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EUROPEAN LUNG CANCER CONFERENCE

Geneva, Switzerland
13-16 APRIL 2016

Final Recommendation on N in TNM Classification of Lung Cancer

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APPLICANT CITY

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Disclosures:

Lecture fee from (greater than 5,000 USD)

1. **Johnson and Johnson, Co.**
2. **Covidien Japan, Co.**

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UICC 7th Edition: General Rules

Anatomical Regions and Sites

The sites in this classification are listed by code number of the International Classification of Diseases for Oncology.[17] Each region or site is described under the following headings:

- Rules for classification with the procedures for assessing the T, N, and M categories
- Anatomical sites, and subsites if appropriate
- Definition of the regional lymph nodes
- TNM Clinical classification
- pTNM Pathological classification
- G Histopathological grading
- Stage grouping
- Summary

TNM Clinical Classification

The following general definitions are used throughout:

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1–T4	Increasing size and/or local extent of the primary tumour

[17] *WHO International Classification of Diseases for Oncology ICD-O*, 3rd ed. Fritz A, Percy C, Jack A, et al., eds. Geneva: WHO; 2000.

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1–N3	Increasing involvement of regional lymph nodes

M – Distant Metastasis*

M0	No distant metastasis
M1	Distant metastasis

Note: *The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone. (The use of MX may result in exclusion from staging.)

The category M1 may be further specified according to the following notation:

Pulmonary	PUL (C34)	Bone marrow	MAR (C42.1)
Osseous	OSS (C40, 41)	Pleura	PLE (C38.4)
Hepatic	HEP (C22)	Peritoneum	PER (C48.1,2)
Brain	BRA (C71)	Adrenals	ADR (C74)
Lymph nodes	LYM (C77)	Skin	SKI (C44)
Others	OTH		

Subdivisions of TNM

Subdivisions of some main categories are available for those who need greater specificity (e.g., T1a, T1b, or N2a, N2b).

UICC 7th Edition: General Rules for pTNM

pTNM Pathological Classification

The following general definitions are used throughout:

pT – Primary Tumour

pTX	Primary tumour cannot be assessed histologically
pT0	No histological evidence of primary tumour
pTis	Carcinoma in situ
pT1–4	Increasing size and/or local extent of the primary tumour histologically

pN – Regional Lymph Nodes

pNX	Regional lymph nodes cannot be assessed histologically
pN0	No regional lymph node metastasis histologically
pN1–3	Increasing involvement of regional lymph nodes histologically

Notes

1. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.
2. Tumour deposits (satellites), i.e., macro- or microscopic nests or nodules, in the lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion (V1/2) or a totally replaced lymph node. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node, and each such nodule should be counted separately as a lymph node in the final pN determination.
3. Metastasis in any lymph node other than regional is classified as a distant metastasis.
4. [illegible] urement is made of the metastasis, not of the entire lymph node.
5. Cases with micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of '(mi)', e.g., pN1(mi).
6. The number of resected and positive nodes should be recorded.

Sentinel Lymph Node

The sentinel lymph node is the first lymph node to receive lymphatic drainage from a primary tumour. If it contains metastatic tumour this indicates that other lymph nodes may contain tumour. If it does not contain metastatic tumour, other lymph nodes are not likely to contain tumour. Occasionally there is more than one sentinel lymph node.

The following designations are applicable when sentinel lymph node assessment is attempted:

pNX(sn)	Sentinel lymph node could not be assessed
pN0(sn)	No sentinel lymph node metastasis
pN1(sn)	Sentinel lymph node metastasis

Isolated Tumour Cells

Isolated tumour cells (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or immunohistochemistry. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section. ITCs do not typically show evidence of metastatic activity

- **Direct extension** of the primary tumor is LN metastasis.
- LN metastasis in **outside the local region is M**.
- The **number** of resected and positive LNs should be recorded.

UICC 7th Edition: Lung

T2 Tumour more than 3 cm but not more than 7 cm; or tumour with *any* of the following features[2]
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension

T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension

T3 Tumour r… invades … (including … phrenic … pericardiu… less than … involveme… ectasis or … lung or separate tumour nodule(s) in the same lobe as the primary

T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

…in a contralat… …ural nodules or …rdial effusion[3]

…g tumour of any …ited to the bron… …imal to the main bronchus, is also classified as T1a.

2. T2 tumours with these features are classified T2a if 5 cm or less, or if size cannot be determined and T2b if greater than 5 cm but not larger than 7 cm.
3. Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Based on ANATOMY

UICC 7th Edition: Esophagus

Regional Lymph Nodes

The regional lymph nodes, irrespective of the site of the primary tumour, are those in the oesophageal drainage area including coeliac axis nodes and paraesophageal nodes in the neck, but not supraclavicular nodes.

TNM Clinical Classification

T – Primary Tu

TX Primary t
T0 No evide
Tis Carcinom

T1 Tumour
mucosa
T1a Tu
cu
T1b Tu

T2 Tumour
T3 Tumour
T4 Tumour
T4a Tu
diaphragm
T4b Tumour invades other adjacent structures such as aorta, vertebral body, or trachea

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–2 regional lymph nodes
N2 Metastasis in 3–6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories. For pM see page 15.

