research article

Real-life long-term outcomes of upfront surgery in patients with resectable stage I-IIIA non-small cell lung cancer

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Background. Treatment of early-stage non-small cell lung cancer (NSCLC) is rapidly evolving. When introducing novelties, real-life data on effectiveness of currently used treatment strategies are needed. The present study evaluated outcomes of stage I–IIIA NSCLC patients treated with upfront radical surgery in everyday clinical practice, between 2010–2017.

Patients and methods. Data of 539 consecutive patients were retrieved from a prospective hospital-based registry. All diagnostic, treatment and follow-up procedures were performed at the same thoracic oncology centre according to the valid guidelines. The primary outcome was overall survival (OS) analysed by clinical(c) and pathological(p) TNM (tumour, node, metastases) stage. The impact of clinicopathological characteristics on OS was evaluated using univariable (UVA) and multivariable regression analysis (MVA).

Results. With a median follow-up of 53.9 months, median OS and 5-year OS rate in the overall population were 90.4 months and 64.4%. Five-year OS rates by pTNM stage I, II and IIIA were 70.2%, 60.21%, and 49.9%, respectively. Both cTNM and pTNM stages were associated with OS; but only pTNM retained its independent prognostic value ($p = 0.003$) in MVA. Agreement between cTNM and pTNM was 69.0%. Next to pTNM, age ($p = 0.001$) and gender ($p = 0.004$) retained their independent prognostic value for OS.

Conclusions. The study showed favourable outcomes of resectable stage I–IIIA NSCLC treated with upfront surgery in real-life. Relatively low agreement between cTNM and pTNM stages and independent prognostic value of only pTNM, observed in real-life data, suggest that surgery remains the most accurate provider of the anatomical stage of disease and important upfront therapy.

Key words: resectable NSCLC; upfront surgery; real-life data; overall survival; prognostic factors

Introduction

Lung cancer is a major public health issue worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2020 making it the second most common cancer and the leading cause of cancer death worldwide.[1] After decades of poor control of lung cancer, the mortality rates began to decrease in the last two decades.[1] This trend coincides with a slow, but steady increase in lung cancer survival rates, that was up to now mostly noticeable in localized (stage I and II) non-small cell lung cancer

(NSCLC). Currently the 5-year net survival of localized lung cancer is around 60%.[2,3]

Localized lung cancer accounts for around 25% of newly diagnosed lung cancers, with a vast majority of them having NSCLC histology.[3] Surgery with curative intent remains fundamental treatment for stage I–II and for selected stage IIIA NSCLC patients.[4] With the introduction of novel, less invasive surgical techniques, such as video-assisted thoracoscopic surgery and improved perioperative care, the outcomes of patients with resectable NSCLC improved substantially.[3,4] Platinum-based adjuvant chemotherapy, which is nowadays considered as a standard adjuvant treatment of early-stage NSCLC, further improved cure rates.[5] With the incorporation of novel targeted therapies and immunotherapy with immune checkpoint inhibitors (ICIs) additional increase in overall survival is expected. Targeted therapy with osimertinib, which led to significant reduction in distant recurrence or death in a prospective phase 3 trial has already been incorporated into treatment recommendations for epidermal growth factor receptor (EGFR) positive patients.[5] Based on the positive results of some recently published adjuvant trials, it is expected that ICIs will soon become a part of standard adjuvant therapy for early-stage NSCLC as well. There is growing evidence that neoadjuvant treatment with ICI leads to major or even complete pathologic responses in a substantial percentage of patients without compromising surgery for resectable NSCLC[6], thus making neoadjuvant immunotherapy an appealing approach in the future.

It is expected that the percentage of patients diagnosed with resectable NSCLC will increase in the next years. Several international clinical trials, including the European NELSON study confirmed the efficacy of low-dose CT screening in decreasing lung cancer mortality in the high-risk population of heavy smokers.[7,8] With the introduction of screening programs, we expect not only an increase of patients diagnosed with localized NSCLC but it might also become necessary to redefine treatment paradigms for early-stage NSCLC.

