论　著　　临床研究

HER2低表达乳腺癌病理完全缓解的影响因素及其与预后的相关性分析

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[摘要]　**目的**　探究人表皮生长因子受体2(HER2)低表达乳腺癌新辅助化疗(NAC)后病理完全缓解(pCR)的影响因素及其与预后的相关性。**方法**　回顾性分析2018年2月28日—2021年2月28日于九江学院第二附属医院接受NAC的HER2低表达乳腺癌患者的临床资料，根据是否获得pCR将其分为pCR组(获得pCR，*n*=143)与非pCR组(未获得pCR，*n*=300)。收集并比较两组患者临床病理资料，包括年龄、手术方式、NAC方案、是否接受术后放疗、肿瘤临床分期、肿瘤cT分期、肿瘤cN分期、病理类型、肿瘤Nottingham分级、激素受体(HR)状态、Ki-67状态、月经状态以及是否接受内分泌治疗等，采用二元logistic回归分析NAC后pCR的影响因素。采用1∶1倾向性评分平衡两组的基线资料，比较匹配后两组患者的基线资料，采用Kaplan-Meier法对平衡后两组患者进行生存分析，采用多因素Cox比例风险回归模型分析平衡后pCR对HER2低表达乳腺癌无病生存期(DFS)及总生存期(OS)的影响。**结果**　共纳入443例接受NAC的HER2低表达乳腺癌患者，年龄(49.5±8.0)岁。二元logistic回归分析结果显示，肿瘤临床分期(*OR*=0.498，95%CI 0.267~0.930)、HR状态(*OR*=0.513，95%CI 0.328~0.801)、Ki-67状态(*OR*=2.580，95%CI 1.366~4.874)、肿瘤Nottingham Ⅲ级(*OR*=3.197，95%CI 1.147~8.910)、内分泌治疗(*OR*=0.513，95%CI 0.328~0.801)为HER2低表达乳腺癌NAC后pCR的独立影响因素(*P*<0.05)。倾向性评分匹配后，pCR组与非pCR组各80例，两组临床病理特征差异均无统计学意义(*P*>0.05)，中位随访时间分别为45.0个月(95%CI 43.1~46.9)与43.0个月(95%CI 41.0~45.0)，pCR组无病生存率高于非pCR组(87.5% *vs.* 70.0%，*P*=0.004)，但两组总生存率差异无统计学意义(88.8% *vs.* 85.0%，*P*=0.438)。多因素Cox比例风险回归模型分析显示，pCR是HER2低表达乳腺癌患者DFS的独立影响因素(*HR*=0.312，95%CI 0.142~0.688，*P*=0.004)，但不是OS的独立影响因素。**结论**　肿瘤临床分期低、HR阴性、Ki-67高表达、肿瘤Nottingham分级高、未接受内分泌治疗的HER2低表达乳腺癌患者更易获得pCR，且获得pCR能显著延长患者的DFS，但对其OS并无明显改善。

[关键词]　HER2低表达乳腺癌；新辅助化疗；病理完全缓解；无病生存期；总生存期

Analysis of factors influencing pathologic complete response and its correlation with prognosis in HER2-low breast cancer

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[**Abstract**]　**Objective**　To investigate the factors influencing pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) and its correlation with prognosis in patients with human epidermal growth factor receptor 2 (HER2)-low breast cancer. **Methods**　A retrospective analysis was conducted on patients with HER2-low breast cancer who underwent NAC at

