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Impact of DLL-3 expression as prognostic factor in extensive stage of small cell lung cancer treated with first-line chemotherapy

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Directed by Professor Seungtaek Lim

The Master′s Thesis
submitted to the Department of Medicine,
Wonju College of Medicine Graduate School, Yonsei University
in partial fulfillment of the requirements
for the degree of Master of Medical Science

Hohyung Nam

December 2022

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This certifies that the Master's Thesis of
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ACKNOWLEDGEMENTS

For those who have been supporting me throughout whole painful but fruitful process of writing thesis, I would like to thank you all.

Above all, I would like to thank my supervisor, professor Seungtaek Lim, for invaluable advices, unconditional love and persistent patience for me.

Also, I would like to thank professors of my thesis committee, Jee Hyun Kong and Shin Yong Hyun, for their passion and love supervising my thesis as well as Taesun Shim for his excellent English proofreading.

Last but not least, I would thank my family and my fiancé, who have been encouraging me and guiding me to the light of learning.

I love you all more than anything.

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ABSTRACT

Impact of DLL-3 expression as prognostic factor in extensive stage of small-cell lung cancer treated with first-line chemotherapy

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(Directed by Professor Seungtaek Lim)

Introduction: Small cell lung cancer (SCLC) is known for its high proliferative rate and poor prognosis. Delta-like ligand 3 (DLL-3) is specifically expressed on the surface of SCLC, but the association of DLL-3 with prognosis of SCLC is not yet well known. Hence, we aimed to evaluate the prognostic role of DLL-3 in extensive-stage small-cell lung cancer treated with first-line chemotherapy.

Materials and Methods: A total of 54 patients with extensive-stage SCLC (ES-SCLC) treated with first-line chemotherapy - whose tissue specimen were prepared for immunohistochemical staining for DLL-3 - and their clinicopathologic data, as well as survival data including progression-free survival (PFS) and overall survival (OS) were obtained. DLL-3 expression and the percentage of tumor cells with DLL-3 positive among total cancer cells were analyzed microscopically, and DLL-3 high and DLL-3 low were defined as the percentage of DLL-3 positive tumor cells versus total cancer cells $\geqq$75% and <75%, respectively.

Results: Patients' clinicopathologic characteristics, including age at diagnosis, sex, response to first-line chemotherapy, history of second-line chemotherapy, and number of metastatic sites, were not correlated to DLL-3 expression. However, response to first-line chemotherapy and number of metastatic sites were correlated to PFS, while DLL-3 expression and number of metastatic sites were correlated to OS.

Conclusions: DLL-3 was highly expressed in SCLC but not associated with any clinicopathologic characteristics. In determining survival outcome, DLL-3 was correlated with worse OS, which suggests the prognostic role of DLL-3 in ES-SCLC.

Keywords: DLL-3; small cell lung cancer; survival outcome

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I. INTRODUCTION

Small cell lung cancer (SCLC), accounting for 15% of all lung cancers, is known for its high proliferative rate and poor prognosis[1]. Because early metastasis is commonly observed at diagnosis, only one-third of SCLC are diagnosed as a limited stage disease with potential curative treatment[1]. For extensive-stage small-cell lung cancer (ES-SCLC), immune checkpoint inhibitors (ICIs) such as atezolizumab or durvalumab in combination with platinum-based chemotherapy became the standard first line treatment option due to phase III studies demonstrating the survival benefit of ICIs in addition to platinum based chemotherapy[2,3]. ES-SCLC is well known for its initial sensitivity to chemotherapy, but it rapidly acquires resistance to the chemotherapy, eventually culminating in patient death[4]. Although topotecan has been approved for relapsed SCLC based on a phase III clinical trial in patients who progressed after platinum doublet chemotherapy, the survival benefit was only modest, resulting in a dismal prognosis of ES-SCLC patients[5]. Hence, there is clearly an unmet need for new therapeutic options for highly lethal malignancy.

