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The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma

Running Title: Revisions of the N descriptors for pleural mesothelioma

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On behalf of the Mesothelioma Domain of the International Association for the Study of Lung Cancer (IASLC) International Staging and Prognostic Factors Committee (SPFC).

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*See Appendix

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Abbreviations:

MPM	Malignant pleural mesothelioma
KM	Kaplan-Meier
c-stage	Clinical-stage
p-stage	Pathologic-stage
HR	Hazard ratio
TNM	Tumor, nodes, metastases
IASLC	International Association for the Study of Lung Cancer
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control
IMIG	International Mesothelioma Interest Group
MD-ATS	Mountain/Dressler-American Thoracic Society
SPFC	Staging and Prognostic Factors Committee
EDC	Electronic data capture
EBUS-TBNA	Endobronchial ultrasound transbronchial needle aspiration

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EPP	Extrapleural pneumonectomy
PD	Pleurectomy decortication
NOS	Not otherwise specified
mo	Months
n	Number

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ABSTRACT (Word count = 250)

Introduction

Nodal categories for malignant pleural mesothelioma (MPM) are derived from the lung cancer staging system and have not been adequately validated. The International Association for the Study of Lung Cancer (IASLC) developed a multinational database to generate evidence-based recommendations to inform the 8th edition of the tumor, node metastasis classification of MPM.

Methods

Data from 29 centers were entered prospectively (n=1,566) or by transfer of retrospective data (n=1,953). Survival according to the 7th edition N categories was evaluated using Kaplan-Meier (KM) survival curves and Cox proportional hazards regression analysis. Survival was measured from the date of diagnosis.

Results

There were 2,432 analyzable cases: 1,603 had clinical (c) staging; 1,614 had pathologic (p) staging; and 785 had both. For clinically staged tumors there was no separation in KM curves between cN0, cN1 or cN2 (cN1 vs. cN0 HR 1.06, p=0.77 and cN2 vs. cN1 HR 1.04, p=0.85). For pathologically staged tumors, patients with pN1 or pN2 tumors had worse survival than those with pN0 tumors (HR 1.51, p<0.0001) but no survival difference was noted between those with pN1 and pN2 (HR 0.99, p=0.99). Patients with both pN1 and pN2 nodal involvement had poorer survival than those with pN2 only (HR 1.60, p=0.007) or pN0 (HR 1.62, p<0.0001).

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Conclusions

A recommendation to collapse both clinical and pathological N1 and N2 categories into a single N category comprising ipsilateral, intrathoracic nodal metastases (N1) will be made for the 8th edition staging system. Nodes previously categorized as N3 will be reclassified as N2.

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Introduction

Malignant pleura mesothelioma (MPM) carries a poor prognosis for the majority of patients, and survival is known to be particularly poor in patients with nodal metastases.[1-4] This has been reflected in several staging systems that have developed over the last four decades.[5-8] The current 7th edition of the tumor, nodes, metastasis (TNM) classification of MPM of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) TNM-based staging systems for MPM was developed in 1994 following a staging workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG), and was derived from analyses of several single institution retrospective series as well as expert opinion.[8-10] This staging system has remained unchanged for two decades and has been criticized because it largely reflects outcome of patients who have undergone cytoreductive surgery and uses several staging descriptors that can only be determined by pathologic review. Thus, the general applicability of this staging system for clinical staging of tumors in non-surgical patients (which form the majority of patients with MPM) is questionable. Furthermore, the nodal categories (N0-3) in the AJCC/UICC staging system were adopted from those used in lung cancer staging and are based on the Mountain/Dressler-American Thoracic Society (MD-ATS) and Naruke classification systems, without much supporting MPM-specific evidence. In fact, there are significant anatomic differences between the lymphatic drainage pathways of the pleura and the lung parenchyma, and data from several single institutional retrospective series have yielded conflicting evidence as to whether

there is indeed a prognostic difference between patients with pathologic (p) N1 and N2 pleural mesothelioma. These facts warranted further evaluation of the appropriateness of the current nodal categories. [11]

Accordingly, the Mesothelioma Domain of the IASLC International Staging and Prognostic Factors Committee (SPFC) coordinated development of a large international multicenter database to collect data that could inform staging in MPM, much like what had previously been done for lung cancer, and which led to the 7th edition of the TNM classification.[12] The initial IASLC MPM database amalgamated retrospective data from 15 institutions worldwide on 3,101 surgically treated patients with mesothelioma and initial analyses published in 2012 suggested that certain changes in the TNM-based staging system might be justifiable, however there was insufficient granularity in the data on individual T, N and M descriptors to allow evidence-based revisions to be made. Therefore, a second database was created which contained more detailed data elements for TNM descriptors and which was populated prospectively using a web-based electronic data capture (EDC) system. Importantly, data on patients treated both surgically and non-surgically were collected. Additionally to increase the proportion of patients who were treated non-operatively, retrospective data, which conformed to the common data elements, were included from participating centers. These data were used to derive evidence-based recommendations regarding nodal categories.

Methods

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Data were submitted from 29 centers around the world including Europe (48%), North America (33%), Asia (10%) and Australia (9%). Data were prospectively collected via the EDC in 1,566 (45%) and by transfer of retrospective data in 1,953 (55%) cases. Though cases from as early as 1995 were included, most were diagnosed between 2000 and 2013. Cases diagnosed after June 30, 2013 were excluded and analyses were undertaken at the end of 2014, allowing a minimum potential follow-up of 18 months. Data management and statistical analyses were provided by co-investigators at Cancer Research And Biostatistics in Seattle, Washington, USA. A total of 3,519 cases were collected of which 2,432 had a complete set of TNM data (by either clinical or pathological staging), known histologic type, and survival follow-up (Table 1). Pre-treatment (i.e. clinical) TNM staging information was available in 1,603 patients, post-surgical (i.e. pathological) staging data in 1,614 patients, and both in 785 cases. Clinical staging included all tests and imaging studies done for initial extent-of-disease evaluation and information obtained from mediastinoscopy, endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) or laparoscopy, where these procedures had been performed, but not from thoracotomy. 23 of the 29 participating centers submitted data on clinical classification (positive, negative, or not done) for individual nodal stations, comprising a total of 1,322 cases. Pathological nodal sampling results were available from 20 centers, a total of 851 patients (Figure 1). There was no standardization regarding method or extent of intraoperative nodal sampling and this varied significantly across institutions. Node classification was based on the current 7th edition TNM classification whereby N0