-pN0 Histological examination of a regional lymph-
include

ut the
classify

Based on NUMBER of METASTATIC NODES

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UICC 7th Edition: Stomach

Anatomical Subsites

1. Fundus (C16.1)
2. Corpus (C16.2)
3. Antrum (C16.3) and pylorus (C16.4)

Regio

The regional lymph
rigastric nodes alo
vatures, the nodes
hepatic, splenic, an
toduodenal nodes.
Involvement of ot
such as retropancre
classified as distant

TNM Cl

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosa
- T1a Tumour invades lamina propria or muscularis mucosae
- T1b Tumour invades submucosa

T2 Tumour invades muscularis propria
T3 Tumour invades subserosa

T4 Tumour perforates serosa or invades adjacent structures[1, 2, 3]
- T4a Tumour perforates serosa
- T4b Tumour invades adjacent structures[1, 2, 3]

Notes: 1. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intes-

Based on NUMBER of METASTATIC NODES

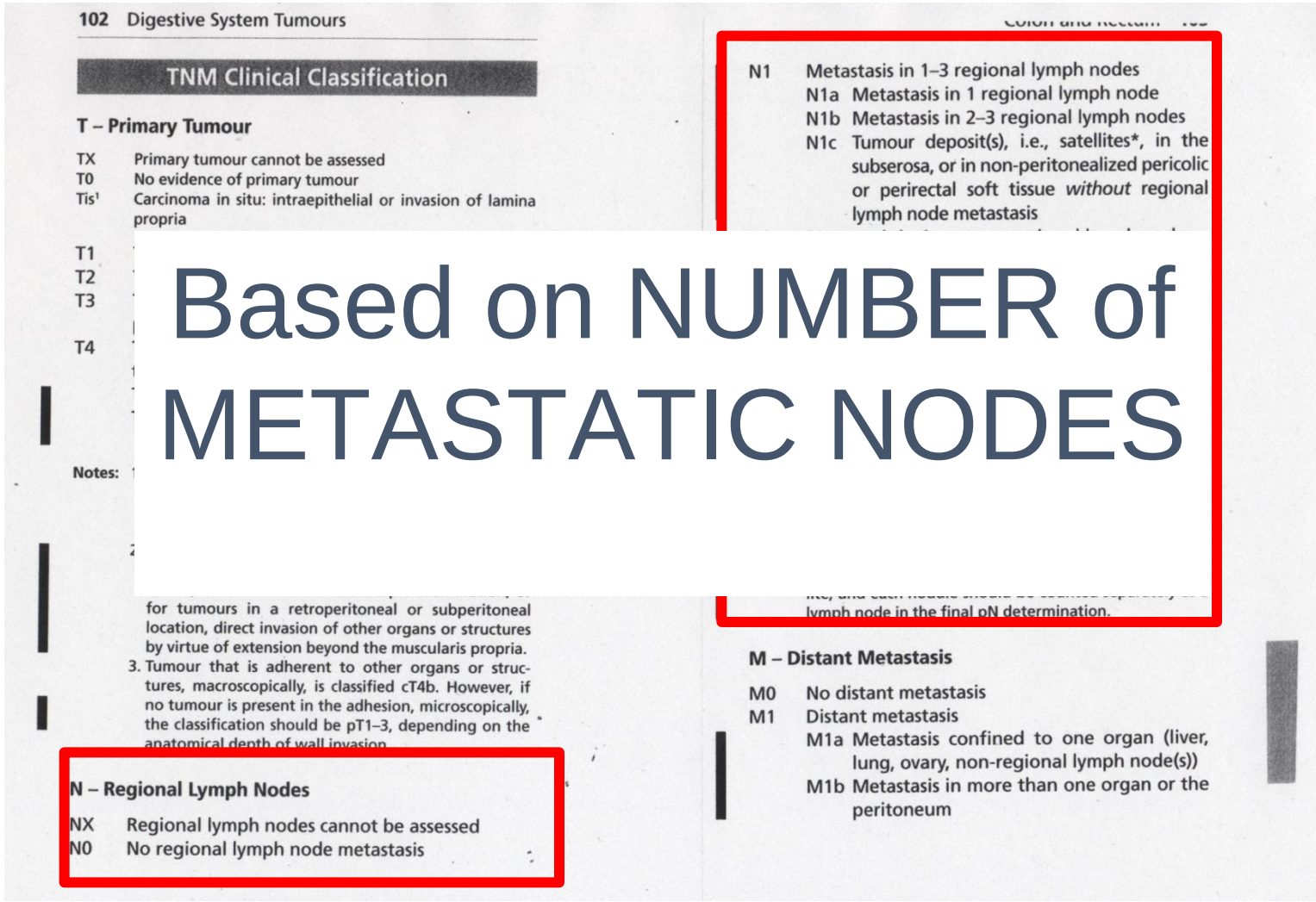
N3a Metastasis in 7–15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

Note: Distant metastasis includes peritoneal seeding, positive peritoneal cytology, and omental tumour not part of continuous extension.

