



· 论 著 ·

放射性淋巴细胞减少对局限期小细胞肺癌患者预后的影响：一项队列研究

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[摘要] 背景与目的: 尽管放射性淋巴细胞减少与某些恶性肿瘤的不良生存结局相关, 但是关于小细胞肺癌 (small cell lung cancer, SCLC) 的研究证据仍较少。本研究旨在探讨放疗前后淋巴细胞计数是否能预测局限期SCLC (limited-stage SCLC, LS-SCLC) 患者的临床预后。方法: 本研究为一项单中心回顾性队列研究。回顾性分析2007年1月—2017年12月在复旦大学附属肿瘤医院接受根治性放化疗的LS-SCLC患者。纳入标准包括: (1) 经病理学检查确认为SCLC; (2) 通过正电子发射计算机断层成像 (positron emission tomography and computed tomography, PET/CT)、脑增强磁共振成像 (magnetic resonance imaging, MRI) 诊断为局限期 [美国癌症联合会 (American Joint Committee on Cancer, AJCC) 第8版TNM分期M0]; (3) 接受了根治性放化疗; (4) 具有放疗前、放疗期间及放疗后1个月的血常规数据; (5) 可获得完整的生存、复发及末次随访信息。排除标准包括: (1) 基线远处转移 (AJCC第8版TNM分期M1, 包括任何远处淋巴结、器官或骨髓转移); (2) 放疗剂量小于50 Gy [以等效生物剂量2 Gy/次计算, 即生物有效剂量 (biological effective dose, BED) <40 Gy]; (3) 放疗前、放疗期间及放疗后的数据不完整; (4) 无法获知生存、复发状态或末次随访记录不完整。本研究获得复旦大学附属肿瘤医院伦理委员会的批准 (伦理编号: 2303271-15), 并豁免了患者的知情同意。采集的临床数据包括患者年龄、性别、美国东部肿瘤协作组体能状态 (Eastern Cooperative Oncology Group performance status, ECOG PS) 评分、吸烟史、肿瘤TNM分期、化疗方案与周期、放疗剂量与分割方式、是否同步放化疗、是否接受预防性颅脑照射 (prophylactic cranial irradiation, PCI); 实验室检查数据包括LS-SCLC患者在放疗前、放疗期间及放疗后1个月的淋巴细胞计数, 根据不良事件通用术语标准 (Common Terminology Criteria for Adverse Events, CTCAE) 4.0版对淋巴细胞减少进行分级。使用Kaplan-Meier方法估计无进展生存期 (progression-free survival, PFS) 和总生存期 (overall survival, OS), 并用log-rank检验进行比较。结果: 共纳入170例患者。患者的中位年龄为57岁, 男性占77.6%。中位放疗剂量为60 Gy (范围: 45~66 Gy)。整组人群的中位PFS为22.0个月, 5年PFS率为31.3%, 10年PFS率19.8%; 中位OS为38.0个月, 5年OS率为37.5%, 10年OS率24.2%。放疗前, 有14例 (8.2%) 患者出现1~2级淋巴细胞减少; 在放疗期间, 出现1、2、3、4级淋巴细胞减少的患者分别为7例 (4.1%)、22例 (12.9%)、111例 (65.3%)、24例 (14.1%); 在放疗后1个月, 1级、2级、3级、4级淋巴细胞减少的患者分别有36例 (21.2%)、36例 (21.2%)、11例 (6.5%)、1例 (0.6%)。无论放疗前、中、后, 各级淋巴细胞减少患者之间的PFS和OS均无显著差异。结论: 在免疫治疗前, 放疗引起的淋巴细胞减少似乎不影响LS-SCLC患者的预后。

[关键词] 局限期小细胞肺癌; 淋巴细胞减少; 放疗; 预后; 生存分析; 队列研究

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Impact of radiation-induced lymphopenia on prognosis in patients with limited-stage small cell lung cancer: a cohort study WANG Yihua^{1,2}, LI Yaqi¹, PEI Yulei¹, WU Kailiang¹, FAN Xingwen¹ (1. Department of Thoracic Radiation Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China; 2. Department of Oncology, Taiyuan Central Hospital/The Ninth Clinical Medical College of Shanxi Medical University, Taiyuan 030009, Shanxi Province, China)

