TREATMENT
(Prof. A. Riccardi)
TREATMENT OF LUNG CARCINOMA

* overall treatment approach to pts with LC formulated after:
  - histologic diagnosis, and
  - anatomic and physiologic staging
SUMMARY OF TREATMENT APPROACH
NON SMALL CELL LUNG CARCINOMA

Summary of treatment approach. I.
Stages IA, IB, IIA, IIB and some IIIA

* Stages IA, IB, IIA, and IIB = surgical resection;
* Stage IIIA with "minimal N2 involvement" (discovered at thoracotomy or mediastinoscopy) = surgical resection with complete mediastinal lymph node dissection;
  - Consider neoadjuvant CT;
  - Postoperative RT for pts with N2 disease (if no neoadjuvant CT given);
  - Discussion of risks / benefits of adjuvant CT with individual pts;
* Potential curative RT for "nonoperable" pts
NON SMALL CELL LUNG CARCINOMA

Summary of treatment approach. II.

Stage IIIA with selected types of stage T3

* tumors with chest wall invasion (T3) = en bloc resection of tumor with involved chest wall (± postoperative RT);

* superior sulcus (Pancoast's, T3) tumors = preoperative RT (30-45 Gy) → en bloc resection of involved lung and chest wall (± postoperative RT or intraoperative brachytherapy)

* proximal airway involvement (< 2 cm from carina, T3) without mediastinal nodes = sleeve resection (preserving distal normal lung) or pneumonectomy
NON SMALL CELL LUNG CARCINOMA
Summary of treatment approach. III.
Stages IIIA "advanced, bulky, clinically evident N2" (discovered preoperatively) and IIIB disease includible in tolerable RT port

* curative potential RT + CT (with reasonable PS and general medical condition) or RT alone (if otherwise);
* consider neoadjuvant CT and surgical resection for IIIA disease with advanced N2 involvement
NON SMALL CELL LUNG CARCINOMA

Summary of treatment approach. IV.
Stage IIIB with carinal invasion (T4) but no N2 involvement.

* consider pneumonectomy with tracheal sleeve resection with direct reanastomosis to contralateral mainstem bronchus
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Figure 4. Right upper lobe bronchial sleeve resection. Tumor at origin of right upper lobe bronchus prevents standard lobectomy. Resection of right main and intermediate bronchial sleeve allows for adequate margins around tumor. Bronchial reanastomosis preserves uninvolved right lower and middle lobes.
NON SMALL CELL LUNG CARCINOMA
Summary of treatment approach. V.
More advanced stage IIIIB and stage IV disease

* RT to symptomatic local sites;
* CT for ambulatory pts;
* chest tube drainage of large malignant pleural effusions;
* consider resection of primary tumor and isolated brain or adrenal metastases
SMALL CELL LUNG CARCINOMA
Summary of treatment approach

* **limited stage** (good performance status) = combination CT + chest RT;

* **extensive stage** (good performance status) = combination CT;
  - complete responders *(all stages)*: prophylactic cranial RT;

* poor-performance-status pts *(all stages)*:
  - modified-dose combination CT;
  - palliative RT
LUNG CARCINOMA
All pts

* radiotheraphy for brain metastases, spinal cord compression, weight-bearing lytic bony lesions, symptomatic local lesions (nerve paralyses, obstructed airway, hemoptysis if not responding to CT);
* appropriate diagnosis and treatment of other medical problems and supportive care;
* encouragement to stop smoking;
* entrance into clinical trial
TREATMENT
OF NON SMALL CELL LUNG CARCINOMA
TREATMENT OF NON SMALL CELL LUNG CARCINOMA LOCALIZED OR LOCALLY ADVANCED DISEASE SURGERY
NSCLC, STAGE I

STAGE IA
T1 N0 M0
- T ≤ 3 cm
- no infiltration of lobar bronchus

STAGE IB
T2 N0 M0
one of following:
- T > 3 cm;
- T invading main bronchus > 2 cm from carina;
- T invading visceral pleura;
- T with incomplete lung atelectasis

N0 = no lymph node involvement
M0 = no distant metastasis
NSCLC, STAGE II

STAGE IIA
T1 N1 M0

- T ≤ 3 cm
- no infiltration of lobar bronchus

N1: regional lymph node involvement

STAGE IIB
T2 N1 M0
T3 N0 M0

one of following:
- T invading main bronchus < 2 cm from carina;
- T infiltrating thoracic wall, diaphragm, mediastinal pleura, pericardium;
- T with complete lung atelectasis

