CURRENT CONCEPTS

LUNG CANCER-DIAGNOSIS AND STAGING

INTRODUCTION

- Lung cancer – leading cause of cancer death globally

- Accounts for 18% of cancer deaths & > 1 million deaths per year

  Rosen G. A History of Public Health. Expanded ed.Baltimore,MD: Johns Hopkins University Press; 1993

- No of deaths/yr > no of deaths from Ca breast+colon+prostate/yr

- 85% lung cancer – “smoking”

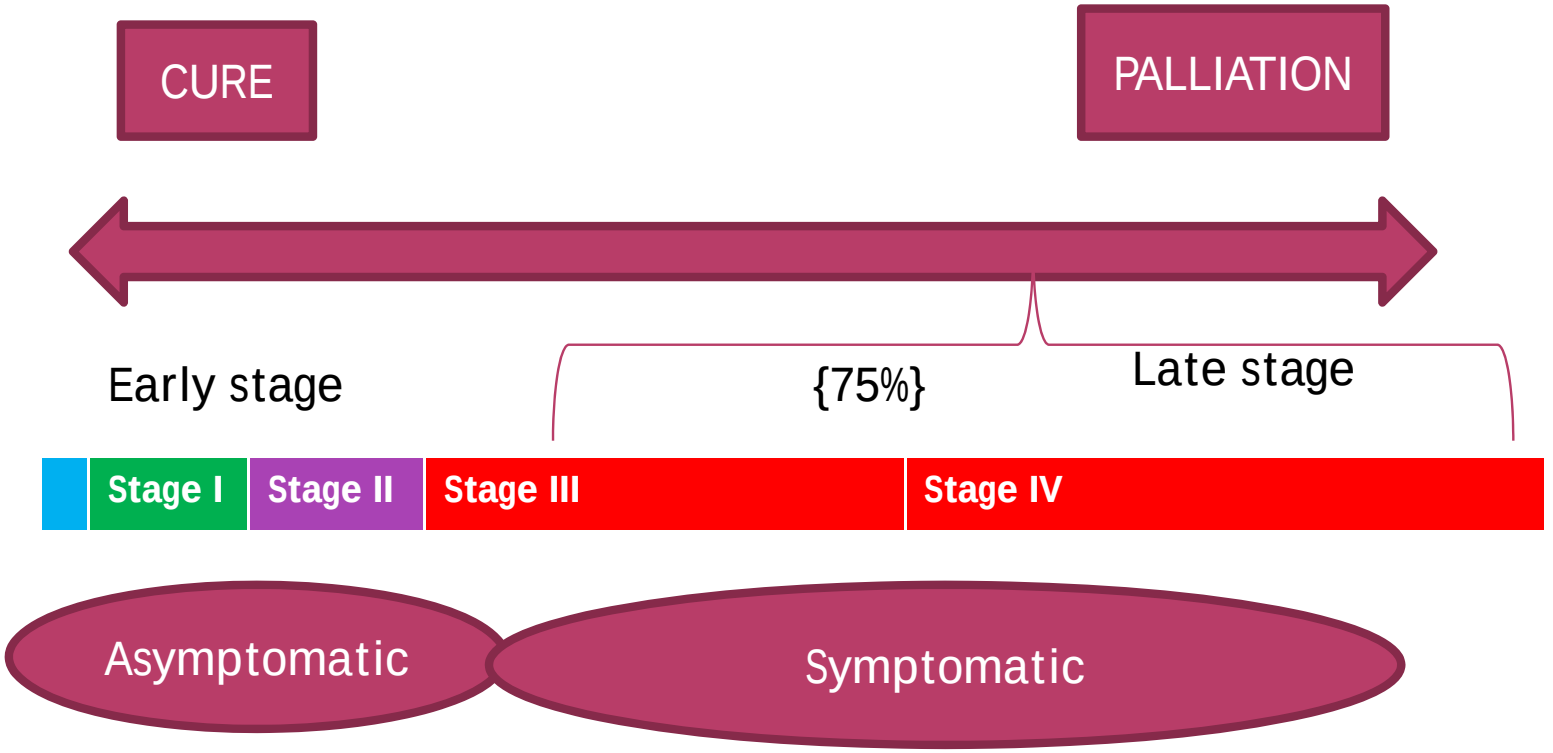
PREVENTABLE

SURVIVAL

- 1 year relative survival has increased from 35% (1975-79) to 42% (2002-05)
- 5 year survival rate combined for all stages is 16%
- 5 year survival rate for localized disease is 53%, but only 15% are diagnosed at this early stage
- 5 year survival rate is 6% for SCLC and 17% for NSCLC