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the Second Affiliated Hospital of Jiujiang College from February 28, 2018 to February 28, 2021. Patients were divided into pCR group (achieved pCR, *n*=143) and non-pCR group (did not achieve pCR, *n*=300) based on pCR status. General clinicopathological data were collected and compared between the two groups, including age, surgical method, NAC regimen, postoperative radiotherapy, clinical tumor stage, tumor cT stage, tumor cN stage, pathological type, tumor Nottingham grade, hormone receptor (*HR*) status, Ki-67 status, menopausal status, and endocrine therapy. Binary logistic regression analysis was used to identify factors influencing pCR after NAC. Propensity score matching (1∶1) was employed to balance baseline characteristics between the two groups. The matched groups' baseline data were compared. Kaplan-Meier method was used for survival analysis of the matched cohorts. Multivariate Cox proportional hazards regression models were used to analyze the independent influence of pCR on disease-free survival (DFS) and overall survival (OS) in HER2-low breast cancer after matching. **Results** A total of 443 patients with HER2-low breast cancer receiving NAC were included, with a mean age of (49.5±8.0) years. Binary logistic regression analysis identified clinical tumor stage (*OR*=0.498, 95%CI 0.267-0.930), HR status (*OR*=0.513, 95%CI 0.328-0.801), Ki-67 status (*OR*=2.580, 95%CI 1.366-4.874), tumor Nottingham grade Ⅲ (*OR*=3.197, 95%CI 1.147-8.910), and endocrine therapy (*OR*=0.513, 95%CI 0.328-0.801) as independent factors influencing pCR after NAC (*P*<0.05). After propensity score matching, 80 patients remained in each group (PCR and non-PCR). No significant differences were found in clinicopathological characteristics between the matched groups (*P*>0.05). The median follow-up time was 45.0 months (95%CI 43.1-46.9) for pCR group and 43.0 months (95%CI 41.0-45.0) for non-pCR group. The DFS rate was significantly higher in pCR group than that in non-pCR group (87.5% *vs*. 70.0%, *P*=0.004), but there was no significant difference in OS rate (88.8% *vs*. 85.0%, *P*=0.438). Multivariate Cox regression analysis showed that pCR was an independent factor influencing on DFS (*HR*=0.312, 95%CI 0.142-0.688, *P*=0.004), but not OS in HER2-low breast cancer patients. **Conclusions** Patients with HER2-low breast cancer who have a lower clinical tumor stage, HR-negative status, high Ki-67 expression, high tumor Nottingham grade, and absence of endocrine therapy are more likely to achieve pCR. Achieving pCR prolongs DFS significantly but does not significantly improve OS in these patients.

[**Key words**] HER2-low breast cancer; neoadjuvant chemotherapy; pathological complete response; disease-free survival; overall survival

乳腺癌的发病率仅次于肺癌，居所有恶性肿瘤的第2位，也是全球癌症死亡的主要原因之一[1]。人表皮生长因子受体2(human epidermal growth factor receptor 2，HER2)是影响乳腺癌患者预后的重要标志物，也是乳腺癌病理分子分型的重要依据之一[2]。目前，HER2阳性判定标准为免疫组化(immunohistochemistry，IHC)(+++)或(++)而荧光原位杂交(fluorescence *in situ* hybridization，FISH)阳性[3]。随着靶向治疗(抗HER2治疗)研究的不断深入，HER2阳性乳腺癌的疗效显著提高。既往IHC(+)或(++)/FISH阴性乳腺癌被认为是HER2阴性乳腺癌，其与无HER2表达[IHC(−)]的乳腺癌均不能从抗HER2治疗中获益[4-5]。因此，IHC(+)或(++)/FISH阴性乳腺癌被归类为管腔型或三阴性乳腺癌，其治疗方法与IHC−的乳腺癌相同。近年来随着新型抗HER2药物的出现，HER2低表达的概念再次受到关注。目前多数研究将IHC(+)或(++)/FISH阴性乳腺癌定义为HER2低表达乳腺癌，占全部乳腺癌类型的45%~55%[6-8]。有研究表明，HER2低表达乳腺癌具有相对独特的临床病理特征[9]，相较IHC(−)的乳腺癌，其组织学分级低、临床分期早，但腋窝淋巴结及脑转移的风险高。此外，HER2低表达也可影响乳腺癌患者的预后。Zhang等[10]发现，HER2低表达乳腺癌新辅助化疗(neoadjuvant chemotherapy，NAC)后病理完全缓解(pathologic complete response，pCR)率低，但长期生存预后更佳。Tan等[11]分析了28 280例HER2阴性非转移性乳腺癌患者，发现HER2低表达患者的无复发生存率和总生存率明显高于IHC(−)者，表明HER2低表达乳腺癌预后较好。恩美曲妥珠单抗(trastuzumab emtansine，T-DM1)是一种新型抗HER2药物，为曲妥珠单抗和抗微管剂maytansine衍生物的结合物，具有HER2靶向特性和T-DM1的细胞内递送能力。T-DM1通过HER2介导的内吞作用进入细胞，诱导细胞产生毒性[12]。德曲妥珠单抗(trastuzumab deruxtecan，T-DXd)由人源化单克隆抗体曲妥珠单抗、基于GGFG四肽序列的可裂解连接子和新型DNA拓扑异构酶Ⅰ抑制剂DXd组成，其药物抗体比高达8∶1。DESTINY-Breast04研究[13]是评估T-DXd治疗HER2低表达晚期乳腺癌疗效和安全性的首个随机Ⅲ期临床试验，结果表明HER2低表达乳腺癌可从抗HER2治疗中获益，并不完全类似于IHC(−)的乳腺癌。已有研究表明，乳腺癌NAC后的pCR与预后具有明显相关性[14-15]，但在HER2低表达乳腺癌患者中，pCR与预后的关系尚未明确。本研究探究HER2低表达乳腺癌患者NAC后pCR的影响因素及其与预后的相关性，以期加深临床对HER2低表达乳腺癌的认识。