denotes an absence of nodal metastases; N1 denotes metastases to nodes contained within the pleural reflection (hilar and parenchymal, stations 10 to 14); N2 denotes metastases in ipsilateral mediastinal nodes outside the pleural reflection (stations 2 to 9) as well as ipsilateral internal mammary, intercostal, diaphragmatic and pericardial nodes; and N3 denotes supraclavicular (station 1, ipsilateral or contralateral) and all contralateral intrathoracic nodes. Known differences between the Naruke and MD-ATS nodal maps include the designation of nodes along the inferior border of the mainstem bronchus (station 10 vs. station 7) and along the upper paratracheal region (stations 1 and 2 vs. station 1). As only 10% of cases were submitted from centers in Asia it is unlikely that these minor differences in nomenclature significantly influenced the overall results. Nodal stations excluded from the Naruke and MD-ATS node maps but often involved in MPM including internal mammary, intercostal, pericardial and diaphragmatic nodes, were collectively referred to as non-mediastinal intrathoracic nodes.

Statistical Methods

The prognostic capabilities of N categories according to the current system were evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression analysis with and without adjustment for age and geographical region. Alternative N category schemes, based on a combination of location and number of positive nodal stations were explored using Kaplan-Meier survival analysis and Cox proportional hazards regression. Cox regression analyses were performed using the SAS System for Windows Version 9.4.

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Results

Overall Survival According to Clinical N Categories

1,322 patients had cM0 tumors and had complete information on clinical N categories with supporting results for individual nodal stations. The majority of patients had tumors staged as clinical (c) N0 (78%) with only 16% staged as cN2 and 3% as cN1 or cN3. Median survival for cN0 patients was 19 months versus 17.6 and 16.2 months for cN1 and cN2, respectively (Figure 2). Perhaps due to the small number of cN1, survival for cN1 did not differ significantly from cN0 (HR = 1.15, p = .49). There was no significant difference between cN1 and cN2 (HR = 1.06, p= .78). When cN1 and cN2 (cN+) were combined and compared to cN0 patients adjusting for region and sex, median overall survival was 17.1 vs. 19.0 months, respectively (HR 1.18, p=.04). No difference in survival was noted between patients with tumors clinically staged as having single station metastases compared to those with multiple station nodal involvement (median 17.1 vs. 17.2 months, p=0.84).

Overall Survival according to Pathological N Staging

851 patients with pathologic M0 tumors had surgical confirmation of nodal status. Of these, 530 (62%) were classified pN0, 58 (7%) pN1, 256 (30%) pN2 and 7 (1%) as pN3. Because of small patient numbers, the 7 patients with pN3 disease were excluded from further survival analyses. Median survival of patients with pN0 tumors was 24.0 months compared to 16.9 (HR 1.51, p=0.006) and 17.4 months (HR 1.56, p<0.001) for patients with pN1 and pN2 tumors, respectively (Figure 3). No

significant difference in survival was noted between patients with pN1 and pN2 disease (p=0.84). Patients with pN1 or pN2 were therefore analyzed together (pN+) which resulted in a significantly worse overall survival prognosis compared to pN0 (HR 1.55, p<0.0001).

Survival in Relationship to the Extent of pN1 and pN2 Metastases

Exploratory analyses were performed to determine whether the pattern or extent of nodal involvement influenced survival in cases with detailed pathologic N category information. No significant survival differences were noted for patients with single or multistation pN1 or pN2 metastases (HR 1.11, p=0.44) (Figure 4). As the presence of skip metastases (i.e. single station N2 without N1 metastases) has been associated with improved survival in patients with lung cancer, we examined whether this held true in our patient population. 54% of patients with N2 disease did not have any N1 nodal involvement. Survival for patients with pN0 was significantly different from patients with pN2 involvement only (median 24.0 vs. 18.5 months, p=0.044). Patients with both N1 and N2 metastases (n=117) had significantly worse survival compared to pN0 (HR 1.63, p<0.0001) and those who were pN2 only (HR 1.60, p=0.0007) (Figure 5). No survival difference was noted between patients with pN2 only and pN1 only tumors (HR=0.83, p=0.28). Analysis of survival by number of involved lymph nodes, lymph node ratio (number of positive nodes over number of nodes biopsied) and nodal distribution (upper mediastinal vs. lower mediastinal vs. non-mediastinal) did not reveal any significant trends, however, individual patient numbers are small.

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Relationship Between Tumor Thickness and Presence of Nodal Metastases

As outlined in the companion manuscript on T categories (this issue), prospectively obtained measurements of tumor thickness by axial computed tomography imaging were available for 472 patients who also had complete N category information. These measurements were obtained at 3 predefined regions within the affected hemithorax (upper, middle and lower) and running log rank tests were performed to identify which tumor thickness cutpoints predicted survival. Additionally, however, cutpoints based on the maximal thickness of the 3 levels, or on the sum of the 3 levels, also predicted risk of nodal metastases. Patients with tumor of maximal thickness of less than 5.1 mm had a 14% risk of nodal metastases, whereas this rose to 38% in patients with tumors maximal thickness greater than 5.1mm ($p<0.0001$). Similarly, tumor thickness cutpoints (based on 3-level summation) of <13mm, 13-60mm and >60mm and were associated with nodal metastases in 14%, 37% and 47% of cases ($p<0.0001$). It should be stressed that these findings are exploratory only and will require further investigation and validation with larger patient numbers.

Accuracy of Clinical N Categories

Both clinical and pathologic N stage data were available for 572 patients. Although 480 patients had tumors clinically staged as cN0, a minority (38%) had some form of pre-treatment nodal histologic confirmation (endobronchial ultrasound, mediastinoscopy, etc). Overall, clinical staging underestimated N status in 33% of

patients and overestimated it in 6% of cases. The Kappa statistic for agreement between clinical and pathological stage determinations was 0.16 (95% C.I. 0.09-0.22), which indicates only slight agreement (Figure 6).