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[**Abstract**] **Background and purpose:** Despite Radiation-induced lymphopenia has been associated with poor survival outcomes in certain solid tumors, there is limited evidence for small cell lung cancer (SCLC). The purpose of this study was to investigate whether the absolute lymphocyte count before and after radiotherapy could predict the clinical outcomes for limited-stage SCLC (LS-SCLC) patients. **Methods:** This was a single-center, retrospective cohort study. A retrospective analysis of patients evaluated at Fudan University Shanghai Cancer Center from January 2007 to December 2017 was conducted. Inclusion criteria: (1) pathologically confirmed small-cell lung cancer; (2) limited-stage disease defined by positron emission tomography and computed tomography (PET/CT) and contrast-enhanced brain magnetic resonance imaging (MRI) [American Joint Committee on Cancer (AJCC) 8th edition TNM stage M0]; (3) receipt of definitive chemoradiotherapy; (4) availability of complete blood counts before, during and within 1 month after radiotherapy; (5) complete survival, relapse, and last-follow-up information retrievable. Exclusion criteria: (1) distant metastasis at baseline (AJCC 8th edition TNM stage M1, including any distant nodal, visceral, or bone-marrow involvement); (2) total radiotherapy dose <50 Gy [calculated as an equivalent biological dose at 2 Gy/fraction, i.e., a biological effective dose (BED) <40 Gy]; (3) incomplete laboratory data at any scheduled time point; (4) inability to ascertain survival or relapse status or insufficient follow-up records. The study protocol was approved by the ethics committee of Fudan University Shanghai Cancer Center (approval number: 2303271-15), and the requirement for informed consent was waived. Clinical data extracted comprised age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS) score, smoking history, TNM stage, chemotherapy regimen and number of cycles, radiotherapy dose and fractionation schedule, use of concurrent chemoradiotherapy and administration of prophylactic cranial irradiation (PCI). Laboratory data comprised serial absolute lymphocyte counts obtained within 1 month before, during and after radiotherapy; lymphopenia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared with the log-rank test. **Results:** A total of 170 patients were included. The median age of the patients was 57 years, with 77.6% being male. The median radiation therapy dose was 60 Gy (range: 45-66 Gy). For the entire cohort, the median PFS was 22.0 months, the 5-year PFS rate was 31.3%, and the 10-year PFS rate was 19.8%. The median OS was 38.0 months, the 5-year OS rate was 37.5%, and the 10-year OS rate was 24.2%. Before radiation therapy, 14 patients (8.2%) had grade 1-2 lymphocytopenia. During radiation therapy, the number of patients with grade 1, 2, 3 and 4 lymphocytopenia was 7 (4.1%), 22 (12.9%), 111 (65.3%), and 24 (14.1%), respectively. One month after radiation therapy, the number of patients with grade 1, 2, 3 and 4 lymphocytopenia was 36 (21.2%), 36 (21.2%), 11 (6.5%) and 1 (0.6%), respectively. There were no significant differences in PFS and OS among patients with different grades of lymphocytopenia before, during, or after radiation therapy. **Conclusion:** Before immunotherapy, radiotherapy-induced lymphopenia did not appear to affect the prognosis of patients with LS-SCLC.

[**Key words**] Limited-stage small cell lung cancer; Lymphopenia; Radiotherapy; Prognosis; Survival analysis; Cohort study

小细胞肺癌 (small cell lung cancer, SCLC) 是恶性程度最高的肺癌类型, 约占所有肺癌的 15%, 其中局限期 SCLC (limited-stage SCLC, LS-SCLC) 占 SCLC 的 1/3^[1]。同步放化疗是 LS-SCLC 的标准治疗, 最新研究^[2-3]显示, 放疗后加上度伐利尤单抗巩固治疗可以进一步延长患者的生存期。虽然 SCLC 对放化疗敏感, 但仍有相当多的患者会出现复发和转移。放疗效果较差的原因有很多, 其中一个指向为放疗引起的淋巴细胞减少, 影响机体免疫系统的正常功能^[4-8]。

在乳腺癌、食管癌、宫颈癌及非小细胞肺癌 (non-small cell lung cancer, NSCLC) 等恶性肿瘤中, 都观察到放疗期间出现的淋巴细胞严重减少症与患者预后不良有关^[9-12]。但也有不同的

结果, 头颈部肿瘤患者放疗期间的淋巴细胞减少与患者预后无关^[13-14]。在 LS-SCLC 中, 放疗导致的淋巴细胞减少是否会影响患者的预后尚未见报道。本研究旨在分析 LS-SCLC 患者在放疗前、放疗期间及放疗后出现的淋巴细胞减少与预后的关系。

