# Taipei Veterans General Hospital
# Practices Guidelines
# Radiation Oncology

# *Lung Cancer*

**Version 2022**

# General principles

- More advanced technologies are appropriate when needed to deliver curative RT safely.
- These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, and motion management.
- Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.
- In a prospective trial of definitive chemo/RT for stage III NSCLC (RTOG 0617), IMRT was associated with a nearly 60% decrease in high-grade radiation pneumonitis and similar survival and tumor control outcomes despite a higher proportion of stage IIIB and larger treatment volumes compared to 3D-CRT; as such, IMRT is preferred over 3D-CRT in this setting.

# General principles

- **The interaction of strong VEGF inhibitors with prior or subsequent dose-intensive RT involving the proximal bronchial tree, hilar vessels, or esophagus can lead to serious toxicity. Careful coordination of medical and radiation oncology on the therapeutic strategy is important.**

# Early-stage NSCLC(Stage I, node negative Stage IIA)

- SABR(also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation.
- Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival.
- Close follow-up and salvage therapy for isolated local and/or locoregional recurrence after SABR have been shown to improved overall survival in a large retrospective study.
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.
- In patients treated with surgery, postoperative radiotherapy is not recommended unless there are positive margins or upstaging to N2.

# Locally advanced NSCLC(Stage II-III)

- **The standard of care for patients with inoperable stage II (node positive) and stage III is currently CCRT.**
- **RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.**
- **In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.(*)(**)**
- **Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy and concurrently with chemotherapy for positive resection margins.**

# Advanced/Metastatic NSCLC(Stage IV)

- **Definitive local therapy to isolated or limited metastatic sites (oligometastasis) (including not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease. Definitive RT to oligomestasis(limited number is not universally defined but clinical trials have included up to 3-5 metastases), particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.**
- **In the setting of progression at a limited number of sites on a given line of systemic therapy(oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.**
- **When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/hypofractionated conformal radiation therapy regimes may be used.**

# Principles of Radiation Therapy

## Radiation Simulation, Planning and Delivery

Treatment planning should be performed by CT scans obtained in the treatment position, with a slice thickness of 3~5mm. IV contrast may be considered for better target delineation whenever possible, especially in patients with central tumors or with nodal disease. PET-CT is preferable in cases with significant atelectasis. PET-CT can significantly improve the target accuracy. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrence, and a trend toward improved overall survival with PET/CT RT planning.(***)

# Principles of Radiation Therapy

## Radiation Simulation, Planning and Delivery

Recommended methods of accounting for tumor motion, per guideline, include:

1) Motion-encompassing methods such as slow CT scanning, **inhale and exhale breath-hold CT**, four-dimensional (4-D) respiration-correlated CT;

2) Respiratory gating methods using an external respiration signal or using internal fiducial markers;

3) **Breath-hold methods by deep-inspiration breath-hold**, active-breathing control (ABC) device, SDX spirometric voluntary breath hold system, surface guided radiotherapy, or self breath-hold with or without respiratory monitoring; forced shallow breathing with abdominal compression; and real-time tumor-tracking methods.

# Principles of Radiation Therapy

## Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy

- Postoperative radiation dose should be based on margin status. Lung tolerance to radiation after surgery is remarkably smaller than those with the presence of both lungs.

- For patients receiving postoperative RT, more strict DVH parameters should be considered for the lung.
- Pre-radiotherapy and post-radiotherapy lung function tests should be obtained.

# Principle of Target volume delineation

## Gross Target Volume (GTV) delineation

- The pulmonary extent of lung tumors should be delineated on pulmonary windows, and the mediastinal extent of tumors should be delineated using mediastinal windows.

- The PET images can help to categorize suspected mediastinal and hilar adenopathy and differentiate between collapsed lung tissue from tumor. However, false-positive PET scans can be caused by inflammation, and a biopsy is recommended if there is any question.

## Principle of Target volume delineation

# Clinical Target Volume (CTV) delineation

- –includes the area of subclinical involvement around the GTV. For the lung parenchymal disease, a margin of 5-10 mm is recommended.
- –In the absence of radiographic proof of invasion, the CTV of the primary lesion should not extend into the chest wall or mediastinum.
- –5-10 mm expansions of involved nodes of the CTV is recommended, but not extend into the major airways or lung, chest wall, or vertebral body without evidence of invasion.

