lek. Marcin Cackowski

Znaczenie nowych czynników prognostycznych przerzutów do węzłów chłonnych śródpiersia u chorych z niedrobnokomórkowym rakiem płuca w odniesieniu do klasyfikacji TNM.

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: dr hab. n. med. Dariusz Dziedzic

Klinika Chirurgii Instytutu Gruźlicy i Chorób Płuc

Warszawa 2023

Spis treści

Wykaz dorobku naukowego i zawodowego

Wykształcenie

2015–2021

Lekarz, Wydział Lekarski, Warszawski Uniwersytet Medyczny

Stypendium Rektora dla najlepszych studentów 4x (2015/16, 2017/18, 2019/20, 2020/21)
Złota Odznaka Studenckiego Towarzystwa Naukowego za wybitne osiągnięcia naukowe

Praktyki zagraniczne

08.2019

Chungnam National University Hospital | Daejeon, Korea Południowa
Oddział Chirurgii Ogólnej

Studia podyplomowe

2021-2022

Medycyna Estetyczna
Śląska Wyższa Szkoła Medyczna w Katowicach

Doświadczenie zawodowe

2022-nadal

Lekarzy rezydent w dziedzinie chirurgii klatki piersiowej
Klinika Chirurgii, Instytut Gruźlicy i Chorób Płuc

2021-2022

Lekarz stażysta
Szpital Praski p.w. Przemienienia Pańskiego Sp. z o.o.

Publikacje

1. Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, D. A., & Orłowski, T. M. (2020). Alternative methods of lymph node staging in lung cancer: a narrative review. *Journal of thoracic disease*, *12*(10), 6042–6053.
2. Dziedzic, D. A., Cackowski, M. M., Zbytniewski, M., Gryszko, G. M., Woźnica, K., Orłowski, T. M., & Polish Lung Cancer Study Group (PLCSG) (2021). The influence of the number of lymph nodes removed on the accuracy of a newly proposed N

descriptor classification in patients with surgically-treated lung cancer. *Surgical oncology*, *37*, 101514.

3. Dziedzic, D. A., Zbytniewski, M., Gryszko, G. M., Cackowski, M. M., Langfort, R., & Orlowski, T. M. (2021). Video-assisted versus open thoracotomy lobectomy: comparison on lymphadenectomy and survival in early stage of lung cancer. *Journal of thoracic disease*, *13*(1), 101–112
4. Gryszko, G. M., Cackowski, M. M., Zbytniewski, M., Woźnica, K., Orłowski, T. M., Dziedzic, D. A., & Polish Lung Cancer Study Group (PLCSG) (2021). The impact of left lower paratracheal (4L) lymph node dissection on survival in patients with surgically treated left-sided NSCLC. *European journal of cardio-thoracic surgery*, *60*(5), 1201–1209.
5. Cackowski M.M., Zbytniewski M., Gryszko M., Dziedzic M., Woźnica K.,. Orłowski T.M., Dziedzic D.A. on behalf of the Polish Lung Cancer Study Group (PLCSG) (2022) Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study. *Journal of thoracic disease.* 14(9), 3265–3276.
6. Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, M., Woźnica, K., Orłowski, T. M., Dziedzic, D. A., & Polish Lung Cancer Study Group (PLCSG) (2023). The absence of lymph nodes removed (pNx status) impacts survival in patients with lung cancer treated surgically. *Surgical oncology,* 48, 101941.
7. Trojnar, A., Domagała-Kulawik, J., Sienkiewicz-Ulita, A., Zbytniewski, M., Gryszko, G. M., Cackowski, M. M., Dziedzic, M., Woźnica, K., Orłowski, T. M., & Dziedzic, D. A. (2022). The clinico-pathological characteristics of surgically treated young women with NSCLC. *Translational lung cancer research,* 11(12), 2382–2394.
8. Trojnar, A., Domagała-Kulawik, J., Sienkiewicz-Ulita, A., Zbytniewski, M., Gryszko, G. M., Cackowski, M. M., Dziedzic, M., Woźnica, K., Orłowski, T. M., Dziedzic, D. A., & Polish Lung Cancer Study Group (PLCSG) (2022). Sex differences in clinico-pathologic characteristics and long-term survival among 17,192 surgically treated NSCLC patients: Nationwide population-based propensity score-matching study. *Surgical oncology*, 45, 101873.
9. Zbytniewski M., Gryszko G. M., Cackowski M. M., Sienkiewicz-Ulita A. W., Woźnica K., Dziedzic M., Orłowski T. M. , Dziedzic D. A.; on behalf of the Polish Lung Cancer Study Group (PLCSG). The effectiveness of surgical treatment of lung cancer in polish academic and nonacademic centers. *Translational Lung Cancer Research* 2023. 12(8):1717-1727

10. Krawczyk P., Cackowski M., Dziubek Ł. (2020) The participation of the defender and the actions of handball goalkeepers in situation of throws from backcourt positions. International Journal of Performance Analysis in Sport Vol 20/2020 (3) 445-455.
11. Cackowski M., Rosiek A., Jóźwiak J. Rozdział: Increased incidence of CNS tumours in Parkinson's Disease Monografia: Advances in Biomedical Research – selected topics. Str 139-146. ISBN 978-83-65932-55-6

Języki

Angielski poziom C2 – certyfikat EFSET

Hiszpański - podstawowy

Polski Język Migowy - podstawowy

Działalność popularyzująca naukę

Wielokrotny współorganizator studenckich konferencji naukowych
(Postępy w Badaniach Biomedycznych, Po drugiej stronie medalu - Medycyna w Sporcie)

Wielokrotny organizator warsztatów szycia chirurgicznego dla studentów

Założyciel i przewodniczący Studenckiego Koła Naukowego Torakochirurgii

Wykaz publikacji stanowiących prace doktorską

1. Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, D. A., & Orłowski, T. M. (2020). Alternative methods of lymph node staging in lung cancer: a narrative review. *Journal of thoracic disease*, *12*(10), 6042–6053. https://doi.org/10.21037/jtd-20-1997

   Impact Factor 3.005
   70 punktów MEiN

2. Cackowski, M. M., Zbytniewski, M., Gryszko, G. M., Dziedzic, M., Woźnica, K., Orłowski, T. M., & Dziedzic, D. A. (2022). Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study. *Journal of thoracic disease*, 14(9), 3265–3276. https://doi.org/10.21037/jtd-21-1957

   Impact Factor 3.005
   70 punktów MEiN

3. Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, M., Woźnica, K., Orłowski, T. M., Dziedzic, D. A., & Polish Lung Cancer Study Group (PLCSG) (2023). The absence of lymph nodes removed (pNx status) impacts survival in patients with lung cancer treated surgically. *Surgical oncology*, 48, 101941. Advance online publication. https://doi.org/10.1016/j.suronc.2023.101941

   Impact Factor 2.388
   100 punktów MEiN

Słowa kluczowe: niedrobnokomórkowy rak płuca, chirurgia klatki piersiowej, limfadenektomia, staging, węzły chłonne, stacja 3a, status pNx

Keywords: non-small-cell lung cancer, thoracic surgery, lymphadenectomy, staging, lymph nodes, 3a station, pNx status

Wykaz skrótów

IASLC: Międzynarodowe Stowarzyszenie do Badań nad Rakiem Płuca

TNM: klasyfikacja Tumour, Node, Metastasis

PET-CT: pozytonowa emisyjna tomografia komputerowa

VATS: wideotorakoskopia

3ALN+: grupa pacjentów u których pobrano węzeł grupy 3a

3ALN-: grupa pacjentów u których nie pobrano węzła grupy 3a

MLND: całkowite wycięcie węzłów chłonnych śródpiersia

MLNS: systematyczny sampling węzłów chłonnych śródpiersia

Streszczenie w języku polskim

Wstęp i cele

Status węzłów chłonnych w niedrobnokomórkowym raku płuca jest jednym z najważniejszych czynników rokowniczych. Jednakże, nadal toczy się wiele kontrowersji i dyskusji dotyczących tego aspektu. Z tego powodu zdecydowaliśmy się przeanalizować następujące zagadnienia dotyczące limfadenektomii w raku płuca:

I. przegląd alternatywnych metod klasyfikacji węzłów chłonnych w klasyfikacji TNM raka płuca,
II. istotność kliniczną i wpływ resekcji węzła przednaczyniowego 3A na ogólną przeżywalność pacjentów z prawostronnym rakiem płuca,
III. istotność kliniczną oraz wpływ zjawiska braku pobrania węzłów chłonnych (pNx) na ogólną przeżywalność w raku płuca.

Materiał i Metody

I. Dokonaliśmy przeglądu bazy danych PubMed na podstawie następujących klasyfikacji węzłów chłonnych: dotychczasowa klasyfikacja TNM, liczba pozytywnych węzłów chłonnych, liczba negatywnych węzłów chłonnych, liczba pobranych węzłów chłonnych, stosunek węzłów chłonnych pozytywnych do pobranych, modyfikacja tego stosunku za pomocą logarytmu, łańcuchy węzłów chłonnych, klasyfikacja oparta na strefach węzłów chłonnych oraz klasyfikacja oparta na liczbie stacji węzłów chłonnych. Uwzględniliśmy również kombinacje tych klasyfikacji.

II. Dane z bazy danych Polskiej Grupy Raka Płuca dotyczące 6348 pacjentów, którzy byli poddani resekcji miąższu płucnego w latach 2005-2015, zostały retrospektywnie przeanalizowane. Resekcja węzłów 3A została wykonana u 221 pacjentów (3ALN+), podczas gdy u 6217 pacjentów nie dokonano takiej resekcji (3ALN-). Przeprowadziliśmy Propensity score matching by zminimalizować stronniczość wyboru oraz zwiększyć siłę statystyczną pracy. Sparowano 221 pacjentów z grupy 3ALN+ i 221 z grupy 3ALN-.

III. Dokonaliśmy retrospektywnej analizy bazy danych Polskiej Grupy Raka Płuca. Zjawisko pNx zostało zdefiniowane jako 0 pobranych węzłów chłonnych. Uwzględniliśmy 17192 pacjentów.

Wyniki

I. Analiza dotychczasowej literatury pokazała, że obecna klasyfikacja węzłów chłonnych może prowadzić do niedokładnego grupowania chorych. Klasyfikacje oparte na liczbie pozytywnych węzłów chłonnych, stosunku węzłów chłonnych lub jego matematycznej modyfikacji są najbardziej przebadane w licznych pracach. Z tego powodu na podstawie wspomnianych licznych danych powinny być uwzględnione w pierwszej kolejności jako potencjalne dodatkowe czynniki w klasyfikacji cechy N w TNM.

II. Częstość występowania przerzutów do węzłów 3a wynosiła 8% i rosła wraz z stadiami pT. Między pT1c oraz pT2a zauważono istotny wzrost częstości, który został podwojony z 4% do 9%. W przypadku pT4 częstość wynosiła aż 15%. Największa częstość była zauważona wśród pacjentów poddanych pneumonektomii (10%) oraz w podgrupach N2b1 i N2b2 (33% i 64%). W analizie jednozmiennej nie znaleźliśmy istotnych różnic w 5-letniej ogólnej przeżywalności między grupami 3ALN+ a 3ALN- (51% vs 51%, $p=0.74$). Natomiast przerzutowe węzły i nieprzerzutowe węzły 3ALN+ już różniły się istotnie ($p<0.0001$). Podgrupy pN2 (pN2a1, pN2a2, pN2b1 i pN2b2) po analizie Propensity Score Matching nie różniły się istotnie pod względem przeżywalności. Przerzut w węźle 3a nie był niezależnym czynnikiem prognostycznym w analizie wielozmiennej w całej grupie po Propensity Score Matching jak i w podgrupach pN2.

III. U 1080 pacjentów (6%) nie pobrano żadnych węzłów chłonnych (pNx). Pacjenci w tej grupie częściej byli młodsi, częściej były to kobiety oraz mieli inny rozkład stadiów pT, częściej mieli raka podstawnokomórkowego, częściej byli poddani torakotomii, częściej byli operowani w ośrodkach nieakademickich, mieli niższy odsetek niektórych chorób współistniejących. Chorzy z pNx częściej byli cN0 niż inni chorzy z pN1 i pN2, ale rzadziej niż chorzy z pN0 ($p<0.001$). W przypadku chorych pNx rzadziej dokonywano inwazyjnej diagnostyki węzłów śródpiersia niż

u chorych z pN1 oraz pN2, ale częściej niż u chorych z pN0 (p<0.001). Ogólne 5-letnie przeżycia wynosiły 64% dla pN0, 45% dla pN1, 32% dla pN2, 50% dla pNx. W porównaniu par pN, wszystkie pary pN różniły się istotnie od siebie (wszystkie p<0.0001 oprócz pNx vs pN1 p=0.016). Umiejscowienie krzywej przeżywalności oraz ogólnej 5 letniej przeżywalności chorych z pNx zależało od histopatologicznego rozpoznania, dostępu chirurgicznego oraz stadium pT. W analizie wielozmiennej, pNx był niezależnym czynnikiem ryzyka zgonu (HR=1.37, 95%CI: 1.23-1.51, p<0.01).

Wnioski

I. Na podstawie przeanalizowanej literatury można wnioskować, że następne edycje cechy N w klasyfikacji TNM mogą ulec ulepszeniu poprzez dodanie czynnika ilościowego. Ponadto powinno się dojść do konsensusu w zakresie minimalnej limfadenektomii w raku płuca, ponieważ zwiększa to jakość stagingu. Niemniej wprowadzenie takich nowych klasyfikacji wymaga międzynarodowych prospektywnych badań walidacyjnych, by ustalić odpowiednie punkty odcięcia, grupy prognostyczne oraz by zdecydować, która z klasyfikacji ilościowych powinna być użyta.

II. Pomimo tego, że węzły stacji 3A nie były niezależnym czynnikiem prognostycznym w naszej kohorcie, częstość przerzutów w tej stacji rośnie znamiennie w bardziej zaawansowanych stadiach nowotworu. Odsetek przerzutów w tej stacji jest porównywalny do innych, bardziej rutynowych stacji węzłów chłonnych. Stąd limfadenektomia z uwzględnieniem tej stacji węzłów chłonnych może być korzystna dla pacjentów z zaawansowanym prawostronnym rakiem płuca.

III. Resekcja węzłów chłonnych w raku płuca pozostaje istotnym etapem leczenia operacyjnego. Przeżywalność podgrupy pNx jest porównywalna do podgrupy pN1. Istnieje zależność przeżywalności pacjentów z pNx w zależności od innych czynników co może być użyteczne w codziennej praktyce i decyzjach klinicznych.

Streszczenie w języku angielskim

Background

Lymph node status in non-small cell lung cancer is one of the most important prognostic factors. However, many controversies and discussions persist regarding this aspect. For this reason, we decided to explore the following issues regarding lymphadenectomy in lung cancer:

I. narrative review of alternative methods of lymph node classification in TNM classification of lung cancer

II. clinical relevance, impact of 3A prevascular lymph node resection on overall survival in right-sided lung cancer

III. clinical relevance and the effect of zero lymph node retrieval (pNx) phenomenon on overall survival in lung cancer.

Material and Methods

I. We reviewed the PubMed database based on the following lymph node classifications: ongoing TNM classification, number of positive lymph nodes, number of negative lymph nodes, number of lymph nodes retrieved, lymph node ratio, mathematical modification of this ratio by logarithm, lymph node chains, lymph node zones, and number of lymph node stations. We also included combinations of these classifications.

II. We analyzed the data from the Polish Lung Cancer Group database on 6348 patients who underwent lung resection between 2005 and 2015. 3A node resection was performed in 221 patients (3ALN+), while 6217 patients did not undergo such resection (3ALN-). We performed Propensity score matching to minimize selection bias and to increase statistical significance of the study. We paired 221 patients from the 3ALN+ group and 221 from the 3ALN- group.

III. We performed a retrospective analysis of the Polish Lung Cancer Group database. The pNx phenomenon was defined as zero lymph nodes retrieved. We included 17192 patients.

Results

I. Review of literature has shown that the current classification of lymph nodes may lead to inaccurate staging of patients. Classifications based on the number of positive lymph nodes, lymph node ratio or its mathematical modifications are the most studied in numerous papers. For this reason, based on these numerous data, they should be considered first as potential additional factors in the classification of the N feature in TNM classification**.**

II. The incidence of 3a lymph node metastasis was 8% and it increased with pT stages. A significant increase in frequency was noted between pT1c and pT2a, which was doubled from 4% to 9%. For pT4, the frequency was as high as 15%. The highest frequency was noted among patients undergoing pneumonectomy (10%) and in the N2b1 and N2b2 subgroups (33% and 64%, respectively). In univariable analysis, we found no significant difference in 5-year overall survival between the 3ALN+ and 3ALN- groups (51% vs 51%, p=0.74). But metastatic lymph nodes and non-metastatic lymph nodes of 3ALN+ differed significantly ($p<0.0001$). The pN2 subgroups (pN2a1, pN2a2, pN2b1 and pN2b2) were not significantly different in terms of survival after Propensity Score Matching analysis. 3A lymph node metastasis was not an independent prognostic factor in multivariable analysis in the entire group after Propensity Score Matching as well as in the pN2 subgroups.

III. In 1080 patients (6%), no lymph nodes were resected (pNx). Patients in this group were more likely to be younger, more likely to be female, had a different distribution of pT stages, were more likely to have squamous cell carcinoma, were more likely to have undergone thoracotomy, were more likely to have been operated on in non-academic centers, and had a lower rate of certain comorbidities. Patients with pNx were more often cN0 than other patients with pN1 and pN2 but less often than patients with pN0 ($p<0.001$). Patients with pNx underwent invasive diagnostics of mediastinal nodes less frequently than patients with pN1 and pN2 but more frequently than patients with pN0 ($p<0.001$). Overall, 5-year survival was 64% for pN0, 45% for pN1, 32% for pN2, and 50% for pNx. In the pairwise comparison of pN subgroups, all pN pairs were significantly different from each other (all $p<0.0001$ except pNx vs pN1 $p=0.016$). The location of the survival curve and overall, 5-year survival of patients with pNx depended on histopathological diagnosis, surgical approach and pT stage. In multivariable analysis, pNx was an independent risk factor for death (HR=1.37, 95%CI: 1.23-1.51, $p<0.01$).

Conclusions

I. Based on the literature reviewed, it seems that, next editions of the N feature in the TNM classification may benefit from adding a quantitative factor. In addition, there should be a consensus on minimal lymphadenectomy in lung cancer, as this increases the quality of staging. However, the introduction of such new classifications requires international prospective validation studies to establish appropriate cutoff values and prognostic groups and to decide which quantitative classification should be used.

II. Although lymph nodes of station 3A were not an independent prognostic factor in our cohort, the frequency of metastasis in this station increases significantly in more advanced stages of cancer. The rate of metastasis in this station is comparable to other, more routine lymph node stations. Hence, including this lymph node station in lymphadenectomy may be beneficial for patients with advanced right-sided lung cancer.

III. Lymph node resection in lung cancer remains a key step in surgical treatment. The survival of the pNx subgroup is comparable to the pN1 subgroup. The survival of pNx patients depends on other factors which may be useful in daily practice and clinical decisions.

Wstęp

Epidemiologia

W 2019 roku w Polsce rak płuca był drugim najczęstszym nowotworem wśród kobiet (tuż po raku piersi) i wśród mężczyzn (tuż po raku prostaty). Został on zdiagnozowany u odpowiednio 16,1% mężczyzn z nowotworem złośliwym oraz u 9,9% kobiet z nowotworem złośliwym. Natomiast w 2019 roku rak płuca był najczęstszą przyczyną zgonu z powodu nowotworu złośliwego wśród kobiet i mężczyzn. Odpowiadał on za 17,9% zgonów nowotworowych u kobiet oraz 27,4% zgonów nowotworowych u mężczyzn [1].

W ujęciu światowym rak płuca jest najczęstszym nowotworem złośliwym wśród mężczyzn (14,3%) a w przypadku kobiet zajmuje on trzecie miejsce pod względem częstości występowania (8,4%). Biorąc pod uwagę śmiertelność rak płuca zajmuje pierwsze miejsce wśród mężczyzn z nowotworem złośliwym (21,5% zgonów), a w przypadku kobiet zajmuje on drugie miejsce (13,7% zgonów). Współczynnik zachorowań (wystandaryzowany względem wieku) jest niższy u kobiet (14,6 na 100 tys. osób) niż u mężczyzn (31,5 na 100 tys. osób). Podobnie współczynnik umieralności (wystandaryzowany względem wieku) jest niższy u kobiet (11,2 na 100 tys. osób) niż u mężczyzn (25,9 na 100 tys osób) [2].

Czynniki ryzyka

Najważniejszym czynnikiem ryzyka związanym z rakiem płuca jest palenie papierosów [3]. Palacze stanowią 85-90% wszystkich przypadków zachorowań na raka płuca. Niemniej bierne narażenie na dym tytoniowy również przyczynia się do zwiększenia ryzyka zachorowania [4]. W 2019 roku palenie papierosów zadeklarowało 21% Polaków. Liczba palaczy od lat stale spada, jednak wśród kobiet można zauważyć względną stagnację odsetka palaczek [5]. Zaprzestanie palenia papierosów wśród osób chorujących już na raka płuca poprawia rokowanie [6].

Współcześnie, smog i zanieczyszczenia odgrywają istotną rolę w etiopatogenezie raka płuca [7]. Do rzadziej występujących, ale nadal ważnych czynników ryzyka zalicza się narażenie na radon, spalanie węgla oraz biomasy w domu, azbest, arsen i wiele innych [4].

Klasyfikacja

Ósma edycja klasyfikacji Tumour, Node, Metastasis (TNM) jest używana, by stratyfikować pacjentów do odpowiednich stadiów zaawansowania (stage) nowotworu. Cecha T jest oceniana na podstawie rozmiaru guza oraz naciekania okolicznych struktur. Cecha M jest oceniania na podstawie występowania przerzutów odległych. Ocenę cech T i N dokonuje się przedoperacyjnie (cT, cN) oraz pooperacyjnie (pT, pN) [8]

Cecha N jest oceniania na podstawie lokalizacji przerzutów do węzłów chłonnych. Cecha N0 oznacza brak przerzutów w węzłach chłonnych. Cecha N1 oznacza przerzuty w węzłach chłonnych przywnękowych, przyoskrzelowych oraz wewnątrzpłucnych po tej samej stronie. Cecha N2 oznacza przerzuty w węzłach chłonnych śródpiersia i/lub podostrogowych po tej samej stronie. Cecha N3 oznacza przerzuty w wyżej wymienionych węzłach chłonnych po stronie przeciwnej lub w węzłach chłonnych nadobojczykowych lub mięśnia pochyłego. W leczeniu operacyjnym raka płuca ta cecha budzi szczególne kontrowersje [8, 9]. Nietypowe zjawiska takie jak „przeskakujący" przerzut w węzłach N2 bez przerzutów w węzłach grupy N1 (tzw. skip N2), mikroprzerzuty w węzłach chłonnych czy klinicznie nieme przerzuty pN2 sprawiają niemałe problemy zarówno dla naukowców jak i praktyków [10-12]. Międzynarodowe Stowarzyszenie do Badań nad Rakiem Płuca (IASLC) badało dołączenie do cechy N aspektu ilościowego w dwóch ostatnich pracach dotyczących klasyfikacji cechy N [9, 13] Warto wspomnieć, że w niektórych nowotworowych złośliwych aspekt ilościowy jest uwzględniony w klasyfikacji TNM (np. rak przełyku) [8].

Z punktu widzenia histopatologicznego najważniejszym podziałem jest rozróżnienie raka płuca na typ drobnokomórkowy oraz na niedrobnokomórkowy. Drobnokomórkowy rak płuca z reguły jest nowotworem nieoperacyjnym, szybko-przerzutującym, z dużo gorszym rokowaniem. Rola chirurgii w takich przypadkach jest bardzo ograniczona [14, 15]. Z tego powodu wyżej wymienione klasyfikacje mają zastosowanie głównie w niedrobnokomórkowym raku płuca. W przypadku raka drobnokomórkowego stosuje się podział na 2 typy – postać ograniczoną i uogólnioną [15].

Rokowanie

W populacji polskiej w latach 2014-2016 ogólna 3-letnia ogólna przeżywalność chorych z rakiem płuca wynosiła odpowiednio 17% u mężczyzn i 24% u kobiet [16]. W populacji amerykańskiej 5-letnia ogólna przeżywalność pacjentów z rakiem płuca wynosi 19%. Zasadniczo ogólna przeżywalność chorych z rakiem płuca jest dużo gorsza niż chorych z innymi nowotworami złośliwymi [17].

Niska przeżywalność pacjentów z rakiem płuca spowodowana jest niespecyficznymi objawami skutkującymi rozpoznaniem choroby w stadiach nieoperacyjnych. Ponadto, nawet pacjent z mało zaawansowanym nowotworem może być zdyskwalifikowany z operacji z powodu złego stanu ogólnego i współchorobowości. Rak płuca to w głównie choroba siódmej i ósmej dekady życia [18]. Bardzo często jest związany z innymi odtytoniowymi chorobami takimi jak przewlekła obturacyjna choroba płuc, choroba niedokrwienna serca i wiele innych [19]. Przykładowo w populacji koreańskiej w 2012 roku zaledwie 25% chorych na raka płuca było

poddanych operacji, co i tak było znaczącym wzrostem od wcześniejszych 16% w 2003 roku [20].

Pięcioletnie ogólne przeżycia w zależności od cechy pN wynoszą odpowiednio: 75% dla pN0, 49% dla pN1, 36% dla pN2 oraz 20% dla pN3 [9].

Diagnostyka przedoperacyjna

Podczas diagnostyki przedoperacyjnej pacjent najczęściej przechodzi przez szereg badań obrazowych (radiogram klatki piersiowej, tomografia komputerowa, rzadziej rezonans magnetyczny) oraz bronchoskopię. Proces diagnostyczny raka płuca w Polsce niestety zajmuje zbyt dużo czasu.