UICC 7th Edition: Colorectum



102 Digestive System Tumours

TNM Clinical Classification

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis[1] Carcinoma in situ: intraepithelial or invasion of lamina propria

T1
T2
T3
T4

Notes:

for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria.
3. Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1–3, depending on the anatomical depth of wall invasion

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–3 regional lymph nodes
N1a Metastasis in 1 regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumour deposit(s), i.e., satellites*, in the subserosa, or in non-peritonealized pericolic or perirectal soft tissue *without* regional lymph node metastasis

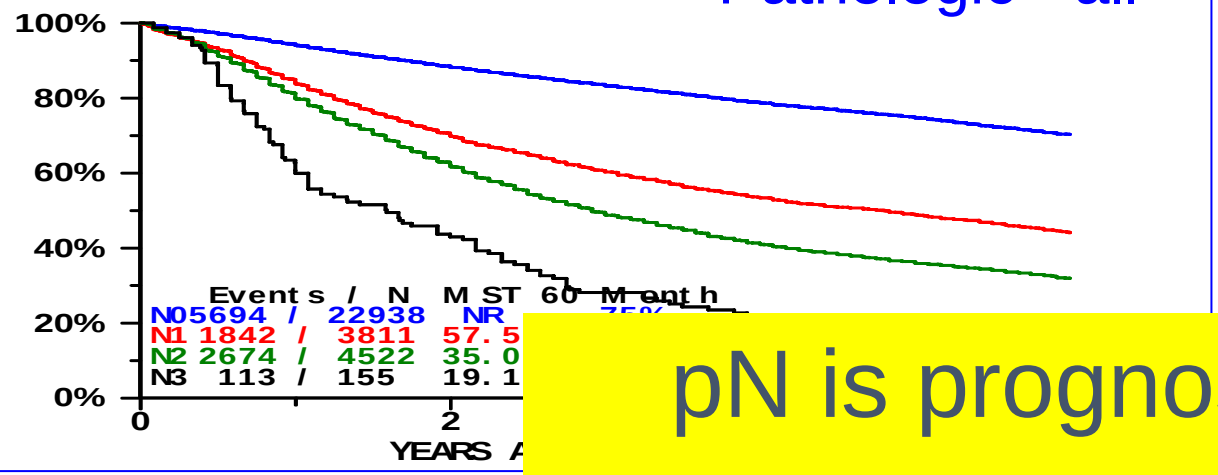
lymph node in the final pN determination.

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s))
M1b Metastasis in more than one organ or the peritoneum

Based on NUMBER of METASTATIC NODES

N: results

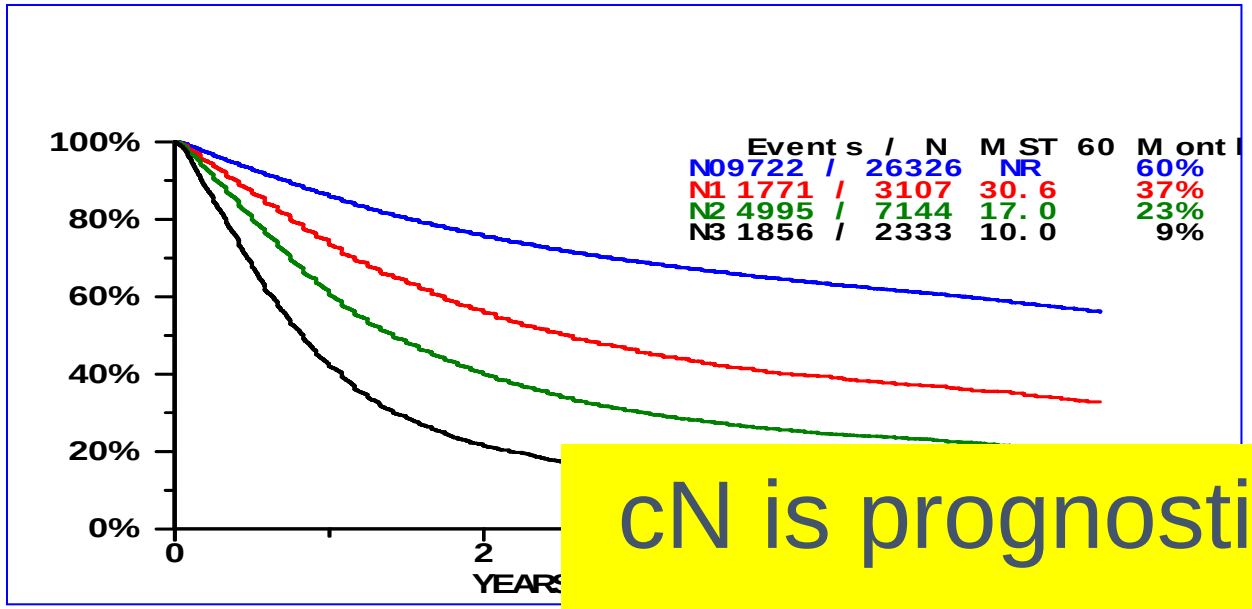


Asamura H et al. J Thorac Oncol 2015;10:1675-84

pN is prognostic very well.

