Turkish Journal of Thoracic and Cardiovascular Surgery 2023;31(4):530-537

ORIGINAL ARTICLE / ÖZGÜN MAKALE

Prognostic significance of mediastinal standardized uptake value on positron emission tomography/computed tomography in patients with left upper lobe non-small cell lung cancer: Is invasive staging of aortopulmonary window lymph nodes necessary?

Sol üst lob küçük hücreli dışı akciğer kanseri hastalarında pozitron emisyon tomografi/bilgisayarlı tomografide mediastinal standardize tutulum değerinin prognostik önemi: Aortopulmoner pencere lenf nodlarının invaziv evrelemesi gerekli mi?

Volkan Erdoğu[1], Necati Çıtak[2], Nisa Yıldız[1], Mustafa Vedat Doğru[1], Merve Özbek[1], Celal Buğra Sezen[1], Yaşar Sönmezoğlu[1], Özkan Saydam[1], Levent Cansever[1], Muzaffer Metin[1]

Institution where the research was done:
Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Türkiye

Author Affiliations:
[1]Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Türkiye
[2]Department of Thoracic Surgery, Health Sciences University, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Türkiye

ABSTRACT

Background: This study aims to investigate whether the invasive staging of aortopulmonary window lymph nodes could be omitted in the presence of a suspected isolated metastasis in the aortopulmonary window lymph node on positron emission tomography/computed tomography.

Methods: Between January 2010 and January 2016, a total of 67 patients (54 males, 13 females; mean age: 59.9±8.7 years; range, 44 to 76 years) with metastatic left upper lobe tumors to aortopulmonary window lymph nodes were retrospectively analyzed. According to positron emission tomography/computed tomography findings in clinical staging, the patients were classified as positive (+) (n=33) and negative (-) (n=34) groups.

Results: There was a statistically significant difference between the two groups in terms of sex distribution, lymph node diameter on computed tomography, maximum standardized uptake value of aortopulmonary window lymph nodes, and tumor diameter (p<0.001 for all). A trend toward significance was found to be in pT status, LN #6 metastases, and pathological stage between the two groups (p=0.067). The five-year overall survival rate for all patients was 42.4% and there was no significant difference between the groups (p=0.896). The maximum standardized uptake value of the aortopulmonary window lymph nodes was a poor prognostic factor for survival (area under the curve=0.533, 95% confidence interval: 0.407-0.675, p=0.648).

Conclusion: Invasive staging of aortopulmonary window lymph nodes can be omitted in patients with isolated suspected metastasis to aortopulmonary window lymph nodes in non-small cell lung cancer of the left upper lobe.

Keywords: Aortopulmonary window lymph nodes, invasive staging, left upper lobe lung cancer, prognosis.

ÖZ

Amaç: Bu çalışmada pozitron emisyon tomografi/bilgisayarlı tomografide aortopulmoner pencere lenf nodlarında şüpheli izole metastaz varlığında aortopulmoner pencere lenf nodlarının invaziv evrelemesinin göz ardı edilip edilemeyeceği araştırıldı.

Çalışma planı: Ocak 2010 - Ocak 2016 2016 tarihleri arasında, izole olarak aortopulmoner pencere lenf nodlarına metastaz yapan sol üst lob tümörlü toplam 67 hasta (54 erkek, 13 kadın; ort. yaş: 59.9±8.7 yıl; dağılım, 44-76 yıl) retrospektif olarak incelendi. Klinik evrelemede pozitron emisyon tomografi/bilgisayarlı tomografi bulgularına göre hastalar pozitif (+) (n=33) ve negatif (-) (n=34) olarak gruplara ayrıldı.

Bulgular: İki grup arasında cinsiyet dağılımı, bilgisayarlı tomografide lenf nodu çapı, aortopulmoner pencere lenf nodlarının maksimum standardize tutulum değeri ve tümör çapı açısından istatistiksel olarak anlamlı bir fark görüldü (tümü için p<0.001). İki grup arasında pT statüsü, LN #6 metastazları ve patolojik evre açısından anlamlılığa doğru bir eğilim izlendi (p=0.067). Tüm hastalarda beş yıllık genel sağkalım oranı %42.4 olup, gruplar arasında anlamlı bir fark yoktu (p=0.896). Aortopulmoner pencere lenf nodlarının maksimum standardize tutulum değeri, sağkalım açısından kötü bir prognostik faktör idi (eğri altında kalan alan=0.533, %95 güven aralığı: 0.407-0.675, p=0.648).