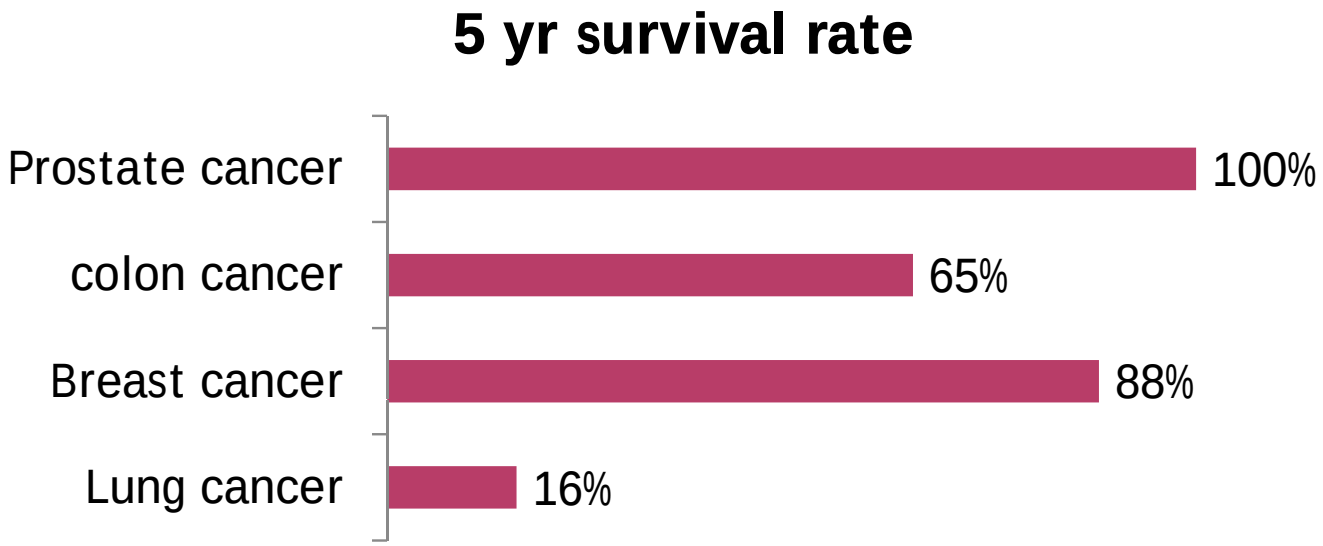
American Cancer Society. Cancer Facts & Figures 2010

