Provincial Non-Small Cell Lung Cancer Treatment Guidelines

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Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Benefits and risk of the proposed should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

SCREENING

Screening low dose CT chest showed mortality improvement however there are many unanswered questions such as identification of at risk population, duration of follow-up and incorporation of smoking cessation program. Canadian Partnership Against Cancer is currently working on publishing lung cancer screening guidelines for the provinces to implement.

WORK-UP

1. Biopsy: For peripheral lesion consider CORE biopsy. For central lesion consider bronchoscopy/endobronchial ultrasound guided (EBUS) or mediastinoscopy. Goal of the biopsy is obtain maximal amount of tissue for immunohistochemical stains and molecular studies.
2. Molecular studies: Currently EGFR and ALK mutation in non-squamous carcinoma for stage IIIB and stage IV is funded by SCA.
3. History & Physical Exam, Performance status, Weight loss.
4. Basic Labs: CBC, Renal Panel, LFTs.
5. CT chest and upper abdomen.
6. PET/CT
7. Mediastinal lymph node staging after CT and PET/CT: Consider work-up for central located tumour or identifiable non-bulky lymph nodes with EBUS or mediastinoscopy.
8. CT/MRI brain as clinically indicated and consider if stage II or higher.
9. Bone scan as clinically indicated.
10. PFTs if surgery or chest radiotherapy is considered.

LOCAL AND OPERABLE DISEASE

1. Lobectomy and mediastina lymph node dissection (with minimum of six lymph nodes of stations) is the CURRENT standard of care.

2. Minimal surgical resection (segmentectomy or wedge resection)
   - For impaired PFTs or significant comorbidities and in small peripheral tumours less than 2 cm.

3. External beam radiation with curative intent OR stereotactic radiosurgery with curative intent
   - For medically inoperable or those who decline surgery.
   - Radiation dose 66-70Gy. Hypofractionated schedule of 60Gy in 20 # can be used in selected cases.

4. Adjuvant chemotherapy post-surgery
   - Consider if tumour 4 cm or greater OR lymph node are positive.
   - Cisplatin + Vinorelbine x 4 cycles (See Appendix)
   - If unable to tolerate Cisplatin consider Carboplatin + Paclitaxel x 4 cycles (See Appendix)

5. Positive margin post-surgery
   - Re-resection if feasible for positive margin.
   - If re-resection not possible for positive margin, 60-66Gy external beam radiation to tumour bed.

6. Incidental N2 disease post-surgery
   - After adjuvant chemotherapy
   - Consider adjuvant EBRT, 50-54Gy to area of resected N2 disease with no gross residual disease. 60-66Gy to any gross residual disease.

LOCALLY ADVANCED DISEASE

1. Induction chemo-RT → surgery
   - Highly selected patients, upfront resectable, stage IIIA disease, non-bluky single mediastinal lymph node (lymph node size less than 2 cm).
   - Superior sulcus/chest wall tumour.
   - Induction chemoradiation: Cisplatin 50 mg/m2 iv d1, 8, 29 and 36 + Etoposide 50 mg/m2 iv d1-5 and 29-33. Radiotherapy 45Gy- 60Gy in 1.8 to 2Gy per fraction.
   - Surgical resection 3-5 weeks later
   - Consider adjuvant chemotherapy: Cisplatin 50 mg/m2 iv d1, 8, 29 and 36 + Etoposide 50 mg/m2 iv d1-5 and 29-33
   - If unable to use cisplatin → Weekly Carboplatin AUC 2 + Paclitaxel 45 mg/m2 weekly with RT followed by surgery and 2 cycles of Carboplatin AUC 6 + Paclitaxel 200 mg/m2 as consolidation chemotherapy.

2. Concomitant chemoradiation (standard of care)
   - Cisplatin 50mg/m2 d 1, 8 + Etoposide 50mg/m2 d 1-5 every 4 weeks x 4 with RT cycles OR Weekly Carboplatin AUC 2 + Paclitaxel 45 mg/m2 weekly with RT followed by 2 cycles of Carboplatin AUC 6 + Paclitaxel 200 mg/m2 as consolidation chemotherapy OR Cisplatin 80mg/m2 d 1 + Vinorelbine 20 mg/m2 d 1, 8 every 4 weeks with RT x 4 cycles.
   - EBRT 60-66Gy to gross disease. Preferably with cycle-1 of chemotherapy.

3. Chemotherapy +/- followed by sequential radiation
   - For patients in whom radical radiation can not be delivered concurrently upfront due to technical or medical reasons.
   - Platinum based doublets regimens.
   - EBRT 60-66Gy to gross disease.

4. Radiation alone with a radical intent
   - Only for patients with contraindications for chemotherapy.
   - EBRT 66Gy-70Gy to gross disease.

ADVANCED / METASTATIC DISEASE

1. Solitary brain metastasis on MRI
   - Surgical resection may be considered of solitary metastasis followed by WBRT (Example, 36Gy in 12#)
   - WBRT followed by Stereotactic boost is also a reasonable option.
   - Lung disease may be treated as deemed appropriate by multidisciplinary team.

2. Systemic therapy
   - 1st line: Platinum based doublet or EGFR inhibitor (if EGFR mutation positive) or ALK inhibitor (if ALK mutation positive). Consider maintenance therapy after 4 to 6 cycles of 1st line doublet chemotherapy with Pemetrexed.
   - 2nd line: Single agent chemotherapy OR Immunotherapy with Nivolumab (squamous histology) OR EGFR inhibitors (if not used earlier and EGFR mutation is positive) OR ALK inhibitor (if ALK mutation is positive).
   - 3rd line: Single agent chemotherapy OR Immunotherapy with Nivolumab (squamous histology) OR EGFR inhibitors (if not used earlier and EGFR mutation is positive) OR ALK inhibitor (if not used earlier and ALK mutation is positive).

     Note: Use Pemetrexed only in non-squamous histology. Use of Bevacizumab (non-squamous histology) as first line and Ramucirumab as second line with Docetaxel has shown minimal overall survival improvement.

3. Palliative RT for symptoms or impending findings on CT likely to pose problems if left alone.
   - Multiple dose schedules can be used based on clinical scenario. 8Gy in 1#, 20Gy in 5#, 30Gy in 10#, 36Gy in 12#, 40Gy in 16# are all reasonable options if RT is delivered alone.

FOLLOW UP
- In patients treated with curative intent, perform a history and physical examination every 3-6 months for the first 3 years, every 6-12 months for the next 2 years, annually thereafter.
- In patients who might be candidates for additional treatment on relapse or progression, Chest X-ray or CT chest may be performed every 3-6 months for the first 2 years and then annually, although there is currently no randomized evidence to justify this approach.
- Routine use of blood tests, PET scanning, sputum cytology, tumour markers and bronchoscopy should only be performed as clinically indicated.

Appendix (adjuvant chemotherapy for **4 cycles**)

1	Cisplatin 75 to 80mg/2 Day 1 + Vinorelbine 25 mg/m2 Day 1, 8	Every 21 days
2	Cispaltin 50mg/m2 Day 1, 8 + Vinorelbine 25mg/m2 Day 1, 8, 15, 22	Every 28 days
3	Carboplatin AUC 6 Day 1+ Paclitaxel 200mg/m2 Day 1	Every 21 days

NOTE: Most patients do not tolerate day 22 of vinrolebine (can omit) and paclitaxel dose can be reduced to 175mg/m2.