N0 vs N1 vs N2 vs N3 Comparisons Adjusted for Histology (adeno vs others), Sex, Age 60+ , R0 resection, and Region. (Cox PH regression on all cases)		
comparison	**HR**	**P**
N1 vs N0	2.13	<0.0001
N2 vs N1	1.74	<0.0001
N3 vs N2	1.66	<0.0001

Clinical N: all cases



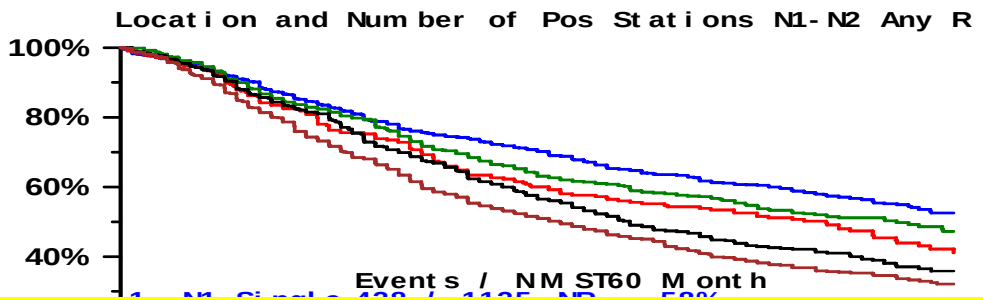
cN is prognostic very well, too.

ons
x, Age 60+, and
Region (Cox PH regression)

comparison	HR	P
N1 vs N0	1.68	<0.0001
N2 vs N1	1.42	<0.0001
N3 vs N2	1.38	<0.0001

Asamura H et al. J Thorac Oncol 2015;10:1675-84

Pathological – any R



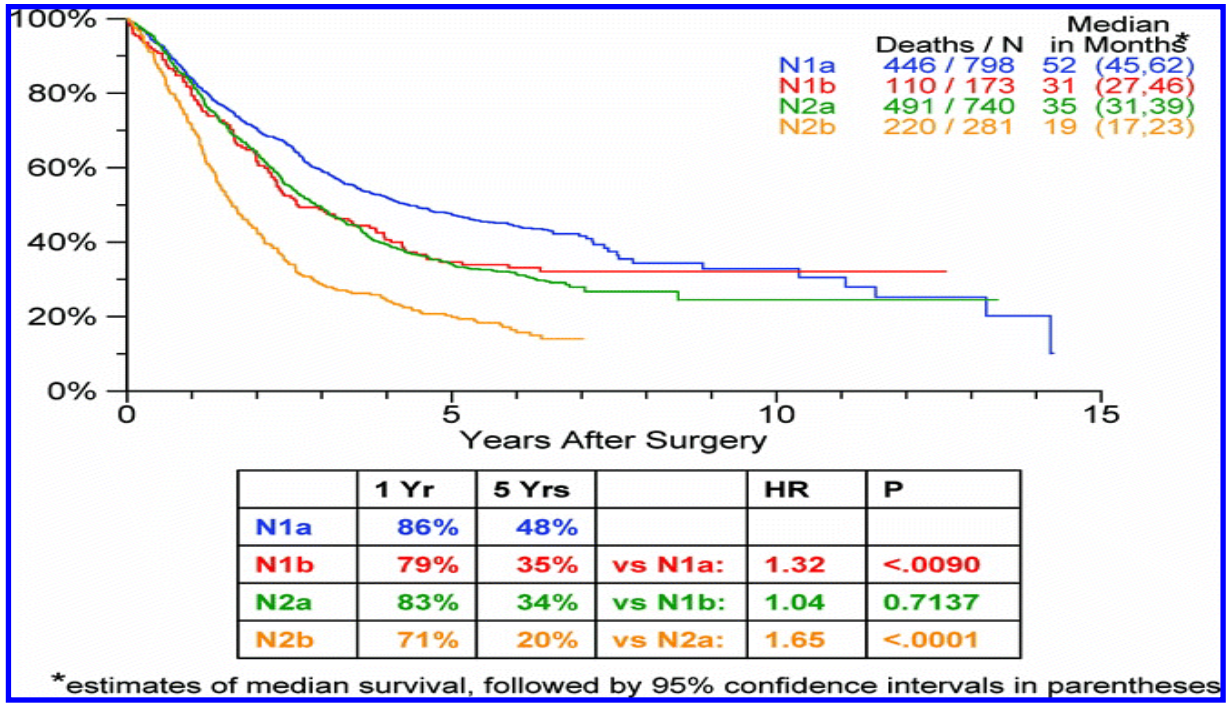
N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 (“skip mets”) = N2a1
N2 Single N2 + N1 = N2a2

Combination of anatomy and number of metastatic stations (single versus multiple station) is also prognostic in pN.

comparison	HR	P
N1b vs N1a	1.38	0.0005
N2a1 (skip) vs N1b	0.92	0.4331
N2a2 vs N2a1 (skip)	1.37	0.0002
N2b vs N2a2	1.21	0.0117
N2a2 vs N1b	1.26	0.0197

Asamura H et al. J Thorac Oncol 2015;10:1675-84

Nodal zones, 7th ed.



