Small cell lung carcinoma: advances and state of the art

Staging update

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Disclosure slide

Type of affiliation / financial interest	Name of commercial company
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Limited disease - by tumours confined to one hemithorax, although local extension and ipsilateral or supraclavicular nodes could also be present if they could be encompassed in the same radiation portal as the primary tumour.

Extensive disease - All other cases were classified as extensive disease.

Veterans Administration Lung Study Group

Stahel, R.A., Ginsberg, R., Havemann, K. et al. Staging and prognostic factors in small cell lung cancer: a consensus report. Lung Cancer. 1989; 5: 119–126

IASLC – SCLC 7th Edition

Shepherd FA et al JTO 2007:2:1067-77

- TNM classification is recommended for SCLC, and stratification in stages I-III should be used in clinical trials or early disease.
- Further studies are needed re:
  - M1a
    - Pleural effusion (+/- tumour)
  - N3 disease
    - Relevance of ipsilateral supraclavicular vs contralateral mediastinal

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Proposals for the 8th edition of TNM for lung cancer

Chair – Ramon Rami-Porta

- **SCLC Subcommittee**
- *Andrew G. Nicholson, DM,*
- *Kari Chansky, MS,*
- *John Crowley, PhD,*
- *Ricardo Beyruti, MD,*
- *Kaoru Kubota, MD,*
- *Andrew Turrisi, MD,*
- *Wilfried E.E. Eberhardt, MD,*
- *Jan van Meerbeeck, MD,*

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Summary of Retrospective Data Collected for the 8th edition of TNM for lung cancer (NSCLC and SCLC)

The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer.
Rami-Porta R et al. *J Thorac Oncol. 2014;9:1618-24*

- 94,708 cases initially submitted from 12 databases and retrospective data entered via EDC system

Submitted	94,708
Included in initial analyses NSCLC SCLC	77,265 71,076 6189
Excluded	17,443
Carcinoid	745
Other or unknown histology	5986
Outside 1999-2010 timeframe	525
Incomplete Survival data	938
Incomplete stage information	9177
Multiple Synchronous Tumours	72

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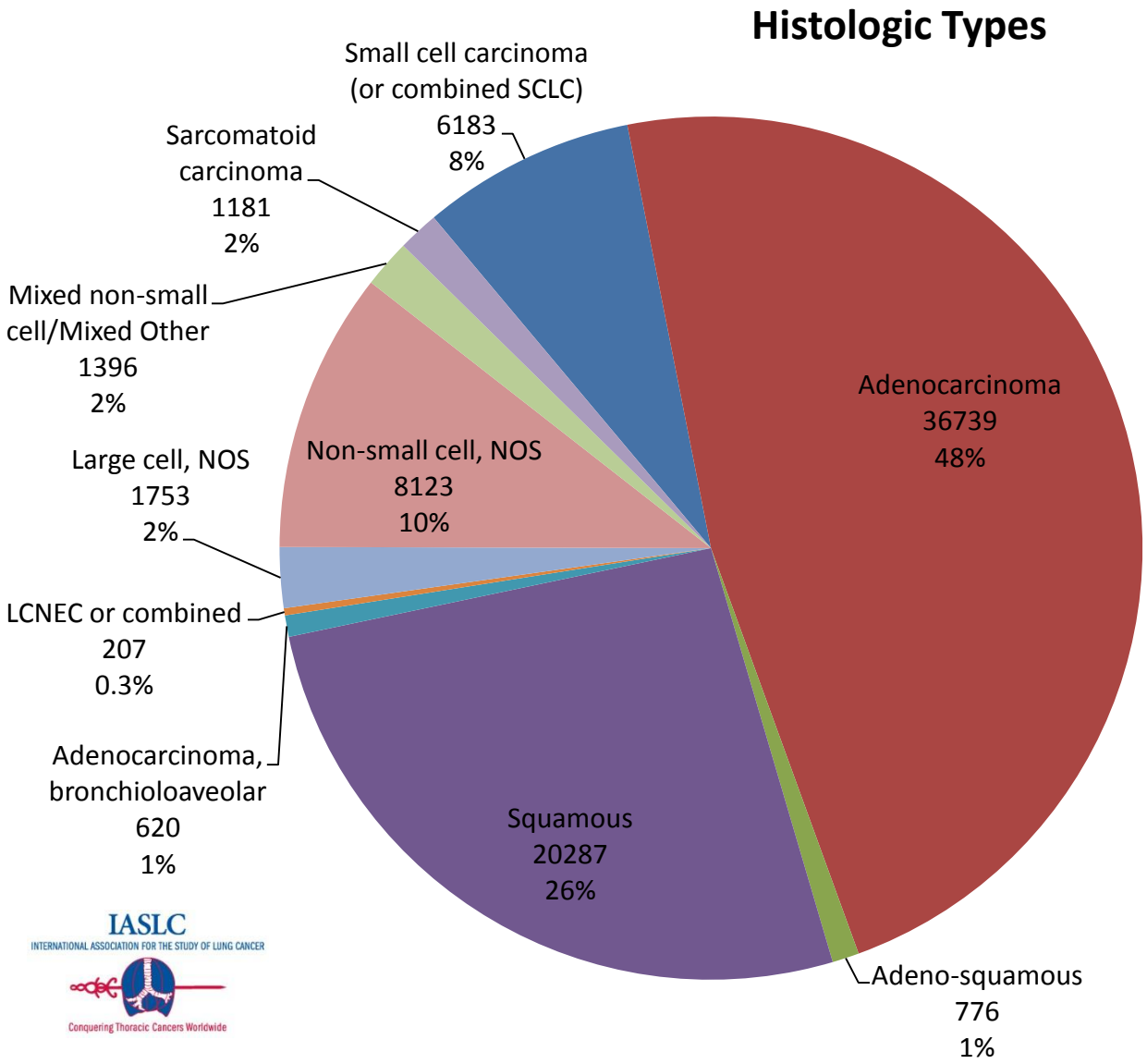
IASLC Lung Cancer Retrospective Staging Data for 8th Ed TNM Proposals
Diagnosed from 1990 through 2010
N=77,265 NSCLC and SCLC Included Cases