W przypadku stwierdzenia podejrzanych zmian w węzłach chłonnych w tych badaniach obrazowych (>10mm węzeł chłonny) przeprowadza się inwazyjną diagnostykę. Wykorzystuje się do tego celu bronchofiberoskopię z ultrasonografią wewnątrz-oskrzelową i biopsją aspiracyjną (tzw. EBUS-TBNA) oraz ezofagoskopię z ultrasonografią wewnątrz-przełykową i biopsją aspiracyjną (tzw. EUS-FNA). W przypadku niekonkluzywnych wyników w metodach endoskopowych przeprowadza się bardziej inwazyjne, operacyjne zabiegi – mediastinoskopię i/lub mediastinotomię [15]. Ponadto w Polsce coraz częściej wykonuje się pozytonową emisyjną tomografia komputerowa (PET-CT). Jeszcze kilka lat temu dostępność tej metody była bardzo ograniczona, ale obecnie większość pacjentów przechodzi te badanie w celu wykluczenia przerzutów regionalnych i odległych, w tym również do węzłów chłonnych. Dodatni wynik PET-CT w zakresie węzłów chłonnych również jest wskazaniem do inwazyjnej diagnostyki [15, 21].

Jak można zauważyć przedoperacyjna diagnostyka węzłów chłonnych śródpiersia jest szczególnie wnikliwa. Wykrycie przerzutu w tych stacjach węzłowych (cN2) jest niesamowicie ważnym czynnikiem podczas decyzji o ewentualnym zabiegu operacyjnym. Taki przerzut wstępnie dyskwalifikuje chorego do zabiegu. Dopiero po stwierdzonej odpowiedzi na neoadjuwantową chemioterapię, pacjenta można zakwalifikować do leczenia operacyjnego [15].

Wyniki badania NELSON oraz National Lung Screening Trial udowodniły skuteczność przesiewowego badania metodą Niskodawkowej Tomografii Komputerowej w redukcji śmiertelności wśród wybranych grup ryzyka [22, 23]. W Polsce badania przesiewowe z zastosowaniem tej metody są obecnie w fazie pilotażu. Badanie skierowane jest do osób palących ≥20 paczkolat w wieku 55-74 lat lub w wieku 50-74 lat w przypadku dodatkowych czynników ryzyka [24, 25].

Leczenie operacyjne

Mimo braku randomizowanych badań porównujących resekcję i brak interwencji, obecnie chirurgia pozostaje najlepszą opcją pacjentów z niedrobnokomórkowym rakiem płuca na całkowite wyleczenie [26]. Resekcja miąższu w granicach anatomicznych z usunięciem węzłów chłonnych wnęki płuca oraz śródpiersia jest złotym standardem leczenia u pacjentów z potencjalnie resekcyjnym rakiem (stadia I, II i wybrane IIIA). Poza resekcyjnością nowotworu innym czynnikiem ograniczającym możliwość leczenia operacyjnego jest stan ogólny chorego i współchorobowość [15].

W przypadku nowotworów niezaawansowanych (stadium I i niektóre II) istnieje możliwość przeprowadzenia zabiegu metodą małoinwazyjną poprzez torakoskopię (ang. video-assisted thoracic surgery – VATS) [15]. W bardziej zaawansowanych przypadkach zastosowanie tej metody budzi kontrowersje, gdyż dowiedziono znamiennie mniejszą liczbę pobranych węzłów chłonnych podczas operacji [21]. W ostatnich latach coraz więcej uwagi i prac poświęca się zastosowaniu robotyki w leczeniu chirurgicznym raka płuca [27].

Biorąc pod uwagę rozległość resekcji tkanki płucnej operatorzy najczęściej przeprowadzają lobektomie. Czasem ze względu na umiejscowienie lub rozległość procesu nowotworowego wymagane jest wykonanie resekcji rozszerzonej (tj. bilobektomie, pneumonektomie, resekcje rękawowe itp.). Z drugiej strony ze względu na współistnienie chorób ograniczających wydolność oddechową może istnieć konieczność przeprowadzenia resekcji mniej rozległej (sublobektomii). Są to najczęściej segmentektomie. a wykonywanie resekcji klinowych w tej chorobie jest często uważane za niezalecane [15]. Niemniej wyniki dwóch ostatnich badań randomizowanych potwierdziły skuteczność i doszczętność onkologiczną segmentektomii a nawet resekcji klinowej w przypadku małych guzków (<2cm – T1a) [28, 29]. Ponadto resekcje klinowe są często pierwszym etapem operacji w celu wysłania materiału do śródoperacyjnego badania histopatologicznego, co pozwala na ustalenie wstępnego rozpoznania i dalszego postępowania operacyjnego.

Limfadenektomia w raku płuca

Dokładna limfadenektomia pozwala na ustalenie właściwego stopnia zaawansowania pN i ma kluczowe znaczenie w kwalifikacji pacjentów do leczenia adjuwantowego [30]. Do klasyfikacji stacji węzłów chłonnych do odpowiednich grup cechy N oraz ich lokalizacji używa się mapy węzłów chłonnych IASLC [31]. Jednak zakres limfadenektomii śródpiersia dzieli naukowców i praktyków od wielu lat. Po pierwsze toczy się wiele dyskusji na temat minimalnej akceptowalnej liczby wezłów chłonnych pobranych podczas operacji. Wytyczne European Society of Thoracic Surgeons zalecają pobranie co najmniej 3 stacji węzłów z grupy N1 i 3 stacji węzłów z grupy N2 [32]. Ludwig i wsp. wykazali, że rokowanie pacjentów leczonych

operacyjnie wzrasta wraz z rosnącą liczbą pobranych węzłów chłonnych aż do wartości 16 [33]. Z drugiej strony pojawiają się również głosy, że liczba węzłów chłonnych jest zmienna osobniczo i zgodna z rozkładem normalnym Gaussa [34]. Całkowity brak pobranych węzłów chłonnych został przewidziany w klasyfikacji TNM (pNx). Wówczas rokowanie jest gorsze oraz porównywalne bardziej do pN1 lub nawet pN2 niż pN0 [8].

Po drugie, kolejnym punktem sporu jest technika operacyjna resekcji węzłów chłonnych śródpiersia. Wyróżnia się kilka zakresów limfadenektomii w zależności od ich rozległości. Najbardziej rozległym i posiadającym wielu zwolenników jest całkowite wycięcie węzłów chłonnych śródpiersia (ang. Mediastinal Lymph Node Dissection - MLND). Taki zabieg obejmuje resekcję następujących stacji węzłów chłonnych: 2R, 4R, 7, 8, 9 po stronie prawej oraz 4L, 5, 6, 7, 8, 9 po stronie lewej. Resekcja obejmuje usunięcie wszystkich węzłów wzdłuż odpowiednich granic anatomicznych [35]. Inną nieco mniej rozległą, ale również popularną techniką jest jest systematyczny sampling węzłów chłonnych śródpiersia (ang. Mediastinal Lymph Node Sampling – MLNS). Ten zabieg z kolei obejmuje podobne stacje węzłów chłonnych lub ich nieco mniejszy zakres na przykład następujące grupy węzłów chłonnych: 2R, 4R, 7 i 10R po stronie prawej oraz 5, 6, 7 i 10L po stronie lewej. Istotną różnicą jest natomiast pobranie jednego lub kilku najbardziej reprezentatywnych węzłów chłonnych z danej grupy. Pozostałe węzły chłonne pozostają nieusunięte [35]. Szczególnie ważne było randomizowane kontrolowane badanie, które wykazało, że obie te metody są porównywalne pod względem przeżyć chorych we wczesnych stadiach zaawansowania nowotworu. Mniej inwazyjny sampling zyskał wtedy wielu zwolenników [35]. Pojawiają się również głosy przeciwne, wykazujące wyższość metody rozleglejszej [36]. Bardziej kontrowersyjne są metody jeszcze mniej rozległe niż sampling. Są to Random Sampling – polegający na losowym wyborze stacji węzłów chłonnych oraz resekcja węzłów chłonnych w zależności od lokalizacji guza (ang. Lobe Specific Lymph node dissection). Przykładowo w przypadku górnej lewej lobektomii pobiera się węzły z stacji: 4L, 5, 6. W kilku pracach naukowych dowiedziono, że metoda ta nie jest gorsza niż poprzednie [37, 38]. Rak płuca może przerzutować poza typowy spływ chłonki. Zjawisko węzła wartowniczego nie zawsze występuje, a przerzuty węzłowe mogą się pojawić bezpośrednio w węzłach grupy N2 lub poza spływem charakterystycznym dla danego płata płuca [39]. Istnieje więc pewne ryzyko pominięcia węzła chłonnego z przerzutami w przypadku mniej rozległych metod limfadenektomii [40].

Innym aspektem limfadenektomii w raku płuca jest zakres obowiązków poszczególnych specjalistów. W dużym uproszczeniu patolodzy są odpowiedzialni za „wycięcie" węzłów chłonnych wewnątrzpłucnych z preparatu – fragmentu płuca. Z kolei zadanie chirurgów polega na wycięciu węzłów chłonnych śródpiersia oraz wnęki płuca podczas operacji. Dlatego też, aspekty komunikacyjne, oznaczenie, transport oraz preparatyka próbek mają również

znaczenie w tym procesie. Przykładowo w jednej z prac 9% przypadków pN0 oraz 11% przypadków pN2 nie miało żadnych pobranych węzłów z stacji grupy N1. Mimo resekcji tkanki płucnej, węzłów chłonnych wewnątrzpłucnych z nieznanych powodów nie wykryto [41].

Uzasadnienie połączenia publikacji wraz z komentarzem osiągnięcia naukowego

Manuskrypt o tytule „Alternative methods of lymph node staging in lung cancer: a narrative review" (Impact Factor 3.005, 70 punktów MEiN) jest przeglądem literatury na temat alternatywnych metod stagingu węzłów chłonnych w raku płuca. W manuskrypcie wymieniliśmy parametry, które były sugerowane przez badaczy jako zastąpienie dotychczasowej klasyfikacji TNM lub jako dodatek do tej klasyfikacji. W literaturze były to głównie parametry ilościowe. Praca również podkreśla, że im bardziej wyszukana metoda klasyfikacji węzłów chłonnych tym większe znaczenie ma adekwatna limfadenektomia.

Manuskrypt o tytule „Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study" (Impact Factor 3.005, 70 punktów MEiN) jest retrospektywną analizą wpływu resekcji stacji węzłów chłonnych 3a na podstawie bazy danych Polskiej Grupy Raka Płuca. W pracy zastosowano tzw. Propensity Score Matching by zwiększyć siłę statystyczną prezentowanych wyników. Mimo, że nie udało się udowodnić bezpośredniego wpływu na ogólne 5-letnie przeżycia chorych leczonych operacyjnie na prawostronnego raka płuca, udało nam się dojść do innych, istotnych wniosków. Po pierwsze częstość występowania przerzutów w stacji 3a rośnie wraz z stopniem zaawansowania nowotworu. Po drugie częstość występowania przerzutów w tej stacji może być porównywalna do innych stacji węzłowych, które są rutynowo pobierane podczas operacji. Po trzecie lokalizacja guza w dolnym płacie nie wyklucza istnienia przerzutu w tej stacji. Z tego powodu resekcja stacji węzłów chłonnych 3a, szczególnie w przypadku, gdy podejrzewamy przerzuty do węzłów chłonnych śródpiersia i/lub nowotwór płuca jest duży, może być korzystna dla pacjentów. Jest to również dodatkowy węzeł chłonny pobrany podczas operacji, co może przekładać się na zwiększenie jakości limfadenektomii.

Manuskrypt o tytule "The absence of lymph nodes removed (pNx status) impacts survival in patients with lung cancer treated surgically" (Impact Factor 2.388, 100 punktów MEiN) jest retrospektywną analizą wpływu zjawiska pNx (brak pobranych węzłów chłonnych) na podstawie bazy danych Polskiej Grupy Raka Płuca. Mimo upływu lat, zjawisko pNx nadal pozostaje istotnym problemem klinicznym. Przeżywalność tej podgrupy jest gorsza niż pN0 i bardziej porównywalna do podgrup pN1 czy też nawet pN2. Zjawisko pNx może skutkować pozostawieniem komórek nowotworowych w węzłach chłonnych i dyskwalifikacją z leczenia

adjuwantowego, co potencjalnie przekłada się na gorszą przeżywalność. Co ciekawe przeżywalność ta zależy od innych czynników. Generalnie czynniki pogarszające rokowanie lub związane z zwiększonym stopniem zaawansowania nowotworu przesuwają krzywą przeżywalności w stronę krzywej pN2. Nawet u pacjentów po pneumonektomii takie zjawisko występuje, co jest zaskakujące, gdyż materiał z węzłów N1 powinien być bardzo obfity w takim preparacie. Kolejnym zaskakującym przykładem jest możliwość wystąpienia przypadków cN2-pNx. Usystematyzowanie limfadenektomii w raku płuca oraz poprawa komunikacji patolog-chirurg klatki piersiowej są niezbędne by ograniczyć występowanie tego zjawiska.

Założenia i cel pracy

Kontrowersje i problemy limfadenektomii są przedmiotem wielu debat i prac naukowych na temat raka płuca. Mimo upływu lat i kolejnych badań wciąż brak jest konsensusu dotyczących wielu aspektów tego zagadnienia. Dlatego, głównym celem niniejszej pracy doktorskiej było zbadanie niektórych z tych kontrowersji oraz problemów dotyczących limfadenektomii w niedrobnokomórkowym raku płuca. Szczegółowe cele pracy były następujące:

- Analiza ilościowych parametrów dotyczących liczby pobranych i/lub przerzutowych węzłów chłonnych oraz ich ocena jako zamiennik lub dodatek do dotychczasowej cechy N w klasyfikacji TNM.
- Zbadanie wpływu pobrania dodatkowego węzła chłonnego ze stacji 3a na ogólną przeżywalność wśród pacjentów leczonych na prawostronnego raka płuca.
- Zidentyfikowanie czynników ryzyka przerzutów do stacji 3a oraz częstości występowania tych przerzutów w zależności od stopnia zaawansowania nowotworu.
- Zbadanie częstości występowania oraz czynników ryzyka zjawiska całkowitego braku pobranych węzłów chłonnych (pNx) u chorych z rakiem płuca.
- Analiza wpływu zjawiska pNx na ogólną przeżywalność chorych oraz porównanie przeżyć do innych grup pN.
- Zidentyfikowanie podgrup, w których zjawisko pNx rokuje dużo gorzej niż zwykle.

Review Article

Alternative methods of lymph node staging in lung cancer: a narrative review

Marcin M. Cackowski^, Grzegorz M. Gryszko#^, Marcin Zbytniewski#^, Dariusz A. Dziedzic, Tadeusz M. Orłowski

Department of Thoracic Surgery, National Research Institute of Chest Diseases, Warsaw, Poland

Contributions: (I) Conception and design: DA Dziedzic; (II) Administrative support: TM Orłowski; (III) Provision of study materials or patients: MM Cackowski, GM Gryszko, M Zbytniewski; (IV) Collection and assembly of data: MM Cackowski, GM Gryszko, M Zbytniewski; (V) Data analysis and interpretation: MM Cackowski, GM Gryszko, M Zbytniewski; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Marcin M. Cackowski. Department of Thoracic Surgery, National Research Institute of Chest Diseases, Plocka 26 Street, 01-038 Warsaw, Poland. Email: cackowskimm@gmail.com.

Abstract: The nodal status indicator in non-small cell lung cancer is one of the most crucial prognostic factors available. However, there are still many arguments among scientists regarding whether the currently used nodal status descriptor should be changed in the forthcoming editions of the Tumor Node Metastasis classification or whether it is precise enough and should be maintained as is. We reviewed studies concerning nodal factor classifications to evaluate their accuracy in non-small cell lung cancer patients and to address the previously mentioned challenge. We reviewed the PubMed database regarding the following classifications: ongoing 8th edition of the Tumor Node Metastasis classification, number of positive lymph nodes, number of negative lymph nodes, number of dissected lymph nodes, lymph node ratio, nodal chains, log odds of positive lymph nodes, zone-based classification and one that is based on the number of lymph node stations involved. Moreover, we analysed data regarding various combinations of these classifications. Our analysis showed that the present nodal staging may not accurately categorize every lung cancer patient. The number of positive lymph nodes and lymph node ratio or the log odds of positive lymph nodes (as the mathematical modification of lymph node ratio) are more legitimate, as they possess very robust data and should be considered initially as additional factors that can be incorporated in ongoing nodal staging systems. Forthcoming non-small cell lung cancer staging systems could benefit from the addition of quantitative-based parameters. Additionally, the minimal extent of lymphadenectomy should be established as staging benefits from it. International, prospective validation studies need to be performed to optimize the cut-off values and prognostic groups and to confirm the superiority of the newly suggested descriptors in non-small cell lung cancer nodal staging.

Keywords: Lung cancer; nodal staging; lymphadenectomy; review

Submitted May 22, 2020. Accepted for publication Sep 01, 2020.
doi: 10.21037/jtd-20-1997
View this article at: http://dx.doi.org/10.21037/jtd-20-1997

^ ORCID: Marcin M. Cackowski: 0000-0002-3183-6789; Grzegorz M. Gryszko: 0000-0002-4257-4470; Marcin Zbytniewski: 0000-0002-5507-8812.

Introduction

Lung cancer is one of the most common cancers in the world. According to statistics, in the United States, nearly 1.8 million people are diagnosed with lung cancer each year only, and more than 600,000 people died because of this malignancy in 2019 (1). According to the literature, the 5-year overall survival (OS) rate of patients with non-small cell lung cancer (NSCLC), accounting for approximately 80% of all cases of lung cancer, is 18% (2). The current clinical nodal (cN) and pathological nodal (pN) NSCLC classifications are based only on the anatomical location of nodal metastases. The nodal stages are used to predict the 5-year OS rates both in clinical staging (60%, 37%, 23%, and 9% for cN0-3, respectively) and in pathological staging (75%, 49%, 36%, and 20% for pN0-3, respectively) (3). The International Association for the Study of Lung Cancer (IASLC) did not introduce any changes in nodal categorization since the 6th edition (4). Nonetheless, the current classification has some limitations. Ongoing N descriptors of the 8th Tumor Node Metastasis classification (TNM) create heterogeneous divisions of NSCLC patients due to situations such as skip N2 metastases, microscopic nodal metastases, and clinically occult pN2 disease (3,5,6). However, clinically, such anatomical staging is a valuable and easy system for making treatment decisions and is relatively visible and distinguishable in preoperative imaging and invasive nodal staging. Many alternative classifications have been suggested. In propositions for both the 7th and 8th editions of the NSCLC staging system, the IASLC suggested quantitative factors that were not ultimately adopted (3,4). In this study, we present a review of various suggested factors analysed as potential additions or successors to the current nodal staging of NSCLC. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1997).

Material and methods

We searched the PubMed database regarding ongoing and newly suggested lymph node descriptors in lung cancer. We used the following search terms and their combinations: "lung cancer", "NSCLC", "lymph node staging", "number of positive lymph nodes", "number of negative lymph nodes", "number of dissected lymph nodes", "lymph node ratio", "log odds of positive lymph nodes", "lymph node stations", "skip N2 metastasis", "lymph node zones", and "nodal chains". After the first search, we included additional articles retrieved from a manual search of cited references and articles that cited articles about particular classifications via a PubMed search. The inclusion criteria were as follows: original articles and articles published from 1990 to present. The exclusion criteria were as follows: no full text available and abstract/full text not in English.

Number of lymph nodes

Number of positive lymph nodes

The quantity of metastatic lymph nodes is a meaningful prognostic factor. Unlike lung cancer, the number of positive lymph nodes (NPLN) has already demonstrated a crucial role in the clinical and/or pathological TNM staging of various malignancies (e.g., breast cancer). Notably, esophageal cancer staging is also based on the NPLN despite the anatomical surroundings and lymph node drainage being comparable to those of lung cancer (7). There are many studies regarding the importance and usefulness of the NPLN in NSCLC. As shown in *Table 1*, we summarized the impact of the NPLN on OS. Various approaches were made towards use of the NPLN in staging. Some researchers used the number of metastatic lymph nodes as an addition to ongoing pN descriptors to subdivide patients (8-12,15). Promising results were achieved. pN2 patients with a few positive lymph nodes (PLN) (range from 1 to 3) had a better survival rate than pN2 patients with more PLN (range from 4 to 6). The subdivision of pN1 patients was not significant; however, the pN2 subgroup with 1–3 PLN had a similar OS rate as the pN1 subgroup. Skip N2 metastases and single-station disease were associated with fewer PLN, indicating the complex relationship of various factors for the revision of N staging (8). The significance of pN2 subdivision and the insignificance of pN1 subdivision were similarly observed in another study (NPLN groups: 1–3, 4–14, and ≥15) (9). However, in another study, pN1 subdivision was significant. Differences between pN2 with 1–3 PLN were not significantly different from pN1 with more PLN (range from 4 to 6). The authors suggested merging these two subgroups into a single prognostic group. However, no significance between the two subgroups could be a result of the small population included in these two subdivisions (10). This combined group was also used in another study (11). Rearrangement of the IIIA and IIIB stages of NSCLC based on the NPLN, values was suggested (15). Patients with less than 3 PLN had relatively

Table 1 Impact of NPLN on 5-year OS

Author	N	pN stage	NPLN	5-year OS
Fukui *et al.* (8)	289	pN0	0	77.0%
		pN1	1–3	57.0% (NS)
			4–6	57.0% (NS)
		pN2	1–3	59.0%
			4–6	40.0%
			≥7	6.0%
Lee *et al.* (9)	1,081	pN1, pN2	0	69.0%
			1–3	42.9%
			4–14	30.0%
			≥15	11.5%
Saji *et al.* (10)	689	pN0	0	79.2%
		pN1	1–3	69.2%
			≥4	48.6%†
		pN2	1–3	48.6%†
			≥4	30.8%
Lee *et al.* (11)	1,487	pN0	0	76.0%
		pN1	1–3	62.0%
			≥4	45.2%†
		pN2	1–3	45.2%†
			≥4	39.4%
Hanagiri *et al.* (12)	121	pN2	1	51.0%
			2	58.9%
			3	34.2%
			4	30.0%
			>5	20.4%
Wei *et al.* (13)	1,659	pN0	0	89.2%
		pN1, pN2	1–2	65.1%
			3–6	42.1%
			≥7	22.4%
Matsuguma *et al.* (14)	749	pN1, pN2	0	76.0%
			1–2	54.3%
			≥3	39.8%
			3–5	45.6%
			>5	31.7%

†, those high NPLN pN1 and low NPLN pN2 subgroups were merged as single prognostic groups. N, number of patients; NPLN, number of positive lymph nodes; NS, not significant; OS, overall survival.

Table 2 Suggested values of minimal NDLN as proper lymphadenectomy

Author	N	Minimal NDLN
Doddoli *et al.* (20)	465	10
Ludwig *et al.* (21)	16,800	11–16
Saji *et al.* (16)	928	10
Yang *et al.* (22)	428	7
Osarogiagbon *et al.* (23)	24,650	18–21
Becker *et al.* (24)	33,463	16
Bria *et al.* (25)	415	10
Dai *et al.* (26)	121	10
Liang *et al.* (27)	44,511	16
Ou *et al.* (28)	2,545	11–15
Samayoa *et al.* (29)	98,970	10
Shapiro *et al.* (30)	4,975	10
Wen *et al.* (31)	549	12

N, number of patients; NDLN, number of dissected lymph nodes.

better survival than those with more than 2 PLN (12).

Other researchers suggested changing N staging completely and using the NPLN alone (13). The number of metastatic lymph nodes (groups: 0; 1–2; 3–6; and ≥7) was a better prognostic factor than the pN1 and pN2 stages, which, in this study, were statistically insignificant and worse than the NPLN in the multivariate analysis. Subdivision of the pN1 and pN2 subgroups based on the NPLN was significant; nonetheless, subdivision of the NPLN categories into pN1 and pN2 was not. This result might imply that the NPLN creates more homogeneous subgroups and that the location of metastatic lymph nodes may not be related to survival (13). Nonetheless, the higher the pN status is, the larger the NPLN, which indicates the relationship of the anatomical extent of the N stage and the NPLN (9,13).

According to the literature, the NPLN cut-off values vary between studies. Additionally, as it highly depends on proper lymphadenectomy, the minimal number of dissected lymph nodes (NDLN) must be addressed to stage patients properly. One study, for example, suggested an NPLN cut-off value of 4 and proper lymphadenectomy for a minimum of 10 dissected nodes (16).

Number of negative lymph nodes

The number of negative lymph nodes (NNLN), as the antithesis of the NPLN, may also be used to predict patient survival. The NNLN has been studied in various cancers (e.g., esophageal cancer), but only a few analyses have been performed in terms of NSCLC (17). The most recent work (n=1,019) revealed that the new classification, based on current pN categories combined with the NNLN (cut-off equal to 8), has the strongest predictive value [compared to pN alone, NPLN and even lymph node ratio (LNR)] (18). The NPLN and LNR were excluded in the multivariate analysis, unlike pN-NNLN (18). Nonetheless, in another study from 2017 (n=482), the NNLN (cut-offs equal to 10 and 30) failed to be an independent prognostic factor in the multivariate analysis, unlike the LNR (cut-offs =20% and 55%). However, researchers suggested combining the classification based on the NNLN groups with the LNR subgroups (the classification based on the opposite LNR groups with NNLN subgroups was not significant), which stratified patients better than pN (19). The NNLN alone has an impact on survival. In one analysis, OS in patients with fewer NNLN (≤15) was better than that in patients with more NNLN (>15) (P=0.002). The survival curves were similar to those generated with pN0; however, differences were observed in the pN1 and pN2 subgroups (14).

Number of dissected lymph nodes

The NDLN is essentially the sum of the two parameters mentioned above (NDLN = NPLN + NNLN). Thus, the NDLN might also be used to predict patient survival. In the TNM classifications of many cancers, the minimum number of removed lymph nodes is determined (e.g., breast 6, colon 12, and stomach 16) (7). Many studies on the minimal NDLN in NSCLC have been performed. As shown in *Table 2*, we summarized the suggested minimal NDLN that were prognostically significant. It is possible that the number of lymph nodes is an individual characteristic of the patient and distributed as a Gaussian curve in the population. Thus, in this study, the NDLN had no impact on OS, unlike the extent of nodal metastasis (single-station *vs.* multi-station) (32).