On the surface of SCLC tumor cells, delta-like ligand 3 (DLL-3) is specifically expressed[6]. DLL-3 expression promotes SCLC migration and invasion through controlling the epithelial mesenchymal transition protein, SNAI1[7]. Rovalpituzumab tesirine (Rova-T), a first-in-class antibody-drug conjugate directed against DLL-3, is a promising targeted therapeutic for individuals with SCLC[8]. In a phase I trial[9], Rova-T demonstrated a higher response rate in patients with tumors with a higher level of DLL-3 than those with a lower level of DLL-3 expression, indicating DLL-3 expression can be considered a potential biomarker for response or Rova-T. However, incidence of high DLL-3 expression and its prognostic value in SCLC patients remains to be discussed.

Hence, based on these previous studies, the value of DLL-3 as a prognostic marker in extensive-stage small-cell lung cancer (ES-SCLC) patients has been investigated.

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II. MATERIALS AND METHODS

1. Patient enrollment

We enrolled patients with ES-SCLC who were diagnosed and treated with palliative chemotherapy at the Department of Hemato-oncology, Wonju Severance Christian Hospital, Yonsei University, from 2015 to 2018. We included patients whose tumor samples were available for immunohistochemical staining of DLL-3. Patients' information including sex, age at diagnosis, biopsy site, metastatic site, first-line and second-line chemotherapy regimen, response to first-line chemotherapy, and survival data (status at the end of 2018, date of death or date of last follow-up), were obtained through medical chart review. This study was approved by the institutional review board of Wonju Severance Christian Hospital, Yonsei University and conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical Research Involving Human Subjects.

2. DLL-3 immunohistochemistry

All tissue specimen were prepared for immunohistochemical staining in 4-μm-thick formalin-fixed, paraffin-embedded tissue sections mounted on glass slides. DLL-3 staining was performed via an anti-DLL-3 mouse monoclonal antibody (AbbVie-Stemcentrx, North Chicago, Illinois, U.S.A.). In this study. DLL-3 positive was defined as any cytoplasmic or membranous staining at any intensity in tumor cells and was determined by a pathologist specialized in thoracic oncology. DLL-3 expression and the percentage of tumor cells with DLL-3 positive among total cancer cells were analyzed microscopically. DLL-3 high and DLL-3 low were defined as the percentage of DLL-3 positive tumor cells versus total cancer cells $\geqq$75% and <75%, respectively, as described previously[10].

3. Statistical analysis

Differences in clinicopathologic factors, including age at biopsy, sex, response to first-line chemotherapy, history of second-line chemotherapy, and number of metastatic sites between DLL-3 expression were assessed based on Student's t-test and Chi-square test. Overall survival (OS) was defined as the time from the first day of treatment to death, and progression-free survival (PFS) was calculated from the first day of treatment to disease progression or death. Univariate analysis of association between patients′ characteristics and survival outcomes was conducted on the Kaplan-Meier test with log rank test. Multivariate analysis of association between survival outcomes and various clinicopathologic factors was conducted by the Cox proportional hazard model. A p-value of <0.05 was considered statistically significant. All statistical analysis was performed via SPSS Statistics 29.0 (IBM, Armonk, New York, U.S.A.).

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III. RESULTS

1. Patient characteristics

The baseline characteristics of the participants in this study were summarized in Table 1. A total of 54 patients diagnosed with ES-SCLC at the Department of Hemato-oncology, Wonju Severance Christian Hospital, Yonsei University from 2015 to 2018 were analyzed in the study. All 54 tumor specimens were available for immunohistochemical staining for DLL-3, whose representative images are shown in Figure 1. The median age was 66.5 with a range of 44 to 86, and the majority (n=48, 87.3%) were male. Most of the patients (n=50, 92.6%) have been treated with etoposide-cisplatin followed by etoposide-carboplatin (n=3, 5.5%) and belotecan (n=1, 1.8%). The most frequent metastatic site was lymph nodes (n=39, 72.2%), and the second most frequent was lung and bone (n=20, 37.0%, each) followed by pleural effusion (n=14, 25.9%). A total of 47 patients were evaluable for response to first-line chemotherapy, and the number of patients who have shown complete and partial response was 29 (61.7%), whereas those who had shown stable and progressive disease were 18 (38.3%).