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Source of Staging and Type of Database Submission for the 5002 Cases in the Small Cell Lung Cancer Database

Type of Database Submission	Available TNM Staging			Geographic Region				Total
	Clinical TNM	Patholo-gical TNM	Clinical and Pathological TNM	Asia	Australia	Europe	North/ South America	
Consortium	1688	97	417	1400	0	802	0	2202
Registry	2645	46	7	0	15	2683	0	2698
Series	87	11	4	31	9	31	31	102
Total	4420	154	428	1431	24	3516	31	5002

- In total, there were 5002 patients, of whom 4848 were clinically staged, 582 were pathologically staged, and 428 both. Among the 4,848 patients considered in the analyses of clinical stage, 577 (12%) were surgically managed

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Type of Management by Clinical Stage, from the Small Cell Lung Cancer Clinically Staged Database

	Treatment				
Clinical Stage (7th ed)	**Surgery (%)**	**Chemotherapy/ Radiotherapy, Nonsurgical (%)**	**No Tx (%)**	**Missing Rx Data, Nonsurgical (%)**	**Total**
IA	273 (100)	0	0	0	273
IB	81 (93)	5 (6)	1 (1)	0	87
IIA	60 (95)	2 (3)	0	1 (2)	63
IIB	35 (32)	48 (44)	0	27 (25)	110
IIIA	84 (17)	290 (57)	2 (<1)	128 (26)	504
IIIB	14 (2)	602 (70)	5 (<1)	245 (28)	866
IV	30 (1)	1984 (67)	38 (1)	893 (31)	2945
Total	577 (12)	2931 (60)	46 (1)	1294 (27)	4848

- In total, there were 5002 patients, of whom 4848 were clinically staged, 582 were pathologically staged, and 428 both. Among the 4,848 patients considered in the analyses of clinical stage, 577 (12%) were surgically managed

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* yP, R1, R2 not included in path staged cases.

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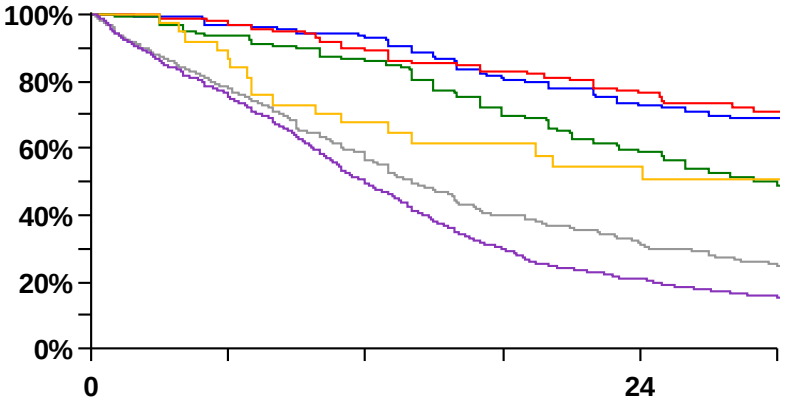
T

