



KELIM及BRCA突变状态对晚期高级别浆液性卵巢癌 中间型肿瘤细胞减灭术预后的影响*

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【摘要】目的 探讨CA125消除速率常数(CA125 elimination rate constant k, KELIM)对接受新辅助化疗联合中间型肿瘤细胞减灭术(neoadjuvant chemotherapy followed by interval debulking surgery, NACT-IDS)的晚期高级别浆液性卵巢癌(high-grade serous ovarian cancer, HGSOc)患者疗效及预后的预测价值,并分析其与乳腺癌易感基因(breast cancer susceptibility gene, BRCA)突变状态的联合预后意义。**方法** 回顾性纳入106例接受NACT-IDS治疗的晚期HGSOc患者。计算NACT期间的KELIM,以1.0为界分为高、低两组。比较两组临床病理特征、R0切除率及铂敏感率。采用Logistic回归分析R0切除的预测因素,采用Kaplan-Meier法和Cox回归分析无进展生存期(progression free survival, PFS)的影响因素。进一步根据KELIM与BRCA状态进行联合分层,分析各亚组的铂耐药复发风险。**结果** KELIM $\geq$ 1组R0切除率高于KELIM<1组(77.1% vs 55.2%),差异有统计学意义($P=0.024$)。多因素Logistic分析显示, KELIM是R0切除的独立预测因子($OR=2.922$, 95% CI: 1.112 ~ 7.678)。生存分析显示, KELIM $\geq$ 1组的PFS长于KELIM<1组(33.0个月 vs 18.0个月),差异具有统计学意义($P<0.001$)。多因素Cox回归显示, KELIM $\geq$ 1与PFS进展风险降低相关($HR=0.481$, 95% CI: 0.280 ~ 0.826);联合分层分析显示,“KELIM $\geq$ 1且BRCA阳性”亚组未观察到铂耐药复发(0/21),与KELIM<1且BRCA阴性组相比较,其铂耐药复发风险较低($OR=0.053$, 95% CI: 0.003 ~ 0.932, $P=0.006$)。**结论** KELIM是预测NACT-IDS患者手术结局和PFS的有效动态标志物。KELIM与BRCA状态联合分层能更精准地识别铂耐药复发风险极低的“双重有利”人群,为晚期HGSOc的个体化治疗与风险分层管理提供重要依据。

【关键词】 高级别浆液性卵巢癌 中间型肿瘤细胞减灭术 新辅助化疗 CA125消除速率常数K
BRCA基因

Effect of Cancer Antigen-125 Elimination Rate Constant K and BRCA Mutation Status on the Prognosis of Interval Debulking Surgery in Advanced High-Grade Serous Ovarian Cancer

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[Abstract] Objective To investigate the predictive value of the cancer antigen-125 elimination rate constant K (KELIM) for treatment response and prognosis in patients with advanced high-grade serous ovarian cancer (HGSOc) undergoing neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS), and to analyze the combined prognostic significance of KELIM and the mutation status of breast cancer susceptibility gene (BRCA). **Methods** A total of 106 patients with advanced HGSOc who had undergone NACT-IDS were retrospectively enrolled. The KELIM values during neoadjuvant chemotherapy were calculated, and patients were divided into high- and low-KELIM groups using a cutoff value of 1.0. Clinicopathological characteristics, R0 resection rates, and platinum sensitivity rates were compared between the two groups. Logistic regression analysis was performed to identify predictive factors for R0 resection, while Kaplan-Meier survival analysis and Cox proportional hazards regression were performed to evaluate factors associated