There is no doubt that major changes in the detection and treatment of early-stage NSCLC are expected shortly. To better predict and evaluate the effectiveness of those novel strategies in everyday clinical practice and to develop individualized risk-adjusted treatment strategies for individual patients, more data on clinicopathological characteristics and outcomes of early-stage NSCLC patients treated in a real-life before the introduction of those novelties, are needed. The International Association for the Study of Lung Cancer (IASLC) recommendations for TNM classification scheme, based on a database of nearly 90.000 patients[9] as well as some IASCL validation studies performed on the Caucasian population[10] provide valuable data on survival of patients treated in routine clinical practice. Next to the IASLC data, there is almost complete lack of information on the outcomes of the cohorts of resectable stage I–IIIA NSCLC patients, treated in a real-life scenario in the last decade. Most of the real-life observational trials reported recently present data for specific subpopulations of resectable NSCLC, such as patients treated with adjuvant chemotherapy[11] or patients with stage IIIA or N2 disease.[12-14] Our study aimed to evaluate overall survival of consecutive resectable TNM stage I–IIIA NSCLC patients treated with upfront radical surgery in a real-life practice, using prospectively collected hospital-based registry data. We also assessed the impact of clinicopathological characteristics, particularly TNM stage, on survival.

Patients and methods

Data source and study population

Data were retrieved from the hospital-based lung cancer registry, which prospectively collects demographics, clinicopathological, treatment, and survival data for all lung cancer patients diagnosed and treated at the centre. In hospital follow-up data are supplemented with the death certificates provided by the National Health Institute on a regular basis. All data was collected in an anonymised fashion. For the purpose of this study, survival status was updated and the data were retrieved in January 2020.

We retrieved the data of consecutive patients with resectable cTNM stage I–III NSCLC, treated with upfront radical surgical resection at a single thoracic oncology centre in Slovenia, between January 2010 and December 2017. All patients had pathologically confirmed NSCLC. Diagnostic and treatment procedures were performed as recommended by the international guidelines valid at the time.[15,16] Lymph nodes showing (18) F-fluorodeoxyglucose (FDG) uptake on preoperative PET-CT scans, or their short axis > 1 cm on CT scans were marked as clinically positive. In patients with clinically positive mediastinal lymph nodes endobronchial ultrasound-guided lymph node biopsy (EBUS TBNB) was performed, whenever

feasible. For all patients, including those with cN2 disease, the institutional multidisciplinary tumour board concluded that they have resectable NSCLC and were referred to upfront surgery.

All patients underwent radical surgical resection (R0) with lobectomy, bilobectomy, or pneumonectomy with complete lymph node dissection as a standard surgical procedur.[16,17] Adjuvant chemotherapy and/or postoperative radiotherapy were performed according to the international guidelines valid at that time.[15,16] Patients with neoadjuvant treatment were not included in the study population.

Clinical stage was defined as the last stage determined before surgical resection. All resected tissue including lymph nodes was examined by board certified pathologists. Clinical and pathological stages were assigned based on the 7th edition TNM classification for NSCLC[17], valid at the time. Testing for EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangements has been introduced gradually as recommended by the international societies.[18] Testing was performed on formalin fixed, paraffin embedded tumour tissue specimens or different cytological specimens. For EGFR testing allele-specific PCR method with commercial kits, either Cobas EGFR mutation test (Roche, USA) or Therascreen EGFR PCR Kit (Qiagen, UK). ALK immunohistochemical detection was based on ALK CDx assay (Ventana, Roche, USA). Patients were followed-up with physical examination and chest CT scan, first biannually and after two years annually.

The hospital-based registry data collection and all subsequent analyses for academic purposes were approved by the Slovenian National Committee for Medical Ethics (approval number 135/07/09 and 40/04/12). All patients consented for data collection and subsequent analyses.

Outcome measures and statistical analyses

The primary endpoint was overall survival (OS), defined as the time in months from the date of surgery until either the date of death from any cause or the date the patient was last known to be alive (censored data). Patient and treatment characteristics were analysed using descriptive statistics. The agreement between clinical and pathological TNM staging variables was calculated as simple percent agreement to ease the interpretation of the results. Survival curves were estimated using the Kaplan-Meier estimator. The independent prognostic value of each included characteristic was tested in a Cox proportional hazards regression model. All variables with $p \leq 0.250$ in univariable regression analysis (UVA) were considered for and included in the multivariable regression analysis (MVA), except EGFR and ALK status due to being applicable only to a subset of patients. A p-value below 0.05 was considered statistically significant. All reported p-values are two-tailed. All statistical analyses were carried out using IBM SPSS Statistics software (version 21).