1 资料和方法

1.1 纳入和排除标准

本研究为一项单中心回顾性队列研究。回顾性分析 2007 年 1 月—2017 年 12 月在复旦大学附属肿瘤医院接受根治性放化疗的 LS-SCLC 患者。纳入标准: (1) 经病理学检查确认为 SCLC; (2) 通过正电子发射计算机断层成像 (positron emission

tomography and computed tomography, PET/CT)、脑增强磁共振成像(magnetic resonance imaging, MRI)诊断为局限期[美国癌症联合会(American Joint Committee on Cancer, AJCC)第8版TNM分期M0];(3)接受了根治性放疗;(4)具有放疗前、期间、放疗后1个月的血常规数据;(5)可获得完整的生存、复发及末次随访信息。排除标准:(1)基线远处转移(AJCC第8版TNM分期M1,包括任何远处淋巴结、器官或骨髓转移);(2)放疗剂量小于50 Gy[以等效生物剂量2 Gy/次计算,即生物有效剂量(biological effective dose, BED) <40 Gy];(3)放疗前、中、后数据不完整;(4)无法获得生存、复发状态或末次随访记录不完整。本研究获得复旦大学附属肿瘤医院伦理委员会的批准(伦理编号:2303271-15),并豁免了患者的知情同意。

1.2 数据收集

采集的临床数据包括患者年龄、性别、美国东部肿瘤协作组体能状态(Eastern Cooperative Oncology Group performance status, ECOG PS)评分、吸烟史、肿瘤TNM分期、化疗方案与周期、放疗剂量与分割方式、是否同步放化疗、是否接受预防性颅脑照射(prophylactic cranial irradiation, PCI);实验室检查数据包括LS-SCLC患者在放疗前、放疗期间及放疗后1个月的淋巴细胞计数。放疗期间淋巴细胞数取所有检测中的最小值;放疗后2~6周检查的淋巴细胞数量归入放疗后1个月,取最大值。根据不良事件通用术语标准(Common Terminology Criteria for Adverse Events, CTCAE)4.0版,1、2、3、4级淋巴细胞减少分别定义为0.8~0.9、0.5~0.7、0.3~0.4、0.0~0.2。随访资料来源于复旦大学附属肿瘤医院门诊病历、住院记录、电话随访及上海市肿瘤登记系统。观察起点统一设定为患者首次接受抗肿瘤治疗(化疗或放疗)之日,随访截至2025年6月30日,中位随访时间为95.0个月(范围:4.1~207.3个月)。每3~6个月复查病史、体格检查、胸部增强计算机体层成像(computed tomography, CT)±腹部CT/MRI及脑MRI(可疑复发时),直至死亡或失访。总生存期(overall survival, OS)定义为观察起点至任何原因死亡的时间;无进展生存期(progression-free survival, PFS)定义为观察起点至影像学或病理学检查证实进展、任何原因死亡或末次随访

的时间,以先发生者为准。失访定义为末次成功联系后连续12个月无任何生命或疾病状态记录;删失病例在生存分析中按末次已知存活日期处理。删失数据在Kaplan-Meier曲线中标记为“+”,并纳入COX模型计算。

1.3 统计学处理

中位随访时间采用反向Kaplan-Meier法计算,并采用Kaplan-Meier法进行单因素生存分析,采用log-rank检验进行组间差异检验,采用COX比例风险模型进行多因素分析。检验水准 α 为0.05,双侧检验。使用SPSS 26.0软件对数据进行统计学分析。 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 患者特征

筛选后共有170例患者纳入本研究(图1)。患者年龄31~76岁(中位年龄57岁),73.5%的患者ECOG PS评分为0或1分,77.6%的患者为男性,62.0%的患者目前或曾经吸烟,96.5%的患者接受了3个周期及以上的化疗,90.6%的患者接受了同步放化疗。处方剂量的中位数为60 Gy(范围:45~66 Gy)。80.0%的患者接受了PCI,详见表1。

2.2 整体预后状态

截至2025年6月,中位随访95.0个月,65%的患者在治疗后达到部分缓解或完全缓解。整组人群的中位PFS为22.0个月,2、5和10年PFS率分别为48.0%、31.3%和19.8%;中位OS为38.0个月,2、5和10年OS率分别为69.0%、37.5%和24.2%。

