


# Staging in thoracic malignancy-from 8th to 9th TNM system

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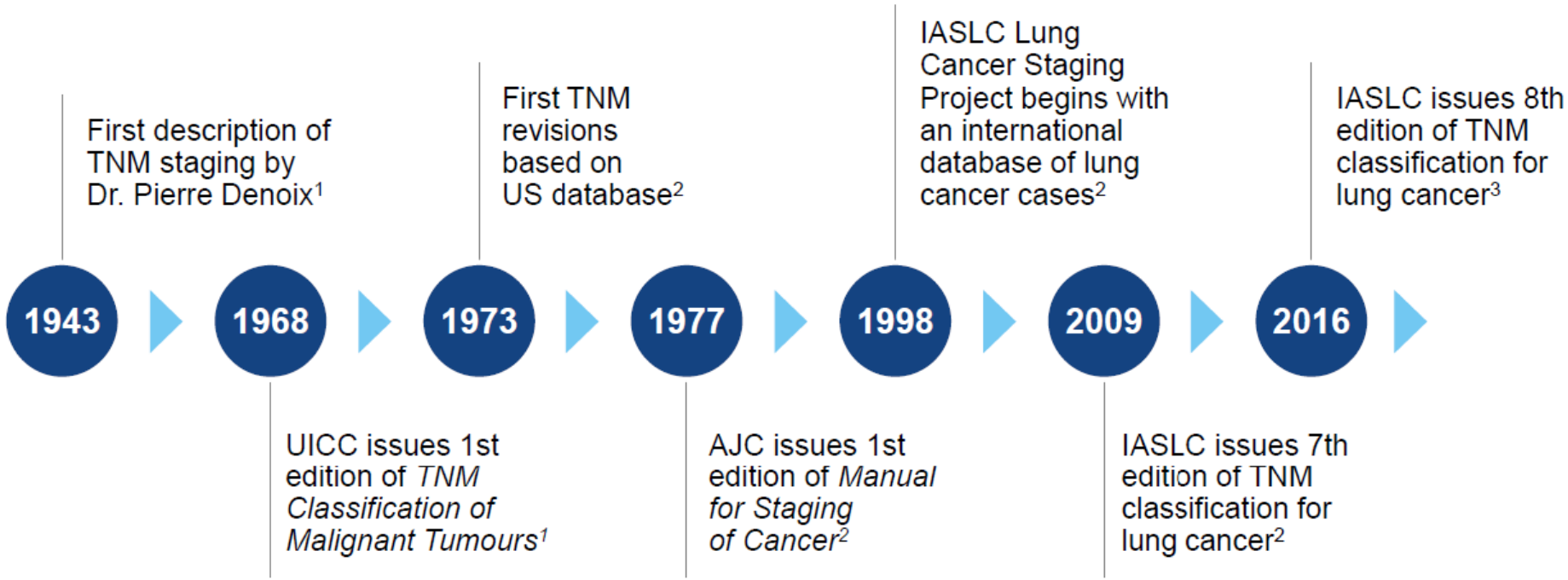
張時杰

2024/08/25

# Evolution of the TNM Classification of Lung Cancer

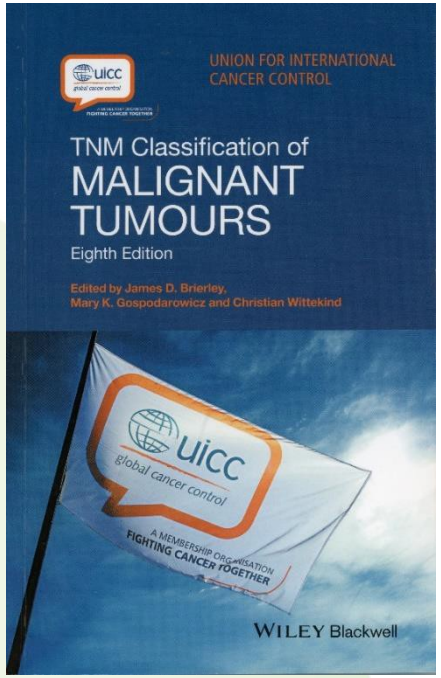
## Timeline of Key Events



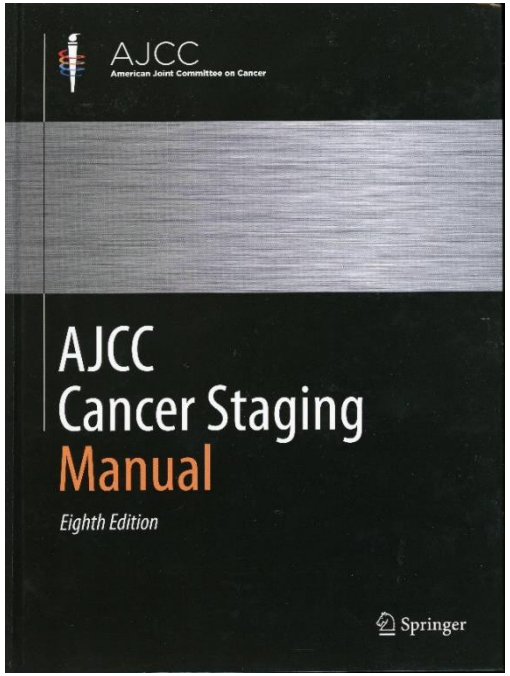

UICC=Union for International Cancer Control. AJC=American Joint Committee for Cancer Staging and End Results Reporting.

1. Goldstraw P. *J Thorac Oncol.* 2006;1:281-286.
2. Goldstraw P. *IASLC Staging Manual in Thoracic Oncology*. 2009.
3. Rami-Porta R. *Staging Manual in Thoracic Oncology*. 2nd ed. 2016.

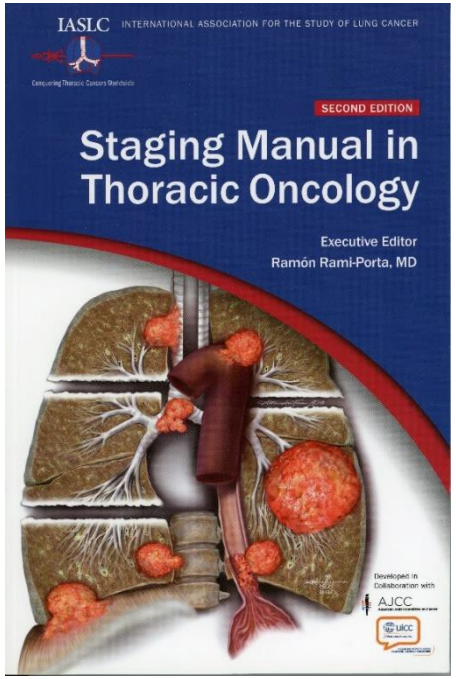
# TNM classifications




**UICC**




**AJCC**




**IASLC**

Identical classifications for thoracic malignancies

| UICC (1943) | AJCC (1959) |
| --- | --- |
| 1st edition 1968 | |
| 2nd edition 1975 | |
| | 1st edition 1977 |
| 3rd edition 1978 (1982) | |
| | 2nd edition 1983 |
| 4th edition 1987 | |
| | 3rd edition 1988 |
| | 4th edition 1993 |
| **IASLC** 5th edition 1997 (5319 cases) | |
| 6th edition 2002 | |
| 7th edition 2010 (67725 cases, 1990-2000), Participating Institutions | |
| P. Perng, Taiwan Lung Cancer Society, Taiwan | |
| 8th edition 2016 | |

# Comparison of 7th and 8th Edition of the TNM Classification for Lung Cancer

## Lung TNM Staging 7th Edition[1]

| T/M | Subgroups | N0 | N1 | N2 | N3 |
|---|---|---|---|---|---|
| **T1** ≤ 3cm surrounded by lung or visceral pleura, w/o invasion more proximal than the lobar bronchus | **T1a** ≤ 2cm | IA | IIA | IIIA | IIIB |
| | **T1b** > 2cm, ≤ 3cm | IA | IIA | IIIA | IIIB |
| **T2** > 3, ≤ 7cm or (1) involves main bronchus ≥ 2cm distal to carina; (2) invades visceral pleura; (3) associated with atelectasis or obstructive pneumonitis that extends to the hilar region | **T2a** > 3cm, ≤ 5cm | IB T2a= 4 cm | IIA | IIIA | IIIB |
| | **T2b** > 5cm, ≤ 7cm | IIA | IIB | IIIA | IIIB |
| **T3** > 7 cm or (1) invades parietal pleural, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; (2) tumor in the main bronchus < 2cm to the carina; (3) atelectasis/obstructive pneumonitis of entire lung; (4) separate tumor nodule(s) in the same lobe | T3 > 7cm | IIB | IIIA | IIIA | IIIB |
| | **T3** Invasion | IIB | IIIA | IIIA | IIIB |
| | **T3** Same lobe nodule/satellite | IIB | IIIA | IIIA | IIIB |
| **T4** Any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe | **T4** Invas/ extension | IIIA | IIIA | IIIB | IIIB |
| | **T4** Ipsil, non prim lobe nodule | IIIA | IIIA | IIIB | IIIB |
| **M1** | **M1a** Contr Nod | IV | IV | IV | IV |
| | **M1a** Pl Dissem | IV | IV | IV | IV |
| | **M1b** Distant mets | IV | IV | IV | IV |

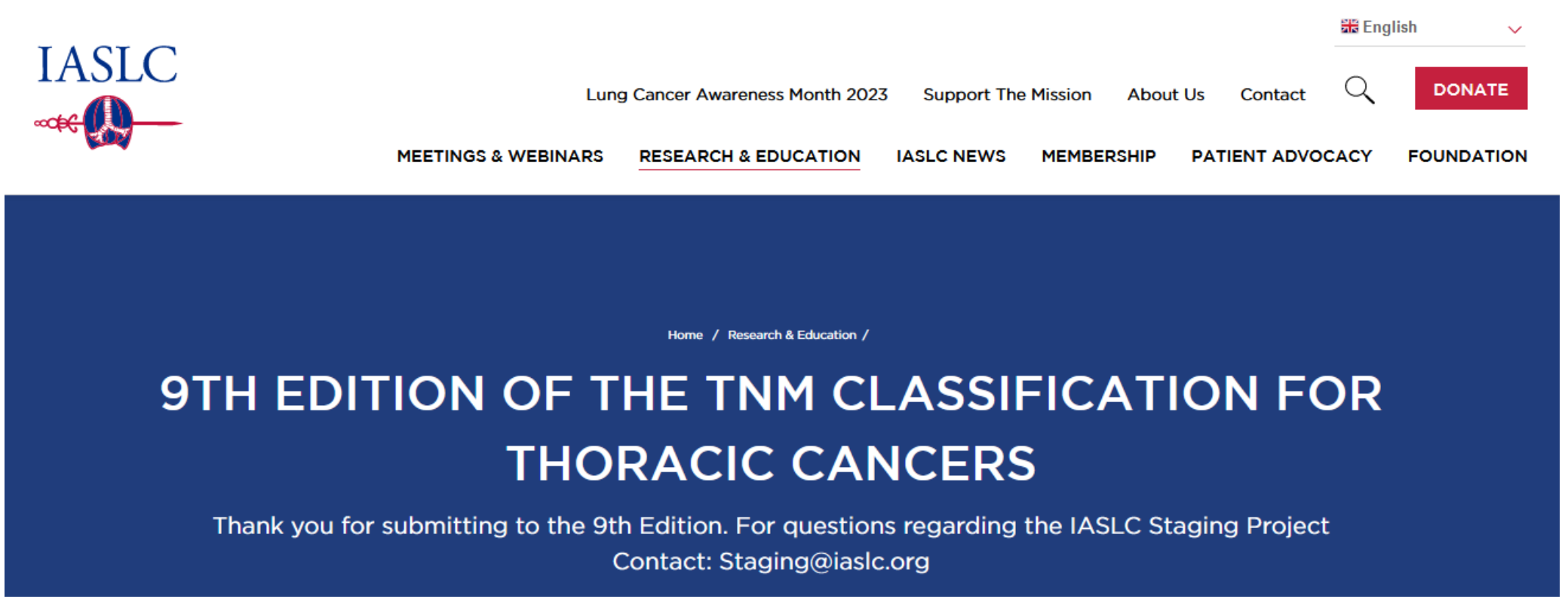
## Lung TNM Staging 8th Edition[2]

| T/M | Subgroups | N0 | N1 | N2 | N3 |
|---|---|---|---|---|---|
| **T1** ≤ 3cm surrounded by lung or visceral pleura, w/o invasion more proximal than the lobar bronchus | **T1a** ≤ 1cm | IA1 | IIB | IIIA | IIIB |
| | **T1b** > 1cm,≤ 2cm | IA2 | IIB | IIIA | IIIB |
| | **T1c** > 2cm,≤ 3cm | IA3 | IIB | IIIA | IIIB |
| **T2** > 3, ≤ 5cm or (1) involves main bronchus but w/o involvement of the carina; (2) invades visceral pleura; (3) associated with atelectasis or obstructive pneumonitis that extends to the hilar region | **T2a** > 3cm, ≤ 4cm, OR Cent, Visc Pl | IB T2a= 4 cm | IIB | IIIA | IIIB |
| | **T2b** > 4cm, ≤ 5cm | IIA | IIB | IIIA | IIIB |
| **T3** > 5, ≤ 7cm or directly invading chest wall, phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe | **T3** > 5cm, ≤ 7cm | IIB | IIIA | IIIB | IIIC |
| | **T3** Invasion | IIB | IIIA | IIIB | IIIC |
| | **T3** Satellite | IIB | IIIA | IIIB | IIIC |
| **T4** > 7cm or any size invading diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or separate tumor nodule(s) in an ipsilateral lobe different from the primary | **T4** > 7cm | IIIA | IIIA | IIIB | IIIC |
| | **T3** Invasion | IIIA | IIIA | IIIB | IIIC |
| | **T4** Ipsil, non prim lobe nodule | IIIA | IIIA | IIIB | IIIC |
| **M1** Distant metastasis | **M1a** Contr Nod | IVA | IVA | IVA | IVA |
| | **M1a** Pl Dissem | IVA | IVA | IVA | IVA |
| | **M1b** Single met | IVA | IVA | IVA | IVA |
| | **M1b Multi mets** | IVB | IVB | IVB | IVB |

- Here we see a comparison of the 7th and 8th edition of the TNM classification for lung cancer.

M = distant metastasis; N = regional lymph nodes; T = primary tumor; w/o = without; NSCLC = non-small cell lung cancer.

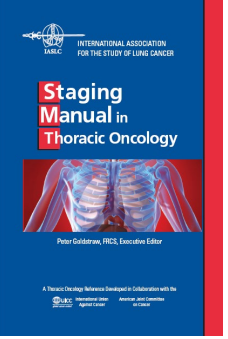
1. Detterbeck FC et al. *Chest*.2009;136:260-271. 2. Detterbeck FC et al. Chest. 2017;151(1):193-203.3. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. Published online 12 September 2022. doi:10.1016/S1470-2045(22)00518-6.




Data source: IASLC members and other thoracic oncology professional

Eligible patient: lung cancer diagnosed between Jan 1, 2011 – Dec 31, 2019

Deadline: Dec 31, 2021




# New Lung Cancer Staging System: The IASLC Lung Cancer Staging Project (International Association for the Study of Lung Cancer)

# IASLC 第九版胸重學會登錄工作計畫

- 2021/02/06 第18屆肺腫瘤委員會第一次會議決議擴展國際參與-參加IASLC 9th lung cancer staging project
- 2021/02/26 本會王鶴健理事長與IASLC及CRAB完成Data Use Agreement Signature並取得本會登錄帳號(100373)
- 2021/03/17 提供IASLC staging Project IRB範本予13家參與醫院
- 2021/05/15 舉辦IASLC staging 登錄工作坊研討會並成立Line工作群組
- **2021/12/31** IASLC new data collection window is closed
- 2022/02/25共有1515筆登錄資料，排除13筆空號及確診日期不符合適應症後，最後有1502筆登錄資料通過審查
- 2023/10/05第18屆肺腫瘤委員會第六次會議IASLC登錄工作計畫結案

IN WITNESS WHEREOF, as of the Effective D
has duly executed this Data Use Agreement.