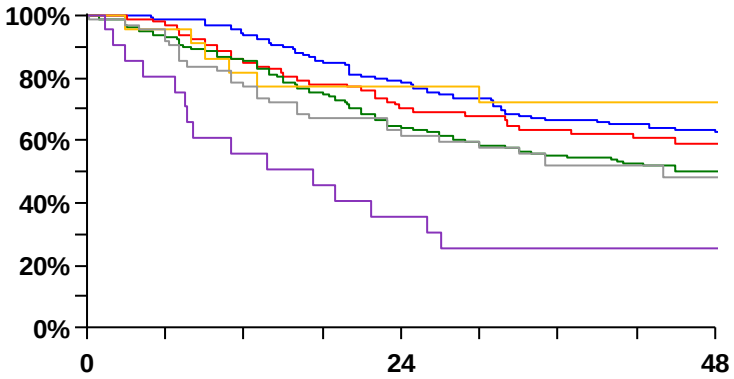
Survival according to clinical T categories, seventh edition.



Notes: c: clinical; N: number of cases; MST: median survival time.

cT	Events / N	MST	12 Month	24 Month
T1a	86 / 208	NR	93%	73%
T1b	50 / 142	NR	89%	76%
T2a	75 / 140	29.0	86%	59%
T2b	20 / 39	33.0	67%	54%
T3	312 / 408	14.0	56%	31%
T4	800 / 966	12.0	49%	21%

Survival according to pathological T categories, seventh edition.



pT	Events / N	MST	24 Month
T1a	60 / 165	NR	78%
T1b	37 / 99	NR	70%
T2a	96 / 196	48.9	64%
T2b	8 / 22	NR	77%
T3	33 / 65	44.0	61%
T4	18 / 21	17.3	35%

T1 vs T2 vs T3 vs T4 Comparisons Unadjusted, and Adjusted for surgical vs. not (Cox PH regression)

comparison	Unadjusted HR	P	Adjusted HR	P
T2 vs. T1	1.63	0.0003	1.52	0.0019
T3 vs. T2	2.24	<.0001	1.51	0.0047
T4 vs. T3	1.30	0.0001	1.21	0.0045

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The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. Rami-Porta R et al. *J Thorac Oncol.* 2015;10:990-1003

Recommended changes are as follows:

- to subclassify T1 into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm);
- to subclassify T2 into T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm);
- to reclassify tumors greater than 5 to less than or equal to 7 cm as T3;
- to reclassify tumors greater than 7 cm as T4; to group involvement of main bronchus as T2 regardless of distance from carina;
- to group partial and total atelectasis/pneumonitis as T2;
- to reclassify diaphragm invasion as T4;
- to delete mediastinal pleura invasion as a T descriptor.

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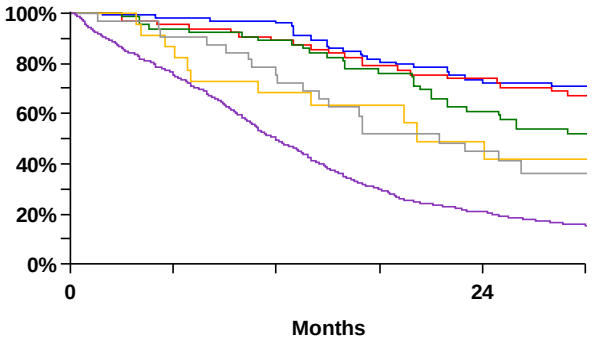
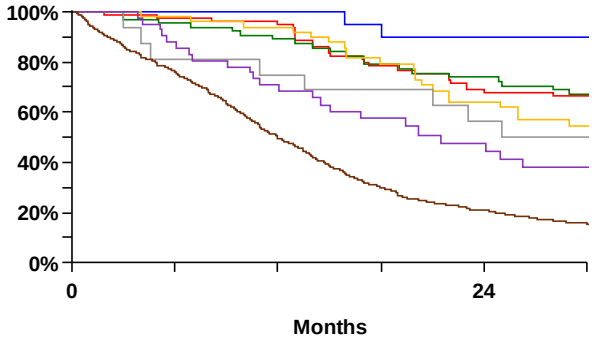
Figure 4. Survival according to a) seventh edition clinical T categories and b) proposed eighth edition clinical T categories in the subset of cases where tumour descriptor data was sufficient to classify according to proposed eighth edition.