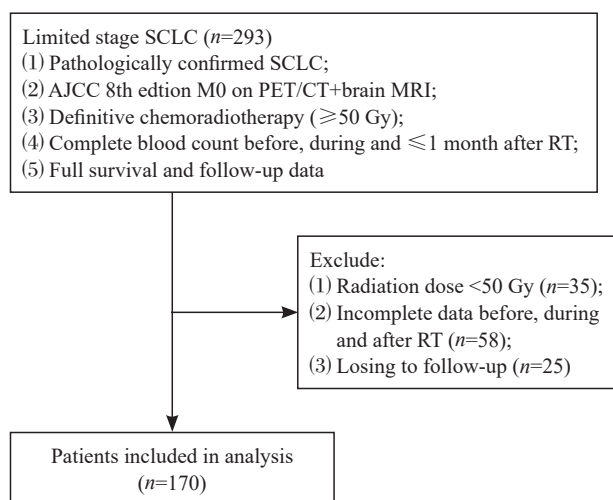


图1 患者纳入及排除标准流程图

Fig. 1 Patient inclusion and exclusion criteria flowchart

表1 170例LS-SCLC根治性化疗患者的基线临床特征

Tab. 1 Baseline clinical characteristics of 170 LS-SCLC patients receiving definitive chemoradiotherapy

Characteristic	Number	[n(%)]
Median age (range)/year	57	(31-76)
Age/year		
≥60	70	(41.2)
<60	100	(58.8)
ECOG PS score		
0-1	125	(73.5)
2	45	(26.5)
Gender		
Male	132	(77.6)
Female	38	(22.4)
TNM stage		
II	69	(40.6)
III	101	(59.4)
Smoking		
Yes	105	(62.0)
No	65	(38.0)
Chemotherapy cycle		
≤4	164	(96.5)
>4	6	(3.54)
Radiation dose/Gy		
≥60	103	(60.6)
<60	67	(39.4)
Concurrent chemoradiotherapy		
Yes	154	(90.6)
No	16	(9.4)
PCI		
No	34	(20.0)
Yes	136	(80.0)

2.3 淋巴细胞数量

在放疗前, 1、2级淋巴细胞减少的患者分别有8例(4.7%)、6例(3.5%); 在放疗期间, 1、2、3、4级淋巴细胞减少的患者分别有7例(4.1%)、22例(12.9%)、111例(65.3%)、24例(14.1%); 在放疗后1个月, 1、2、3、4级淋巴细胞减少的患者分别有36例(21.2%)、36例(21.2%)、11例(6.5%)、1例(0.6%)。放疗期间出现3、4级淋巴细胞减少的患者, 在放疗结束1个月后, 有33.3%可以恢复到正常水平, 14.8%可以恢复到1级水平, 17.8%可以恢复到2级水平。

2.4 淋巴细胞减少与患者预后的关系

在放疗前, 淋巴细胞数量正常组与降低组的PFS及OS差异无统计学意义($P=0.84$ 和 0.81)。在放疗期间, 淋巴细胞减少各组间的PFS和OS差异也无统计学意义($P=0.27$ 和 0.55)。在放疗结束1个月后, 各级淋巴细胞减少间的PFS及OS差异仍无统计学意义($P=0.83$ 和 0.55 , 图2)。

通过log-rank检验进行单因素分析, 结果显示, 放疗前、放疗期间及放疗后各淋巴细胞减少等级组的OS及PFS差异均无统计学意义($P>0.05$)。其他临床变量差异也无统计学意义($P>0.05$, 表2)。

COX模型纳入年龄、分期、PCI及淋巴细胞减少等变量进行多因素分析, 结果显示, 放疗前、放疗期间及放疗后各级淋巴细胞减少均非OS或PFS的独立影响因素($P>0.05$); 仅PCI与PFS呈临界相关[风险比(hazard ratio, HR)=2.57, 95% CI: 1.30~5.09, $P=0.007$, 表3]。未发现本组人群中的性别、分期、吸烟史、是否同步化疗与PFS及OS有相关性。

3 讨论

在本研究中, 79.4%的患者在放疗期间会出现3、4级淋巴细胞减少, 但到放疗结束1个月后, 50.6%的患者可以恢复到正常水平。我们未发现放疗前、放疗期间及放疗后的淋巴细胞数量与患者预后存在相关性, 这与我们在NSCLC中观察到的情况不同^[15-16], 这可能与SCLC独特的生物学行为有关。SCLC对放化疗高度敏感, 其疗效更取决于放化疗的直接杀伤作用, 而非免疫系统的间接作用^[17-19]; 而对于NSCLC这类放化疗中度敏感的肿瘤, 其疗效更依赖于免疫系统的激活^[20-23]。