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with progression-free survival (PFS). Furthermore, the patients were stratified according to both KELIM and *BRCA* status to assess the risk of platinum-resistant recurrence in each subgroup. **Results** The R0 resection rate was higher in the $KELIM \geq 1$ group than in the $KELIM < 1$ group (77.1% vs 55.2%), and the difference was statistically significant ($P = 0.024$). Multivariate logistic regression analysis showed that KELIM was an independent predictor of R0 resection (odds ratio [OR] = 2.922, 95% CI: 1.112–7.678). Survival analysis demonstrated longer PFS in the $KELIM \geq 1$ group compared with that in the $KELIM < 1$ group (33.0 months vs 18.0 months), and the difference was statistically significant ($P < 0.001$). Multivariate Cox regression analysis showed that $KELIM \geq 1$ was associated with a reduced risk of disease progression (hazard ratio [HR] = 0.481, 95% CI: 0.280–0.826). Combined stratification analysis revealed that no platinum-resistant recurrence was observed in the subgroup with both $KELIM \geq 1$ and a *BRCA*-positive status (0/21). Compared with patients with $KELIM < 1$ and a *BRCA*-negative status, this subgroup exhibited a lower risk of platinum-resistant recurrence (OR = 0.053, 95% CI: 0.003–0.932, $P = 0.006$). **Conclusion** KELIM is an effective dynamic biomarker for predicting surgical outcomes and PFS in patients undergoing NACT-IDS. Combined stratification by KELIM and *BRCA* status allows more precise identification of the patient population with both $KELIM \geq 1$ and *BRCA*-positive status, who have an extremely low risk of platinum-resistant recurrence, thereby providing an important basis for individualized treatment and risk stratification management in patients with advanced HGSOC.

[Key words] High-grade serous ovarian cancer Interval debulking surgery Neoadjuvant chemotherapy Cancer antigen-125 elimination rate constant K *BRCA* gene

卵巢癌是病死率最高的妇科恶性肿瘤,其中晚期高级别浆液性卵巢癌(high-grade serous ovarian cancer, HGSOC)是最常见的亚型。因其早期症状隐匿,超过70%的患者确诊时已属晚期。对于肿瘤负荷大、伴有大量腹水或一般状况无法耐受初次肿瘤细胞减灭术(primary debulking surgery, PDS)的患者,新辅助化疗联合中间型肿瘤细胞减灭术(neoadjuvant chemotherapy followed by interval debulking surgery, NACT-IDS)已成为标准治疗模式之一^[1]。然而,患者对NACT的反应存在异质性,部分患者即使完成治疗,仍面临快速复发与铂类耐药的问题,导致预后不良。研究显示,尽管乳腺癌易感基因(breast cancer susceptibility gene, *BRCA*)突变患者通常对铂类药物更为敏感且生存期较长,但仍有部分患者出现耐药与早期复发^[2-3]。因此,如何在治疗前或治疗早期准确评估患者对铂类药物的敏感性,成为指导临床决策、改善疗效的关键。

目前,肿瘤标志物 CA125是广泛应用的血清标志物,但其单点测定特异性有限^[4-5]。You等^[6]提出的KELIM,通过动力学模型定量评估化疗中肿瘤标志物CA125的清除速率,为预测疗效提供了新思路。尽管KELIM在PDS患者中的预后价值已得到验证,但针对NACT-IDS人群的研究仍有限,且较少将其与*BRCA*基因状态结合分析^[7-12]。为此,本研究旨在通过回顾性分析106例接受NACT-IDS治疗的HGSOC患者的CA125动力学数据,评估KELIM对IDS后R0切除率、无铂间期(platinum free interval, PFI)、PFS及总生存期(overall survival, OS)的预测能力,并探讨其与*BRCA*状态的联合预后意义,为晚期HGSOC的风险

分层与个体化治疗提供依据。

1 资料与方法

1.1 研究对象

本研究为一项单中心回顾性分析。选择2019年1月—2024年12月期间于本院妇产科接受治疗的晚期HGSOC患者106例。共筛查171例,按排除标准排除65例,最终纳入106例(图1)。所有患者均接受NACT后行IDS。NACT方案以铂类联合紫杉类为主,每3周为1个周期,通常完成3~4个周期后评估是否进入IDS,术后按残余病灶评估减瘤效果,定义R0为无肉眼残余,R1/R2为存在肉眼残余。*BRCA* 1/2检测来源于胚系和/或体细胞检测,将致病或可能致病变异定义为*BRCA*阳性(*BRCA*+),未检出致病或意义未明变异定义为*BRCA*阴性(*BRCA*-)。IDS后患者接受标准辅助化疗完成一线治疗;复发后按临床实践给予二线及后续治疗方案。