A.



cT 7th Ed.	Events / N	MST	12 Month	24 Month
T1a	39 / 104	NR	96%	72%
T1b	25 / 68	NR	89%	74%
T2a	34 / 68	33.0	89%	61%
T2b	12 / 24	20.2	68%	49%
T3	21 / 35	21.5	75%	45%
T4	800 / 966	12.0	49%	21%

B.



cT Proposed	Events / N	MST	12 Month	24 Month
T1a	5 / 20	NR	100%	90%
T1b	34 / 84	NR	95%	68%
T1c	25 / 68	NR	89%	74%
T2a	26 / 53	33.0	94%	64%
T2b	8 / 17	NR	75%	56%
T3	26 / 44	21.5	71%	48%
T4	807 / 979	12.0	50%	21%

Notes: c: clinical; N: number of cases; MST: median survival time.

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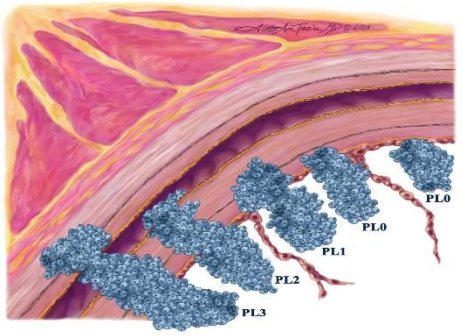
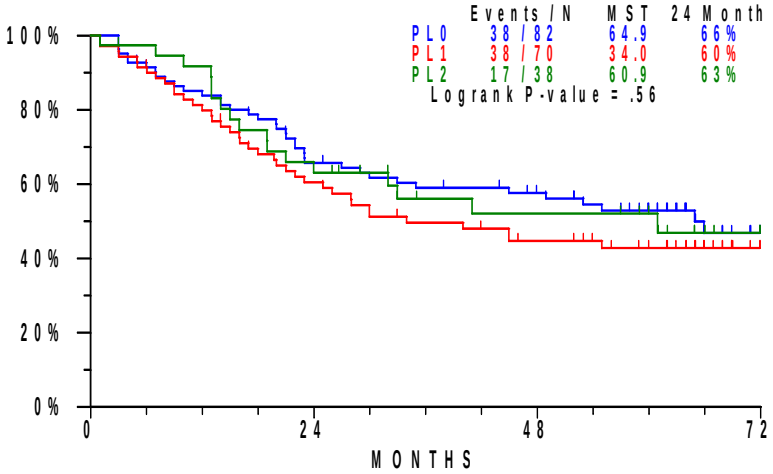
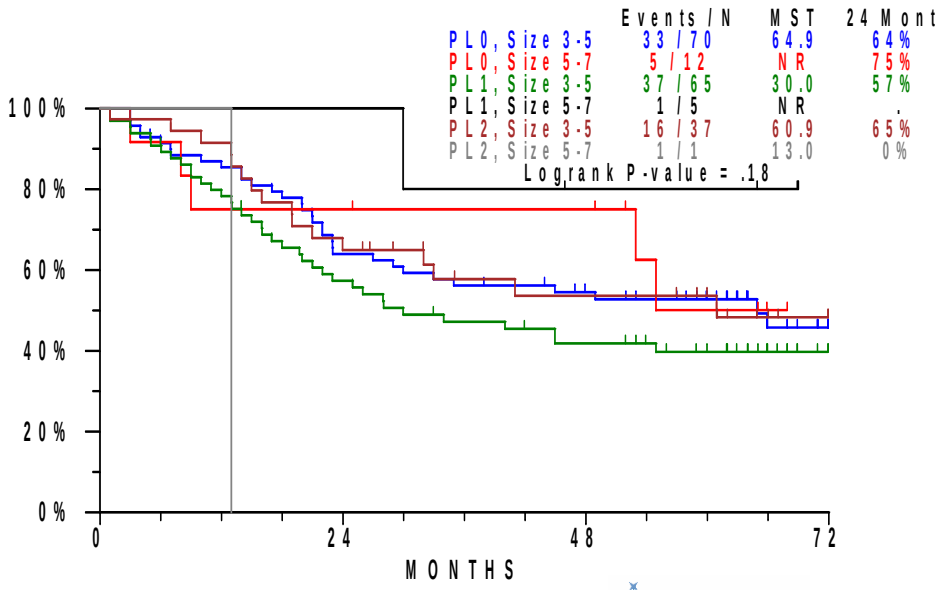
SCLC T Components

Path Stage T2 – Depth of pleural invasion and size

- **PL0: tumour within the subpleural lung parenchyma, or invades superficially into the pleural connective tissue beneath the elastic layer*.**
- **PL1: tumour invades beyond the elastic layer.**
- **PL2: tumour invades to the pleural surface.**
- **PL3: tumour invades into any component of the parietal pleura.**







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N

The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer.
Asamura H et al. J Thorac Oncol. 2015;10:1675-84

- Current N descriptors adequately predict the prognosis and therefore should be maintained in the forthcoming staging system.