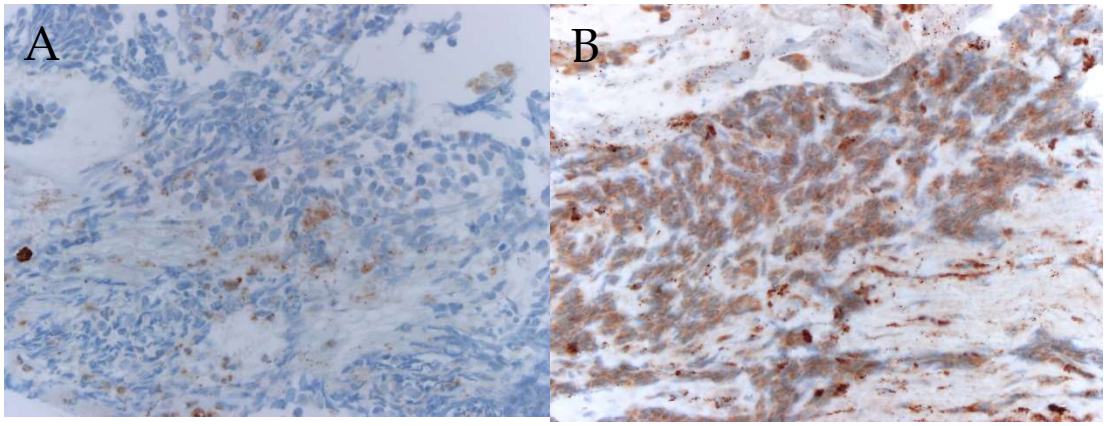

Figure 1. Representative immunohistochemical staining of DLL-3 in SCLC tissue specimens.

A: 5% cancer cells (+) for DLL-3 (low)

B: 100% cancer cells (+) for DLL-3 (high)

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Table 1. General characteristics of study subjects

Characteristics	*n*	%
Age (years)		
Median	66.5	
Range	44 to 86	
Age at diagnosis		
<65 years	16	29.6
≧65 years	38	70.4
Sex		
Male	48	88.9
Female	6	11.1
First-line chemotherapy		
Etoposide+cisplatin	50	92.6
Etoposide+carboplatin	3	5.6
Belotecan	1	1.8
History of second-line chemotherapy		
Received	19	35.2
None	35	64.8
Response to first-line chemotherapy		
CR+PR	29	61.7
SD+PD	18	38.3
Metastatic sites		
Liver	15	27.8
Lung	20	37.0
Bone	20	37.0
Brain	9	16.7
Pericardial effusion	1	1.9
Pleural effusion	14	25.9
Adrenal gland	2	3.7
Lymph nodes	39	72.2
Number of metastatic sites		
<3	38	71.7
≧3	15	28.3

(CR: complete response, PR: partial response, SD: stable disease, PD: partial disease)