Distribution of Nodal Metastases

Complete data on nodal sampling (i.e. where data entry included if nodal stations positive, negative or not biopsied) was available for 642 cases from 16 contributing centers, of which 274 (43%) had positive N1 or N2 nodes. The mean number of separate stations biopsied per patient was 4.7 (range 1 to 18), with a mean of 2.7 N1 stations and 2.0 N2 stations sampled. The distribution of biopsied nodal stations is shown in Table 2 with stations 4, 7 and 10 being sampled most frequently.

Of 314 patients with N1 or N2 disease, metastases were most commonly identified in the subcarinal (43%), hilar (36%) and lower paratracheal stations (20%); however these stations were also those most commonly biopsied (Table 2). On a per-station sampled basis, nodes in the internal mammary chain had the highest frequency of positivity, harboring metastases in 24 of 58 (41%) stations sampled. More nodal stations were evaluated in patients who underwent extrapleural pneumonectomy (EPP) compared to those who had pleurectomy decortication (PD) or extended PD (mean 5.5 vs. 3.8 stations, $p<.0001$). Patients with epithelioid histology were more likely to be pathological node positive compared to patients with non-epithelioid tumors (41% vs. 27%, $p=.0003$), although this may have been influenced by differences in the degree of surgical resection, with more aggressive

approaches such as EPP (and potentially more thorough node dissections) being favored in patients with epithelioid tumors.

Discussion

The presence of nodal metastases is known to adversely affect outcome in patients with MPM, reducing long term survival by as much as 50%.[1,2,13] Lymph node metastases are frequent and are reported in between 35% to 50% of patients undergoing cytoreductive surgery (Table 3) and a recent postmortem study reported the presence of nodal metastases in 76% of autopsies.[14] The 7th edition of the TNM classification classifies any ipsilateral nodal involvement as stage III and categorizes ipsilateral nodes as either N1 (intrapleural including hilar and intraparenchymal nodes) or N2 (extrapleural including mediastinal and non-mediastinal such as internal mammary, peridiaphragmatic, pericardial and intercostal nodes).[9] Although evidence from most retrospective studies supports assigning tumors with nodal metastases a stage higher than that of N0 tumors of equivalent T category, the current TNM classification system, which has remained unchanged for almost two decades, is not evidence-based, having been largely empirically derived from limited retrospective surgical series. Though the N categories for lung cancer are logical in as much that N1 nodes generally become involved with metastatic disease before N2 nodes do, the same orderly progression is not known to occur for mesothelioma, a tumor that chiefly involves the pleura, which is known to have a pattern of lymphatic drainage distinct to that of the lung parenchyma.[15,16] Indeed, it has been postulated that extrapleural nodes (N2) may, in

fact, be the initial site of nodal metastases in patients with mesothelioma, with N1 nodes becoming secondarily involved only when invasion of lung parenchyma occurs.[17] Therefore, a more data driven assessment of the significance of nodal metastases as they relate to incidence and prognosis was warranted for the upcoming 8th edition of the TNM classification for mesothelioma.[11]

The current report presents data from the largest multi-national, multi-institutional database established to date of patients with MPM. Though a majority of patients underwent some form of surgery, a significant proportion (28%) received non-operative treatment. As most patients who present with MPM are not candidates for surgery, inclusion of non-operative patients in this database was of great importance for clinical staging as outcomes may be more relevant to the population as a whole. In addition, although more than half of the cases were derived from retrospective institutional databases, a significant proportion (45%) was prospectively entered electronically by participating centers. These factors, coupled with more detailed information on anatomic N descriptors make the current database significantly more robust than the previous iteration of the IASLC MPM staging database originally reported by Rusch and colleagues.[12]

Analysis of the original IASLC database, which included 1,056 patients with pN-category information, revealed survival differences between patients with node negative (pN0) versus node positive (pN1 or pN2) disease but no difference between pN1 and pN2 [12]. Additionally, in a small subset of 181 patients in whom data were available, no difference in survival was observed according to the number of nodes harboring metastases. The present study, which included a slightly smaller

number of patients with pathologic N-category information (n=851), corroborated these findings revealing a significant survival difference between patients with pN0 and pN1 or pN2 disease, but again no survival difference existed between pN1 and pN2. This supports current stage grouping whereby patients with N1 or N2 metastases are assigned the same overall stage (currently stage III). However, since the anatomic location of ipsilateral nodal metastases did not appear to influence prognosis, data do not support maintaining the anatomic differentiation of current N1 and N2 categories and suggest that intrapleural (N1) and extrapleural (N2) should be collapsed into a single N category (N1) with N3 nodes becoming N2 in the 8th edition of the TNM classification for MPM (Figure 7).

The surgical literature varies with respect to the impact on survival of N1 versus N2 metastases (Table 4). Several authors report no differences in survival between patients with N1 and N2 metastases.[4,12,18,19] In a retrospective analysis of 50 patients undergoing EPP, dePerrot et al. reported identical median survival of 10 months for patients with N1 (n=8) and N2 (n=21) metastases [4]. In a larger series of 212 patients undergoing either EPP or PD, Nakas et al. reported median survival for N1 positive patients (n=23) of 11 to 12 months, which was not significantly different from the 11 to 14 month survival seen in patients with N2 metastases (n=99) [19]. In contrast, in a series of 348 patients who underwent cytoreduction, Flores et al reported median survival of 19 months in 22 patients with N1 metastases (similar to pN0 patients), which was significantly better than that of pN2 patients (10 months, n=110), although notably the number of N1 patients was small [3]. More recently, in the largest series reported to date including 529 patients with

epithelioid MPM who underwent EPP, Sugarbaker et al. demonstrated significantly better survival in patients with N1 metastases (17 months, n=116) compared to those with N2 involvement (13 months, n=181).[20] It is difficult to interpret the reported literature for many reasons. A minority of patients (approximately 12%) present with isolated N1 disease, therefore in most retrospective series the true impact of N1 nodes is likely to be statistically insignificant purely because of numerical insufficiency. Additionally, the reported incidence of nodal metastases is dependent on the extent of nodal sampling, which varies between surgeons and institutions (as we observed in the present study) and is also dependent on the type of resection performed - with more N1 nodes being typically evaluated with EPP than with PD. In the present study only 58 patients (6%) had pN1 tumors, which is similar to the proportion reported by Flores et al (7%) but low compared to many other studies.[3] It is therefore conceivable that N1 nodes may have been undersampled and perhaps included in the group of tumors staged as N0. If this is true, had patients with N1 tumors been identified perhaps overall survival of the pN0 group would have been better. Additionally, the median survival we observed in patients with N1 metastases (17 months from date of diagnosis, which preceded date of surgery by a median of 3.6 months) is lower than that reported by Flores et al. and Sugarbaker et al., and the median survival of N2 patients (17 months) is on the higher end of the range reported in the literature, which may account for why survival differences were not observed between pN1 and pN2 patients in the present study.[3,20]