- Furthermore, we recommend that physicians record the number of metastatic lymph nodes (or stations) and to further classify the N category using new descriptors, such as N1a, N1b, N2a, N2b, and N3, for further testing.

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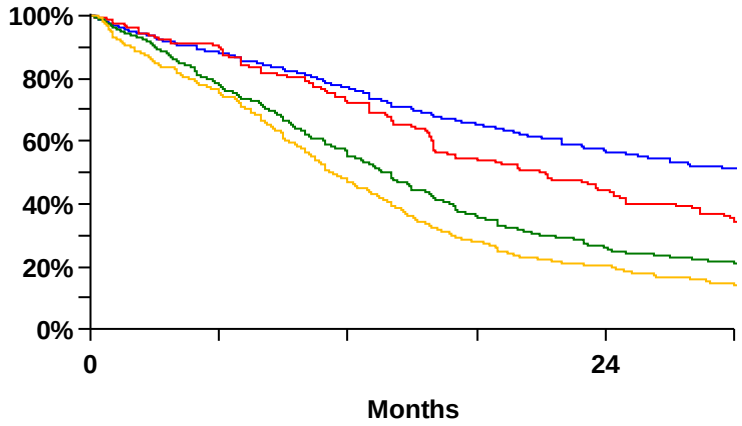
Survival according to clinical N categories, seventh edition.

Application of the N component categories from the seventh edition, independent of T category, showed better survival trends for clinical N0 through to N3



cN	Events / N	MST	12 Month	24 Month
N0	347 / 637	32.0	77%	57%
N1	104 / 149	21.0	72%	44%
N2	489 / 621	13.8	55%	26%
N3	403 / 496	11.2	47%	20%

Notes: c: clinical; N: number of cases; MST: median survival time.

Comparison	Unadjusted HR	P-Value	Adjusted* HR	P
Clinical N categories				
N1 vs N0	1.55	<.0001	1.13	0.2689
N2 vs N1	1.48	0.0003	1.15	0.2056
N3 vs N2	1.24	0.0013	1.11	0.1115

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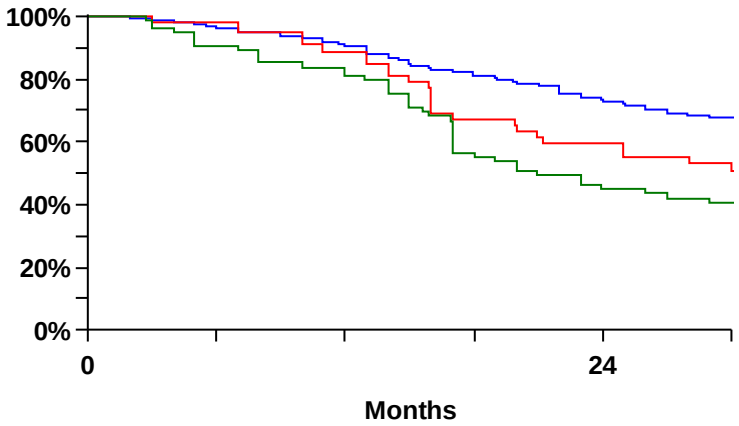
In cases that underwent surgery, independent of T category, there was a significant difference between N0 patients and those with node positive disease for both clinical and pathological staging

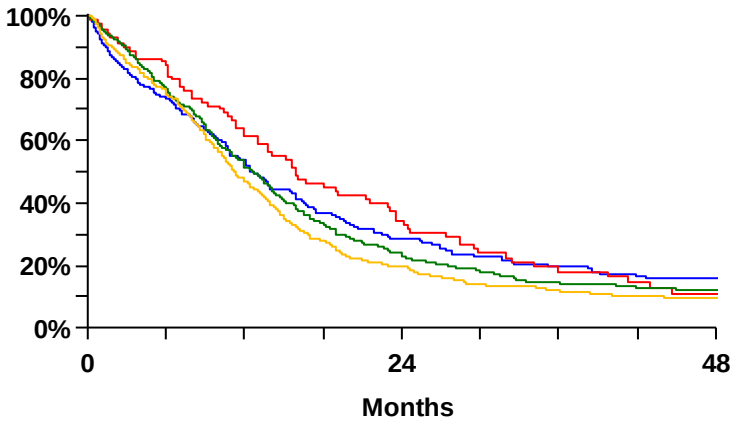
Survival according to clinical N categories, surgically resected cases (6 cases with N3 disease omitted)