LUNG CANCER- CURRENT SCENARIO



Surgery/RT +Adjunctive CT	**Combined CT+RT**	**Targeted molecular therapies**

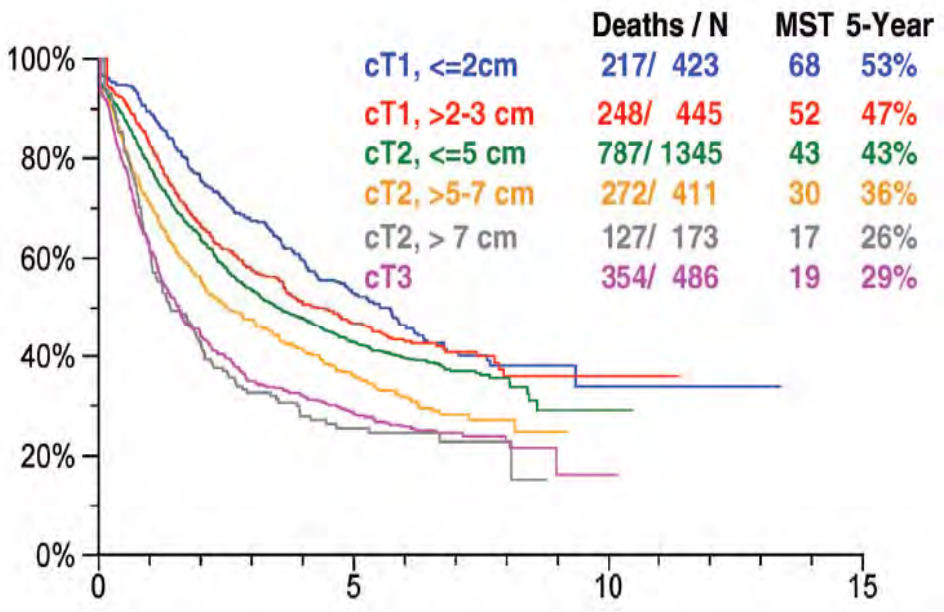
RATIONALE FOR EARLY DETECTION



American Cancer Society. Cancer Facts & Figures 2010

LUNG CANCER OUTCOME

- Strongly related to size and stage: small tumors do better



After surgery

(Rami-Porta R et al.Journal of Thoracic Oncology. 2007;2:593-602)

RATIONALE FOR EARLY DETECTION

- Early Stage disease
  - Radically treatable
  - Better survival

- Clear Risk Factors
  - Smoking –length & dose
  - Asbestos exposure
  - COPD

POTENTIAL SCREENING TOOLS

- Radiological
  - CXR
  - Low dose CT
  - PET
  - SPECT
- Sputum
  - Cytology
  - Molecular markers
- Spirometry
- Autofluorescence bronchoscopy
- Serum proteomics

SCREENING FOR LUNG CANCER

- The current position of the American Cancer Society and the U.S. Preventive Services Task Force is that there is no role for screening for lung cancer, even in high-risk individuals

RCTS OF LUNG CANCER SCREENING WITH CHEST RADIOGRAPHY WITH OR WITHOUT SPUTUM CYTOLOGY

Study	Intervention	No. of Participants	No. of Lung Cancers Detected at First Screening (Prevalence)	No. of Lung Cancers Detected After First Screening	No. of Stage III and IV Cancers*	Lung Cancer Mortality†‡	5-year Survival (%)†
Memorial Sloan-Kettering (11,12)					173	NA	35
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	4968	30	146	…	…	…
Control arm	Annual chest radiography	5072	23	155	…	…	…
Johns Hopkins (13,14)					NA		NA
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	5226	39	194	…	3.4/1000 PY	…
Control arm	Annual chest radiography	5161	40	202	…	3.8/1000 PY	…
Mayo Lung Project (15–17)			91 in all§				
Experimental arm	Chest radiography, sputum cytology every 4 mo	4618	…	206	123‖	4.4/1000 PY	35
Control arm	Recommended annual chest radiography, sputum cytology	4593	…	160	119‖	3.9/1000 PY	19
Czechoslovakian RCT (18,19)			19 in all§				NA
Experimental arm	Chest radiography and sputum cytology every 6 mo × 3 years, annually after year 3	3171	…	108	53	7.8%	…
Control arm	Chest radiography and sputum cytology annually after year 3	3174	…	82	46	6.8%	…

Radiology doi:10.1148/radiol.10091808

OUTCOME

- More cancers detected in screened groups
- Most early stage
- No mortality reduction
- Questions raised are
  - Most studies didn't have 'no-screening' arm
  - Inadequate sample size
  - Unrealistic set goal: 50% reduction in mortality

Chest 2003; 123:72S-82S
Am Rev Respir Dis 1984; 130:561-565.

PROSTATE, LUNG, COLORECTAL AND OVARIAN CANCER SCREENING TRIAL

- Largest RCT-(1993 to 2001)
- Participants of 154942
- Age 55-74
- CXR at baseline and annually thrice (if smoker) or twice (non-smoker)

Stage I 44 %

Result	Baseline screening chest radiograph		
	All	Women	Men
No. screened	67038	32899	34139
No. positive screens	5991	2700	3291
% positive of total screened	8.9	8.2	9.6
No. patients examined by biopsy	206	100	106
% of positive screens examined by biopsy	3.4	3.7	3.2
No. lung cancers diagnosed	126	59	67
PPV of screening test, %	2.1	2.2	2.0
(95% CI for PPV)*	(1.7 to 2.5)	(1.6 to 2.7)	(1.6 to 2.5)
% of biopsy examinations positive	61.2	59.0	63.2
No. lung cancers per 1000 screens	1.9	1.8	2.0

