
- Sufficient functional status for definitive treatment.
- Recommendation for concurrent chemotherapy and radiation therapy.

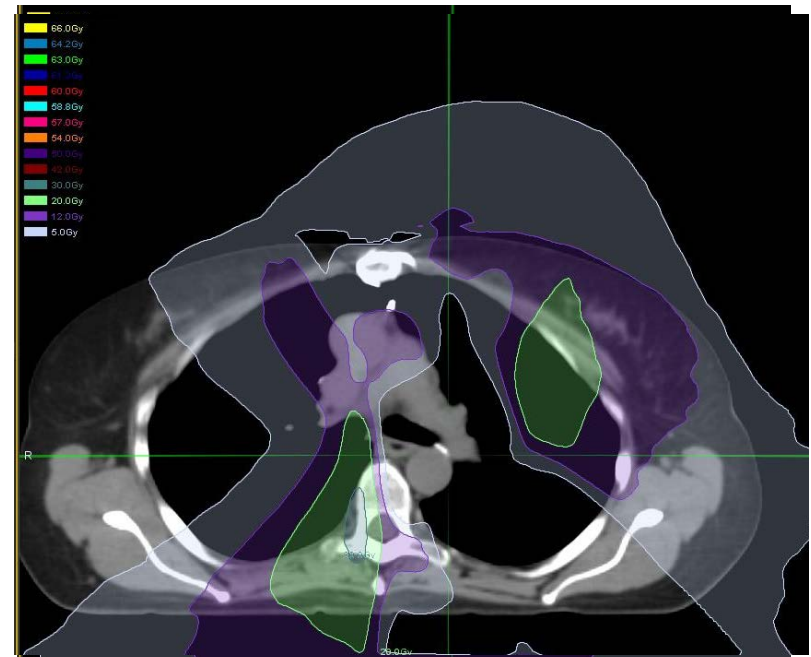
- Suboptimal with RT excess dose delivered



# PROTON therapy and lung cancer sample cases

- 71 year old male with stage IIIA non-small cell lung cancer.
- Not a candidate for surgery due to multi-station lymph node involvement.
- Sufficient functional status for definitive treatment.
- Recommendation for concurrent chemotherapy and radiation therapy.

- Suboptimal with RT excess dose delivered



# PROTONS – SHOULD WE USE it for lung cancer?

- National Comprehensive Cancer Network Guidelines currently limit the use of ‘advanced technology’ to situations where needed to deliver ‘curative RT safely.’
  - Many of these are considered standard: PET imaging, motion management or image guidance.
  - Proton therapy is listed in this category.
- Proton therapy demonstrates clear dosimetric advantages and superiority in many cases of local regional lung cancer.
- Proton therapy has shown improved toxicity and survival in non-randomized and single institution studies.
- Proton therapy in lung cancer remains *controversial*.