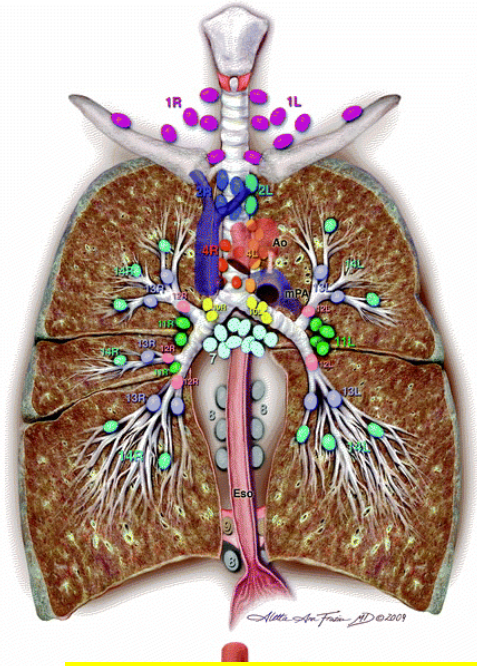
	1 Yr	5 Yrs		HR	P
N1a	86%	48%			
N1b	79%	35%	vs N1a:	1.32	<.0090
N2a	83%	34%	vs N1b:	1.04	0.7137
N2b	71%	20%	vs N2a:	1.65	<.0001

*estimates of median survival, followed by 95% confidence intervals in parentheses

- Derived from pathologic classification
- Most data (60%) from Asia
- No geographical validation
- No clinical validation

Rusch VW et al. JTO 2007; 2: 603-612

IASLC Lymph node map



Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

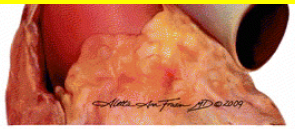
SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

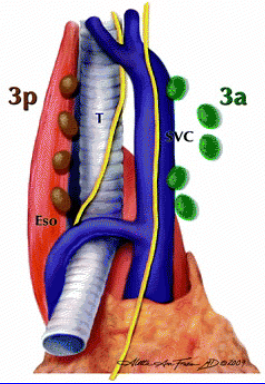
AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

Needs consensus among thoracic surgeons.



Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament



N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Rusch V et al.
J Thorac Oncol 2009; 4: 568-577

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Recommendations

- To **keep the present descriptors as they are**
- To propose new descriptors for **prospective testing**:
  - pN1a: involvement of single pN1 nodal station
  - pN1b: involvement of multiple pN1 nodal stations
  - pN2a1: involvement of single pN2 nodal station without pN1 (skip pN2)
  - pN2a2: involvement of single pN2 nodal station with pN1
  - pN2b: involvement of multiple pN2 nodal stations

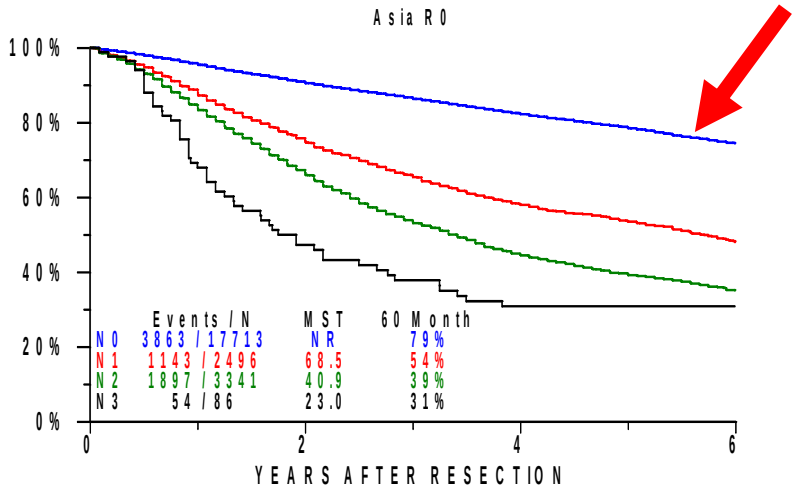
Asamura H et al. J Thorac Oncol 2015;10:1675-84

Issues around N

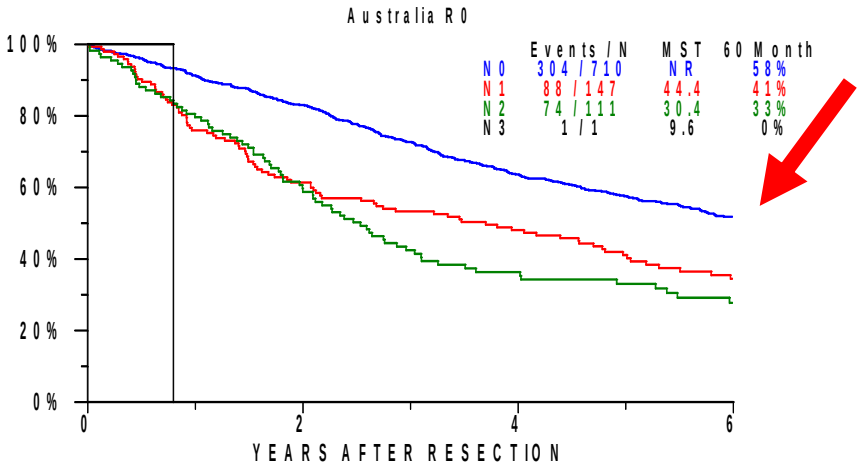
1. Why regional difference in N-specific prognosis?
2. Imbalance of data source, which might have affected the results.
3. Method of pathological evaluation, not standardized.
4. Can nN be used clinically?