J Natl Cancer Inst 2005;97:1832 – 9

LOW DOSE SPIRAL CT AS A SCREENING TOOL

Observational studies	Baseline	Annual repeat
Total scans	13,122	10,245
Number of Tumors	112	55
Stage I (%)	**55-85**	**60-100**
Stage III,IV (%)	3-36	0-36
Rate of Cancer (%)	0.4-2.7	0.07-1.1
Mean diameter (mm)	14-21	10-16
Invasive procedures for benign lesions (%)	4-22	14-15
Interval cancers (%)	NA	0-22

ALCA: Anti Lung Cancer Association, Japan
ELCAP: Early Lung Cancer Action Project, USA
Mayo Clinic Study, USA
Lung Cancer Screening study, Milan, Italy
Hitachi Health Center, Japan

N Eng J Med, 2005

I-ELCAP RESULTS

- Large multicenter, multinational, nonrandomized trial
- 31,567 baseline and 27,456 repeat scans 7-18 months after baseline
- 484 cancer cases detected
- All cases: 10-yr survival 80%
- Stage I resected cases (85%): 10-yr survival 92%
- Stage I untreated cases (n=8): dead within 5-yrs

N Engl J Med 2006; 355:1763-1771

I-ELCAP: CONTROVERSIES

- No control arm
- Cannot rule out lead-time, length-time and overdiagnosis biases
- Does not account for potential harm

N Engl J Med 2006; 355:1763-1771

2 COCHRANE REVIEWS

LOW-DOSE CT LUNG CA SCREENING -APRIL 08

CLINICAL & COST EFFECTIVENESS OF LUNG CA SCREENING - AUG 08

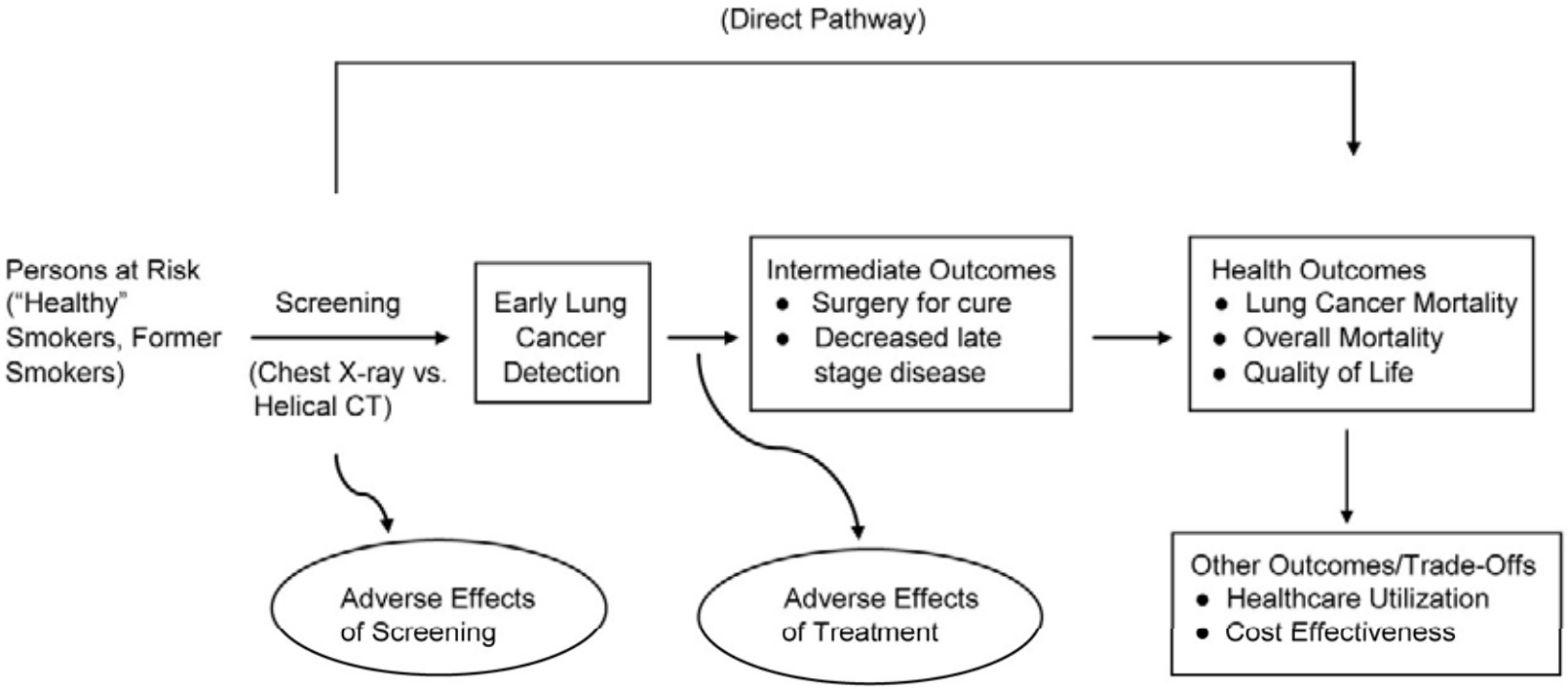
15/ 12 Trials 2 RCT, 3 CCT, 10 cohort N= 29607/ 25749 screened 2 RCT: - CT vs nil - CT vs CXR	CT better than CXR Positive tests ranged 5.1%- 51% Ca diagnosis ranged 1.8% - 32% +ve predictive value: <20% Stage 1 80% (53 -100%) Inadequate data on mortality