1 资料与方法

1.1 研究对象 回顾性分析2018年2月28日—2021年2月28日于九江学院第二附属医院接受治疗的女性乳腺癌患者。所有患者在接受NAC前均接受空芯针穿刺活检。纳入标准：(1)病理检查结果为Ⅱ—Ⅲ期乳腺癌；(2)HER2低表达乳腺癌；(3)接受规范、标准的NAC；(4)行乳腺癌手术治疗。排除标准：(1)双侧乳腺癌；(2)失访；(3)临床数据缺失；(4)伴有其他原发性肿瘤；(5)术后未行规范辅助治疗。本研究获九江学院医学伦理委员会审批(2024-022)。根据纳入标准共筛选出510例接受NAC的HER2低表达女性乳腺癌患者，根据排除标准排除67例，最终纳入443例，其中未获得pCR(非pCR组)300例，获得pCR(pCR组)143例。按照1:1的比例进行倾向性评分匹配后，共160例被纳入生存分析，其中未获得pCR(非pCR组)80例，获得pCR(pCR组)80例。研究人群筛选过程见图1。

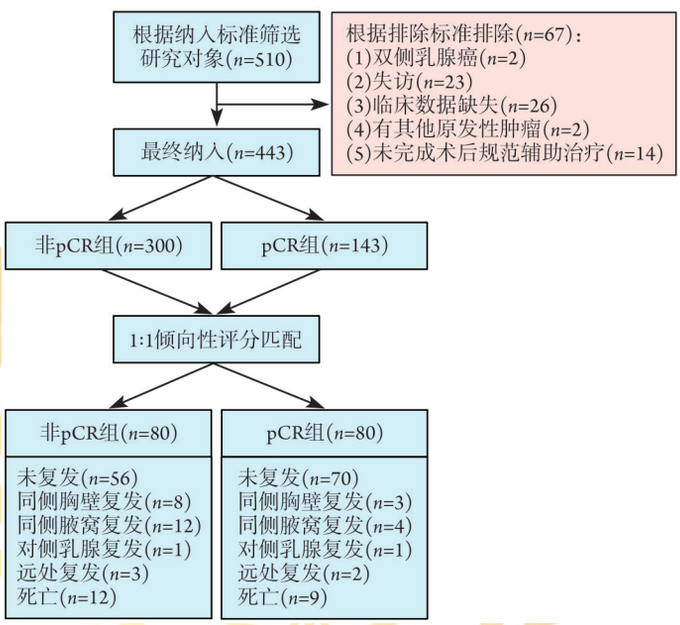


图1 人表皮生长因子受体2(HER2)低表达乳腺癌研究人群筛选流程

Fig.1 Flow chart of illustrate the study participants with human epidermal growth factor receptor 2 (HER2)-low breast cancer

1.2 NAC方案及疗效评估标准 NAC方案：表柔比星联合环磷酰胺序贯多西他赛或紫杉醇每周1次[EC-T(wP)]，表柔比星联合环磷酰胺每2周1次序贯紫杉醇每周或每2周1次(dEC-wP/dDP)，或多西他赛联合表柔比星及环磷酰胺或多西他赛/紫杉醇联合卡铂(TEC或TCb/PCb)。所有患者的术后辅助化疗和后续辅助放疗均按照患者确诊时最新的NCCN指南执行。NAC临床疗效根据实体瘤疗效评价标准(RECIST 1.1版)[16]进行评估。根据患者术后病理，将NAC临床疗效分为疾病进展(disease progression，PD)、疾病稳定(disease stabilization，SD)、部分缓解(partial response，PR)或完全缓解(complete response，CR)，pCR定义为CR，而非pCR则定义为PD、SD或PR。