M0: no distant metastase
NSCLC, STAGE IIIA

T3 N1 M0
T1 N2 M0

T3 N2 M0
T2 N2 M0

N1: homolateral peribronchial and / or hilas nodes;
N2: homolateral mediastinal and / or subcarenal nodes;
M0: no distant metastases
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Localized disease. I. Surgery

* complete pulmonary resection = treatment of choice in pts with:
  - stages IA, IB, IIA and IIB (T1-2, N0-1) disease;
  - stage IIIA (T3, N0-1 + T1-3, N2) with favorable age, cardiopulmonary function and anatomy;
* 5 - yr survival for N1 and N2 disease ~ 50% and 20%, respectively;
* however, technically resectable only 20% of pts with N2 disease (most resectable pts discovered to have N2 disease at thoracotomy)
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Localized disease. II. Surgery for N2 disease

* = the most controversial area in surgical management of LC;
- pts with are divided into "minimal" disease (involvement of only one node with microscopic foci, usually discovered at thoracotomy or mediastinoscopy) and more common "advanced, bulky" disease (preoperatively obvious on CT scan)
NSCLC, STAGE IIIB

any T, N3, M0

T4, any N, M0

scalene
supraclavicular

any T

any N

N3: contralateral mediastinal or hilar nodes; scalene or supraclavicular nodes, omo- or contralateral

T (any volume) invading mediastinum, hearth, large vessels, trachea, esophagus, vertebral bodies, carina; pleural effusion CTM+
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Locally advanced disease. III. Stage IIIB

* stage IIIB for N3 disease = pts with contralateral+ or bilateral+ mediastinal (N3) nodes or fixed nodes not candidates for conventional resection;

* stage IIIB for T3 - 4 disease = new surgical approaches making resection possible include chest wall resection (for direct extension of tumor) and tracheal sleeve pneumonectomy and sleeve lobectomy (for lesions near carina)
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Surgery for localized disease. IV.

* extent of resection is a surgical judgment based on findings at exploration;
  - in general, conservative resection encompassing all known tumor → survival = to that obtained with more extensive procedures;
  - → lobectomy preferred to pneumonectomy [and to wedge resections and segmentectomies (↑ rate of local relapse)]
RIGHT PNEUMONECTOMY
LEFT LOBECTOMY
LOBECTOMY VS LIMITED RESECTION IN STAGE I NSCLC

*↓ in local recurrence for pts treated with lobectomy compared with pts treated with limited excision but no significant difference in overall survival (Ginsberg & Rubinstein, Ann Thorac Surg 95)
* wedge resections and segmentectomies, potentially by VATS (video-assisted thoracic surgery via thoracoscopy, not usually used for curative LC resection) for pts with poor pulmonary reserve and small peripheral lesions
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Surgery for localized disease. VI.

Outcome of thoracotomy

* 43% (43 / 100) of pts with LC undergo thoracotomy:

- 76% (= 33 pts) definitive resection;
- 12%: explored only for disease extent, and
- 12%: palliative procedure with known disease left behind;

* 30 - day hospital mortality = 3 and 6% for lobectomy and pneumonectomy, respectively
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Surgery for localized disease. VII. Survival

* ~ 30% of pts (10 pts) treated with “curative resection” survive 5 yrs [~ 15% (5 pts) survive for 10 yrs];
- most pts ultimately die of metastatic disease (usually within 5 yrs from surgery)
* response to neoadjuvant (preoperative) chemotherapy (50 - 60% of pts) → unresectable disease to become resectable
PREOPERATIVE (NEOADJUVANT) CT IN STAGES IB-IIIA

* randomized trial of neoadjuvant CT (mitomycin, ifosfamide and cisplatin) vs surgery alone in stages IB - IIIA NSCLC;
  - responders received two postoperative cycles (and pT3 or pN2 pts RT too);
  * at a median follow up of 80 mos, the benefit of neoadjuvant therapy is confined to pts with N0 and N1 disease

Depierre et al JCO 2002

A = PCT = primary CT
B = PRS = primary surgery
* 1867 radically operated pts (36% stage I, 25% stage II, 39% stage III) randomized between receiving or not receiving adjuvant cisplatin-based CT;

- 2 and 5 yr disease-free survival = 6 and 39% in CT arm vs 55 and 34% in control arm at 2 and 5 yrs respectively (p < .003).
- 2 and 5-yr survival = 70 and 45% in CT arm vs 67 and 40% in control arm respectively (p < .03)
TREATMENT OF NSCL
Localized disease. X.
Postoperative UFT in stage I adenocarcinoma

* 999 pts with resected T1 and T2 disease randomized (1994 - 97) between oral UFT for 2 yrs and no CT;
  - 5-yr OS increased in UFT- with respect to control- arm due to greatly increased OS of pts with T2 disease in UFT arm (84.9 vs 73.5%) (p = .005) (no # among pts with T1 disease)

Kato et al NEJM 2004
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
LOCALLY ADVANCED DISEASE
RADIOThERAPy
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Radiotherapy for locally advanced (stage IIIIB) disease. I.

