Non-Small Cell Lung Cancer

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Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

INITIAL EVALUATION

- Pathology[1] consistent with non-small cell lung cancer
- History and physical
- Chest x-ray
- Laboratory studies to include hematologic and full chemistry panels
- CT chest and upper abdomen
- ECG if history of heart disease

T1-3, N0 (Stage I)
T1-3, N1 (Stage II)

PET scan (optional for T1,N0)

CLINICAL STAGE

T1-2, N0 (Stage I)

Central lesion?

No → See Page 2, central lesion with negative mediastinal nodes or peripheral lesion

Yes

T1-2, N1 (Stage II)

PRE-TREATMENT EVALUATION

- Bronchoscopy
- Mediastinoscopy or endobronchial ultrasound-fine needle aspiration (EBUS-FNA)
- Brain MRI for symptomatic patients T1-2, N0
- Pulmonary function tests

Negative mediastinal nodes → See Page 2, central lesion with negative mediastinal nodes or peripheral lesion

Positive mediastinal nodes

- T1-3, N2 (Stage IIIA) → See Page 4, box **B**
- T1-3, N3 (Stage IIIB) → See Page 5, box **C**

T3, N0 (Stage IIB) → See Page 3, box **A**

T3, N1 (Stage IIIA) → See Page 3, box **A**

[1] Consider MD Anderson approved Thoracic biomarkers https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-biomarkers-web-algorithm.pdf

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PRE-TREATMENT EVALUATION

Central lesion with negative mediastinal nodes or peripheral lesion[1]

Medically operable?

No
- Stereotactic body radiation therapy
- Conventional definitive radiation therapy
- Consider local ablation therapy

Yes
- Surgical exploration and resection

POST-OPERATIVE SURGICAL FINDINGS

T1, N0 (Stage IA)
- Margins negative → Observe **or** Adjuvant chemotherapy in high risk patients[2]
- Margins positive → Reresection **or** Consider concurrent chemotherapy/ radiation therapy → Observe **or** Adjuvant chemotherapy in high risk patients[2]

T2, N0 (Stage 1B) T1-2, N1 (Stage IIA-B)
- Margins negative → Observation (excluding T1-2, N1) **or** Adjuvant chemotherapy[3]
- Margins positive → Consider re-resection followed by Post-op adjuvant therapy: radiation therapy[4] followed by chemotherapy[3] or chemotherapy[3] followed by radiation therapy[4]

T1-2, N2-3 (Stage IIIA-B)
- Margins negative and no extracapsular spread → Adjuvant chemotherapy[3] followed by radiation therapy[4]
- Margins positive or extracapsular spread → Post-op adjuvant therapy: radiation therapy[4] followed by chemotherapy[3] or chemotherapy[3] followed by radiation therapy[4]

Unresectable
- Radiation therapy or chemoradiation[5] for selected patients

Surveillance, see Page 7

[1] In case of small (less than or equal to 2 cm) peripheral lesions that will undergo resection with a complete mediastinal and hilar lymph node dissection, integrated PET/CT has a high negative predictive value. EBUS-FNA is recommended but not required.
[2] High risk patients display poorly differentiated tumors, vascular invasion, wedge resection, tumors greater than 4 cm, visceral pleural involvement, and unknown lymph node status
[3] Platinum-based doublet therapy for selected patients
[4] Radiation therapy alone or concurrent chemoradiation
[5] Either concurrent radiation therapy followed by 2 cycles of posterior chemotherapy or 2 cycles of induction chemotherapy followed by concurrent chemoradiation