Lymph node ratio

The LNR is defined as the ratio of the NPLN to the total

Table 3 Impact of LNR on 5-year OS and mean survival

Author	N	pN stage	LNR	5-year OS	Mean survival (months)
Taylor *et al.* (35)	302	pN1, pN2	<0.34	51.0%	–
			>0.34	18.0%	–
Wang *et al.* (36)	301	pN1, pN2	≤0.18	40.3%	38.0
			>0.18	10.5%	16.0
Matsuguma *et al.* (14)	651	rNO†	0.00	76.0%	–
		rN1†	<0.12	58.8%	–
		rN2†	>0.12	35.0%	–
		rN2a†	0.12–0.26	40.0%	–
		rN2b†	>0.26	27.5%	–
Hsieh *et al.* (37)	108	pN2	<0.4	–	62.0
			>0.4	–	24.0
Urban *et al.* (38)	11,324	pN1	<0.125	–	43.0
			0.125–0.249	–	40.0
			0.25–0.499	–	30.0
			>0.5	–	23.0
		pN2	<0.125	–	40.0
			0.125–0.249	–	32.0
			0.250–0.499	–	27.0
			>0.5	–	22.0
Renaud *et al.* (39)	152	pN2	<0.33	–	30.0
			≥0.33	–	16.0

†, suggested rN staging based solely on LNR value. LNR, lymph node ratio; N, number of patients; OS, overall survival.

number of all resected nodes $\left(LNR = \frac{NPLN}{NPLN + NNLN}\right)$. The role of the LNR has been well proven in many malignancies (e.g., esophageal malignancies) (33). Additionally, many scientific works have proven its role in lung cancer. One of the largest and most important studies regarding the role of the LNR in NSCLC was a recent meta-analysis of 20 high-quality retrospective studies (total n=76,929). Generally, the lower the LNR is, the better OS (hazard ratio 1.954, 95% CI: 1.746–2.169, P<0.001). Similar results were observed in terms of disease-free survival and cancer-specific survival (fewer studies were included, however, due to a lack of data). Although the group may have been heterogeneous, the subgroup analysis (pN1 and pN2 or type of lymph node dissection) remarkably diminished heterogeneity (34). As shown in *Table 3*, we summarized the results of various studies on the LNR to depict diverse suggested cut-off values and their impact on OS. When compared to other classifications, the LNR (followed by the NPLN) was far superior to pN (14). Additionally, the combination of pN and the LNR demonstrated superiority in comparison to pN, the LNR, the NPLN, and pN-NPLN (40). In one study, the LNR (cut-off 0.35) and its impact on survival were significant in the pN1 subgroup but not in the pN2 subgroup (41), but in many other studies, the LNR had a significant impact on survival in the case of pN2 (35-37). pN1 patients with a high LNR could create a single prognostic group with pN2 patients with a low LNR (35,36).

Many studies have aimed to determine optimal LNR values for the selection of patients who could benefit from adjuvant therapy. For example, among the pN2 groups, patients with an LNR higher than 0.50 should

undergo postoperative therapy (38). Interestingly, the survival outcomes of patients with an LNR less than 0.18 were not different regardless of whether they underwent chemotherapy (36). The usefulness of the LNR was also confirmed when predicting the survival of patients who underwent neoadjuvant therapy (39) and in predicting brain metastases of NSCLC (42). The LNR could be an alternative to positron emission tomography scans according to one study. In terms of the prediction of recurrence, an LNR >0.12 was the second-best predictor after the maximum standardized uptake value (>6.5). Thus, the LNR could be a great compromise for countries where these scans are not accessible due to various reasons (43).

Despite having robust usefulness and being generally better than the NPLN, the LNR also has some limitations. Heterogeneity in this system is also possible. For instance, when 0 of 2 resected lymph nodes is positive and 0 of 17 resected lymph nodes is positive (both 0), the ratio is equal to 0. Mathematically, more situations such as these are possible (e.g., 2/2 and 14/14 are both equal to 1). The log odds of positive lymph nodes (LODDS) would discriminate such situations, as its formula would yield different results. This was proven in the work by Deng *et al.*, where the LODDS was particularly better than the LNR in the case of an LNR equal to 0 and 1 (44). When the minimal NDLN is agreed on, situations such as those observed with the LNR could be avoided, at least partially. This was also proven in that study. The LODDS was superior to the LNR only when the NDLN was less than 10. In the case of proper lymphadenectomy, the LODDS was surpassed (44).

Log odds of positive lymph nodes

The LODDS is defined as the logarithm of the ratio of the NPLN to the NNLN. $LODDS = \log \frac{NPLN + 0.5}{NNLN + 0.5}$. The aim of adding 0.5 to both the numerator and the denominator is to avoid an infinite value. The importance of the LODDS has already been well established in various cancers (e.g., esophageal cancer) (45). There is also increasing interest in making use of this indicator in the staging of lung cancer. Nonetheless, only a few studies regarding its role in NSCLC have been conducted.

In various studies, the LODDS was found to be a better descriptor than the LNR and current pN staging (44,46-48). Lv *et al.* even suggested the so-called TLM (Tumor, LODDS, Metastases) staging, which was identified as an independent risk factor, unlike the current TNM staging. This descriptor was good at diminishing heterogeneity in pN and in cases of an LNR less than 0.036 (46). The LODDS was especially better in higher-stage patients. In the case of lower stage survival, the curves for pN, the LNR and the LODDS were similar. Only the LODDS was identified as an independent risk factor in the multivariable analysis. However, in that study, only the adenocarcinoma group was included (47). Introducing the LODDS into the staging system would allow us to classify some pN1 patients into the pN2 group and pN2 patients into the pN1 group based on survival (48). As already mentioned in other classifications, the LODDS is becoming increasingly important, especially in the case of 0 PLN and an LNR equal to 1 (44). Zero PLN (thus pN0) seems to be particularly interesting because some programmes treat selected pN0 patients postoperatively because of their poor prognosis. Additionally, in the case of the LODDS, cut-off values vary between studies. In two studies, there was a single cut-off value: –1.142 (46) and 0.26 (44). In one study, there were 4 different groups based on values ranging from –2.10 to 1.74 (47). Even more groups (seven) existed in the most recent work, where values ranged from –6 to 2 (48).

In comparison to the NPLN or LNR, the LODDS seem to be the least faulty system (especially when there is no consensus on the minimal NDLN). Its usefulness is narrow due to limited data; nonetheless, as the mathematical modification of the ratio, it may be very robust. Previous descriptors are usually reported in pathological results or can be easily calculated.

Single or multiple station involvement

In 2015, the IASLC suggested a new subclassification of N staging in lung cancer for the 8th edition of the TNM staging system based on single/multiple station disease and skip metastases (3). Although it was not accepted, as data were not sufficient, in the future, such a system might be adapted into everyday practice. The subclassification of N descriptors is as follows: pN1 is subdivided into single (pN1a) and multiple (pN1b) stations, and pN2 is also subdivided into single (pN2a) and multiple (pN2b) stations. Further, pN2a is again subdivided into a lack of N1 involvement (pN2a1, so-called skip-N2) and with N1 involvement (pN2a2). pN3 remains intact. All of these subdivisions yielded significantly distinct groups (3). Since then, many studies have been performed to validate this classification (*Table 4*). Additional N2b subdivision into N2b1 and N2b2 based on skip N2 metastases might be

Table 4 Impact of single/multiple-station status and skip metastases presence on 5-year OS

Author	N	5-years overall survival (%)										
		pN0	pN1	pN1a	pN1b	pN2	pN2a	pN2a1	pN2a2	pN2b	pN2b1	pN2b2
Asamura *et al.* (3)	26,236	75.0	49.0	58.0	50.0*	36.0	47.0	52.0*	41.0	36.0	–	–
Chen *et al.* (49)	570	76.1	53.4	60.0	39.3*	26.3	40.3*	NS	NS	15.3	33.3*	11.4
Yun *et al.* (50)	3,971	82.8	62.6	64.6	51.7	45.3	–	61.8	47.9	34.6	–	–
Park *et al.* (51)†	1,228	–	–	62.6*	57.0*	–	–	64.7*	48.4	42.8	–	–
Park *et al.* (51)†	1,228	–	–	62.6	57.0*	–	–	64.7*	48.4*	42.8	–	–
Bertoglio *et al.* (52)	93	–	–	–	–	33.0	–	45.5	31.5*	23.5*	–	–
Sayar *et al.* (53)	181	75.0	45.0	45.0	32.0*	31.0	31.0*	–	–	0.0	–	–
Keller *et al.* (54)	488	–	52.0	–	–	32.0	NS	–	–	NS	–	–
Sezen *et al.* (55)	119	–	–	–	–	29.3	38.6	–	–	11.0	–	–
Ichinose *et al.* (56)	402	–	–	–	–	31.0	43.0	–	–	17.0	–	–
Nakagiri *et al.* (57)	121	–	–	–	–	42.0	45.5	–	–	38.5	–	–
Martini *et al.* (58)	214	–	39.0	45.0	31.0	–	–	–	–	–	–	–

†, Park *et al.* suggested two potential combined prognostic groups: pN1a + pN1b + pN2a1 or pN1b + pN2a1 + pN2a2; *, represent potential merged prognostic groups. NS, not significant; N, number of patients; pN1a, single-station pN1; pN1b, multiple-station pN1; pN2a, single-station pN2; pN2a1, pN2a with skip metastasis; pN2a2, pN2a without skip metastasis; pN2b, multiple-station pN2b; pN2b1, pN2b with skip metastasis; pN2b2, pN2b without skip metastasis.

used. N2b1 and N2b2 are significantly distinct groups. Unlike other works, the N2a1 and N2a2 subgroups showed no significant difference (49). Potential combined prognostic groups seem to vary, and based on statistical significance, researchers have suggested many possibilities (*Table 4*) Nonetheless, some of combinations may be the result of small samples in subgroups (50,51). Compared with other propositions, this system is worse than the LNR and NPLN (52).

Years before Asamura's idea, many studies were made on the role of multiple and single station disease in the prognosis of NSCLC patients were performed. In some studies, the difference between pN1 subgroups was not significant, as was sometimes the case for pN2 subgroups (54). In other works, the distinction between multiple stations and a single station was significant in both N1 (53,58) and N2 (55-57) patients. Interestingly, tumor location might have an impact on single and multiple station statuses (56,59). Skip N2 metastases, as a distinct prognostic group, were also either significant or insignificant in various analyses (55,57).

Even the authors of the largest IASLC study noted limitations because most of the records were based on the Japanese population and nodal staging was based on the Naruke-Japanese nodal map (3). Currently, only the Mountain-Dresler modification of the American Thoracic Society is recommended. The recognition of each nodal station might be challenging, and errors are possible. Some stations could be indistinguishable because of their adjacency (e.g., to the paratracheal), and this could lead to an incorrect diagnosis. That is why some researchers suggested grouping nodal stations into zones (levels).

Other classifications

During propositions for the 7th edition of the TNM staging system in 2007, the IASLC suggested a system for grouping lymph node stations into zones (levels) that was not implemented and eventually discarded (4). Compared to the LNR and NPLN, zone-based staging is inferior and not as prognostic (60). Propositions for the 7th and 8th editions of the TNM staging system were combined into a single staging system by Yun *et al.* (based on single/multiple zones and skip metastasis). In comparison to the station-based system, the zone-based system is as equal, and some patients (7.1%) are downstaged (50).

All suggestions disregarded extranodal metastases, which are important according to the nodal chains (NC) system.

Each NC consists of at least one lymph node vessel and various lymph nodes at different stations. This staging classification was studied as the ratio between positive and resected NC (61). Excluding extranodal metastases, NC are an intermediate system between zones and stations and could have a single status or multiple statuses (62).

Interestingly, when multiple-station cases are limited to a single-zone or single-chain, survival is as good as single-station cases (50,62). Unfortunately, these and other systems (e.g., systems based on a relationship between tumor location and station/zone of the involved lymph node) extend beyond the framework of our article (63).

Discussion

The minimal number of resected lymph nodes in NSCLC has not been established, and according to various studies and our opinion, it has to change. In the 8th edition of the TNM staging system, it is suggested that at least 6 lymph nodes should be resected for adequate staging; however, it is not enforced as mandatory, and it is not an appropriate number according to various studies (7). Among these studies, 10 was the most frequent minimal value of harvested lymph nodes that was prognostically significant (*Table 2*). More extensive lymph node resection might be even more beneficial; for instance, an NDLN equal to 16 was the best value in regard to OS, and the other best value ranged from 18 to 21, which demonstrated the best benefit for patients (21,23). Nonetheless, such numbers might not be achieved in some cases because of anatomical interindividual differences (32). Regardless, we should aim to achieve such values and, if not possible, approach such patients individually (e.g., by the LODDS) or classify and treat such patients at least as pNx. In practice, there are many possibilities for proper nodal dissection. Lymphadenectomy provides good staging, and sampling decreases the surgery time and complication rate (20,64). The lobe-specific method allows the dissection of lymph nodes according to lymphatic drainage and anatomy (65). Targeted sampling decreases the rate of the dissection of dangerous lymph nodes (e.g., station 7 and postoperative ischaemic bronchitis) (66).

The main limitation of the studies included in our review is their retrospective nature. Selection bias could be possible. Additionally, most of the studies used different inclusion or exclusion criteria (e.g., minimal NDLN).

In this review, we summarized the most important and prominent suggestions to consider as potential pN descriptors in NSCLC. The vastness of newly suggested NSCLC classifications and IASLC suggestions indicate the need for upcoming changes. As we already mentioned in our criticism of the ongoing 8th edition of the TNM staging system, heterogeneity in N descriptors is the main reason behind the need for such changes. It is necessary to determine the optimal pN classification to refer eligible patients for adequate adjuvant therapies. When considering other organs, multiple classifications are applied. The staging of esophageal cancer, an anatomically related malignancy to NSCLC, is based on the NPLN (7). Therefore, based on the reviewed papers, a quantity-based pN descriptor should be introduced. All of the suggested methods have their pros and cons. Each of the proposed classifications tends to eliminate NSCLC subgroup heterogeneity while potentially being able to create new prognostic groups. Interestingly, only the LODDS is superior in terms of pN0 heterogeneity elimination (44). Cut-off values and potential prognostic groups vary from study to study, and they must be validated and determined in prospective international studies (e.g., IASLC Lung Cancer Staging Project). Additionally, in such a study, we could determine which of the descriptors is superior and should be introduced. Data regarding the NPLN and LNR are more robust (albeit retrospective) than other suggested N classifications, which need additional analyses. Hence, in our opinion, these 2 parameters or the LODDS (as the mathematical modification of the LNR) are more legitimate and should be considered first. Many more studies, especially regarding other classifications, need to be performed in the future. The minimal NDLN, in addition to being a good assessment of lymphadenectomy, is a factor that can be used to increase the objectivity of various proposed staging methods. The LODDS is potentially superior when minimal lymphadenectomy is not established. The NPLN is highly dependent on having a proper minimal NDLN. The LNR also benefits from more dissected lymph nodes, which was proven by Deng *et al.* (44).

It seems necessary that pN and cN descriptors should be divided (as in breast cancer), as quantity parameters of lymph nodes are not easily accessible in preoperative imaging and staging (7). For cN, ongoing TNM staging seems to be a good compromise for making treatment decisions. Additionally, as most of the data reviewed here are based on a population of resectable NSCLC patients (thus mostly pN), any changes regarding cN would not be appropriate. Even if a new nodal classification is introduced to the pathological staging of lung cancer, the nodal clinical

staging would probably remain unchanged.

To summarize our review:

(I) Minimal lymphadenectomy in NSCLC should be settled;

(II) A quantity-based descriptor of lymph node metastases should be considered as an addition in the next TNM staging system;

(III) Prospective international validation study or studies need to be performed to validate optimal cut-off values and prognostic groups and to determine which newly suggested descriptor is superior.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1997

Peer Review File: Available at http://dx. doi. org/10. 21037/jtd–20–1997

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1997). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:1675-84.
4. Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2007;2:603-12.
5. Garelli E, Renaud S, Falcoz PE, et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;50:322-8.
6. Bille A, Woo KM, Ahmad U, et al. Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. Eur J Cardiothorac Surg 2017;51:674-9.
7. Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, 8th edition. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc., 2017.
8. Fukui T, Mori S, Yokoi K, et al. Significance of the number of positive lymph nodes in resected non-small cell lung cancer. J Thorac Oncol 2006;1:120-5.
9. Lee JG, Lee CY, Park IK, et al. Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. Ann Thorac Surg 2008;85:211-5.
10. Saji H, Tsuboi M, Shimada Y, et al. A proposal for combination of total number and anatomical location of involved lymph nodes for nodal classification in non-small cell lung cancer. Chest 2013;143:1618-25.
11. Lee GD, Kim DK, Moon DH, et al. A comparison of the proposed classifications for the revision of N descriptors for non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;49:580-8.
12. Hanagiri T, Takenaka M, Oka S, et al. Clinical significance in the number of involved lymph nodes in patients that underwent surgery for pathological stage III-N2 non-small

cell lung cancer. J Cardiothorac Surg 2011;6:144.
13. Wei S, Asamura H, Kawachi R, et al. Which is the better prognostic factor for resected non-small cell lung cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? J Thorac Oncol 2011;6:310-8.
14. Matsuguma H, Oki I, Nakahara R, et al. Proposal of new nodal classifications for non-small-cell lung cancer based on the number and ratio of metastatic lymph nodes. Eur J Cardiothorac Surg 2012;41:19-24.
15. Fan Y, Du Y, Sun W, et al. Including positive lymph node count in the AJCC N staging may be a better predictor of the prognosis of NSCLC patients, especially stage III patients: a large population-based study. Int J Clin Oncol 2019;24:1359-66.
16. Saji H, Tsuboi M, Yoshida K, et al. Prognostic impact of number of resected and involved lymph nodes at complete resection on survival in non-small cell lung cancer. J Thorac Oncol 2011;6:1865-71.
17. Ma M, Tang P, Jiang H, et al. Number of negative lymph nodes as a prognostic factor in esophageal squamous cell carcinoma. Asia Pac J Clin Oncol 2017;13:e278-83.
18. Liu H, Yan T, Zhang T, et al. Proposal of a new nodal classification for operable non-small cell lung cancer based on the number of negative lymph nodes and the anatomical location of metastatic lymph nodes. Medicine (Baltimore) 2019;98:e15645.
19. Wang S, Zhang B, Li C, et al. Prognostic value of number of negative lymph node in patients with stage II and IIIa non-small cell lung cancer. Oncotarget 2017;8:79387-96.
20. Doddoli C, Aragon A, Barlesi F, et al. Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg 2005;27:680-5.
21. Ludwig MS, Goodman M, Miller DL, et al. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. Chest 2005;128:1545-50.
22. Yang M, Cao H, Guo X, et al. The number of resected lymph nodes (nLNs) combined with tumor size as a prognostic factor in patients with pathologic N0 and Nx non-small cell lung cancer. PLoS One 2013;8:e73220.
23. Osarogiagbon RU, Ogbata O, Yu X. Number of lymph nodes associated with maximal reduction of long-term mortality risk in pathologic node-negative non-small cell lung cancer. Ann Thorac Surg 2014;97:385-93.
24. Becker DJ, Levy BP, Gold HT, et al. Influence of Extent of Lymph Node Evaluation on Survival for Pathologically Lymph Node Negative Non-Small Cell Lung Cancer. Am J Clin Oncol 2018;41:820-5.
25. Bria E, Milella M, Sperduti I, et al. A novel clinical prognostic score incorporating the number of resected lymph-nodes to predict recurrence and survival in non-small-cell lung cancer. Lung cancer 2009;66:365-71.
26. Dai Y, Long H, Lin P, et al. Impact of the number of resected and involved lymph nodes on the outcome in patients with stage II non-small cell lung cancer. Zhonghua Zhong Liu Za Zhi 2010;32:436-40.
27. Liang W, He J, Shen Y, et al. Impact of Examined Lymph Node Count on Precise Staging and Long-Term Survival of Resected Non-Small-Cell Lung Cancer: A Population Study of the US SEER Database and a Chinese Multi-Institutional Registry. J Clin Oncol 2017;35:1162-70.
28. Ou S-HI, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. J Thorac Oncol 2008;3:880-6.
29. Samayoa AX, Pezzi TA, Pezzi CM, et al. Rationale for a Minimum Number of Lymph Nodes Removed with Non-Small Cell Lung Cancer Resection: Correlating the Number of Nodes Removed with Survival in 98,970 Patients. Ann Surg Oncol 2016;23:1005-11.
30. Shapiro M, Mhango G, Kates M, et al. Extent of lymph node resection does not increase perioperative morbidity and mortality after surgery for stage I lung cancer in the elderly. Eur J Surg Oncol 2012;38:516-22.
31. Wen YS, Xi KX, Xi KX, et al. The number of resected lymph nodes is associated with the long-term survival outcome in patients with T2 N0 non-small cell lung cancer. Cancer Manag Res 2018;10:6869-77.
32. Riquet M, Legras A, Mordant P, et al. Number of mediastinal lymph nodes in non-small cell lung cancer: a Gaussian curve, not a prognostic factor. Ann Thorac Surg 2014;98:224-31.
33. Chen SB, Weng HR, Wang G, et al. Lymph node ratio-based staging system for esophageal squamous cell carcinoma. World J Gastroenterol 2015;21:7514-21.
34. Zhou J, Lin Z, Lyu M, et al. Prognostic value of lymph node ratio in non-small-cell lung cancer: a meta-analysis. Jpn J Clin Oncol 2020;50:44-57.
35. Taylor MD, LaPar DJ, Thomas CJ, et al. Lymph node ratio predicts recurrence and survival after R0 resection for non-small cell lung cancer. Ann Thorac Surg 2013;96:1163-70.
36. Wang CL, Li Y, Yue DS, et al. Value of the metastatic lymph node ratio for predicting the prognosis of non-small-cell lung cancer patients. World J Surg 2012;36:455-62.

37. Hsieh CP, Fu JY, Liu YH, et al. Prognostic factors in resectable pathological N2 disease of non-small cell lung cancer. Biomed J 2015;38:329-35.
38. Urban D, Bar J, Solomon B, et al. Lymph node ratio may predict the benefit of postoperative radiotherapy in non-small-cell lung cancer. J Thorac Oncol 2013;8:940-6.
39. Renaud S, Falcoz PE, Olland A, et al. Mediastinal downstaging after induction treatment is not a significant prognostic factor to select patients who would benefit from surgery: the clinical value of the lymph node ratio. Interact Cardiovasc Thorac Surg 2015;20:222-7.
40. Ding X, Hui Z, Dai H, et al. A Proposal for Combination of Lymph Node Ratio and Anatomic Location of Involved Lymph Nodes for Nodal Classification in Non-Small Cell Lung Cancer. J Thorac Oncol 2016;11:1565-73.
41. Qiu C, Dong W, Su B, et al. The prognostic value of ratio-based lymph node staging in resected non-small-cell lung cancer. J Thorac Oncol 2013;8:429-35.
42. Ding X, Dai H, Hui Z, et al. Risk factors of brain metastases in completely resected pathological stage IIIA-N2 non-small cell lung cancer. Radiat Oncol 2012;7:119.
43. Ohtaki Y, Shimizu K, Kaira K, et al. Risk factors associated with recurrence of surgically resected node-positive non-small cell lung cancer. Surg Today 2016;46:1196-208.
44. Deng W, Xu T, Wang Y, et al. Log odds of positive lymph nodes may predict survival benefit in patients with node-positive non-small cell lung cancer. Lung cancer 2018;122:60-6.
45. Yang M, Zhang H, Ma Z, et al. Log odds of positive lymph nodes is a novel prognostic indicator for advanced ESCC after surgical resection. J Thorac Dis 2017;9:1182-9.
46. Lv P, Chen G, Zhang P. Log odds of positive lymph nodes are superior to other measures for evaluating the prognosis of non-small cell lung cancer. Thorac Cancer 2014;5:570-5.
47. Zhao Y, Li G, Zheng D, et al. The prognostic value of lymph node ratio and log odds of positive lymph nodes in patients with lung adenocarcinoma. J Thorac Cardiovasc Surg 2017;153:702-9.e1.
48. Dziedzic D, Piotr R, Langfort R, et al. Log odds of positive lymph nodes as a novel prognostic indicator in NSCLC staging. Surg Oncol 2017;26:80-5.
49. Chen W, Zhang C, Wang G, et al. Feasibility of nodal classification for non-small cell lung cancer by merging current N categories with the number of involved lymph node stations. Thorac Cancer 2019;10:1533-43.
50. Yun JK, Lee GD, Choi S, et al. Comparison between lymph node station- and zone-based classification for the future revision of node descriptors proposed by the International Association for the Study of Lung Cancer in surgically resected patients with non-small-cell lung cancer. Eur J Cardiothorac Surg 2019;56:849-57.
51. Park BJ, Kim TH, Shin S, et al. Recommended Change in the N Descriptor Proposed by the International Association for the Study of Lung Cancer: A Validation Study. J Thorac Oncol 2019;14:1962-9.
52. Bertoglio P, Ricciardi S, Ali G, et al. N2 lung cancer is not all the same: an analysis of different prognostic groups. Interact Cardiovasc Thorac Surg 2018;27:720-6.
53. Sayar A, Turna A, Kilicgun A, et al. Prognostic significance of surgical-pathologic multiple-station N1 disease in non-small cell carcinoma of the lung. Eur J Cardiothorac Surg 2004;25:434-8.
54. Keller SM, Vangel MG, Wagner H, et al. Prolonged survival in patients with resected non-small cell lung cancer and single-level N2 disease. J Thorac Cardiovasc Surg 2004;128:130-7.
55. Sezen CB, Aksoy Y, Sonmezoglu Y, et al. Prognostic factors for survival in patients with completely resected pN2 non-small-cell lung cancer. Acta Chir Belg 2019. [Epub ahead of print].
56. Ichinose Y, Kato H, Koike T, et al. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. J Thorac Cardiovasc Surg 2001;122:803-8.
57. Nakagiri T, Sawabata N, Funaki S, et al. Validation of pN2 sub-classifications in patients with pathological stage IIIA N2 non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2011;12:733-8.
58. Martini N, Burt ME, Bains MS, et al. Survival after resection of stage II non-small cell lung cancer. Ann Thorac Surg 1992;54:460-5; discussion 466.
59. Misthos P, Sepsas E, Kokotsakis J, et al. The significance of one-station N2 disease in the prognosis of patients with nonsmall-cell lung cancer. Ann Thorac Surg 2008;86:1626-30.
60. Ito M, Yamashita Y, Tsutani Y, et al. Classifications of n2 non-small-cell lung cancer based on the number and rate of metastatic mediastinal lymph nodes. Clin Lung Cancer 2013;14:651-7.
61. Cao Q, Zhang B, Zhao L, et al. The impact of positive nodal chain ratio on individualized multimodality therapy in non-small-cell lung cancer. Tumour Biol 2015;36:4617-25.
62. Zheng H, Wang LM, Bao F, et al. Re-appraisal of N2 disease by lymphatic drainage pattern for non-small-cell lung cancers: by terms of nodal stations, zones, chains, and

a composite. Lung Cancer 2011;74:497-503.
63. Baba T, Uramoto H, Kuwata T, et al. Survival impact of node zone classification in resected pathological N2 non-small cell lung cancer. Interact Cardiovasc Thorac Surg 2012;14:760-4.
64. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann Thorac Surg 2005;80:268-74; discussion 274-5.
65. Shapiro M, Kadakia S, Lim J, et al. Lobe-specific mediastinal nodal dissection is sufficient during lobectomy by video-assisted thoracic surgery or thoracotomy for early-stage lung cancer. Chest 2013;144:1615-21.
66. Satoh Y, Okumura S, Nakagawa K, et al. Postoperative ischemic change in bronchial stumps after primary lung cancer resection. Eur J Cardiothorac Surg 2006;30:172-6.