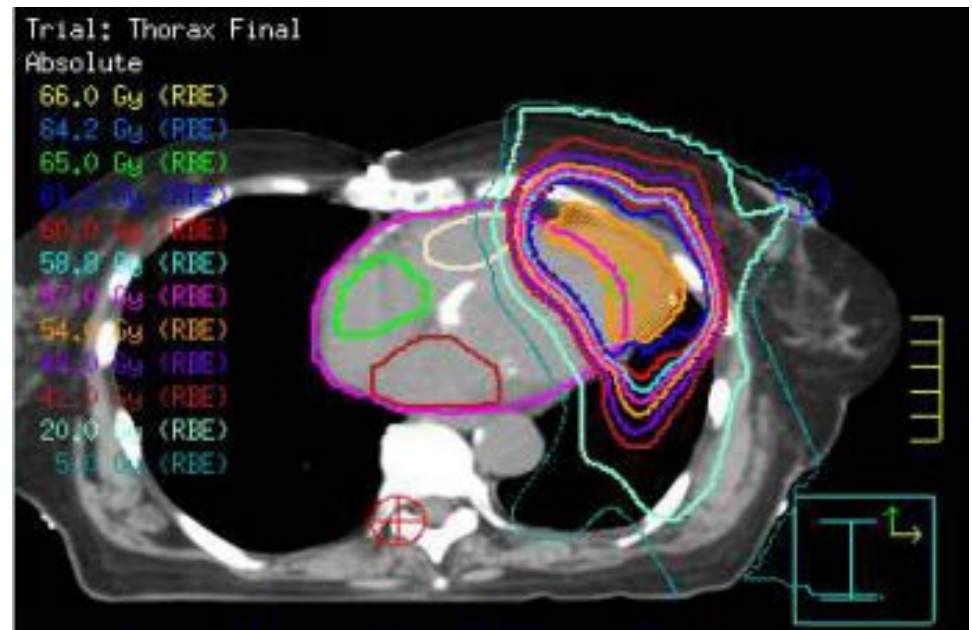


# PROTONS – Should we use it for lung cancer?

- Recent data have shown unexpected results.
- RTOG 0617 revealed decreased survival with increasing radiation dose (60Gy vs 74Gy) using x-rays.
  - Some data point towards a link to worse survival with higher acute toxicity.
  - Data suggest survival is tied to increased low to moderate heart radiation dose.
- A relatively small randomized trial of proton therapy versus IMRT failed to show improvement in a mixed toxicity and survival endpoint.
- The jury is out for the widespread use of proton therapy in lung cancer.
  - RTOG 1308 is an appropriately sized multi-center randomized trial evaluating proton therapy in inoperable non-small cell lung cancer.
  - In the meantime, proton therapy is limited to difficult to treat cases and those with inarguable dosimetric advantages certain to result in decreased toxicity and improved safety.

# PROTONS – Should we use it for lung cancer?

- 75 year old female with a history of CABG presented with a single episode of hemoptysis.
- Found to have a small adenocarcinoma in the lingula.
- Otherwise in good condition. Surgical resection attempted but aborted due to direct left ventricular invasion.
- The patient underwent salvage definitive proton beam radiation therapy.





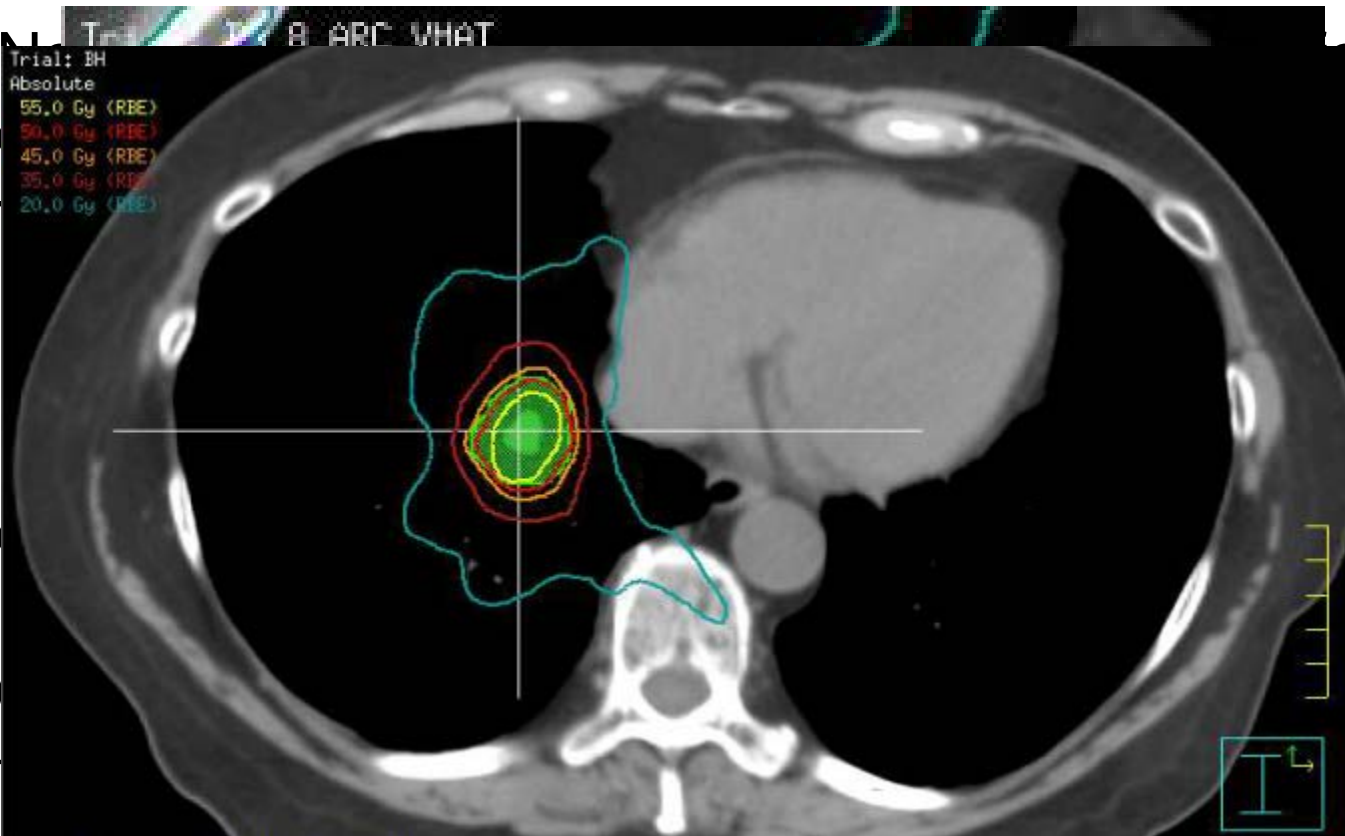
# Stereotactic body radiation therapy (SBRT)

- Surgery, specifically lobectomy, remains the gold standard in the management of early stage non-small cell lung cancer.
  - Control rates of up to 97%.
  - Intraoperative lymph node assessment.
  - Robust, decades long track record.
- For inoperable patients, SBRT has emerged as the standard of care.
  - Delivery of targeted, motion-managed, high dose radiotherapy over 1 to 5 fractions usually within a 2 week span.
  - Excellent local control of 90%+ at three years.