Sonuç: Sol üst lobun küçük hücreli dışı akciğer kanserinde aortopulmoner pencere lenf nodlarına izole metastaz şüphesi olan hastalarda, aortopulmoner pencere lenf nodlarının invaziv evrelemesi göz ardı edilebilir.

Anahtar sözcükler: Aortopulmoner pencere lenf nodları, invasiv evreleme, sol üst lob akciğer kanseri, prognoz.

Corresponding author: Volkan Erdoğu.
E-mail: verdogu@gmail.com

Doi: 10.5606/tgkdc.dergisi.2023.24627

Received: January 07, 2023
Accepted: April 06, 2023
Published online: October 19, 2023

Cite this article as: Erdoğu V, Çıtak N, Yıldız N, Doğru MV, Özbek M, Sezen CB, et al. Prognostic significance of mediastinal standardized uptake value on positron emission tomography/computed tomography in patients with left upper lobe non-small cell lung cancer: Is invasive staging of aortopulmonary window lymph nodes necessary?. Turk Gogus Kalp Dama 2023;31(4):530-537. doi: 10.5606/tgkdc.dergisi.2023.24627.

One of the most significant survival markers in non-small cell lung cancer (NSCLC) is the nodal status.[1] Nodal spreads vary depending on the localization of the tumor in the lung.[2] The number and type of invasion into mediastinal lymph nodes (LNs) have a crucial prognostic effect on survival.[3] In general, the established treatment strategy in selected clinical (c), single N2/T1-T2, and T3 (non-invasive) cases is neoadjuvant chemotherapy (CTx) or concurrent chemoradiotherapy (CRT), followed by surgery in cases with mediastinal downstage.[4] Since the aortopulmonary window LNs (APW-LNs) exhibit a distinct form of lymphatic drainage, studies have claimed that left upper lobe (LUL) tumors with isolated metastasis to the subaortic (#5) and/or paraaortic (#6) LNs located in the APW have higher survival rates compared to other N2 cases.[5,6] Thoracic computed tomography (CT) and positron emission tomography (PET)/CT may be insufficient for evaluating metastatic LNs in APW, therefore, sampling of this region with invasive methods may be required.[7] Whether these interventions can or cannot change the course of treatment is a controversial issue, as these cases have a better expected prognosis.[7] The group with the best survival rates among N2s is the incidental N2 patient group, whose N2 metastasis cannot be detected in the clinical evaluation, but can be confirmed in the postoperative pathological examination.[8] To the best of our knowledge, there are no studies in the literature regarding whether patients with unexpected N2 LNs show better survival, particularly in LUL tumors with isolated metastasis to APW-LNs.

In the present study, we aimed to evaluate the preoperative clinical stages of NSCLC of the LUL that underwent upfront surgery and had N2 isolated to APW-LNs in the pathological examination. We also aimed to investigate whether the presence or absence of suspected metastases to APW-LNs had an impact on survival using PET/CT results.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery between January 2010 and January 2016. We prospectively collected data of a total of 98 cases diagnosed with NSCLC of the LUL with isolated metastasis to #5 and/or #6 LN(s) which were pathologically proven after surgery. Twelve patients who underwent neoadjuvant therapy for tumor (T) extension or cN2 except for APW-LNs were excluded from the study. Patients with histological subtypes other than adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and large cell carcinoma were also excluded (n=5). Besides, patients with incomplete resections (R1-2) (n=4) and wedge resections (n=6), a case with multiple N2 detected in APW-LNs and subcarinal and/or paratracheal LNs in the pathological examination (n=1), cases with mortality within the first 30 days (n=3) were excluded. In the study design, to maintain the homogeneity of patients, we did not consider patients with isolated metastases to 5-6 station(s) of left lower lobe tumors, as overall survival (OS) may differ in upper lobe tumors.[9] The remaining 67 patients (54 males, 13 females; mean age: 59.9±8.7 years; range, 44 to 76 years) were included.

Patients whose lung capacity and general condition were eligible for resection were operated. In the preoperative period, the mediastinal staging (paratracheal and subcarinal LNs) was routinely performed with endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) and/or cervical mediastinoscopy, except for patients diagnosed with cT1N0M0 squamous cell carcinoma.

On PET/CT, if the maximum standardized uptake value (SUV_{max}) of the APW-LN(s) was above 2.5 and the diameter was greater than 1 cm, then the LN was considered suspicious for metastasis.

The patients with suspected metastases in APW-LNs according to PET/CT findings was named PET-apw (+) group (n=33) in the study, while the patients without suspected metastases in this region was named PET-apw (-) group (n=34).