Cite this article as: Cackowski MM, Gryszko GM, Zbytniewski M, Dziedzic DA, Orłowski TM. Alternative methods of lymph node staging in lung cancer: a narrative review. J Thorac Dis 2020;12(10):6042-6053. doi: 10.21037/jtd-20-1997

Original Article

Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study

Marcin M. Cackowski[1]^, Marcin Zbytniewski[1]^, Grzegorz M. Gryszko[1]^, Michał Dziedzic[2], Katarzyna Woźnica[3], Tadeusz M. Orłowski[1], Dariusz A. Dziedzic[1]^; on behalf of the Polish Lung Cancer Study Group (PLCSG)

[1]Department of Thoracic Surgery, National Research Institute of Chest Diseases, Warsaw, Poland; [2]Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland; [3]Faculty of Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland

Contributions: (I) Conception and design: MM Cackowski, DA Dziedzic; (II) Administrative support: TM Orłowski, DA Dziedzic; (III) Provision of study materials or patients: DA Dziedzic, TM Orlowski; (IV) Collection and assembly of data: DA Dziedzic, MM Cackowski, M Dziedzic; (V) Data analysis and interpretation: MM Cackowski M Zbytniewski, GM Gryszko, K Woźnica; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dariusz A. Dziedzic. Department of Thoracic Surgery, National Research Institute of Chest Diseases, Plocka 26 Street, 01-138 Warsaw, Poland. Email: drdariuszdziedzic@gmail.com.

Background: We aimed to assess the clinical significance and impact on survival of prevascular mediastinal lymph nodes (3A) in patients with right-sided lung cancer.

Methods: Prospective data of 6,348 patients, who underwent lung resection from 2005 to 2015, were retrospectively analysed. There were 221 patients who underwent 3A dissection (3ALN+), while 6,127 did not (3ALN–). We performed propensity score matching (PSM) to decrease selection bias (221 *vs.* 221).

Results: The incidence of 3A metastasis was 8%, and it elevated with pT stage. Between pT1c and pT2a, there was a significant increase in the 3A metastasis incidence, which doubled from 4% to 9%. For pT4, the incidence was 15%. The highest incidence was found among patients undergoing pneumonectomy (10%) and in the N2b1 and N2b2 subgroups (33% and 64%). In univariable analysis, we found no differences in 5-year survival between 3ALN+ and 3ALN– (51% *vs.* 51%, P=0.74). But, non-metastatic 3ALN+, 3ALN–, and metastatic 3ALN+ differed significantly (P<0.0001). pN2 subgroups (pN2a1, pN2a2, pN2b1, pN2b2) within PSM analysis did not differ significantly in terms of survival. 3A metastasis failed to be an independent prognostic factor in the multivariable analysis of matched pN2 subgroups.

Conclusions: Regardless of 3A lymph nodes failing to be an independent prognostic factor in our cohort, the incidence of metastases in lymph nodes increases notably in advanced stages. 3A metastasis rate is comparable to other lymph node stations. Therefore, superior mediastinal lymphadenectomy in advanced cancers may improve from resections of the 3A lymph node station.

Keywords: Lung cancer; lymph node dissection; surgery; prevascular mediastinal lymph nodes; overall survival

Submitted Dec 17, 2021. Accepted for publication May 25, 2022.
doi: 10.21037/jtd-21-1957
View this article at: https://dx.doi.org/10.21037/jtd-21-1957

^ ORCID: Marcin M. Cackowski, 0000-0002-3183-6789; Marcin Zbytniewski, 0000-0002-5507-8812; Grzegorz M. Gryszko, 0000-0002-4257-4470; Dariusz A. Dziedzic, 0000-0002-3931-8636.

Introduction

For decades, surgery has been the primary treatment in early-stage non-small-cell lung carcinoma (NSCLC) patients. It typically includes tumour resection with lymph node dissection (1). Unfortunately, the influence of lymph node dissection on patient survival is unclear. Furthermore, the optimal extent of lymph node dissection is still under discussion and generally depends on a surgeons' experience. International medical societies related to lung cancer surgery [e.g., the European Society of Thoracic Surgeons (ESTS)] focus solely on the quantity of lymph nodes (e.g., a minimum of 6 resected) or anatomical location (i.e., N1 or N2 lymph node stations) without focusing on particular stations (e.g., 3A station) (2,3).Considering the on-going debate about which particular lymphadenectomy method is superior, additional studies in this field remain crucial

In most of the cases, only stations 2, 4, 7, 8, and 9 are commonly dissected in right-sided NSCLC, while station 3A is usually omitted. Station 3A nodes are the prevascular mediastinal lymph nodes, which are not adjacent to the trachea and lie within the fatty tissue of the anterior mediastinum (4). Aside from the technical difficulties of 3A dissection, station 3A is an uncommon place for lymphatic spread because of the phrenic nerve and superior vena cava blockage and generous communications between the stations superior 10R, 4R, and 2R (5). Also, these adjacent anatomical structures are potential sites of complications. According to a few other studies, metastasis of the 3A station is not rare and occurs in between 15.3% and 17.8% of cases (6,7). Hence, 3A resection might be an important aspect of lymph node dissection in NSCLC.

In this study, we aimed to assess the clinical significance of prevascular mediastinal lymph nodes (3A) and their impact on survival in patients with right-sided NSCLC. This was accomplished using a large multicentre database from the Polish Lung Cancer Study Group. We also used propensity score matching (PSM) to minimize the potential selection bias. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1957/rc).

Methods

The Prospective Polish Lung Cancer Study Group database (24 thoracic centres) was analysed retrospectively. We included 6,348 cases with right-sided NSCLC. Two subgroups were created: patients with 3A station resection (3ALN+) (n=221) and patients without 3A station resection (3ALN–) (n=6,127). For further analysis, we divided the 3ALN+ group into non-metastatic subgroup (N3ALN) with 204 patients and metastatic subgroup (M3ALN) with 17 patients.

Patients were staged accordingly to the 8th edition of TNM classification (8). Lymph nodes were assessed according to The International Association for the Study of Lung Cancer lymph node map (9). Around 57 per cent of patients underwent adjuvant chemotherapy or radiotherapy. Exact data regarding adjuvant treatment regimens are not available. However, cisplatin and vinorelbine were the most common ones. We performed PSM to reduce selection bias. In case of conversion from thoracoscopy to thoracotomy, the procedure was reported as thoracotomy in the database. The ethics committee of the National Research Institute of Chest Diseases, Warsaw, Poland approved our study (91/2020), and waived the requirement for informed consent for the retrospective analysis. We conducted our study in accordance with the Declaration of Helsinki (as revised in 2013).

New pN descriptors

IASLC's new pN descriptors were used with the modifications proposed by Chen *et al.* Therefore, we were able to assess the impact of single or multiple status of pN2 station or the skip metastasis phenomenon. This allowed us to answer whether 3A station solely has an impact on survival. The definitions are as follows: N1a: single station N1; N1b multiple station N1; N2a1 single station N2 without N1 involvement (skip metastasis); N2a2: single station N2 with N1 involvement; N2b1: multiple station N2 without N1 involvement (skip metastasis); N2b2: multiple station N2 with N1 involvement (9,10).

Lymph node dissection

Mediastinal lymph node dissection (MLND) consists of nodal stations #2, #4, #7, #8, and #9 (2). In Poland, most thoracic surgeons use MLND as the technique of choice. Station 3A is not resected routinely. To our knowledge, there are two major reasons of 3A resection: intraoperative findings and/or surgeon personal experience (e.g., to increase lymph node retrieval yield). There were no preoperative findings in 3A as cN2-IIIA cases were excluded. Resection of 3A is possible via both thoracoscopy

and thoracotomy.

Inclusion and exclusion criteria

In this study, we included patients with confirmed right-sided NSCLC after radical resection (R0) from 2005 to 2015 and after mediastinal lymph node dissection or lymph node sampling. The patients had to have minimum 6 resected lymph nodes from hilar and mediastinal stations according to the ESTS guidelines (2) and complete clinical data. We excluded patients if they had minor resection, non-radical resection (R1), pNx status, neoadjuvant therapy prior to surgery (IIIA-cN2), clinical information that was lost or recorded incompletely, or failure to complete the follow-up period. Later, we excluded right middle lobes (RML) from the analysis due to an insignificant number of cases in this subgroup.

Preoperative staging and follow up

In case of radiological imaging findings [chest radiograph, computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET)], patients underwent invasive diagnostics (endobronchial ultrasound transbronchial needle aspiration, oesophageal ultrasound fine-needle aspiration, mediastinoscopy, and mediastinotomy).

After the surgery, the surgeon consulted patients within 2–3 weeks. Patients underwent follow-up diagnostics every three to five months for 5 years, which included chest radiographs, CT, or PETs in justified cases. Failure patterns were evaluated by imaging studies and data from invasive diagnostics similar to those in preoperative staging. Hilar and/or mediastinal failure was defined as a new or enlarging lymph node greater than 1 cm on the short axis in CT and/or hypermetabolism in PET imaging, in which the patient's consecutive clinical follow-up was consistent with disease progression. Cancer recurrence was divided into two categories: locoregional and distant recurrence. Locoregional recurrence was within the ipsilateral hemithorax or mediastinum. Other anatomical locations were defined as distant metastasis. PET availability increased from 25% of cases (early study years) to nearly 75% of cases (late study years). In case of missing data or loss to follow-up, polish national personal identity databases were checked for missing data. But, we excluded 159 patients because of incomplete data or loss to follow-up.

Statistical analysis

We identified the mean with the standard deviation and the median with a range of values as continuous variables. The Mann-Whitney U-test was implemented to ascertain significant differences in continuous variables between groups. We summarised every group with categorical variables with a frequency and incidence. Every group with categorical variables is summarised with an incidence and frequency of the investigated population. We applied the Chi-squared test to conduct a statistical comparison between these groups. We approximated survival curves with the Kaplan-Meier method, and we used the log-rank test to contrast differences between groups. We used the Cox proportional hazards model in univariable and multivariable analysis to examine the influence on patients' risk of death. We selected predictive variables based on univariable models ($P<0.05$). In accordance with the results, we established the following factors as important in the univariable analysis: age, sex, pT, pN, resection type, pathological stage, surgical approach, and comorbidities (kidney failure, insulin-dependent diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases). The hazard ratio of the entire cohort of patients using subgroup analysis by pN was estimated in the Cox multivariable analysis. All tests were two-sided, and a $P<0.05$ was considered statistically significant. For pairwise comparison of more than 2 groups, the FDR adjustment was used. We conducted all analyses using survminer and survival packages in R-software.

Propensity score matching

Because of the disproportion in variables, we performed a case-matched analysis to acquire comparable subgroups. This allowed us to enhance the statistical power of the study and to confirm results found in unmatched cohorts. We used the PSM method in identical pN stages separately. Logistic regression was used to calculate propensity scores for cohort cases. We used the following variables in the PSM method: sex, age, smoking status, histopathology of cancer, stage, and pT descriptor. We reproduced Cox Multivariable analysis after the PSM.

Results

A total of 6,348 patients were included in the study (221 in

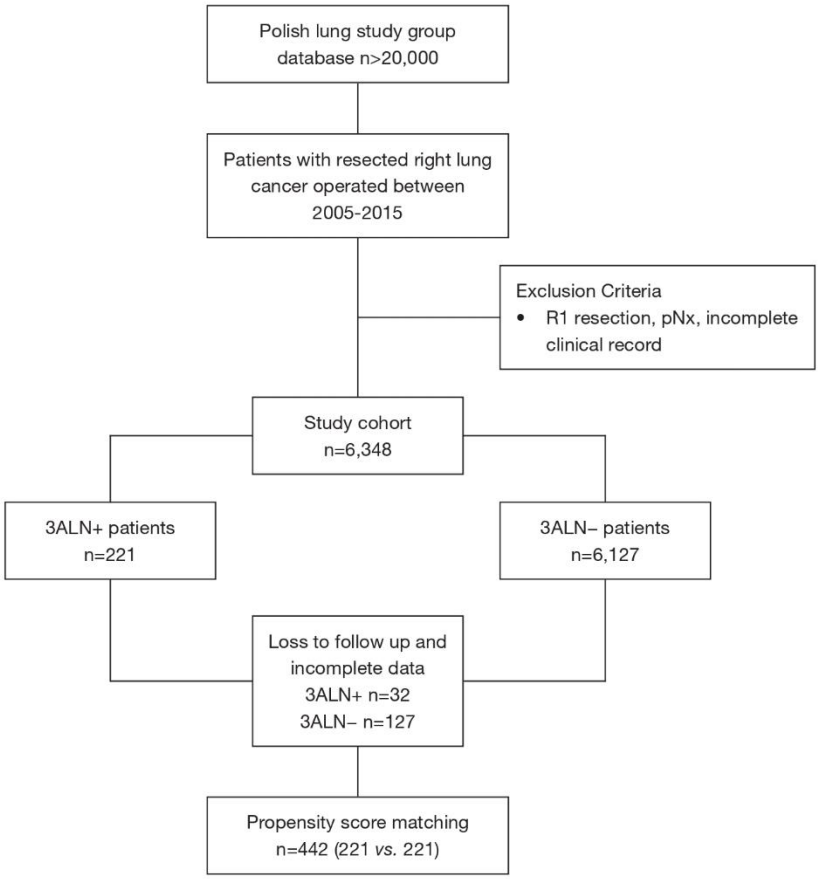


Figure 1 Patients flowchart. 3ALN+, patients with prevascular node resection; 3ALN–, patients without prevascular node resection.

the 3ALN+ group and 6,127 in the 3ALN– group). The patients' flow chart is presented in *Figure 1*. After PSM, 221 *vs.* 221 patients were matched. Before PSM, groups differed significantly in terms of stage (P=0.0351), pN descriptors (P<0.001), new pN descriptors (P=0.00124), type of resection (P=0.0214), and surgical approach (P=0.0133). After PSM, all these variables were comparable (P>0.99), but the surgical approach remained significantly different (P=0.0433). Also, after PSM, new significant differences were found in terms of age (P=0.0101). In both groups, the incidence of mediastinoscopy was similar both before and after PSM (P>0.05). Detailed data about the included cases before and after PSM are listed in *Table 1*.

Incidence of metastasis in 3A lymph node station

In the entire cohort, the incidence of patients with 3A nodes removed was 3.5%. In 3ALN group, the mean incidence of observed M3ALN was 8% (*Table 2*). The incidence of diagnosed 3A nodal metastases depended on the type of resection, tumour size, and the presence of mediastinal nodal metastases. The highest incidence of M3ALN was found among patients undergoing pneumonectomy (10%) and in the N2b1 and N2b2 subgroups (33% and 64%). These subgroups also had higher incidence of 3A nodes retrieved (4.8%, 8.3%, and 8.1%, respectively). There was no difference in the M3ALN incidence between the right upper lobe (RUL) and right lower lobe (RLL) (7% and 6%). Regarding tumour size, a notable increase in the metastatic 3ALN incidence was found between pT1c and pT2a (from 4% to 9%), and for pT4, it was 15%.

Incidence of M3ALN (8%) was lower than metastasis rate in station 4R (10%), but higher than metastasis rate in stations 2R (5%), 7 (7%), 8 (4%) and 9 (2%). Comparison of 3A resection and metastasis rate in comparison to routine MLND lymph node stations (depending on surgery type) is

Table 1 Patient characteristic before and after propensity score matching

Variable	Entire cohort (N=6,348)			Propensity score matching (N=442)		
	3ALN− (N=6,127)	3ALN+ (N=221)	P value (SMD)	3ALN− (N=221)	3ALN+ (N=221)	P value (SMD)
Age			0.326 (0.058)			0.0101 (0.214)
Mean (SD)	62.6 (8.25)	63.1 (7.93)		61.3 (8.55)	63.1 (7.93)	
Median [1Q, 3Q]	62.0 [22.0, 87.0]	63.0 [38.0, 81.0]		61.0 [42.0, 83.0]	63.0 [38.0, 81.0]	
Sex			1.0 (0)			0.68 (0.049)
Female	1,942 (31.7)	70 (31.7)		70 (31.1)	70 (31.7)	
Male	4,185 (68.3)	151 (68.3)		156 (70.6)	151 (68.3)	
Stage			0.0351 (0.26)			1.0 (0.019)
IA1	59 (1.0)	2 (0.9)		2 (0.9)	2 (0.9)	
IA2	568 (9.3)	16 (7.2)		16 (7.2)	16 (7.2)	
IA3	544 (8.9)	14 (6.3)		14 (6.3)	14 (6.3)	
IB	1,480 (24.2)	45 (20.4)		45 (20.4)	45 (20.4)	
IIA	532 (8.7)	13 (5.9)		13 (5.9)	13 (5.9)	
IIB	1,426 (23.3)	55 (24.9)		55 (24.9)	55 (24.9)	
IIIA	1,244 (20.3)	59 (26.7)		60 (27.1)	59 (26.7)	
IIIB	274 (4.5)	17 (7.7)		16 (7.2)	17 (7.7)	
Smoking	4,265 (69.6)	144 (65.2)	0.181 (0.095)	154 (69.7)	144 (65.2)	0.361 (0.097)
Comorbidities						
Diabetes I	177 (2.9)	3 (1.4)	0.254 (0.106)	3 (1.4)	3 (1.4)	1.0 (0.0)
Myocardial infarction	385 (6.3)	10 (4.5)	0.357 (0.078)	17 (7.7)	10 (4.5)	0.233 (0.133)
Nervous diseases	49 (0.8)	0 (0.0)	0.345 (0.127)	1 (0.5)	0 (0.0)	1 (0.095)
Heart failure	153 (2.5)	20 (3.0)	0.685 (0.04)	13 (5.9)	7 (3.2)	0.253 (0.131)
Kidney failure	49 (0.8)	7 (3.2)	0.0508 (0.119)	0 (0.0)	5 (2.3)	0.072 (0.215)
COPD	1,485 (24.2)	52 (23.5)	0.872 (0.017)	48 (21.7)	52 (23.5)	0.733 (0.043)
Hypertension	2,342 (38.2)	85 (38.5)	0.999 (0.005)	70 (31.7)	85 (38.5)	0.163 (0.143)
Coronary disease	400 (6.5)	11 (5.0)	0.435 (0.067)	17 (7.7)	11 (5.0)	0.329 (0.112)
pT			0.64 (0.14)			1.0 (0.015)
1a	71 (1.2)	2 (0.9)		2 (0.9)	2 (0.9)	
1b	668 (10.9)	23 (10.4)		23 (10.4)	23 (10.4)	
1c	721 (11.8)	23 (10.4)		23 (10.4)	23 (10.4)	
2a	2,124 (34.7)	67 (30.3)		68 (30.8)	67 (30.3)	
2b	818 (13.4)	31 (14.0)		31 (14.0)	31 (14.0)	
3	1,113 (18.2)	48 (21.7)		48 (21.7)	48 (21.7)	
4	612 (10.0)	27 (12.2)		26 (11.8)	27 (12.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Entire cohort (N=6,348)			Propensity score matching (N=442)		
	3ALN– (N=6,127)	3ALN+ (N=221)	P value (SMD)	3ALN– (N=221)	3ALN+ (N=221)	P value (SMD)
cN			0.797 (0.029)			0.445 (0.059)
0	4,599 (75.1)	164 (74.2)		152 (68.8)	164 (74.2)	
1	839 (13.7)	29 (13.1)		36 (16.3)	29 (13.1)	
pN			<0.001 (0.239)			1.0 (0.0)
0	4,267 (69.6)	131 (59.3)		131 (59.3)	131 (59.3)	
1	1,065 (17.4)	44 (19.9)		44 (19.9)	44 (19.9)	
2	795 (13.0)	46 (20.8)		46 (20.8)	46 (20.8)	
New pN			0.00124 (0.272)			1.0 (0.0)
N0	4,267 (69.6)	131 (59.3)		131 (59.3)	131 (59.3)	
N1a	917 (15.0)	38 (17.2)		38 (17.2)	38 (17.2)	
N1b	148 (2.4)	6 (2.7)		6 (2.7)	6 (2.7)	
N2a1	277 (4.5)	14 (6.3)		14 (6.3)	14 (6.3)	
N2a2	294 (4.8)	12 (5.4)		12 (5.4)	12 (5.4)	
N2b1	66 (1.1)	6 (2.7)		6 (2.7)	6 (2.7)	
N2b2	158 (2.6)	14 (6.3)		14 (6.3)	14 (6.3)	
Extent of resection			0.0214 (0.185)			0.993 (0.011)
Lower lobectomy	1,752 (28.6)	50 (22.6)		50 (22.6)	50 (22.6)	
Upper lobectomy	3,418 (55.8)	123 (55.7)		124 (56.1)	123 (55.7)	
Pneumonectomy	957 (15.6)	48 (21.7)		47 (21.6)	48 (21.7)	
Approach			0.0133 (0.239)			0.0433 (0.226)
Thoracotomy	5,886 (96.1)	220 (99.5)		213 (96.4)	220 (99.5)	
VATS	241 (3.9)	1 (0.5)		8 (3.6)	1 (0.5)	
Histopathology			0.435 (0.058)			0.923 (0.018)
Adenocarcinoma	3,288 (53.7)	125 (56.6)		127 (57.5)	125 (56.6)	
Squamous	2,839 (46.3)	96 (43.4)		94 (42.5)	96 (43.4)	
Mediastinoscopy	702 (11.5)	26 (11.8)	0.973 (0.01)	24 (10.9)	26 (11.8)	0.881 (0.029)

3ALN+, patients with prevascular node resection; 3ALN–, patients without prevascular node resection; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; VATS, video-assisted thoracic surgery.

presented in *Table 3*.

Univariable survival analysis

The median follow-up time in the entire study group was 1,913 days. There was no statistical difference in survival between 3ALN+ and 3ALN– before PSM (51% *vs.* 51%, P=0.74) and after PSM (51% *vs.* 48%, P=0.58). With regard to the type of resection in the whole group, after the PSM the lowest survival rate was found in patients after pneumonectomy (37%), while no differences were found between RUL and RLL (54% *vs.* 52%). For comparison, survival in the M3ALN subgroup was 9% and was significantly lower than in both 3ALN– and N3ALN

Table 2 Characteristics of 3A lymph node station depending on pN and pT descriptors

Variable	n	Positive rate[a]	Examined (%)
Overall	6,348	8%	221 (3.5%)
New pN			
N0	4,398	0%	131 (3.0%)
N1a	955	0%	38 (4.0%)
N1b	154	0%	6 (3.9%)
N2a1	291	21%	14 (4.8%)
N2a2	306	25%	12 (3.9%)
N2b1	72	33%	6 (8.3%)
N2b2	172	64%	14 (8.1%)
pT			
1a	73	0%	2 (2.7%)
1b	691	4%	23 (3.3%)
1c	744	4%	23 (3.1%)
2a	2,191	9%	67 (3.1%)
2b	849	10%	31 (3.7%)
3	1161	4%	48 (4.1%)
4	639	15%	27 (4.2%)

n, number of patients; [a], % positive if lymph nodes station was examined.

(P<0.0001) (*Figure 2*).

In the subgroup analysis of the 3ALN+ and 3ALN– survival rates, no significant differences were found in terms of extent of resection, pT, pN, and new pN (*Table 4*). Also, in the analysis with the M3ALN subgroup, no differences were found in subgroups N2a1, N2a2, N2b1, and N2b2. Survival rates of 3ALN+ and 3ALN– as a function of new pN subgroups are presented in Figure S1.

Multivariable survival analysis

In the entire cohort after PSM, the multivariable analysis showed that the independent prognostic risk factors were pneumonectomy (HR =1.73, 95% CI: 1.16–2.57, P=0.007), heart failure (HR =1.96, 95% CI: 1.13–3.46, P=0.017), and coronary disease (HR =2.06, 95% CI: 1.33–3.20, P=0.001). In contrast, removal of the 3A lymph nodes as well as the presence of 3A nodal metastases were not shown to be independent prognostic factors (HR =0.91, 95% CI: 0.71–1.18, P=0.50 and HR =1.08, 95% CI: 0.60–1.93, P=0.79) (*Table 5*). Also, the multivariable analysis after PSM in the subgroups of patients with mediastinal metastases (subgroups pN2a1, pN2a2, pN2b1, and pN2b2) did not show that removal of 3A nodes or 3A nodal metastases is an independent prognostic factor in any given group for any of the stages. Detailed results of multivariable analysis of pN2 subgroups are presented in Table S1.

Discussion

Lymphadenectomy of mediastinum is an integral part of the surgical treatment of NSCLC. However, as shown by clinical data, biopsy or resection of the lymph nodes is not performed in some cases. Osarogiagbon and Yu showed that the incidence of these cases reaches 15%, which results in inadequate staging of patients. Thus, survival is worse and more similar to pN1 rather than pN0 (3). In turn, Little *et al.* showed that only 57.8% of patients underwent mediastinal lymph node sampling (MLNS) or MLND (11). In a recently published study by Ray *et al.*, this incidence was 10%, and 75% of cases did not even meet the sampling criteria (12). Many authors have proposed liberalizing the extent of lymph node resection. In a prospective and randomized study, Darling *et al.* showed that there is no statistical difference between MLNS and MLND (13). In recent years, the number of supporters of lobe-specific lymph nodes dissection (LS-LND) has increased, especially in the early stages of lung cancer (14,15). However, a large group of opponents still support MLND as the standard of care in the surgical treatment of lung cancer. Riquet *et al.* showed that the incidence of metastases in the upper mediastinum in the case of lower lobectomies is similar to that of upper lobectomies. This supports systemic resection of all nodal groups (16). Also, Maniwa *et al.* showed that in the LS-LND group, the incidence of local and distant recurrences was higher than in the MLND group (P=0.005) (17).