Results

We identified 539 consecutive stage I–IIIA NSCLC patients treated with upfront radical surgery. Demographic, clinicopathological, and treatment characteristics of the study population are presented in Table 1. The median age was 64 years (range, 39–83), males accounted for 58.4% of patients. Most patients were current or former smokers, with only 12.7% of never smokers included in the study. Adenocarcinoma appeared most frequently (63.3%), followed by squamous-cell carcinoma (36.2%) and other rare types of NSCLC (0.6%). EGFR mutations and ALK rearrangements were detected in 12.3% and 5.3 % of tested patients, with low completeness of ALK testing due to the introduction of testing to routine clinical practice from 2014 onward. Lobectomy was performed in a vast majority of patients, bilobectomy or pneumonectomy was required in only 5.8% and 9.1% of patients, respectively. Adjuvant platinum doublet chemotherapy was delivered in 146 (27.1%) of patients, the vast majority of whom had pathologically confirmed lymph node involvement. Postoperative radiotherapy was used in 36 (6.7%) patients; all of them had pathological N2 disease.

PET-CT was performed in 94.8% of patients (511/539). EBUS TBNB was gradually introduced in the routine clinical practice during the study period and was applied in 112 patients, with cN1 and cN2 disease according to CT and/or PET-CT scan. Lymph node involvement was confirmed in 65.5% of the samples obtained from the patients with cN2 disease. Mediastinoscopy was performed in five patients with cN2 and negative EBUS TNBN of mediastinal nodes; all lymph node samples obtained by mediastinoscopy were negative. Most patients were diagnosed with clinical stage I (57.3%) or stage II (26.9%). Clinical stage IIIA was determined in 15.8% of patients. All patients had either a single zone cN2 involvement or cT3/T4 disease without

TABLE 1. Demographic, clinicopathological and treatment characteristics of study population

Characteristic	N (%)
No. of patients	**539**
Age in years: median (range)	64 (39–83)
< 65 years	271 (50.3)
≥ 65 years	268 (49.7)
Gender	
Male	315 (58.4)
Female	224 (41.6)
Smoking status (n = 537; completeness = 99.6 %)	
Current	257 (47.8)
Former	212 (39.5)
Never	68 (12.7)
Histology	
Adenocarcinoma	341 (63.3)
Squamous-cell carcinoma	195 (36.2)
NSCLC other rare types	3 (0.6)
EGFR[a] status in non-squamous NSCLC (n = 334; completeness = 99.7%)	
Positive	41 (12.3)
Negative	292 (87.7)
ALK[b] status in non-squamous NSCLC (n = 334; completeness = 39.2%)	
Positive	7 (5.3)
Negative	124 (94.7)
Clinical TNM stage[c]	
I	309 (57.3)
II	145 (26.9)
IIIA	85 (15.8)
Clinical T stage	
T1	242 (44.9)
T2	193 (35.8)
T3	96 (17.8)
T4	8 (1.5)
Clinical N stage	
N0	393 (72.9)
N1	102 (18.9)
N2	44 (8.2)
Pathological TNM stage[c] (n = 532; completeness = 98.7%)	
I	296 (55.6)
II	150 (28.2)
III	86 (16.2)
Pathological T stage (n = 537; completeness = 99.6%)	
T1	223 (41.5)
T2	248 (46.2)
T3	58 (10.8)
T4	8 (1.5)
Pathological N stage (n = 534; completeness = 99.1%	
N0	386 (72.3)
N1	81 (15.2)
N2	67 (12.5)
Surgery type	
Lobectomy	459 (85.2)
Bilobectomy	31 (5.8)
Pneumonectomy	49 (9.1)
Adjuvant treatment	146 (27.1)
Platinum-based chemotherapy	36 (6.7)
Postoperative radiotherapy	

