



GUIDELINES FOR THE MANAGEMENT OF LUNG CANCER

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CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF UNRESECTABLE NON-SMALL CELL LUNG CANCER

PURPOSE:

- To minimize the inappropriate practice variations.
- To justify the financial costs of therapy in relation to its outcome
- To clarify the optimal management of patients with unresectable disease
- To define what is important to patients, the quality or the quantity of survival in situations where palliation, not cure, is the goal.

Introduction:

Lung cancer remains worldwide a public health problem for both men and women. The impact on and cost of this disease to society are staggering. In the USA alone, an estimated 171,600 new cases were diagnosed and 159,900 deaths occurred in 1999. This death toll is greater than that attributed to colorectal, breast and prostate cancer (the second through fourth leading causes of cancer mortality) combined.

- Non small cell histologies account for approximately 80% of lung cancer cases.
- For clinical stage I and II patients, 5-year survival rates of approximately 40% are anticipated with standard surgical resection.
- 70% of patients with NSCLC present with advanced, poor-prognosis stage III & IV disease.
- Locoregionally advanced (stage III) and distant metastatic (stage IV) disease are generally approached differently.
- The 5-year survival rates for the former group (stage III) range from 5% to 30% depending on resectability and extent of disease. Fewer than 20% of such patients have disease that is resectable for cure at presentation.
- For patients with distant metastatic disease, median survival times with best available therapies are typically 6-10 months and most patients have died of cancer within 1-2 years of diagnosis.
- Best supportive care, radiation therapy, and chemotherapy are the most commonly applied options; surgery is used only in a very selective manner.
- Chemotherapy, ideally a platinum-based regimen is recommended for selected patients who have a good performance status with both unresectable, locally advanced, and metastatic NSCLC.
- In patients with unresectable stage III NSCLC, two or more cycles of Cisplatin-based chemotherapy with or followed by radiation has been proven to enhance survival (not more than 8 cycles); ongoing maintenance chemotherapy is of unproven benefit.
- Initial treatment with an investigational agent is appropriate, provided a standard regimen is then given if the disease does not respond after two cycles.
- Delaying chemotherapy until symptoms develop may negate the survival benefits of treatment.
- There is no proof that 2nd line chemotherapy improves survival in patients with nonresponding or progressive NSCLC.

Methods

1. Panel composition
2. Process overview
3. Literature review and data collection
4. Consensus development based on evidence
5. Guidelines and conflict of interest
6. Revision dates.

Diagnostic Evaluation of patients with advanced lung cancer

- History
- Physical examination
- Blood studies
 - CBC, Platelet
 - Chemistry (including Cr+Ca)

I- Staging Locoregional Disease

a- Chest x-ray and CT scan of chest → should include liver and both adrenals.

- To characterize the size and location of the primary tumor and its relationship to other thoracic structures.
- To identify pathologically enlarged hilar and mediastinal LN's (LN's > 1 cm).
- To identify satellite and other ipsilateral or contralateral pulmonary nodules.
- To identify potential metastasis to the liver and adrenal glands, both common metastatic sites.

b- Biopsy of mediastinal LN's (>1cm) found on CAT scan.

By mediastinoscopy and anterior mediastinostomy (Chamberlin Procedure).

CT scan sensitivity to detected pathologically enlarged LN's of 0.79 0 specificity 0.78 (a meta-analysis involving 42 studies).

For adenoca Sensitivity by CAT scan is 61%.

For Sq.cell ca Sensitivity 86% for both specificity is the same.

<u>Mediastinoscopy</u>	Sensitivity	87%
	Specificity	100%
+ve	predictive value	100%
-ve	predictive value	93%
	overall accuracy	95%

MRI

- Has not been demonstrated to improve the accuracy of nodal staging
- It may be useful for delineating the extent of direct tumor invasion into chest wall, Mediastinum and /or other structures.

Staging Distant Metastatic Disease

a- Bone

A bone scan should be performed only in symptomatic patients
Patients with elevated alkaline phosphatase and/or calcium.
9% to 15% with newly diagnosed NSCLC patients have bony metastasis at presentation.

b- Brain

- CT scan or MRI should be done only in symptomatic patients indicating CNS disease.
- Routine CT scan can detect metastasis in 3% to 8% in asymptomatic patients and potentially operable.
- In symptomatic patients with negative CT scan obtaining an MRI scan may be helpful.

c- Adrenal

- In potentially resectable patients, the finding of an isolated adrenal mass on CT scan examination requires biopsy to rule out metastasis.
- NSCLC metastasize to adrenal glands in 18% to 38% of cases.
- 2/3 of adrenal masses in NSCLC patients are benign adenomas.
- Needle biopsy of adrenal gland had 96% accuracy.
- MRI to differentiated benign vs malignant adrenal tumor gives high false-positive rate.
- PET scan for differentiation is still investigational.
- Nuclear a images using iodo cholesterol analogue gives better result (especially in benign lesion 100% sensitivity).
- No non invasive study has been identified that currently can replace adrenal biopsy.

d- Liver

- The finding of an isolated hepatic mass on CT scan requires a biopsy to rule out metastases in patient with potentially resectable lesion.
5% will have metastases
30% hepatic hemangioma / (atypical)hepatic cysts.