Several authors have reported differences in survival outcomes related to the pattern and extent of nodal involvement. Both Edwards et al and Flores et al observed that the number of metastatically involved nodes was predictive of survival, however there was no survival difference among patients with pN1 plus pN2 nodes involved compared to those with N2 metastases only, or between patients with nodal metastases in the paratracheal and subcarinal nodes versus other sites.[3,21] Conversely, Richards et al suggested that patients with metastases to paratracheal nodal stations (2-4) had worse survival than patients with involvement of internal mammary or lower mediastinal (5-9) stations (median survival 13 vs 7 months).[22] The same group subsequently reported worse outcomes in patients who had N1 plus N2 metastases (median survival 13 months) compared to those with either N1 or N2 involvement only (median survival 17 and 16 months, respectively).[23] Though we did not collect information regarding nodal number (because of the inherent inaccuracies of reporting node number due to fragmentation), we analyzed survival according to whether single or multiple stations were metastatically involved and observed no difference (median survival 18 vs. 17 months, p=0.44). However, like Sugarbaker et al. we found significantly worse survival in patients with N1 plus N2 involvement versus those with involvement of only N1 or N2 nodes alone (median survival 14 months vs. 17 and 19 months, respectively, p=0.0007).[20] No significant survival differences existed between the latter (pN1 only or pN2 only), suggesting that anatomic location of nodal metastases, per se, may not influence prognosis as much as the cumulative extent of metastatic nodal involvement. However, definitive recommendations

regarding the appropriateness of reclassifying N1 plus N2 as a separate N category will need to be based on future larger studies that standardize prospectively the extent of nodal sampling or dissection across institutions.

The present study also highlighted the known inaccuracies of clinical N staging.[12,24] Only 22% of tumors in 1,029 patients were clinically staged as having nodal metastases whereas the incidence of positive nodes in patients who underwent surgery was 38% (321 of 851 patients with surgical stage information). In fact, clinical assessment of N categories did not predict outcome as survival curves for all cN categories were superimposed. In the subset of patients in whom both clinical and pathologic N categories were known, clinical staging was inaccurate in predicting pathologic N status (Kappa statistic, 0.16), which underscores the inability of current staging modalities to reliably determine N categories preoperatively. Of note, only 56% of clinically staged patients had PET imaging and only 7% had mediastinoscopy. A more liberal use of invasive pretreatment nodal sampling is therefore recommended to improve accuracy of clinical nodal staging, although a significant proportion of positive nodes are located at anatomic regions inaccessible to mediastinoscopy or even endoscopic techniques such as endobronchial and esophageal ultrasound (e.g. internal mammary nodes, peridiaphragmatic nodes etc.).[25] Other non-invasive predictors of nodal involvement (and hence survival) would also be highly useful and in this regard the exploratory analysis we performed, which showed association between tumor thickness and nodal involvement, is very intriguing.

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In conclusion, the data do not support maintaining the current anatomical-based classification of ipsilateral intrathoracic nodes as N1 and N2, as these nodal categories are not associated with different survival. Rather, survival appears to be more influenced by the extent of nodal involvement than on the specific location of the involved nodes. For these reasons, we recommend redefining any ipsilateral, intrathoracic node with metastatic involvement as N1 for the upcoming 8th edition of the TNM classification of MPM. Ipsilateral supraclavicular or contralateral nodes (previously N3) should be reclassified as N2 (Table 5). Electronic capture of reliable and detailed data documenting tumor involvement at specific nodal stations is planned to continue and may allow more accurate analysis regarding the prognostic significance of anatomic location and pattern of node metastases, which may lead to further refinement of N categories in the future. For now, since metastatic involvement of any lymph nodes is associated with poor prognosis, and especially in cases where both intrapleural and extrapleural nodes harbor metastases, surgeons should be encouraged to perform detailed node dissections for all patients undergoing cytoreductive surgery and to document precise locations of any metastatically involved lymph nodes. This will facilitate more accurate analyses to be performed in future iterations of the TNM classification system for pleural mesothelioma.

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Figure Legends:

Figure 1. Cases analysed and reasons for exclusion.

Figure 2. Kaplan Meier curve for survival by 7th edition AJCC clinical N category in cases with N descriptor support.

Figure 3. Kaplan Meier curve for survival by 7th edition AJCC pathologic N category in cases with N descriptor support.

Figure 4. Survival by 7th edition AJCC pathologic N category, single versus multiple nodal station involvement.

Figure 5. Survival by 7th edition AJCC pathologic N category, N1 + N2 involvement versus N0, pN1 and pN2 only (i.e. without N1).

Figure 6. Proportion of overstaged and understaged patients according to pre-treatment (clinical) N category in patients with confirmatory data on pathologic N category.

Figure 7. Kaplan Meier curve for survival by proposed 8th edition N category in cases with N descriptor support; a, clinical staging; b, pathological staging; c, 'best' staging.

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Appendix

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Table 1. Summary of cases meeting the requirements for inclusion in the primary N category analysis. Clinical and/or pathologic stage with supporting nodal station data was required. NOS, not otherwise specified.