1.3 临床与病理评估标准 乳腺癌临床TNM分期以第八届美国癌症联合委员会(American Joint Committee on Cancer，AJCC)分期手册为标准[17]。根据美国临床肿瘤学会/美国病理学家学会(American Society of Clinical Oncology/College of American Pathologists，ASCO/CAP)的推荐，本研究通过超声引导下穿刺活检的标本诊断结果对NAC前乳腺癌进行确诊。由本院至少两名经验丰富的病理科医师进行病理染色、阅片，评估IHC结果，雌激素受体和孕激素受体的IHC评估标准遵循最新的ASCO/CAP指南，雌激素受体/孕激素受体阳性定义为≥1%的浸润性肿瘤细胞经IHC染色呈阳性[18]；Ki-67评估根据国际乳腺癌Ki-67工作组推荐的标准进行[19]；HER2的检测根据ASCO/CAP指南[20]进行，IHC(+++)定义为HER2阳性，IHC(−)/(+)定义为HER2阴性；IHC(++)则需进行FISH检测，FISH阳性为HER2平均拷贝数≥6.0且HER2/染色体计数探针(chromosome enumeration probes 17，CEP17)<2.0或HER2平均拷贝数≥4.0且HER2/CEP17≥2.0，FISH阴性为HER2平均拷贝数<4.0且HER2/CEP17<2.0；在IHC(++)的患者中，若FISH检测阳性则定义为HER2阳性，FISH检测阴性则定义为HER2阴性；IHC(+)或(++)伴FISH

检测阴性定义为HER2低表达[21]。

1.4 资料收集 收集并比较两组患者的临床病理资料，包括年龄、手术方式、NAC方案、是否接受术后放疗、肿瘤临床分期、肿瘤cT分期、肿瘤cN分期、病理类型、肿瘤Nottingham分级、激素受体(hormone receptor，HR)状态、Ki-67状态、月经状态及是否接受内分泌治疗等。将单因素分析中P<0.05的因素纳入二元logistic回归进行多因素分析。为确保组间基线资料的可比性，采用1:1倾向性评分对两组患者进行匹配，卡钳值设置为0.001。

1.5 HER2低表达乳腺癌患者的生存分析 采用Kaplan-Meier法对两组患者进行生存分析，绘制生存曲线并进行log-rank检验。主要研究终点为总生存期(overall survival，OS)，是指乳腺癌患者首次治疗至死亡(任何原因导致)或随访结束的时间；次要终点为无病生存期(disease-free survival，DFS)，是指乳腺癌患者首次治疗至首次发生事件(包括局部、区域或远处复发、对侧乳腺癌或随访结束)的时间。随访自接受NAC治疗开始，截至2024年2月28日。

1.6 HER2低表达乳腺癌患者的预后影响因素分析 采用多因素Cox比例风险回归模型分析pCR对HER2低表达乳腺癌患者预后的影响，多因素Cox回归变量筛选采用Enter法(全部变量进入)。检验水准α=0.05。

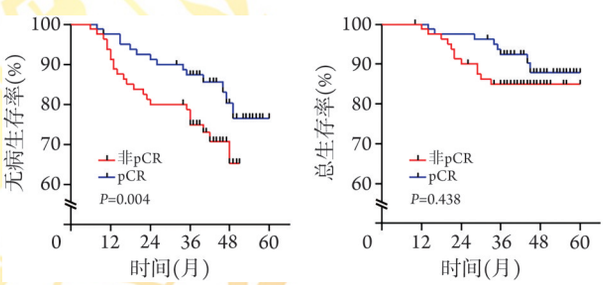
1.7 统计学处理 采用SPSS 27.0和GraphPad Prism 8.0软件进行统计分析。采用Shapiro-Wilk法检验计量资料，符合正态分布者以$\bar{x}\pm s$表示，两组间比较采用独立样本t检验；不符合正态分布者以$M(Q_1, Q_3)$表示，两组间比较采用Mann-Whitney U非参数检验。计数资料以例(%)表示，两组间比较采用Pearson χ^2或Fisher确切概率法。P<0.05为差异有统计学意义。

2 结 果

2.1 两组临床病理资料比较 共443例HER2低表达乳腺癌患者接受了NAC，年龄(49.5±8.0)岁。其中，143例(32.3%)获得pCR(pCR组)，300例(67.7%)未获得pCR(非pCR组)。与非pCR组比较，pCR组患者年龄较小(P=0.045)，肿瘤cN分期(P=0.006)、肿瘤临床分期(P<0.001)、HR阳性比例(P=0.006)、接受内分泌治疗的比例(P=0.006)较低，Ki-67>14%比例(P=0.018)、肿瘤Nottingham分级(P=0.037)较高；两组NAC方案差异有统计学意义(P=0.030)(表1)。

2.2 HER2低表达乳腺癌NAC后pCR的多因素logistic回归分析 以pCR为因变量，将单因素分析中P<0.05的因素作为为自变量(赋值见附表1，https://dx.doi.org/10.11855/j.issn.0577-7402.1142.2025.0627FJ)纳入二元logistic回归分析，采用向后法逐步筛选变量，结果显示，肿瘤临床分期、HR状态、Ki-67状态、肿瘤Nottingham分级、是否接受内分泌治疗为HER2低表达乳腺癌NAC后pCR的独立影响因素(P<0.05，表2)。