Notes: c: clinical; N: number of cases; MST: median survival time.

cN	Events / N	MST	12 Month	24 Month
N0	161 / 405	NR	91%	73%
N1	33 / 60	33.0	89%	59%
N2	51 / 76	21.0	81%	45%

Survival according to clinical N categories, non-surgical cases only.



cN	Events / N	MST	24 Month
N0	186 / 232	12.6	28%
N1	71 / 89	15.9	35%
N2	438 / 545	12.6	23%
N3	399 / 490	11.2	20%

Comparison	Unadjusted HR	P-Value
Clinical N categories, Non-surgical cases only		
N1 vs N0	0.89	0.3974
N2 vs N1	1.21	0.1318
N3 vs N2	1.14	0.0537
Clinical N categories, Surgical cases only		
N1 vs N0	1.76	0.0031
N2 vs N1	1.34	0.19
N3 vs N2	1.08	0.8805

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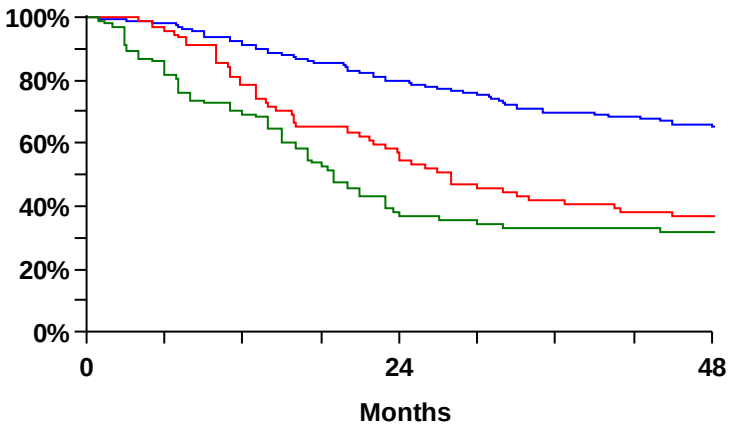
Survival according to pathological N Categories. 2 cases with N3 disease omitted.



pN	Events / N	MST	24 Month
N0	132 / 380	NR	80%
N1	55 / 93	28.0	55%
N2	64 / 93	19.0	37%

Notes: p: pathological; N: number of cases; MST: median survival time.

Concordance between Clinical and Pathological N Categories

	Pathological N Category				
N Category Concordance (M0 Cases)	N0	N1	N2	N3	Percent Agreement
cN0	253	37	32	0	79
cN1	14	24	8	0	52
cN2	16	3	23	0	55
cN3	0	1	2	1	25
cN0	253	37	32	0	79
cN1	14	24	8	0	52

73% of cases (301/414) show agreement; 9% (36/414) are overstaged and 18% (77/414) are understaged clinically.

…Highlights the importance of pathological confirmation of nodal disease

M

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The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer.

Eberhardt WE et al. J Thorac Oncol. 2015;10:1515-22

- Cases with pleural/pericardial effusions, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or a combination of multiple of these parameters should continue to be grouped as M1a category.

- Single metastatic lesions in a single distant organ should be newly designated to the M1b category.

- Multiple lesions in a single organ or multiple lesions in multiple organs should be reclassified as M1c category.

- This new division can serve as a first step into providing rational definitions for an oligometastatic disease stage in non-small-cell lung cancer in the future.

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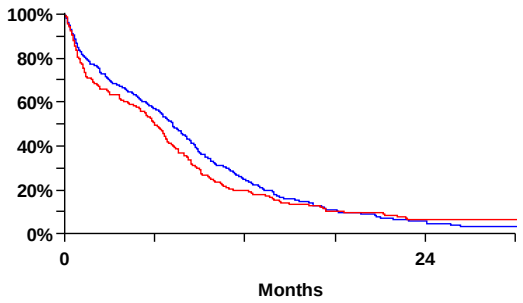
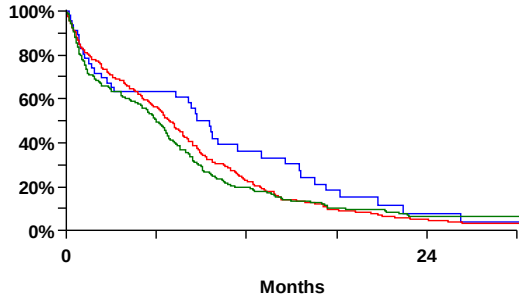
Evaluation of metastatic sites: a) single site metastases versus multiple sites, M1 cases; b) single-site metastases to the brain, versus other sites; c) single versus multiple site metastases with or without pleural effusion.