在免疫治疗时代, 放疗期间的淋巴细胞保护是当前的热点话题。有研究者^[24-25]提出, 将高危区未明确转移或经诱导治疗后完全缓解的淋巴结豁免照射, 以缓解放疗引起的淋巴细胞减少和淋巴结功能障碍。我们认为, 至少在LS-SCLC中, 这种想法是不适用的, 原因如下: 第一, LS-SCLC放疗过程中的淋巴细胞减少并未影响患者疗效; 第二, 淋巴细胞对放射线高度敏感, 小幅度的照射体积减少不会显著影响到淋巴细胞数量; 第三, 对于高度敏感的肿瘤, 放射线的直接杀伤作用是最可靠的^[26-29]。因此, 在防止淋巴结漏照射和淋巴细胞保护两方面, 我们更倾向于前者。在心肺损伤可控的前提下, 尽可能减少淋

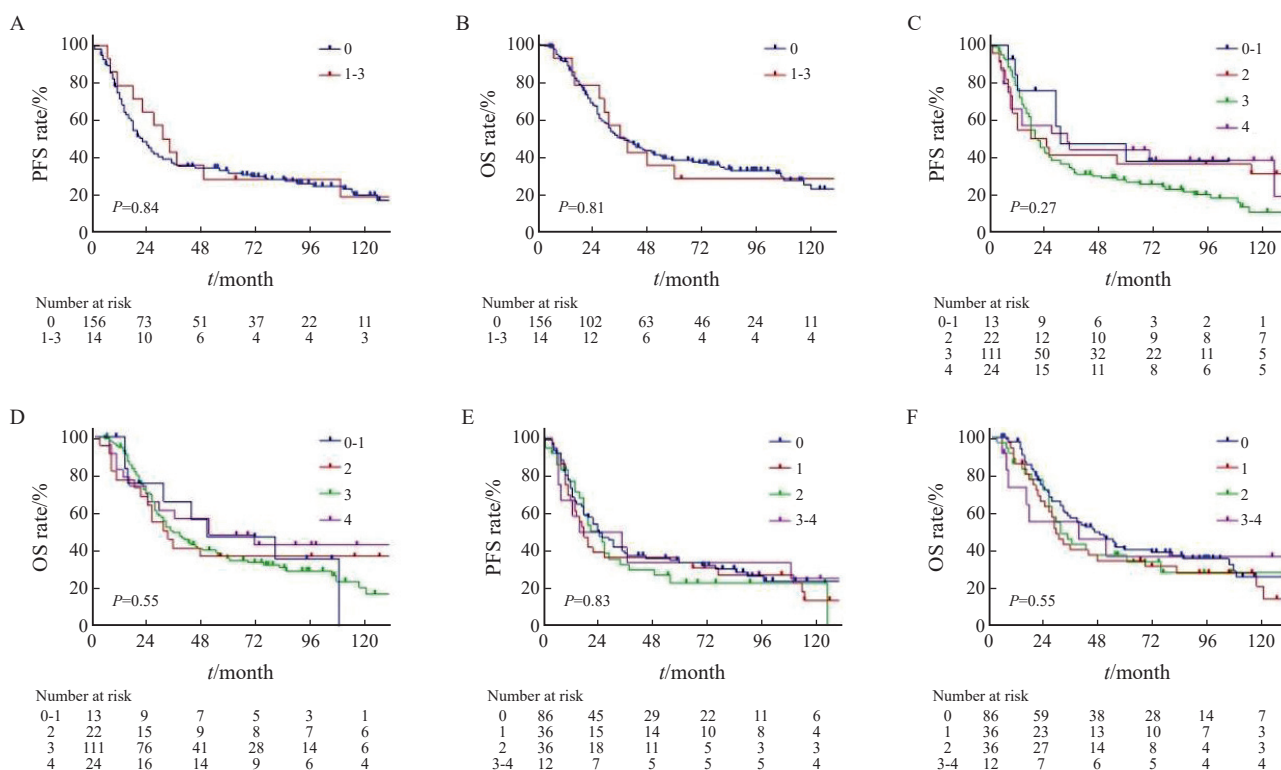


图2 放疗前、放疗期间及放疗后1个月的淋巴细胞减少与生存率的关系

Fig. 2 Lymphopenia before, during and 1 month after radiotherapy and survival

A, B: Lymphopenia before radiotherapy; C, D: Lymphopenia before radiotherapy; E, F: Lymphopenia 1 month after radiotherapy.