		Available TNM Staging					
	TOTAL	Both		Clinical Only		Pathologic Only	
		n	(%)	n	(%)	n	(%)
REGION							
Asia	213	85	(39%)	123	(57%)	5	(2%)
Australia	109	1	(0%)	108	(99%)	0	0
Europe	529	61	(11%)	224	(42%)	244	(46%)
North America	695	379	(54%)	287	(41%)	29	(4%)
Turkey	55	46	(83%)	8	(14%)	1	(1%)
SEX							
Female	313	126	(40%)	126	(40%)	61	(19%)
Male	1288	447	(34%)	623	(48%)	218	(16%)
HISTOLOGY							
Biphasic	243	93	(38%)	91	(37%)	59	(24%)
Epithelioid	1150	436	(37%)	507	(44%)	207	(18%)
Other/NOS	133	33	(24%)	93	(69%)	7	(5%)
Sarcomatoid	75	11	(14%)	58	(77%)	6	(8%)
Total	1601	573	(35%)	749	(46%)	279	(17%)

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Table 2. Distribution of sampled lymph node stations.

Lymph node station	Stations sampled (n=642)	Stations positive (n=314)	Positive/Sampled stations (%)
2	89 (14%)	5 (2%)	6%
3	101 (16%)	15 (5%)	15%
4	292 (45%)	63 (20%)	22%
5	214 (33%)	53 (17%)	25%
6	129 (20%)	22 (7%)	17%
7	500 (78%)	134 (43%)	27%
8	222 (35%)	44 (14%)	20%
9	198 (31%)	36 (11%)	18%
10	361 (56%)	112 (36%)	31%
11	187 (29%)	30 (10%)	16%
12	185 (29%)	33 (11%)	18%
13	119 (19%)	8 (3%)	7%
14	113 (18%)	4 (1%)	4%
Internal mammary	58 (9%)	24 (8%)	41%
Percardial	63 (10%)	5 (2%)	8%
Peridiaphragmatic	61 (10%)	8 (3%)	13%
Intercostal	68 (11%)	10 (3%)	15%
Retrocrural	48 (7%)	2 (1%)	4%

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Table 3. Series of patients with prevalence of nodal metastases. EPP, extrapleural pneumonectomy; PD, pleurectomy-decortication.

Author	**Year**	**EPP/PD (n)**	**N0 n (%)**	**N1 n (%)**	**N1 (any) n (%)**	**N1+N2 n (%)**	**N2 only n (%)**	**N2 (any) n (%)**
Edwards[21]	2006	92 EPP	48 (52%)	9 (10%)	30 (33%)	21 (23%)	14 (15%)	35 (38%)
dePerrot[4]	2007	50 EPP	21 (42%)	8 (16%)	21 (42%)	13 (26%)	8 (16%)	21 (42%)
Rice[13]	2007	100 EPP	46 (46%)	12 (12%)	-	-	-	42 (42%)
Rea[26]	2007	21 EPP	14 (67%)	2 (10%)	-	-	-	5 (24%)
Rahman[17]	2008	49 EPP	11 (22%)	7 (14%)	25 (51%)	18 (37%)	13 (27%)	31 (63%)
Flores[3]	2008	223 EPP 125 PD	192 (59%)	22 (7%)	87 (25%)	65 (20%)	45 (14%)	110 (34%)
Buduhan[18]	2009	46 EPP	26 (57%)	4 (9%)	-	-	-	16 (35%)
Richards[22]	2010	353 EPP	162 (46%)	86 (24%)	-	-	-	105 (30%)
Friedberg[27]	2012	38 PD	9 (24%)	4 (11%)	-	-	-	24 (63%)
Nakas[19]	2012	127 EPP 85 PD	94 (44%)	23 (11%)	-	-	-	99 (47%)
Rusch (IASLC)[12]	2012	1,191 EPP 299 PD	889 (61%)	179 (12%)	-	-	-	386 (27%)
Bovolato[28]	2014	301 EPP 202 PD	258 (51%)	47 (9%)	-	-	-	100 (20%)
Lang-Lazdunski[29]	2014	102 PD	68 (67%)	8 (8%)	-	-	-	26 (25%)
Lauk[30]	2014	251 EPP	152 (61%)	34 (34%)	-	-	-	62 (25%)
Spaggiari[23]	2014	516 EPP	305 (59%)	65 (13%)	-	-	-	146 (28%)
Sugarbaker[20]	2014	523 EPP	226 (43%)	116 (22%)	256 (49%)	136 (26%)	45 (9%)	181 (35%)
Baldini[31]	2015	169 EPP	86 (51%)	18 (11%)	-	-	-	52 (31%)
Bece[32]	2015	49 EPP	35 (71%)	2 (4%)	-	-	-	12 (24%)
Williams[33]	2015	117 PD	51 (44%)	8 (7%)	-	-	-	37 (32%)
Current		516 EPP 253 PD (82 other)	530 (63%)	58 (6%)	110 (13%)	52 (6%)	204 (24%)	256 30%)

Table 4. Survival of patients undergoing cytoreductive surgery with respect to N1 and N2 involvement. IASLC, International Association for the Study of Lung Cancer; EPP, extrapleural pneumonectomy; PD, pleurectomy/decortication; mo, months.

Author	Year	n	N0 (mo)	N1 (mo)	N2 (m0)	N1 vs. N2	Comment
Edwards[21]	2006	92 EPP	28 (N1,N0)		14	NS	Number of positive nodes significant
dePerrot[4]	2007	50 EPP	29	10	10	NS	
Flores[3]	2008	324	19	19	10	<0.001	Number of positive nodes significant
Buduhan[18]	2009	46 EPP	34	10	12	NS	
Richards[22]	2010	354 EPP	26	19	11	<0.0001	Superior mediastinal (stations 2-4) N2 had worse prognosis
Nakas[19]	2012	127 EPP	22	12	14	NS	
	2012	85 PD	16	11	11		
Rusch (IASLC)*[12]	2012	1191 EPP/ 299 PD	21	17	13	NS	
Sugarbaker[20]	2014	529 EPP	26	17	13	<0.05	N1 only and N2 only had simmilar survival. N1+N2 had worse survival.
Current*		516 EPP/ 253 PD	24	17	17	NS	

* Survival calculated from date of diagnosis (median 3.6 months prior to surgery)