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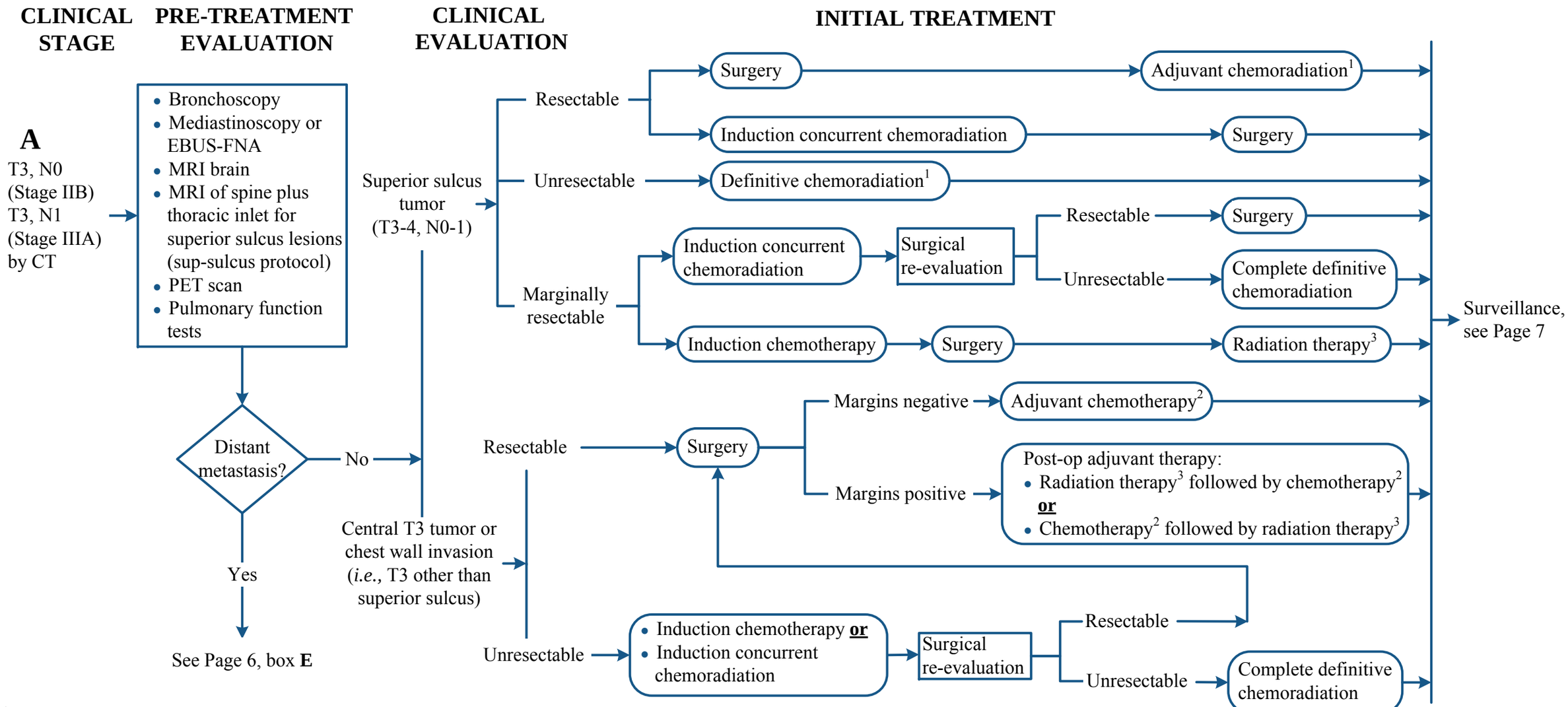

[1] Either concurrent radiation therapy followed by 2 cycles of posterior chemotherapy or 2 cycles of induction chemotherapy followed by concurrent chemoradiation
[2] Platinum-based doublet therapy for selected patients
[3] Radiation therapy alone or concurrent chemoradiation

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CLINICAL STAGE

B

T1-3, N2 (Stage IIIA)

PRE-TREATMENT EVALUATION

- MRI brain
- PET scan
- Pulmonary function tests

- Pleural/pericardial effusion → See Page 6, box **D**
- Distant metastasis → See Page 6, box **E**
- N3 disease → See Page 5, box **C**
- Clinical N2 disease

- Bronchoscopy
- EBUS-FNA
- Consider mediastinoscopy if EBUS-FNA negative

INITIAL AND ADJUVANT TREATMENT

- N2, N3 nodes negative → Surgical resection with mediastinal lymph node dissection
  - N0-1 → Adjuvant chemotherapy; Surveillance if T1-2, N0
  - N2-3 → Adjuvant chemotherapy[1] followed by radiation therapy[2]
  - Margins positive → Post-op adjuvant therapy: Radiation therapy[2] followed by chemotherapy[3] **or** Chemotherapy[3] followed by radiation therapy[2]
- N2 nodes positive
  - Induction chemotherapy versus induction chemoradiation → Surgical re-evaluation
    - Unresectable → Complete definitive chemoradiation
    - Resectable → Surgical resection with adjuvant radiation, if eligible
  - Definitive chemoradiation[4]
- N3 nodes positive → See Page 5, box **C**
- Metastasis → See Page 6, box **E**