纳入标准:(1)经病理组织学确诊为高级别浆液性卵巢癌;(2)年龄 ≥ 18 岁;(3)FIGO分期为Ⅲ-Ⅳ期;(4)接受NACT ≥ 2 个周期,且随后行IDS;(5)NACT期间具有完整的血清CA125监测数据(至少3个时间点),可用于计算KELIM。排除标准:(1)合并其他恶性肿瘤;(2)外院手术或未规范治疗;(3)临床随访资料严重缺失。本研究经医院伦理委员会批准(2022-KY045),患者知情同意。

1.2 资料收集

通过医院电子病历系统回顾性收集患者资料,主要包括:①人口学及临床特征:年龄、体质质量指数(body mass index, BMI)、FIGO分期;②治疗信息:NACT周期

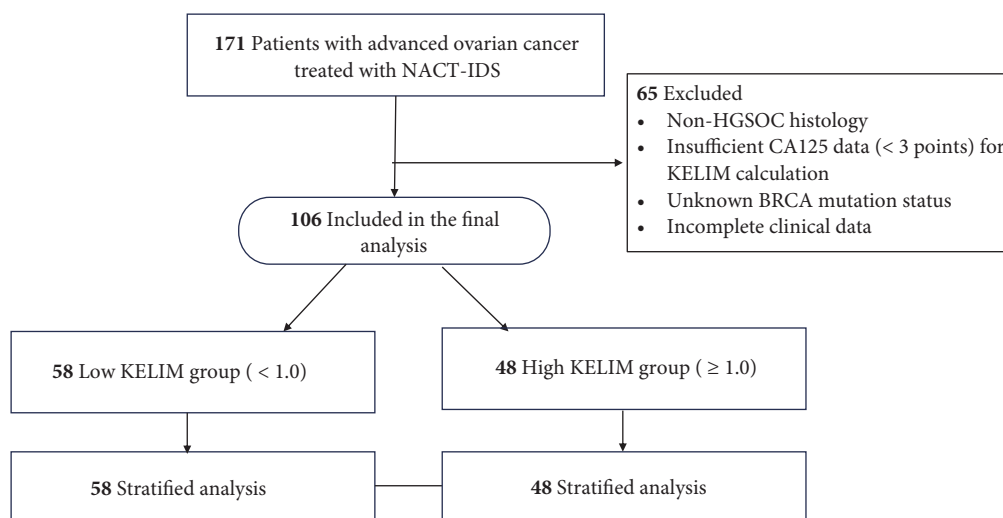


图1 晚期HGSOE患者研究队列的入组标准及数据处理流程

Fig 1 Study cohort enrollment criteria and data processing flowchart for advanced HGSOE patients

数、IDS手术结局;③生物标志物:BRCA 1/2基因状态;④随访信息:疾病进展、生存状态,随访截止日期为2025年12月31日。OS:从初次就诊起至患者因任何原因死亡或随访结束的时间。PFS:从初次就诊起至肿瘤进展或复发或随访结束的时间。PFI:一线治疗中最后一次含铂给药至出现进展或复发或随访结束的时间。PFI>6个月被称为铂敏感,PFI≤6个月定义为铂耐药^[13]。

1.3 KELIM计算:

本研究收集了患者在NACT期间血清CA125的数据。通过记录化疗开始后100 d内的至少3次CA125测量值及对应的化疗时间,利用在线非线性混合效应模型计算CA125的模型化消除速率常数(KELIM)(使用在线工具<http://www.biomarker-kinetics.org/CA125>进行计算)。该指标用于评估患者在NACT期间CA125水平的动态下降速率。随后,以KELIM = 1.0为阈值,将患者分为两组:KELIM<1(低KELIM组),KELIM≥1(高KELIM组)。

1.4 统计学方法

采用SPSS 26.0软件进行数据分析。计量资料(连续变量)根据其分布情况描述:符合正态分布者以 $\bar{x} \pm s$ 表示,组间比较分别采用 t 检验或Mann-Whitney U 检验;计数资料以例数(%)表示,组间比较采用 χ^2 检验或Fisher确切检验。以IDS后是否R0切除为结局构建Logistic回归模型,报告OR及95% CI;以PFS和OS为结局构建Cox比例风险回归模型,报告HR及95% CI。采用Kaplan-Meier法绘制生存曲线并以Log-rank检验比较差异。鉴于本研究为回顾性观察性研究,为降低混杂因素影响,多因素模型纳入临床上可能与手术结局及预后相关且本研究可获得的变量进行调整。Logistic模型纳入年龄、绝经状态、BMI、