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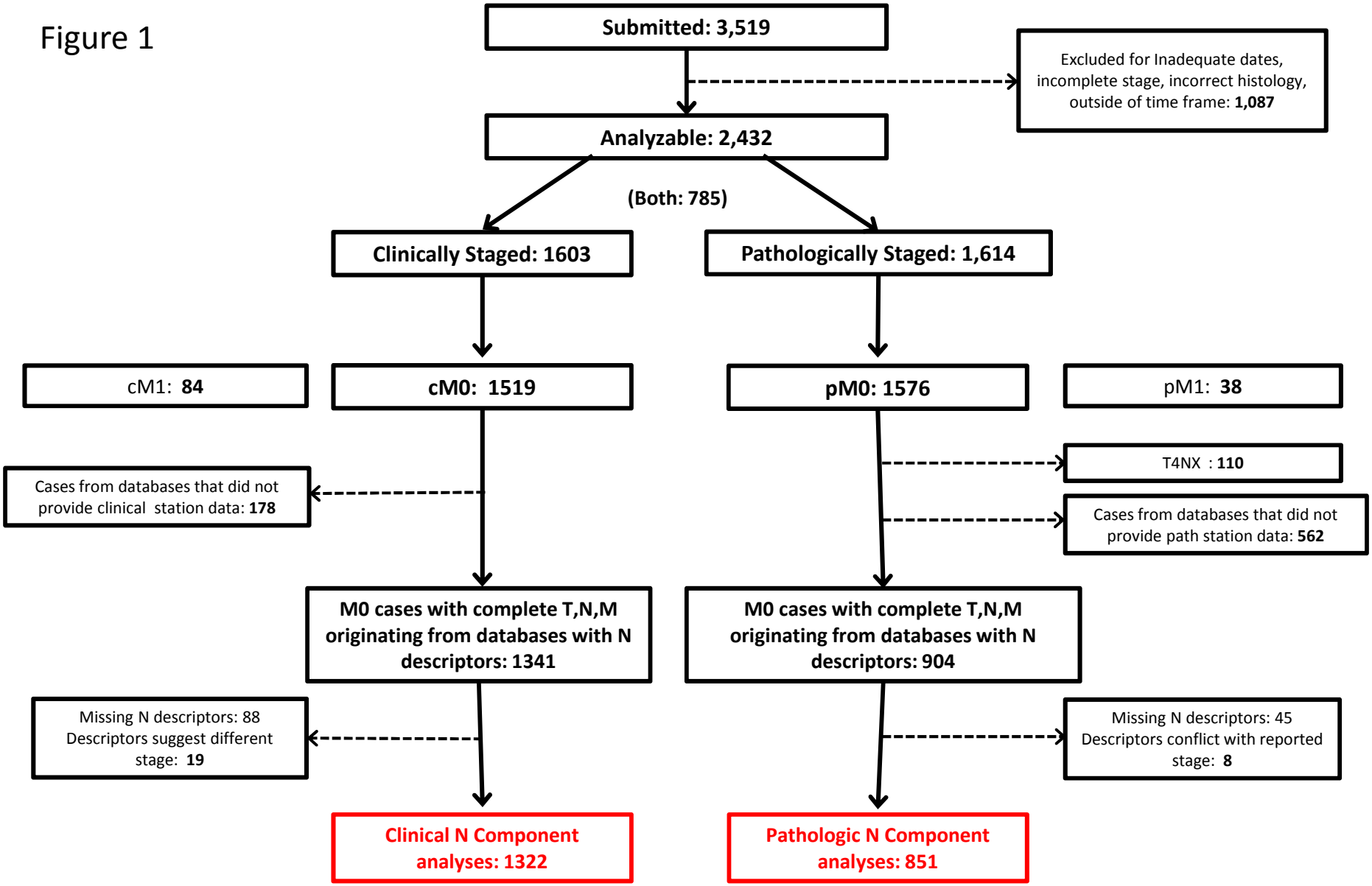
Table 5. Final recommendations for N descriptors for the 8th Edition of the AJCC/IUCC staging handbook.

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes
N2	Metastases in the contralateral bronchopulmonary, hilar or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes

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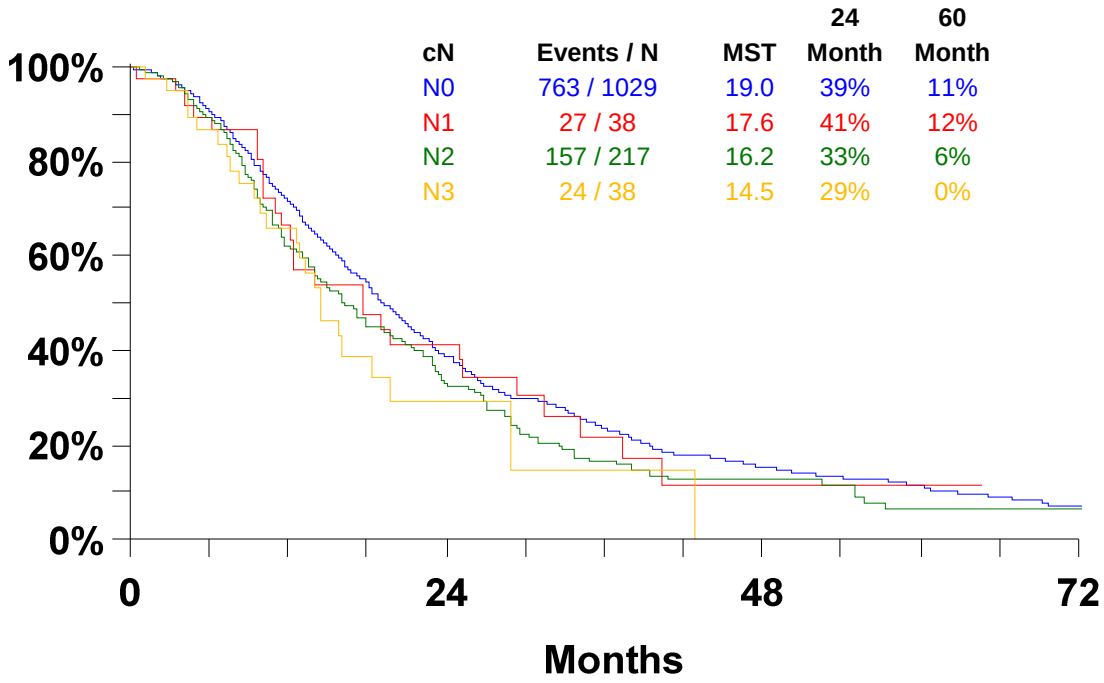
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Figure 1