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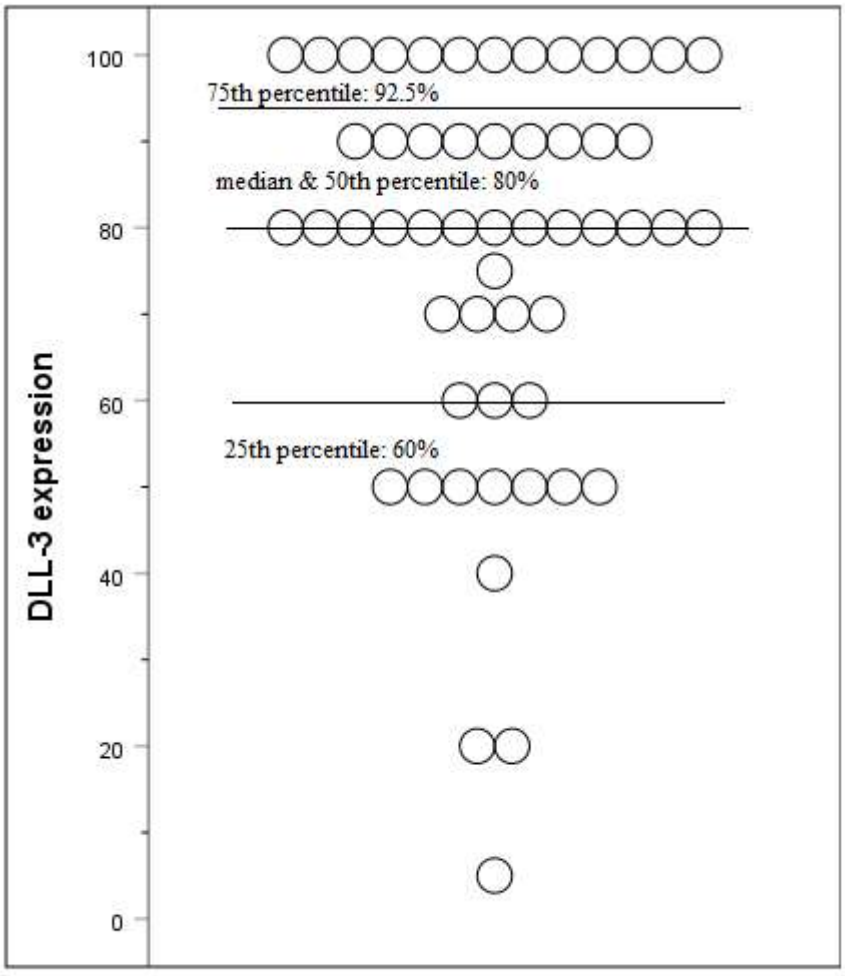
2. Expression status of DLL-3 and relationship between clinical parameters and survival

The dot plot for the percentage of tumor cells positively stained for DLL-3 was presented in Figure 2. Among all 54 patients, DLL-3 high was observed in 70.4% of patients (n=38). The mean of DLL-3 expression and the standard deviation of DLL-3 were 76.3% and 22.86 respectively. Patient demographics, clinical characteristics and metastatic sites according to DLL-3 expression was summarized in Table 1. The expression level of DLL-3 was not correlated to any characteristics: sex, age at biopsy, response to first-line chemotherapy, history of second-line chemotherapy, and number of metastatic sites. (Table 2).



DLL-3 positive cells/total cancer cells	Number of patients (%)
≧75% (DLL-3 high)	38 (70.4)
<75% (DLL-3 low)	16 (29.6)

Figure 2. Dot plot for the percentage of tumor cells staining positive for DLL-3 in all patients. Median of DLL-3 expression was 80%, and 25th percentile was 60%, 50th percentile 80%, and 75th percentile was 92.5%.

(DLL-3: delta-like ligand 3)

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Table 2. Association between various patients' characteristics and DLL-3 expression

Factor	Number	*p*
Sex		
Male vs. female	48 vs. 6	0.833
Age at diagnosis (years)		
≧65 vs. <65	31 vs. 23	0.256
Response to first-line chemotherapy		
CR+PR vs. SD+PD	29 vs. 18	0.869
History of second-line chemotherapy		
Received vs. None	19 vs. 35	0.309
Number of metastatic sites		
≧3 vs. <3	15 vs. 39	0.767

(CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease)