2.3 倾向性评分匹配后两组生存结局比较 经1:1倾向性评分匹配后，pCR组与非pCR组各纳入80例患者，其中，pCR组未复发70例、复发10例、死亡9例，非pCR组未复发56例、复发24例、死亡12例。两组临床病理特征比较差异均无统计学意义(P>0.05，附表2，https://dx.doi.org/10.11855/j.issn.0577-7402.1142.2025.0627FJ)。Kaplan-Meier生存分析显示，pCR组与非pCR组的中位随访时间分别为45.0个月(95%CI 43.1~46.9)与43.0个月(95%CI 41.0~45.0)；pCR组无病生存率高于非pCR组(87.5% *vs.* 70.0%，P=0.004)，但两组总生存率差异无统计学意义(88.8% *vs.* 85.0%，P=0.438)(图2)。



pCR.病理完全缓解

图2 倾向性评分匹配后非pCR组与pCR组患者生存率的比较

Fig.2 Comparison of survival rate of patients in non-pCR group and pCR group after propensity score matching

2.4 HER2低表达乳腺癌预后影响因素分析 单因素Cox比例风险回归模型分析结果显示，肿瘤cT分期(Ⅲ *vs.* Ⅱ)、肿瘤cN分期(Ⅲ *vs.* 0)、肿瘤临床分期(Ⅲ *vs.* Ⅱ)、HR阳性、接受内分泌治疗、pCR为HER2低表达乳腺癌DFS的影响因素(P<0.05)；肿瘤cN分期(Ⅲ *vs.* 0)、肿瘤临床分期(Ⅲ *vs.* Ⅱ)、HR阳性、接受内分泌治疗为HER2低表达乳腺癌OS的影响因素(P<0.05，表3)。将单因素分析中P<0.05的变量纳入多因素Cox比例风险回归模型，结果显示，肿瘤临床分期(Ⅲ *vs.* 0)为HER2低表达乳腺癌DFS的独立影响因素(P<0.05)，肿瘤临床分期(Ⅲ *vs.* 0)亦为HER2低表达乳腺癌OS的独立影响因素(P<0.05)；HR阳性、接受内分泌治疗、pCR为HER2低表达乳腺癌DFS的独立保护因素(P<0.05)，HR阳性、接受内分泌治疗为HER2低表达乳腺癌OS的独立保护因素(P<0.05，表4)。

3 讨 论

HER2低表达乳腺癌的出现，导致现有乳腺癌的

表 1 两组 HER2 低表达乳腺癌患者的临床病理资料比较

Tab.1 Clinicopathological characteristics between the two groups of patients with HER2-low breast cancer

项目	总体(n=443)	非 pCR 组(n=300)	pCR 组(n=143)	P
年龄[岁, $M(Q_1, Q_3)$]	49.0(43.0, 55.0)	50.0(44.0, 55.0)	47.0(42.0, 54.0)	0.045
月经状态[例(%)]				0.187
已绝经	184(41.5)	131(43.7)	53(37.1)	
未绝经	259(58.5)	169(56.3)	90(62.9)	
肿瘤 cT 分期[例(%)]				0.055
Ⅱ期	242(54.6)	153(51.0)	89(62.2)	
Ⅲ期	179(40.4)	129(43.0)	50(35.0)	
Ⅳ期	22(5.0)	18(6.0)	4(2.8)	
肿瘤 cN 分期[例(%)]				0.006
0 期	100(22.6)	63(21.0)	37(25.9)	
Ⅰ期	198(44.7)	125(41.7)	73(51.0)	
Ⅱ期	102(23.0)	74(24.7)	28(19.6)	
Ⅲ期	43(9.7)	38(12.7)	5(3.5)	
肿瘤临床分期[例(%)]				<0.001
Ⅱ期	203(45.8)	121(40.3)	82(57.3)	
Ⅲ期	240(54.2)	179(59.7)	61(42.7)	
浸润性导管癌[例(%)]				0.974
是	335(75.6)	227(75.7)	108(75.5)	
否	108(24.4)	73(24.3)	35(24.5)	
HR 状态[例(%)]				0.006
阴性	250(56.4)	156(52.0)	94(65.7)	
阳性	193(43.6)	144(48.0)	49(34.3)	
Ki-67 状态[例(%)]				0.018
≤14%	77(17.4)	61(20.3)	16(11.2)	
>14%	366(82.6)	239(79.7)	127(88.8)	
肿瘤 Nottingham 分级[例(%)]				0.037
Ⅰ级	25(5.6)	19(6.3)	6(4.2)	
Ⅱ级	215(48.5)	156(52.0)	59(41.3)	
Ⅲ级	203(45.8)	125(41.7)	78(54.5)	
手术方式[例(%)]				0.157
乳房全切	278(62.8)	195(65.0)	83(58.0)	
保乳	165(37.2)	105(35.0)	60(42.0)	
NAC 方案[例(%)]				0.030
EC-T(wP)	107(24.2)	77(25.7)	30(21.0)	
dEC-wP/dDP	134(30.2)	79(26.3)	55(38.5)	
TEC	141(31.8)	105(35.0)	36(25.2)	
TCb/PCb	61(13.8)	39(13.0)	22(15.4)	
术后放疗[例(%)]				0.878
无	213(48.1)	145(48.3)	68(47.6)	
有	230(51.9)	155(51.7)	75(52.4)	
内分泌治疗[例(%)]				0.006
否	250(56.4)	156(52.0)	94(65.7)	
是	193(43.6)	144(48.0)	49(34.3)	