INSTITUTION

Signed: Hao-chien Wang

Name: Taiwan Society of Pulmonary and Critical Care Medicine

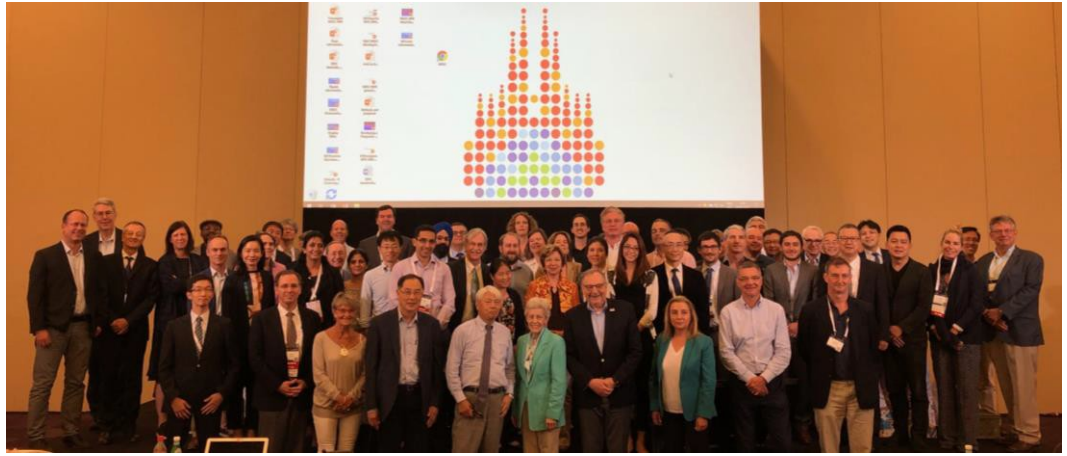
Title: President

Date: Feb 26, 2021

CANCER RESEARCH AND BIOSTATISTICS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

# Staging and Prognostic Factors Committee (SPFC)



**SPFC**

**CRAB**

**Steering Committee, SC**

**LUNG CANCER DOMAIN**
**Chair: Paul Van Schil**

**THYMIC DOMAIN**
**Chair: Enrico Ruffini**

**MESOTHELIOMA DOMAIN**
**Chair: Valerie Rusch**

**ESOPHAGEAL DOMAIN**
**Chair: Wentao Fang**

**14 SUBCOMMITTEES**

**T, N, M, NEUROENDOCRINE, STAGE, LEPIDIC-AIS, LYMPH NODE CHART, VALIDATION-METHODOLOGY, MULTPLE NODULES, PROGNOSTIC FACTORS, R-FACTOR, MOLECULAR, IMAGING, DATABASE**

| | | |
|---|---|---|
| Chair: | **Hisao Asamura** | (Japan) |
| Chair-Elect: | **Valerie Rusch** | (USA) |
| Past Chair: | **Ramón Rami-Porta** | (Spain) |

The SPFC consists of 112 members, including 28 advisory board members.

CRAB
Cancer Research And Biostatistics

# IASLC 9th Edition TNM Stage Proposal

## WCLC-Singapore 2023

CRAB
Cancer Research And Biostatistics

Katie Nishimura (CRAB)/Hisao Asamura

Updated August 12, 2023

# The IASLC Lung Cancer Staging Project 1990-

6th edition

7th edition
1st Staging Project

8th edition
2nd Staging Project

9th edition
3rd Staging Project

| | | | | |
|---|---|---|---|---|
| **Chairperson** | **Clifton Mountain** | **Peter Goldstraw** | **Ramón Rami-Porta** | **Hisao Asamura** |
| **Publication** | **2002** | **2010** | **2017** | **2024** |
| **Period of diagnosis** | **1975-** | **1990 to 2000** | **1999 to 2010** | **2011 to 2019** |
| **Total patients submitted** | **5,319** | **100,869** | **94,708** | **124,581** |
| **Geographical origin** | | | | |
| **-Europe** | **0** | **58,701 (58%)** | **46,560 (49%)** | **30,827 (25%)** |
| **-North America** | **5,319 (100%)** | **21,130 (21%)** | **4,660 (5%)** | **19,608 (16%)** |
| **-Asia/Australia** | **0** | **21,038 (21%)** | **43,298 (46%)** | **69,749 (56%)** |
| **-South/Central America** | **0** | **0** | **190 (0.3%)** | **4,225 (3%)** |
| **-Africa/Middle East** | **0** | **0** | **0** | **172 (0.1%)** |
| **Patients included in analysis** | | **81,495** | **77,154** | **87,339** |
| **-NSCLC** | **5,253 (99%)** | **68,463 (84%)** | **70,967 (92%)** | **72,278 (83%)** |
| **-SCLC** | | **13,032 (16%)** | **6,189 (8%)** | **5,561 (7%)** |
| **Treatment modalities** | | | | |
| -Surgery alone | **mostly populated with surgical cases** | **41%** | **58%** | **47%** |
| -Radiotherapy + surgery | | **5%** | **2%** | **2%** |
| -Chemotherapy + surgery | | **4%** | **21%** | **13%** |
| -Chemotherapy alone | | **23%** | **9%** | **11%** |
| -Radiotherapy alone | | **11%** | **2%** | **3%** |
| -Chemotherapy + radiotherapy | | **12%** | **5%** | **6%** |
| -Trimodality | | **3%** | **4%** | **13%** |
| **Type of data** | | | | |
| **-Electronic data capture** | | | **3,905 (5%)** | **21,505 (25%)** |
| **-Batch** | | | **73,251 (95%)** | **65,834 (75%)** |

# Anticipated publication list for the 9th edition TNM classification: 28 papers

**Red letters indicate core articles.**

## LUNG CANCER

| | | Paper Title | Lead Author |
|---|---|---|---|
| **Core Recommendations** | 1 | **Data overview** | Hisao Asamura Already published |
| | 2 | **T descriptors** | Paul Van Schil Already published |
| | 3 | **N descriptors** | James Huang Already published |
| | 4 | **M descriptors** | Kwun Fong Already published |
| | 5 | **Stage grouping** | Ramon Rami-Porta Already published |
| | 6 | Neuroendocrine | Ming Tsao, Andrew Nicholson |
| | 7 | Molecular | David Carbone, Fred Hirsch |
| | 8 | R factor | John Edwards |
| | 9 | Prognostic factor | Frank Detterbeck |
| | 10 | Prognostic grouping | Frank Detterbeck, David Carbone, Fred Hirsch |
| Additional Recommendations | 11 | Lepidic & AIS | William Travis |
| | 12 | STAS | William Travis Already published |
| | 13 | Multiple nodules | Frank Detterbeck |
| | 14 | Imaging | Jin Mo Goo |
| | 15 | Lymph node chart | Shun-ichi Watanabe |
| | 16 | Database | Paula Ugalde |
| Validation and Methodology | 17 | Validation & Methodology | Frank Detterbeck |

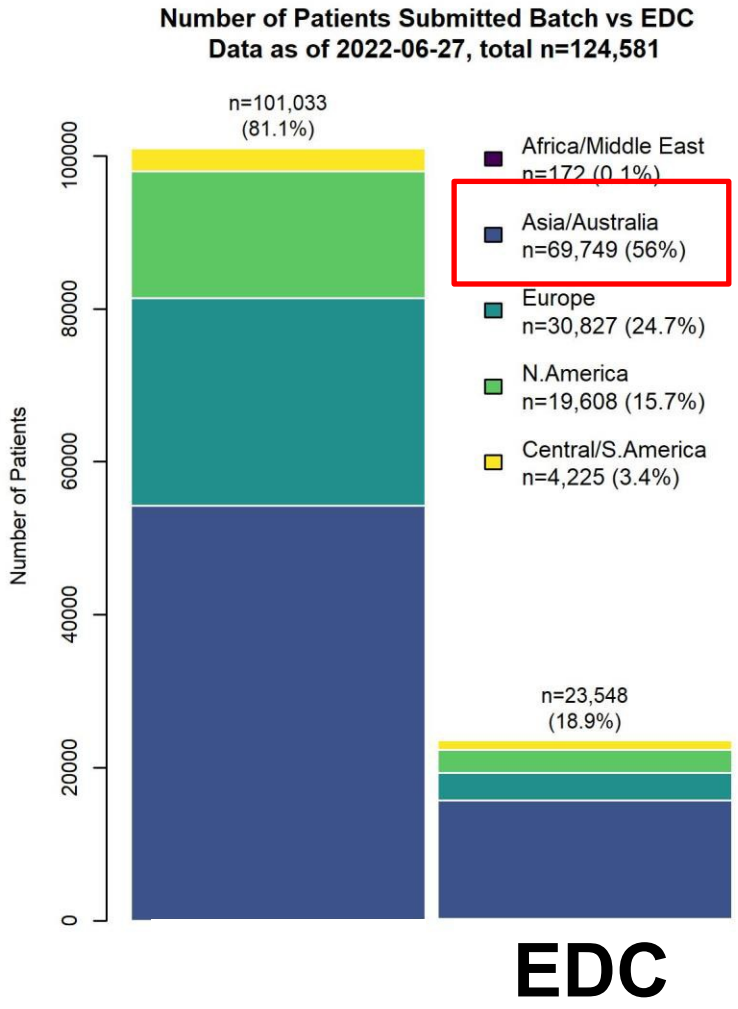
## THYMIC

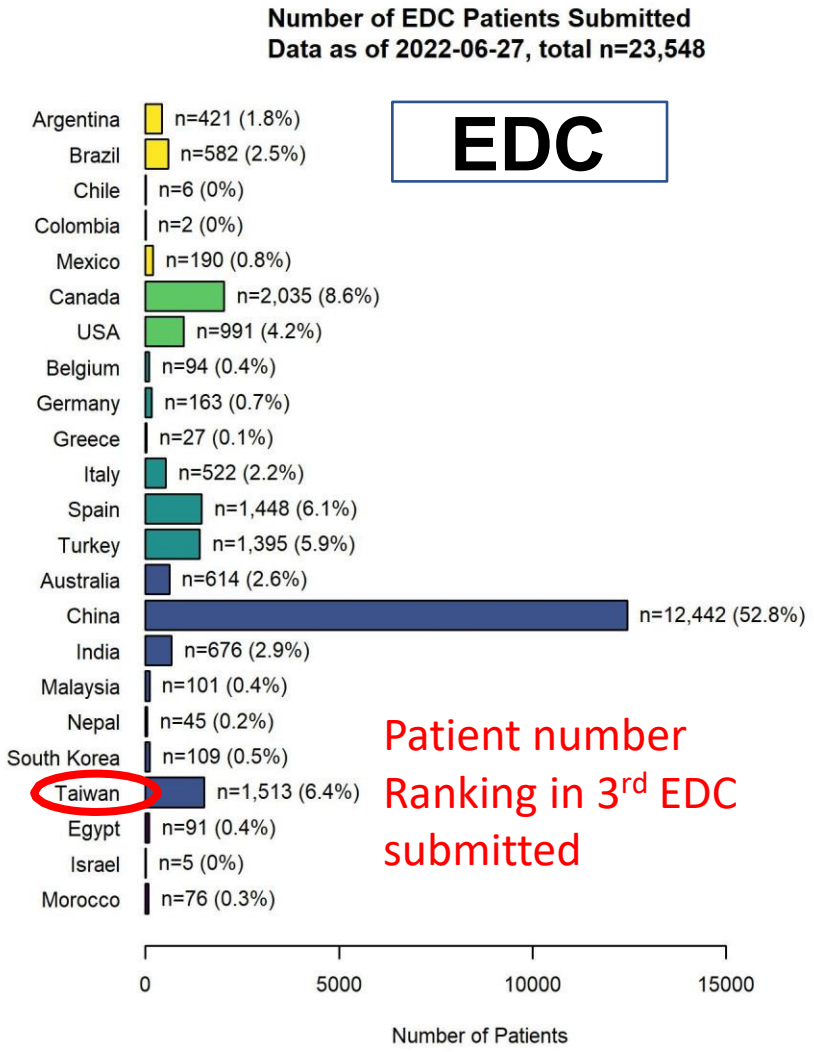
| | Paper Title | Lead Author |
|---|---|---|
| 18 | **Overview** | Enrico Ruffini, Andreas Rimner |
| 19 | **T descriptor** | Meinoshin Okumura, Mirella Marino |
| 20 | **N descriptors** | Vincent Fang |
| 21 | **M descriptors** | Nicolas Girard |
| 22 | **Stage grouping** | Enrico Ruffini, James Huang |
| 23 | Lymph node chart | Edith Marom |

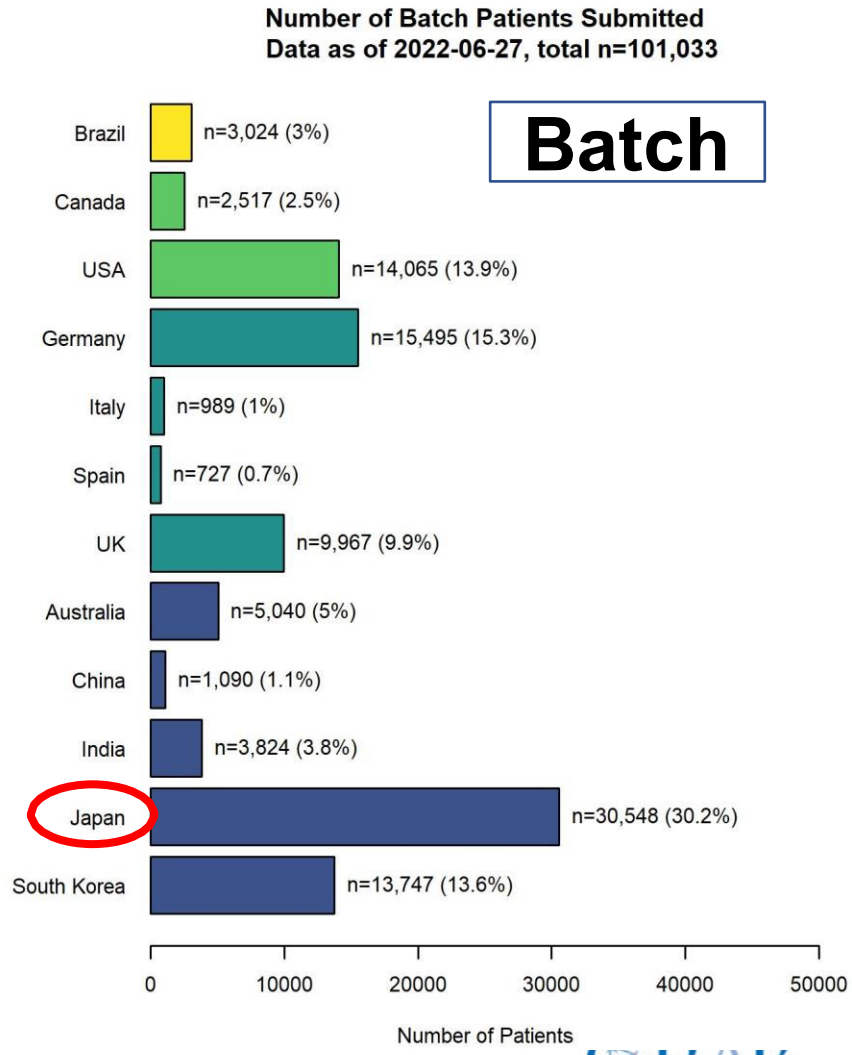
## MESOTHELIOMA

| | Paper Title | Lead Author |
|---|---|---|
| 24 | **Overview** | Andrea Wolf |
| 25 | **T descriptor** | Ritu Gill, Anna Nowak |
| 26 | **N descriptor** | Andrea Bille |
| 27 | **M descriptor** | Hedy Kindler |
| 28 | **Stage grouping** | Anna Nowak |

# Data submitted for the 9th Edition TNM Staging Project

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# 2022/02/16 已完成登錄1502 case (115.5%)-超過目標數1300

| 醫院 | 人數 | 審查狀態 |
|---|---|---|
| 台大醫院 (NTUH) | 253人 | 複審後通過 |
| 台北榮總 (TVGH) | 100人 | 審查通過 |
| 三總醫院 (TSGH) | 100人 | 審查通過 |
| 台中榮總 (VGHTC) | 116人 | 複審後通過 |
| 陽交大醫院 (YMUH) | 27人 | 審查通過 |
| 林長 (CGMH- LK) | 120人 | 複審後通過 |
| 高長 (CGMH-KS) | 100人 | 複審後通過 |
| 成大 (NCKUH) | 150人 | 複審後通過 |
| 高醫 (KMUH) | 120人 | 複審後通過 |
| 大林慈濟 (DLTZU) | 101人 | 複審後通過 |
| 雙和 (SHH) | 100人 | 複審後通過 |
| 中國 (CMUH) | 100人 | 複審後通過 |
| 馬偕(MMH) | 115人 | 複審後通過 |

ORIGINAL ARTICLE

# IASLC Lung Cancer Staging Project: The New Database to Inform Revisions in the Ninth Edition of the TNM Classification of Lung Cancer

Check for updates

## Appendix 3

*Participating Institutions in the Third Phase of the IASLC Lung Cancer Staging Project*