* stage III (as stages I - II refusing surgery or poor candidates for medical reasons) → high-dose radiation therapy with curative intent;

  - not candidate for curative radiation pts with distant metastases, supraclavicular nodes+, pleural effusion or cardiac involvement;

* median survival for unresectable NSCLC localized to chest is < 1 yr (6% alive at 5 yrs and possibly cured)
Radiotherapy for locally advanced (stage IIIb) disease. II.

* usually midplane doses of 55 - 60 mGy (5500 to 6000 rad, either split course or continuous fraction radiotherapy);

- major concern: amount of lung parenchyma and other thoracic organs (spinal cord, heart, and esophagus) included in treatment plan;

* deleterious effects of radiation on pulmonary function often hampers treatment in pts with major underlying pulmonary disease
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Radiotherapy for locally advanced (stage IIIB) disease. III. Side effects.

Radiation pneumonitis

* risk proportional to dose of radiation and volume of lung within radiation field;
  - full clinical syndrome (dyspnea, fever, and radiographic infiltrate corresponding to treatment port) in 5% of cases
RADIATION PNEUMONITIS
CT findings: a) homogeneous slight increase in attenuation (2-4 mos after therapy); b) patchy consolidation (1-12 mos after therapy); c) non-uniform discrete consolidation (most common; 3 mos to 10 yrs after therapy)
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Radiotherapy for locally advanced (stage III B) disease. III. Radiation esophagitis and spinal cord injury

* acute radiation esophagitis during treatment usually self-limited;

* spinal cord injury avoided by careful treatment planning
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Radiotherapy for locally advanced (stage IIIB) disease. IV.

* continuous hyperfractionated, accelerated RT (CHART) = delivery of 36 treatments of 1.5 Gy 3 times/day for 12 consecutive days (total dose of 54 Gy);
  - 2-yr survival rate > 20 - 30% (with more esophagites);

* brachytherapy (local radiotherapy delivered by placing radioactive "seeds" in a catheter in tumor bed) delivers a ↑ local dose with sparing surrounding normal tissue.
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Radiotherapy for locally advanced (stage IIIb) disease. V.

* beside potentially curative, radiotherapy may control primary tumor and increase quality and length of life of noncured pts
TREATMENT OF NON SMALL CELL CARCINOMA LOCALLY ADVANCED DISEASE COMBINED MODALITY THERAPY
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Combined modality therapy. I.
Adjuvant chemo - radiotherapy in early disease

* overall, adjuvant chemo - radiotherapy after apparently complete resection does not improve survival [from meta - analyses, deleterious of radiotherapy in pts with stage I and II (and IIIA?) disease]
Postoperative radio ± chemotherapy (cisplatin + etoposide) in resected stage I - IIIA NSCLC

Keller et al (for Eastern Cooperative Oncology Group), NEJM 2000
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Combined modality therapy for locally advanced (stage IIIb) disease. II. Pancoast’s syndrome

* for superior pulmonary sulcus LC (producing Pancoast's syndrome) usual preoperative staging procedures (including mediastinoscopy and CT scans, for tumor extent) + neurologic examination (sometimes with nerve conduction studies) for neurologic abnormalities;

- histologic diagnosis sometimes not made, but combination of tumor location and pain distribution allows diagnostic accuracy > 90%
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Combined modality therapy for locally advanced (stage IIIB) disease. III. Pancoast’s syndrome

* after mediastinoscopy, two curative approaches:
  - combined radiotherapy and surgery [preoperative irradiation (30 Gy in 10 treatments) → en bloc resection of tumor and involved chest wall 3 - 6 wks later (3 yr survival = 42% for epidermoid and 21% for adeno- and large cell- carcinomas)];
  - standard fractionation radiotherapy alone in curative doses (survival ~ to that from combined - modality therapy)
* in overall localized NSCLC, adjuvant CT containing cisplatin after resection = survival benefit (meta-analysis = 9387 pts from 52 randomized trials → 13% reduction in risk of death at 5 yrs in favor of CT, but wide confidence intervals);
- confirmation needed before adjuvant CT recommended for general use
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Combined modality therapy
for locally advanced (stage IIIB) disease. V.
Neoadjuvant chemotherapy

* major benefits with CT given preoperatively (neoadjuvant) in early stage IIIA disease;
* CT → RT in other locally advanced conditions (bulky stage IIIA and stage IIIB disease) ↑ median survival (10 → 14 mos) and 5 - yr survival (7 → 17%) than with RT alone
**TREATMENT OF NON SMALL CELL LUNG CARCINOMA**

Combined modality therapy for locally advanced (stage IIIb) disease. VIII.