HER2. 人表皮生长因子受体 2；pCR. 病理完全缓解；HR. 激素受体；NAC. 新辅助化疗；EC-T(wP). 表柔比星联合环磷酰胺序贯多西他赛密或紫杉醇每周 1 次；dEC-wP/dDP. 表柔比星联合环磷酰胺每 2 周 1 次序贯紫杉醇每周或每 2 周 1 次；TEC 或 TCb/PCb. 多西他赛联合表柔比星及环磷酰胺或多西他赛/紫杉醇联合卡铂

表2 HER2低表达乳腺癌NAC后pCR的多因素logistic回归分析

Tab.2 Multivariate logistic regression analysis of influencing factors for pCR after NAC in HER2-low breast cancer

变量	*β*	*OR*	95%CI	*P*
年龄	−0.023	0.977	0.953~1.002	0.070
肿瘤cN分期(Ⅰ期*vs.*0期)	0.363	1.437	0.794~2.601	0.231
肿瘤cN分期(Ⅱ期*vs.*0期)	0.220	1.246	0.520~2.987	0.622
肿瘤cN分期(Ⅲ期*vs.*0期)	−1.041	0.353	0.104~1.199	0.095
肿瘤临床分期(Ⅲ期*vs.*Ⅱ期)	−0.697	0.498	0.267~0.930	0.029
HR状态	−0.668	0.513	0.328~0.801	0.003
Ki-67状态	0.948	2.580	1.366~4.874	0.003
肿瘤Nottingham分级(Ⅱ级*vs.*Ⅰ级)	0.623	1.864	0.671~5.178	0.232
肿瘤Nottingham分级(Ⅲ级*vs.*Ⅰ级)	1.162	3.197	1.147~8.910	0.026
NAC方案[dEC-wP/dDP*vs.*EC-T(wP)]	0.594	1.732	0.968~3.100	0.064
NAC方案[TEC*vs.*EC-T(wP)]	0.053	1.054	0.574~1.938	0.864
NAC方案[TCb/PCb*vs.*EC-T(wP)]	0.732	2.080	0.988~4.377	0.054
内分泌治疗	−0.668	0.513	0.328~0.801	0.003

HER2.人表皮生长因子受体2；pCR.病理完全缓解；HR.激素受体；NAC.新辅助化疗；EC-T(wP).表柔比星联合环磷酰胺序贯多西他赛密或紫杉醇每周1次；dEC-wP/dDP.表柔比星联合环磷酰胺每2周1次序贯紫杉醇每周或每2周1次；TEC或TCb/PCb.多西他赛联合表柔比星及环磷酰胺或多西他赛/紫杉醇联合卡铂

表3 HER2低表达乳腺癌患者DFS及OS的单因素Cox比例风险回归分析

Tab.3 Univariate Cox regression analysis of influencing factors for DFS and OS in HER2-low breast cancer patients