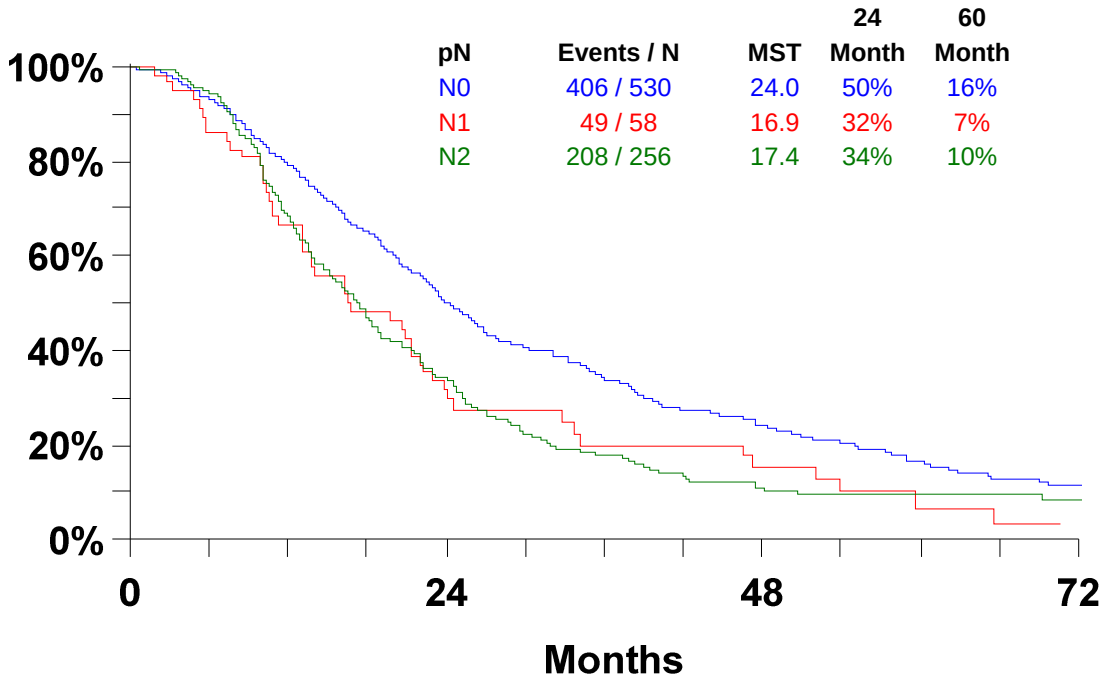
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Figure 2



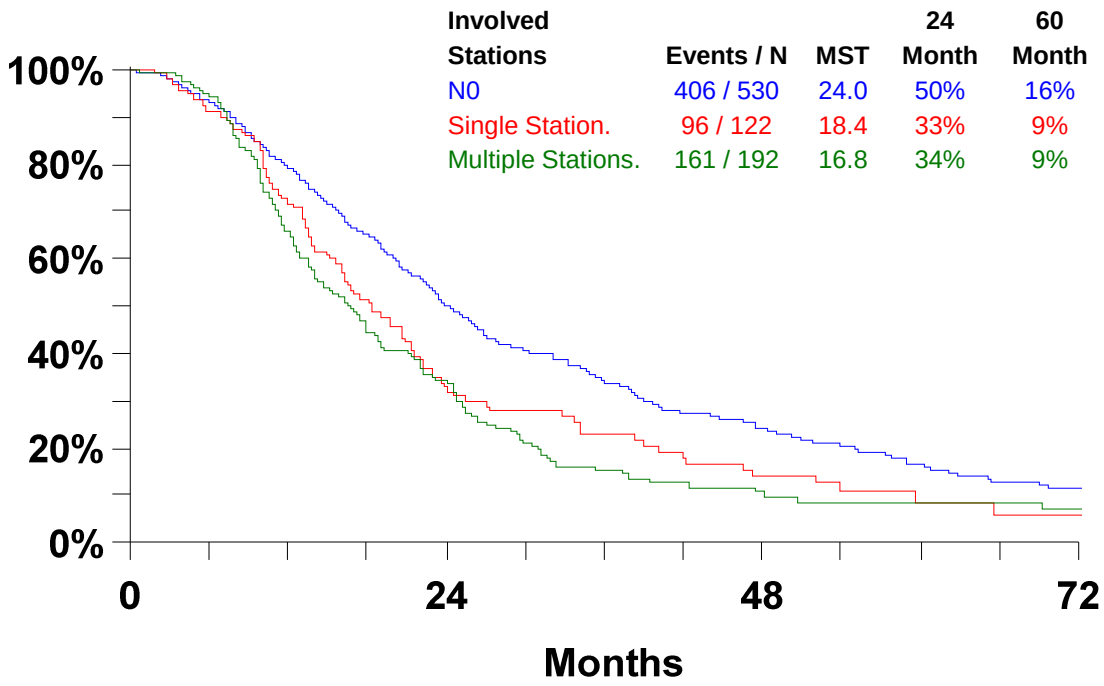
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Figure 3