[a]EGFR: epidermal growth factor receptor; [b]ALK: anaplastic lymphoma kinase; [c]stage defined by American Joint Committee on Cancer staging

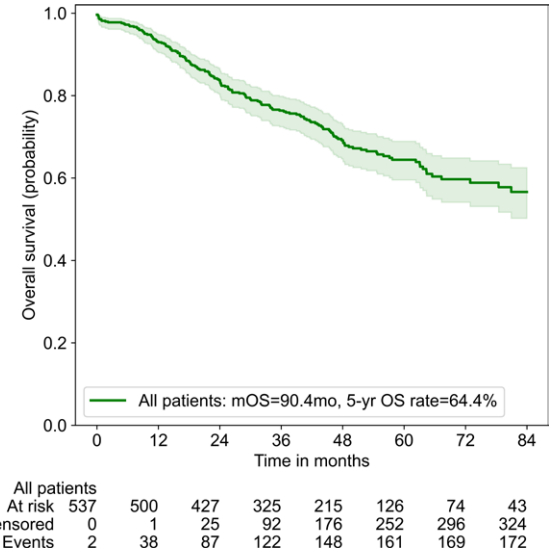

FIGURE 1. Overall survival of patients with completely resected stage I–III A non-small cell lung cancer.

tumour invasion to the adjacent vessels or organs. Postoperative pathological examination and staging also revealed high rate of pathological stage I (55.6%) or stage II (28.2%), with low percentage of stage IIIA disease (16.2%). However, the agreement between clinical and pathological staging was relatively low.

Table 2 shows the comparison between clinical (cTNM) and pathological (pTNM) staging according to TNM staging categories. The agreement between cTNM and pTNM stages was the highest for stage I (81%) and much lower for stage II (55%) and stage IIIA (49%). Of note, cTNM stage IIIA turned out to be pTNM stage II or stage I in 36% and 14% of patients, respectively. When analysing T and N descriptors separately, the accuracy of cT-descriptor decreased with increasing stage while for cN-descriptor the lowest accuracy rate was observed for cN1 stage. The overall agreement between clinical and pathological stage were quite similar for all three descriptors, TNM stage, T stage and N stage, i.e., 69.0%, 72.3% and 71.9%, respectively.

The median follow-up time was 53.9 (50.9–56.9) months. At the end of follow-up, 177/539 patients (32.8%) died. The median OS (mOS) for the whole cohort of patients was 90.4 months (95% CI calculation unreliable due to few events after mOS), with an estimated 5-year OS rate of 64.4% (Figure 1). The overall survival of patients grouped by cTNM, pTNM, cN and pN stage is depicted in Figure 2. The mOS has not been reached in the majority of the subgroups. The estimated 5-year OS rates for patients with cTNM stage I, stage II, and stage IIIA were 70.6%, 56.9%, and 55.3%; while the estimated 5-year OS rates for patients with pTNM stage I, stage II, and stage IIIA were 70.2%, 60.2%, and