NATIONAL LUNG SCREENING TRIAL

- Multicenter, RCT
- LDCT vs CxR in screening current & former heavy smoker (≥ 30 pack-year)
- 53,456 participants (sept 02- april 04)
- Primary end poind – lung ca mortality
- 20% mortality reduction

Posted 4/11/10 -www.cancer.gov

Process and outcomes in the NLST.



Radiology doi:10.1148/radiol.10091808

Radiology

OVERVIEW ONGOING RCT'S

Trials	No screened	Control arm	MSCT	Volu metry	DT*	Stage I,II
NELSON	6814	N	16 -detector	Y	Y	76%
Denmark	1889	N	16- detector	Y	Y	50%
ITALUNG-CT	1019	N	4-16 detector	N	N	47%

* Doubling time

LUNG CANCER: RECOMMENDATIONS

- Chest X-rays cannot be recommended for screening of lung cancer.
  - Recommendation IA

- Low-dose CT scan cannot yet be used for screening of lung cancer unless in a clinical trial.
  - Recommendation IIC

Annals of Oncology 21 (Supplement 5): v103–v115, 2010

DIAGNOSIS OF LUNG CANCER

- Symptomatic
- Asymptomatic with abnormal CxR

- Concomittant risk factors
  - Age > 50 yrs
  - Smoking history (current or past)
  - Occupational exposure – asbestos, arsenic, cadmium, radon
  - Positive family history for malignancy
  - h/o malignancy in past

SYMPTOMS OF LUNG CANCER

Primary tumor	Local extension	Metastases	Systemic/ Paraneoplastic
Cough Hemoptysis Chest pain Wheezing Dyspnea	Chest pain SVC syndrome Hoarseness of voice Dysphagia	Lymph node enlargement Bone pain Neurologic deficits Skin & subcutaneous lesions	Fever Anorexia Weight loss SIADH Hypercalcemia HOAP* Dementia Cerebellar ataxia Myelopathy Peripheral neuropathy

*Hypertrophic osteoarthopathy

DIAGNOSIS AND STAGING OF LUNG CANCER

- Diagnosis
  - Central vs Peripheral
  - SCLC (15-18%) vs NSCLC (82-85%)
  - Subtypes: Sq Cell Ca, Adenocarcinoma, Large cell
  - Molecular markers: EGFR mutations, K ras mutations

- Staging
  - TNM staging 7th edition – NSCLC
  - Limited vs Extensive disease - SCLC

STAGING OF NSCLC: TWO METHODS

- Clinical staging
  - Based on biospy and imaging modalities
  - Inaccurate
  - Poorer outcomes
  - Widely used
- Pathological staging
  - Determined after surgical resection
  - Applicable in patients undergoing operative treatment
  - Accurate – reference standard

Overall level of agreement betwenen two system 35-55%

TNM STAGING OF NSCLC

5th & 6th Edition

- Proposed by AJCC & UICC
- Single center (MD Anderson Cancer Center, Houston, TX)
- 1977-1988 (includes pre-CT era)
- 5319 NSCLC patients
- Cases mostly Sx treated
- Lacked validation (esp external)

7th Edition

- IASLC
- 46 registries in 20 countries
- >100,000 patients
- 1990-2000 (post CT era)
- Validated internally and externally to some extend