表2 OS和PFS的单因素分析

Tab. 2 Univariate analyses for OS and PFS

Factor	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
Age (<60 years vs ≥60 years)	1.306	0.816-2.089	0.266	1.302	0.847-1.999	0.229
Gender (female vs male)	1.554	0.796-3.035	0.197	1.612	0.874-2.971	0.126
TNM stage (III vs II)	2.188	0.966-4.960	0.061	1.446	0.762-2.745	0.259
Concurrent chemoradiotherapy (yes vs no)	1.087	0.336-3.512	0.890	0.872	0.349-2.184	0.771
Smoker (yes vs no)	1.209	0.643-2.275	0.555	1.126	0.656-1.933	0.667
PCI (no vs yes)	0.801	0.357-1.797	0.590	1.630	0.905-2.938	0.104
Lymphopenia before radiotherapy (yes vs no)	1.115	0.599-2.075	0.731	1.025	0.578-1.818	0.654
Lymphopenia during radiotherapy (G3-4 vs G0-2)	0.931	0.572-1.514	0.772	1.084	0.638-1.843	0.720
Lymphopenia after radiotherapy (G3-4 vs G0-2)	1.117	0.587-2.125	0.736	1.109	0.624-1.970	0.663

巴结的漏照射。

尽管本研究未发现SCLC放疗期间的淋巴细胞减少与患者预后的相关性，但是并不意味着不需要重视放射性淋巴细胞减少的危害。事实上，在临床上观察到一部分患者在放疗后出现带状疱疹、反复感染等，都可能与放疗对免疫系统的摧毁有关。考虑到淋巴细胞对射线高度敏感，降低损伤很难，本课题组目前将研究重心聚焦在如何促进免疫系统恢复。基础研究^[30-32]表明，细胞

因子如白细胞介素 (interleukin, IL) -7和IL-15可以促进淋巴细胞增殖。这些细胞因子的临床应用价值尚待进一步验证。

本研究是回顾性研究，存在筛选患者的偏倚。放疗期间及放疗后的血常规检查时间点并不统一，可能会影响到研究结果。本研究的患者均未接受过免疫治疗，在免疫治疗时代，放疗期间的淋巴细胞减少或放疗后的淋巴细胞恢复情况是否会影响免疫治疗的效果，尚有待进一步观

表3 OS和PFS的多因素分析

Tab. 3 Multivariate analyses for OS and PFS

Factor	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
Lymphopenia before radiotherapy (yes vs no)	1.356	0.552-3.329	0.507	1.226	0.569-2.643	0.603
Lymphopenia during radiotherapy (G3-4 vs G0-2)	1.327	0.598-2.945	0.486	1.257	0.638-2.477	0.509
Lymphopenia after radiotherapy (G3-4 vs G0-2)	0.702	0.197-2.504	0.585	0.758	0.299-1.925	0.560
Age (<60 years vs ≥60 years)	1.417	0.741-2.708	0.292	1.472	0.843-2.569	0.174
Gender (female vs male)	0.637	0.215-1.883	0.414	0.434	0.175-1.075	0.071
TNM stage (III vs II)	2.307	0.989-5.382	0.053	1.260	0.639-2.489	0.505
Concurrent chemoradiotherapy (yes vs no)	0.797	0.237-2.683	0.714	0.780	0.299-2.031	0.780
Smoker (yes vs no)	1.185	0.536-2.619	0.676	0.989	0.515-1.900	0.974
PCI (no vs yes)	1.038	0.431-2.499	0.934	2.574	1.301-5.092	0.007

Lymphopenia at three time points was separately entered into the model, with other factors adjusted as confounding variables.

察。本研究提供了免疫治疗之前对局限期小细胞肺癌患者进行放疗的基线数据, 有望为未来评估免疫治疗联合放化疗对淋巴细胞减少的影响提供参考。免疫治疗可能依赖功能性淋巴细胞, 此时放疗引起的淋巴细胞减少是否会影响疗效值得进一步研究。

综上所述, 本研究分析了LS-SCLC放疗前、放疗期间及放疗后的淋巴细胞数量, 并未发现放疗引起的淋巴细胞减少会影响患者预后。

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