In our center, although cases with suspected metastasis in APW-LN(s) were sampled with extended cervical mediastinoscopy (ECM) in previous years, there have been some patient-based changes in our general approach over the years while conducting the study.[10] In cases whose paratracheal and subcarinal LNs were reported free of metastasis after cervical mediastinoscopy while having radiological evidence of metastasis in APW-LNs, APW-LNs were not staged as invasive, and upfront surgery was performed. However, in cases with N2 metastasis in APW-LNs in the final pathological examination, we applied adjuvant treatment. In staging with cervical mediastinoscopy, in case of radiological suspicion of metastasis in APW-LNs of those with single station metastasis in frozen-section examination in paratracheal or subcarinal LNs, the aortopulmonary

region was invasively sampled with ECM or video-assisted thoracoscopic surgery (VATS). In case of detection of additional metastasis in APW-LN(s), the patient was considered "multiple N2" and was referred to the Department of Medical Oncology for definitive treatment without considering surgery.

The general approach to surgical intervention was lobar lung resection with complete LN dissection, including mediastinal fat tissue (*en bloc* resection).

All patients who had single or multi-level N2 disease after surgery were referred to adjuvant CTx ± radiation

Table 1. Demographic and clinicopathological characteristics of the patients

	Total (n=67)			PET-APW (-) group (n=34)			PET-APW (+) group (n=33)			
Variables	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59.9±8.7			61.5±9.2			58.2±8.0	0.080
<65	45	67.2		20	58.8		25	75.8		0.140
≥65	22	32.8		14	41.2		8	24.2		
Sex										**0.01**
Male	54	80.6		23	67.6		31	93.9		
Female	13	19.4		11	32.4		2	6.1		
LN diameter in CT			1.1±0.5			0.7±0.3			1.5±0.4	**<0.001**
<1.5	44	65.7		32	94.1		12	36.4		
≥1.5	23	34.3		2	5.9		21	63.6		**<0.001**
SUV_{max} value of APW-LNs			4.3±5.7			0.2±0.6			8.6±5.4	<0.001
Cervical mediastinoscopy	51	76.1		24	70.6		27	81.8		0.281
Resection type										0.109
Lobectomy	41	61.2		24	70.6		20	60.7		
Pneumonectomy	26	38.8		10	29.4		13	39.3		
Tumor diameter			4.9±2.5			4.0±1.9			5.8±2.7	**<0.001**
Histological type										0.686
Adenocarcinoma	26	38.8		14	41.2		12	36.4		
Non-adenocarcinoma	41	61.2		20	58.8		21	63.6		
PL status										0.874
PL0	42	62.7		21	61.8		21	63.6		
PL1/2/3*	25	37.3		13	38.2		12	36.4		
pT status										0.067
T1/T2	36	53.7		22	64.7		14	42.4		
T3/T4	31	46.3		12	35.3		19	57.6		
pN status										0.517
pN2a1	9	13.4		5	14.7		4	12.1		
pN2a2	38	56.7		21	61.8		17	51.5		
pN2b	20	29.9		8	23.5		12	36.4		
pN2 subtype#										
Ln 5+	56	83.6		30	88.2		26	78.8		0.340
Ln 6+	31	46.3		12	35.3		19	57.6		0.067
pStage										0.067
Stage IIIA	36	53.7		22	64.7		14	42.4		
Stage IIIB	31	46.3		12	35.3		19	57.6		

PET: Positron emission tomography; APW: Aortopulmonary window; SD: Standard deviation; CT: Computed tomography; SUV_{max}: Maximum standardized uptake value; LN: Lymph node; p: Pathological; T: Tumor; N: Node; N2a1: Involvement of a single N2 nodal station without N1 involvement (skip metastasis); N2a2: Involvement of a single N2 nodal station with N1 involvement; N2b: Involvement of multiple N2 nodal stations; * 10 patients have PL1, 5 patients have PL2, and 10 patients have PL3; In # 20 patients, both #5 and #6 were positive. Therefore, the total is more than 67; Bold *p*-values show statistical significance. P values in italics indicate a significant trend towards; PL0: No Visceral Pleural inv.; PL1: Penetration beyond the elastic layer of visceral pleura; PL2: Invasion of visceral pleura; PL3: Parietal pleura invasion.

therapy (RT). Platinum-based CTx regimens were administered with a median of four cycles. However, some patients may refuse this treatment or may not be able to finish the procedure properly due to the side effects of the treatment and comorbidities or advanced age. Adjuvant RT was administered only to patients with N2 disease with extracapsular extension.