Eur Respir J 2010; 36: 401–407

7TH EDITION OF THE TNM STAGING SYSTEM FOR LUNG CANCER

Comparison of the 6th and 7th Editions of the TNM Staging System for Lung Cancer

Category	6th Edition	7th Edition	Reason for Revision*
Tumor			
Size	T1: ≤3 cm	T1a: ≤2 cm	5-year survival rate = 77%
		T1b: >2 cm but ≤3 cm	5-year survival rate = 71%
	T2: >3 cm	T2a: >3 cm but ≤5 cm	5-year survival rate = 58%
	. . .	T2b: >5 cm but ≤7 cm	5-year survival rate = 49%
	. . .	T3: >7 cm	5-year survival rate = 35%
Tumor nodule(s) separate from primary mass			
Same lung and lobe as primary mass	T4	T3	5-year survival rate = 28% (similar to that for T3 and better than that for T4)
Same lung but not same lobe as primary mass	M1	T4	5-year survival rate = 22% (similar to that for T4)
Contralateral lung	M1	M1a	5-year survival rate = 3% (consistent with that for other intrathoracic metastatic disease)

RadioGraphics 2010; 30:1163-1181

Comparison of the 6th and 7th Editions of the TNM Staging System for Lung Cancer

Node			
Lymph node map	Lymph node staging primarily from the MD-ATS (Mountain-Dresler–American Thoracic Society) map	New IASLC lymph node map published (Fig 7)	New IASLC map reconciles differences between earlier lymph node maps and provides new descriptions of the nodal anatomy with respect to anatomic borders to ensure accurate localization of lymph nodes (cf Table 3)
Malignant pleural or pericardial effusion	T4	M1a	5-year survival rate = 2% (similar to that for tumors in the intrathoracic metastatic category, compared with a 5-year survival rate of 15% in other patients with T4 tumors
Metastasis			
Metastatic disease	M0: absent	M0: absent	. . .
	M1: present	M1a: local thoracic metastatic disease	Additional nodules in the contralateral lung (M1a) result in a median survival time of 10 months and a 1-year survival rate of 45%
		M1b: distant or extrathoracic metastatic disease	Extrathoracic metastases result in a median survival time of 6 months and a 1-year survival rate of 22%

RadioGraphics 2010; 30:1163-1181

Revisions to Stage Groupings in the Seventh Edition of the TNM Classification for Lung Tumors Compared With the Sixth Edition

Stage in Seventh Edition	Stage in Sixth Edition	N0	N1	N2	N3
T1a	T1	IA	IIA	IIIA	IIIB
T1b	T1	IA	IIA	IIIA	IIIB
T2a	T2	IB	**IIA** (IIB)	IIIA	IIIB
T2b	T2	IIA	IIB	IIIA	IIIB
T3 (> 7 cm)	T2	**IIB** (IB)	**IIIA** (IIB)	IIIA	IIIB
T3 (invasion)	T3	IIB	IIIA	IIIA	IIIB
T3 (satellite nodule, same lobe)	T4	**IIIB** (IIIA)	**IIIA** (IIIB)	**IIIA** (IIIB)	IIIB
T4 (invasion)	T4	**IIIA** (IIIB)	**IIIA** (IIIB)	IIIB	IIIB
T4 (ipsilateral nodule, different lobe)	M1	**IIIA** (IV)	**IIIA** (IV)	**IIIB** (IV)	**IIIB** (IV)
M1a (pleural or pericardial dissemination)	T4	**IV** (IIIB)	**IV** (IIIB)	**IV** (IIIB)	**IV** (IIIB)
M1a (contralateral lung nodules)	M1	IV	IV	IV	IV
M1b (distant metastatic disease)	M1	IV	IV	IV	IV

Note—Cells in bold indicate a change in the stage from the sixth edition. Adjacent stage in parentheses represents staging from the sixth edition.