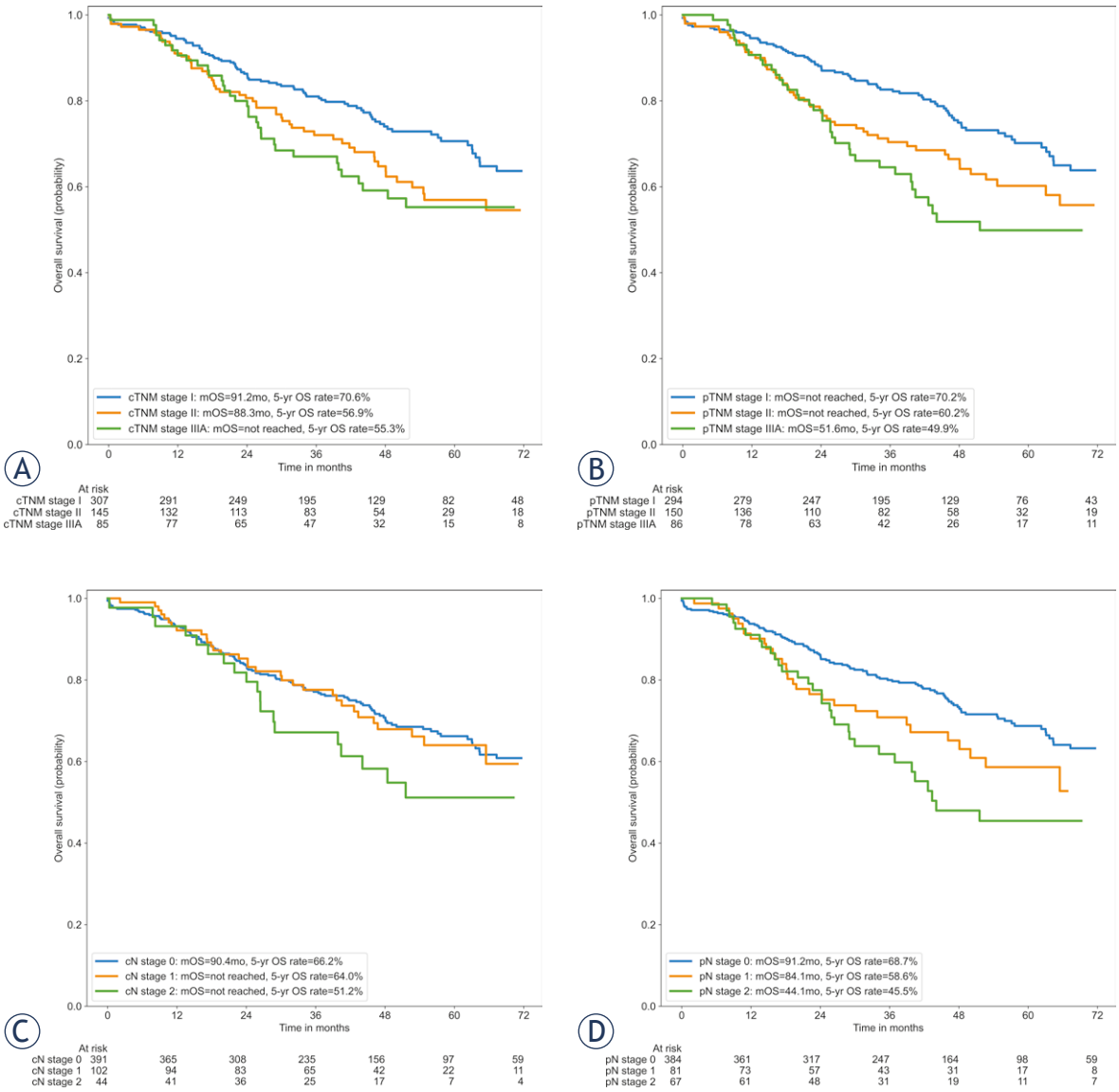

FIGURE 2. Overall survival by clinical TNM stage **(A)**, pathological TNM stage **(B)**, clinical N stage **(C)** and pathological N stage **(D)**.

49.9%, respectively, (Figures 2A and 2B). When observing the N status alone, Figures 2C and 2D show that pN stage provides a much clearer separation of survival curves than cN stage – as also demonstrated by UVA below.

In UVA the factors significantly associated with shorter overall survival were age ≥ 65 years and male gender. Furthermore, with respect to the anatomical stages, all stage categories, except cN (p = 0.313), were significantly associated with OS in the UVA (Table 3). However, in MVA that included either cTNM or pTNM stage as a determinator of the anatomical extent of disease, pTNM retained its significant and independent impact on OS (p = 0.003), next to age and gender, while cTNM stage lost its independent prognostic value (p = 0.092) (Table 4). Of note, TNM stage (clinical or pathological) was always included in the model for multivariate analyses, while the other factors were included in the stepwise procedure (thus only the significant factors are reported in Table 4).