变量	DFS		OS	
	HR(95%CI)	*P*	*HR*(95%CI)	*P*
年龄	1.004(0.964~1.046)	0.843	0.974(0.921~1.029)	0.349
月经状态	1.119(0.565~2.217)	0.748	1.260(0.522~3.040)	0.608
肿瘤*c*T分期(Ⅲ*vs.*Ⅱ)	2.035(1.019~4.064)	0.044	2.244(0.929~5.419)	0.072
肿瘤*c*T分期(Ⅳ*vs.*Ⅱ)	1.411(0.186~10.724)	0.739	2.268(0.285~18.029)	0.439
肿瘤cN分期(Ⅰ*vs.*0)	0.961(0.379~2.438)	0.933	1.042(0.330~3.283)	0.945
肿瘤cN分期(Ⅱ*vs.*0)	2.182(0.859~5.548)	0.101	1.577(0.456~5.448)	0.472
肿瘤cN分期(Ⅲ*vs.*0)	7.517(2.547~22.188)	<0.001	5.471(1.463~20.455)	0.012
肿瘤临床分期(Ⅲ*vs.*Ⅱ)	3.485(1.708~7.109)	<0.001	3.167(1.277~7.856)	0.013
浸润性导管癌	1.357(0.633~2.910)	0.432	1.080(0.396~2.949)	0.881
HR状态	0.347(0.151~0.797)	0.013	0.295(0.099~0.877)	0.028
Ki-67状态	1.259(0.487~3.255)	0.635	1.901(0.443~8.164)	0.387
肿瘤Nottingham分期(Ⅱ*vs.*Ⅰ)	1.197(0.273~5.249)	0.811	1.528(0.194~12.073)	0.687
肿瘤Nottingham分期(Ⅲ*vs.*Ⅰ)	0.995(0.228~4.342)	0.995	1.434(0.185~11.134)	0.731
手术方式(保乳*vs.*全切)	0.958(0.479~1.916)	0.903	0.717(0.290~1.778)	0.473
NAC[dEC-wP/dDP*vs.*EC-T(wP)]	1.066(0.436~2.609)	0.889	1.780(0.558~5.675)	0.330
NAC[TEC*vs.*EC-T(wP)]	0.831(0.321~2.156)	0.704	0.935(0.251~3.482)	0.920
NAC[TCb/PCb*vs.*EC-T(wP)]	1.053(0.344~3.219)	0.928	0.840(0.154~4.585)	0.840
术后放疗	1.581(0.789~3.166)	0.196	1.453(0.602~3.506)	0.406
内分泌治疗	0.347(0.151~0.797)	0.013	0.295(0.099~0.877)	0.028
pCR	0.350(0.167~0.735)	0.006	0.711(0.299~1.690)	0.440

HER2.人表皮生长因子受体2；DFS.无病生存期；OS.总生存期；HR.激素受体；NAC.新辅助化疗；EC-T(wP).表柔比星联合环磷酰胺序贯多西他赛密或紫杉醇每周一次；dEC-wP/dDP.表柔比星联合环磷酰胺每2周一次序贯紫杉醇每周或每2周一次；TEC或TCb/PCb.多西他赛联合表柔比星及环磷酰胺或多西他赛/紫杉醇联合卡铂；pCR.病理完全缓解

分子分型受到了前所未有的冲击。基于HER2低表达乳腺癌独特的临床与生物学特征[22-24]，本研究对HER2低表达乳腺癌患者NAC后pCR的影响因素进行了分析。HER2低表达乳腺癌的病理学特征尚未完

表4 HER2低表达乳腺癌患者DFS及OS的多因素Cox比例风险回归分析

Tab.4 Multivariate Cox regression analysis of influencing factors for DFS and OS in HER2-low breast cancer patients

变量	DFS		OS	
	HR(95%CI)	*P*	*HR*(95%CI)	*P*
肿瘤cT分期(Ⅲ *vs.* Ⅱ)	0.891(0.371~2.141)	0.796		
肿瘤cT分期(Ⅳ *vs.* Ⅱ)	0.337(0.039~2.948)	0.326		
肿瘤cN分期(Ⅰ *vs.* 0)	0.490(0.145~1.655)	0.251	0.380(0.073~1.962)	0.248
肿瘤cN分期(Ⅱ *vs.* 0)	0.677(0.126~3.643)	0.649	0.275(0.035~2.148)	0.218
肿瘤cN分期(Ⅲ *vs.* 0)	1.448(0.254~8.265)	0.677	0.850(0.103~6.983)	0.880
肿瘤临床分期(Ⅲ *vs.* Ⅱ)	4.720(1.011~22.050)	0.048	5.654(1.094~29.218)	0.039
HR状态	0.303(0.129~0.709)	0.006	0.292(0.098~0.871)	0.027
内分泌治疗	0.303(0.129~0.709)	0.006	0.292(0.098~0.871)	0.027
pCR	0.312(0.142~0.688)	0.004	–	