AJR 2010; 194:562–573

IASLC LYMPH NODE STATIONS

Nodal zones	5 yr survival
N0	42%
N1	29%
N2	16%
N3	7%

AJR 2010; 194:562–573

SURVIVAL DIFFERENCE BETWEEN SINGLE VS MULTIPLE LN METASTASIS

Factor	Median survival (months)
Single N1 zone	52
Multiple N1 zone	31
Single N2 zone	35
Multiple N2 zone	19

No statistical significance due to small numbers

STAGING OF SCLC

- Exclusively seen in smokers
- Rapid doubling time, high growth fraction and early metastasis
- Chemo and radiosensitive
- Staged as limited and extensive disease
- Poor survival outcome than NSCLC

IASLC study of SCLC
13290/81015 (16.7%)
3430 cases - full data for TNM staging
Survival reduces as staging increased
TNM predict survival better – recommends TNM staging

STAGING OF BRONCHOPULMONARY CARCINOID TUMOR

- Malignant neuroendocrine tumor
- low-grade typical carcinoid → intermediate- grade atypical carcinoid → high-grade small cell carcinomas and large cell carcinomas
- Survival analysis performed on 1,829 pathologically staged patients
- As T, N, and M designations of bronchopulmonary carcinoid tumors independently increased → statistically significant decrease in 5-year survival
- Recommended to use newly revised TNM classification

LIMITATIONS OF 7TH TNM STAGING

- Retrospective data
- Databases not specifically designed to study the TNM classification
- Precise information except T size and exact extent of LN involvement omitted
  - T3 & T4 classification remains mostly unchanged
  - No changes made to N classification despite significant survival differences in those with single versus multiple nodal zone involvement
- Presence or absence of lymphangitic spread of tumor not evaluated
- Prognostic information based on tumor biology and tumor genetics was not included
- Reliability and accuracy of imaging in clinical staging and the prognostic impact of PET imaging were not addressed
- Staging and treatment strategies were not uniform
- Prospective validation required

LUNG CANCER DIAGNOSIS & STAGING

Non invasive staging techniques

- CxR
- CT chest
- PET
- MRI
- Search for metastasis
  - Bone scan
  - CT/MRI head
  - Adrenal & hepatic imaging

Invasive diagnostic and staging techniques

- Transthoracic Needle Aspiration
- Fiberoptic Bronchoscopy
- Endoscopic Ultrasound
- Endobronchial Ultrasound
- Mediastinoscopy
- Thoracoscopy

WHAT IS NEXT STEP?

1. Surgical resection leading to diagnosis and pathological staging?
2. Confirm diagnosis by tissue sampling from nodule and/or hilar LN then go for surgery with pathological staging?
3. Confirm diagnosis and preoperative clinical staging then decide management?
    1. PET/CT scan
    2. Mediastinoscopy
    3. EBUS/EUS

SURGERY WITH PATHOLOGICAL STAGING

- 10% of surgeries explorative thoracotomy but NO Tumour Resection (advanced mediastinal disease not detected pre-op)
- 25–35% of apparently curative resections unsuccessful due to early post-op recurrence
- Surgery futile & unnecessary in up to 45% of operated pts of NSCLC because stage more advanced than expected pre-op

CT SCAN

- Used in staging since its introduction in seventies
- Localizes site, size and extent of tumor, locoregional extent
- Usually CECT chest with upper abdomen (including adrenals) are advised
- Spiral/MDCT with better algorithm → 3D images of tumor and its extent to fissures, pleura, chestwall, mediastinum: decide resectability

CT SCAN- MEDIASTINAL LYMPH NODES

- Determining size (short axis ≥ 10mm)
- Accuracy has been evaluated in 2 metaanalysis with sensitivity and specificity around 61%& 79%* and 64% & 74%**
- Systematic review of medical literature performed by Duke University Evidence-Based Practice Center reported a pooled sensitivity and specificity of 51% &86%***
- In clinical stage IA (T1N0M0) – 6%
- 60% of the nodes identified as malignant turns out to be benign, similarly, approximately 20% of all nodes identified as benign by CT criteria are actually malignant

PET SCAN

- Relies on physiological rather than anatomical features of tumor cells/tissues
- Based on fact that malignant tumors have greater glucose utilization than normal tissue.
- Pt injected with 18F-fluoro-deoxy-D-glucose (radiolabeled glucose analog) → Cellular uptake ~ glucose → Phosphorylation → No further metabolism → Trapped within cells→Accumulation of isotope identified using a PET camera

PET

- Indications
  - Evaluation of nodules and masses
  - Locoregional & Extrathoracic staging
  - F/U & Dx of recurrence
  - Prognostic information

- Molecular applications
  - Early assessment of CT
  - Assessment of molecular targeted therapy