Ginsberg et al Ann Thorac Surg 1995  
Tandberg et al Cancer 2018

# Stereotactic body radiation therapy (SBRT)

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Trial: BH  
Absolute  
55.0 Gy (RBE)  
50.0 Gy (RBE)  
45.0 Gy (RBE)  
35.0 Gy (RBE)  
20.0 Gy (RBE)

formed  
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surgery.  
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atment with  
appropriate safeguards.

Sun et al. Cancer 2017  
Bezjak et al IJROBP 2016

# Advanced disease – incorporating local therapy

- Radiation therapy's role in metastatic disease has traditionally been limited to palliation.
  - Pain, hemoptysis, cough, spinal cord compression, brain metastasis, etc.
- Exception in patients with limited metastatic disease at presentation, i.e. oligometastatic disease.
  - Define by the NCCN as 'limited.' More often considered four or fewer.
  - These patients are managed with aggressive local therapy to the primary tumor and sites of metastatic disease.
- Improving systemic therapy options has opened the door to expanding this principle.
  - An example is the emerging concept of oligoprogression.

# Advanced disease – incorporating local therapy

- Locally ablative treatment long used for limited intracranial metastatic disease.
  - Referred to as stereotactic radiosurgery.
  - Now the favored standard treatment with 4 or fewer brain metastasis due to excellent disease control and improved toxicity versus whole brain radiation treatment.
- For extracranial disease, progression at any site prompted change in therapy.
  - Subsequent lines in therapy are often more toxic and less likely to achieve objective response or stable disease.

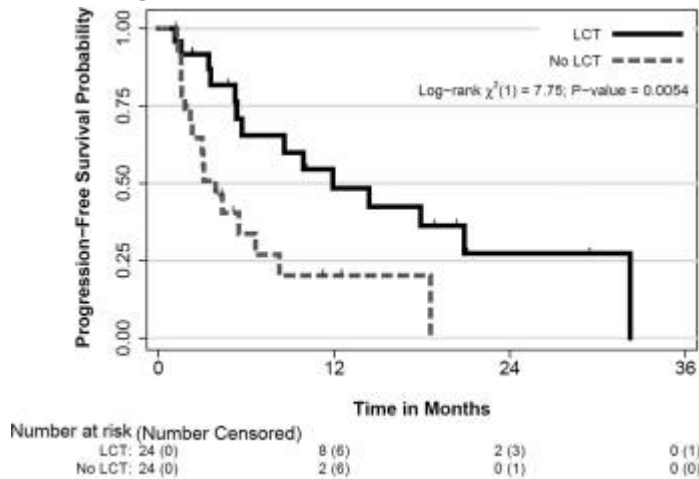
# Advanced disease – incorporating local therapy

- Among lung cancers with EGFR, ALK or ROS-1 mutations, first lines of therapy are highly effective oral targeted agents with favorable toxicity profile.
  - Progression may lead to change of therapy to traditional cytotoxic chemotherapy.
- Often, progression occurs in only limited sites (i.e. oligoprogression).
  - Multiple small retrospective series have explored continuing a targeted agent after ablative treatment to the progressing site only.
  - Results demonstrate excellent local control as well as increased time to further progression and time on the targeted therapy.
  - Local treatment and continued targeted therapy is now the standard recommendation in national guidelines such as NCCN.

Shukuya et al Lung Cancer 2011  
Weickhardt et al J Thorac Oncol 2012  
Gan et al IJROBP 2014

# Advanced disease – incorporating local therapy

- Phase II studies by Gomez et al. and Iyengar et al. have supported applying local ablative therapies to non-small cell lung cancer patients without targetable mutations as well.



- Both trials led to remarkable improvements in progression free survival.
- In the study by Dr. Gomez, PFS improved from 3.9 to 11.9 months.
- In the study by Dr. Iyengar, PFS improved from 3.5 to 9.7 months.

— This is now the subject of a multi-center cooperative group trial run by NRG.

Gomez et al Lancet Oncol 2017  
Iyengar et al IJROBP 2017

# Advanced disease – incorporating local therapy

- The principal of ablation for limited extracranial metastatic progression is being applied beyond lung cancer as well:
  - Colorectal adenocarcinoma
  - Renal cell carcinoma
  - Melanoma
  - Sarcoma
  - Breast cancer

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# Thank you!