A.



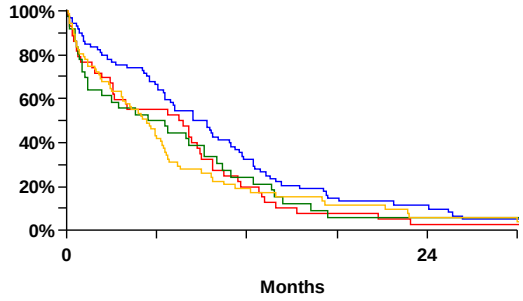
Mets Sites	Events / N	MST	12 Month	24 Month
Single Site	308 / 336	7.2	25%	6%
Multiple Sites	185 / 205	5.9	20%	7%

B.



SSM	Events / N	MST	12 Month	24 Month
Brain Only	38 / 47	9.5	36%	8%
Other Single	270 / 289	6.8	23%	5%
Multiple Sites	185 / 205	5.9	20%	7%

C.



Mets and PE	Events / N	MST	12 Month	24 Month
Single Site,PE(-)	71 / 87	8.4	32%	12%
Single Site,PE(+)	41 / 44	7.7	20%	3%
Mult. Sites,PE(+)	33 / 38	6.5	24%	6%
Mult. Sites,PE(-)	64 / 73	5.3	19%	6%

Notes: N: number of cases; MST: median survival time, PE: pleural effusion, SSM: single site metastasis.

A. Analyses of patients with clinical stage M1b showed no significant difference between patients who had either a single site metastasis (SSM) or multiple site disease.

B. However, when SSMs was subdivided into those with brain involvement only, there was an apparent difference between this group and other sites of SSM and multiple site disease.

C. In addition, patients with a SSM and no pleural effusion showed an improved survival when compared with patients who had either pleural effusions or multiple -metastatic sites, or both (P= 0.02, HR = .71.)

OVERALL STAGE

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The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer.

Goldstraw P et al. J Thorac Oncol. 2016;11:39-51

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a–c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a–c**	**N2**	**M0**
	T2a–b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a–c**	**N3**	**M0**
	T2a–b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

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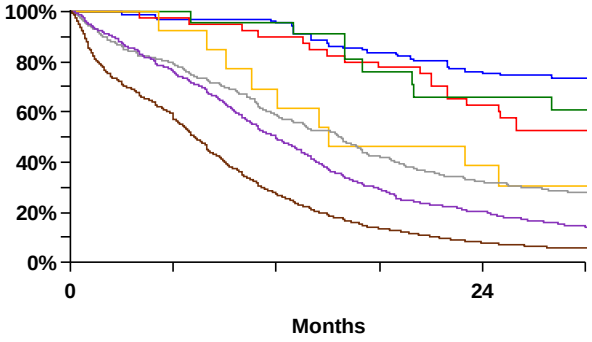
Figure 5. Survival according to a) seventh edition clinical TNM stages and b) proposed eighth edition clinical TNM stages in cases where tumour descriptor data was sufficient to classify according to proposed eighth edition.

A.

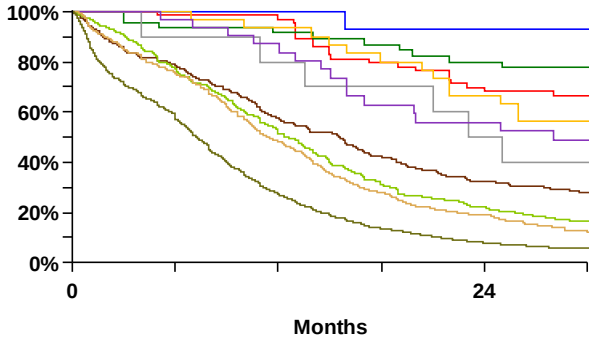
B.