Discussion

This observational cohort study presents real-life data on long-term survival and the impact of clinicopathological characteristics on overall survival

of resectable stage I–IIIA NSCLC patients, treated with upfront radical surgery at a single thoracic oncology centre in the period 2010–2017. The median OS time of 90.4 months and estimated 5-year survival rate of 64.4% observed in our real-life cohort of 539 consecutive patients are encouraging. Our data exceed the median OS of 63 months observed in a German cohort of patients with radically resected stage I–IIIB NSCLC, treated at a single academic centre in a very similar period (from 2009 to 2014), which also included patients with a higher stage IIIB disease.[10] When comparing by pTNM stage I, II and IIIA, the estimated 5-year survival rates of 70.2%, 60.2% and 49.9%, respectively, observed in our study, correspond very well to the 5-year survival rates in the German study.[10] Our findings also slightly exceed the 5-year survival rates of 83%–71%, 57%–49% and 36% for pTNM stage IA–B, II A–B and IIIA, published by IASLC.[9] Furthermore, our findings are also in line with 5-year survival rates between 37%–47%, observed in real-life cohorts of patients with resectable stage IIIA–N2 NSCLC, treated with upfront surgery in a similar period.[12-14] Thus, our observation supports the idea that selected patients with stage IIIA NSCLC might have a favourable outcome when treated by upfront radical surgery followed by adjuvant chemotherapy and/or irradiation.

As expected, the observed survival rates decreased with increasing stage of all staging variables (T, N, and TNM). But of note, while significant differences in survival were observed according to both clinical and pathological T and both clinical and pathological TNM stage, clinical N stage (as opposed to pathological N stage) did not prove a significant prognostic factor already in the UVA. Furthermore, in the multivariate analyses in which only TNM stage as a comprehensive denominator of T and N stages was included, only pTNM stage retained its significant and independent impact on overall survival, while cTNM stage failed to do so (likely due to its N stage part). This clearly points towards a much stronger prognostic value of pathological compared to clinical staging variables in resectable NSCLC. Also, in many previous studies evaluating prognostic impact of clinical and pathological TNM or N stage on OS the information on pathological stage improved prognostic value of the model.[9,14,17] There is evidence suggesting quite a high rate of disagreement between clinical and pathological staging in operable NSCLC patients treated in everyday practice. Even in studies performed after introduction of PET-CT and EBUS TBNB in routine clinical practice, relatively high rate of disagreement between clinical and pathological N and TNM staging was observed. In the Dutch observational study performed in patients with pathological stage IIIA disease, the agreement between clinical and pathological T and N stage was 57.1% and 28.5%, respectively.[19] The agreement rates observed in our study were relatively high for all three descriptors T, N and TNM stage (72.3%, 71.9% and 69.0%, respectively), but still not optimal. However, EBUS TBNB have only been introduced in our everyday clinical practice during the study period. With the incoming era of neoadjuvant systemic therapy, the accurate non-surgical staging of not only mediastinal lymph nodes but also hilar lymph nodes were becoming important. In our study the lowest agreement between clinical and pathological N status was observed particularly for cN1 stage (33%). Very interesting and clinically important observation is that almost half (48%) of cN1 patients were down staged to pN0, while upgrading to pN2 was found in a smaller, 19% proportion of patients. With recent dilemmas whether more invasive mediastinal lymph node

TABLE 2. Comparison between clinical (c) and pathological (p) TNM staging

2A. Comparison between clinical and pathological TNM stage (n = 532; completeness = 98.7%)

	c Stage I (N = 303) N (%)	c Stage II (N = 144) N (%)	c Stage IIIA (N = 85) N (%)
p Stage I	**246 (81%)**	38 (26%)	12 (14%)
p Stage II	40 (13%)	**79 (55%)**	31 (36%)
p Stage IIIA	17 (6%)	27 (19%)	**42 (49%)**

Overall agreement: 367 out of 532 cases (69.0%)

2B. Comparison between clinical and pathological T stage (n = 537; completeness = 99.6%)

	cT1 (N = 240) N (%)	cT2 (N = 193) N (%)	cT3 (N = 96) N (%)	cT4 (N = 8) N (%)
pT1	**187 (78%)**	24 (13%)	10 (10%)	2 (25%)
pT2	46 (19%)	**158 (82%)**	41 (43%)	3 (37%)
pT3	5 (2%)	9 (4%)	**42 (44%)**	2 (25%)
pT4	2 (1%)	2 (1%)	3 (3%)	**1 (13%)**

Overall agreement between: 388 out of 537 cases (72.3%)