In many studies, lymph nodes of the 3A station are not routinely included in both the MLNS and MLND groups (18). Therefore, when analysing this nodal group, it is not surprising that the incidence of patients in whom it is removed is usually small. In our study, only 3.5% of patients had 3A nodes removed. Also, the current international recommendations do not take this node station into consideration (2). Therefore, in practice, 3A nodes are rarely removed. Only a few who are devoted to lymphadenectomy in lung cancer include this nodal station in their analyses or daily practice.

Table 3 Distribution of examination and metastasis in the lymph node stations regarding surgery type

Lymph node station	Right lower lobectomy (n=1,802)	Right upper lobectomy (n=3,541)	Pneumonectomy (n=1,005)	Overall (n=6,348)	P value
2R					
Examined (%)	521 (28.9%)	1,381 (39.0%)	360 (35.8%)	2,262 (35.6%)	0.0101
% positive*	5%	5%	6%	5%	0.436
3A					
Examined (%)	50 (2.8%)	123 (3.5%)	48 (4.8%)	221 (3.5%)	0.0214
% positive*	6%	7%	10%	8%	0.695
4R					
Examined (%)	1,179 (65.4%)	2,827 (79.8%)	755 (75.1%)	4,761 (75.0%)	<0.001
% positive*	5%	10%	14%	10%	<0.001
7					
Examined (%)	1,478 (82.0%)	2,795 (78.9%)	898 (89.4%)	5,171 (81.5%)	<0.001
% positive*	11%	3%	16%	7%	<0.001
8					
Examined (%)	582 (32.3%)	972 (27.4%)	401 (39.9%)	1,955 (30.8%)	<0.001
% positive*	8%	1%	5%	4%	<0.001
9					
Examined (%)	737 (40.9%)	1,041 (29.4%)	379 (37.7%)	2,157 (34.0%)	<0.001
% positive*	2%	1%	3%	2%	<0.001

*, positive if lymph node station was examined, n: number of patients.

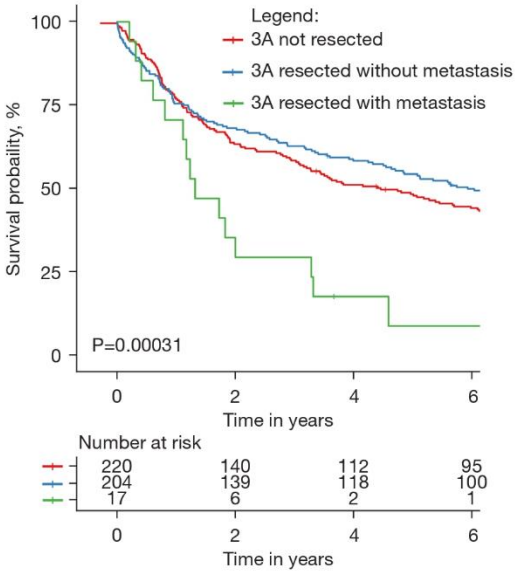


Figure 2 Impact of prevascular lymph node station (3A) resection and metastasis on 5-year overall survival.

In the work of Liang *et al.*, the incidence of removed 3A nodes for RUL, RML, and RLL were 3.2%, 5.4%, and 1.8%, respectively. At the same time, the incidence of 3A node metastases were 12.2%, 20%, and 7.4%, respectively (19). In other study by Liu *et al.*, the incidence of 3A nodes removed was 29.9%, and 15.3% had metastases. Also, the authors showed that the metastasis rate of station 3A was second only to that of stations 4 and 3A was significantly higher than those of stations 8 and 9 (6). In a study by Yang *et al.*, the incidence of removed and metastatic 3A nodes were 24% and 11.4% (RUL), 28.2% and 12.1% (RML), and 23.7% and 5% (RLL), respectively (20). In our study, the incidence of positive 3A nodes in the entire group was 8%. The incidence of removed and metastatic nodes were 2.8% and 6% for RUL and 3.5% and 7% for RLL, respectively. Furthermore, there were no statistical differences in the incidence of positive nodes between both types of lobectomy.

Our study also showed that the incidence of 3A nodal

Table 4 Five-year overall survival rates of the patients after propensity score matching

Subgroup	3ALN+	3ALN−	P value
Overall	51%	48%	0.58
Extent of pulmonary resection			
Right lower lobectomy	56%	48%	0.35
Right upper lobectomy	54%	54%	0.69
Pneumonectomy	40%	34%	0.35
pN descriptor			
pN0	64%	60%	0.69
pN1	45%	39%	0.46
pN2	19%	24%	0.96
New classification of pN descriptor			
pN0	64%	60%	0.84
pN1a	45%	34%	0.39
pN1b	50%	67%	0.81
pN2a1	36%	21%	0.39
pN2a2	17%	42%	0.26
pN2b1	17%	17%	0.62
pN2b2	0%	14%	0.77
pT descriptor			
pT1a	50%	50%	0.81
pT1b	78%	74%	0.67
pT1c	57%	52%	0.48
pT2a	54%	59%	0.22
pT2b	48%	42%	0.36
pT3	50%	39%	0.58
pT4	22%	19%	0.43

3ALN+, patients with prevascular node resection; 3ALN−, patients without prevascular node resection.

Table 5 Multivariable analysis after propensity score matching

Variable	Hazard risk (95% CI)	P value
Comorbidities	Reference = lack of disease	
Coronary disease	2.06 (1.33–3.20)	0.001
Heart failure	1.96 (1.13–3.46)	0.017
cN		
cN0	Reference	
cN1	0.99 (0.69–1.42)	0.951
pN		
pN0	Reference	
pN1a	0.78 (0.37–1.61)	0.496
pN1b	0.51 (0.18–1.44)	0.202
pN2a1	0.57 (0.11–2.93)	0.497
pN2a2	0.53 (0.10–2.69)	0.444
pN2b1	0.46 (0.09–2.24)	0.338
pN2b2	0.70 (0.16–3.18)	0.649
Mediastinoscopy (reference = lack of mediastinoscopy)	1.16 (0.79–1.68)	0.452
Surgery		
Lower lobectomy	Reference	
Upper lobectomy	1.08 (0.78–1.51)	0.629
Pneumonectomy	1.73 (1.16–2.57)	0.007
Approach		
Thoracotomy	Reference	
VATS	0.19 (0.03–1.38)	0.100
pT		
pT1a	Reference	
pT1b	1.41 (0.34–5.94)	0.639
pT1c	1.97 (0.46–8.44)	0.360
pT2a	1.76 (0.47–6.55)	0.399
pT2b	2.54 (0.69–9.35)	0.162
pT3	1.10 (0.58–2.09)	0.767
Stage		
IA1	Reference	
IA2	0.25 (0.03–2.10)	0.204
IA3	0.29 (0.03–2.38)	0.249
IB	0.30 (0.04–2.17)	0.235
IIA	0.25 (0.03–1.90)	0.182
IIB	0.64 (0.13–3.19)	0.589
IIIA	1.56 (0.36–6.81)	0.551
IIIB	4.53 (0.65–31.75)	0.129
3A station		
Not-resected	Reference	
Resected and non-metastatic	0.91 (0.71–1.18)	0.497
Resected and metastatic	1.08 (0.60–1.93)	0.793

VATS, video-assisted thoracic surgery.

metastases may increase with the size of the tumour. There was a difference between pT1c and pT2a where the incidence of positive nodes doubled (4% *vs.* 9%). A similar observation between the tumour size and the incidence of positive 3A nodes was demonstrated by Zheng *et al.* However, it was not confirmed by the multivariable analysis (7).

Earlier analyses of 3A nodes have shown that survival in the group with positive 3A nodes was worse than in other pN2 patients. In the study by Zheng *et al.*, the 3-year survival in the group with positive 3A nodes was lower than in the other cases and amounted to 22% and 63%, respectively (P<0.001). Moreover, there were differences between single and multistation nodal involvement (72% *vs.* 33%, P<0.001) (7). On the other hand, Liu *et al.* showed differences in 5-year survival between 3ALN+ and 3ALN– (58.8% *vs.* 48.7%, P=0.007), finding better survival in stages II and III. Notably, the multivariable analysis showed that 3A nodal removal is an independent prognostic factor for survival (HR =0.76, 95% CI: 0.64–0.90, P=0.001) (6). But in our study, both univariable and multivariable analyses (after PSM) for 3ALN+ and 3ALN– showed no significant differences in survival. Also, the multivariable analysis after PSM in the subgroups of pN2 patients with single/multistation 3A or with/without pN1 involvement (N2a1, N2a2, N2b1, and N2b2) did not show the presence of 3A metastases as an independent prognostic factor. However, other factors such as age, sex, comorbidities, and the severity of the disease had a significant influence on the long-term results.

Nevertheless, we believe that, 3A station resection has significant clinical importance. First, the incidence of 3A metastases is the second highest after 4R nodes, which is true for both upper and lower lobe tumours (*Table 3*). This is especially important in LS-LND, for which removal of the upper mediastinal nodes is not recommended in inferior lobectomy. Also, 3A metastasis rate is higher overall than other routine MLND stations: 2R, 7, 8, 9. This is even more apparent in upper lobe cases (*Table 3*) Moreover, even in the nodes of the 3A station that are 5-10 mm in size, the incidence of metastatic changes reaches 22.2% (7). In the context of the arguments presented above, an important reservation is raised by the low incidence of patients with 3A nodes removed, which amounts to 3.5%. This result is also comparable with the data of some of the previously cited study (19).

Several reasons could explain why 3A resection would potentially enhance patients survival. Undiscovered metastasis during nodal staging obviously lowers the survival due to patients not being eligible for beneficial adjuvant therapy. In our study pN0 and pN1 cases had better survival within the 3ALN+ subgroup compared to the 3ALN–, but it was without statistical significance. This might suggest there were undetected 3A metastases in 3ALN– subgroups. The second important reason is micrometastasis, which cannot be detected macroscopically or during image diagnostics. Thus, a patient would not undergo neoadjuvant therapy or would not be disqualified from surgery (21). And as we stated before some surgeons resect 3A based on intraoperative findings. Thus, micrometastatic 3A would not draw an attention of these surgeons. Thirdly, residual disease, which is a presence of single metastatic cells, is another explanation. This phenomenon could be missed even by experienced pathologists and result in future recurrence (22).

Our study has several significant limitations. First of all, it is a retrospective study, which significantly affects the errors in the clinical evaluation of the issue. This effect was partially offset by the use of PSM in both univariable and multivariable analyses. The second important limitation was the very low incidence of patients with 3A nodes removed, despite observing data from several centres. Relatively high metastasis rate in 3A (in comparison to MLND lymph node stations) might be due to intraoperative findings, which affected surgeon decision. Important reservations can be made with regard to preoperative diagnostics, particularly the use of PET-CT, which was very low in the initial period of the study. Also, the incidence of mediastinoscopy performed in the 3ALN+ and 3ALN– groups is too low (11.8% and 11.5%, respectively), considering the very high pN2 incidence of 20.8% in the 3ALN+ group. From a statistical point of view, in the multivariable analysis concerning pN2 subgroups, the population of individual subgroups after PSM was too small, which may limit the statistical value of the presented results. Prospective studies are needed, especially as a low 3A resection rate makes retrospective studies (even with big cohorts) hard to analyse correctly. Also, due to incompleteness of our database some important variables could not be introduced in this analysis (e.g., relapse-free survival, cancer specific survival or detailed complication analysis)

To sum up, the incidence of 3A node metastases in the pN2 patient group is high and increases in advanced stages. Also, 3A metastasis rate is comparable to routine MLND lymph node stations. The location of the tumour in the inferior lobe does not exclude the presence of 3A node metastases. Removal of the 3A station may

be recommended as a routine procedure in superior mediastinal lymphadenectomy in all cases of suspected mediastinal node metastases.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1957/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1957/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1957/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the National Research Institute of Chest Diseases, Warsaw, Poland (91/2020) and the requirement for informed consent was waived for the retrospective analysis.

References

1. Watanabe S, Asamura H. Lymph node dissection for lung cancer: significance, strategy, and technique. J Thorac Oncol 2009;4:652-7.
2. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30:787-92.
3. Osarogiagbon RU, Yu X. Nonexamination of lymph nodes and survival after resection of non-small cell lung cancer. Ann Thorac Surg 2013;96:1178-89.
4. Zieliński M, Rami-Porta R. Proposals for changes in the Mountain and Dresler mediastinal and pulmonary lymph node map. J Thorac Oncol 2007;2:3-6.
5. Riquet M, Arame A, Foucault C, et al. Prognostic classifications of lymph node involvement in lung cancer and current International Association for the Study of Lung Cancer descriptive classification in zones. Interact Cardiovasc Thorac Surg 2010;11:260-4.
6. Liu C, Wei S, Guo C, et al. Clinical Significance of Station 3A Lymph Node Dissection in Patients with Right-Side Non-Small-Cell Lung Cancer: A Retrospective Propensity-Matched Analysis. Ann Surg Oncol 2021;28:194-202.
7. Zheng H, Gao W, Fei K, et al. Prognostic role of station 3A mediastinal nodes for non-small-cell lung cancers. Interact Cardiovasc Thorac Surg 2013;17:447-54.
8. Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, 8th edition. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc; 2017.
9. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:1675-84.
10. Chen W, Zhang C, Wang G, et al. Feasibility of nodal classification for non-small cell lung cancer by merging current N categories with the number of involved lymph node stations. Thorac Cancer 2019;10:1533-43.
11. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. Ann Thorac Surg 2005;80:2051-6; discussion 2056.
12. Ray MA, Smeltzer MP, Faris NR, et al. Survival After Mediastinal Node Dissection, Systematic Sampling, or Neither for Early Stage NSCLC. J Thorac Oncol 2020;15:1670-81.
13. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery

Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-70.
14. Adachi H, Sakamaki K, Nishii T, et al. Lobe-Specific Lymph Node Dissection as a Standard Procedure in Surgery for Non-Small Cell Lung Cancer: A Propensity Score Matching Study. J Thorac Oncol 2017;12:85-93.
15. Deng HY, Qin CL, Li G, et al. Can lobe-specific lymph node dissection be an alternative to systematic lymph node dissection in treating early-stage non-small cell lung cancer: a comprehensive systematic review and meta-analysis? J Thorac Dis 2018;10:2857-65.
16. Riquet M, Rivera C, Pricopi C, et al. Is the lymphatic drainage of lung cancer lobe-specific? A surgical appraisal. Eur J Cardiothorac Surg 2015;47:543-9.
17. Maniwa T, Okumura T, Isaka M, et al. Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small-cell lung cancer. Eur J Cardiothorac Surg 2013;44:e59-64.
18. Fang L, Xu J, Ye B, et al. Is lobe specific lymph node dissection adequate for cN0-1 non-small cell lung cancer? J Cardiothorac Surg 2020;15:46.
19. Liang RB, Yang J, Zeng TS, et al. Incidence and Distribution of Lobe-Specific Mediastinal Lymph Node Metastasis in Non-small Cell Lung Cancer: Data from 4511 Resected Cases. Ann Surg Oncol 2018;25:3300-7.
20. Yang MZ, Hou X, Liang RB, et al. The incidence and distribution of mediastinal lymph node metastasis and its impact on survival in patients with non-small-cell lung cancers 3 cm or less: data from 2292 cases. Eur J Cardiothorac Surg 2019;56:159-66.
21. Coello MC, Luketich JD, Litle VR, et al. Prognostic significance of micrometastasis in non-small-cell lung cancer. Clin Lung Cancer 2004;5:214-25.
22. Frisone D, Friedlaender A, Addeo A. The Role and Impact of Minimal Residual Disease in NSCLC. Curr Oncol Rep 2021;23:136.

Cite this article as: Cackowski MM, Zbytniewski M, Gryszko GM, Dziedzic M, Woźnica K, Orłowski TM, Dziedzic DA; on behalf of the Polish Lung Cancer Study Group (PLCSG). Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study. J Thorac Dis 2022. doi: 10.21037/jtd-21-1957

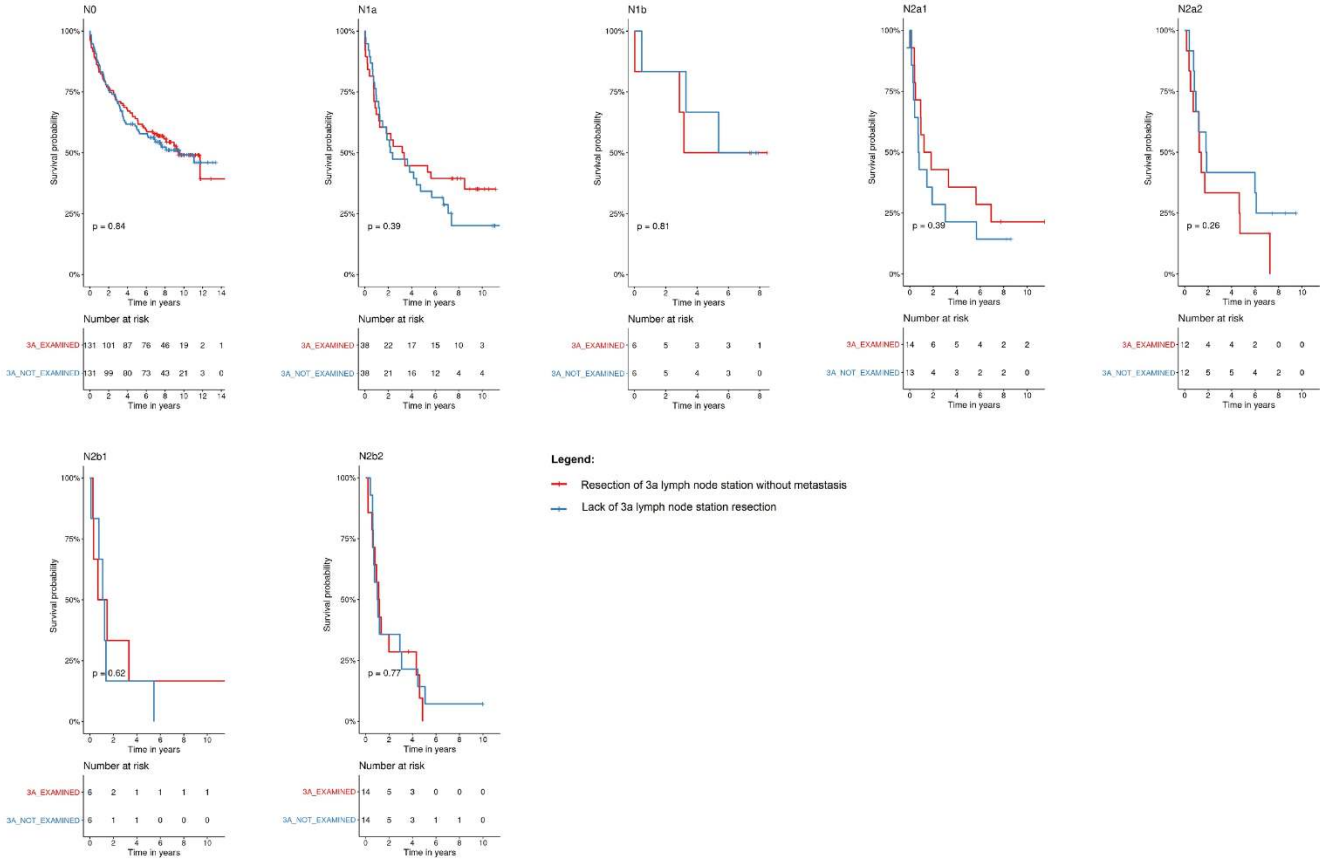


Figure S1 Impact of prevascular lymph node station resection status on 5-year overall survival in new pN subgroups.

https://dx.doi.org/10.21037/jtd-21-1957

Table S1 Multivariable analysis after Propensity Score Matching in new pN2 subgroups

Variable	N2a1		N2a2		N2b1		N2b2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Surgery								
Right lower lobectomy	Reference							
Right upper lobectomy	10.48 (1.81–60.66)	0.001	2.67 (0.46–15.43)	0.27	2.96 (0.19–4.63)	0.44	5.93 (0.08–4.14)	0.60
Pneumonectomy	10.0 (1.53–65.37)	0.02	1.17 (0.13–10.98)	0.89			5.41 (0.72–40.39)	0.01
pT								
1a	Reference							
1b	2.54 (0.22–29.51)	0.46	0.03 (0.002–0.53)	0.02			9.71 (0.07–12.63)	0.98
1c	3.13 (0.30–32.35)	0.34					9.49 (1.01–88.99)	0.049
2a	5.41 (0.45–64.58)	0.18	0.23 (0.04–1.46)	0.12	0.47 (0.01–2.15)	0.70	2.04 (0.55–7.57)	0.29
2b								
3					13.12 (0.34–5.09)	0.17		
4								
3A station								
3ALN−	Reference							
N3ALN	0.58 (0.17–2.0)	0.39	4.68 (1.24–17.75)	0.02	0.07 (0.003–1.49)	0.09	1.30 (0.31–5.50)	0.73
M3ALN	0.62 (0.15–2.55)	0.51	2.96 (0.54–16.23)	0.21	2.0 (0.22–1.87)	0.54	1.11 (0.34–3.64)	0.86
Comorbidities (reference = absence of disease)								
Myocardial infarction	3.81 (0.35–41.20)	0.27 13.12 (1.46–117.75)		0.02			8.81 (1.58–49.19)	0.01
Mediastinoscopy (reference = lack of mediastinoscopy)	1.63 (0.19–14.23)	0.66	0.44 (0.09–2.03)	0.29			1.95 (0.56–6.81)	0.30
Stage (reference = Stage IA1)								
IIIA	0.04 (0.003–0.46)	0.01	12.68 (1.25–128.55)	0.03	3.23 (0.17–6.00)	0.43	0.18 (0.03–1.05)	0.06

3ALN−, patients without prevascular node resection; M3ALN, patients with prevascular node resection with metastasis; N3ALN, patients with prevascular node resection without metastasis.

https://dx.doi.org/10.21037/jtd-21-1957

Surgical Oncology 48 (2023) 101941

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

The absence of lymph nodes removed (pNx status) impacts survival in patients with lung cancer treated surgically

Marcin M. Cackowski [a], Grzegorz M. Gryszko [a], Marcin Zbytniewski [a], Michał Dziedzic [b], Katarzyna Woźnica [c], Tadeusz M. Orłowski [a], Dariusz A. Dziedzic [a,*], on behalf of the Polish Lung Cancer Study Group (PLCSG)

[a] Department of Thoracic Surgery, National Research Institute of Chest Diseases, Plocka Street 26, 01-138, Warsaw, Poland
[b] Faculty of Medicine, Medical University of Gdansk, Sklodowska-Curie Street 3, 80-210, Gdansk, Poland
[c] Faculty of Mathematics and Information Science, Warsaw University of Technology, Koszykowa Street 75, 00-662, Warsaw, Poland

ARTICLE INFO

Keywords:
pNx status
Non-small-cell lung cancer
Lymph node resection
Thoracic surgery
Lymph node staging

ABSTRACT

Objectives: We aimed to study the clinical significance of the lack of lymph node assessment (pNx status) and its impact on survival in non-small-cell lung cancer patients.
Methods: We retrospectively analysed the Polish Lung Cancer Study Group database. pNx status was defined as 0 lymph nodes removed. We included 17,192 patients.
Results: A total of 1080 patients (6%) had pNx status. pNx patients were more likely to be younger, be female, have a different pT distribution, have squamous cell carcinoma, undergo open thoracotomy, be operated on in non-academic hospitals, and have a lower rate of some comorbidities. pNx was more likely to be cN0 than pN1 and pN2 but less likely than pN0 ($p < 0.001$). pNx patients were less likely to undergo preoperative invasive mediastinal diagnostics than pN1 and pN2 patients but more likely than pN0 patients ($p < 0.001$). Overall, the five-year overall survival rates were 64%, 45%, 32% and 50% for pN0, pN1, pN2 and pNx, respectively. In pairwise comparisons, all pN descriptors differed significantly from each other (all $p < 0.0001$ but pNx vs. pN1 $p = 0.016$). The placement of the pNx survival curve and survival rate depended on histopathology, surgical approach and pT status. In multivariable analysis, pNx was an independent prognostic risk factor (HR = 1.37, 95%CI: 1.23–1.51, $p < 0.01$).
Conclusion: The resection of lymph nodes in lung cancer remains a crucial step in the surgical treatment of this disease. The survival of pNx patients is similar to that of pN1 patients. pNx survival curve placement depends on the other variables which could be useful in clinical decisions.

1. Introduction

In Poland in 2019, lung cancer was the second most frequent cancer among men and women. Specifically, it was diagnosed in 9.9% of female and 16.1% of male cancer patients. However in terms of mortality, it was the most frequent cause of cancer deaths among both women and men (17.9% and 27.4% of cancer deaths, respectively) [1]. From 2014 to 2016, the 3-year overall survival (OS) was 24% among women and 17% among men [2]. Surgery is the treatment of choice in cases of stage I-II and some cases of stage III non-small-cell lung cancer (NSCLC) if the patient is sufficiently healthy for surgery. Radical resection significantly improves survival [3].

In surgery for lung cancer, intraoperative lymphadenectomy is one of the most crucial steps of the procedure. It includes the resection of intrapulmonary, peribronchial, hilar and mediastinal lymph nodes. The eighth edition of the Tumour Node Metastasis (TNM) classification is used to properly differentiate patients in different stages and define survival prognosis [4]. Whether the nodal aspect of TNM of lung cancer should be changed or enhanced by additional factors (e.g., quantitative factors) is an ongoing topic of debate [5].

Abbreviations: EBUS-TBNA, endobronchial-ultrasound transbronchial-needle-aspiration; EUS-FNA, oesophageal-ultrasound fine-needle-aspiration; NSCLC, non-small-cell lung cancer; OS, Overall Survival; PET-CT, positron emission tomography-computed tomography; PLCSG, Polish Lung Cancer Study Group; TNM, Tumour-Node-Metastasis classification; VATS, Video-assisted thoracic surgery.