→ Surveillance see Page 7

[1] Concurrent chemoradiation for gross residual disease
[2] Radiation therapy alone or concurrent chemoradiation
[3] Platinum-based doublet therapy for selected patients
[4] Either concurrent radiation therapy followed by 2 cycles of posterior chemotherapy or 2 cycles of induction chemotherapy followed by concurrent chemoradiation

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Non-Small Cell Lung Cancer

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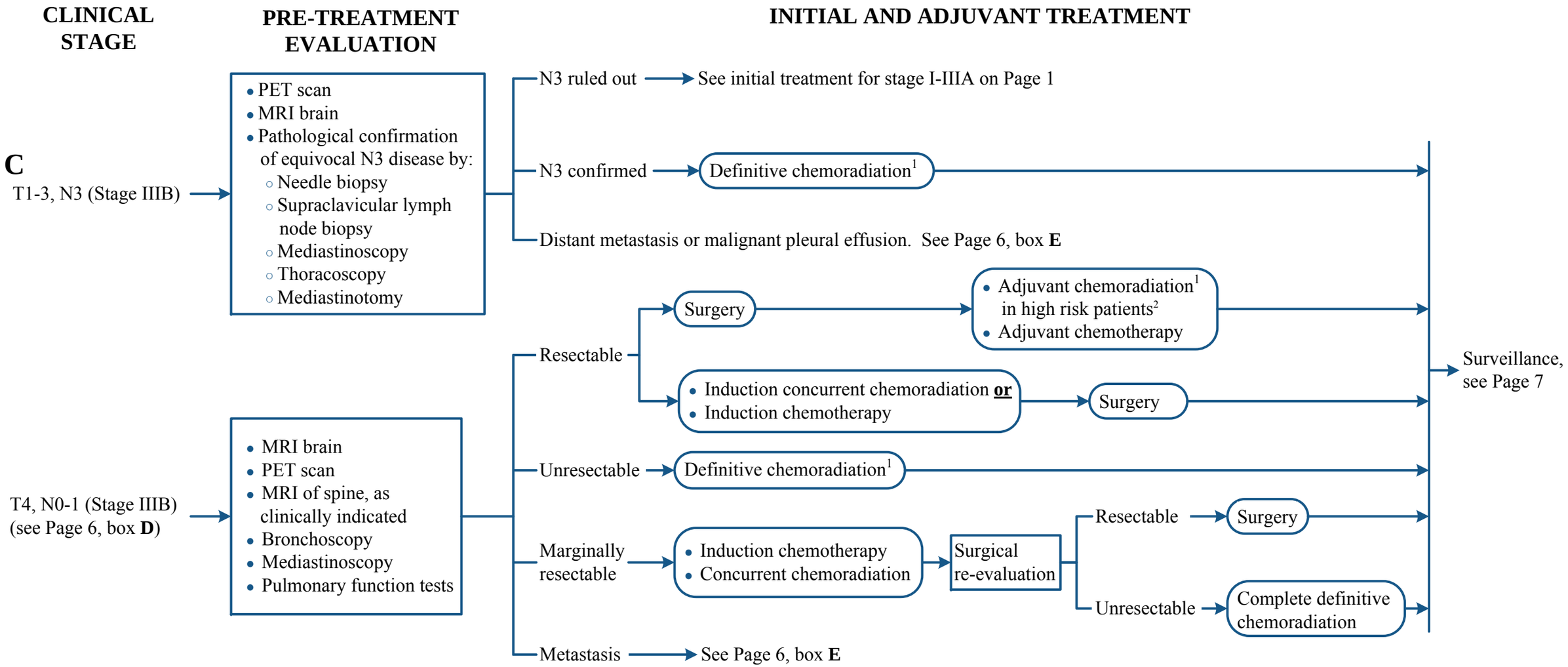

[1] Either concurrent radiation therapy followed by 2 cycles of posterior chemotherapy or 2 cycles of induction chemotherapy followed by concurrent chemoradiation
[2] High risk patients display poorly differentiated tumors, vascular invasion, wedge resection, tumors greater than 4 cm, visceral pleural involvement, and unknown lymph node status