3. Survival outcomes according to DLL-3 expression

The median PFS and OS in all patients was 175 days and 250 days respectively. We performed a survival analysis of all 54 patients to clinical characteristics and DLL-3 expression. In our univariate analysis, response to first-line chemotherapy and the number of metastatic sites were correlated with both PFS and OS. Patients with higher DLL-3 expression tended to have worse median PFS (159 vs 221 days, p=0.373, 95% CI: 0.405 ~ 1.404) and worse median OS (226 vs. 312 days, p=0.098, 95% CI: 0.306 ~ 1.105), although both had no statistical significance (Table 3, Figure 3). We also conducted multivariate analysis for PFS and OS. Response to first-line chemotherapy and the number of metastatic sites were independent adverse prognostic factor of PFS. Further, multivariate analysis revealed that DLL-3 high expression was an independent adverse prognostic factor of OS in addition to the number of metastatic sites.

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Table 3. Univariate and multivariate analysis of survival data: A. Univariate and multivariate analysis of patients' characteristics on PFS, B. Univariate and multivariate analysis of patients' characteristics on OS.

A.

PFS						
Characteristics	Univariate analysis		Multivariate analysis			
	MST (days)	*p*	Factor	HR	95% CI	*p*
Sex		0.454		Not included		
Male	175					
Female	156					
Age		0.203	≧65 vs. <65	1.910	0.944 ~ 3.864	0.072
≧65	152					
<65	233					
Response to first-line chemotherapy		<0.001	CR+PR vs. SD+PD	0.265	0.127 ~ 0.553	<0.001
CR+PR	203					
SD+PD	103					
History of second-line chemotherapy		0.483		Not included		
None	159					
Received	233					
DLL-3 expression		0.370	High vs. Low	1.333	0.678 ~ 2.622	0.405
High	159					
Low	221					
Number of metastatic sites		<0.001	≧3 vs. <3	4.428	2.012 ~ 9.746	<0.001
≧3	90					
<3	222					

(MST: median survival time, HR: hazard ratio, PFS: progression-free survival, SD: stable disease, PD: progressive disease, CR: complete response, PR: partial response, DLL-3: Delta-like ligand 3)

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B.

Characteristics	OS					
	Univariate analysis		Multivariate analysis			
	MST (days)	*p*	Factor	HR	95% CI	*p*
Sex		0.454		Not included		
Male	226					
Female	542					
Age		0.203	≧65 vs. <65	1.719	0.857 ~ 3.447	0.127
≧65	165					
<65	312					
Response to first-line chemotherapy		<0.001	CR+PR vs. SD+PD	0.594	0.281 ~ 1.255	0.172
CR+PR	372					
SD+PD	159					
History of second-line chemotherapy		0.483		Not included		
None	165					
Received	288					
DLL-3 expression		0.370	High vs. Low	2.343	1.078 ~ 5.090	0.031
High	226					
Low	312					
Number of metastatic sites		<0.001	≧3 vs. <3	2.641	1.200 ~ 5.811	0.016
≧3	123					
<3	288					

(MST: median survival time, HR: hazard ratio, PFS: progression-free survival, SD: stable disease, PD: progressive disease, CR: complete response, PR: partial response, DLL-3: Delta-like ligand 3)

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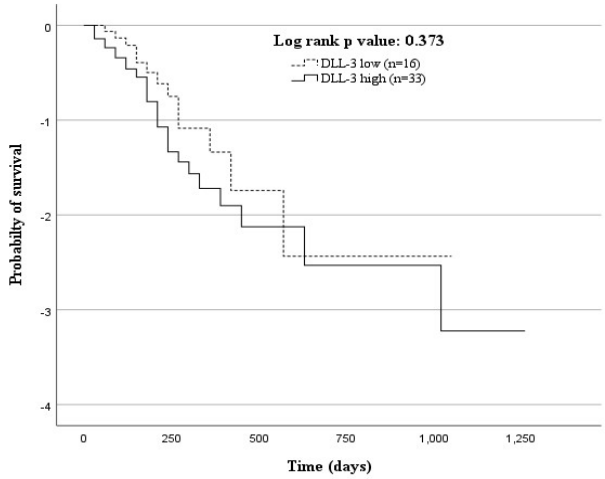
A