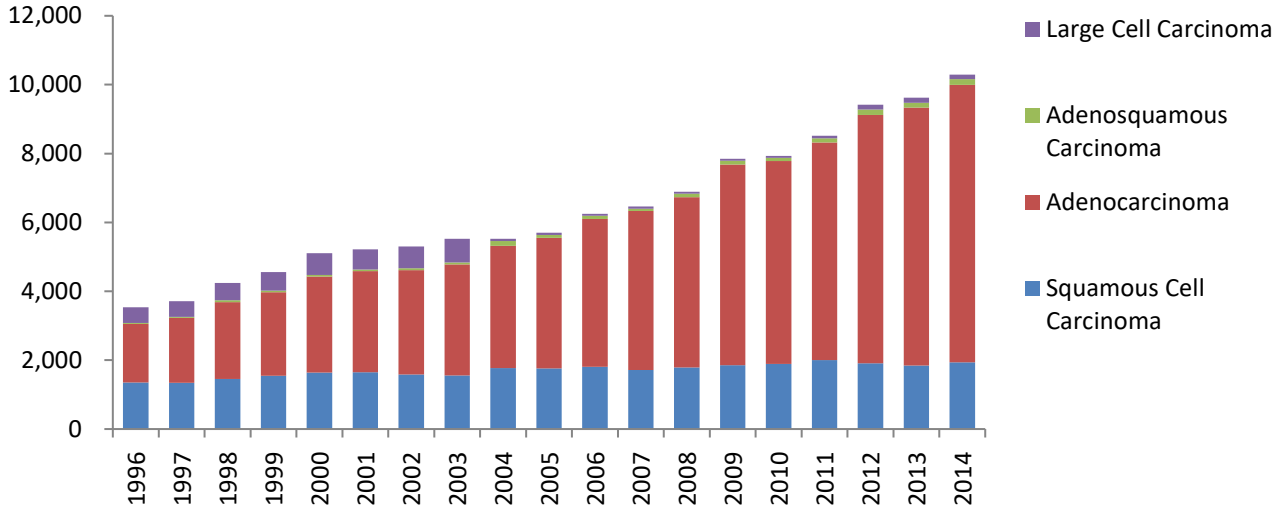
Columbus, Ohio, USA (1819 cases); J. Shih, Taiwan Society of Pulmonary and Critical Care Medicine, Taipei, Taiwan (1481 cases); E. Lim, Royal Brompton & Hare-

- Total global patients submitted: 124581→ 87339 (only 70.1% included for analysis)
- Total Taiwan patients submitted: 1513 → 1481 (up to **97.9**% included for analysis)

Hisao Asamura, et al, J Thorac Oncol. 2023 May; 18: 564-575

# Histology distribution of new database for the 9th Edition TNM Staging Project

| | Histology | Total N | Total % |
|---|---|---|---|
| Total | | 87,043 | 100 |
| NSCLC | Adenocarcinoma | 52,069 | 59.8 |
| | Squamous | 15,872 | 18.2 |
| | NSCLC NOS | 1957 | 2.2 |
| | AIS | 1142 | 1.3 |
| | Adenosquamous | 1100 | 1.3 |
| | Large cell | 1057 | 1.2 |
| NET | SCLC | 5530 | 6.4 |
| | Typical carcinoid | 1215 | 1.4 |
| | LCNEC | 689 | 0.8 |
| | Atypical carcinoid | 369 | 0.4 |
| | Mixed SCLC/NSCLC | 173 | 0.2 |
| | Carcinoid, NOS | 54 | 0.1 |
| | NET-DIN | 15 | 0.0 |
| Other | Other | 3465 | 4.0 |
| | Sarcomatoid | 615 | 0.7 |
| | Salivary type | 146 | 0.2 |
| | Multiple synchronous primary tumor | 1575 | 1.8 |




*Taiwan Lung Cancer Registry 2000-2014*

Hisao Asamura, et al, J Thorac Oncol. 2023 May; 18: 564-575

# T-category

9th Edition

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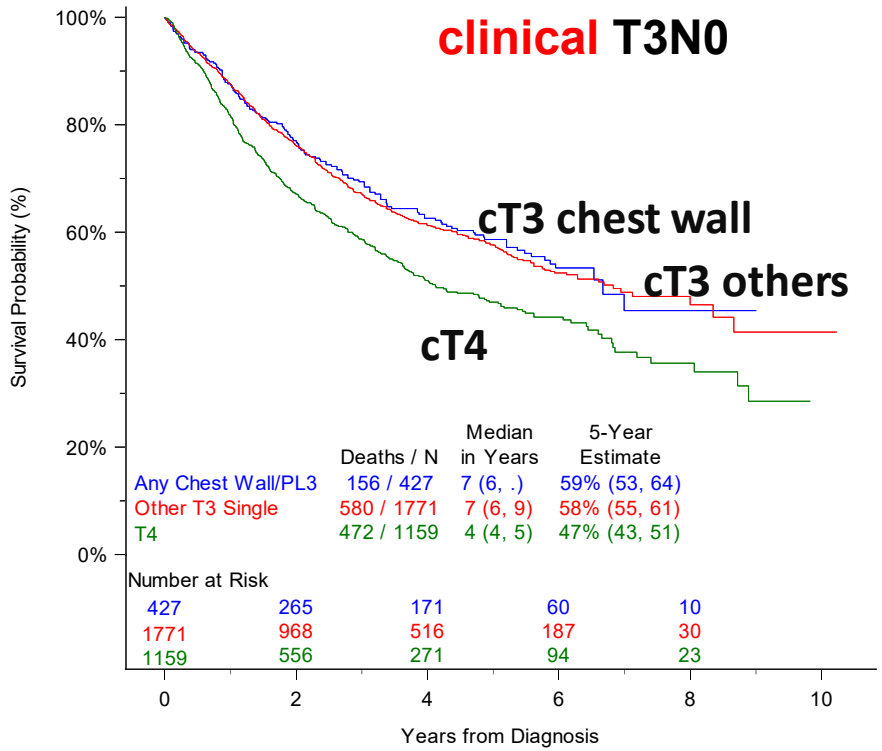
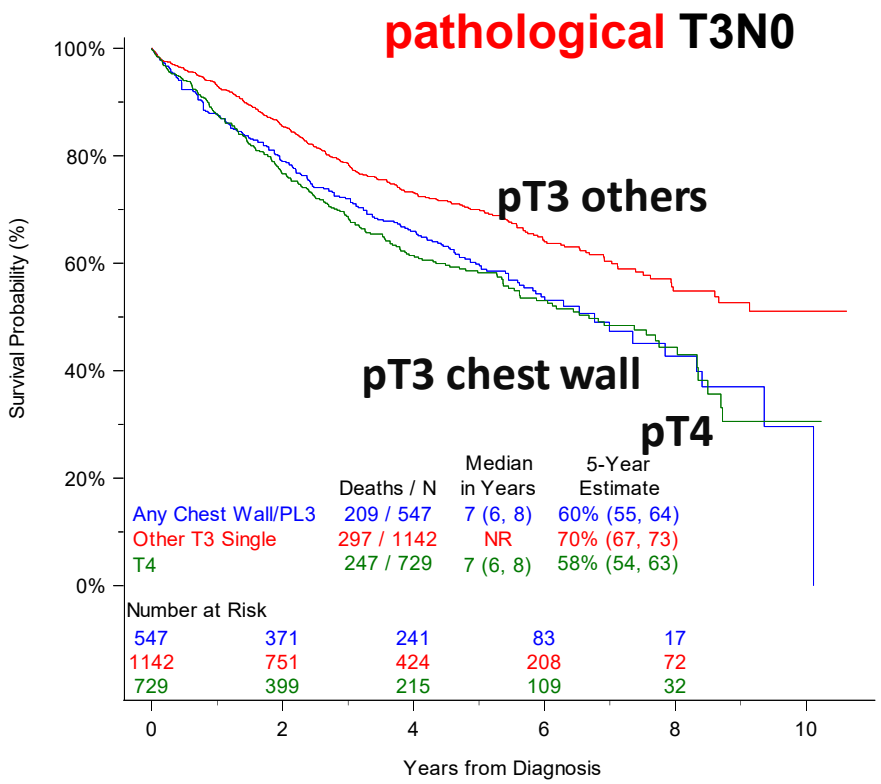
# IASLC 9th Edition, T-category:
# No change

| Proposed 9th Edition T-categories | | | 9th Edition |
|---|---|---|---|
| TX | | Primary tumor cannot be assessed | No changes |
| T0 | | No evidence of primary tumor | No changes |
| Tis | | Carcinoma in situ<br>Tis(AIS): adenocarcinoma<br>Tis(SCIS): squamous cell carcinoma | No changes |
| T1 | | Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. | No changes |
| | T1mi | Minimally invasive adenocarcinoma | No changes |
| | T1a | Tumor 1 cm or less in greatest dimension | No changes |
| | T1b | Tumor more than 1 cm but not more than 2 cm in greatest dimension | No changes |
| | T1c | Tumor more than 2 cm but not more than 3 cm in greatest dimension | No changes |
| T2 | | Tumor more than 3 cm but not more than 5 cm; or tumor with any of the following features. T2 tumors with these features are classified T2a if 4 cm or less, or if size cannot be determined; and T2b if greater than 4 cm but not larger than 5 cm.<br>• Involves main bronchus regardless of distance to the carina, but without involving the carina<br>• Invades visceral pleura<br>• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung | No changes |
| | T2a | Tumor more than 3 cm but not more than 4 cm in greatest dimension | No changes |
| | T2b | Tumor more than 4 cm but not more than 5 cm in greatest dimension | No changes |
| T3 | | Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary | No changes |
| T4 | | Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary | No changes |

# T3 analysis

- **Chest Wall/PL3** was hypothesized to have worse survival than the other T3 descriptors.
- Given inconsistent findings in clinical vs path, the consensus was that there was insufficient evidence to change the Chest Wall/PL3 classification as a T3 descriptor.



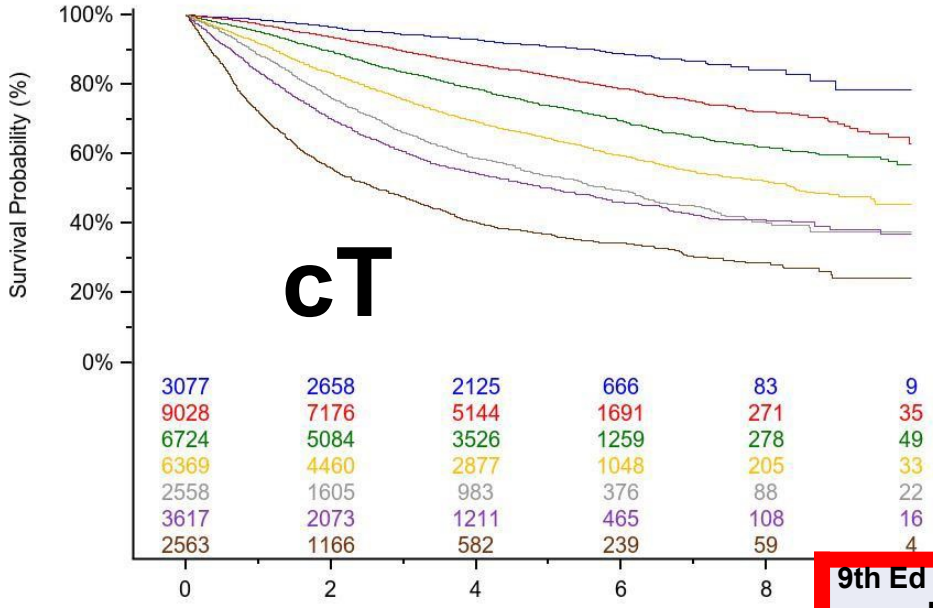

**9thEd publication will not recommend any changes to the current 8thEd T criteria.**

# IASLC 8th/9th Edition T-category

| | cT |
|---|---|
| T1a vs T1b | <0.0001 |
| T1b vs T1c | <0.0001 |
| T1c vs T2a | <0.0001 |
| T2a vs T2b | <0.0001 |
| T2b vs T3 | 0.0002 |
| T3 vs T4 | <0.0001 |

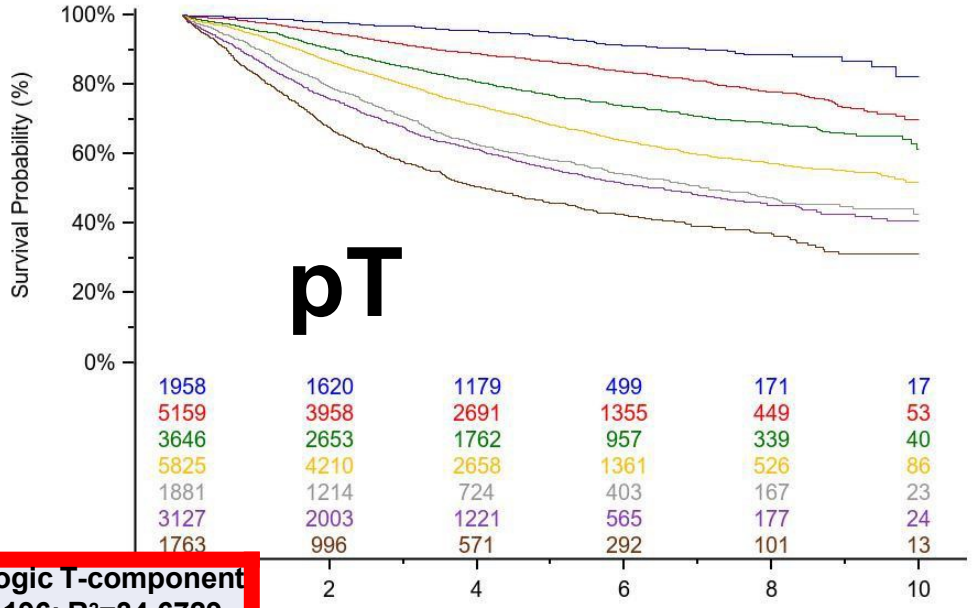
| | pT |
|---|---|
| T1a vs T1b | <0.0001 |
| T1b vs T1c | <0.0001 |
| T1c vs T2a | <0.0001 |
| T2a vs T2b | <0.0001 |
| T2b vs T3 | 0.0337 |
| T3 vs T4 | <0.0001 |

8th Ed Staging Criteria in 9th Ed Dataset
Clinical Pre-Treatment T-Categories
M0, Any N, Any R




| | Deaths / N | Median in Years | 5-Year Estimate |
|---|---|---|---|
| T1A | 271 / 3077 | NR | 91% (90, 92) |
| T1B | 1435 / 9028 | NR | 83% (82, 83) |
| T1C | 1595 / 6724 | NR | 74% (73, 75) |
| T2A | 2029 / 6369 | 8 (8, 9) | 64% (63, 66) |
| T2B | 1041 / 2558 | 6 (5, 6) | 54% (51, 56) |
| T3 | 1573 / 3617 | 5 (5, 6) | 50% (48, 52) |
| T4 | 1411 / 2563 | 3 (2, 3) | 37% (35, 39) |

8th Ed Staging Criteria in 9th Ed Dataset
Pathologic Post-Surgical T-Categories
M0, Any N, Any R




| | Deaths / N | Median in Years | 5-Year Estimate |
|---|---|---|---|
| T1A | 120 / 1958 | NR | 94% (93, 95) |
| T1B | 653 / 5159 | NR | 87% (86, 88) |
| T1C | 746 / 3646 | NR | 77% (75, 79) |
| T2A | 1659 / 5825 | NR | 68% (67, 70) |
| T2B | 695 / 1881 | 7 (7, 8) | 58% (56, 61) |
| T3 | 1252 / 3127 | 7 (6, 7) | 56% (54, 58) |
| T4 | 859 / 1763 | 4 (4, 5) | 46% (43, 49) |

| 9th Ed Adjusted HR | Clinical T-component n=33,523; $R^2$=36.3488 | | Pathologic T-component n=23,196; $R^2$=34.6729 | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| T1b (vs T1a) | 1.79 (1.58-2.04) | <.0001 | 1.97 (1.62-2.39) | <.0001 |
| T1c (vs T1b) | 1.54 (1.43-1.65) | <.0001 | 1.63 (1.46-1.81) | <.0001 |
| T2a (vs T1c) | 1.36 (1.27-1.45) | <.0001 | 1.40 (1.29-1.53) | <.0001 |
| T2b (vs T2a) | 1.35 (1.25-1.45) | <.0001 | 1.30 (1.18-1.42) | <.0001 |
| T3 (vs T2b) | 1.10 (1.02-1.19) | 0.0157 | 1.13 (1.03-1.24) | 0.0107 |
| T4 (vs T3) | 1.52 (1.41-1.63) | <.0001 | 1.33 (1.22-1.45) | <.0001 |

# T-descriptors for Lung Cancer with Multiple Lesions for the 9th Edition TNM Staging Project

Are there multiple malignant lung lesions? No

**If yes, complete the section below.**

☐ Synchronous, non-related, primary tumour(s)

T3/T4 ☐ Separate Tumour Nodules with similar histopathologic features in same lung (intrapulmonary metastases)

M1a ☐ Separate Tumour Nodules with similar histopathologic features in opposite lung (interpulmonary metastases)