Clinical follow-ups of the patients were performed every three months for the first two years, every six months up to five years, and annually thereafter. Computed tomography was performed every six months. The PET/CT was performed, when recurrence or metastasis was suspected.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Student t-test was used for the comparisons of the groups. The Pearson chi-square test was used for the analysis of qualitative variables, while the Fisher exact test was used to analyze the sample size. Non-parametric continuous variables were compared using the Mann-Whitney U tests. Survival was estimated using the Kaplan-Meier method compared between the groups with a log-rank analysis. Multivariate survival analyses were performed using a Cox proportional hazards model to examine the association between survival and potential prognostic factors. The optimal cut-off values of the PET/CT SUV_{max} of the APW-LNs for survival in all patients were determined using the highest sensitivity and specificity values, which were calculated in the receiver operating characteristic (ROC) curve analysis. The ROC curves were drawn and the areas under the ROC curves (AUCs) were calculated. The number of days for ROC analysis was defined as the time from surgery until death called combined event (time-dependent ROC analysis). A p value of <0.05 was considered statistically significant.

RESULTS

Demographic and clinicopathological characteristics of the patients are summarized in Table 1. The mean pathological tumor diameter was 4.9±2.3 (range, 1.7 to 13) cm. The mean SUV_{max} for APW-LNs on PET/CT was 4.3±3.7 (range, 0 to 23), while the mean APW-LN size on CT was 1.1±1.2 (range, 0.2 to 3) cm.

There was a statistically significant difference in the sex distribution (p<0.001), LN diameter on CT (p<0.001), APW-LN SUV_{max} (p<0.001), and tumor diameter on PET/CT (p<0.001) between the PET-apw (-) and PET-apw (+) groups. There was also a significant trend toward the differences between the groups in terms of pT status, LN #6 positivity, and pathological stage (p=0.067).

The five-year OS rate for all patients was 42.4% (median: 49.2 months, 95% confidence interval [CI]: 30.4-68.0) (Figure 1). The five-year OS rate in the PET-apw (-) group was 44.1% (median: 39.4 months, 95% CI: 21.5-57.2), while it was 40.0% in the PET-apw (+) group (median: 53.5 months, 95% CI: 30.4-68.0). However, it did not reach statistical significance (p=0.896, hazard ratio [HR]=1.041, 95% CI: 0.564-1.922) (Figure 2).

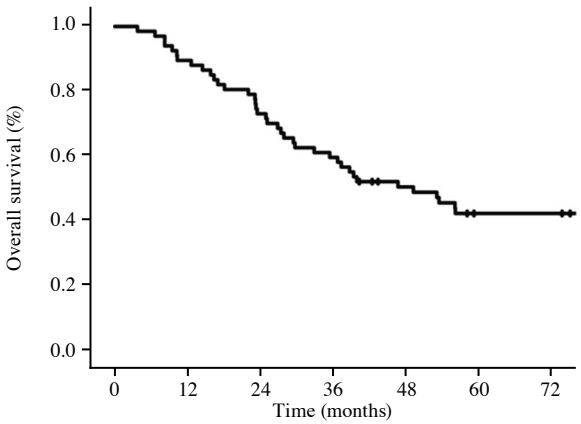

Figure 1. Overall survival of all patients.

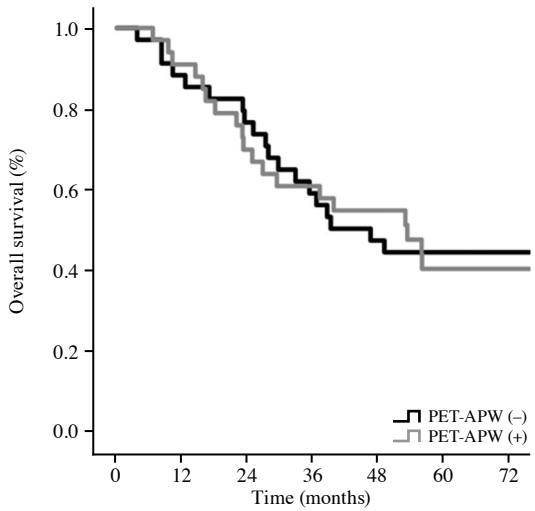

Figure 2. Overall survival of PET-APW (+) and (-) patient groups.
PET: Positron emission tomography; APW: Aortopulmonary window.