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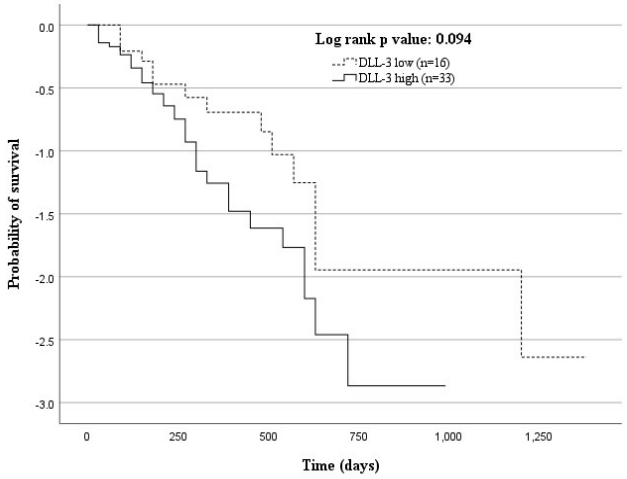

Figure 3. Survival data study plotted via Kaplan-Meier curves: (A) Kaplan-Meier curves of PFS according to DLL-3 expression, (B) Kaplan-Meier curves of according to DLL-3 expression.

(DLL-3: Delta like ligand 3, PFS: progression-free survival, OS: overall survival)

IV. DISCUSSION

DLL-3 controls the Notch pathway, which is highly upregulated and aberrantly expressed on the cell surface in SCLC[11]. The Notch signal pathway is downregulated during neuroendocrine tumor growth and is inhibited by DLL-3 expression[12]. Achaete-scute homolog 1 (ASCL1), a transcriptional factor that plays a role in the development of pulmonary neuroendocrine cells and is an oncogenic driver in SCLC, controls DLL-3 expression. In contrast to its cytoplasmic expression in normal adult tissue, DLL-3 is expressed at the cell surface in SCLC, which can be a high-value target for cancer cell-specific treatment with an antibody-drug conjugate.

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Rova-T, a DLL-3 antibody drug conjugate demonstrated rapid and prolonged response in PDX mice model. It showed modest clinical activity in ORR in phase I and II studies, but a phase III study comparing Rova-T to topotecan as second-line therapy for SCLC (TAHOE, NCT3061812) was halted due to shorter OS in the Rova-T arm compared with the topotecan arm. Nevertheless, clinical studies to develop Rova-T as a new treatment option for ES-SCLC continue. Modification of the Rova-T molecule or implementation of a different dose and schedule of Rova-T are required. In addition, the enrollment of a study of Rova-T as a maintenance therapy following first-line platinum-based chemotherapy (MERU, NCT03033511) is ongoing. All in all, DLL-3 is still regarded as a promising new drug for SCLC.

The primary aim of this study was to evaluate DLL-3 as a prognostic factor in ES-SCLC patients who received first-line chemotherapy. In univariate analysis, expression of DLL-3 was not associated with PFS or OS, although it showed a tendency of worse PFS and OS. Instead, response to first-line chemotherapy and the number of the metastatic sites were prognostic factors for both worse PFS and worse OS. In our multivariate analysis, expression of DLL-3 was an independent prognostic factor for worse OS and the number of metastatic sites, suggesting the prognostic role of DLL-3 in ES-SCLC patients treated with first-line chemotherapy. There have been a number of studies (Table 4) regarding the prognostic role of DLL-3 in patients with SCLC that report conflicting results: some studies showed that patients with high DLL-3 expression had worse OS[13], whereas other studies indicated that DLL-3 had no correlation with survival[14] or a better prognostic factor[15]. The reason behind this discrepancy is not well known. The ethnic difference of the prognostic value of DLL-3 suggested by one meta-analysis could be one reason[16]. It could also be due to heterogeneity of the various detection methods and cut-off values for DLL-3 expression used in each study. In this study, DLL-3 high was defined as ≧75% of tumor cell expression as used in previous literatures. For better understanding, future research should investigate the optimal cutoff and detection methods for DLL-3 expression.