2C. Comparison between clinical and pathological N stage (n = 534; completeness = 99.1%)

	cN0 (N = 388) N (%)	cN1 (N = 102) N (%)	cN2 (N = 44) N (%)
pN0	**324 (84%)**	49 (48%)	13 (30%)
pN1	42 (11%)	**34 (33%)**	5 (11%)
pN2	22 (6%)	19 (19%)	**26 (59%)**

Overall agreement: 384 out of 534 cases (71.9%)

TABLE 3. Univariate analyses of overall survival

Factor	p-value	HR (95% CI)
Age		
< 65		1
≥ 65	0.002	1.59 (1.18 – 2.15)
Gender		
Male		1
Female	0.001	0.59 (0.43 – 0.81)
Smoking status		
never		1
current or former	0.115	1.50 (0.91 – 2.47)
Histology		
adenocarcinoma or NOS		1
squamous cell carcinoma	0.111	1.28 (0.95 – 1.73)
EGFR status[a] (positive vs negative)		
negative		1
positive	0.111	0.56 (0.27 – 1.14)
Clinical TNM stage	0.027*	
I		1
II	0.034	1.44 (1.03 – 2.02)
IIIA	0.025	1.57 (1.06 – 2.34)
Clinical T stage	0.001*	
T1		1
T2	0.882	0.97 (0.69 – 1.38)
T3 or T4	0.001	1.86 (1.29 – 2.68)
Clinical N stage	0.317*	
N0		1
N1	0.958	0.99 (0.67 – 1.46)
N2	0.137	1.44 (0.89 – 2.34)
Pathological TNM stage	0.003*	
I		1
II	0.030	1.46 (1.04 – 2.06)
IIIA	0.001	1.90 (1.29 – 2.79)
Pathological T stage	0.007*	
T1		1
T2	0.019	1.49 (1.07 – 2.07)
T3 or T4	0.004	1.92 (1.23 – 2.98)
Pathological N stage	0.002*	
N0		1
N1	0.054	1.48 (0.99 – 2.20)
N2	0.001	1.93 (1.29 – 2.87)

[a]only in non-squamous NSCLC; *for the whole variable

staging might change the treatment paradigm and outcomes of NSCLC patients with cN1 disease our data become even more appealing.

Notably, the survival rates observed in our current study far exceed those observed in a retrospective analysis of NSCLC patients treated at our centre in 2006.[20] The latter revealed much shorter median overall survival rates for all clinical TNM stages I, II and IIIA NSCLC with the largest differences observed in stages II–IIIA. In that analysis all consecutive patients were included, regardless of whether they received treatment with curative intent or not, which is definitively one of the reasons for worse survival rates. But still, improvement in overall survival achieved over the last years is obvious. This can be attributed to major advances in diagnostic procedures, surgical techniques, postoperative care and adjuvant therapies for early NSCLC that we witnessed in the last decade and their rapid transfer into everyday clinical practice at our institution.[21]

The clinicopathological characteristics of our cohort of patients mirror the typical population of NSCLC patients in our country and region at the beginning of this century, with prevailing smokers and squamous-cell histology.[21] Next to pTNM stage, age and gender retained their significant and independent prognostic value for OS in MVA; while smoking status and histology failed to show prognostic value already in the UVA. Our results are in concordance with the observations made on a large series of patients with NSCLC confirming older age and male gender as independent prognostic factors for worse survival.[22,23] Male gender was confirmed as an independent prognostic factor for worse survival in published trials, however this has been seen particularly in patients with advanced NSCLC and adenocarcinomas.[23] In our study male gender turned out to be an independent predictor of worse survival in early-stage NSCLC and irrespective of histology, thus suggesting other probable causes of poor survival in male NSCLC patients which need to be further investigated.