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CLINICAL STAGE	PRE-TREATMENT EVALUATION	INITIAL AND ADJUVANT TREATMENT
D Pleural/ pericardial effusion	• Thoracentesis or pericardiocentesis, if indicated • Thoracoscopy, if thoracentesis indeterminate	Benign → Treatment according to T and N stage Malignant → • Treatment for distant metastasis or malignant pleural effusion • If pleural effusion is recurrent, consider either pleurodesis or indwelling pleural catheter
E Metastasis Stage IV		Solitary brain metastasis → • Resect brain lesion with or without whole brain radiation therapy **or** • Stereotactic radiosurgery with or without whole brain radiation therapy Solitary metastasis elsewhere → Consider local ablation surgery, radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT) Multiple metastatic disease No metastasis → Workup as clinically indicated → Systemic chemotherapy with or without palliative radiation therapy (see principles of radiation therapy and chemotherapy) → Surveillance, see Page 7

Non-Small Cell Lung Cancer

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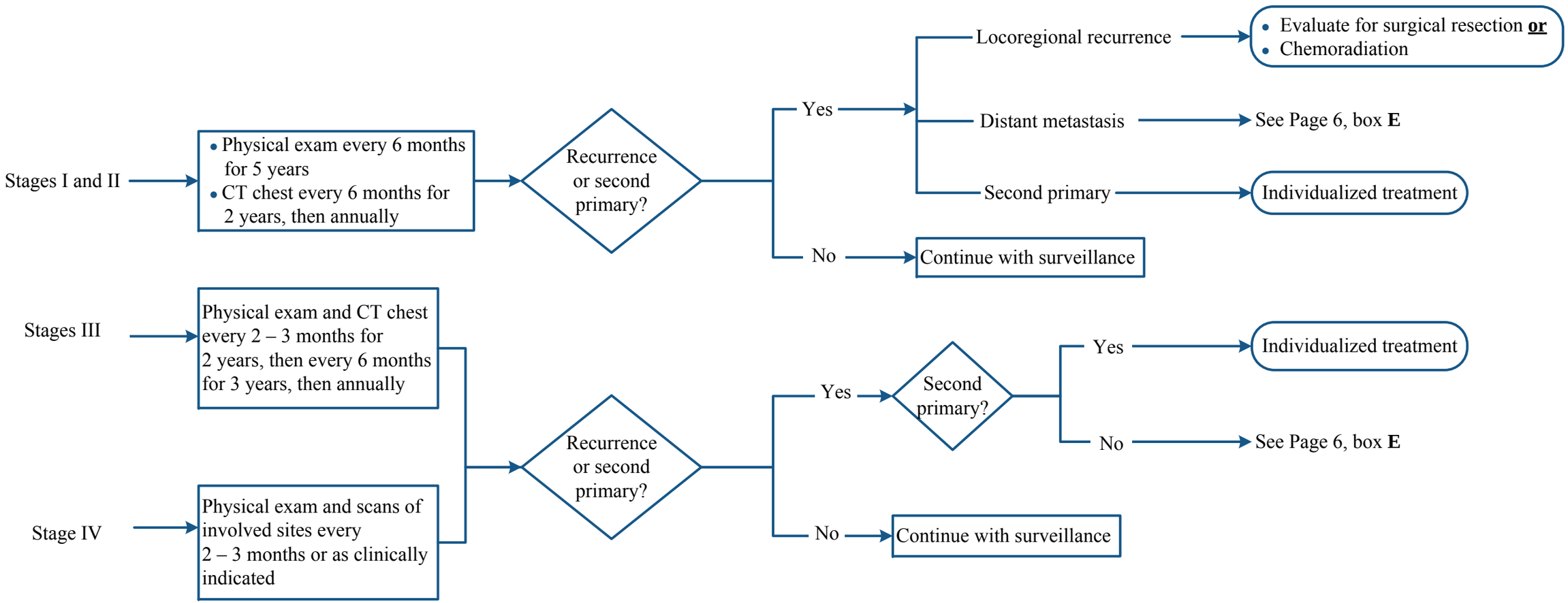
SURVEILLANCE

THERAPY FOR RECURRENCE AND METASTASIS



Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF CHEMOTHERAPY FOR PATIENTS WITH STAGE III DISEASE RECEIVING CHEMORADIATION