Table 2. The Cox proportional multivariate analysis for survival

	Multivariate analysis		
Variables	HR	95% CI	*p*
Age (year)	1.067	1.018-1.119	**0.006**
Sex (male *vs*. female)	0.577	0.199-1.557	0.228
LN diameter in CT	0.577	0.256-1.301	0.187
SUV_{max} value of APW-LNs	1.090	1.005-1.183	**0.03**
Cervical mediastinoscopy (No *vs*. Yes)	1.357	0.565-3.256	0.496
Resection type (pneumonectomy *vs*. lobectomy)	1.750	0.742-4.128	0.203
Tumor diameter	0.995	0.815-1.215	0.962
Histological type (Adc *vs*. Non-adc)	3.120	0.493-19.723	0.228
PL status (PL1/2/3 *vs*. PL0)			
PL1/2/3*	1.236	0.582-2.623	0.582
pN status			
pN2a1	1		
pN2a2	0.395	0.135-1.139	0.108
pN2b	1.139	0.358-3.671	0.825
pT status (T3/T4 *vs*. T1/T2)	1.076	0.643-1.795	0.781

HR: Hazard ratio; CI: Confidence interval; LN: Lymph node; CT: Computed tomography; SUV_{max}: Maximum standardized uptake value; APW: Aortopulmonary window; Adc: Adenocarcinoma; p: Pathological; T: Tumor; N: Node; Boldface indicates statistical significance; PL0: No Visceral Pleural inv.; PL1: Penetration beyond the elastic layer of visceral pleura; PL2: Invasion of visceral pleura; PL3: Parietal pleura invasion.

In the multivariate analysis, age (p=0.006, HR=1.067, 95% CI: 1.018-1.119) and SUV_{max} for APW-LNs (p=0.03, HR=1.090, 95%CI: 1.005-1.183) were found to be significant prognostic factors for survival (Table 2). The five-year OS rate was calculated as 41.7% (median: 49.2 months) for Stage IIIA disease and as 44.4% (median: 32.9 months) for Stage IIIB disease (p=0.669).

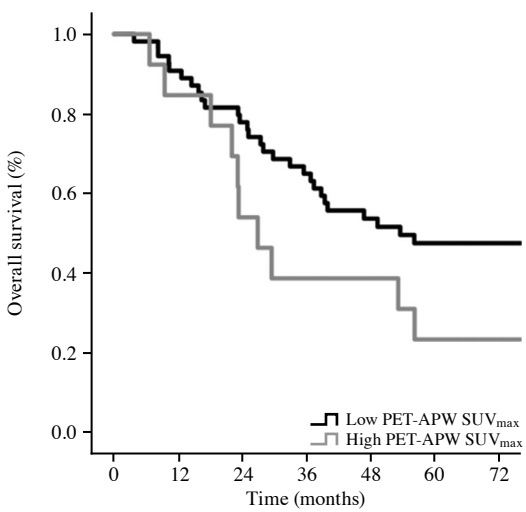

Figure 3. Overall survival of low and high PET-APW SUV_{max} patient groups.

PET: Positron emission tomography; APW: Aortopulmonary window; SUV_{max}: Maximum standardized uptake value.

The ROC analysis was performed to examine the relationship of SUV_{max} of APW-LNs with survival, and the SUV_{max} of APW-LNs was found to be a poor prognostic factor for survival (AUC=0.533, 95% CI: 0.407-0.675, p=0.648). The most optimal cut-off value for SUV_{max} of APW-LNs on PET/CT was 8 (sensitivity 24.3%, specificity 88.4%). When the patients were classified as those with high SUV_{max} (n=13) and those with low SUV_{max} (n=54) according to this cut-off value, a difference regarding survival was observed (median survival 26.8 months *vs*. 53.5 months, respectively). However, the difference was not statistically significant (p=0.152) (Figure 3).

DISCUSSION

Left upper lobe tumors with isolated metastasis to APW-LNs are a unique group and, in these cases, the necessity of sampling the APW-LNs with minimally invasive or invasive methods and the treatment algorithms to be performed are still controversial. Due to different drainage pathways, LUL tumors frequently have mediastinal metastases to APW-LNs.[11] The accepted approach for resectable NSCLC patients

with clinical single-station, non-bulky N2 disease is to perform surgery after neoadjuvant CTx±RT, if mediastinal downstage can be achieved.[4]

Although mediastinal LN metastasis is a poor prognostic factor in NSCLC, single-station N2, microscopic metastasis, unexpected N2 disease, skip N2, and metastasis of LUL tumors to APW-LNs are the groups with the best prognosis among N2 diseases.[12-14] Skip N2 is detected more frequently in LUL tumors, that is also another reason for good prognosis.[15]