CT VS PET SCAN

Imaging for mediastinal metastasis	Sensitivity	Specificity	(+) LR	(-) LR
CT scan	51%	86%	3.4	0.6
PET scan	74%	58%	4.9	0.3

Potential causes of falsely positive and negative results in PET/CT studies

False positive	False negative
Infection (including tuberculosis)	Bronchoalveolar cell cancer
Inflammation (sarcoidosis, pulmonary fibrosis, amyloidosis, vasculitis)	Tumours or involved nodes <8 mm diameter
Pulmonary infarction	Recent chemotherapy
Physiological uptake (brown fat, muscle, vessel walls)	
Recent surgery, radiotherapy, chemotherapy	
Non-pathological rib or spinal fractures	

Potential causes of falsely positive and negative results in PET/CT studies

INVASIVE MEDIASTINAL STAGING

- Mediastinoscopy
- TBNA
- TTNA
- EBUS-TBNA
- EUS-NA
- VATS

MEDIASTINOSCOPY

- Under GA/LA via suprasternal notch incision
- Nodes that are accessible via this approach are:
  - Right and left high and low paratracheal nodes (stations 2R, 2L, 4R, and 4L),
  - Pretracheal nodes (stations 1 and 3), and
  - Anterior subcarinal nodes (station 7)
- Following nodes are not approachable
  - Posterior subcarinal nodes (station 7),
  - Inferior mediastinal nodes (stations 8 and 9),
  - Aortopulmonary window (APW) nodes (station 5), and
  - Anterior mediastinal nodes (station 6) node groups cannot be biopsied with this technique.
- Ideally, five nodal stations (stations 2R, 4R, 7, 4L, and 2L) should routinely be examined, with at least one node sampled from each station

MEDIASTINOSCOPY

- Average sensitivity and false negative (FN) rate of mediastinoscopy is about 80% and 10% while the specificity and false positive rate is 100% and 0%, respectively

- Among the false negative cases approximately 42 to 57% are due to nodes that were not accessible by the mediastinoscope

- Mediastinoscopy is associated with a complication rate of 2–3% and a surgical mortality rate of around 0.1%

ESOPHAGEAL ENDOSCOPIC ULTRASOUND WITH NEEDLE ASPIRATION (EUS-NA)

- Particularly useful for inferior pulmonary ligament, esophageal, subcarinal, and APW nodes (stations 9, 8, 7, and 5).
- Overall sensitivity, specificity, FN and FP rate, was 84%, 99.5%, 19% (range, 0 to 61%) and 0.4%, respectively
- Detect metastatic disease to subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes, and the liver.
- Evaluation for the presence of direct tumor invasion into the mediastinum
- Major limitation is the inability to assess nodes in the anterior mediastinum, resulting in an imperfect sensitivity

ENDOBRONCHIAL ULTRASOUND WITH NEEDLE ASPIRATION (EBUS-NA)

- Targeted nodal sampling
- Paratracheal (stations 2 and 4), subcarinal (station 7), hilar and intrapulmonary nodes (stations 10 and 11) can be reached
- Compared with mediastinoscopy, EBUS-TBNA has the advantage of routinely accessing posterior mediastinal (level 7) and hilar lymph nodes (levels 10 and 11).
- The main blind spots for EBUS-TBNA are the lymph nodes in the aortopulmonary window, para-aortic station, paraoesophageal stations and the inferior pulmonary ligament.
- By localizing the lymph nodes with EBUS, the sensitivity of TBNA can be greatly increased up to the tune of 85%
- *As compared to CT and PET, EBUS-TBNA has a high sensitivity as well as specificity for mediastinal and hilar lymph node*

APPROACH TO INCIDENTAL DETECTION OF SUBCENTRIMETRIC PULMONARY NODULE

- < 8 mm in size
- Prevalence 23-51% - majority benign
- Not reliably characterized by imaging and difficut in tissue sampling
- ACCP guidelines recommend against the use of FDG-PET in patients with nodules that measure <8 mm in diameter

CONCLUSIONS

- Till date no role of screening for lung cancer even for high risk population
- Early detection and effective treatment improves overall survival
- Proper staging and diagnosis of lung cancer improves survival – aggressive approach
- Tissue diagnosis from suspected distant mets if patient tumor is resectable to confirm staging