## Principle of Target volume delineation

# Clinical Target Volume (CTV) delineation

- Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial and should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. **Involved field RT to high dose without ENI** has been shown to allow higher dose radiation with acceptable toxicity and low risk of isolated nodal relapse.

- In patients who receive postoperative RT, CTV should consist of the bronchial stump and high-risk draining lymph node stations.(****)

## Principle of Target volume delineation

# Planning Target Volume (PTV)

- When patients are immobilized with a Vac-Loc bag or other devices, expansion along all axes of 7 mm is recommended.

- When daily image-guided setup is used, the setup uncertainty can be reduced.

- Typically CTV could be expanded 0.5-1 cm in all directions (****)

# Commonly Used Doses for Conventionally Fractionated and Palliative RT (NCCN v3. 2022)

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

| Treatment Type | Total Dose | Fraction Size | Treatment Duration |
|---|---|---|---|
| Definitive RT with or without chemotherapy | 60–70 Gy | 2 Gy | 6–7 weeks |
| Preoperative RT | 45–54 Gy | 1.8–2 Gy | 5 weeks |
| Postoperative RT | | | |
| • Negative margins | 50–54 Gy | 1.8–2 Gy | 5–6 weeks |
| • Extracapsular nodal extension or microscopic positive margins | 54–60 Gy | 1.8–2 Gy | 6 weeks |
| • Gross residual tumor | 60–70 Gy | 2 Gy | 6–7 weeks |
| Palliative RT | | | |
| • Obstructive disease (SVC syndrome or obstructive pneumonia) | 30–45 Gy | 3 Gy | 2–3 weeks |
| • Bone metastases with soft tissue mass | 20–30 Gy | 4–3 Gy | 1–2 weeks |
| • Bone metastases without soft tissue mass | 8–30 Gy | 8–3 Gy | 1 day–2 weeks |
| • Brain metastases | CNS GLs* | CNS GLs* | CNS GLs* |
| • Symptomatic chest disease in patients with poor PS | 17 Gy | 8.5 Gy | 1–2 weeks |
| • Any metastasis in patients with poor PS | 8–20 Gy | 8–4 Gy | 1 day–1 week |

*NCCN Guidelines for Central Nervous System Cancers

- RTOG 0617 (74 Gy vs. 60 Gy, CCRT): no overall survival benefit.
- While optimal RT dose intensification remains a valid question, higher doses of 74 Gy are not currently recommended for routine use.

# Recommended Dose/Volume Limit for Lung

- **QUANTEC is recommended by NCCN guideline 2022**
- **For conventional fractionation, definitive RT:**
  - V20 ≦ 30–35% and MLD ≦ 20–23 Gy to limit the risk of radiation pneumonitis to ≦ 20%
  - Limiting the dose to the central airways to ≦ 80 Gy to reduce the risk of bronchial stricture

- **Reference : *Radiation dose-volume effects in the lung.*** *Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S70-6.*

**QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic**
**V20 = % of whole lung receiving ≥ 20 Gy**
**MLD = Mean Lung Dose**

# Normal Tissue Constraints (NCCN v3. 2022)

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy*

| OAR | Constraints in 30–35 fractions |
|---|---|
| Spinal cord | Max ≤50 Gy |
| Lung | V20 ≤35%–40%†; MLD ≤20 Gy |
| Heart** | V50 ≤25%; Mean ≤20 Gy |
| Esophagus | Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable |
| Brachial plexus | Median dose ≤69 Gy |

Vxx = % of the whole OAR receiving ≥xx Gy.

*These constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given organ at risk should typically be lower than these constraints, approaching them only when there is close proximity to the target volume.

†Use V20 <35%, especially for the following: elderly ≥70 years, taxane chemotherapy, and poor PFTs (such as FEV1 or DLCO <50% normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IDP)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized).

Atlas:
http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx

# Node-Negative Early-Stage SABR

- SABR is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation.
- SABR is also an appropriate option for patients with high surgical risk.
- Intensive regimens of $BED_{10}$ ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.
- For centrally located tumors (within 2 cm of the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe, while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.
- Treatment-related mortality was 1.0% when the biologically equivalent normal tissue dose ($BED_3$) of the radiation schedule was ⩽210 Gy

# Node-Negative Early-Stage SABR

- **Most commonly used for tumors up to 5 cm in size.**
- **Prescription doses incompletely describe the actual delivered doses, which also depend strongly on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm. All of these must be considered when interpreting or emulating regimens from prior studies.**