Several studies have shown that metastasis to APW-LNs in LUL tumors has a better prognosis than other N2 cases.[16,17] Patterson et al.[6] reported that direct surgery could be performed, rather than evaluating metastases to the APW-LNs as mediastinal LN metastases in LUL tumors. Okada et al.,[17] on the other hand, found that unlike other N2 metastases, metastases to APW-LNs showed the same survival as metastases to hilar LNs. Even in the study of Çitak et al.,[5] in a completely different geography, this group of patients showed similar survival rates to cases with hilar LN metastasis. In an ongoing prospective study, LUL tumors with isolated metastasis to APW-LNs had a survival rate similar to Stage II rather than Stage IIIA.[18] Currently, there is no consensus on the approach to LUL tumors with isolated metastasis to the APW-LNs. Therefore, a different preoperative evaluation may come to the fore in these cases. Such that, in these cases, if the presence of N2 in the APW-LNs does not cause a significant negative effect on survival, detection of N2 disease by sampling this region may be omitted and CT and/or RT may be saved for adjuvant therapy. It is well known, contrary to the standard approach for single cN2 lung cancer patients (neoadjuvant treatment followed by surgery), that some thoracic surgery clinics apply upfront surgery, followed by adjuvant treatment as a treatment option.[19] By omitting invasive staging, patients are not exposed to an additional surgical intervention such as VATS or anterior mediastinotomy for the region in which standard mediastinoscopy cannot reach. Lee et al.[20] also emphasized this issue and reported that skipping invasive diagnostic methods in these cases with suspected cN2a could reduce the total medical cost and shorten the workup time.

Review of the literature reveals no study comparing the results of neoadjuvant therapy followed by resection and resection followed by adjuvant therapy in cases of, never particularly, cN2 isolated to the APW-LNs in the LUL tumors. Some authors have suggested that when there is a suspicion of contralateral nodal involvement (N3) or multi-station N2 disease (N2b) in the LUL tumors, further diagnostic workup would be appropriate.[21] Consistent with our opinion, they have also proposed that if there is no evidence of mediastinal LN metastasis other than in the APW-LNs, the idea remains unclear whether any further invasive diagnostic procedure is necessary. Cerfolio et al.,[7] in APW examination with PET/CT, recommended that this region should be sampled if there was suspicion, and neoadjuvant therapy should be given if metastases were detected. Nevertheless, they also concluded that upfront surgery might be an option and further randomized studies are needed on this subject.

In another study, Maniva et al.[22] reported that good survival was observed in cases with cN2a detected on PET/CT examination of tumors located in the LUL and that upfront surgery should be an option in these cases. Tsitsias et al.[21] also found a similar result in their study and reported that the survival of single-zone cN2a cases was similar to the unexpected pN2 patient group. In our study, there was no significant difference in the survival rates between the cN2/pN2 and cN0-1/pN2 cases, consistent with the study of Tsitsias et al.[21]

Multiple N2 cases show a poorer prognosis than single N2 cases.[13] However, the limited number of patients in studies related to LUL tumors makes it difficult to draw a firm conclusion on this issue. In the current study, we observed no significant difference in the survival rates between pN2a1, pN2a2, and pN2b cases; however, the low number of patients should be considered while evaluating the results, and the results should be interpreted with caution.

Sensitivity and specificity of PET/CT for staging the mediastinal region are 93% and 71%, respectively, and these values are not sufficient for staging this region.[23] In a study evaluating 360 cases, cN0/pN2 was detected at a rate of 15% in mediastinal staging.[24] In particular, in terms of granulomatous diseases, the diagnosis rate is decreasing in endemic regions. If detection of metastasis in the APW-LNs is required, minimally invasive or invasive sampling should be performed.[25] Although many patients were excluded from our study, 34 pN2 cases in our case series were interpreted as false-negatives on PET/CT. Nevertheless, in the current study, the presence or the absence -as false-negative- of suspected metastasis in this region by PET/CT evaluation did not affect survival of the patients. This result may eliminate the necessity of preoperative invasive sampling of this area in cases of suspected APW-LN metastases.

Another remarkable result in our study was that the SUV_{max} of APW-LNs were poor predictors of survival, although increases in SUV_{max} in the multivariate analysis affected survival adversely. This is probably related to greatly increased tumor burden. Likewise, the tumor diameter was larger in cases with high SUV_{max}. It is well known that cases with microscopic N2 positivity and bulky N2 or N2 with extracapsular spread show different survival rates.[17] In our study, the cut-off value of SUV_{max} for poor prognosis was found to be 8, and a survival difference of approximately 27 months was observed between the two groups. Therefore, considering neoadjuvant treatment by the invasive sampling of this region at a high SUV_{max}, and considering upfront surgery without sampling at a lower SUV_{max} may be a new perspective to the treatment algorithm. Nonetheless, there is an obvious need for further larger-scale studies to draw more reliable conclusions on this subject.