☐ Multifocal adenocarcinoma with GGO/lepidic features

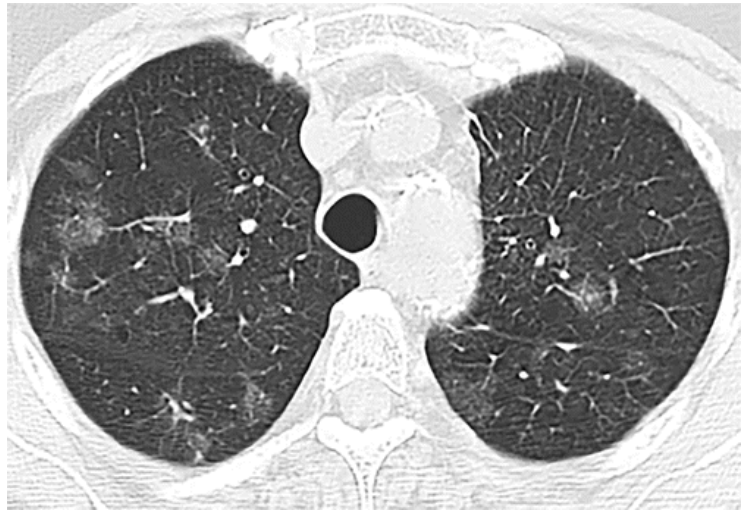
If checked, number of lesions:

☐ Diffuse pneumonic-type lung adenocarcinoma

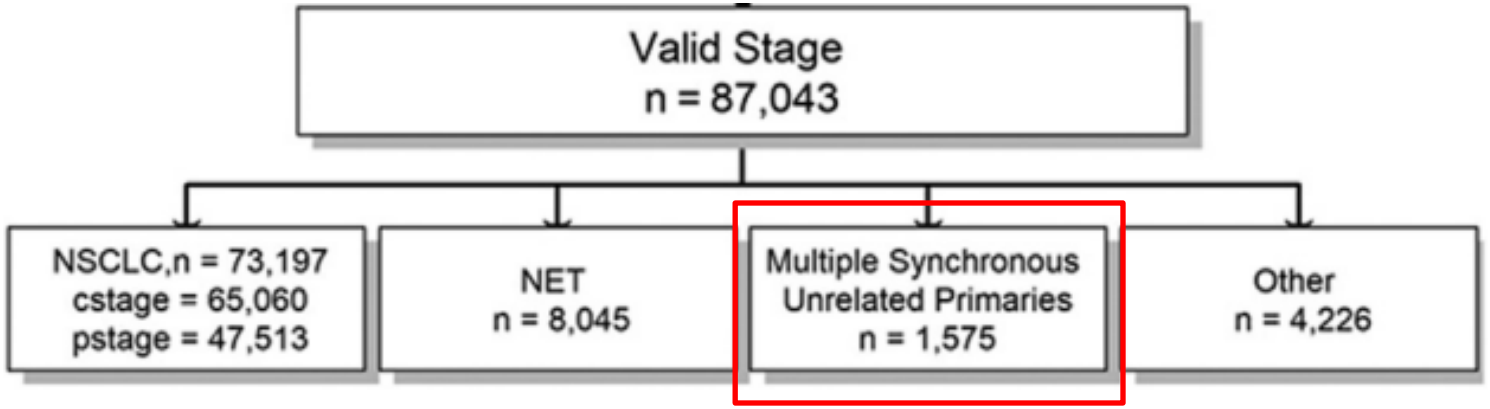
Hisao Asamura, et al, J Thorac Oncol. 2023 May; 18: 564-575

# T-descriptors for Lung Cancer with Multiple Lesions for the 9th Edition TNM Staging Project

| Lung cancer type | TNM classification |
|---|---|
| **Second Primary tumor** | Separate T, N, M for each tumor |
| **Separate tumor nodules (intrapulmonary metastasis)** | T3 if same lobe<br>T4 if same side (other lobe)<br>M1a if different side<br>Single N and M for all |
| **Multifocal adenocarcinoma with GGO/lepidic features** | T according to lesions with highest T, with (#/m) indicating multiplicity<br>Singal N and M for all lesions |
| **Diffuse, pneumonic type adenocarcinoma** | T3 if same lobe<br>T4 if same side (other lobe)<br>M1a if different side<br>Single N and M for all |

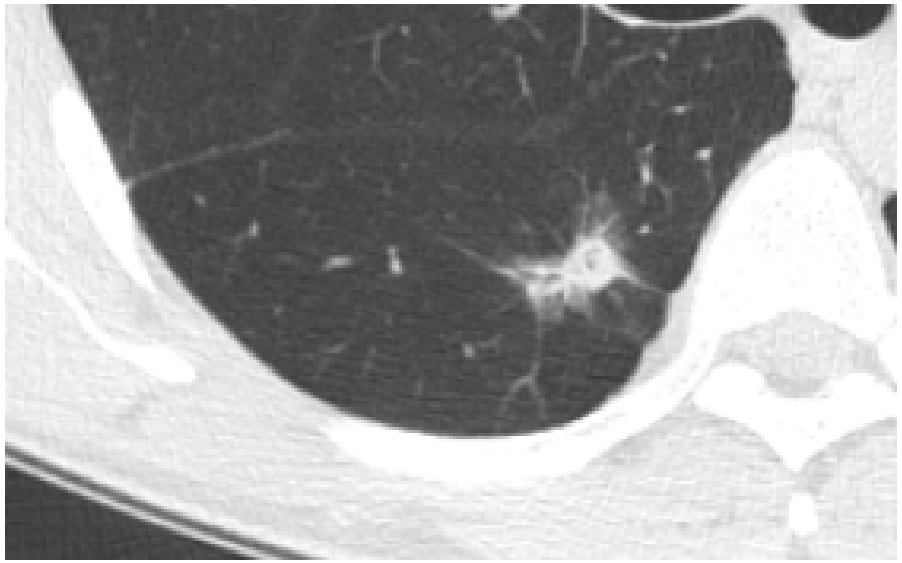


Hisao Asamura, et al, J Thorac Oncol. 2023 May; 18: 564-575

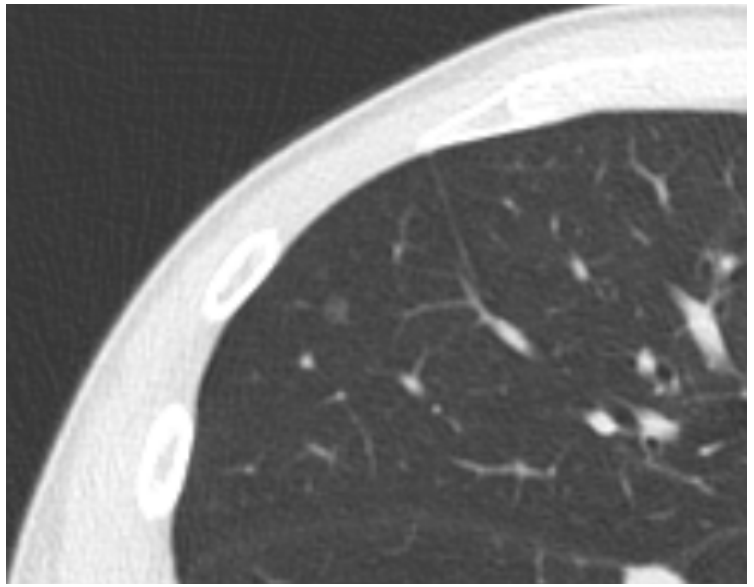



| | Separate primary tumors | A single tumor source |
|---|---|---|
| May be considered | Different **histology** (eg. ADC vs SqCC)<br>Clearly different by comprehensive histological assessment<br>SqCC that arise from **SCIS** | Exactly **matching CGH** (comparative genomic hybridization) results |
| Argument but favored | Different **radiological appearance** or **SUV in PET**<br>Different **biomarker (driver mutation)**<br>Different **rate of growth**<br>Absence of **nodal or systemic metastasis** | Similar **radiological appearance**<br>Same **biomarker pattern** (driver mutation)<br>Similar **rate of growth**<br>Significant **nodal or systemic metastasis** |

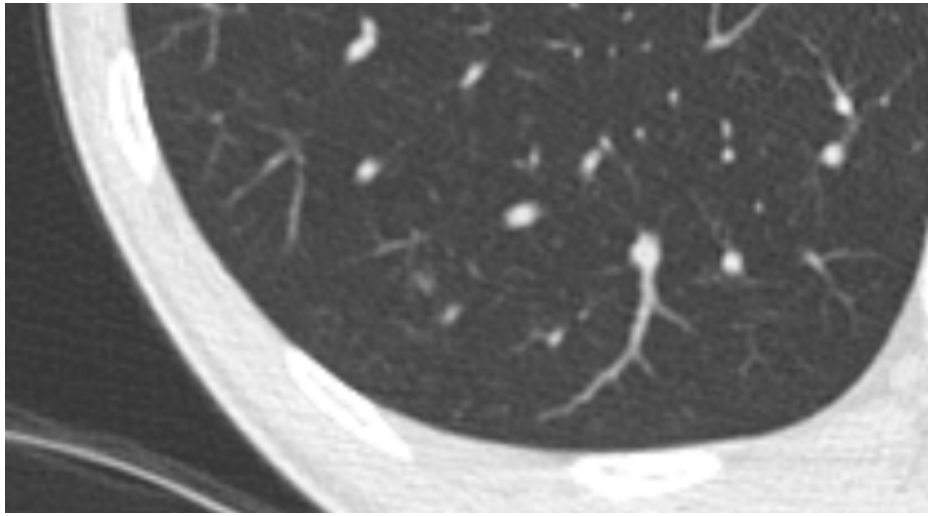
# 48 y/o man, never smoker received LDCT screening



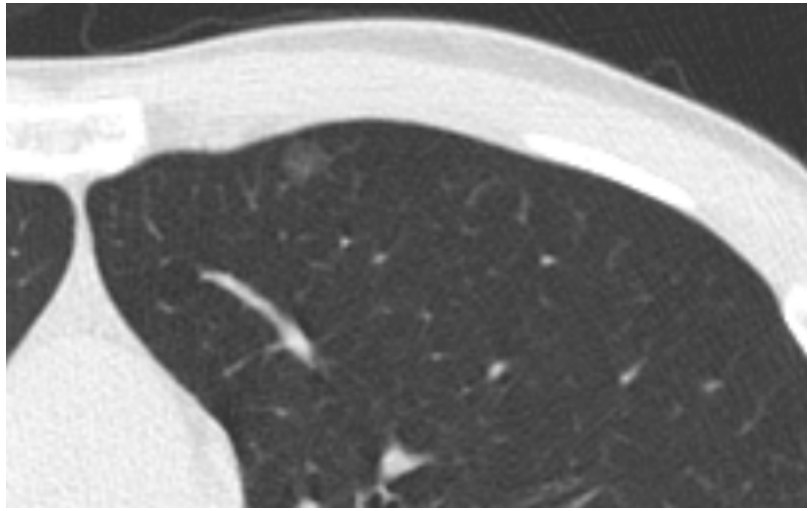
RLL 25 mm adenocarcinoma (exon 19 deletion)



RML 3.5 mm AIS wide type



RLL 3 mm AIS exon 20 in frame insertion



LUL 7 mm (not resected)

# Surgical Results of Synchronous Multiple Primary Lung Cancers: Similar to the Stage-Matched Solitary Primary Lung Cancers?

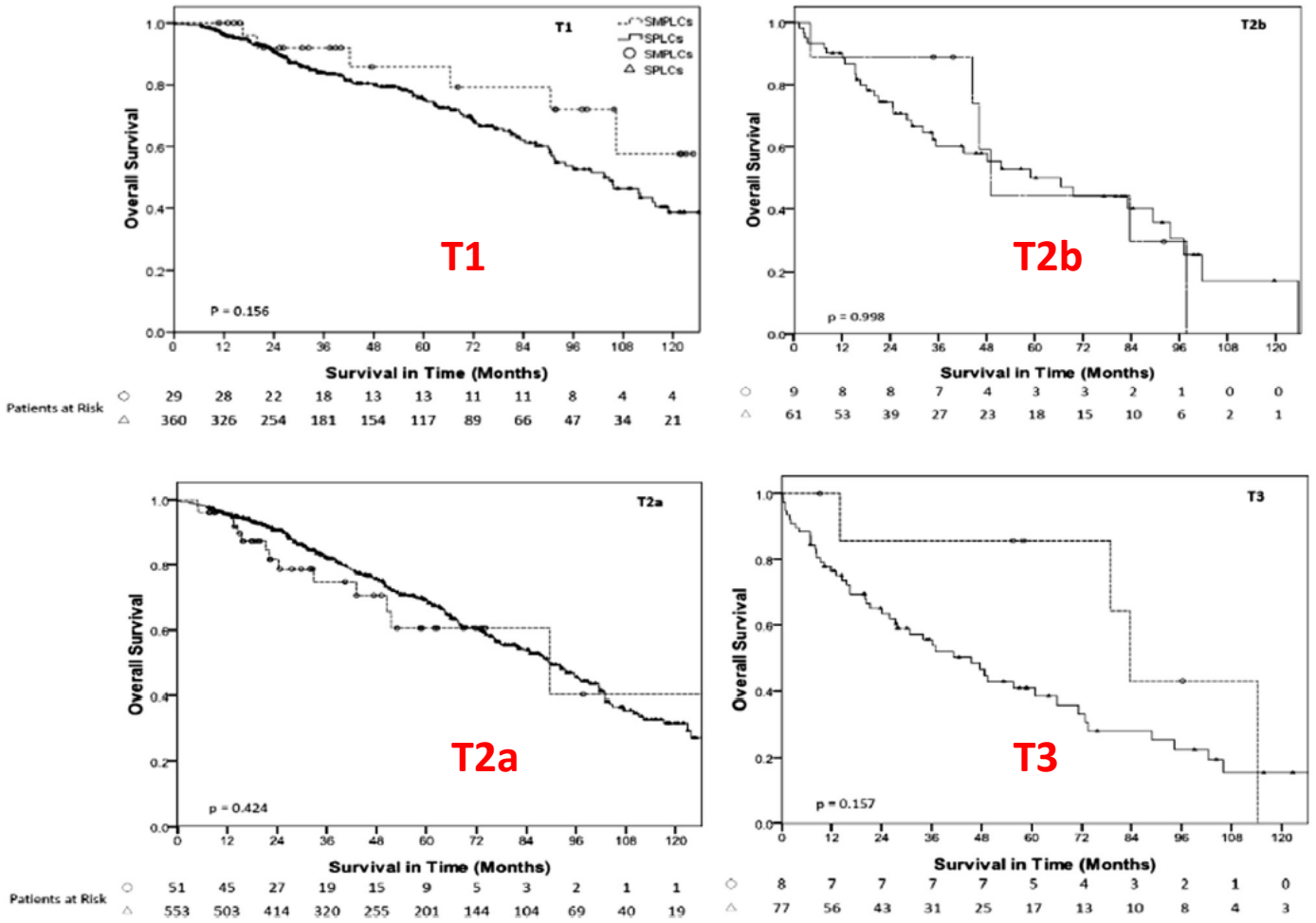



*Fig 3. Subgroup comparison of the overall survival between the highest T stage of synchronous multiple primary lung cancers (SMPLC) and the matched T stage of solitary pulmonary lung cancers (SPLC): (upper left) T1; (lower left) T2a; (upper right) T2b; and (lower right) T3. Circles indicate SMPLC; triangles indicate SPLC.*

- Between 2001 and 2011, 1995 patients underwent pulmonary resection for lung cancer
- 97 (5%) patients met the modified criteria of Martini and Melamed for SMPLC
- No significant difference in overall survival between the matched-stage SMPLC and SPLC.
- Tumor size (T stage): independent predictor of survival

Ann Thorac Surg 2013;96:1966–74

# N-category

9th Edition

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Cancer Research And Biostatistics

# Clinical and Pathologic N Category

**Instructions: Indicate N-category.** [Click here for the 8th edition criteria]

**N Category:** N0

Set all stations to "-"

**Supraclavicular**
#1R - #1L -

**Upper paratracheal**
#2R - #2L -

**Pre-vascular**
#3aR - #3aL -

**Retrotracheal**
#3p -

**Lower paratracheal**
#4R - #4L -

**Sub-aortic**
#5 -

**Para-aortic**
#6 -

**Subcarinal**
#7 -

**Paraoesophageal**
#8R - #8L -

**Pulmonary ligament**
#9R - #9L -

**N2**

**Hilar**
#10R - #10L -

**Interlobar**
#11R - #11L -

**Lobar**
#12R - #12L -

**Segmental**
#13R - #13L -

**Subsegmental**
#14R - #14L -

**Size of largest node:** cm

Method of measurement: CT

**Extracapsular involvement?** No

If 'Yes', N3 extracapsular involvement:

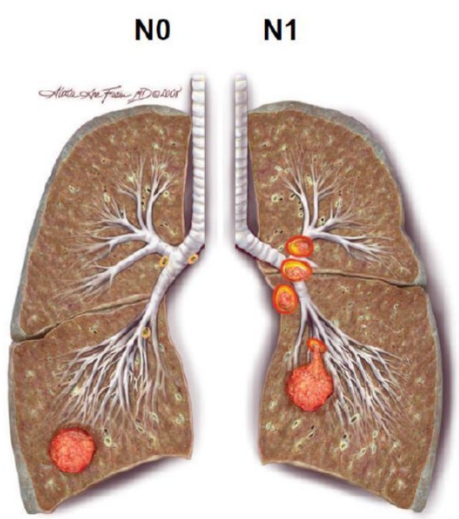
If 'Yes', N2 extracapsular involvement:

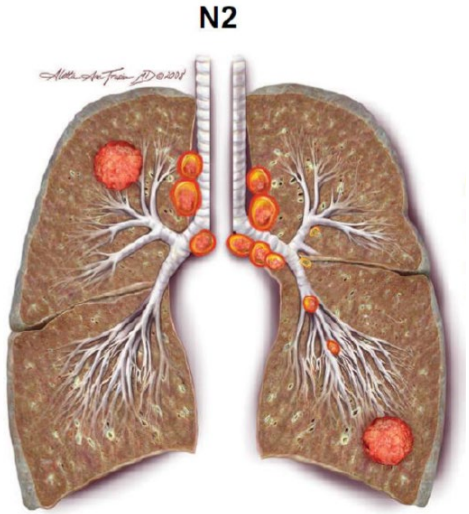
If 'Yes', N1 extracapsular involvement:

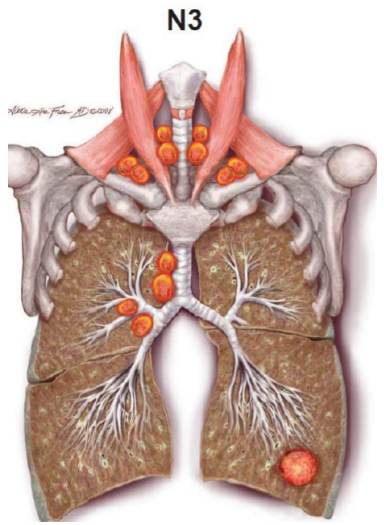
**Number of N3 nodes explored:** 0 **Number of positive N3 nodes:** 0

**Number of N2 nodes explored:** 0 **Number of positive N2 nodes:** 0

**Number of N1 nodes explored:** 0 **Number of positive N1 nodes:** 0



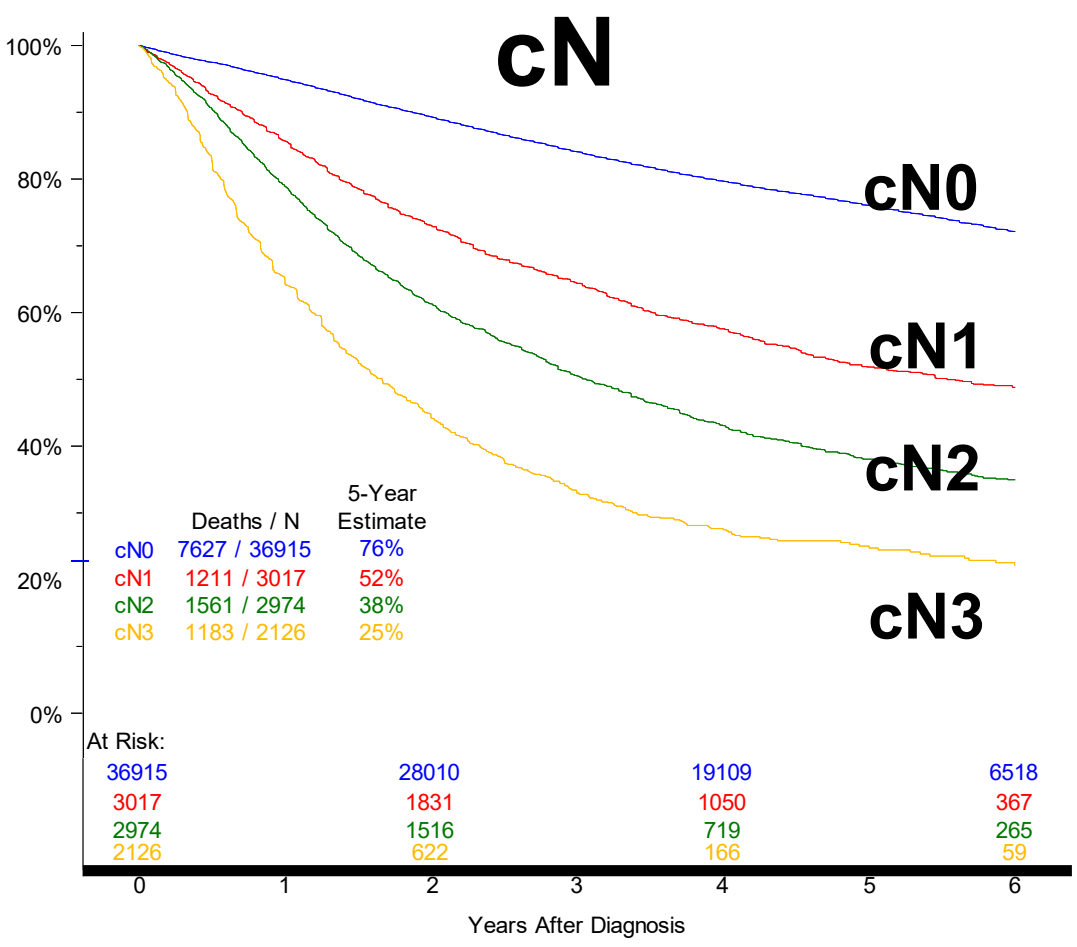

Hisao Asamura, et al, J Thorac Oncol. 2023 May; 18: 564-575

# IASLC 9th Edition, N-category:
# Split N2 into N2a and N2b

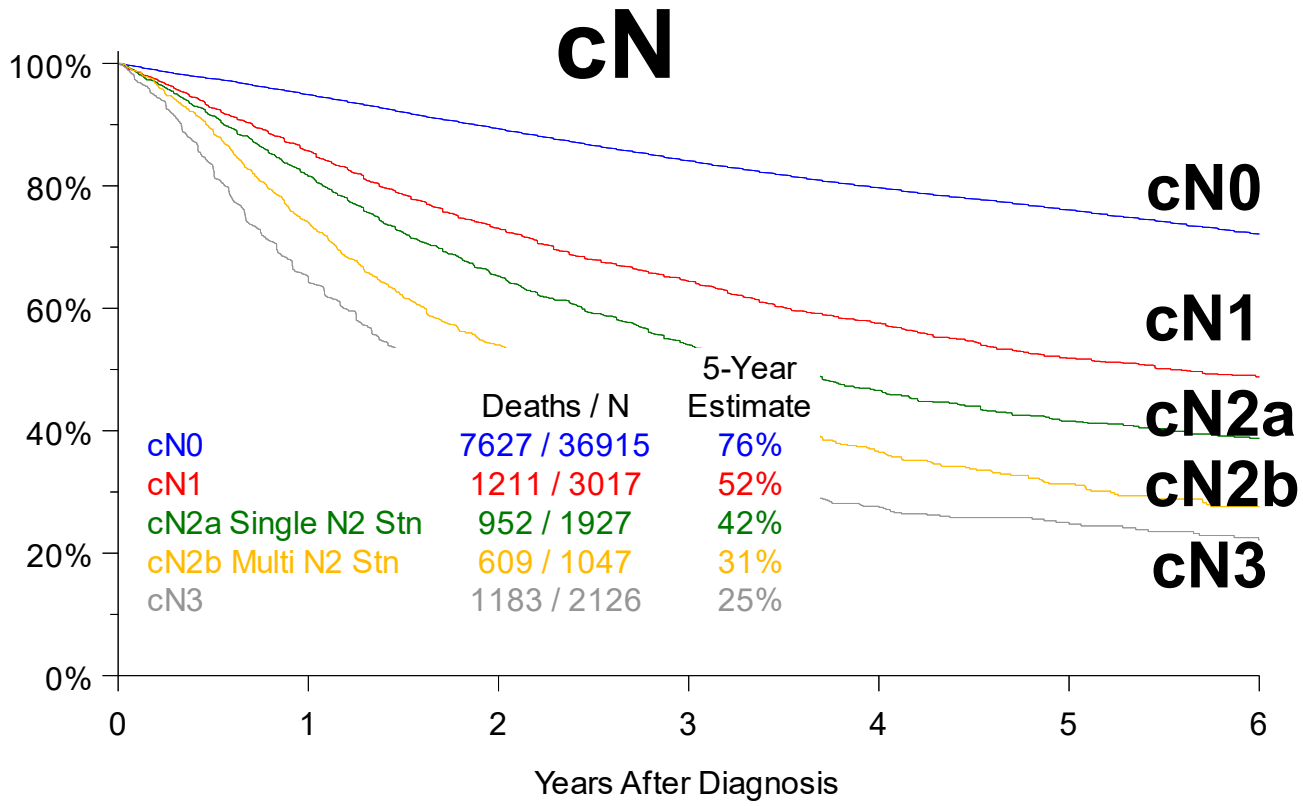
| Proposed 9th Edition N-categories | | | 9th Edition |
|---|---|---|---|
| NX | | Regional lymph nodes cannot be assessed | No changes |
| N0 | | No regional lymph node metastasis | No changes |
| N1 | | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension | No changes |
| N2 | | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) | |
| | N2a | Single N2 station involvement | Subdivided |
| | N2b | Multiple N2 station involvement | Subdivided |
| N3 | | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) | No changes |

# IASLC 8th vs 9th Edition N-category - Clinical

## 8th Edition Clinical N-category




## 9th Edition Clinical N-category




| 9th Ed Adjusted HR | cN (44,309 patients) | |
|---|---|---|
| | HR (95% CI) | P-value |
| N1 vs N0 | 1.96 (1.84, 2.08) | <0.0001 |
| N2a vs N1 | 1.42 (1.28, 1.56) | <0.0001 |
| N2b vs N2a | 1.27 (1.13, 1.43) | <0.0001 |
| N3 vs N2b | 1.51 (1.35, 1.70) | <0.0001 |

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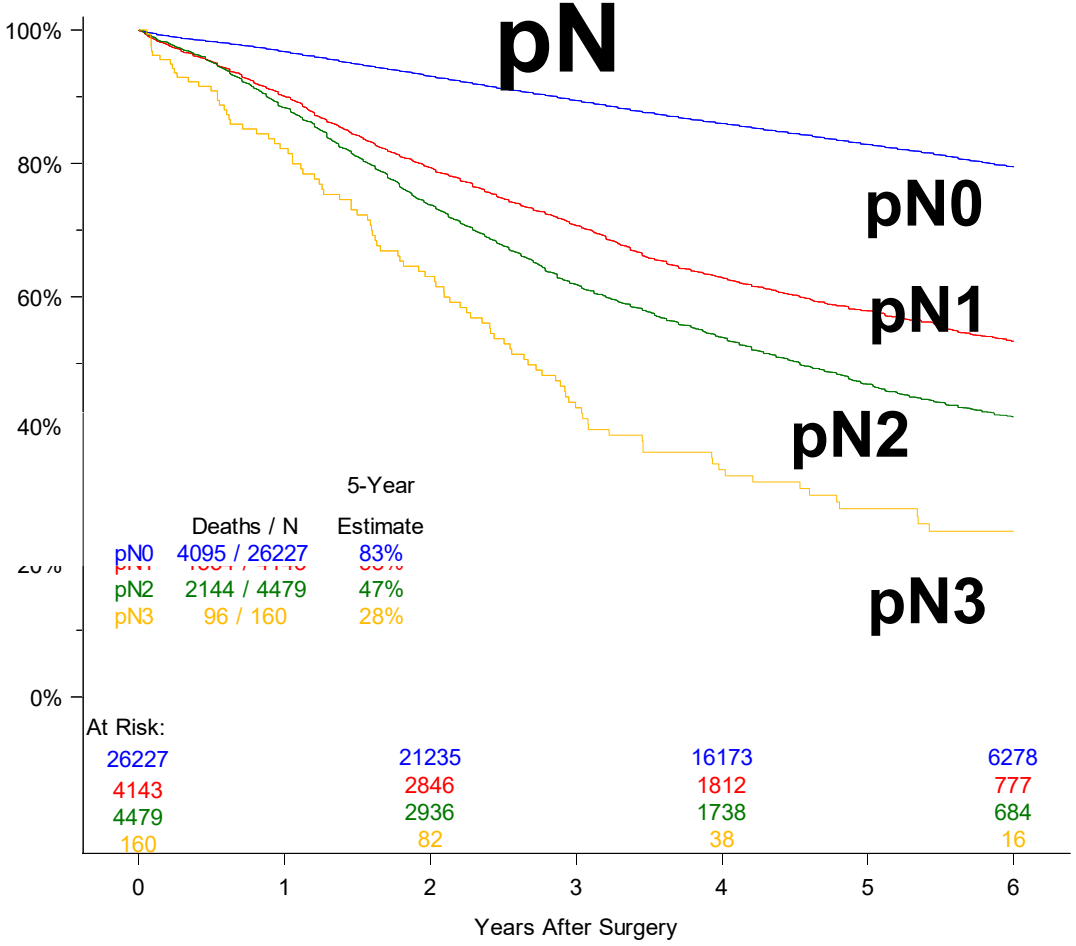
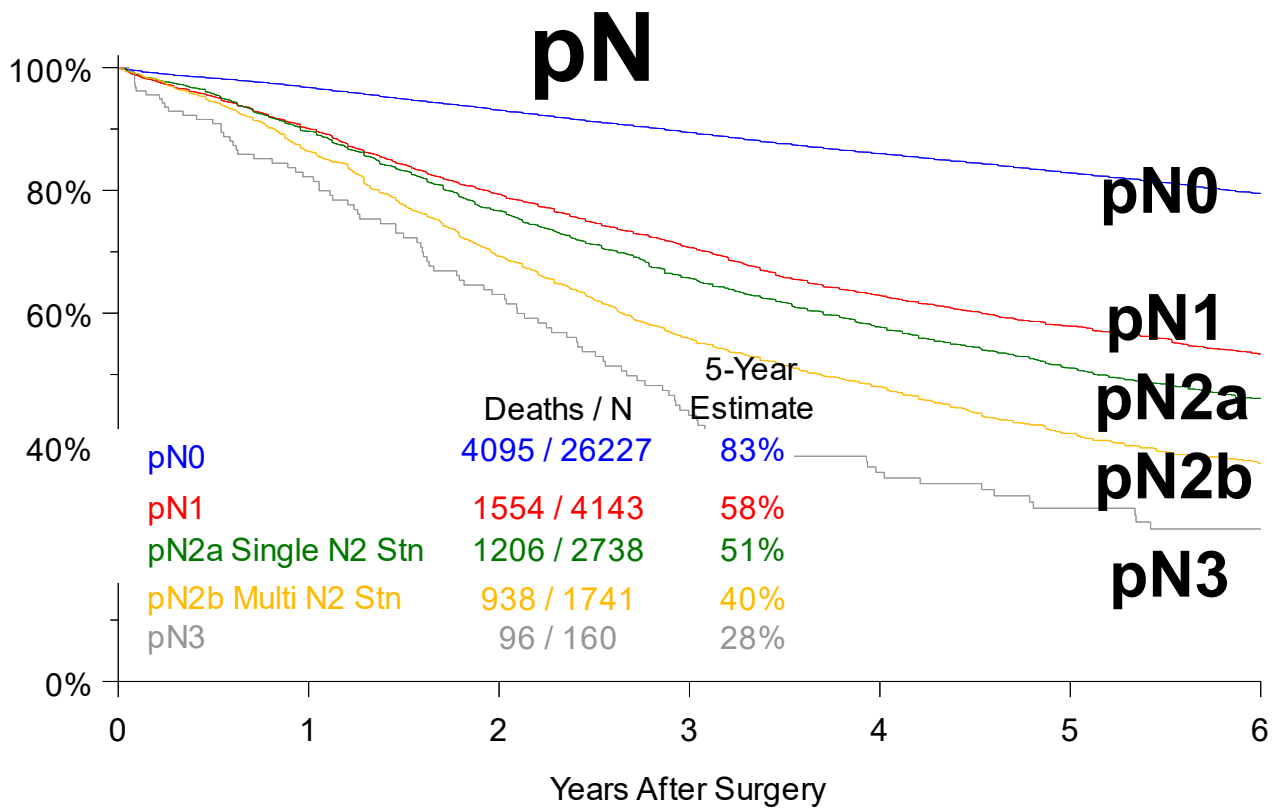
# IASLC 8th vs 9th Edition N-category - Pathologic