# SABR (NCCN v3. 2022)

Table 2. Commonly Used Doses for SABR

| Total Dose | # Fractions | Example Indications |
|---|---|---|
| 25–34 Gy | 1 | Peripheral, small |
| 45–60 Gy | 3 | Peripheral tumors |
| 48–50 Gy | 4 | Central or peripheral tumors <4–5 cm |
| 50–55 Gy | 5 | Central or peripheral tumors |
| 60–70 Gy | 8–10 | Central tumors |

Table 3. Maximum Dose Constraints for SABR*

| OAR/Regimen | 1 Fraction | 3 Fractions | 4 Fractions | 5 Fractions |
|---|---|---|---|---|
| Spinal Cord | 14 Gy | 18 Gy (6 Gy/fx) | 26 Gy (6.5 Gy/fx) | 30 Gy (6 Gy/fx) |
| Esophagus | 15.4 Gy | 27 Gy (9 Gy/fx) | 30 Gy (7.5 Gy/fx) | 105% of PTV prescription^ |
| Brachial Plexus | 17.5 Gy | 24 Gy (8 Gy/fx) | 27.2 Gy (6.8 Gy/fx) | 32 Gy (6.4 Gy/fx) |
| Heart/ Pericardium | 22 Gy | 30 Gy (10 Gy/fx) | 34 Gy (8.5 Gy/fx) | 105% of PTV prescription^ |
| Great Vessels | 37 Gy | NS | 49 Gy (12.25 Gy/fx) | 105% of PTV prescription^ |
| Trachea & Proximal Bronchi | 20.2 Gy | 30 Gy (10 Gy/fx) | 34.8 Gy (8.7 Gy/fx) | 105% of PTV prescription^ |
| Rib | 30 Gy | 30 Gy (10 Gy/fx) | 40 Gy (10 Gy/fx) | NS |
| Skin | 26 Gy | 24 Gy (8 Gy/fx) | 36 Gy (9 Gy/fx) | 32 Gy (6.4 Gy/fx) |
| Stomach | 12.4 Gy | NS | 27.2 Gy (6.8 Gy/fx) | NS |

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^for central tumor location. NS = not specified

# Principles of Radiation Therapy for Small cell lung cancer

## Definitive RT for limited disease:

Simulation, planning and delivery similar to NSCLC

ENI may be considered (No ENI in current trials: RTOG 0538, EORTC 08072)

Dose: 45 Gy (1.5 Gy bid) or **56-70** Gy (1.8-2.0 Gy qd)

## Prophylactic cranial irradiation (PCI)

30Gy / 15 Fx or
25Gy / 10 Fx

## Consolidative thoracic RT

Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC with good response to systemic therapy. Dosing may be individualized within the range of 30 Gy/ 10 Fx to 60 Gy/ 30 Fx.

# Acronym

- 3D-CRT: 3D Conformal Radiation Therapy
- CCRT: Concurrent chemoradiotherapy
- CT: computed tomography
- CTV: Clinical Target Volume
- DVH: dose-volume histogram
- ENI: elective nodal irradiation
- Fx: fraction
- GTV: Gross Tumor Volume
- HDR: High dose rate
- IGRT: Image-Guided Radiation Therapy
- IMRT: Intensity Modulated Radiation Therapy
- LDR: Low dose rate
- MRI: Magnetic Resonance Image
- PET: Positron Emission Tomography
- PTV: Planning Target Volume
- RT: Radiation Therapy
- SABR: Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
- BED: Biologically effective dose

# References:


- (*) Douillard, Jean-Yves, et al. "Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non–small-cell lung cancer treated with adjuvant chemotherapy: The Adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial." *International Journal of Radiation Oncology* Biology* Physics* 72.3 (2008): 695-701.
- (**) Lally, Brian E., et al. "Postoperative radiotherapy for stage II or III non–small-cell lung cancer using the surveillance, epidemiology, and end results database." *Journal of clinical oncology* 24.19 (2006): 2998-3006.
- (***) Ung, Y., et al. "An Ontario Clinical Oncology Group (OCOG) randomized trial (PET START) of FDG PET/CT in patients with stage III non-small cell lung cancer (NSCLC): Predictors of overall survival." *Journal of Clinical Oncology* 29.15_suppl (2011): 7018-7018
- (****) Cox, James D., Joe Y. Chang, and Ritsuko Komaki, eds. Image-Guided Radiotherapy of Lung Cancer. CRC Press, 2007.