FIGO分期、NACT疗程、BRCA状态及KELIM分组;Cox模型纳入年龄、FIGO分期、BRCA状态、手术残余病灶(R0/非R0)及KELIM分组。所有检验均为双侧检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 患者临床病理特征

本研究回顾性纳入在本中心接受IDS的晚期卵巢癌患者共171例。根据预设排除标准共排除65例,主要原因包括:非高级别浆液性癌、术前CA125数据不足无法计算KELIM、BRCA基因突变状态未知、临床资料缺失以及合并其他肿瘤等。最终共有106例患者进入统计分析(图1)。全组患者平均年龄为(58.56±9.35)岁,平均BMI为(23.27±3.16)kg/m²。绝大多数患者就诊时已绝经(75.5%, 80 / 106),FIGO分期以Ⅲ期为主(66.0%, 70 / 106)。NACT≤3次者占63.2%(67 / 106),IDS术后达到R0切除者占65.1%(69 / 106)。BRCA阳性率为34.0%(36 / 106),铂敏感患者占81.1%(86 / 106)(表1)。

根据KELIM将患者分为两组(KELIM<1组58例,KELIM≥1组48例),两组在年龄、BMI、绝经状态及FIGO分期方面差异无统计学意义($P>0.05$)。与KELIM≥1组相比,KELIM<1组接受>3次NACT的比例升高(51.7% vs 18.8%, $P=0.001$),且IDS术后R0切除率明显更低(55.2% vs 77.1%, $P=0.024$)。此外,KELIM≥1组的BRCA阳性率呈较高趋势(43.8% vs 25.9%, $P=0.053$),并且铂敏感比例更高(91.7% vs 72.4%, $P=0.012$)(表1)。上述结果提示,较高KELIM与更少的NACT周期、更高的R0切除率及更高的铂敏感率相关,为其后续预后差异提供了临床基础。

表 1 不同KELIM分组患者的临床病理特征比较

Table 1 Comparison of clinicopathological characteristics of patients in different KELIM groups

Characteristics	Overall (<i>n</i> = 106)	KELIM<1 (<i>n</i> = 58)	KELIM≥1 (<i>n</i> = 48)	t/χ^2	<i>P</i>
Age/yr., $\bar{x} \pm s$	58.56 ± 9.35	58.31 ± 8.81	58.85 ± 10.05	0.297	0.767
BMI/(kg/m ²), $\bar{x} \pm s$	23.27 ± 3.16	23.40 ± 3.42	23.12 ± 2.84	1.090	0.277
Menopausal status/case (%)				1.582	0.208
Yes	80 (75.5)	41 (70.7)	39 (81.3)		
No	26 (24.5)	17 (29.3)	9 (18.8)		
FIGO stage/case (%)				0.288	0.592
III	70 (66.0)	37 (63.8)	33 (68.8)		
IV	36 (34.0)	21 (36.2)	15 (31.2)		
NACT cycles/case (%)				10.903	0.001
≤ 3 cycles	67 (63.2)	28 (48.3)	39 (81.3)		
> 3 cycles	39 (36.8)	30 (51.7)	9 (18.8)		
Residual disease/case (%)				5.549	0.024
R0	69 (65.1)	32 (55.2)	37 (77.1)		
Non-R0	37 (34.9)	26 (44.8)	11 (22.9)		
BRCA status/case (%)				3.747	0.053
BRCA ⁺	36 (34.0)	15 (25.9)	21 (43.8)		
BRCA ⁻	70 (66.0)	43 (74.1)	27 (56.3)		
Platinum sensitivity/case (%)				6.360	0.012
Platinum-sensitive	86 (81.1)	42 (72.4)	44 (91.7)		
Platinum-resistant	20 (18.9)	16 (27.6)	4 (8.3)		

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics; NACT: neoadjuvant chemotherapy; BRCA: breast cancer susceptibility gene.