Notes: ed.: edition; N: number of cases; MST: median survival time.



cTNM 7th Ed.	Events / N	MST	12 Month	24 Month
IA	45 / 129	NR	95%	75%
IB	22 / 42	32.4	90%	63%
IIA	10 / 28	41.0	96%	66%
IIB	10 / 14	15.0	69%	38%
IIIA	203 / 270	15.7	59%	32%
IIIB	641 / 782	12.0	49%	20%
IV	2620 / 2926	7.3	27%	8%

Comparison	Unadjusted HR	p Value	Adjusted HR[a]a	Adjusted p Value
Clinical TNM stages (7th ed)				
IB vs. IA	1.67	0.05	1.49	0.13
IIA vs. IB	0.82	0.60	0.87	0.70
IIB vs. IIA	2.30	0.06	2.17	0.08
IIIA vs. IIB	1.22	0.54	0.75	0.40
IIIB vs. IIIA	1.36	<0.0001	1.23	0.01
IV vs. IIIB	1.68	<0.0001	1.68	<0.0001



cTNM Proposed	Events / N	MST	12 Month	24 Month
IA1	3 / 14	NR	100%	93%
IA2	27 / 67	NR	97%	68%
IA3	15 / 48	NR	91%	80%
IB	16 / 32	33.0	93%	67%
IIA	6 / 10	24.1	80%	50%
IIB	17 / 38	28.0	87%	56%
IIIA	191 / 254	15.6	58%	32%
IIIB	326 / 402	12.6	52%	22%
IIIC	330 / 400	11.4	48%	19%
IV	2620 / 2926	7.3	27%	8%

Comparison	Unadjusted HR	p Value	Adjusted HR[a]a	Adjusted p Value
Clinical TNM stages (7th ed)				
IB vs. IA	1.67	0.05	1.49	0.13
IIA vs. IB	0.82	0.60	0.87	0.70
IIB vs. IIA	2.30	0.06	2.17	0.08
IIIA vs. IIB	1.22	0.54	0.75	0.40
IIIB vs. IIIA	1.36	<0.0001	1.23	0.01
IV vs. IIIB	1.68	<0.0001	1.68	<0.0001

Concordance between Clinical and Pathological TNM Stage, in Cases where Both Clinical and Pathological Stage Data were Available

	Pathological TNM Category							
Stage Concordance	IA	IB	IIA	IIB	IIIA	IIIB	IV	Percent Agreement
cIA	129	34	26	10	18	1	1	59
cIB	1	49	5	3	12	0	1	69
cIIA	6	5	24	5	7	1	0	50
cIIB	0	4	7	8	5	0	1	32
cIIIA	6	4	1	6	28	2	1	58
cIIIB	1	0	1	0	3	2	1	25
cIV	1	1	1	0	2	0	4	44

57% of cases (244/428) show agreement; 12% (50/428) are overstaged and 31% (134/428) understaged clinically.

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CONCLUSIONS (1)

- **TNM classification for SCLC continues to show prognostic stratification (validated using 7th TNM categories and also using proposed 8th T, N, M and stage (TNM) categories**

- **N component**

  Survival differences in relation to the N categories were lost in nonsurgical cases independent of the T component, with comparisons of c and p staging showing under-staging predominating.

  No change in extent of under-staging comparing 7th and 8th TNM data

- **M component**
  - Single site metastasis (SSM)/Pleural Effusion(PE) -ve have better survival than SSM/PE+ve and multiple sites/PE + or –ve.
  - Brain metastasis as a SSM has better survival than other SSM
  - Use M1a, M1b and M1c as recommended for NSCLC

- Important to undertake systematic nodal staging at surgery

  ? Impact of TBNA in next decade for non-surgical cases (unable to analyse in current data)
- Insufficient data to assess the value of pleural (and pericardial) effusion +/- tumour
- Insufficient data on specific site of N3 involvement

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CONCLUSIONS (2)

For future revisions of the TNM staging system, we recommend documenting prospectively for patients with metastases:

(1) the number of extrathoracic metastatic sites.

(2) the exact number and locations in metastatic organs involved.

(3) the diameter as surrogate for volume of individual metastatic sites, including involved lymph nodes beyond the nodal stations shown in the IASLC lymph node map.

(4) investigations performed to undertake staging (e.g. TBNA).

(5) whether presentation with brain metastases was symptomatic or asymptomatic.

With higher patient numbers within these individual subgroups, answering clinically important questions relevant to SCLC might be possible

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The IASLC Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer

Andrew G. Nicholson, DM, Kari Chansky, MS, John Crowley, PhD, Ricardo Beyruti, MD, Kaoru Kubota, MD, Andrew Turrisi, MD, [5] Jan van Meerbeeck, William Eberhardt and Ramón Rami-Porta, MD, FETCS on behalf of the Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions

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