This study has some limitations. First, the study has a single-center and retrospective design. However, taking the advantage of being a single-center study, we were able to use standard treatment approaches. Second, since it has a retrospective nature, disease-free survival times were unable to be evaluated. Third, due to the limited number of patients, the results should be interpreted with caution. In particular, as in many studies, the number of patients in the pN2b (#5+#6) group was quite low and it was an assertive judgment to speculate that there was no significant difference in survival between the pN2b and pN2a groups. One of the most important limitations of the study is that no neoadjuvant patient group was included in the study. If we could have compared our patient group with the patient group who underwent neoadjuvant therapy followed by surgery for APW-LN(s) metastases, we could have achieved more accurate results. However, we had a very small number of patients in this group and the T factor played an important role in the neoadjuvant treatment decisions of these groups of patients. Despite all these limitations, the main strength of this study was that cN2/pN2 and cN0/pN2 cases showed similar survival rates.

In conclusion, in non-small cell lung cancer of the left upper lobe with pathologically isolated aortopulmonary window lymph node metastases, the presence or absence of suspicious metastases on positron emission tomography/computed tomography in the preoperative radiological evaluation of aortopulmonary window lymph nodes did not affect survival. In cases where metastases are not suspected radiologically in aortopulmonary window lymph nodes, invasive sampling of this region is not performed. In the presence of suspected aortopulmonary window lymph node metastases on positron emission tomography/computed tomography, if maximum standardized uptake value is not very high in aortopulmonary window lymph nodes, invasive staging of this region can be omitted, since the maximum standardized uptake value is a poor prognostic factor for survival.

Ethics Committee Approval: The study protocol was approved by the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (date: 28.07.2021, no: 302-06). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Design: Ö.S., V.E.; Control/supervision: V.E., N.E.; Data collection and/or processing: L.C., M.M.; Analysis and/or interpretation: M.Ö., N.Y.; Literature review: N.Ç.; Writing the article: M.V.D.; Critical review: Ö.S., V.E.; Materials: C.B.S., Y.S.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. 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. doi: 10.1097/JTO.0000000000000678.
2. Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the mediastinal nodes. An anatomic study on 260 adults. J Thorac Cardiovasc Surg 1989;97:623-32.
3. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, et al. The IASLC Lung Cancer Staging Project: External validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2017;12:1109-21. doi: 10.1016/j.jtho.2017.04.011.
4. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Nonsmall Cell Lung Cancer, Version 2, 2021. Published 2021 [Cited 21 Nov 2018.] Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