Issues #1: Regional Differences

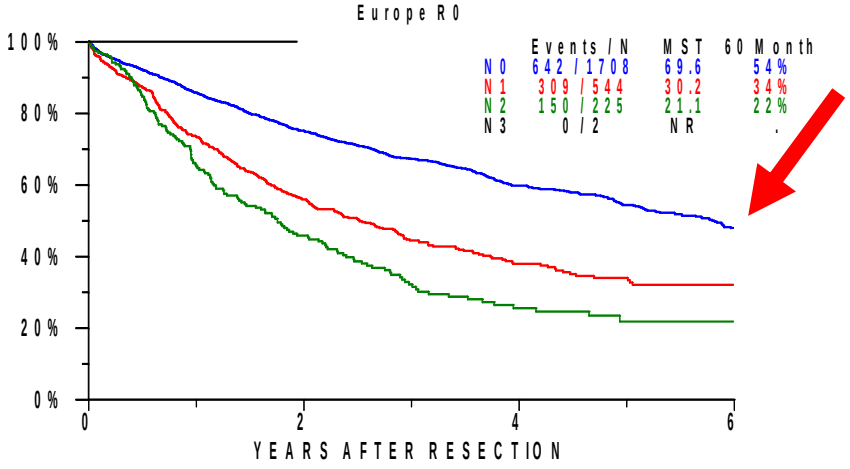
Asia



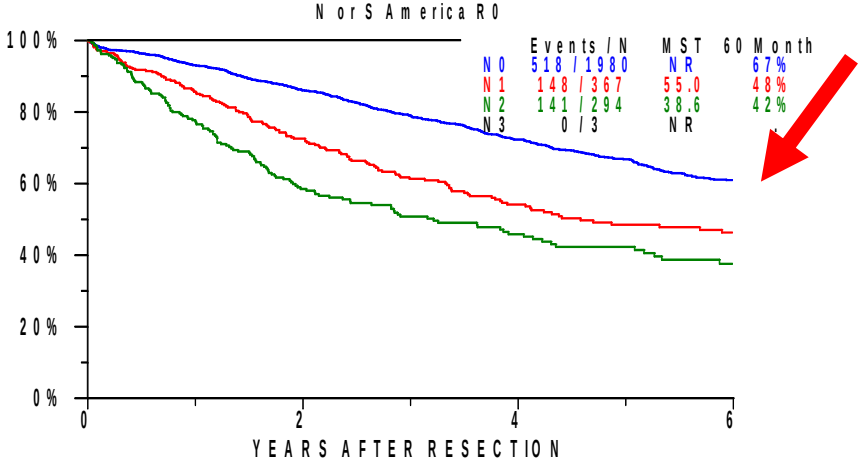
Australia



Europe



North/South America



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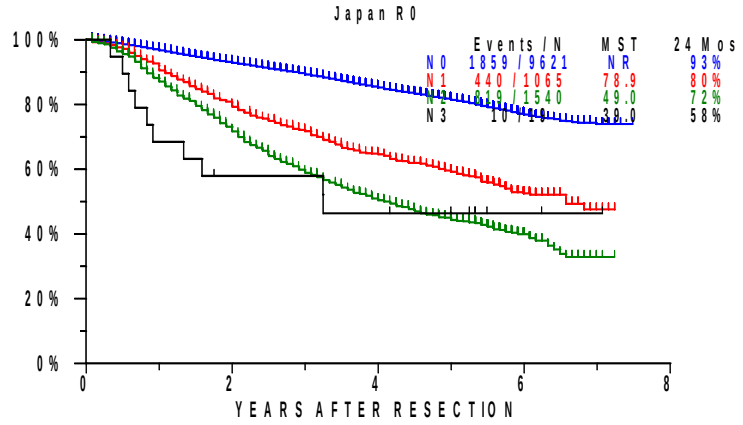
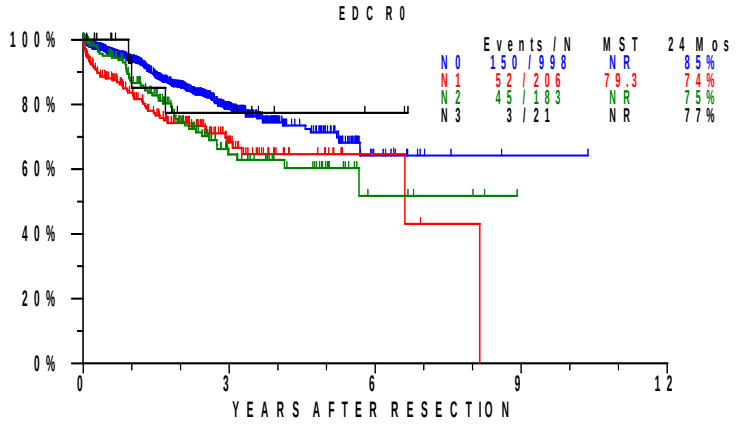
Issues #1: Regional (Institutional) Differences