8th Edition Pathologic N-category




9th Edition Pathologic N-category




| 9th Ed Adjusted HR | pN (34,379 patients) | |
|---|---|---|
| | HR (95% CI) | P-value |
| N1 vs N0 | 2.40 (2.26, 2.55) | <0.0001 |
| N2a vs N1 | 1.45 (1.31, 1.60) | <0.0001 |
| N2b vs N2a | 1.46 (1.32, 1.62) | <0.0001 |
| N3 vs N2b | 1.62 (1.29, 2.03) | <0.0001 |

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# M-category

9th Edition

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Cancer Research And Biostatistics

# 1.10 M-Descriptors, by Pre-Treatment/Evaluative Findings

Are there any distant (extrathoracic) metastases? No

| Sites of distant metastases | Presence/Number of Lesions | If multiple lesions, specify number of lesions | Size of largest lesion (solid) cm |
|---|---|---|---|
| Bone: | Absent | | |
| Liver: | Absent | | |
| Brain: | Absent | | |
| Abdominal lymph nodes: | Absent | | |
| Other distant lymph nodes: | Absent | | |
| Peritoneum: | Absent | | |
| Adrenals: | Absent | | |
| Skin: | Absent | | |
| Bone Marrow: | Absent | | |
| Other: | Absent | | |

若有遠Distant metastasis則需輸入轉移部位、數量及病灶最大長度公分數

# IASLC 9th Edition, M-category:
# Divide M1c into two subcategories

| Proposed 9th Edition M-categories | | | 9th Edition |
|---|---|---|---|
| M0 | | No distant metastasis | No changes |
| M1 | | Distant metastasis | No changes |
| | M1a | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor. | No changes |
| | M1b | **Single** extrathoracic metastasis in a **single** organ and involvement of a single distant (non-regional) node | No changes |
| | M1c1 | **Multiple** extrathoracic metastases in a **single** organ system | Subdivided |
| | M1c2 | **Multiple** extrathoracic metastases in **multiple** organ systems | Subdivided |

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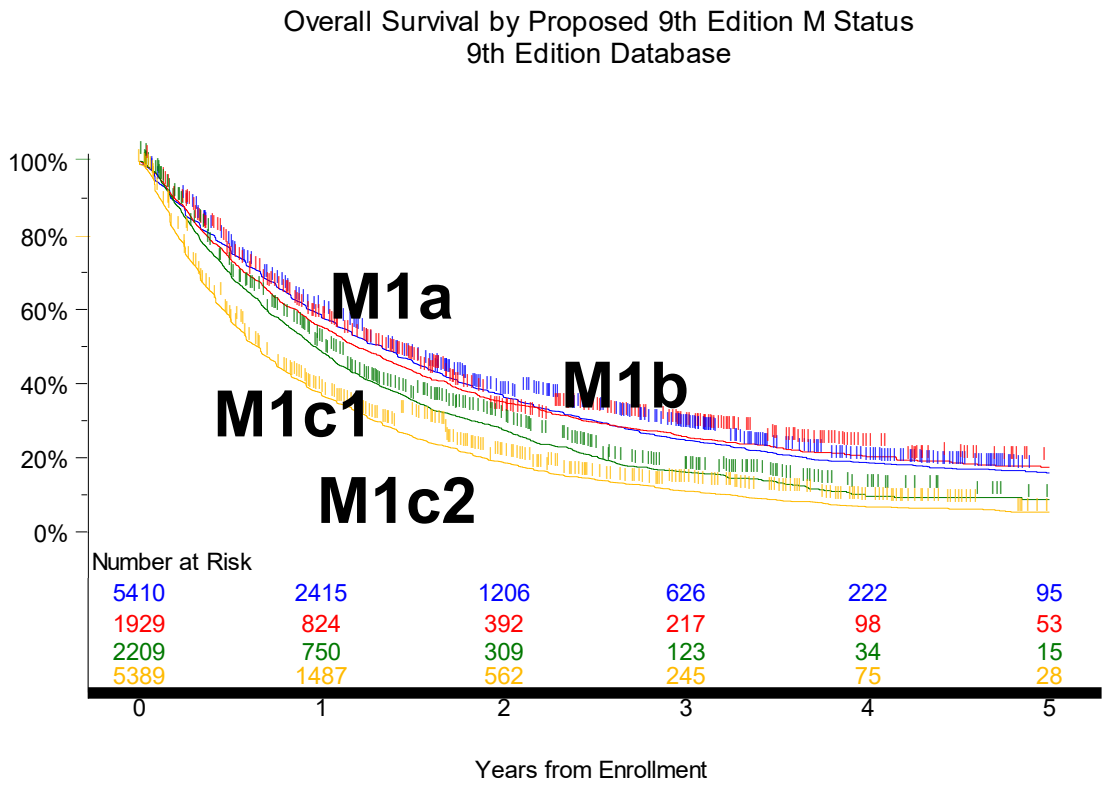
# IASLC 8th vs 9th Edition M-category – Clinical: Divide M1c into two Subcategories

**M1c1 = Multiple extrathoracic lesions in a single organ system,**

**M1c2 = Multiple extrathoracic lesions in multiple organ systems**

**M1a, M1b remain as previously defined.**

| | cM (14,937 patients) | |
|---|---|---|
| **9th Ed Adjusted HR** | **HR (95% CI)** | **P-value** |
| **M1b vs M1a** | 1.06 (0.99, 1.13) | 0.1101 |
| **M1c1 vs M1b** | 1.27 (1.17, 1.37) | <0.0001 |
| **M1c2 vs M1b** | 1.39 (1.31, 1.48) | <0.0001 |




| | Deaths / N | Median in Years | 2-Year Estimate |
|---|---|---|---|
| Group 1: M1A | 3280 / 5410 | 1.3 (1.2, 1.4) | 36% (35, 38) |
| Group 2: One site, one lesion | 1158 / 1929 | 1.2 (1.1, 1.3) | 35% (33, 38) |
| Group 3: One site, multiple lesions | 1368 / 2209 | 1 (0.9, 1) | 27% (25, 30) |
| Group 4: Multiple sites | 3923 / 5389 | 0.6 (0.6, 0.7) | 19% (17, 20) |

Log-rank p-value < .0001

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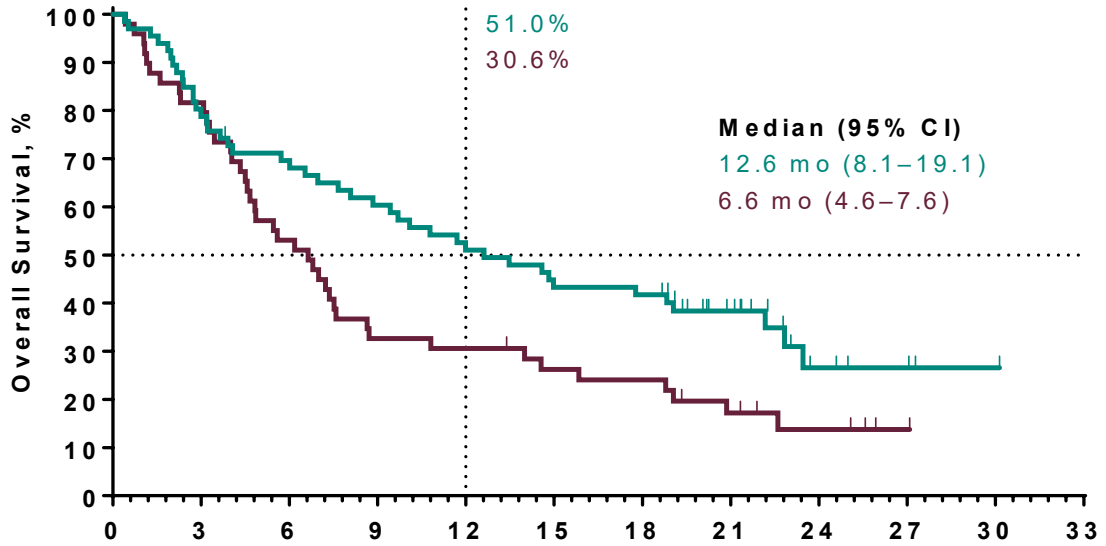
| | | FLAURA2 | NEJ009 | MARIPOSA | RAMOSE | NEJ026 | RELAY |
|---|---|---|---|---|---|---|---|
| Treatment arm | | Osimertinib + chemotherapy vs. Osimertinib | Gefitinib + chemotherapy vs. Geftinib | Amivantamab+lasertinib vs. Osimertinib (vs. lasertinib) | Osimertinib+Ramucirumab vs. Osimertinib | Erlotinib+Bevacizumab vs. Erlotiinb | Erlotinib+Ramucirumab vs. Erlotinib |
| PFS | | 25.5m vs. 16.7m<br>HR: 0.62 (0.49, 0.79); p<0.0001 | 20.9m vs.11.2m<br>HR: 0.49 (0.39-0.62; p<0.001) | 23.7m vs. 16.6m<br>HR: 0.7(0.58-0.85)<br>P<0.001 | 24.8m vs. 15.6m<br>HR: 0.55 (0.32-0.93)<br>P=0.026 | 16.9m vs. 13.3m<br>HR: 0.61 (0.42-0.88); P=0.016 | 19.4m vs. 12.4m<br>HR: 0.59 (0.46-0.76) |
| OS | | NR vs. NR<br>HR 0.90 (0.65-1.24) | 50.9m vs 38.8m<br>HR: 0.722 (0.5–0.95; p=0.021) | NR vs. NR<br>HR 0.80 (0.61-1.05) | NA | 50.7m vs. 46.2m<br>HR: 1.01 (0.68-1.49) | NR vs. NR<br>HR: 0.83 (0.53-1.30) |
| Del19 | PFS | 27.9m vs. 19.4m<br>HR: 0.60 (0.44-0.83) | NA<br>HR 0.47 (0.34-0.64) | NA<br>HR: 0.65 (0.51-0.85) | NA<br>HR: 0.49 (0.26-0.92) | 16.6m vs. 12.4m<br>HR: 0.69 (0.41-1.16) | 19.6m vs. 12.5m<br>HR: 0.65 (0.47-0.90) |
| | OS | NA | NA<br>HR: 0.65 (0.44-0.97) | NA | NA | 41.9m vs. NR<br>HR: 1.34 (0.76-2.37) | NR |
| L858R | PFS | 24.7m vs. 13.9m<br>HR: 0.63 (0.44-0.90) | NA<br>HR 0.55 (0.38-0.80) | NA<br>HR: 0.78 (0.59-1.02) | NA<br>HR: 0.66 (0.25-1.72) | 17.4m vs. 13.7m<br>HR: 0.57 (0.33-0.97) | 19.4m vs. 11.2m<br>HR: 0.62 (0.44-0.87) |
| | OS | NA | NA<br>HR: 0.80 (0.53-1.20) | NA | NA | 50.7m vs. 38.2m<br>HR: 0.79 (0.46-1.36) | NR |
| CNS mets subgroup | PFS | 24.9m vs. 13.8m<br>HR: 0.47 (0.33-0.66) | NA<br>HR: 0.32 (0.19-0.53) | NA<br>HR: 0.69 (0.53-0.92) | NA<br>HR: 0.65 (0.32-1.31) | 12.7m vs. 11.2m<br>HR: 0.78 (0.42-1.43) | Baseline CNS mets excluded |
| | OS | NA | NA<br>HR: 0.66 (0.40-1.07) | NA | NA | NR vs. 38.2m<br>HR: 0.84 (0.43-1.63) | Baseline with CNS metastases were excluded |
| Most common AE | TKI combination | anemia (47%), diarrhea (44%), nausea (43%) | Anemia (66.5%), rash (64.7%), leukopenia/neutropenia (59.4%) | Paronychia (68%), IRR (63%), rash (61%), hypoalbuminemia (48%),VTE (37%) peripheral edema (36%) | Diarrhea (67%), fatigue (53%), headache (47), epistaxis (38%), hypertension(35) | Rash (88%), diarrhea (47%), hypertension (46%), proteinuria (32%) | Diarrhea (63%), dermatitis acneiform (53%), bleeding or haemorrhage (53%), paronychia (49%) |
| | TKI alone | Diarrhea (40%), paronychia (26%), dry skin (24%) | Rash (80.7%), liver dysfunction (59.6%), diarrhea (36.8%) | Diarrhea (45%), rash (31%), paronychia (28.5%) | Diarrhea (61%), fatigue (35%), rash (30%), Lymphopenia (25%) | Diarrhea (41%), increase aminotransferase (30%), paronychia (16%) | Diarrhea (70%), dermatitis acneiform (59%), paronychia (48%) |

# Overall Survival: Liver Metastases (KN-189) Nonsquamous NSCLC

## With Liver Metastases

| | Events, n (%) | HR (95% CI) |
|---|---|---|
| Pembro/Pem/Plat | 43 (65.2) | 0.62 (0.39–0.98) |
| Placebo/Pem/Plat | 41 (83.7) | |

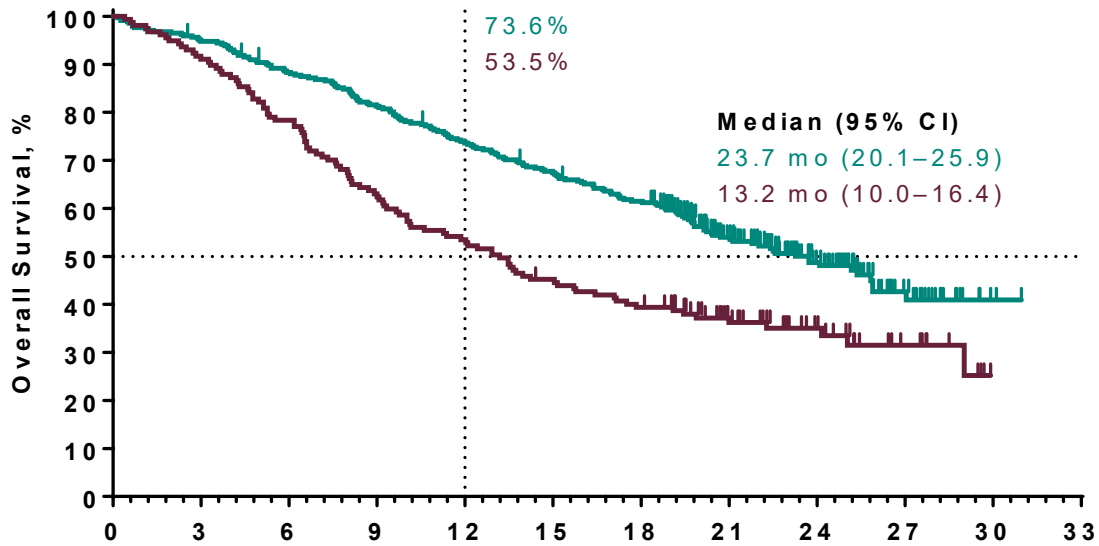



No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro/Pem/Plat | 66 | 52 | 45 | 39 | 33 | 28 | 27 | 16 | 5 | 2 | 1 | 0 |
| Placebo/Pem/Plat | 49 | 40 | 26 | 16 | 15 | 12 | 11 | 7 | 4 | 0 | 0 | 0 |

## Without Liver Metastases

| | Events, n (%) | HR (95% CI) |
|---|---|---|
| Pembro/Pem/Plat | 170 (49.4) | 0.58 (0.45–0.74) |
| Placebo/Pem/Plat | 103 (65.6) | |




No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro/Pem/Plat | 344 | 325 | 301 | 277 | 250 | 228 | 207 | 128 | 74 | 26 | 1 | 0 |
| Placebo/Pem/Plat | 157 | 143 | 123 | 99 | 84 | 70 | 61 | 38 | 22 | 10 | 0 | 0 |

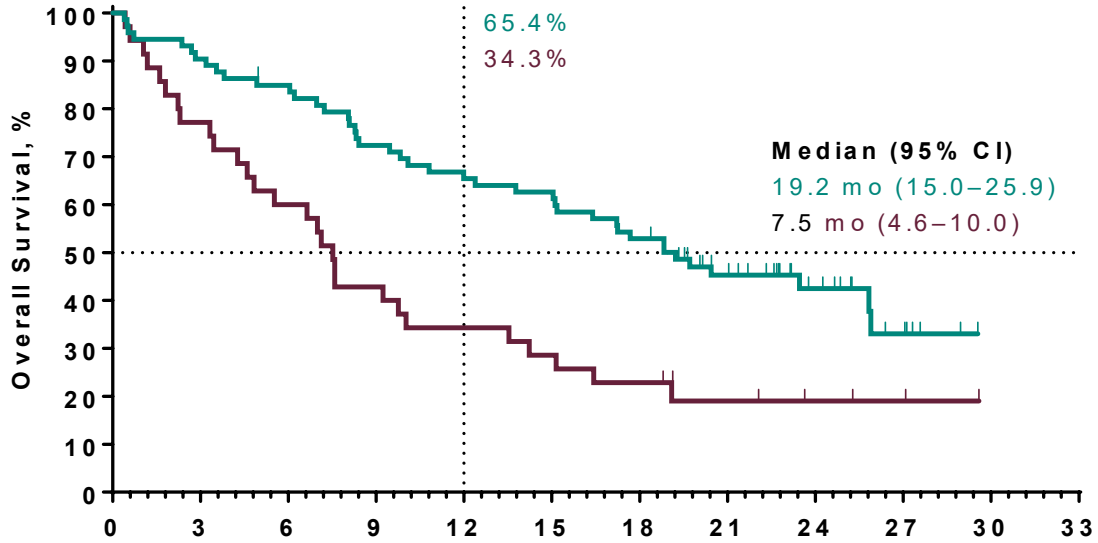
Data cutoff date: September 21, 2018.