Treatment

A-The Role of Chemotherapy.

1- Stage III

- Chemotherapy in association with definitive thoracic irradiation is the treatment for selected patients with unresectable , locally advanced NSCLC (stage III).
- 5% survival with XRT alone 4% to 8%
- CALGB study
XRT arm 6%]
XRT + chemotherapy 17%] 5 y. survival
- The optional sequencing of chemotherapy and radiation is not definitively established (sequential v alternating v concurrent.)
- Controlled studies of concurrent chemotherapy with daily low dose less toxic administration of drugs have been documented to prolong survival compared with radiation.

2-StageIV NSCLC

- Chemotherapy improves median survival in patients with IV disease compared with best supportive care, but is not curative.

- 3 published metaanalysis indicate that Cisplatin based chemotherapy yield an improvement in median survival approximately 6-8 w in stage IV NSCLC.
- 2 recent studies include Cisplatin + Paclitaxel produced significant higher response rates and survival advantages compared with etoposide and Cisplatin. No survival advantage with higher doses of paclitaxel.
- Cisplatin and Vinorelbine combination is superior to Cisplatin and etoposide with 1 y. survival rates of 35% to 40%.

3- Patient Selection

- In both stage IIIB and stage IV, patients must have good performance status. ECOG 0,1 and possibly 2.
- Patients with stage III respond better than those of stage IV.
- Absence of weight loss
- Pretreatment factors
- Age
- Serum lactate dehydrogenase
- Hb level
- Leucocyte count
- Location and number of metastatic sites
- Cutaneous metastasis → poor prognosis.

4-Selection of Drugs

- Platinum based chemotherapy
- The best combination is not well defined Cisplatin or carboplatin + Vinorelbine or paclitaxel or Gemcitabine.
- Cisplatin dose
50 mg/m² to 120 mg/m².
Randomized trials using low dose (50 to 60 mg/m²) vs high dose (100 - 120 mg/m²) and very high dose 200mg/m² → have failed to prove a dose response effect but there was significant increased toxicity.

New agents

- Docetaxel alone or in combination with Cisplatin.
- CPT-11 alone or in combination with Cisplatin
- All are studied in phase I clinical trials only

4- Duration of therapy

Stage III NSCLC combination chemotherapy + radiotherapy.

Chemotherapy duration should be between 2 to 8 cycles.

2 cycles followed by definitive thoracic radiation

The role of post treatment surgery in initially unresectable patients is undefined

Stage IV NSCLC

No more than 8 cycles

Imaging studies after 2-4 cycles

5- Timing of Treatment

Chemotherapy may best be started soon after diagnosis of unresectable stage III. NSCLC delaying chemotherapy until performance status worsens or weight loss develops may negate the survival benefits of treatment.

6- Second Line Therapy

- There is no current evidence that second line chemotherapy improves survival in non responding or progressing patients with advanced NSCLC.
- 2nd line therapy may be used:
 - 1- As investigational protocol with good performance status.
 - 2- After an initial good response to the I" line chemotherapy with a long progression free interval off treatment.

B-Radiotherapy

Should be included in the treatment of unresectable stage III NSCLC in those with good performance status ECOG 0, 1,2. And those with adequate pulmonary function disease confined to the thoracic wall.

Patients with malignant effusion are not appropriate for definitive XRT.

Dose of XRT: 60 Gy in 1.8 to 2 Gy fractions.

- As palliative in metastatic bone and brain disease in stage IV disease.

C- Surgery

Role of Resection for Distant Metastasis

- In patients with controlled disease outside brain and has isolated cerebral metastasis in a resectable area.
- Resect followed by whole - brain radiotherapy is superior to whole brain radiotherapy.
- Combined resection of lung primary (stage I and II) along with with adrenalectomy has been associated with long term survival in a small number of patients.
- No data concerning resection of lung primary and single liver metastatic lesion.

Surveillance and Follow Up Care for Patients with Advanced Lung Cancer

- No consensus has emerged for unresectable NSCLC.
- The great majority of patients with unresectable stage III and IV disease either will not achieve a complete remission, or, if achieved, its duration will be short.
- Intensity of follow-up frequency did not have an impact on survival (2 retrospective studies).

1- History and Physical Examination

- For patients treated with curative intent, in the absence of symptoms, a history and physical examination should be performed every 3 months during the first 2 years, every 6 months thereafter through year 5; and yearly thereafter.

2- Chest Radiographs

- For patients treated with curative intent a yearly chest-x -ray to evaluate for potentially curable second primary cancers may be reasonable.
- Chest -x-ray detect 78.8% of the asymptomatic recurrences.

3- Other Diagnostic Studies

- No role for routine studies in asymptomatic patients, only performed as indicated by the patients symptoms.