- Patients with inoperable stage III disease should be offered definitive concurrent chemoradiation with curative intent, which provides superior survival over radiation therapy alone.
- Concurrent chemoradiation should be used only in patients with a suitable performance status (PS) who have not had excessive weight loss prior to starting treatment (*i.e.*, PS 0-1 and with less than or equal to 5 – 10% weight loss).
- Patients in need of immediate radiation therapy for symptom palliation (*i.e.*, those with symptomatic bronchial obstruction, superior vena cava (SVC) obstruction, pain, etc.) should begin treatment with concurrent chemoradiation, followed by 2 additional cycles of chemotherapy upon completion of their concurrent chemoradiation.
- For patients who do not need immediate radiation therapy for symptom palliation, acceptable sequencing of their chemoradiation is as follows:
  - 2 cycles of induction chemotherapy, followed by concurrent chemoradiation **or**
  - Concurrent chemoradiation, and followed by 2 additional cycles of chemotherapy upon completion of their concurrent chemoradiation ("posterior chemotherapy")
- Acceptable chemotherapy regimens for induction and/or "posterior" chemotherapy include:
  - Paclitaxel 200 mg/m^2 IV plus carboplatin AUC 6 IV, every 21 days
  - Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV, every 21 days
  - Docetaxel 75 mg/m^2 IV plus carboplatin AUC 6 IV, every 21 days
  - Docetaxel 75 mg/m^2 IV plus cisplatin 75 mg/m^2 IV, every 21 days
  - Cisplatin 60 – 80 mg/m^2 IV day 1 plus etoposide 80 – 120 mg/m^2 IV days 1 – 3, every 21 days
- Acceptable chemotherapy regimens for the concurrent chemoradiation phase of treatment include:
  - Paclitaxel 50 mg/m^2 IV plus carboplatin AUC 2 IV, weekly during radiation therapy
  - Docetaxel 20 – 25 mg/m^2 IV plus carboplatin AUC 2 IV, weekly during radiation therapy
  - Docetaxel 20 – 25 mg/m^2 IV plus cisplatin 20 – 25 mg/m2 IV, weekly during radiation therapy
  - Cisplatin 50 mg/m^2 IV days 1, 8 and days 29, 36 plus etoposide 50 mg/m^2 IV days 1 – 5 and days 29 – 33
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for temporary and manageable toxicities, such as esophagitis or myelosuppression, should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks in potentially curable patients. Patients should be evaluated at least once per every 5 fractions to monitor weight changes and toxicity.

Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF CHEMOTHERAPY FOR PATIENTS WITH STAGES IIIB (EFFUSION) AND IV DISEASE

First-line chemotherapy

- Platinum-based combination chemotherapy prolongs survival and improves symptoms and quality of life compared to best supportive care for patients with acceptable PS.
- Platinum-based combination chemotherapy should be offered to all patients with PS of 0 – 1, and to selected patients with PS of 2.
- Patients with PS of 3 – 4 benefit little, if any, from cytotoxic chemotherapy.
- Elderly patients with acceptable PS should be offered chemotherapy, either combination platinum-based therapy or single-agent therapy (depending upon patient's age and co-morbid conditions).
- Most platinum-based combination regimens yielded similar response rates (25% – 35%) and survival (median: 8 – 10 months; 1 year: 30% – 40%; 2 year: 10% – 15%).
- Acceptable first-line chemotherapy regimens include:
  - Paclitaxel 200 mg/m^2 IV plus carboplatin AUC 6 IV, every 21 days
  - Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV, every 21 days
  - Docetaxel 75 mg/m^2 IV plus carboplatin AUC 6 IV, every 21 days
  - Docetaxel 75 mg/m^2 IV plus cisplatin 75 mg/m^2 IV, every 21 days
  - Gemcitabine 1,000 mg/m^2 IV days 1, 8 (plus or minus day 15) plus cisplatin 75 mg/m^2 IV day 1, every 21 days (if using day 1/8 gemcitabine schedule) or every 28 days (if using day 1/8/15 gemcitabine schedule)
  - Gemcitabine 1,200 mg/m^2 IV days 1, 8 plus carboplatin AUC 5 IV day 1, every 21 days
  - Vinorelbine 25 – 30 mg/m^2 IV days 1, 8, and 15 plus cisplatin 80 – 100 mg/m^2 IV day 1, every 28 days
  - Cisplatin 60 – 80 mg/m^2 IV day 1 plus etoposide 80 – 120 mg/m^2 IV days 1 – 3, every 21 days
  - Pemetrexed 500 mg/m^2 IV day 1 plus carboplatin AUC 6 IV day 1, every 21 days
  - Paclitaxel 150 – 200 mg/m^2 IV plus carboplatin AUC 6 IV plus bevacizumab 15 mg/kg IV every 21 days for metastatic non-small cell lung cancer in patients that have non-squamous cell histology
  - Crizotinib[1] if EML4-ALK positive
  - Erlotinib if EGFR mutation present
  - Afatinib[1] if EGFR mutation present
- Patients with non-squamous tumors should have their tumor tested for EGFR mutation, KRAS mutation, and EML4-ALK translocation. Presence of these mutations is predictive of response to tyrosine kinase inhibitors (TKI) and can be used in guiding first-line and second-line chemotherapy in selected patients.