Garassino KN189 AACR 2019

# Overall Survival: Brain Metastases (KN-189) Nonsquamous NSCLC

## With Brain Metastases

| | Events, n (%) | HR (95% CI) |
|---|---|---|
| Pembro/Pem/Plat | 42 (57.5) | 0.41 (0.24–0.67) |
| Placebo/Pem/Plat | 28 (80.0) | |

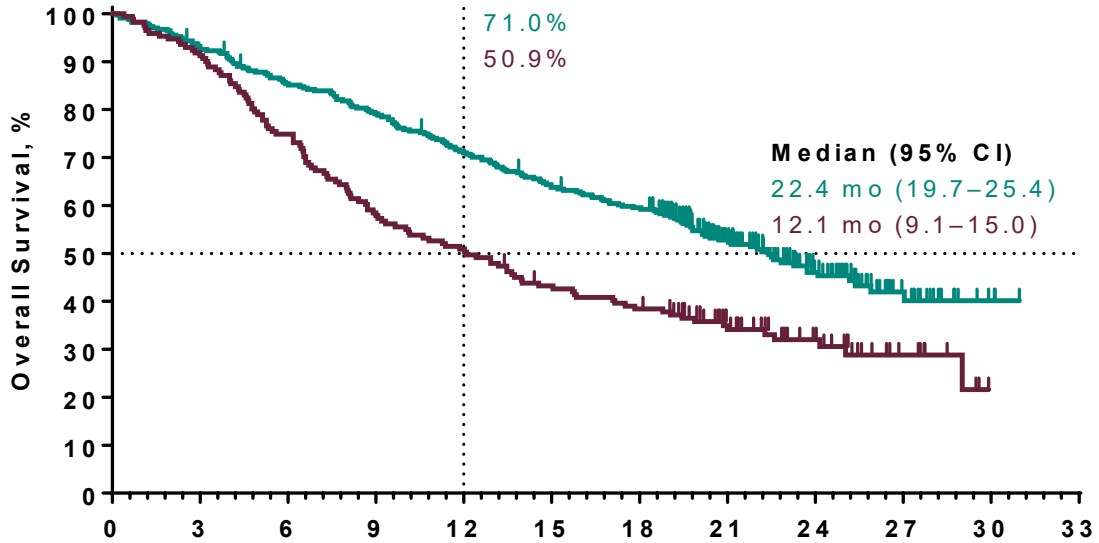



No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro/Pem/Plat | 73 | 66 | 61 | 52 | 47 | 45 | 38 | 25 | 14 | 5 | 0 | 0 |
| Placebo/Pem/Plat | 35 | 27 | 21 | 15 | 12 | 10 | 8 | 5 | 3 | 1 | 0 | 0 |

## Without Brain Metastases

| | Events, n (%) | HR (95% CI) |
|---|---|---|
| Pembro/Pem/Plat | 171 (50.7) | 0.59 (0.46–0.75) |
| Placebo/Pem/Plat | 116 (67.8) | |




No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro/Pem/Plat | 337 | 311 | 285 | 264 | 236 | 211 | 196 | 119 | 65 | 23 | 2 | 0 |
| Placebo/Pem/Plat | 171 | 156 | 128 | 100 | 87 | 72 | 64 | 40 | 23 | 9 | 0 | 0 |

Data cutoff date: September 21, 2018.

Garassino KN189 AACR 2019

# TNM Stage

9th Edition

CRAB
Cancer Research And Biostatistics

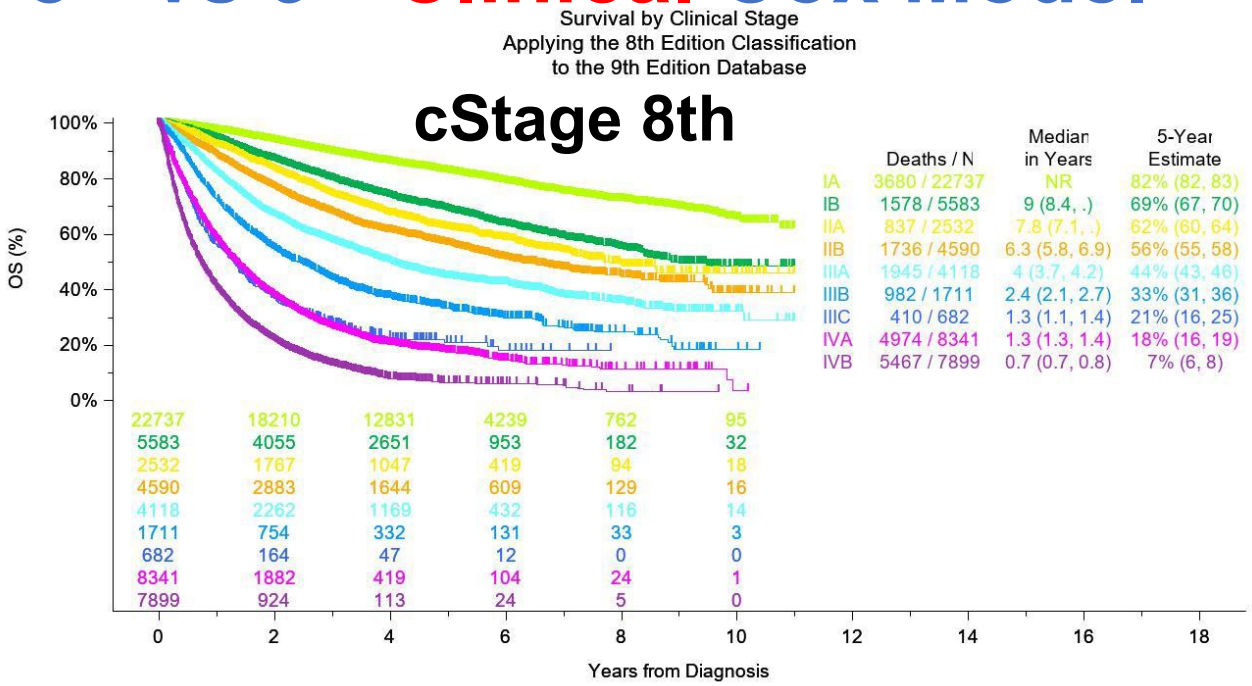
## 8th Ed Categories

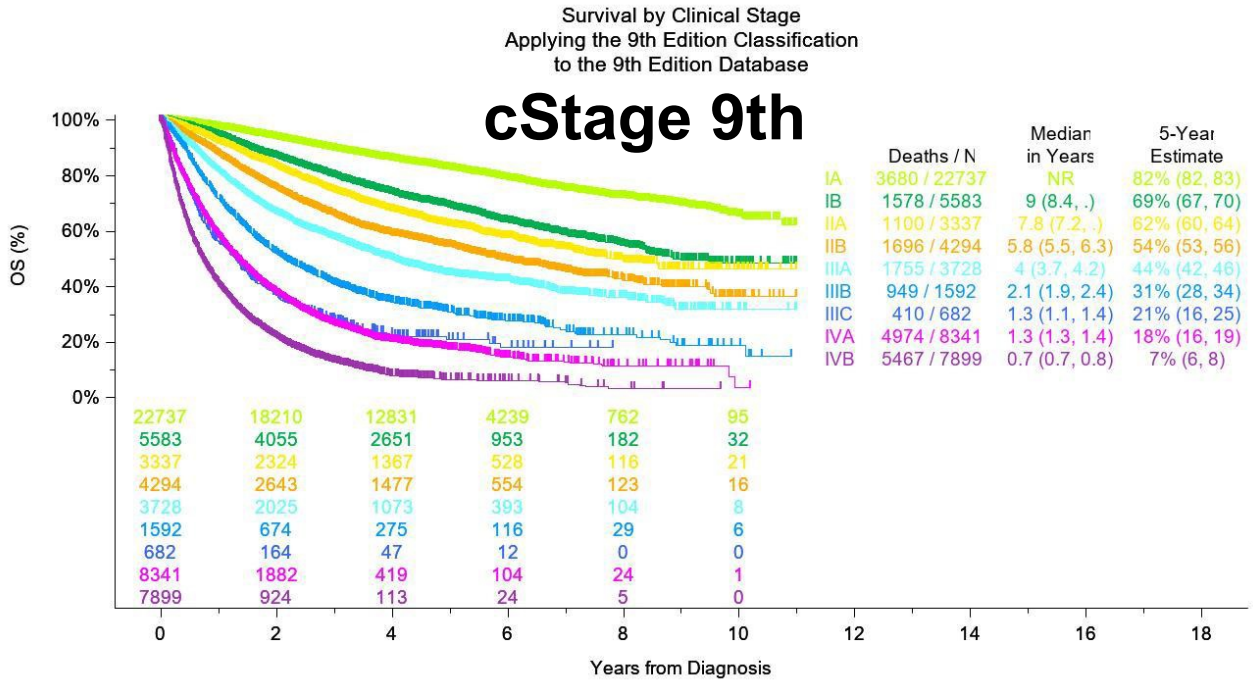
## Proposed 9th Ed TNM Categories

| 8th Ed TNM Categories | | | | | |
|---|---|---|---|---|---|
| T/M | Label | N0 | N1 | N2 | N3 |
| T1 | T1a | IA1 | IIB | IIIA | IIIB |
| | T1b | IA2 | IIB | IIIA | IIIB |
| | T1c | IA3 | IIB | IIIA | IIIB |
| T2 | T2a | IB | IIB | IIIA | IIIB |
| | T2a >3-4 | IB | IIB | IIIA | IIIB |
| | T2b >4-5 | IIA | IIB | IIIA | IIIB |
| T3 | T3 >5-7 | IIB | IIIA | IIIB | IIIC |
| | T3 Inv | IIB | IIIA | IIIB | IIIC |
| | T3 Sat | IIB | IIIA | IIIB | IIIC |
| T4 | T4 > 7 | IIIA | IIIA | IIIB | IIIC |
| | T4 Inv | IIIA | IIIA | IIIB | IIIC |
| | T4 Ipsi Nod | IIIA | IIIA | IIIB | IIIC |
| M1 | M1a Contr Nod | IVA | IVA | IVA | IVA |
| | M1a Pleur | IVA | IVA | IVA | IVA |
| | M1b Single Lesion | IVA | IVA | IVA | IVA |
| | M1c Multiple Lesions | IVB | IVB | IVB | IVB |

| Proposed 9th Ed TNM Categories | | | | | | |
|---|---|---|---|---|---|---|
| T/M | Label | | N1 | N2 | | N3 |
| 9th | | | | N2a | N2b | |
| T1 | T1a ≤1 cm | IA1 | IIA | IIB | IIIA | IIIB |
| | T1b >1 to ≤2 cm | IA2 | IIA | IIB | IIIA | IIIB |
| | | IA3 | IIA | IIB | IIIA | IIIB |
| T2 | T2a | IB | IIB | IIIA | IIIB | IIIB |
| | T2a >3 to ≤4 cm | IB | IIB | IIIA | IIIB | IIIB |
| | T2b >4 to ≤5 cm | IIA | IIB | IIIA | IIIB | IIIB |
| T3 | | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Invasion | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Satellite nodules | IIB | IIIA | IIIA | IIIB | IIIC |
| T4 | T4 > 7 cm | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Invasion | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Ipsilateral nodules | IIIA | IIIA | IIIB | IIIB | IIIC |
| M1 | M1a Contralateral nodules | IVA | IVA | IVA | IVA | IVA |
| | M1a Pleural, pericardial effusion | IVA | IVA | IVA | IVA | IVA |
| | M1b Single Extrathoracic Lesion | IVA | IVA | IVA | IVA | IVA |
| | M1c1 Mult. Lesions, Single Organ system | IVB | IVB | IVB | IVB | IVB |
| | M1c2 Mult. Lesions, Mult. Organ systems | IVB | IVB | IVB | IVB | IVB |