2.2 KELIM对手术结局的预测价值

在完成IDS的患者中,以是否达到R0切除为结局变量进行Logistic回归分析。将KELIM、BMI、疾病分期、NACT疗程、BRCA状态、年龄及绝经状态纳入多因素Logistic回归模型。结果显示,KELIM与R0切除相关(OR=2.922, 95% CI: 1.112 ~ 7.678, $P=0.030$),提示KELIM较高者达到R0切除的可能性更大;此外,BRCA状态与R0切除呈相关趋势(OR=2.423, 95% CI: 0.904 ~ 6.496, $P=0.078$)。其余变量(年龄、绝经状态、BMI、疗程及FIGO分期)与R0切除的相关性均未达到

统计学意义(均 $P>0.05$)(表2)。综上,KELIM为预测IDS手术能否实现R0切除的独立相关因素,提示化疗期间CA125动力学反映的肿瘤生物学敏感性,可能与肿瘤负荷下降及实现满意减灭的可行性相关。

2.3 KELIM对PFS和OS的影响因素分析

根据KELIM将患者分为KELIM<1组与KELIM≥1组后行Kaplan-Meier生存分析。PFS方面,KELIM≥1组的中位PFS为33.0个月,而KELIM<1组为18.0个月;两组PFS曲线差异有统计学意义(Log-rank检验: $\chi^2 = 11.79$, $P<0.001$)(图2)。

为探讨PFS的独立影响因素,我们进行多因素Cox回

表 2 预测R0切除的多因素Logistic回归分析

Table 2 Multivariate logistic regression analysis of predictors for R0 resection

Category	<i>B</i>	SE	χ^2	<i>P</i>	Odds ratio (95% CI)
Age/yr	-0.025	0.033	0.592	0.442	0.975 (0.914-1.040)
Menopausal status	-0.299	0.689	0.188	0.665	0.742 (0.192 ~ 2.864)
BMI/(kg/m ²)	0.049	0.069	0.500	0.480	1.050 (0.917 ~ 1.202)
Chemotherapy cycles	0.386	0.484	0.637	0.425	1.471 (0.570 ~ 3.800)
KELIM	1.072	0.493	4.732	0.030	2.922 (1.112 ~ 7.678)
BRCA status	0.885	0.503	3.096	0.078	2.423 (0.904-6.496)
FIGO stage	0.454	0.478	0.899	0.343	1.574 (0.616 ~ 4.019)

The abbreviations are explained in the note to Table 1. Age and BMI are continuous variables. For categorical variables, the reference groups were as follows, premenopausal for menopausal status, stage III for FIGO stage, BRCA-negative for BRCA status, ≤ 3 cycles for chemotherapy cycles, and KELIM < 1 for KELIM group.

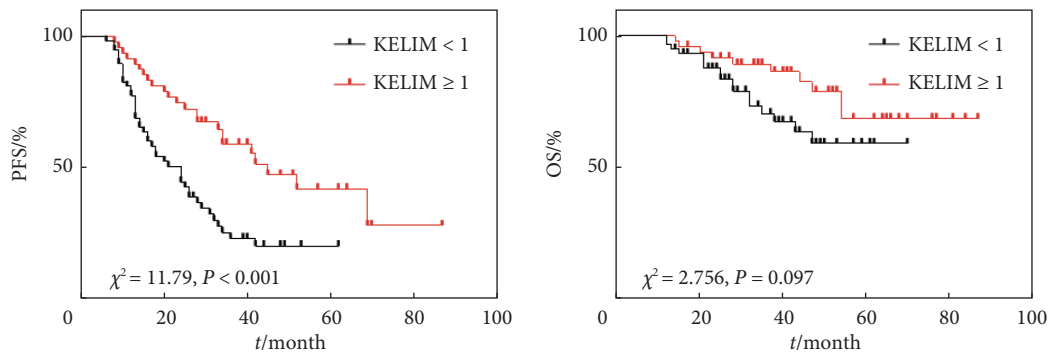


图 2 不同KELIM分组的PFS (A) 与OS (B) 生存曲线

Fig 2 Survival curves for PFS (A) and OS (B) across different KELIM groups

归分析(表3)。在校正年龄、FIGO分期、BRCA状态及手术残余病灶后,KELIM分组和是否R0切除仍与PFS进展风险独立相关。与KELIM<1组相比,KELIM≥1组进展风险降低(HR = 0.481, 95% CI: 0.280 ~ 0.826);与非R0切除组相比,R0切除组进展风险降低(HR = 0.461, 95% CI: 0.275 ~ 0.772)。而年龄、FIGO分期及BRCA状态与PFS的相关性均未达到统计学意义(均P>0.05)。