Our study also provides valuable data on the frequency of EGFR mutations and their prognostic value in early-stage NSCLC. The findings are in line with the results of recently published large individual study[24] which failed to confirm prognostic impact of EGFR status on survival of patients with resectable NSCLC. There are still uncertainties about the percentage of EGFR mutated tumours in early-stage NSCLC. In our study, EGFR testing performed on a large series of 334 patients with resectable non-squamous cell NSCLC, revealed a 12.3% positivity rate which is quite comparable to the 13.8% positivity rate observed in advanced NSCLC in the countries and the centres which participated in the INSIGHT registry trial.[25] Similarly, ALK positivity rate of 5.3% observed in our series of resectable NSCLC corresponds very well with the positivity rates observed in advanced NSCLC.[26]

The results of our study should be considered in the context of its strengths and limitations. The study provides a wealth of information on clinicopathological characteristics and survival outcomes of a large cohort of resectable NSCLC patients, treated with upfront surgery in real-life practice. Additionally, all data were collected prospectively by the hospital-based lung cancer registry. Looking at potential limitations, results from a single centre study might not be generalisable to the overall population in the country or region. However, at our centre more than a half of the country's newly

diagnosed resectable NSCLC are treated, thus representing the entire population quite well. It is also encouraging that the activities on establishing a nationwide register of lung cancer patients collecting detailed data on clinicopathological characteristics and individual treatments at the Cancer Registry of Slovenia are ongoing. Since our hospital-based registry does not capture data on the cause of death, we do not present data on cancer specific survival but on overall survival, which might be influenced by comorbidities and other conditions often present in fairly old population of patients with resectable NSCLC. The hospital registry also does not collect precise data on modality of preoperative staging (imaging *versus* invasive procedures) to determine clinical N stage in each individual patient. Therefore, the data on mediastinal staging by EBUS TNBN and mediastinoscopy were collected retrospectively and might be subject to bias.

Our study with a lengthy follow-up, showed a favourable outcome for patients with resectable stage I–IIIA NSCLC treated with upfront surgery in a real-life setting. Particularly encouraging are the survival rates observed in patients with stage IIIA disease indicating that selected patients with N2 disease are candidates for upfront surgery. Relatively low agreement between cTNM and pTNM stages and the independent prognostic value of pTNM but not cTNM stage observed in our study, suggest that we should aim to further improve preoperative staging. Until then we should always weight our decisions about upfront treatment of resectable NSCLC very carefully for each individual patient. Currently, surgery remains the most reliable provider of information on anatomical TNM stage as one of the strongest prognostic factors and enables us to make an informed decision on adjuvant systemic treatment in each individual patient.

Finally, it is inspiring to notice a substantial improvement in overall survival rates of early-stage NSCLC patients treated over the last decades at the same large thoracic oncology centre. With the aim of further improving our results, we are planning an additional study which will strive to evaluate preoperative staging of nodal involvement more profoundly, thus providing for better multimodality treatment selection for each individual patient.

TABLE 4. Multivariate analyses of overall survival (separate for clinical and for pathological stage)

Cox regression model with clinical stage	p-value	HR (95% CI)
Age		
< 65		1
≥ 65	0.003	1.58 (1.17 – 2.14)
Gender		
Male		1
Female	0.006	0.63 (0.46 – 0.88)
Clinical TNM stage	0.092*	
I		1
II	0.078	1.36 (0.97 – 1.91)
IIIA	0.068	1.46 (0.97 – 2.18)
Cox regression model with pathological stage	**p-value**	**HR (95% CI)**
Age		
< 65		1
≥ 65	0.001	1.68 (1.24 – 2.28)
Gender		
Male		1
Female	0.004	0.62 (0.45 – 0.86)
Pathological TNM stage	0.003*	
I		1
II	0.076	1.37 (0.97 – 1.93)
IIIA	0.001	1.95 (1.32 – 2.88)

*for the whole variable

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The raw data underlying this article are available in the article. Due to data privacy, and hospital registry-related restrictions, the clinicopathological data cannot be made public, i.e., accessible to anyone for any purpose without a review process and without putting an agreement in place.

Data availability statement and author contribution statement

Marko Bitenc: conceptualization, writing – original draft, formal analysis, writing – review & editing. **Tanja Cufer**: conceptualization, formal analysis, writing – original draft, writing – review & editing, supervision. **Izidor Kern**: investigation, writing—original draft, formal analysis. **Martina Miklavcic**: data curation, investigation, writing – original draft, writing – review & editing. **Sabrina Petrovic**: data curation, investigation, writing – original draft. **Vida Groznik**: software, data curation. **Aleksander Sadikov**: software, formal analy-

sis, visualization, writing – review & editing, supervision.

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