This study presents some strengths over other studies. In this study, patients who had been diagnosed with ES-SCLC and treated with first-line chemotherapy (mainly platinum-based doublet chemotherapy) were exclusively included. It also investigated the association of DLL-3 with PFS and ORR as well as OS. Nonetheless, this study also had several limitations. First, patients′ enrollment was relatively small to be statistically significant compared to other studies. Moreover, types of first-line chemotherapy regimen could be further considered. Since platinum-based chemotherapy combined with etoposide without anti-PD1 monoclonal antibody was considered as a standard first-line therapy of ES-SCLC before 2018, all 54 patients in this study did not receive any immune-oncologic therapy as first-line therapy.

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Table 4. Previous researches to investigate prognostic role of DLL-3

n	DLL-3 high (%)	Cutoff	Results	References
335	62.4	H-score≧150	Worse OS	Yan 2019[17]
44	79.5	≧50%	Better OS	Xie 2019[18]
63	23	≧50%	No difference	Tanaka 2018[19]
38	52.6	H-score≧135	Worse OS	Regzedmaa 2019[20]
72	31.9	H-score≧6	Worse OS/PFS/RR	Huang 2019[21]
93	44	≧75%	No difference	Furua 2019[22]
1073	68	≧75%	No difference	Rojo 2020[23]
54	70.4	≧75%	Worse OS	This study

V. CONCLUSION

In summary, DLL-3 was highly expressed in SCLC and was not associated with any clinicopathologic characteristics. In determining survival outcome, DLL-3 was correlated with OS, which suggests the prognostic role of DLL-3 in ES-SCLC.

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ABSTRACT (IN KOREAN)

1 차 항암화학요법을 시행한 확장병기 소세포폐암에서 예후인자로서의 DLL-3 의 가치

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개요: 소세포폐암은 매우 증식속도가 빠르고 예후가 불량한 것으로 알려져 있다. Delta-like ligand 3 (DLL-3)은 소세포폐암의 표면에 표현되어 있으며, DLL-3와 소세포폐암의 예후와의 관련성은 잘 알려져 있지 않다. 이에 1차 항암화학요법을 시행한 확장병기 소세포폐암에서의 DLL-3의 예후인자로서의 역할에 대한 연구를 진행하였다.

재료 및 방법: 총 54명의 확장병기 소세포폐암 환자에게서 임상병리학적 특성과 무진행생존기간과 전체생존기간을 포함하는 생존데이터를 수집하였고, 조직표본을 채취하여 DLL-3 단클론항체로 염색하여 현미경으로 분석하였다. DLL-3 양성인 암세포 대 총 암세포의 비율이 75% 이상인 것을 DLL-3 high, 75% 미만을 DLL-3 low로 각각 정의하였다.

결과: 진단 당시 연령, 1차 항암화학요법에 대한 반응, 2차 항암화학요법의 유무, 전이부위의 개수 등 환자들의 임상병리학적 특성들은 DLL-3 발현과 유의한 관계를 보이지 않았다. 하지만 1차 항암치료에 대한 반응과 총 전이부위 개수는 무진행생존기간과 통계적으로 유의한 관련성을 보였고, DLL-3 발현과 총 전이부위 개수는 전체생존기간과 통계적으로 유의한 관련성을 보였다.

결론: DLL-3는 소세포폐암에서 잘 발현되어 있으며 DLL-3의 발현도는 환자들의 임상병리학적 특성과 관련이 있지 않았다. 생존분석에서는 DLL-3가 발현될수록 전체생존기간이 악화되었으며, 이는 확장병기 소세포폐암에서 DLL-3의 예후인자로서의 가능성을 암시하는 것으로 보인다.

핵심 되는 말: DLL-3; small cell lung cancer; survival outcome