# 8th vs 9th Clinical Cox Model

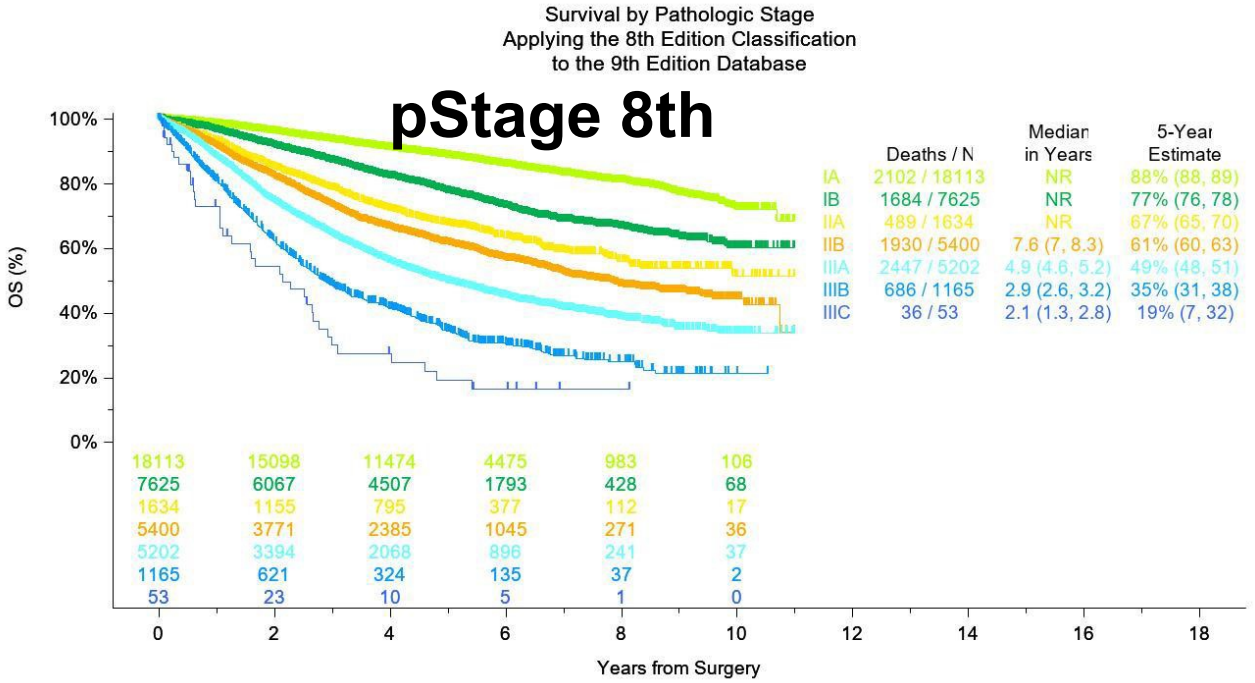


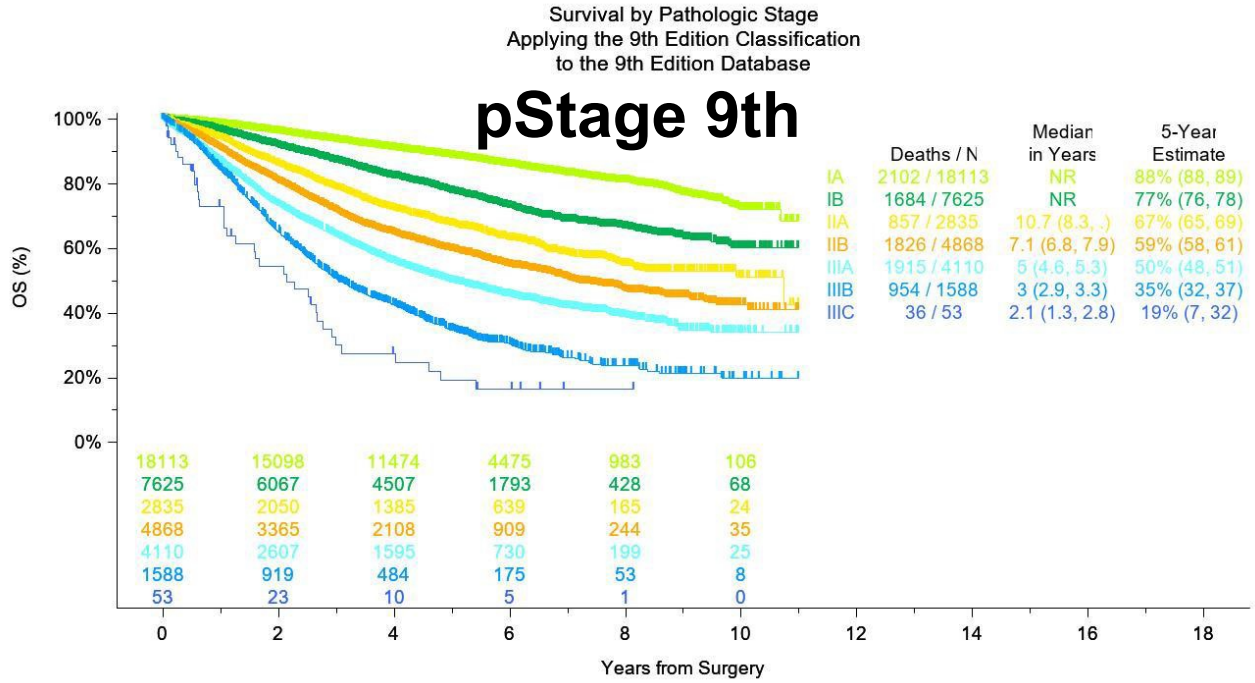




| Multivariable Cox Model | 8th Edition Clinical TNM Stage Groupings n=56,069; $R^2$=64.9103 | | |
|---|---|---|---|
| | n/N (%) | HR (95% CI) | P-value |
| IB (vs IA) | 5,519/56,069 (9.84%) | 1.77 (1.67-1.88) | <.0001 |
| IIA (vs IB) | 2,492/56,069 (4.44%) | 1.18 (1.09-1.29) | 0.0001 |
| IIB (vs IIA) | 4,502/56,069 (8.03%) | 1.21 (1.11-1.31) | <.0001 |
| IIIA (vs IIB) | 3,473/56,069 (6.19%) | 1.40 (1.31-1.50) | <.0001 |
| IIIB (vs IIIA) | 1,609/56,069 (2.87%) | 1.41 (1.30-1.53) | <.0001 |
| IIIC (vs IIIB) | 632/56,069 (1.13%) | 1.72 (1.53-1.94) | <.0001 |
| IVA (vs IIIC) | 7,931/56,069 (14.15%) | 1.10 (0.99-1.23) | 0.0627 |
| IVB (vs IVA) | 7,309/56,069 (13.04%) | 1.68 (1.61-1.75) | <.0001 |
| Age 65 or Older (vs younger than 65) | 31,819/56,069 (56.75%) | 1.43 (1.39-1.47) | <.0001 |
| Female (vs Male) | 27,423/56,069 (48.91%) | 0.83 (0.81-0.86) | <.0001 |
| Europe (vs Asia) | 11,875/56,069 (21.18%) | 1.31 (1.27-1.36) | <.0001 |
| North America (vs Asia) | 9,894/56,069 (17.65%) | 1.10 (1.05-1.14) | <.0001 |
| Rest of World (vs Asia) | 1,294/56,069 (2.31%) | 1.78 (1.63-1.95) | <.0001 |
| Squamous (vs Non-squamous) | 12,308/56,069 (21.95%) | 1.43 (1.38-1.48) | <.0001 |

| Multivariable Cox Model | 9th Edition Clinical TNM Stage Groupings n=56,069; $R^2$=65.0032 | | |
|---|---|---|---|
| | n/N (%) | HR (95% CI) | P-value |
| IB (vs IA) | 5,519/56,069 (9.84%) | 1.77 (1.67-1.88) | <.0001 |
| IIA (vs IB) | 3,286/56,069 (5.86%) | 1.18 (1.10-1.28) | <.0001 |
| IIB (vs IIA) | 3,708/56,069 (6.61%) | 1.25 (1.15-1.35) | <.0001 |
| IIIA (vs IIB) | 3,593/56,069 (6.41%) | 1.33 (1.24-1.43) | <.0001 |
| IIIB (vs IIIA) | 1,489/56,069 (2.66%) | 1.53 (1.41-1.66) | <.0001 |
| IIIC (vs IIIB) | 632/56,069 (1.13%) | 1.62 (1.44-1.83) | <.0001 |
| IVA (vs IIIC) | 7,931/56,069 (14.15%) | 1.10 (0.99-1.23) | 0.0639 |
| IVB (vs IVA) | 7,309/56,069 (13.04%) | 1.68 (1.61-1.75) | <.0001 |
| Age 65 or Older (vs younger than 65) | 31,819/56,069 (56.75%) | 1.43 (1.39-1.47) | <.0001 |
| Female (vs Male) | 27,423/56,069 (48.91%) | 0.83 (0.81-0.86) | <.0001 |
| Europe (vs Asia) | 11,875/56,069 (21.18%) | 1.31 (1.26-1.35) | <.0001 |
| North America (vs Asia) | 9,894/56,069 (17.65%) | 1.10 (1.06-1.15) | <.0001 |
| Rest of World (vs Asia) | 1,294/56,069 (2.31%) | 1.78 (1.62-1.95) | <.0001 |
| Squamous (vs Non-squamous) | 12,308/56,069 (21.95%) | 1.43 (1.38-1.48) | <.0001 |

# 8th vs 9th Pathologic Cox Model




| Multivariable Cox Model | 8th Edition Pathologic TNM Stage Groupings n=38,335; $R^2$=45.5117 | | |
|---|---|---|---|
| | n/N (%) | HR (95% CI) | P-value |
| IB (vs IA) | 7,596/38,335 (19.81%) | 1.87 (1.76-2.00) | <.0001 |
| IIA (vs IB) | 1,623/38,335 (4.23%) | 1.37 (1.24-1.51) | <.0001 |
| IIB (vs IIA) | 5,372/38,335 (14.01%) | 1.27 (1.15-1.41) | <.0001 |
| IIIA (vs IIB) | 4,500/38,335 (11.74%) | 1.60 (1.50-1.70) | <.0001 |
| IIIB (vs IIIA) | 1,155/38,335 (3.01%) | 1.48 (1.36-1.61) | <.0001 |
| IIIC (vs IIIB) | 51/38,335 (0.13%) | 1.81 (1.28-2.56) | 0.0008 |
| Age 65 or Older (vs younger than 65) | 21,520/38,335 (56.14%) | 1.65 (1.58-1.73) | <.0001 |
| Female (vs Male) | 19,860/38,335 (51.81%) | 1.00 (0.95-1.04) | 0.8553 |
| Europe (vs Asia) | 4,227/38,335 (11.03%) | 1.48 (1.39-1.57) | <.0001 |
| North America (vs Asia) | 6,423/38,335 (16.75%) | 1.49 (1.41-1.58) | <.0001 |
| Rest of World (vs Asia) | 1,393/38,335 (3.63%) | 1.51 (1.37-1.67) | <.0001 |
| Squamous (vs Non-squamous) | 8,431/38,335 (21.99%) | 1.43 (1.37-1.50) | <.0001 |

| Multivariable Cox Model | 9th Edition Pathologic TNM Stage Groupings n=38,335; $R^2$=46.0200 | | |
|---|---|---|---|
| | n/N (%) | HR (95% CI) | P-value |
| IB (vs IA) | 7,596/38,335 (19.81%) | 1.87 (1.75-1.99) | <.0001 |
| IIA (vs IB) | 2,819/38,335 (7.35%) | 1.42 (1.30-1.54) | <.0001 |
| IIB (vs IIA) | 4,176/38,335 (10.89%) | 1.27 (1.17-1.38) | <.0001 |
| IIIA (vs IIB) | 4,073/38,335 (10.62%) | 1.45 (1.35-1.55) | <.0001 |
| IIIB (vs IIIA) | 1,582/38,335 (4.13%) | 1.69 (1.56-1.83) | <.0001 |
| IIIC (vs IIIB) | 51/38,335 (0.13%) | 1.71 (1.21-2.41) | 0.0023 |
| Age 65 or Older (vs younger than 65) | 21,520/38,335 (56.14%) | 1.66 (1.58-1.73) | <.0001 |
| Female (vs Male) | 19,860/38,335 (51.81%) | 0.99 (0.95-1.03) | 0.5493 |
| Europe (vs Asia) | 4,227/38,335 (11.03%) | 1.48 (1.39-1.57) | <.0001 |
| North America (vs Asia) | 6,423/38,335 (16.75%) | 1.52 (1.43-1.61) | <.0001 |
| Rest of World (vs Asia) | 1,393/38,335 (3.63%) | 1.54 (1.39-1.70) | <.0001 |
| Squamous (vs Non-squamous) | 8,431/38,335 (21.99%) | 1.47 (1.40-1.54) | <.0001 |

# CheckMate 816 study design[a]

**Key eligibility criteria**

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per AJCC TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358

R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo and/or RT → Follow-up

**Primary endpoints**

- pCR by BIPR
- EFS by BICR

**Secondary endpoints**

- MPR by BIPR
- OS
- TTDM

**Exploratory analyses**

- EFS by surgical outcomes
- pCR and EFS by 4-gene inflammatory signature score

**Database lock date: October 14, 2022. Minimum/median follow-up: 32.9/41.4 months.**

From *The New England Journal of Medicine*, Forde PM, et al, Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, 2022;386:1973-1985.  [a]NCT02998528. [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Included patients with PD-L1 expression status not evaluable and indeterminate. [d]Nonsquamous: pemetrexed + cisplatin or paclitaxel + carboplatin; squamous: gemcitabine + cisplatin or paclitaxel + carboplatin. [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pemetrexed + cisplatin (nonsquamous only), or paclitaxel + carboplatin.

# CheckMate816 enrolled patients population in different TNM edition

**AJCC 7th**

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| **T1a**<br>• ≤2 cm | IA | IIA | IIIA | IIIB |
| **T1b**<br>• >2-3 cm | | | | |
| **T2a**<br>• >3-5 cm<br>• Invades main bronchus >2cm from carina<br>• Atelectasis/pneumonitis of entire lung | IB | | | |
| **T2b**<br>• >5-7 cm | IIA | IIB | | |
| **T3**<br>• >7 cm<br>• Invades diaphragm<br>• Invades main bronchus <2cm from carina | IIB | IIIA | | |
| **T4**<br>• Any size with invasion of mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina | IIIA | | IIIB | |

IASLC/UICC 8th edition[1]

| T/M | Label | N0 | N1 | N2 | N3 |
|---|---|---|---|---|---|
| T1 | $T1a_{\leq 1}$ | IA1 | IIB | IIIA | IIIB |
| | $T1b_{>1-2}$ | IA2 | IIB | IIIA | IIIB |
| | $T1c_{>2-3}$ | IA3 | IIB | IIIA | IIIB |
| T2 | $T2a_{Cent,\ Yisc\ Pl}$ | IB | IIB | IIIA | IIIB |
| | $T2a_{>3-4}$ | IB | IIB | IIIA | IIIB |
| | $T2b_{>4-5}$ | IIA | IIB | IIIA | IIIB |
| T3 | $T3_{>5-7}$ | IIB | IIIA | IIIB | IIIC |
| | $T3_{Inv}$ | IIB | IIIA | IIIB | IIIC |
| | $T3_{Satell}$ | IIB | IIIA | IIIB | IIIC |
| T4 | $T4_{>7}$ | IIIA | IIIA | IIIB | IIIC |
| | $T4_{Inv}$ | IIIA | IIIA | IIIB | IIIC |
| | $T4_{Ipst\ Nod}$ | IIIA | IIIA | IIIB | IIIC |

**Proposed 9th Ed TNM Categories**

| T/M | Label | N0 | N1 | N2 | | N3 |
|---|---|---|---|---|---|---|
| 9th | | | | N2a | N2b | |
| T1 | T1a ≤1 cm | IA1 | IIA | IIB | IIIA | IIIB |
| | T1b >1 to ≤2 cm | IA2 | IIA | IIB | IIIA | IIIB |
| | T1c >2 to ≤3 cm | IA3 | IIA | IIB | IIIA | IIIB |
| T2 | T2a | IB | IIB | IIIA | IIIB | IIIB |
| | T2a >3 to ≤4 cm | IB | IIB | IIIA | IIIB | IIIB |
| | T2b >4 to ≤5 cm | IIA | IIB | IIIA | IIIB | IIIB |
| T3 | T3 >5 to ≤7 cm | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Invasion | IIB | IIIA | IIIA | IIIB | IIIC |
| | T3 Satellite nodules | IIB | IIIA | IIIA | IIIB | IIIC |
| T4 | T4 > 7 cm | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Invasion | IIIA | IIIA | IIIB | IIIB | IIIC |
| | T4 Ipsilateral nodules | IIIA | IIIA | IIIB | IIIB | IIIC |

# Genetic markers, copy number alternation (CNA) and protein alternation collected in 9th Edition

**Genetic Biomarkers for this Subject**

To view complete information for a record, or to edit or delete an record, click on the entry in the Gene column.

| Gene | Sample Date | Sample Type | Platform | Custom Platform | Total Mutation | Pos/Incon? | DNA Variant | Other Variant | Gene Abnorm. |
|---|---|---|---|---|---|---|---|---|---|
| ALK | 12-JUN-2017 | Biopsy | Sanger | Hospital A Panel | | N | ALK Fusions | | |

**CNA Biomarkers for this Subject**

To view complete information for a record, or to edit or delete an record, click on the entry in the CNA column.

| CNA | Date Assessed | Type of Sample | Platform | Custom Platform | CNA Result | Average Gene Copy Number | Genotype | Average Gene Centromere Ratio | Centromere Copy Number |
|---|---|---|---|---|---|---|---|---|---|
| CCND1 11q13 AMP | 12-JUN-2017 | Biopsy | FISH | | Normal | 5 | Homozygous4 | | |

**Protein Alterations for this Subject**

To view complete information for a record, or to edit or delete an record, click on the entry in the Protein column.

| Protein | Date Assessed | Type of Sample | Platform | Antibody | % Tumor cells | Expression | % Immune cells | H-Score |
|---|---|---|---|---|---|---|---|---|
| PD-L1 | 12-JUN-2017 | Biopsy | IHC | DAKO 28-8 | 36 | Positive | 45 | 121 |
| PD-L1 | 15-JUN-2017 | Cytology | Mass spectrometry | | 32 | Negative | 42 | 181 |

# Final proposals for the 9th TNM classification

- Scheduled to be in use in January 2024
- T descriptors: No change

- N descriptors:
  Split N2 into single-station N2 (N2a) vs multiple-station N2 (N2b)

- M descriptors:
  M1a: pleural effusion/dissemination, pericardial effusion, contralateral intrapulmonary metastasis,
  M1b: single metastasis in a single extrathoracic organ
  M1c1: multiple metastases in a single extrathoracic organ system
  M1c2: multiple metastases in multiple extrathoracic organ systems

# The IASLC Lung Cancer Staging Project 1990-

| | 6th edition | 7th edition<br>1st Staging Project | 8th edition<br>2nd Staging Project | 9th edition<br>3rd Staging Project | 10th edition<br>4th Staging Project |
|---|---|---|---|---|---|
| Chairperson | Clifton Mountain | Peter Goldstraw | Ramón Rami-Porta | Hisao Asamura | Valerie Rusch |
| Publication | 2002 | 2010 | 2017 | 2024 | 2031 |
| Period of diagnosis | 1975- | 1990 to 2000 | 1999 to 2010 | 2011 to 2019 | |
| Total patients submitted | 5,319 | 100,869 | 94,708 | 124,581 | |
| Geographical origin | | | | | |
| -Europe | 0 | 58,701 (58%) | 46,560 (49%) | 30,827 (25%) | |
| -North America | 5,319 (100%) | 21,130 (21%) | 4,660 (5%) | 19,608 (16%) | |
| -Asia/Australia | 0 | 21,038 (21%) | 43,298 (46%) | 69,749 (56%) | |
| -South/Central America | 0 | 0 | 190 (0.3%) | 4,225 (3%) | |
| -Africa/Middle East | 0 | 0 | 0 | 172 (0.1%) | |
| Patients included in analysis | | 81,495 | 77,154 | 87,339 | |
| -NSCLC | 5,253 (99%) | 68,463 (84%) | 70,967 (92%) | 72,278 (83%) | |
| -SCLC | | 13,032 (16%) | 6,189 (8%) | 5,561 (7%) | |
| Treatment modalities | | | | | |
| -Surgery alone | mostly populated with surgical cases | 41% | 58% | 47% | |
| -Radiotherapy + surgery | | 5% | 2% | 2% | |
| -Chemotherapy + surgery | | 4% | 21% | 13% | |
| -Chemotherapy alone | | 23% | 9% | 11% | |
| -Radiotherapy alone | | 11% | 2% | 3% | |
| -Chemotherapy + radiotherapy | | 12% | 5% | 6% | |
| -Trimodality | | 3% | 4% | 13% | |
| Type of data | | | | | |
| -Electronic data capture | | | 3,905 (5%) | 21,505 (25%) | |
| -Batch | | | 73,251 (95%) | 65,834 (75%) | |