The potential clinical impact of breathhold technique in radical radiation therapy for NSCLC

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- Radical radiation therapy (RT) is one of the curative options for non-small cell lung cancer (NSCLC), but it is associated with significant complications.
  - Acute pneumonitis
  - Acute esophageal inflammation
  - Lymphopenia
  - Late lung fibrosis
  - Late cardiac complications – arrhythmia, pericarditis, heart failure, valvular disease
- We have many randomized trials informing us on cancer control efficacy (especially on new drugs) but much less emphasis was put on treatment related toxicity, especially for RT
- Can breathing control be a potential technique to reduce toxicity of radical lung radiation therapy?

Methodology

- Consecutive 125 NSCLC patients from 6-2023 to 8-2024
- Proknow retrieval of dosimetry data
- Manual review of clinical data
  - Stage, pathology, SACT
  - OS, PFS
  - Lymphopenia (within 3 months post RT)
  - RT induced lung damage
    - RT/immunotherapy related pneumonitis or pulmonary fibrosis
  - Lymphopenia (within 3 months post RT)

	RTOG	CTCAE v. 5.0	SWOG
Grade 0	No changes	No changes	Normal
Grade 1	Asymptomatic or mild symptoms	Asymptomatic, only radiological, or tomographic findings	Radiographic changes, symptoms do not require steroids
Grade 2	Moderate symptoms of pneumonitis (severe cough) and radiographic changes (radiographic patches)	Symptomatic, does not interfere with daily activities	Steroids required or tap of effusion
Grade 3	Severe symptoms of pneumonitis, dense radiographic changes	Symptomatic, interferes with daily activities, requires supplemental O2	Oxygen required
Grade 4	Symptoms of severe respiratory failure requiring assisted ventilation or continuous O2	Threatens life, requires mechanical ventilation support	Requires assisted ventilation
Grade 5	Death-related late effects of radiotherapy	Death related severe pneumonitis	–

1. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). International Journal of Radiation Oncology*Biology*Physics. 1995;31(5):1341–6.
2. Common Terminology Criteria for Adverse Events (CTCAE) 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
3. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs. 1992;10(4):239–253. doi: 10.1007/BF00944177.

Radiation induced lung damage (grade 2 or above)

Grade 0 – minimal radiological changes: 48 (38.4%)
Grade 1 – asymptomatic radiological changes: 44 (35.2%)
Grade 2 – symptomatic, need steroid: 17 (13.6%)
Grade 3 – symptomatic, required admission / O2: 10 (8%)
Grade 4 – life threatening: 1 (0.8%)
Grade 5 – fatal: 5 (4%)

Grade 3 or above radiation induced lung damage is associated with worse overall survival - HR 3.1, p=0.01

Predictors of RT induced lung damage

- **Auto-immune disease: OR 5.5, p=0.02**
- **Normal Lung volume (1st quartile, >4.5L): OR 0.42, p=0.03**
- Insignificant factors: lung function test results, V20, V40, GTV, PTV, use of concurrent chemo, lower lobe location, immunotherapy

RT induced lymphopenia

- Grade 3-4 (<500/mm^3 within 3 months post-RT): 58%
- Grade 3-4 lymphopenia / lowest lymphocyte count is associated with worse overall survival
  - HR 2.53, p=0.02; HR 0.28, p=0.03
- Predictor of lowest lymphocyte count,
  - V5 (p=0.008), V10 (p=0.016), V20 (p=0.013), V40 (p=0.04), mean lung dose (0.009)
  - Mean h
  - Effecti

$$EDIC = 0.12 \times MLD + 0.08 \times MHD + \left[0.45 + 0.35 \times 0.85 \times \left(\frac{n}{k}\right)^{1/2}\right] \times \frac{ITD}{62 * 10^3}$$

- *RT induced lymphopenia (grade 3 or above) and RT induced lung damage (grade 3 or above) are independent predictors of overall survival (HR 3.3 & 2.6, p=0.004 & 0.015 respectively)*

Jin JY, et al. Higher Radiation Dose to the Immune Cells Correlates with Worse Tumor Control and Overall Survival in Patients with Stage III NSCLC: A Secondary Analysis of RTOG0617. Cancers (Basel). 2021 Dec 8;13(24):6193. doi: 10.3390/cancers13246193.

Discussion

- Potential dual role of breathing control technique in lung cancer RT
  - Reduce RT induced lung damage by increasing total lung volume
  - Reduce RT associated lymphopenia by improving lung / heart mean dose (EDIC)

- Voluntary DIBH may increase lung volume by 50%, CPAP assisted DIBH may increase lung volume by ~100%[1]
- Reducing EDIC by 1 Gy is associated with 8% OS benefit

- Should we formally test breathing control technique in randomized clinical trial with primary endpoint at radiation induced lung damage or overall survival?

Liang E, Dolan JL, Morris ED, Vono J, Bazan LF, Lu M, Glide-Hurst CK. Application of Continuous Positive Airway Pressure for Thoracic Respiratory Motion Management: An Assessment in a Magnetic Resonance Imaging-Guided Radiation Therapy Environment. Adv Radiat Oncol. 2022 Jan 4;7(3):100889.