HER2. 人表皮生长因子受体2；HR. 激素受体；pCR. 病理完全缓解

全阐明，其获得pCR是否意味着较好的预后亦不完全清楚[25]，因此，本研究进一步探究了HER2低表达乳腺癌患者NAC后获得pCR与预后之间的关系，共纳入443例HER2低表达乳腺癌患者，其中143例(32.3%)在接受NAC后获得了pCR，与以往临床研究中观察到的结果相似[7]。

本研究发现，肿瘤临床分期、HR状态、Ki-67状态、肿瘤Nottingham分级、是否接受内分泌治疗是HER2低表达乳腺癌pCR的独立影响因素。肿瘤临床分期是HER2低表达乳腺癌pCR的独立影响因素，即肿瘤临床分期越高，获得pCR的难度越大，与既往其他类型乳腺癌的研究结果一致[26-28]。Ki-67是一种分子量为359 kD的核蛋白，通常用于检测和量化增殖细胞，其表达量的增加与细胞增殖有关[29]。大量研究表明，Ki-67状态是预测NAC治疗乳腺癌疗效的可靠指标，其水平越高，获得pCR的可能性越大，对NAC的敏感性也越高，但HER2低表达乳腺癌患者Ki-67与NAC疗效之间关系的研究则较少[30-32]。本研究发现，Ki-67状态(>14%)是HER2低表达乳腺癌患者NAC后pCR的独立影响因素。在管腔型、HER2阳性以及三阴性乳腺癌中，肿瘤Nottingham分级已被证实是NAC后pCR的独立影响因素[33-35]。本研究进一步证实在HER2低表达乳腺癌中，肿瘤Nottingham分级亦是pCR的独立影响因素。有研究发现，约80.0%的HER2低表达乳腺癌为管腔型乳腺癌[36]。基于乳腺癌PAM50分子分型，Schettini等[6]发现，HER2低表达乳腺癌中管腔型乳腺癌的比例较高，而HER2无表达乳腺癌中三阴性乳腺癌的比例较高。Ilie等[37]的研究纳入了236例HER2低表达乳腺癌，其中72.3%为HR阳性乳腺癌，结果显示，与HR阳性乳腺癌相比，HR阴性乳腺癌的pCR率更高(44.0% *vs.* 4.3%，*P*<0.001)。本研究结果显示，HER2低表达乳腺癌患者的HR阳性率为43.6%，与Ilie等[37]的研究结果不一致；原因可能是由于本研究纳入的研究对象均为接受了NAC的临床分期较晚的乳腺癌患者，在一定程度上造成了选择偏倚。但本研究结果仍显示HR状态是pCR的一个独立影响因素。

CTNeoBC研究表明，对于侵袭性较强的三阴性、HER2阳性/HR阴性、HR阳性/HER2阴性但Nottingham Ⅲ级的乳腺癌患者，NAC后获得pCR预示着较好的预后；对于侵袭性较低的Luminal A型乳腺癌患者，NAC后获得pCR与较好的预后并无明显相关性[14]。已有研究表明，使用抗体偶联药物T-DXd靶向治疗可使HER2低表达乳腺癌患者的生存获益[38]。而pCR是否与较好的预后相关在HER2低表达乳腺癌患者中尚未完全阐明。因此，本研究探究了NAC后获得pCR的HER2低表达乳腺癌患者是否表现出更好的预后，结果显示，pCR组患者的无病生存率高于未获得pCR的患者，表明获得pCR的HER2低表达乳腺癌患者的局部复发率较低；而两组总生存率却无明显差异，表明获得pCR对HER2低表达乳腺癌患者的OS并无获益。因此，pCR对HER2低表达乳腺癌的预后仍具有一定的预测价值。多因素Cox回归分析结果显示，肿瘤临床分期、HR状态、是否接受内分泌治疗、pCR是HER2低表达乳腺癌患者DFS的独立影响因素，肿瘤临床分期、HR状态、是否接受内分泌治疗是HER2低表达乳腺癌患者OS的独立影响因素。目前关于HER2低表达乳腺癌预后影响因素的研究较少，现有研究尚未见到与本研究结论一致的报道[7-8,39]。

综上所述，本研究结果表明，肿瘤临床分期低、HR阴性、Ki-67高表达、肿瘤Nottingham分级高、未接受内分泌治疗的HER2低表达乳腺癌患者更易

获得pCR，且NAC后获得pCR可明显延长其DFS，但OS并无明显改善。本研究存在一些局限性：(1)经倾向性评分匹配后，仅160例患者纳入了生存分析，较小的样本量可能导致统计学偏倚；(2)为单中心回顾性研究，可能会限制研究结果的普适性；(3)随访时间较短，无法分析NAC后获得pCR是否对HER2低表达乳腺癌患者的长期生存产生影响。

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