[1] Formulary restrictions may apply to this agent

Continued on Next Page

Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF CHEMOTHERAPY FOR PATIENTS WITH STAGES IIIB (EFFUSION) AND IV DISEASE (continued)

Second-line (and higher) chemotherapy

- Second-line chemotherapy prolongs survival and improves symptoms and quality of life compared with best supportive care in patients with acceptable PS.
- Second-line chemotherapy should be offered to all patients with PS of 0 – 1, and to selected patients with PS of 2.
- Patients with PS of 3 – 4 are unlikely to benefit from second-line chemotherapy.
- Elderly patients with acceptable PS should be offered second-line chemotherapy.
- Most single agents administered in the second-line setting yield similar response rates (10% partial response plus 30% stable disease) and survival (median: 8 months; 1 year: 20%).
- Second-line therapy should generally be given as sequential single agents. Acceptable second-line drugs include:
  - Docetaxel 75 mg/m^2 IV, every 21 days
  - Pemetrexed 500 mg/m^2 IV, every 21 days
  - Erlotinib 150 mg PO daily
  - Gemcitabine 1,000 mg/m^2 IV days 1, 8, and 15, every 28 days
  - Vinorelbine 25 – 30 mg/m^2 IV days 1, 8, and 15, every 28 days
  - Crizotinib[1] if EML4-ALK positive
  - Erlotinib if EGFR mutation present
  - Ceritinib[1] if EML4-ALK positive
  - Ramucirumab 10 mg/kg IV plus docetaxel 75 mg/m^2 IV, every 21 days
- If available, patients with non-squamous tumors should have their tumor tested for EGFR mutation, KRAS mutation, and EML4-ALK translocation. Presence of these mutations is predictive of response to tyrosine kinase inhibitors (TKI) and can be used in guiding first-line and second-line chemotherapy in selected patients.

[1] Formulary restrictions may apply to this agent

Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF RADIATION THERAPY

- Treatment of patients with potentially curable non-small cell lung cancer (NSCLC) (*i.e.*, stages I – III) should be made after multidisciplinary consultation with a surgical, radiation and medical oncologist. Decisions about radiation therapy should account for patient's stage, PS, tumor bulk, underlying pulmonary function, and potential overlap with normal tissue in the proposed radiation field.
- Patients with medically inoperable stage I or II NSCLC, as well as patients with stage III disease who are not candidates for chemoradiation, should be treated with radiation therapy alone with curative intent, to a total dose of 66 – 74 Gy at 200 cGy per fraction. Stereotactic body radiation therapy can be used for medically inoperable Stage I NSCLC patients.
- Patients with inoperable stage III disease should be offered definitive concurrent chemoradiation with curative intent as follows:
  - Concurrent chemoradiation should be used only in patients with a suitable PS who have not had excessive weight loss prior to starting treatment (*i.e.*, PS 0 – 1 and with less than or equal to 5 – 10% weight loss).
  - The dose of radiation therapy for these patients is 60-70 Gy at 180 – 200 cGy per fraction in 30-35 fractions. The V20 for the total lung should be kept below 35% and total mean lung dose should be kept below 20 Gy considered for patients whose volumes exceed 40%.
  - Patients in need of immediate radiation therapy for symptom palliation (*i.e.*, those with symptomatic bronchial obstruction, superior vena cava (SVC) obstruction, pain, etc) should begin treatment with concurrent chemoradiation, followed by 2 additional cycles of chemotherapy upon completion of their concurrent chemoradiation.
- For patients who do not need immediate radiation therapy for symptom palliation, acceptable sequencing of their chemoradiation is as follows:
  - 2 cycles of induction chemotherapy, followed by concurrent chemoradiation **or**
  - They may begin with concurrent chemoradiation, and then follow that with 2 additional cycles of chemotherapy upon completion of their concurrent chemoradiation
  - See "Non-Small Cell Lung Cancer Principles of Chemotherapy for Patients with Stage III Disease" for details of chemotherapy drugs, dosing and schedule.
  - In patients who are to receive induction chemotherapy prior to beginning radiation or chemoradiation, consideration should be given to obtaining a baseline planning CT prior to starting induction chemotherapy.
- Patients should be well-immobilized for treatment (e.g., Vac-Loc bag, wingboard and T-bar). Fusion with PET/CT, if available, may help to elude involved lymph nodes and differentiate atelectasis from tumor involvement.
- Suggested treatment margins are gross tumor volume to clinical target volume (CTV) of 0.8 cm, and CTV to primary tumor volume of 0.5-1 cm. However, treatment plans should be individualized using 4 dimensional CT as it may be necessary to modify these suggested margins depending upon the specifics of the case.
- In general, elective nodal irradiation should be avoided as it may unnecessarily increase the amount of normal lung tissue in the radiated field.
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for temporary and manageable toxicities, such as esophagitis or myelosuppression, should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks in potentially curable patients. Patients should be evaluated at least once per every 5 fractions to monitor weight changes and toxicity.