* Corresponding author. Department of Thoracic Surgery, National Research Institute of Chest Diseases, Plocka 26 Street, 01-138, Warsaw, Poland.
E-mail address: drdariuszdziedzic@gmail.com (D.A. Dziedzic).

https://doi.org/10.1016/j.suronc.2023.101941
Received 18 December 2022; Received in revised form 12 March 2023; Accepted 28 March 2023
Available online 31 March 2023

Additionally, the pNx descriptor, defined as the impossibility of lymph node assessment, is included in the TNM classification [4]. This phenomenon occurs in between 12.1% and 17.3% of resected cases of NSCLC and results in a worse survival rate than in properly examined cases [6–8]. The pNx survival rate is comparable to pN1 rather than pN0 [7]. The improper examination of lymph nodes may be caused by factors such as inadequate resection or the documentation of mediastinal lymph nodes (N2) by surgeons, the inadequate resection of parenchymal lymph nodes (N1) by pathologists, and communication barriers between these specialties [9].

Despite many improvements in NSCLC lymphadenectomy over the years, the pNx phenomenon persists and requires further studies to evaluate its prevalence and associated factors. Thus, in this work, we aimed to investigate the impact of pNx status on patient survival and to assess pNx prevalence in the Polish Lung Cancer Study Group (PLCSG) database population. We hypothesize, that pNx survival rate is worse than pN0 and pNx survival rate can be predicted based on the other factors.

2. Materials and methods

After approval by the ethics committee of the National Research Institute of Chest Diseases (96/2021), we retrospectively analysed the PLCSG database. The PLCSG database is a nationwide registry of surgically treated lung cancer cases that collects data regarding epidemiology, preoperative evaluation, operation details, pathological examination, postoperative care, treatment and follow-up [10]. We used the eight edition of the TNM classification and IASLC lymph node map [4,5]. Cases, that were classified according to previous TNM classification, were recl assified to the newest one. To our knowledge, mediastinal lymph node dissection is the technique of choice in most thoracic centres in Poland. Various chemotherapy regimens were used (exact data not available), but cisplatin and vinorelbine were the most routinely used. pNx was defined as 0 lymph nodes removed according to the latest TNM classification [4]. cN was defined as preoperative N descriptor and pN was defined as postoperative (pathological) N descriptor.

2.1. Inclusion and exclusion criteria

The study period included the years 2007–2017. We included patients with confirmed NSCLC who received radical resection (R0) with complete clinical data after lobectomy or pneumonectomy. We excluded cases of patients after nonradical resection (R1), after sublobar or extended resections, with incomplete or lost clinical data or who failed to complete follow-up. Neoadjuvant cN2 cases were included in the study; however, they constituted a small portion of the entire cohort (227 cases-1.3%). We decided to keep them to assess the possibility of cN2-pNx.

2.2. Preoperative staging and follow-up

When patients had preoperative findings (>10 mm lymph nodes) during radiological diagnostics (, computed tomography, magnetic resonance imaging or positron emission tomography-computed tomography (PET-CT)), invasive lymph node diagnostics (endobronchial-ultrasound transbronchial-needle-aspiration (EBUS-TBNA), oesophageal-ultrasound fine-needle-aspiration (EUS-FNA), mediastinoscopy, mediastinotomy) were performed.

Thoracic surgeons consulted patients within 2–3 weeks after surgery. Generally, patients underwent follow-up diagnostics every 3–5 months for 5 years. Follow-up included radiological examinations (chest radiograph, computed tomography or, in justified cases, PET-CT or magnetic resonance imaging). In the case of radiological findings, patients underwent an invasive procedure, similar to the preoperative evaluation. Data from imaging tests and invasive procedures allowed us to evaluate failure patterns. Failures in hilar and/or mediastinal lymph nodes were defined as new or enlarging lymph nodes with >10 mm diameter in the short axis on computed tomography or as hypermetabolism on PET-CT. Recurrence in the ipsilateral hemithorax or mediastinum was defined as locoregional. Distant recurrence was defined as recurrence in all other sites. The study period included the implementation times of PET-CT in Poland (from ~25% at the beginning to ~75% of cases at the end).

2.3. Statistical analysis

We divided patients into pN groups. Each cohort's numerical variables were summarized by mean value and standard deviation. The significance of differences between groups was assessed using the Kruskal-Wallis test. Categorical variables were summarized as percentage frequency of occurrence. Statistical differences were evaluated with the chi-squared test. Survival curves were estimated using the Kaplan-Meier method and the log-rank test was used to assess statistical differences between curves. To assess which groups were statistically significantly different from each other, post hoc pairwise tests were applied and the Benjamin-Hochberg multiple testing correction was included. The multivariable Cox model was built on variables assessed as statistically significant in the univariable Cox model. In all statistical tests, 0.05 was considered the significance threshold. We conducted all analyses in R using the survival and survminer packages.

3. Results

We included 17192 patients in our analysis. Overall, 11695 patients had pN0 (68%), 2580 had pN1 (15%), 1837 had pN2 (11%) and 1080 had pNx (6%) disease. Patient characteristics based on pN subgroups are presented in Table 1.

pNx patients showed a different distribution of pT features (e.g., the pT1a percentage (3.1%) was similar to that of pN0 (2.9%) rather than those of pN1 and pN2 (0.6% and 0.9%)($p < 0.001$). The pNx histopathology rates were between pN0 and pN1 (e.g., adenocarcinoma 51.8%, 58.0% and 47.9%, respectively, $p < 0.001$). pNx patients underwent video-assisted thoracic surgery (VATS)(11.8%) less often than pN0 (23.2%) and at a similar rate as pN1 and pN2 patients (both 12.0%)($p < 0.001$). pNx patients were more likely to be operated on in nonacademic centres (63.2%) than pN0, pN1 and pN2 patients (47.9%, 42.5% and 53.1%, respectively; $p < 0.001$). The pNx pneumonectomy rate was between those of pN0 and pN1 (8.1%, 1.8% and 16.7%, respectively; $p < 0.001$).

3.1. Lymph node characteristics

The mean numbers of resected lymph nodes and stations for the entire cohort were 8.26 and 3.22, respectively. The mean numbers of positive lymph nodes and stations were 2.89 and 1.99, respectively. The lymph node yield of the entire cohort is presented in Fig. 1 pNx cases were more likely to be cN0 (89.8%) in comparison to pN1 (53.6%) and pN2 (40.6%) but less likely in comparison to pN0 (95.1%). In the case of cN1 and cN2, the percentages were the second smallest for pNx after pN0 ($p < 0.001$). The pNx group was less likely to undergo mediastinoscopy and EBUS-TBNA/EUS-FNA (4.9% and 8.8%, respectively) than the pN1 (20.6% and 36.4%, respectively) and pN2 groups (32.7% and 62.9%, respectively) but more likely than the pN0 group (1.2% and 3.7%, respectively)($p < 0.001$ and $p < 0.001$, respectively). Detailed lymph node characteristics are presented in Table 2.

3.2. Survival analysis

The median follow-up time was 2429 days (79.86 months) (95%CI: (2343–2549 days). Overall, the five-year OS rates were 64%, 45%, 32% and 50% for pN0, pN1, pN2 and pNx, respectively (Table 3). The pNx survival curve was placed just above the pN1 curve (Fig. 2). In pairwise

Table 1
Patient demographics in pN subgroups.

Variable	pN0(n = 11695)	pN1(n = 2580)	pN2(n = 1837)	pNx(n = 1080)	p-value
Age					
Mean (SD)	64.7 (7.69)	63.8 (7.70)	63.4 (8.33)	63.9 (7.92)	<0.001
Median [Min, Max]	65.0 [22.0, 96.0]	64.0 [32.0, 87.0]	63.0 [31.0, 85.0]	64.0 [39.0, 85.0]	
Sex					
Female	4537 (38.8%)	784 (30.4%)	690 (37.6%)	361 (33.4%)	<0.001
Male	7158 (61.2%)	1796 (69.6%)	1147 (62.4%)	719 (66.6%)	
pT					
1a	340 (2.9%)	15 (0.6%)	16 (0.9%)	34 (3.1%)	<0.001
1b	2030 (17.4%)	213 (8.3%)	140 (7.6%)	151 (14.0%)	
1c	1862 (15.9%)	313 (12.1%)	196 (10.7%)	152 (14.1%)	
2a	3681 (31.5%)	769 (29.8%)	582 (31.7%)	301 (27.9%)	
2b	1259 (10.8%)	402 (15.6%)	266 (14.5%)	120 (11.1%)	
3	1726 (14.8%)	535 (20.7%)	393 (21.4%)	194 (18.0%)	
4	797 (6.8%)	333 (12.9%)	244 (13.3%)	128 (11.9%)	
Histopathology					
Adenocarcinoma	6786 (58.0%)	1235 (47.9%)	1205 (65.6%)	559 (51.8%)	<0.001
Squamous	4909 (42.0%)	1345 (52.1%)	632 (34.4%)	521 (48.2%)	
Approach					
Thoracotomy	8987 (76.8%)	2271 (88.0%)	1617 (88.0%)	953 (88.2%)	<0.001
Video-assisted	2708 (23.2%)	309 (12.0%)	220 (12.0%)	127 (11.8%)	
Procedure					
Lobectomy	11475 (98.2%)	2149 (83.3%)	1472 (80.1%)	993 (91.9%)	<0.001
Pneumonectomy	220 (1.8%)	431 (16.7%)	365 (19.9%)	87 (8.1%)	
Side					
Right	7679 (65.7%)	1420 (55.0%)	1359 (73.9%)	722 (66.9%)	<0.001
Left	4016 (34.3%)	1160 (45.0%)	478 (26.1%)	358 (33.1%)	
Center type					
Academic	6088 (52.1%)	1484 (57.5%)	862 (46.9%)	397 (36.8%)	<0.001
Other	5607 (47.9%)	1096 (42.5%)	975 (53.1%)	683 (63.2%)	
Comorbidities					
Smoking	8259 (70.6%)	1805 (70.0%)	1266 (68.9%)	748 (69.3%)	0.401
Diabetes	427 (3.7%)	87 (3.4%)	60 (3.3%)	38 (3.5%)	0.797
Heart failure	316 (2.7%)	58 (2.2%)	42 (2.3%)	26 (2.4%)	0.46
Kidney failure	146 (1.2%)	23 (0.9%)	12 (0.7%)	5(0.5%)	0.0121
Chronic obstructive pulmonary disease	2841 (24.3%)	611 (23.7%)	406 (22.1%)	194 (18.0%)	<0.001
Hypertension	5535 (47.3%)	1128 (43.7%)	827 (45.0%)	429 (39.7%)	<0.001
Coronary disease	870 (7.4%)	175 (6.8%)	150 (8.2%)	70 (6.5%)	0.227

comparisons, all pN descriptors differed significantly from each other (all $p < 0.0001$ but pNx vs. pN1 $p = 0.016$)(Table 4).

3.3. Subgroup survival analysis

In the adenocarcinoma subgroup, the five-year OS rates were 66%, 42%, 33%, and 53% for pN0, pN1, pN2, and pNx, respectively (Table 3). In pairwise comparisons, all pN descriptors differed significantly from each other ($p < 0.0001$) (Table 4). The pNx survival curve was placed between the pN0 and pN1 curves (Fig. 3).

In the squamous cell carcinoma subgroup, the five-year OS rates were 61%, 48%, 31%, and 47% for pN0, pN1, pN2, and pNx, respectively (Table 3). In pairwise comparisons, almost all pN descriptors differed significantly from each other ($p < 0.0001$), but pNx was not significantly different from pN1 ($p = 0.92$)(Table 4). The pNx survival curve overlapped with the pN1 curve (Fig. 2).

In the open thoracotomy subgroup, the five-year OS rates were 62%, 44%, 32%, and 48% for pN0, pN1, pN2, and pNx, respectively (Table 3). In pairwise comparisons, all pN descriptors differed significantly from each other (pNx vs. pN1 $p = 0.04$, rest pairs $p < 0.001$)(Table 4). The pNx survival curve was placed between the pN0 and pN1 curves (Fig. 3).

In the VATS subgroup, the five-year OS rates were 77%, 64%, 40%, and 75% for pN0, pN1, pN2, and pNx, respectively (Table 3). In pairwise comparisons, pN0 pN1 and pN2 significantly differed from each other, but pNx significantly differed only from pN2 (Table 4). The pNx survival curve overlapped with the pN0 curve (Fig. 3).

The five-year OS rates of each pN descriptor based on pT subgroups are presented in Table 3. Generally, a higher pT stage corresponded to pNx survival that was similar to higher pN stages (see Supplementary Material 1).

3.4. Multivariable analysis

In multivariable analysis, pNx was an independent prognostic risk factor (HR = 1.37, 95%CI: 1.23–1.51, $p < 0.01$). pN1 was also an independent prognostic risk factor (HR = 1.14, 95%CI: 1.01–1.28, $p = 0.029$). We identified other independent prognostic factors: chronic obstructive pulmonary disease, heart failure, stage IIIA, stage IIIB, male sex and age. VATS was an independent prognostic factor for survival (Table 5).

4. Discussion

The adequate resection of lymph nodes is necessary to accurately stage and qualify patients for adjuvant treatment [11]. Additionally, the resection of occult metastasis significantly improves survival [12]. Based on current European Society of Thoracic Surgeons guidelines, adequate lymph node resection in lung cancer surgery is defined as the resection of at least 3 lymph nodes from N1 group stations and 3 lymph nodes from N2 group stations [13]. However, experts have been divided over this issue for almost 20 years. In 2005, Ludwig et al. revealed that the optimal number of resected lymph nodes ranged from 11 to 16 [14]. Further studies did not set optimal cut-off values, but most unanimously recommended the resection of more than 6 lymph nodes [15]. From technical point of view, many surgical techniques of lymphadenectomy are used in daily practice and are investigated in studies. Nevertheless even the least invasive of these techniques require resection of many lymph nodes [16]. [17]. [17]. [18]. [19]. [20]. Additionally, the IASLC proposed a new, more complex pN staging classification that requires more precise lymphadenectomy and a higher lymph node count [5]. Nevertheless, based on the Spanish study, 19.6% of lung cancer resections had fewer than 6 LNs removed, and 21.1% of resections had fewer than 3 LNs removed [23]. All arguments mentioned in this paragraph and many more sources depict the complexity of lymphadenectomy problems in lung cancer.

pNx status, which is a lack of resected lymph nodes, represents the

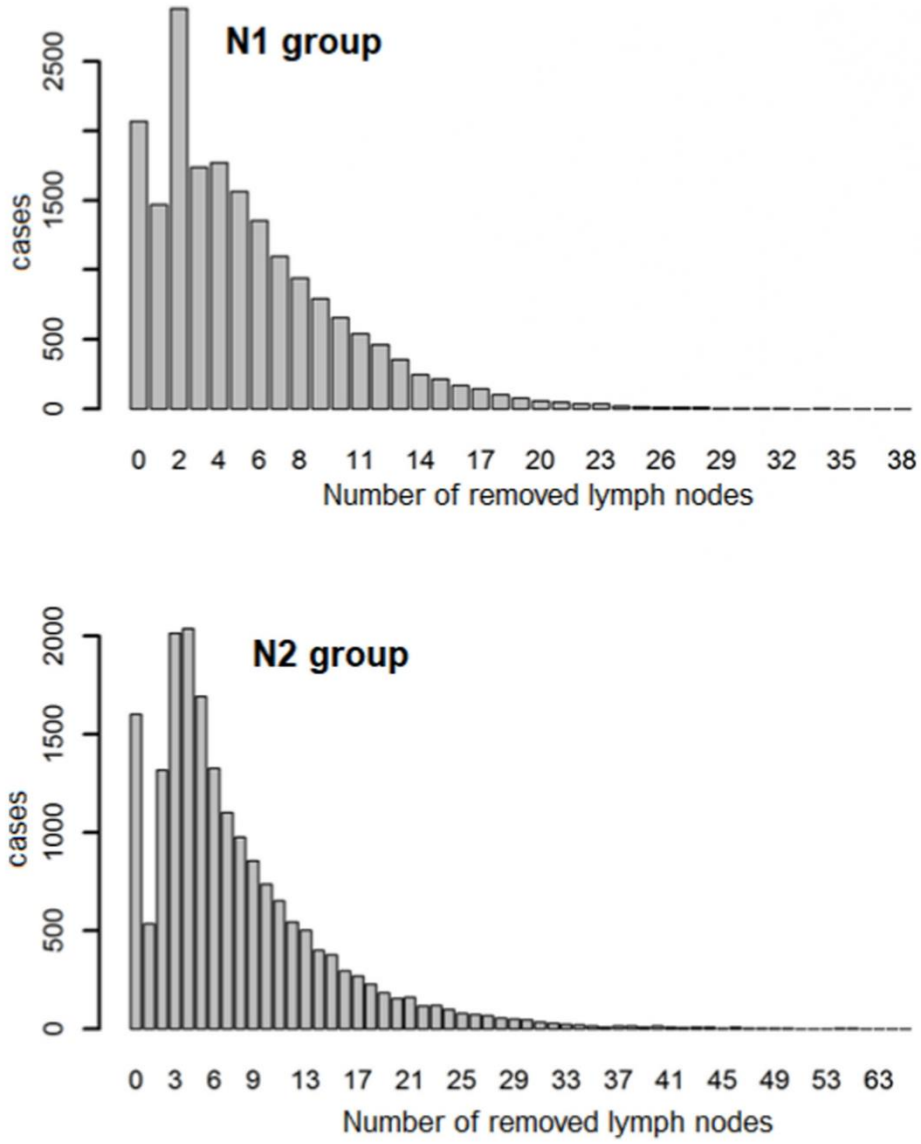


Fig. 1. Lymph node yield.

Table 2
Lymph node characteristics.

Variable	pN0 (11695)	pN1 (2580)	pN2 (1837)	pNX (1080)	p-value
Clinical N-stage					
cN0	11132 (95.1%)	1387 (53.6%)	745 (40.6%)	970 (89.8%)	<0.001
cN1	558 (4.8%)	1132 (43.9%)	950 (51.7%)	108 (10.0%)	
cN2	5(0.1%)	68(2.5%)	142 (7.7%)	12 (0.2%)	
Preoperative diagnostics					
EBUS-TBNA/ /EUS-FNA	437 (3.7%)	938 (36.4%)	1155 (62.9%)	96 (8.8%)	<0.001
Mediastinoscopy	139 (1.2%)	532 (20.6%)	601 (32.7%)	53 (4.9%)	<0.001
Number of resected(mean)					
Lymph nodes	8.61	9.10	9.28		<0.001
Stations	2.27	3.12	3.65		
Number of positive(mean)					
Lymph nodes		3.17	4.41		<0.001
Stations		1.87	2.40		

EBUS-TBNA: Endobronchial-ultrasound transbronchial-needle-aspiration, EUS-FNA: oesophageal-ultrasound fine-needle-aspiration.

Table 3
The 5-year overall survival rates in pN subgroups.

Variable	pN0	pN1	pN2	pNX	p-value
Overall	64%	45%	32%	50%	<0.0001
pT					
1a	79%	51%	44%	67%	0.027
1b	76%	64%	51%	76%	<0.0001
1c	69%	54%	40%	57%	<0.0001
2a	64%	47%	31%	54%	<0.0001
2b	60%	41%	42%	36%	<0.0001
3	56%	38%	25%	42%	<0.0001
4	44%	40%	21%	22%	<0.0001
Histopathology					
Adenocarcinoma	66%	42%	33%	53%	<0.0001
Squamous-cell-carcinoma	61%	48%	31%	47%	<0.0001
Surgery type					
Thoracotomy	62%	44%	32%	48%	<0.0001
Video-assisted thoracic surgery	77%	64%	40%	75%	<0.0001

extreme of the inadequate lymphadenectomy spectrum. Based on the SEER database, pNx occurs in between 8% and 24% of cases depending on the region [7]. A dramatically high incidence of pNx was presented in a study based on audits of pathological and surgical reports (42% and

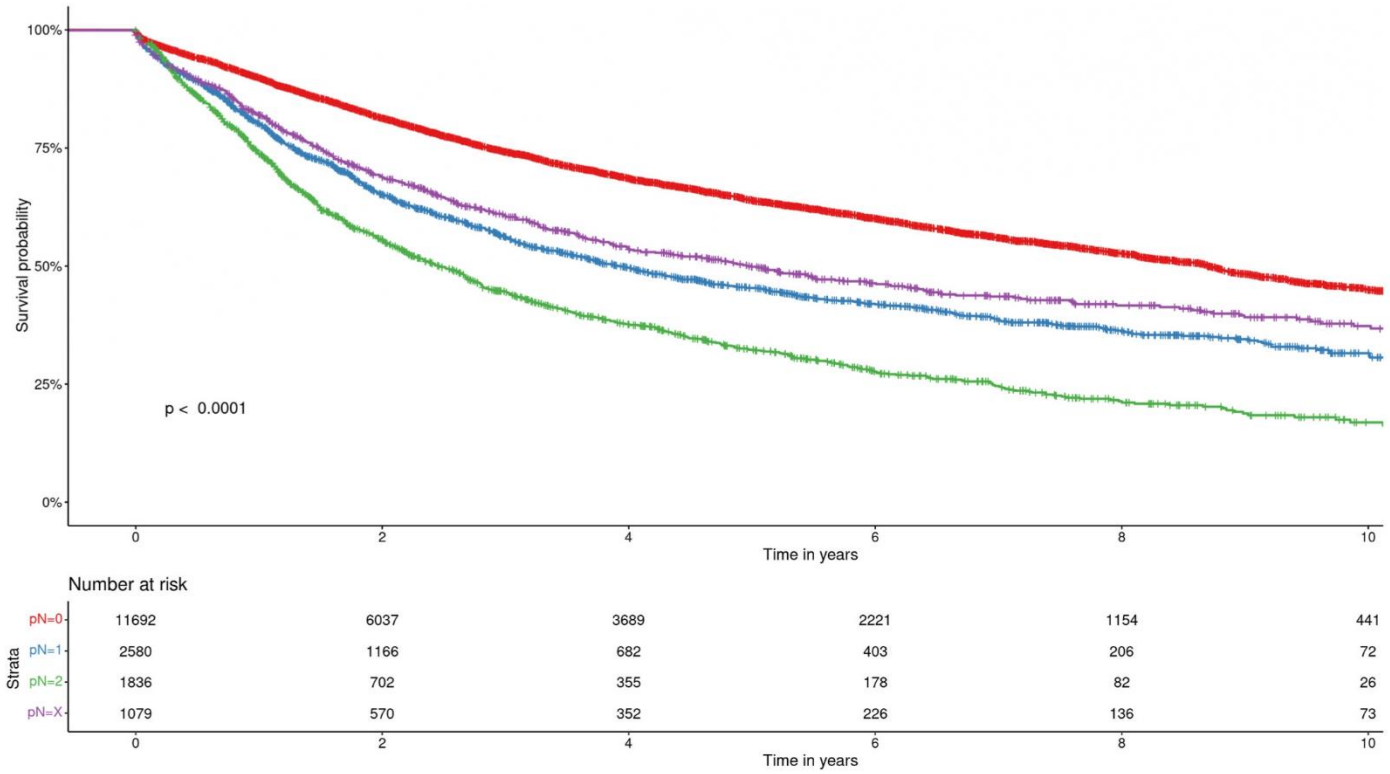


Fig. 2. Impact of pNx status on 5-year overall survival in comparison to other pN descriptors.

Table 4
Pairwise comparison of subgroup survivals.

Variable	Group 1	Group 2	p-value
Overall			
	pN1	pN0	<0.0001
	pN2	pN0	<0.0001
	pN2	pN1	<0.0001
	pNX	pN0	<0.0001
	pNX	pN1	0.0160
	pNX	pN2	<0.0001
Histopathological type			
Adenocarcinoma	pN1	pN0	<0.0001
	pN2	pN0	<0.0001
	pN2	pN1	<0.0001
	pNX	pN0	<0.0001
	pNX	pN1	<0.0001
	pNX	pN2	0.0006
Squamous-cell-carcinoma	pN1	pN0	<0.0001
	pN2	pN0	<0.0001
	pN2	pN1	<0.0001
	pNX	pN0	<0.0001
	pNX	pN1	0.92
	pNX	pN2	<0.0001
Surgical Approach			
Thoracotomy	pN1	pN0	<0.0001
	pN2	pN0	<0.0001
	pN2	pN1	<0.0001
	pNX	pN0	<0.0001
	pNX	pN1	0.04
	pNX	pN2	<0.0001
Video-assisted thoracic surgery	pN1	pN0	0.0032
	pN2	pN0	<0.0001
	pN2	pN1	0.0064
	pNX	pN0	0.68
	pNX	pN1	0.21
	pNX	pN2	0.0007

45% of cases, respectively). This work showed a large discrepancy between the declared technique of lymphadenectomy and the actual number of LNs removed [9]. Little et al. made similar observations in their study, where 53% of samples in mediastinoscopy did not contain lymph node tissue [24]. In our study, the percentage of pNx was 6.3%. In comparison to previous studies, we believe that this percentage is acceptable. Most of the pNx cases were staged preoperatively as cN0 (89.9%). However, the preoperative staging of mediastinal LNs was higher in the pNx group than in the pN0 group (EBUS-TBNA/EUS-FNA 8.8% vs. 3.7% and mediastinoscopy 4.9% and 1.2%, respectively; both $p < 0.001$). This finding indicates awareness of the importance of mediastinal lymph nodes in lung cancer. But, even though most cases were clinically unsuspicious (lymph node wise), something was unusual as invasive lymph node diagnostics were performed more frequently than pN0. Identifying these preoperative factors as potential predictors of pNx status might be essential and further studies are required. Also, mediastinoscopy percentage in pNx is surprising and worrying, because lymph nodes were not retrieved in both mediastinoscopy and thoracotomy/VATS procedures. Additionally, a higher percentage of pNx cases had pneumonectomy (8.1% vs. 1.8%, $p < 0.001$). Thus, despite the numerous N1 lymph nodes in pathological material, pathologists reported none in reports, which is surprising. Simply put, surgeons are responsible for N2 lymph nodes, and pathologists are responsible for N1 lymph nodes [9] Guidelines and frameworks of pathologist lymphadenectomy of intraparenchymal lymph nodes are as important as surgical ones. In one study, almost 9% of pN0 cases and 11% of pN2 cases had no N1 nodes reported. Surgeons certainly removed them with lung parenchyma, but pathologists did not assess or report them. Although these errors may seem oversimplified, the authors revealed the incorrect labelling of lymph nodes, inaccurate procedure descriptions and communications barriers between surgeons and pathologists in final reports [15]. These errors demonstrate the importance of nontechnical skills as a life-saving factor in surgery [25].