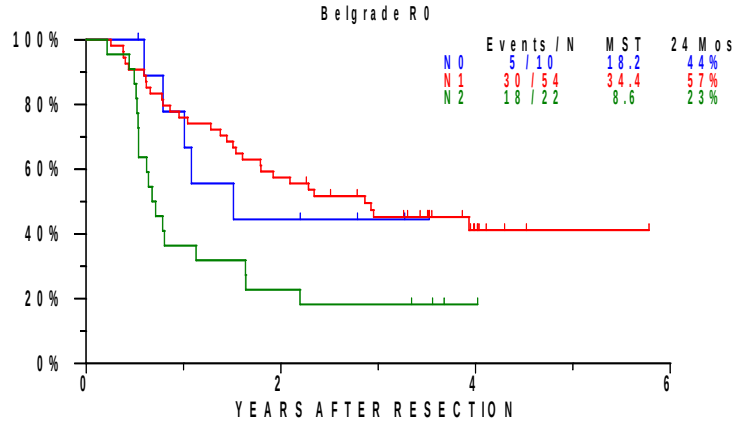
Japan National



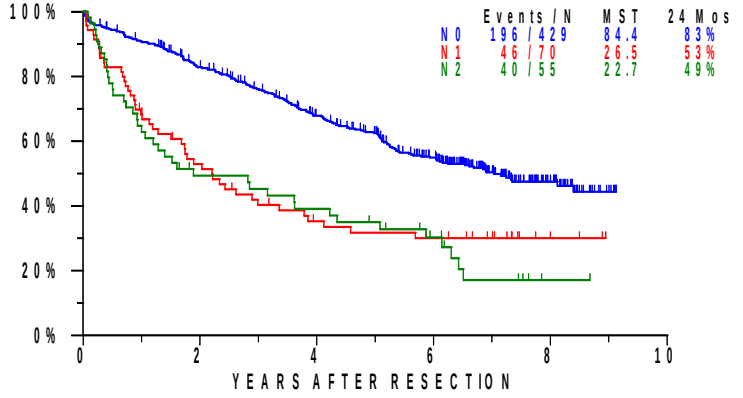
EDC



Belgrade



Hospital A



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Distribution of c-N Categories Across Databases

Table 1. Origin of the data for clinical nodal (c-N) category (n=38,910)

J= 23,012 patients (59.1%) for c-N status

Data source	Clinical N				Total	Follow-up (months)		
	N0	N1	N2	N3		Min	Median	Max
Denmark	6435	845	2690	1390	11360	4	27	124
EDC	1243	182	402	277	2104	<1	22	125
Japan 1999	**8497**	**918**	**1540**	**79**	**11034**	**1**	**66**	**83**
Japan 2002	**450**	**200**	**725**	**391**	**1766**	**1**	**16**	**87**
Japan 2004	**8501**	**683**	**985**	**43**	**10212**	**1**	**62**	**88**
MSKCC	535	97	198	31	861	1	80	122
PrinceCharles	88	13	24	6	131	28	34	39
Sydney	14	1	3	0	18	49	59	98
TurkeyG	563	168	577	116	1424	<1	65	73
Total	26326	3107	7144	2333	**38910**	<1	61	125

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Distribution of p-N Categories Across Databases

Table 2. Origin of the data for pathological nodal (p-N) category (n=38,910)

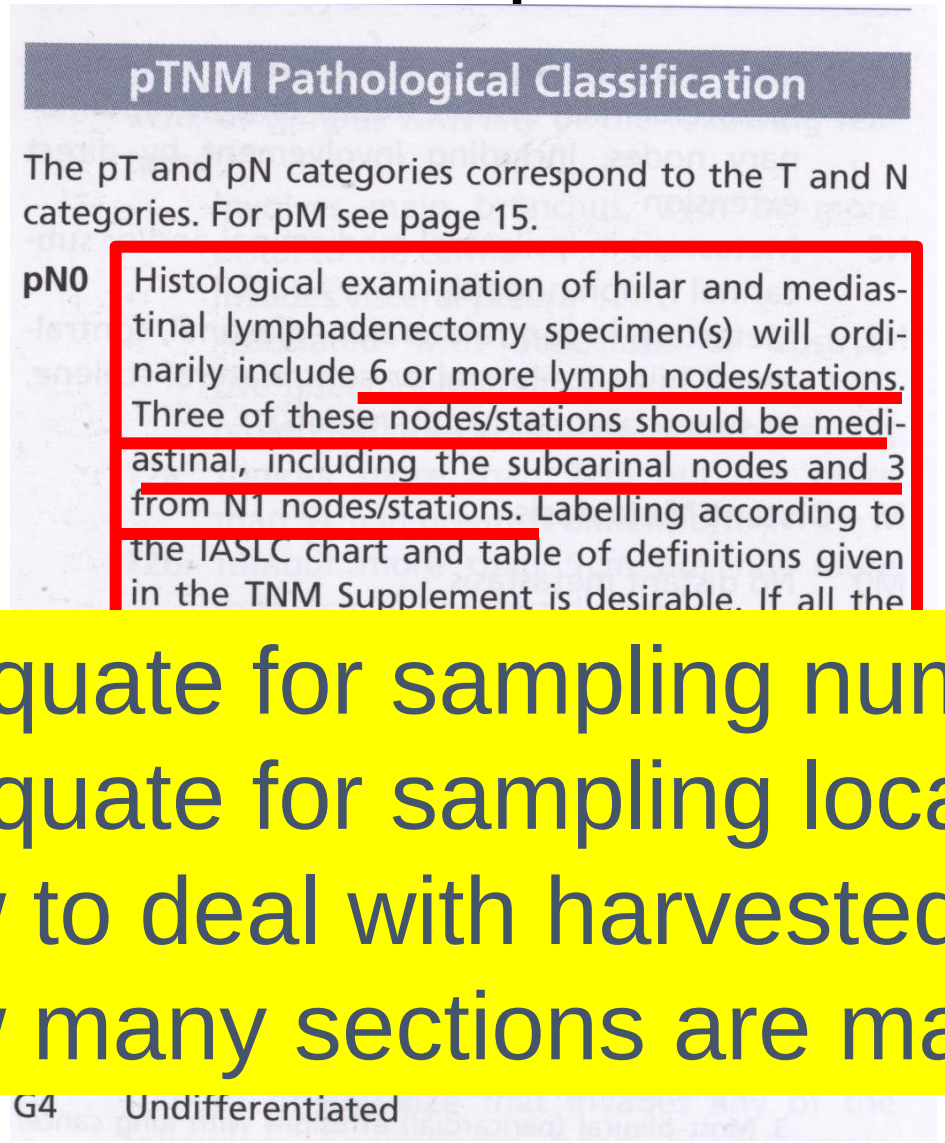
J= 23,463 patients (74.7%) for p-N status