表 3 晚期HGSOC患者PFS的多因素COX回归分析
Table 3 Multivariate Cox regression analysis of PFS in advanced HGSOC patients

Category	HR	95% CI	P
Age ≥ 58 yr. (vs < 58 yr.)	0.998	0.601-1.658	0.995
FIGO stage III (vs stage IV)	0.829	0.494-1.391	0.478
KELIM ≥ 1 (vs KELIM < 1)	0.481	0.280-0.826	0.008
BRCA ⁺ (vs BRCA ⁻)	0.729	0.410-1.296	0.282
R0 (vs Non-R0)	0.461	0.275-0.772	0.003

在OS方面,KELIM≥1组虽呈现更优趋势,但差异未达到统计学意义(Log-rank检验: $\chi^2 = 2.756, P=0.097$);两组中位OS均未达到,提示当前随访期间死亡事件数可能有限。综上,KELIM≥1与更长时间的PFS相关,并在OS方面观察到潜在获益趋势,但仍需更长随访或更大样本进一步验证。

2.4 KELIM与BRCA状态的联合亚组分析

为评估KELIM表型与BRCA基因型联合分层对铂耐药复发风险的影响,根据KELIM评分和BRCA状态将患者分为四个亚组,并以“KELIM<1 + BRCA阴性”为参照组进行比较。结果(表4,图3)显示:参照组的铂耐药复发率为30.2%(13/43)。与参照组相比,KELIM<1 + BRCA阳性组复发率为20.0%(3/15),差异无统计学意义(P=0.522)。KELIM≥1 + BRCA阴性组复发率为14.8%(4/27),复发风险呈下降趋势。值得注意的是,KELIM≥1 + BRCA阳性

组中未观察到铂耐药复发(0/21),因该组出现0事件,OR及95% CI采用连续性校正估计;结果显示其复发风险低于参照组(OR = 0.053, 95% CI: 0.003 ~ 0.932, P=0.006)(表4)。总体比较显示四组铂耐药复发率差异具有统计学意义(总体 χ^2 检验, P=0.032;组间比较P值采用Fisher确切检验)。

表 4 KELIM × BRCA联合分层与铂耐药复发率的影响

Table 4 Association of KELIM × BRCA Combined Stratification with Platinum-Resistant Recurrence

Joint stratification	platinum resistance n / N	Recurrence rate/%	OR	95% CI	P
KELIM < 1 + BRCA ⁻	13 / 43	30.2	1.000	-	-
KELIM < 1 + BRCA ⁺	3 / 15	20.0	0.633	0.164-2.434	0.522
KELIM ≥ 1 + BRCA ⁻	4 / 27	14.8	0.433	0.131-1.429	0.165
KELIM ≥ 1 + BRCA ⁺	0 / 21	0	0.053	0.003-0.932	0.006

The abbreviations are explained in the note to Table 1. The group with KELIM < 1 and BRCA⁻ status serves as the reference. Because the group with KELIM ≥ 1 and BRCA⁺ status had zero events, the odds ratio (OR) and 95% CI were estimated using continuity correction. P values for between-group comparisons were derived from Fisher's exact test.