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Figure 4



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Figure 5

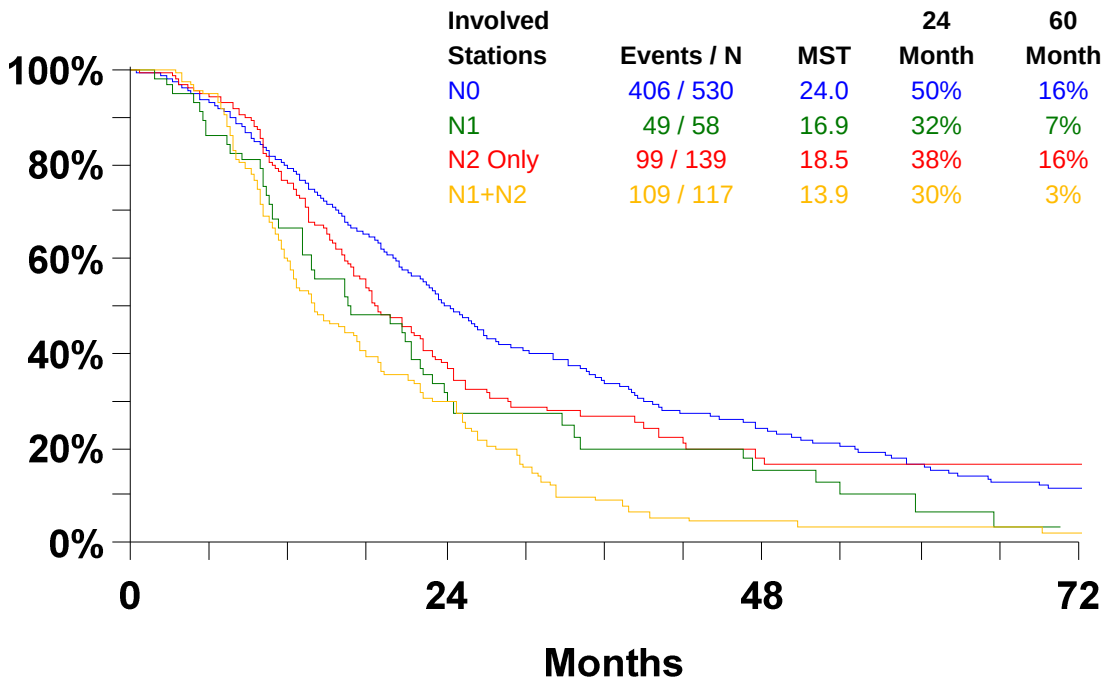
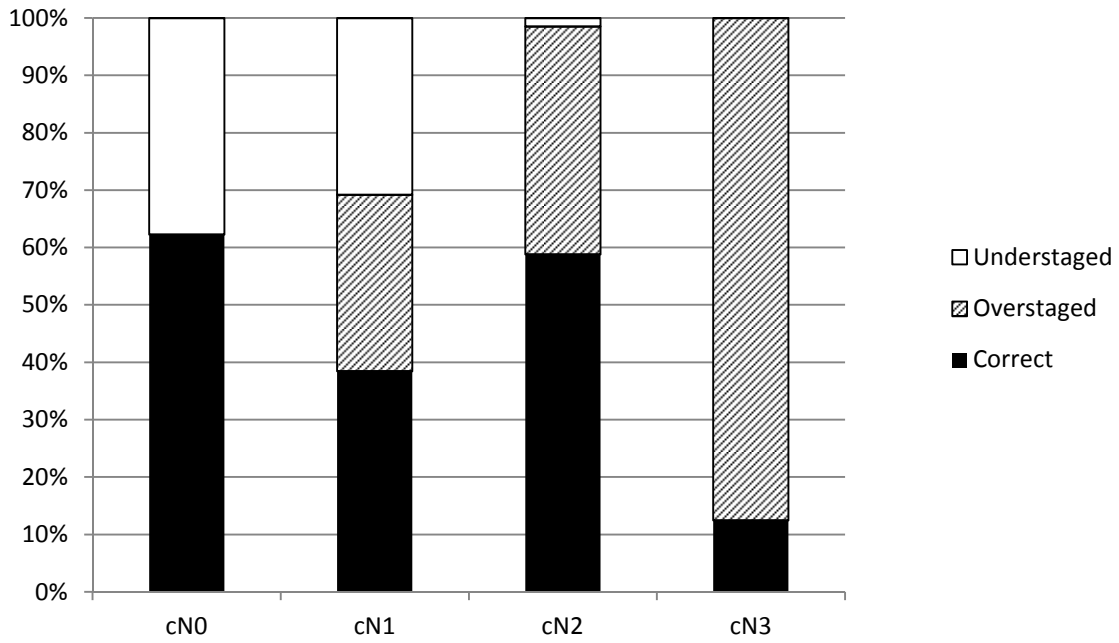
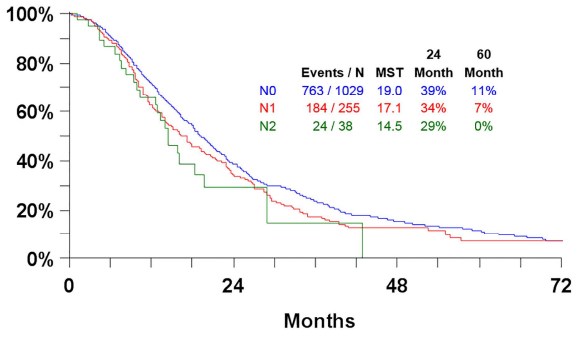
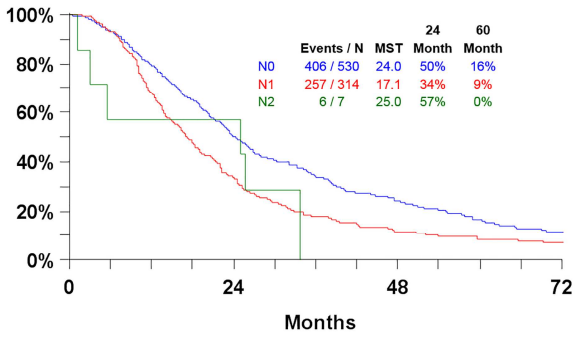


Figure 6

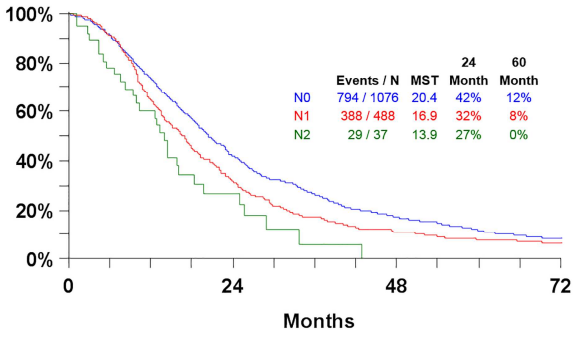

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N1 184 / 255 17.1 34% 7%
N2 24 / 38 14.5 29% 0%
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N1 257 / 314 17.1 34% 9%
N2 6 / 7 25.0 57% 0%
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N2 29 / 37 13.9 27% 0%
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