* randomized clinical phase III trials still needed on usefulness of new agents effective against NSCLC [including taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and camptotecins (topotecan and CPT-11)] in both adjuvant and neoadjuvant settings
TREATMENT OF NON SMALL CELL LUNG CARCINOMA DISSEMINATED DISEASE
NSCLC
Stage IV
any T, any N
M1 (distant metastases)

TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. I.

* poor prognosis for the 70% of pts with not resectable NSCLC:

- median survivals = 34, 25, 17, 8, and 4 wks with performance status of 0 (asymptomatic), 1 (symptomatic, fully ambulatory), 2 (in bed < 50% of time), 3 (in bed > 50% of the time), and 4 (bedridden), respectively;

* cornerstone of management: standard medical care, judicious use of pain medications, and appropriate use of radiotherapy and outpatient chemotherapy
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. II. Radiotherapy

* radiotherapy to primary tumor for pts with symptoms (e.g., bronchial obstruction with pneumonitis, hemoptysis, or upper airway or superior vena cava obstruction);
  - frequencies of relief = hemoptysis, 84%; superior vena cava syndrome, 80%; dyspnea, 60%; cough, 60%; atelectasis, 23%, and vocal cord paralysis, 6%;
  * with closely followed pt, radiation deferred until symptoms, rather than given prophylactically to prevent them
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. III. Radiotherapy

* cardiac tamponade (pericardiocentesis + radiation therapy to entire cardiac silhouette);
* painful bony metastases (relief in 66% of pts), and
  - brachial plexus involvement
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. IV. Radiotherapy

* brain metastases often isolated relapse in adenocarcinoma otherwise controlled by surgery or radiotherapy;
  - no proven value for CT scan of brain or prophylactic cranial irradiation in asymptomatic pts;
  - with proven brain or spinal cord compression → radiotherapy + dexamethasone (25-100 mg / day in 4 divided doses, rapidly tapered to lowest dosage which relieves neurologic symptoms)
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. V. Pleural effusions

* common and usually treated with thoracentesis;
  - if recurring and symptomatic, chest tube drainage
    with a sclerosing agent (intrapleural talc)
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. VI. VATS for pleural effusions

- video - assisted thoracic surgery (VATS) via thoracoscopy used to drain and treat large malignant effusions
meodymium-YAG (yttrium-aluminum - garnet) laser therapy through a flexible fiberoptic bronchoscope (general anesthesia) → palliation in 80 - 90% of pts with symptomatic endobronchial lesions recurred after surgery or RT (or in pts with compromised pulmonary function not treatable with conventional RT)

Figure 1. Obstructing squamous cell carcinoma of the trachea (a) and patent lumen after tumor resection with neodymium:yttrium-aluminum-garnet laser (b).
TREATMENT OF NON SMALL CELL LUNG CARCINOMA

Disseminated disease

VII. Recurring symptomatic endobronchial lesions

* possibilities:
  - brachytherapy,
  - photodynamic therapy (PDT, using a photosensitizing agent) and
  - endobronchial stents

What is PDT?

Day 1: Photofrin® Injection
Day 2: Argon Laser Light Application
Day 7: Tumor Destroyed

Esophagus obstructed by tumor

Photofrin® activated by laser light

Singlet Oxygen Radicals released

Tumor Cell absorbs Photofrin®
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. VIII. Chemotherapy

* careful judgment to balance potential benefits and toxicity;
* combination chemotherapy offers modest (1 - 3 mos) survival benefit and cost-effective symptom palliation and improved quality of life;
* objective response in ~ 30 - 40% of pts (complete in < 5%);
  - median survival = 9 - 10 mos, and
  - 1-yr survival = 40%
TREATMENT OF NON SMALL CELL LUNG CARCINOMA
Disseminated disease. XIII.
Indications of chemotherapy

* reasonable if pt is ambulatory (improved antiemetics allows treatment to be tolerable on an outpatient basis), did not receive prior CT, desires to be treated, and is able to understand and accept the risk / benefit ratio;

* CT must contain cisplatin and one of new drugs with proven activity (including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan);

* all eligible pts encouraged to enter clinical studies designed to determine the benefits and toxicities of these new treatments