5. Çıtak N, Guglielmetti L, Aksoy Y, Isgörücü O, Metin M, Sayar A, et al. Should aortic lymph nodes be considered hilar lymph nodes in patients with completely resected NSCLC? A multicenter study. J Thorac Oncol 2019;1:545-6. doi: 10.1016/j.jtho.2019.08.1139.
6. Patterson GA, Piazza D, Pearson FG, Todd TR, Ginsberg RJ, Goldberg M, et al. Significance of metastatic disease in subaortic lymph nodes. Ann Thorac Surg 1987;43:155-9. doi: 10.1016/s0003-4975(10)60386-4.
7. Cerfolio RJ, Bryant AS, Eloubeidi MA. Accessing the aortopulmonary window (#5) and the paraaortic (#6) lymph nodes in patients with non-small cell lung cancer. Ann Thorac Surg 2007;84:940-5. doi: 10.1016/j.athoracsur.2007.04.078.
8. Casali C, Stefani A, Natali P, Rossi G, Morandi U. Prognostic factors in surgically resected N2 non-small cell lung cancer: The importance of patterns of mediastinal lymph nodes metastases. Eur J Cardiothorac Surg 2005;28:33-8. doi: 10.1016/j.ejcts.2005.03.016.
9. Kudo Y, Saji H, Shimada Y, Nomura M, Usuda J, Kajiwara N, et al. Do tumours located in the left lower lobe have worse outcomes in lymph node-positive non-small cell lung cancer than tumours in other lobes? Eur J Cardiothorac Surg 2012;42:414-9. doi: 10.1093/ejcts/ezs065.
10. Metin M, Citak N, Sayar A, Pekcolaklar A, Melek H, Kök A, et al. The role of extended cervical mediastinoscopy in staging of non-small cell lung cancer of the left lung and a comparison with integrated positron emission tomography and computed tomography: Does integrated positron emission tomography and computed tomography reduce the need for invasive procedures? J Thorac Oncol 2011;6:1713-9. doi: 10.1097/JTO.0b013e318225914e.
11. Riquet M, Manac'h D, Dupont P, Dujon A, Hidden G, Debesse B. Anatomic basis of lymphatic spread of lung carcinoma to the mediastinum: Anatomo-clinical correlations. Surg Radiol Anat 1994;16:229-38. doi: 10.1007/BF01627676.
12. Lee JG, Lee CY, Bae MK, Park IK, Kim DJ, Kim KD, et al. Validity of International Association for the Study Of Lung Cancer proposals for the revision of N descriptors in lung cancer. J Thorac Oncol 2008;3:1421-6. doi: 10.1097/JTO.0b013e31818e0dbd.
13. Inoue M, Sawabata N, Takeda S, Ohta M, Ohno Y, Maeda H. Results of surgical intervention for p-stage IIIA (N2) non-small cell lung cancer: Acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe. J Thorac Cardiovasc Surg 2004;127:1100-6. doi: 10.1016/j.jtcvs.2003.09.012.
14. Ohta Y, Shimizu Y, Minato H, Matsumoto I, Oda M, Watanabe G. Results of initial operations in non-small cell lung cancer patients with single-level N2 disease. Ann Thorac Surg 2006;81:427-33. doi: 10.1016/j.athoracsur.2005.08.018.
15. Riquet M, Assouad J, Bagan P, Foucault C, Le Pimpec Barthes F, et al. Skip mediastinal lymph node metastasis and lung cancer: A particular N2 subgroup with a better prognosis. Ann Thorac Surg 2005;79:225-33. doi: 10.1016/j.athoracsur.2004.06.081.
16. Nakanishi R, Osaki T, Nakanishi K, Yoshino I, Yoshimatsu T, Watanabe H, et al. Treatment strategy for patients with surgically discovered N2 stage IIIA non-small cell lung cancer. Ann Thorac Surg 1997;64:342-8. doi: 10.1016/S0003-4975(97)00535-3.
17. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. Prognosis of completely resected pN2 non-small cell lung carcinomas: What is the significant node that affects survival? J Thorac Cardiovasc Surg 1999;118:270-5. doi: 10.1016/S0022-5223(99)70217-5.
18. ClinicalTrials.gov identifier (NCT number): NCT02555592. Available at: https://clinicaltrials.gov/ct2/show/NCT02555592.
19. Yun JK, Bok JS, Lee GD, Kim HR, Kim YH, Kim DK, et al. Long-term outcomes of upfront surgery in patients with resectable pathological N2 non-small-cell lung cancer. Eur J Cardiothorac Surg 2020;58:59-69. doi: 10.1093/ejcts/ezaa042.
20. Lee K, Jeong YH, Ryu JS, Kim YI, Kim HR, Park SI. Surgical outcomes of non-small cell lung cancer in single-zone N2 in the aortopulmonary zone. Thorac Cardiovasc Surg 2022;70:251-7. doi: 10.1055/s-0041-1727206.
21. Tsitsias T, Boulemden A, Ang K, Nakas A, Waller DA. The N2 paradox: Similar outcomes of pre- and postoperatively identified single-zone N2a positive non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:882-7. doi: 10.1093/ejcts/ezt478.
22. Maniwa T, Shintani Y, Okami J, Kadota Y, Takeuchi Y, Takami K, et al. Upfront surgery in patients with clinical skip N2 lung cancer based on results of modern radiological examinations. J Thorac Dis 2018;10:6828-37. doi: 10.21037/jtd.2018.10.115.
23. Rogasch JMM, Frost N, Bluemel S, Michaels L, Penzkofer T, von Laffert M, et al. FDG-PET/CT for pretherapeutic lymph node staging in non-small cell lung cancer: A tailored approach to the ESTS/ESMO guideline workflow. Lung Cancer 2021;157:66-74. doi: 10.1016/j.lungcan.2021.05.003.
24. Miao H, Shaolei L, Nan L, Yumei L, Shanyuan Z, Fangliang L, et al. Occult mediastinal lymph node metastasis in FDG-PET/CT node-negative lung adenocarcinoma patients: Risk factors and histopathological study. Thorac Cancer 2019;10:1453-60. doi: 10.1111/1759-7714.13093.
25. Werutsky G, Hochhegger B, Lopes de Figueiredo Pinto JA, Martínez-Mesa J, Zanini ML, Berdichevski EH, et al. PET-CT has low specificity for mediastinal staging of non-small-cell lung cancer in an endemic area for tuberculosis: A diagnostic test study (LACOG 0114). BMC Cancer 2019;19:5. doi: 10.1186/s12885-018-5233-5.