Continued on Next Page

Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF RADIATION THERAPY (continued)

- In patients receiving postoperative radiation therapy because of involved mediastinal nodes or resection margins which are close or positive, discussion with the thoracic surgeon and pathologist is helpful in designing appropriate target volumes. Recommended post-operative radiation therapy doses are as follows:
  - N2/N3 nodes 50 Gy
  - T4 primary 50 Gy
  - Extranodal extension 54 Gy
  - Positive margins 60 Gy
  - Gross residual disease 60 – 74 Gy (possibly with concurrent chemotherapy)
- ^{60}Cobalt and orthovoltage beams are not appropriate for curative treatment due to the possibility of under-dosing, particularly of small tumors or tumor extensions.
  In addition , it may be preferable to avoid high-energy photons and instead use lower energies (4 – 10 MeV) in most patients. High-energy photons (15MeV, 18MeV, etc) may be preferable when used to treat larger gross tumor volumes surrounded by consolidated and/or atelectatic lung tissue, bulky lymphadenopathy or large blood vessels, thus achieving a better dose distribution and also an improved therapeutic ratio.

Note: Consider Clinical Trials as treatment options for eligible patients. This algorithm is based on TNM Staging VI.

PRINCIPLES OF SURGICAL RESECTION

- It is strongly recommended that determination of resectablility be performed by thoracic surgical oncologists who perform lung cancer surgery as a prominent part of their practice.
- All patients should undergo pulmonary function testing if considered for surgical resection.
- Patients with an FEV1 less than 70% of predicted should have xenon function studies.
- Patients with a predicted post-resection FEV1 below 35% should have complimentary exercise oxygen consumption testing.
- Patients with enlarged mediastinal nodes by CT scan or PET positive nodes should undergo mediastinal node biopsy prior to thoracotomy either by transthoracic FNA ultrasound guided biopsies via bronchoscopy or esophagoscopy techniques, or mediastinoscopy.
- Patients with co-morbidities require a detailed medical and anesthesia evaluations before surgery.
- All patients need to abstain from smoking a minimum of two weeks prior to thoracotomy. The use of nicotine replacement therapies is encouraged.
- The optimal surgery for non-small cell lung cancer is an anatomical lobectomy or pneumonectomy. In selected patients unable to undergo a lobectomy or pneumonectomy due to physiologic constraints, a more limited resection is an acceptable oncologic alternative.
- N1 and N2 node dissection and mapping should be performed on all patients undergoing a lung cancer resection. Complete node dissection should ideally be performed. When this is not feasible, a minimum of three N2 nodal stations should be sampled.
- Lung-sparing anatomic resections (*i.e.*, sleeve lobectomies) are preferred over pneumonectomies, provided that negative margins can be achieved.
- Lobectomies performed by minimal invasive techniques need to adhere to all of the oncologic principles of complete resection with negative margins and full nodal dissection.

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This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

DEVELOPMENT CREDITS

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