Data source	Pathological N				Total	Followup (months)*		
	N0	N1	N2	N3		Min	Median	Max
Belgrade	10	54	24	0	88	6	42	70
EDC	1002	218	189	21	1430	<1	23	125
MSKCC	451	74	60	1	586	1	79	110
Norway	1193	369	145	1	1708	8	55	96
Sydney	743	158	118	1	1020	<1	69	139
Total	22938	3811	4522	155	**31426**	<1	64	139

- Are these world-wide data?
- Need to encourage data submission from north America

LNs that should be examined: how many, from what part?

3 nodes from N1 and 3 nodes from N2 regions including subcarina.



pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories. For pM see page 15.

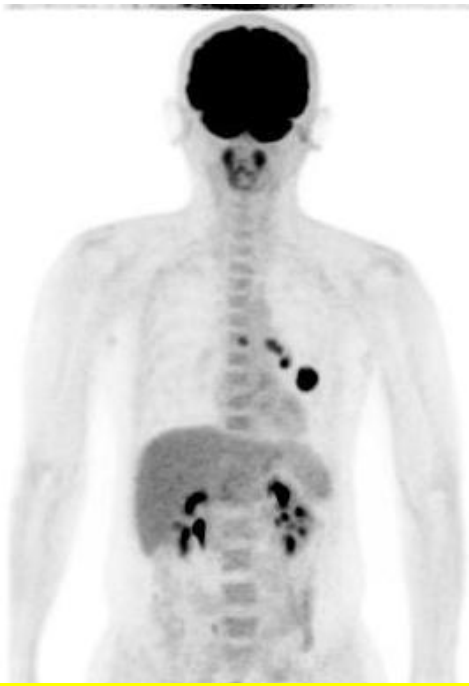
pN0 Histological examination of hilar and mediastinal lymphadenectomy specimen(s) will ordinarily include 6 or more lymph nodes/stations. Three of these nodes/stations should be mediastinal, including the subcarinal nodes and 3 from N1 nodes/stations. Labelling according to the IASLC chart and table of definitions given in the TNM Supplement is desirable. If all the

G4 Undifferentiated

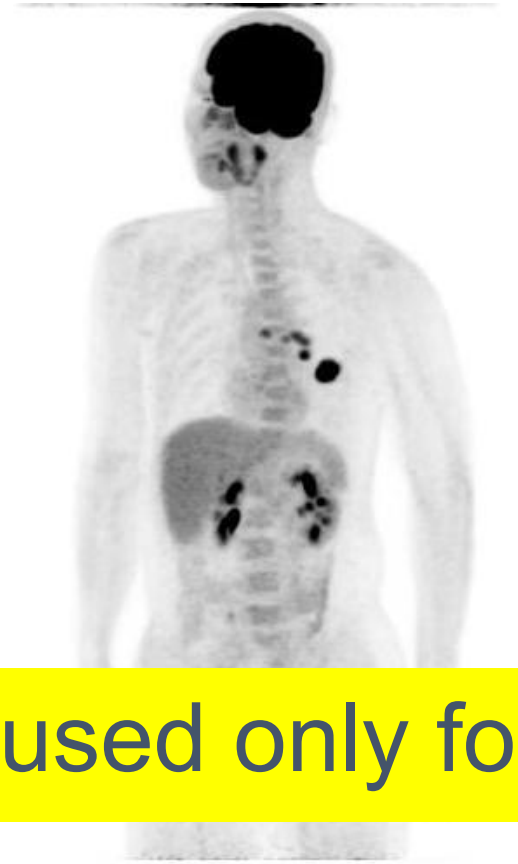
- Adequate for sampling number?
- Adequate for sampling location?
- How to deal with harvested nodes?
- How many sections are made?

How to Count Lymph Nodes?
Can You Do It?
Even “single” metastasis is difficult to identify.

4 nodes



5 nodes



- “Single-multiple” is better used only for pN.