Our study population was dominated by T2a cases, and 53.5% of cases were in stage I. Edwards et al. reported that incomplete

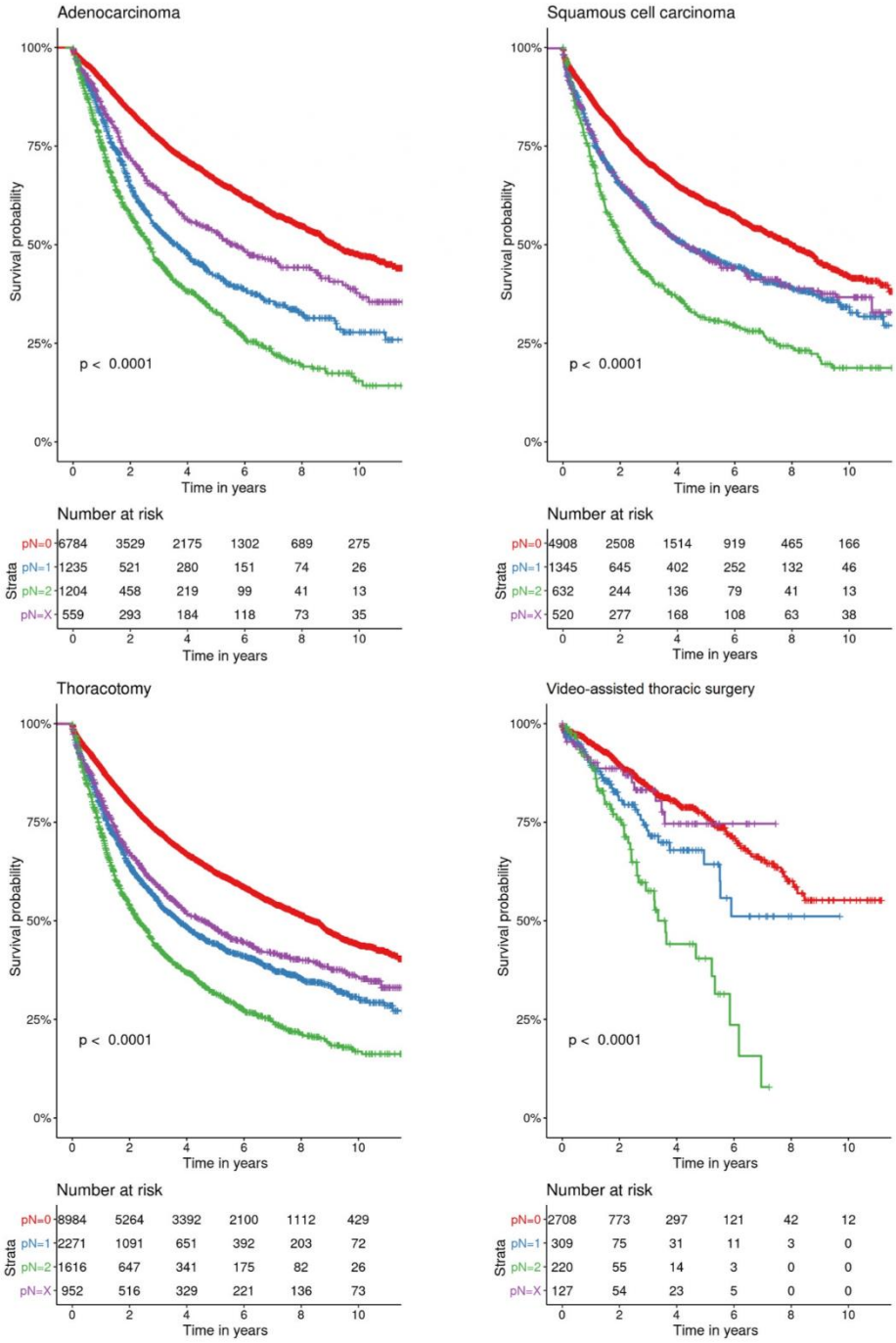


Fig. 3. The subgroup survival analysis of pNx and other pN descriptor.

lymphadenectomy was more frequent in cases T1a and T4 disease than in T2 disease [26]. Some surgeons might have neglected importance of lymphadenectomy in lower stage lung cancers as they believed lymph node metastases are less frequent in such cases. For example some researchers suggested that the extent of lymphadenectomy should be based on tumour size and histology [21]. However, others oppose such recommendations because of the relatively high incidence of metastasis to lymph nodes, even in pT1 tumours (e.g. 41% of pN2 cases had pT1 stage) [15,22]. Regardless of these data and preferences, the number of lymph node retrieved should not be zero. In our opinion, meticulous lymphadenectomy should be performed regardless of tumour size. Additionally, most of our pNx patients were operated on by thoracotomy rather than VATS (88.2% vs. 11.8%, $p < 0.001$) and were operated on at nonacademic centres (63.2% vs. 36.8%, $p < 0.001$). Bilimoria et el. Revealed similar findings in cases of stomach and pancreatic cancer. They found that in academic centres, surgeons resected significantly more lymph nodes (15 vs. 6 and 9 vs. 6, $p < 0.001$, respectively) [27]. Higher thoracotomy rate in pNx cases is surprising as usually VATS is related with smaller number of lymph nodes removed [28]. But access to less invasive techniques and experience in these techniques are better at academic centres. Also, awareness of adequate lymphadenectomy is higher at academic centres because of lifelong learning and academic work, which defines new trends and guidelines. Thus, this might result in lower rate of VATS technique in pNx subgroup in our study.

In our study, the 5-year OS in the pNx group was worse than that in the pN0 group but better than those in the pN1 and pN2 groups (50% vs. 64% vs. 45% vs. 32%, $p < 0.0001$). Additionally, in multivariable analysis, pNx was an independent prognostic factor (HR = 1.37, 95%CI:

Table 5
The multivariable analysis.

Variable	Hazard Risk	95%CI	p-value
pN status			
pN0 = reference			
pN1	1.14	1.01–1.28	0.029
pN2	1.20	0.98–1.48	0.085
pNx	1.37	1.23–1.51	<0.01
Comorbidities			
Lack of disease = reference			
Chronic obstructive pulmonary disease	1.12	1.06–1.19	<0.01
Coronary disease	1.09	0.98–1.22	0.115
Heart failure	1.41	1.22–1.64	<0.01
pT status			
pT1a = reference			
pT1b	1.02	0.51–2.01	0.964
pT1c	1.40	0.72–2.74	0.320
pT2a	1.62	0.84–3.12	0.153
pT2b	1.60	0.83–3.11	0.163
pT3	1.39	0.72–2.70	0.326
pT4	1.46	0.75–2.86	0.267
Stage			
IA1 = reference			
IA2	1.02	0.48–2.16	0.964
IA3	1.00	0.48–2.08	0.992
IB	0.98	0.48–2.03	0.966
IIA	1.15	0.55–2.40	0.706
IIB	1.51	0.73–3.12	0.263
IIIA	2.13	1.02–4.45	0.045
IIIB	3.11	1.42–6.78	<0.01
Histopathology			
Adenocarcinoma = reference			
Squamous cell carcinoma	0.97	0.92–1.03	0.306
Approach			
Open thoracotomy = reference			
Video-assisted thoracic surgery	0.63	0.56–0.70	<0.01
Sex			
Female = reference			
Male	1.39	1.31–1.47	<0.01
Age	1.02	1.02–1.02	<0.01

1.23–1.51, $p < 0.01$). In previous studies, pNx survival was similar to pN1 or pN2 survival [7,8]. The above data suggest that pNx cases were understaged. Thus, possible cancer cells in these lymph nodes were not resected, and the patient did not benefit from potential further adjuvant treatment.

Interestingly, the placement of the pNx survival curve depended on other variables (e.g., approach, histology of tumour or pT), which represents a novel finding. Generally, variables indicating worse prognosis or more malignant processes significantly moved the pNx curve towards the pN1 or even pN2 curve (Fig. 3, Tables 3 and 4, Supplementary Material 1). We hypothesize, that these variables indicate higher probability of lymph node metastases, which remain undetected and untreated in pNx cases. This results in worse prognosis.Thus, clinical decisions on how to stage pNx cases could be based on coexisting other variables, not exclusively on pNx status.

Our study has several limitations. We included a large cohort, but the retrospective character of the study indicates potential selection bias. In the database, lymphadenectomy data are based on pathologist reports without considering surgeon reports. Thus, this assessment is unilateral. Several dozens of centres participate in the database, and operative techniques and lymph node reporting standards may consequently differ. We excluded cases of sublobar or extended resections. However, these groups were relatively small and did not impact the final results. Sadly, the PLCSG database does not include detailed data on pre- and postoperative chemotherapy because oncological treatment is usually performed outside thoracic centres that participate in the database. Neoadjuvant treatment was rare during the study period, and these cases consequently did not significantly affect the final results. We decided to include cN2 cases to assess the probability of the cN2-pNx phenomenon, which is very rare but possible. Additionally, the study period included the times of PET-CT implementation in lung cancer diagnostics in Poland.

In summary, the survival of pNx patients is similar to that of pN1 patients, rather than pN0 Also, pNx status is an independent risk factor of worse prognosis. Therefore, the resection of lymph nodes in lung cancer remains a crucial step in the surgical treatment of NSCLC. pNx overall survival rate and survival curve placement depends on the other variables that could be useful in clinical decisions. Uniform procedures of lymph node resection reports and tight cooperation between thoracic surgeons and pathologists are needed to improve the quality of lymphadenectomy in lung cancer.

Funding

None declared.

Author contributions

Marcin M. Cackowski: Investigation; Methodology; Writing—original draft; Writing—review&editing. **Grzegorz M. Gryszko:** Investigation; Writing—review&editing. **Marcin Zbytniewski:** Investigation; Writing—review&editing. **Michał Dziedzic:** Investigation; Writing—review&editing **Katarzyna Woźnica:** Data curation; Formal analysis; Visualization. **Tadeusz M. Orłowski:** Supervision; Writing—review&editing. **Dariusz A. Dziedzic:** Conceptualization; Methodology; Writing—original draft.

Data availability statement

The data will be shared on request to the corresponding author.

Declaration of competing interest

None declared.

Acknowledgements

Principal investigators of PLCSG: P.Gabryel (Poznan University of Medical Sciences), P.Rudzinski (National Research Institute of Chest Diseases, Warsaw), R.Wlodarczyk (National Cancer Center, Warsaw), W. Laudanski (Bialystok University of Medical Sciences), T.Marjanski (Medical University of Gdansk), K.Buczynski (Lublin University of Medical Science) K.Pawelczyk (Lower Silesia Center of Lung Diseases, Wroclaw), R.Lewandowski (Zabrze Medical University of Silesia), M. Wawrzycki (Lodz University of Medical Science), j A.Bala (Department of Thoracic Surgery, Bydgoszcz), K.Brulinski (Center of Pulmonology and Thoracic Surgery, Bystra Slaska), A.Gebski (Department of Thoracic Surgery, Czerwona Gora), P.Talar (Krakow University of Medical Sciences), M.Lochowski(Department of Thoracic Surgery, Lodz), J.Golota (Olsztyn University of Medical Science), A.Zel (Center of Lung Diseases, Otwock), D.Preis (Department of Thoracic Surgery, Prabuty), K.Wojtun, J.Rybka, A.Lis, G.Kobak (Center of Lung Diseases, Rzeszow), M.Bielewicz (Szczecin University of Medical Sciences), Pawel P.Pryszczek (Department of Thoracic Surgery, Zielona Gora), M.Wilkojc (Department of Thoracic Surgery, Zakopane), M.Bella (Bydgoszcz University of Medical Sciences), M.Chabowski (Military Clinical Hospital with Polyclinic, Wroclaw), J.Nogaj (Kielce University of Medical Science).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2023.101941.

References

[1] J.A. Didkowska, U. Wojciechowska, I. Michałek, F. Caetano dos Santos, P. Olasek, Cancer in Poland in 2019, Centrum Onkologii-Instytut im, Marii Skłodowskiej-Curie., Warsaw, 2021.

[2] J.A. Didkowska, U. Wojciechowska, A. Śliwczyński, Raport dotyczący stopni zaawansowania, leczenia oraz przeżyć chorych na raka płuca zgłoszonych do KRN w latach 2014-2016, Centrum Onkologii-Instytut im, Marii Skłodowskiej-Curie, Warsaw, 2019.

[3] M. Krzakowski, J. Jassem, A. Antczak, K. Błasińska, J. Chorostowska-Wynimko, R. Dziadziuszko, M. Głogowski, T. Grodzki, D. Kowalski, R. Kreńke, R. Langfort, W. Olszewski, T. Orłowski, P. Śliwiński, A. Tysarowski, W. Rzyman, M. Woźniewski, Thoracic neoplasms, Oncol. Clin. Pract. 18 (1) (2022) 1–39.

[4] J. Brierley, M.K. Gospodarowicz, C. Wittekind, TNM Classification of Malignant Tumours, eighth ed., John Wiley & Sons, Inc, Oxford, UK; Hoboken, NJ, 2017.

[5] H. Asamura, K. Chansky, J. Crowley, P. Goldstraw, V.W. Rusch, J.F. Vansteenkiste, H. Watanabe, Y.L. Wu, M. Zielinski, D. Ball, R. Rami-Porta, S. International Association for the Study of Lung Cancer, A.B.M, Prognostic factors committee, I. Participating, the international association for the study of lung cancer lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer, J. Thorac. Oncol. 10 (12) (2015) 1675–1684.

[6] K. Pawelczyk, P. Blasiak, M. Szromek, K. Nowinska, M. Marciniak, Assessment of adequacy of intraoperative nodal staging and factors influencing the lack of its compliance with recommendations in the surgical treatment of non-small cell lung cancer (NSCLC), J. Thorac. Dis. 10 (8) (2018) 4902–4911.

[7] R.U. Osarogiagbon, X. Yu, Nonexamination of lymph nodes and survival after resection of non-small cell lung cancer, Ann. Thorac. Surg. 96 (4) (2013) 1178–1189.

[8] R.U. Osarogiagbon, J.W. Allen, A. Farooq, A. Berry, D. Spencer, T. O'Brien, Outcome of surgical resection for pathologic N0 and Nx non-small cell lung cancer, J. Thorac. Oncol. 5 (2) (2010) 191–196.

[9] R.U. Osarogiagbon, J.W. Allen, A. Farooq, J.T. Wu, Objective review of mediastinal lymph node examination in a lung cancer resection cohort, J. Thorac. Oncol. 7 (2) (2012) 390–396.

[10] P. Rudziński, T.M. Orłowski, R. Langfort, Krajowy Rejestr Raka Płuca, Polish J. Pathol. 1 (Suplement 1) (2010) S80–S84.

[11] S. Burdett, J.P. Pignon, J. Tierney, H. Tribodet, L. Stewart, C. Le Pechoux, A. Aupérin, T. Le Chevalier, R.J. Stephens, R. Arriagada, et al., Adjuvant chemotherapy for resected early-stage non-small cell lung cancer, Cochrane Database Syst. Rev. 3 (2015).

[12] L.L. Wu, J.J. Lai, X. Liu, Y.Y. Huang, P. Lin, H. Long, L.J. Zhang, G.W. Ma, Association between number of dissected lymph nodes and survival in stage IA non-small cell lung cancer: a propensity score matching analysis, World J. Surg. Oncol. 18 (1) (2020) 322.

[13] D. Lardinois, P. De Leyn, P. Van Schil, R.R. Porta, D. Waller, B. Passlick, M. Zielinski, T. Lerut, W. Weder, ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer, Eur. J. Cardio. Thorac. Surg. 30 (5) (2006) 787–792.

[14] M.S. Ludwig, M. Goodman, D.L. Miller, P.A. Johnstone, Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer, Chest 128 (3) (2005) 1545–1550.

[15] R.U. Osarogiagbon, J.W. Allen, A. Farooq, A. Berry, T. O'Brien, Pathologic lymph node staging practice and stage-predicted survival after resection of lung cancer, Ann. Thorac. Surg. 91 (5) (2011) 1486–1492.

[16] V.W. Rusch, H. Asamura, H. Watanabe, D.J. Giroux, R. Rami-Porta, P. Goldstraw, I. S.C. Members of, The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer, J. Thorac. Oncol. 4 (5) (2009) 568–577.

[17] G.E. Darling, M.S. Allen, P.A. Decker, K. Ballman, R.A. Malthaner, R.I. Inculet, D. R. Jones, R.J. McKenna, R.J. Landreneau, V.W. Rusch, J.B. Putnam Jr., Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial, J. Thorac. Cardiovasc. Surg. 141 (3) (2011) 662–670.

[18] S.M. Keller, S. Adak, H. Wagner, D.H. Johnson, Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group, Ann. Thorac. Surg. 70 (2) (2000) 358–365. ; discussion 365-6.

[19] H. Adachi, K. Sakamaki, T. Nishii, T. Yamamoto, T. Nagashima, Y. Ishikawa, K. Ando, K. Yamanaka, K. Watanabe, Y. Kumakiri, M. Tsuboi, T. Maehara, H. Nakayama, M. Masuda, Lobe-specific lymph node dissection as a standard procedure in surgery for non-small cell lung cancer: a propensity score matching study, J. Thorac. Oncol. 12 (1) (2017) 85–93.

[20] D. Lardinois, H. Suter, H. Hakki, V. Rousson, D. Betticher, H.B. Ris, Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer, Ann. Thorac. Surg. 80 (1) (2005) 268–274. ; discussion 274-5.

[21] K. Sugi, K. Nawata, N. Fujita, K. Ueda, T. Tanaka, T. Matsuoka, Y. Kaneda, K. Esato, Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter, World J. Surg. 22 (3) (1998) 290–294. ; discussion 294-5.

[22] A.N. Graham, K.J. Chan, U. Pastorino, P. Goldstraw, Systematic nodal dissection in the intrathoracic staging of patients with non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 117 (2) (1999) 246–251.

[23] J.R. Jarabo Sarceda, S. Bolufer Nadal, R. Mongil Poce, P. López de Castro, R. Moreno Balsalobre, J.C. Peñalver Cuesta, R. Embún Flor, J. Pac Ferrer, F.J. Algar Algar, A.P. Gámez García, M.F. Jiménez, J.G. Sales-Badía, E. Pereira, B. Massuti, M. Provencio, F. Hernando Trancho, Spanish Lung Cancer Group SCAT trial: surgical audit to lymph node assessment based on IASLC recommendations, Transl. Lung Cancer Res. 10 (4) (2021) 1761–1772.

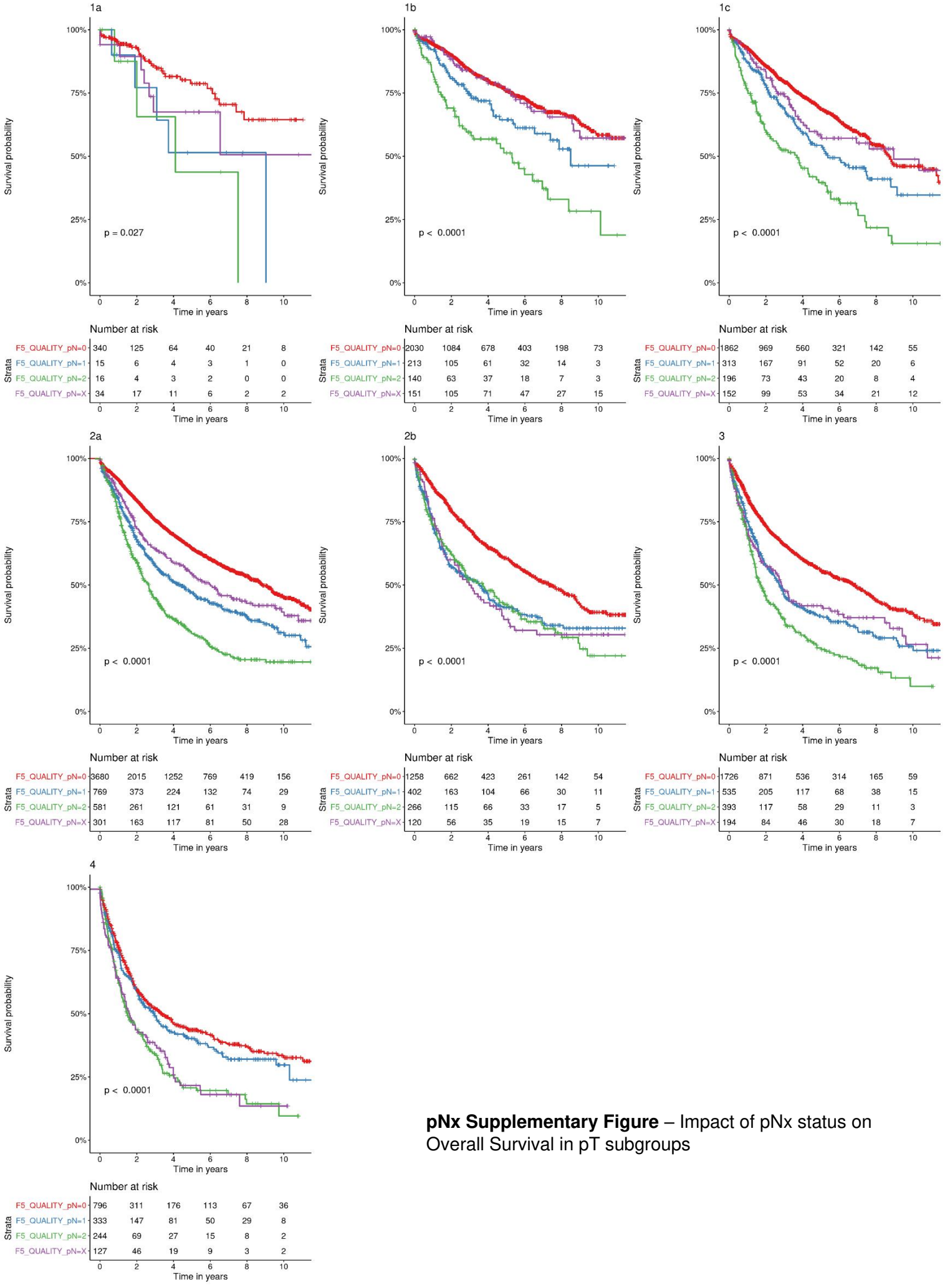
[24] A.G. Little, V.W. Rusch, J.A. Bonner, L.E. Gaspar, M.R. Green, W.R. Webb, A. K. Stewart, Patterns of surgical care of lung cancer patients, Ann. Thorac. Surg. 80 (6) (2005) 2051–2056. ; discussion 2056.

[25] G. Casali, G. Lock, N.M. Novoa, Teaching non-technical skills: the patient centered approach, J. Thorac. Dis. 13 (3) (2021) 2044–2053.

[26] T. Edwards, H. Balata, M. Elshafi, P. Foden, P. Bishop, E. Fontaine, M. Jones, P. Krysiak, K. Rammohan, R. Shah, P. Crosbie, R. Booton, M. Evison, Adequacy of intraoperative nodal staging during surgical resection of NSCLC: influencing factors and its relationship to survival, J. Thorac. Oncol. 12 (12) (2017) 1845–1850.

[27] K.Y. Bilimoria, M.S. Talamonti, J.D. Wayne, J.S. Tomlinson, A.K. Stewart, D. P. Winchester, C.Y. Ko, D.J. Bentrem, Effect of hospital type and volume on lymph node evaluation for gastric and pancreatic cancer, Arch. Surg. 143 (7) (2008) 671–678. ; discussion 678.

[28] D.A. Dziedzic, M. Zbytniewski, G.M. Gryszko, M.M. Cackowski, R. Langfort, T. M. Orlowski, Video-assisted versus open thoracotomy lobectomy: comparison on lymphadenectomy and survival in early stage of lung cancer, J. Thorac. Dis. 13 (1) (2021) 101–112.



pNx Supplementary Figure – Impact of pNx status on Overall Survival in pT subgroups

pT	Group 1	Group 2	p value
1a	1	0	0.15
	2	0	0.12
	2	1	0.57
	X	0	0.26
	X	1	0.57
	X	2	0.57
1b	1	0	0.004
	2	0	≤0.001
	2	1	0.005
	X	0	0.76
	X	1	0.077
	X	2	≤0.001
1c	1	0	≤0.001
	2	0	≤0.001
	2	1	≤0.001
	X	0	0.28
	X	1	0.16
	X	2	≤0.001
2a	1	0	≤0.001
	2	0	≤0.001
	2	1	≤0.001
	X	0	≤0.001
	X	1	0.049
	X	2	≤0.001
2b	1	0	≤0.001
	2	0	≤0.001
	2	1	0.95
	X	0	≤0.001
	X	1	0.95
	X	2	0.95
3	1	0	≤0.001
	2	0	≤0.001
	2	1	≤0.001
	X	0	≤0.001
	X	1	0.86
	X	2	0.004
4	1	0	0.27
	2	0	≤0.001
	2	1	≤0.001
	X	0	≤0.001
	X	1	0.002
	X	2	0.9

Supplementary Table. Pairwise comparison of subgroup survivals concerning pT.