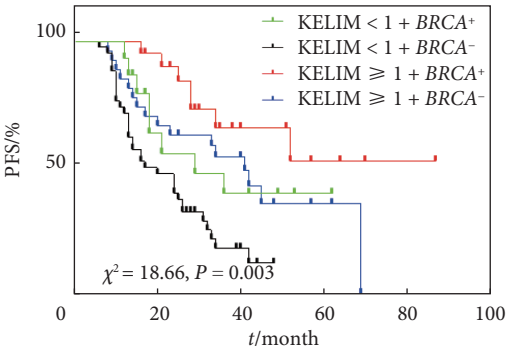


图 3 KELIM + BRCA联合分层的PFS比较
Fig 3 PFS across KELIM and BRCA status combined stratification groups

进一步的Kaplan-Meier分析显示,四组 PFS 曲线分离明显,总体差异具有统计学意义(Log-rank检验 $\chi^2 =$

18.66, $P=0.0003$) (图3), 提示KELIM与BRCA状态的联合分层不仅可区分铂耐药复发风险, 也能进一步识别预后较好的低危人群。

3 讨论

NACT期间肿瘤标志物的动态变化, 为评估晚期卵巢癌的体内药敏反应提供了重要窗口^[11,14]。KELIM通过动力学模型整合了标志物的清除速率与时间信息, 相较于单次绝对值, 能更精准地量化肿瘤对治疗的早期生物学应答^[5-6]。在接受 NACT-IDS 的晚期 HGSOE 队列中, 我们证实 KELIM 具有明确的临床分层价值: 较高的 KELIM (≥ 1) 与更高的R0切除率相关, 并在多因素模型中仍保持独立预测作用, 提示快速 CA125 清除不仅是化疗敏感性的表型体现, 也可能意味着肿瘤负荷更有效地缩减, 从而提升手术可切除性并为手术时机优化提供客观依据^[15-17]。

在预后方面, KELIM ≥ 1 与更高的PFS相关, 进一步印证其对识别化疗获益人群的有效性; 而 OS 未达到统计学差异但呈有利趋势, 可能与随访时间、死亡事件数有限以及后续维持治疗方案差异有关。值得注意的是, 单一指标往往难以覆盖 HGSOE 的生物学复杂性。BRCA 1/2突变作为同源重组修复缺陷的经典分子标志, 代表对铂类及 PARP 抑制剂更敏感的遗传亚群^[2-3,15]。

本研究将反映治疗反应表型的 KELIM 与代表遗传易感基因型的 BRCA 状态联合分析, 观察到更精细的风险分层: 铂耐药复发风险随联合分层呈梯度变化, 且在“KELIM ≥ 1 + BRCA 阳性”亚组未观察到铂耐药复发事件。这一结果提示二者具有互补作用: BRCA 体现潜在药物敏感性, 而 KELIM 捕捉真实发生的早期治疗反应; 即使 BRCA 状态在多因素 Cox 模型中未显示独立相关性, 其与 KELIM 的组合仍可能在临床上提供更具辨识度的风险分层信息。需要强调的是, 0 事件亚组样本量有限且随访长度可能影响事件捕获, 相关结论应理解为“本队列观察结果”, 仍需更大样本与外部队列验证。

从临床应用角度, 联合分层策略可为 NACT-IDS 治疗链条提供更可操作的决策支持: 在 NACT 早期即可基于 CA125 动态计算 KELIM, 用于预判 IDS 的可切除性及复发风险; 其中低 KELIM (尤其合并 BRCA 阴性) 的患者可能属于高风险人群, 提示需要更谨慎地评估手术获益、优化围治疗策略并加强随访管理; 而高 KELIM 合并 BRCA 突变的患者可能预后较好, 但仍应结合影像学肿瘤负荷、手术残余及后续维持治疗进行综合判断^[18-20]。

综上, KELIM可作为NACT-IDS晚期HGSOE患者手术结局与PFS的有效动态预测指标; 与BRCA状态联合分

层可进一步识别铂耐药复发高危与低危人群, 为个体化治疗与随访管理提供重要依据。本研究为单中心回顾性观察性研究, 尽管在多因素 Logistic 与 Cox 模型中对部分可获得的临床变量进行了调整, 但仍可能存在残余混杂。部分影响手术可切除性与预后的关键因素 (如术者经验及手术策略差异、术前肿瘤负荷、患者合并症与体能状态、后续维持治疗策略等) 在回顾性资料中记录不完整或缺失, 未能全部纳入模型。未来研究可进一步优化, 以全面评估其对预后的作用, 并通过多中心前瞻性研究, 结合分子分型与治疗策略信息, 对KELIM以及BRCA联合分层的最优阈值及其对个体化治疗决策的增益进行进一步验证。

* * *

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