Dyskusja

Limfadenektomia w leczeniu operacyjnym niedrobnokomórkowego raka płuca pozostaje jednym z najbardziej istotnych etapów leczenia operacyjnego, ale jednocześnie najbardziej kontrowersyjnym. Przełożyło się to na duże zainteresowanie środowiska naukowego dotyczące tego zagadnienia, w tym również nasze. W pracach uwzględnionych w niniejszej pracy doktorskiej jedynie częściowo przeanalizowaliśmy ten temat. Poza tym w poprzednich pracach naszego zespołu naukowego badaliśmy także inne aspekty limfadenektomii w raku płuca tj. klasyfikację zaproponowaną przez Asamurę i wsp. jako potencjalnego następcę TNM, analizę wpływu resekcji węzła 4L, porównanie VATS kontra torakotomia uwzględniając liczbę pobranych węzłów chłonnych [21, 42, 43]. Wyniki pracy dotyczącej resekcji węzła 4L w lewostronnym raku płuca były niemal tożsame z wynikami pracy o resekcji węzła 3a po stronie prawej. Dostęp mało inwazyjny VATS wiązał się ze znamiennie mniejszą liczbą pobranych węzłów chłonnych w porównaniu do torakotomii. Mimo tego, przeżywalność grupy VATS była znamiennie lepsza niż grupy po torakotomii. Natomiast klasyfikacja Asamury i wsp. wydaje się lepiej stratyfikować pacjentów w grupy prognostyczne. Jednocześnie ze względu na jej złożoność, liczba pobranych węzłów chłonnych ma duży wpływ na jej dokładność. Niemniej to nadal nie uwzględnia całego zbioru różnych kontrowersji i problemów dotyczących węzłów chłonnych w raku płuca. Badacze w swoich pracach analizują przeróżne aspekty: zjawisko „przeskakujących" węzłów chłonnych (skip metastasis), mikroprzerzuty, przedoperacyjnie niewykryte przerzuty pN2 [9, 12, 44]. Biorąc pod uwagę typowy spływ chłonki z płuc, przerzut do grupy N2 powinien również oznaczać przerzut do węzła grupy N1. Jednak nierzadko przerzut nowotworowy omija węzły grupy N1 i trafia bezpośrednio do węzłów grupy N2. Teoretycznie zarówno przypadki z przeskakującym przerzutem, jak i z klasycznymi przerzutami powinny rokować tak samo, bo należą do tej samej grupy prognostycznej N2. Jednak pacjenci ze zjawiskiem skip metastasis rokują znamiennie lepiej. Mikroprzerzuty (zdefiniowane jako <2mm) w węzłach chłonnych grupy N2 również przekładają się na lepsze rokowanie niż przerzuty większe. Brak jakichkolwiek przedoperacyjnych podejrzeń i zmian sugerujących przerzuty w grupie N2 nie wyklucza obecności tych przerzutów w materiale pooperacyjnym. To również nie wyczerpuje całkowicie tematu kontrowersji i nietypowych zjawisk w limfadenektomii w raku płuca.

Takie zjawiska powodują, że grupy chorych w poszczególnych cechach N z klasyfikacji TNM, są heterogenne. Przykładowo chory z cechą pN0, któremu pobrano 1 węzeł chłonny, a chory któremu pobrano takich węzłów 10 to zupełnie dwie różne grupy pod względem przeżywalności, doszczętności leczenia i precyzyjności stagingu. W przypadku tego

pierwszego istnieje dużo większe ryzyko, że chory jest niedodiagnozowany pod względem stopnia zaawansowania z powodu niedostatecznej limfadenektomii, co może pogorszyć rokowanie z powodu nieusunięcia komórek nowotworowych z węzłów chłonnych i nieotrzymania adjuwantowej chemioterapii. Niewątpliwie dotychczasowa cecha N pozwala w prosty sposób stratyfikować chorych i decydować o dalszym postępowaniu. Szczególnie jest to istotne przy klasyfikacji przedoperacyjnej (cN), gdzie dane o pacjencie są mniej pełne niż po operacji. Warto zauważyć, że w niektórych nowotworach staging przedoperacyjny jest oparty na innych kryteriach niż staging pooperacyjny. Przykładowo w raku piersi staging przedoperacyjny węzłów chłonnych oparty jest na lokalizacji i charakterystyce. Natomiast staging pooperacyjny zależy między innymi od liczby przerzutowych węzłów chłonnych [8]. Być może w przyszłości do takiego rozróżnienia dojdzie w stagingu raku płuca. Istotne również jest to, że większość prac naukowych i analiz opiera się na raportach operacyjnych lub patologicznych, więc wyniki i wnioski są adekwatne w stosunku do cechy pN, a niekoniecznie do cechy cN.

Jednym z najbardziej elementarnych zagadnień w limfadenektomi w leczeniu operacyjnym raka płuca jest zakres minimalnej resekcji węzłów chłonnych. Międzynarodowe towarzystwa naukowe takie jak European Society of Thoracic Surgeons oraz National Comprehensive Cancer Network zalecają pobranie co najmniej 6 stacji węzłów chłonnych (3 stacje z grupy N1 i 3 stacje z grupy N2)[45, 46]. Minimalny zakres resekcji węzłów chłonnych jest elementem, który przewija się przez wszystkie publikacje uwzględnione w niniejszej pracy. W przypadku manuskryptu o alternatywnych metodach klasyfikacji węzłów chłonnych, im bardziej złożony system klasyfikacji tym większy wpływ liczby pobranych węzłów chłonnych na funkcjonowanie danej klasyfikacji. Sama liczba pobranych węzłów chłonnych jest istotnym czynnikiem prognostycznym. W przypadku pracy o pobieraniu przednaczyniowej stacji węzłów chłonnych (3a), jest to jedna z metod zwiększenia jakości limfadenektomii i liczby pobranych węzłów chłonnych, szczególnie w bardziej zaawansowanych przypadkach raka płuca. Natomiast praca o zupełnym braku pobrania węzłów chłonnych (pNx) przedstawia ekstremum nieadekwatnej limfadenektomii w raku płuca. Nieadekwatna limfadenektomia nie jest zerojedynkowa, ale jest pewnego rodzaju spektrum. Jak wcześniej wspomnieliśmy międzynarodowe towarzystwa wyznaczyły liczbę 6 stacji węzłów chłonnych [32, 45]. Ludwig i wsp. w swojej pracy wykazali, że przeżywalność pacjentów rośnie aż do wartości 16 pobranych węzłów chłonnych. W innych pracach wartości te były jeszcze większe. Z drugiej strony istnieją głosy i dane stwierdzające, że liczba węzłów chłonnych jest zmienna osobniczo, zgodna z rozkładem normalnym Gaussa [33, 34].

Analiza alternatywnych metod klasyfikacji węzłów chłonnych wskazuje, że aspekt ilościowy cechy N powinien zostać uwzględniony w przyszłych edycjach klasyfikacji TNM. Nawet samo

IASLC w dwóch ostatnich analizach w ramach tzw. Lung Cancer Staging Project zasugerowało i zbadało wprowadzenie aspektu ilościowego w nowych wersjach tej klasyfikacji. Ostatecznie takich zmian nie dokonano ze względu na brak wystarczających danych i konieczność dalszych badań. W 2007 roku IASLC zasugerowało wprowadzenie liczby stref (ang. zone) węzłów chłonnych, a w 2015 roku liczbę stacji węzłów chłonnych z uwzględnieniem zjawiska przeskakujących przerzutów (ang. skip-metastasis). W literaturze można znaleźć dużo więcej przykładów – liczba przerzutowych węzłów chłonnych, stosunek węzłów chłonnych przerzutowych do nieprzerzutowych, modyfikacja tego stosunku za pomocą logarytmu, łańcuchy węzłowe (ang. nodal chain) itp. Warto wspomnieć, że cecha N raka innego narządu klatki piersiowej – przełyku – jest oparta na liczbie pozytywnych węzłów chłonnych [8]. Mnogość tych klasyfikacji, retrospektywny charakter prac, niedostateczna ilość danych sprawiają, że ustalenia docelowej klasyfikacji ilościowej będzie wymagało dużych prospektywnych badań.

Węzeł chłonny przednaczyniowy (3a) jest stosunkowo rzadko pobieranym węzłem chłonnym śródpiersia (3,5% chorych operowanych z prawostronnym rakiem płuca). Zazwyczaj nie jest rutynowo pobierany podczas operacji. Domniemywamy, że torakochirurdzy pobierają je z dwóch głównych powodów – wzbudzają zainteresowanie operatora podczas operacji lub wynika to z preferencji i techniki operacyjnej danego operatora. Z drugiej strony ich lokalizacja i sąsiedztwo z żyłą główną górną i nerwem przeponowym może zniechęcać niektórych ze względu na potencjalne powikłania. Mimo braku wpływu resekcji węzłów 3a na ogólną przeżywalność wśród chorych leczonych operacyjnie na raka płuca, częstość przerzutów do tej stacji węzłów chłonnych jest porównywalna do częstości przerzutów do innych, bardziej rutynowych stacji węzłów chłonnych śródpiersia. Aż 8% pobranych węzłów ze stacji 3a było z przerzutami nowotworu, a w przypadku rutynowo pobieranych węzłów z stacji grupy 7 i 4R było to odpowiednio 7% i 10% Częstość tych przerzutów rośnie wraz ze wzrostem stopnia zaawansowania nowotworu. Przykładowo między pT1c a pT2a nastąpił wzrost z 4% do 9%, a w przypadku podgrupy pT4 częstość przerzutów wśród pobranych węzłów chłonnych wynosiła aż 15%. Lokalizacja guza w płacie dolnym nie wyklucza przerzutu do tej stacji. Częstość przerzutów nie różniła się istotnie statystycznie między lobektomią górną a dolną. Natomiast znacząco rzadziej węzły grupy 3a były pobierane w przypadku dolnych lobektomii. Z tych powodów ta stacja węzłów chłonnych powinna wzbudzić zainteresowanie wszystkich operatorów. Ponadto pobranie dodatkowej stacji węzłów chłonnych śródpiersia może być jedną z metod zwiększenia jakości limfadenektomii w raku płuca.

Zjawisko całkowitego braku pobrania węzłów chłonnych śródpiersia to przykład skrajnej nieadekwatnej limfadenektomii w leczeniu operacyjnym raka płuca. W naszej pracy do takiego zjawiska doszło w 6% przypadków. Wydaje się to być dużo, jednak na tle innych prac

dotyczących tego zagadnienia jest to relatywnie niska wartość. W dużym uproszczeniu w takich przypadkach musiało dojść do dwóch wydarzeń. Po pierwsze chirurg nie pobrał lub nie znalazł żadnego węzła chłonnego śródpiersia i wnęki płuca oraz patomorfolog nie pobrał lub nie znalazł żadnego węzła chłonnego wewnątrz miąższu płuca. Szczególnie zaskakujące jest to, że patolodzy nie znaleźli tych węzłów w materiale po pneumonektomii, a przypadków pNx było nawet więcej w tej grupie (8,1%). Pięcioletnie ogólne przeżycia chorych z pNx nie są tak dobre jak przypadki pN0 jak miałoby to wynikać z klasyfikacji TNM (50%). Przeżycia są gorsze niż pN0 (64%) i bardziej zbliżone do pN1 (45%). Wszystkie przeżycia cech pN (w tym pNx) istotnie statycznie się od siebie różniły. Co ciekawe i nowe w naszej pracy, różne czynniki pogarszające rokowanie przesuwają krzywą przeżycia pNx w stronę pN1, a nawet pN2. Torakotomia, rak płaskonabłonkowy, wyższe stadia pT sprawiają że pacjenci ze zjawiskiem pNx rokują dużo gorzej niż odpowiednio podgrupy z VATS, rakiem gruczołowym czy niższymi stadiami pT. W codziennej praktyce uwzględniając takie czynniki można by przypuszczalnie oszacować rzeczywisty status pN i zaplanować dalsze leczenie. Przykładowo w przypadku cechy pT1b przeżywalność dla pNx wynosiła 76% i nie różniła się istotnie statystycznie od pN0 (76%, p = 0,76). Natomiast w przypadku cechy pT4 przeżywalność dla pNx wynosiła 22% i nie różniła się istotnie statystycznie od pN2 (21%, p = 0,9). W analizie wieloczynnikowej zjawisko pNx było niezależnym czynnikiem prognostycznym co stanowi o jego istotności klinicznej (HR = 1.37, 95%CI: 1.23–1.51, p < 0.01).

Głównym ograniczeniem pracy poglądowej o alternatywnych metodach klasyfikacji węzłów chłonnych w raku płuca jest metodologia omawianych prac. Większość z nich było pracami retrospektywnymi. Różne prace dotyczące tych samych metod klasyfikacji używały różnych wartości punktów odcięcia i poszczególnych podgrup, co sprawia, że ich porównywanie jest nieadekwatne. Ponadto dokonaliśmy jedynie analizy jakościowej bez analizy ilościowej prac zawartych w pracy poglądowej.

W przypadku pracy o węzłach chłonnych grupy 3A największym ograniczeniem pracy jest jej retrospektywny charakter. Z tego powodu zdecydowaliśmy o użyciu tzw. Propensity Score Matching, by zwiększyć jakość i istotność statystyczną pracy. Ze względu na rzadkość pobierania węzłów chłonnych tej grupy kolejnym ograniczeniem jest liczebność analizowanej grupy. Fakt, że mimo tego częstość przerzutów w tych węzłach jest stosunkowa duża, może sugerować, że śródoperacyjne znaleziska wpłynęły na decyzję torakochirurga. W takich przypadkach mogło dojść do stronniczości selekcji. Uwzględniony w pracy zakres lat przypadków przypada na proces wprowadzania badań PET-CT do Polski. Początkowo nie były one dostępne, natomiast pod koniec tego okresu były niemal powszechne. Dodatkowo uwzględnione lata nie umożliwiały analizy podtypów genetycznych nowotworów. Dane w bazie danych nie umożliwiają przeprowadzenia innych analiz długofalowych przeżycia niż przeżycia

ogólne (np. przeżycia wolnego od wznowy). W końcu brak informacji o dalszym leczeniu w ośrodkach onkologicznych. Ze względów organizacyjnych w Polsce leczenie onkologiczne chorych na raka płuca odbywa się głównie poza jednostkami z oddziałami chirurgii klatki piersiowej. Te podmioty nie biorą aktywnego udziału w bazie danych Polskiej Grupy Raka Płuca, przez co wiele informacji nie dociera do wspomnianej bazy danych.

W przypadku pracy o zjawisku pNx istnieje wiele jej ograniczeń, które są podobne do tych z pracy o węzłach 3a. Retrospektywny charakter pracy, uwzględnione czasy wprowadzania PET-CT w Polsce, brak informacji dotyczących genetyki raka, brak innych analiz przeżycia, czy też brak danych z ośrodków onkologicznych to wspólne ograniczenia tych dwóch prac.

Podsumowanie i wnioski

W niniejszej dysertacji doktorskiej wykazano, że limfadenektomia w leczeniu operacyjnym raka płuca pozostaje jednym z najważniejszych elementów leczenia. Jakość limfadenektomii bezpośrednio wpływa na wyniki leczenia. Jednocześnie istnieje wiele kontrowersji, problemów i zagadnień, które wymagają dalszych badań i opracowania. Istniejące klasyfikacje nie są dokładne i prawdopodobnie będą wymagały zmian. W niniejszej dysertacji przedstawiono następujące szczegółowe wnioski:

- Aktualna cecha N w klasyfikacji TNM nie jest dokładna i prawdopodobnie będzie w przyszłości zmieniona
- Istnieje wiele alternatywnych metod klasyfikacji węzłów chłonnych. Szczególnie te uwzględniające aspekt ilościowy wydają się istotne.
- Resekcja węzła przednaczyniowego 3a nie ma wpływu na ogólną przeżywalność
- Niemniej częstość przerzutów do tej stacji węzłów chłonnych jest porównywalna do innych bardziej rutynowych stacji oraz rośnie wraz z zaawansowaniem pT.
- Zjawisko pNx świadczy o gorszym rokowaniu, bardziej zbliżonym do cechy pN1 niż pN0
- Inne czynniki takie jak cecha pT, dostęp operacyjny oraz histologia raka wpływają na umiejscowienie krzywej przeżywalności pNx, co pozwala na oszacowanie rzeczywistego rokowania u pacjentów z cechą pNx.

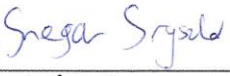
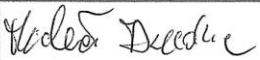
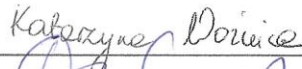
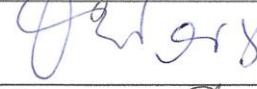
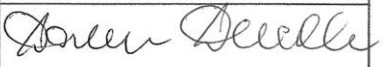
Oświadczenia współautorów publikacji

Warszawa 27.04.2023

Oświadczenie współautorów publikacji

Niniejszym oświadczamy następujący procentowy wkład autorski w publikację:

Cackowski, M. M., Zbytniewski, M., Gryszko, G. M., Dziedzic, M., Woźnica, K., Orłowski, T. M., & Dziedzic, D. A. (2022). Effect of 3A lymph node resection on survival in patients with right-sided NSCLC: a retrospective, multicentre, propensity-score matching study. Journal of thoracic disease, 14(9), 3265–3276. https://doi.org/10.21037/jtd-21-1957

Imię i nazwisko współautora	Procentowy wkład autorski	Podpis współautora
Marcin Cackowski	55	
Marcin Zbytniewski	5	
Grzegorz Gryszko	5	
Michał Dziedzic	5	
Katarzyna Woźnica	10	
prof. Tadeusz. M. Orłowski	10	
dr hab. Dariusz Dziedzic	10	

Warszawa 27.04.2023

Oświadczenie współautorów publikacji

Niniejszym oświadczamy następujący procentowy wkład autorski w publikację:

Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, M., Woźnica, K., Orłowski, T. M., Dziedzic, D. A., & Polish Lung Cancer Study Group (PLCSG) (2023). The absence of lymph nodes removed (pNx status) impacts survival in patients with lung cancer treated surgically. Surgical oncology, 48, 101941. Advance online publication. https://doi.org/10.1016/j.suronc.2023.101941

Imię i nazwisko współautora	Procentowy wkład autorski	Podpis współautora
Marcin Cackowski	55	
Grzegorz Gryszko	5	
Marcin Zbytniewski	5	
Michał Dziedzic	5	
Katarzyna Woźnica	10	
prof. Tadeusz. M. Orłowski	10	
dr hab. Dariusz Dziedzic	10	

Warszawa 27.04.2023

Oświadczenie współautorów publikacji

Niniejszym oświadczamy następujący procentowy wkład autorski w publikację:

Cackowski, M. M., Gryszko, G. M., Zbytniewski, M., Dziedzic, D. A., & Orłowski, T. M. (2020). Alternative methods of lymph node staging in lung cancer: a narrative review. Journal of thoracic disease, 12(10), 6042–6053. https://doi.org/10.21037/jtd-20-1997

Imię i nazwisko współautora	Procentowy wkład autorski	Podpis współautora
Marcin Cackowski	60	
Grzegorz Gryszko	10	
Marcin Zbytniewski	10	
dr hab. Dariusz Dziedzic	10	
prof. Tadeusz. M. Orłowski	10	

Bibliografia

[1] Didkowska J, Wojciechowska U, Olasek P, Caetano dos Santos F, Michałek I. *Nowotwory złośliwe w Polsce w 2019 roku*. Krajowy Rejestr Nowotworów, Centrum Onkologii-Instytut 2021.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*. CA Cancer J Clin 2021;**71**:209-49.

[3] O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. *Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis*. BMJ Open 2018;**8**:e021611.

[4] Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ *et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors*. Clin Cancer Res 2009;**15**:5626-45.

[5] Główny Inspektorat Sanitarny. *Postawy Polaków wobec palenia tytoniu – Raport 2019 r.* https://www.gov.pl/web/gis/postawy-polakow-wobec-palenia-tytoniu--raport-2017 (19.11 2022, date last accessed).

[6] Koshiaris C, Aveyard P, Oke J, Ryan R, Szatkowski L, Stevens R *et al. Smoking cessation and survival in lung, upper aero-digestive tract and bladder cancer: cohort study*. Br J Cancer 2017;**117**:1224-32.

[7] Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM *et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis*. Environ Health Perspect 2014;**122**:906-11.

[8] Brierley J, Gospodarowicz MK, Wittekind C, O'Sullivan B, Mason MD, Asamura H *et al. TNM classification of malignant tumours*. Oxford: Wiley Blackwell, 2017.

[9] Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF *et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer*. J Thorac Oncol 2015;**10**:1675-84.

[10] Wang X, Guo H, Hu Q, Ying Y, Chen B. *The Impact of Skip vs. Non-Skip N2 Lymph Node Metastasis on the Prognosis of Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis*. Front Surg 2021;**8**:749156.

[11] Hüyük M, Fiocco M, Postmus PE, Cohen D, von der Thüsen JH. *A systematic review and meta-analysis of the prognostic impact of lymph node micrometastasis and isolated tumor cells in patients with stage I-IIIA non-small cell lung cancer*. Histopathology 2022.

[12] Bille A, Woo KM, Ahmad U, Rizk NP, Jones DR. *Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients*. Eur J Cardiothorac Surg 2017;**51**:674-79.

[13] Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M *et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer*. J Thorac Oncol 2007;**2**:603-12.

[14] Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. *Lung cancer*. Lancet 2021;**398**:535-54.

[15] Krzakowski M, Jassem J, Antczak A, Błasińska K, Chorostowska-Wynimko J, Dziadziuszko R *et al. Thoracic neoplasms*. Oncology in Clinical Practice 2022;**18**:1-39.

[16] Didkowska J, Wojciechowska U, Śliwczyński A. *Raport dotyczący stopni zaawansowania, leczenia oraz przeżyć chorych na raka płuca zgłoszonych do KRN w latach 2014-2016*. Krajowy Rejestr Nowotworów, Centrum Onkologii-Instytut 2019.

[17] Noone A, Howlader N, Krapcho M, Miller D, Brest A, Yu M *et al. SEER Cancer Statistics Review, 1975-2015*. National Cancer Institute Bethesda, MD 2018.

[18] Torre LA, Siegel RL, Jemal A. *Lung Cancer Statistics*. Adv Exp Med Biol 2016;**893**:1-19.

[19] Leduc C, Antoni D, Charloux A, Falcoz PE, Quoix E. *Comorbidities in the management of patients with lung cancer*. Eur Respir J 2017;**49**.

[20] Kim D, Kim SY, Suh B, Park JH. *Trend Analysis for the Choice and Cost of Lung Cancer Treatment in South Korea, 2003-2013*. Cancer Res Treat 2018;**50**:757-67.

[21] Dziedzic DA, Zbytniewski M, Gryszko GM, Cackowski MM, Langfort R, Orlowski TM. *Video-assisted versus open thoracotomy lobectomy: comparison on lymphadenectomy and survival in early stage of lung cancer*. J Thorac Dis 2021;**13**:101-12.

[22] de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA *et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial*. N Engl J Med 2020;**382**:503-13.

[23] Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM *et al. Reduced lung-cancer mortality with low-dose computed tomographic screening*. N Engl J Med 2011;**365**:395-409.

[24] Ministerstwo Zdrowia. *Program profilaktyki raka płuca.* https://pacjent.gov.pl/programy-profilaktyczne/profilaktyka-raka-pluca (20.11 2022, date last accessed).

[25] Rzyman W, Didkowska J, Dziedzic R, Grodzki T, Orłowski T, Szurowska E *et al. Consensus statement on a screening programme for the detection of early lung cancer in Poland*. Adv Respir Med 2018;**86**:53-74.

[26] Manser R, Wright G, Hart D, Byrnes G, Campbell D, Wainer Z *et al. Surgery for local and locally advanced non-small cell lung cancer*. Cochrane Database of Systematic Reviews 2005;**2010**.

[27] Guo F, Ma D, Li S. *Compare the prognosis of Da Vinci robot-assisted thoracic surgery (RATS) with video-assisted thoracic surgery (VATS) for non-small cell lung cancer: A Meta-analysis*. Medicine (Baltimore) 2019;**98**:e17089.

[28] Saji H, Okada M, Tsuboi M, Nakajima R, Suzuki K, Aokage K *et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial*. Lancet 2022;**399**:1607-17.

[29] Altorki N, Wang X, Kozono D, Watt C, Landrenau R, Wigle D *et al. Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer*. N Engl J Med 2023;**388**:489-98.

[30] Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C *et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer*. Cochrane Database of Systematic Reviews 2015.

[31] Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. *The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer*. J Thorac Oncol 2009;**4**:568-77.

[32] Lardinois D, De Leyn P, Van Schil P, Porta RR, Waller D, Passlick B *et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer*. Eur J Cardiothorac Surg 2006;**30**:787-92.

[33] Ludwig MS, Goodman M, Miller DL, Johnstone PA. *Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer*. Chest 2005;**128**:1545-50.

[34] Riquet M, Legras A, Mordant P, Rivera C, Arame A, Gibault L *et al. Number of mediastinal lymph nodes in non-small cell lung cancer: a Gaussian curve, not a prognostic factor*. Ann Thorac Surg 2014;**98**:224-31.

[35] Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI *et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial*. J Thorac Cardiovasc Surg 2011;**141**:662-70.

[36] Keller SM, Adak S, Wagner H, Johnson DH. *Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group*. Ann Thorac Surg 2000;**70**:358-65; discussion 65-6.

[37] Adachi H, Sakamaki K, Nishii T, Yamamoto T, Nagashima T, Ishikawa Y *et al. Lobe-Specific Lymph Node Dissection as a Standard Procedure in Surgery for Non-Small Cell Lung Cancer: A Propensity Score Matching Study*. J Thorac Oncol 2017;**12**:85-93.

[38] Ishiguro F, Matsuo K, Fukui T, Mori S, Hatooka S, Mitsudomi T. *Effect of selective lymph node dissection based on patterns of lobe-specific lymph node metastases on patient outcome in patients with resectable non-small cell lung cancer: a large-scale retrospective cohort study applying a propensity score*. J Thorac Cardiovasc Surg 2010;**139**:1001-6.

[39] Kawakami Y, Takizawa H, Toba H, Kawakita N, Yoshida M, Kondo K *et al. Diversity of lymphatic flow in patients with lung cancer revealed by computed tomography lymphography*. Interact Cardiovasc Thorac Surg 2021;**33**:871-78.

[40] Kim AW. *Lymph node drainage patterns and micrometastasis in lung cancer*. Semin Thorac Cardiovasc Surg 2009;**21**:298-308.

[41] Osarogiagbon RU, Allen JW, Farooq A, Berry A, O'Brien T. *Pathologic lymph node staging practice and stage-predicted survival after resection of lung cancer*. Ann Thorac Surg 2011;**91**:1486-92.

[42] Dziedzic DA, Cackowski MM, Zbytniewski M, Gryszko GM, Woźnica K, Orłowski TM. *The influence of the number of lymph nodes removed on the accuracy of a newly proposed N descriptor classification in patients with surgically-treated lung cancer*. Surg Oncol 2021;**37**:101514.

[43] Gryszko GM, Cackowski MM, Zbytniewski M, Woźnica K, Orłowski TM, Dziedzic DA. *The impact of left lower paratracheal (4L) lymph node dissection on survival in patients with surgically treated left-sided NSCLC*. Eur J Cardiothorac Surg 2021;**60**:1201-09.

[44] Garelli E, Renaud S, Falcoz PE, Weingertner N, Olland A, Santelmo N *et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer*. Eur J Cardiothorac Surg 2016;**50**:322-8.

[45] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A *et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology*. J Natl Compr Canc Netw 2022;**20**:497-530.

[46] De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R *et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer*. Eur J Cardiothorac Surg 2014;**45**:787-98.