doi: 10.13241/j.cnki.pmb.2020.10.044

乳腺癌患者新辅助化疗后 ER、PR、HER2、Ki67 表达变化及临床意义 *

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摘要 目的：研究乳腺癌患者在新辅助化疗后 ER、PR、HER2、Ki67 的变化及临床意义。**方法：**选择 2012 年 1 月 -2017 年 12 月至我院进行乳腺癌新辅助化疗的患者 176 例进行临床研究。所有患者化疗前及术后行经 B 超引导下核芯针穿刺取病理活检，检测 ER、PR、Ki67、HER2 的表达，分析其变化情况。**结果：**176 例乳腺癌患者新辅助化疗前 ER 阳性为 57 例，新辅助化疗后 ER 阳性为 69 例，新辅助化疗前 ER 阴性为 119 例，新辅助化疗后 ER 阴性 107 例；新辅助化疗前后状态改变了 34 例（19.32%），其中 12 例新辅助化疗前 ER 阴性转变为 ER 阳性，22 例新辅助化疗前 ER 阳性转变为新辅助化疗后 ER 阴性，化疗前后患者 ER 表达变化有统计学差异（x^2=8.044，P=0.037）；176 例乳腺癌患者新辅助化疗前 PR 阳性为 83 例，新辅助化疗后 PR 阳性为 89 例，新辅助化疗前 PR 阴性为 93 例，新辅助化疗后 PR 阴性 87 例；新辅助化疗前后状态改变了 82 例（46.59%），其中 45 例新辅助化疗前 PR 阴性转变为 PR 阳性，37 例新辅助化疗前 PR 阳性转变为新辅助化疗后 PR 阴性，化疗前后患者 PR 表达变化有统计学差异（x^2=6.311，P=0.049）；176 例乳腺癌患者新辅助化疗前 HER2 阳性为 31 例，新辅助化疗后 HER2 阳性为 30 例，新辅助化疗前 HER2 阴性为 145 例，新辅助化疗后 HER2 阴性 146 例；新辅助化疗前后状态改变了 3 例（1.70%），其中 1 例新辅助化疗前 HER2 阴性转变为 HER2 阳性，2 例新辅助化疗前 HER2 阳性转变为新辅助化疗后 HER2 阴性，化疗前后患者 HER2 表达变化无统计学差异（x^2=0.522，P=0.945）；176 例乳腺癌患者新辅助化疗前 Ki67 阳性为 104 例，新辅助化疗后 Ki67 阳性为 95 例，新辅助化疗前 Ki67 阴性为 72 例，新辅助化疗后 Ki67 阴性 81 例；新辅助化疗前后状态改变了 109 例（61.93%），其中 54 例新辅助化疗前 Ki67 阴性转变为 Ki67 阳性，55 例新辅助化疗前 Ki67 阳性转变为新辅助化疗后 Ki67 阴性，化疗前后患者 Ki67 表达变化有统计学差异（x^2=2.936，P=0.048），经过新辅助化疗后，Ki67 出现上调表达最高，为 23.86%，同时也是下调表达最高，为 38.07%。HER2 表达保持不变最高，为 98.30%。**结论：**新辅助化疗会对乳腺癌患者 ER、PR、Ki67 的表达造成影响，其中对 Ki67 的影响最为显著。

关键词：乳腺癌；新辅助化疗；免疫组化；临床研究

中图分类号：R737.9 **文献标识码：**A **文章编号：**1673-6273(2020)10-1997-04

A Clinical Study on the Immunohistochemical Changes of Breast Cancer after Neoadjuvant Chemotherapy and Its Influence on the Changes of Er, PR, HER2 and Ki67*

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ABSTRACT Objective: To study the changes and clinical significance of ER, PR, HER2, Ki67 in breast cancer patients after neoadjuvant chemotherapy. **Methods:** 176 patients with breast cancer undergoing neoadjuvant chemotherapy from January 2012 to December 2017 were selected for clinical study. All patients underwent B-ultrasound-guided core needle aspiration biopsy before chemotherapy and pathological examination after surgery. All pathological specimens were examined by immunohistochemistry. The changes and trends of ER, PR, HER2 and Ki67 before and after adjuvant chemotherapy were observed. **Results:** Among the 176 breast cancer patients, 57 were ER positive before neoadjuvant chemotherapy, 69 were ER positive after neoadjuvant chemotherapy, 119 were ER negative before neoadjuvant chemotherapy, and 107 were ER negative after neoadjuvant chemotherapy. Before and after neoadjuvant chemotherapy, the status of 34 patients (19.32%) changed, including 12 patients who were negative for ER before neoadjuvant chemotherapy to positive for ER, and 22 patients who were positive for ER before neoadjuvant chemotherapy to negative for ER after neoadjuvant chemotherapy. There was a statistical difference in ER expression before and after chemotherapy (x^2=8.044, P=0.037). Among the 176 breast cancer patients, 83 were PR positive before neoadjuvant chemotherapy, 89 were PR positive after neoadjuvant chemotherapy, 93 were PR negative before neoadjuvant chemotherapy, and 87 were PR negative after neoadjuvant chemotherapy. Before and after neoadjuvant chemotherapy, the status of 82 patients (46.59%) changed, among which 45 patients changed from negative PR to positive PR before neoadjuvant

* 基金项目：河北省医学科学研究重点计划项目(20181237)

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（收稿日期：2020-02-03 接受日期：2020-02-28）

chemotherapy, and 37 patients changed from positive PR to negative PR after neoadjuvant chemotherapy. There was a statistical difference in the change of PR expression before and after chemotherapy (x^2=6.311, P=0.049). Among the 176 breast cancer patients, 31 were positive for HER2 before neoadjuvant chemotherapy, 30 were positive for HER2 after neoadjuvant chemotherapy, 145 were negative for HER2 before neoadjuvant chemotherapy, and 146 were negative for HER2 after neoadjuvant chemotherapy. Before and after neoadjuvant chemotherapy, the status of 3 patients changed (1.70%). Among them, 1 patient changed from negative HER2 to positive HER2 before neoadjuvant chemotherapy, and 2 patients changed from positive HER2 to negative HER2 after neoadjuvant chemotherapy. There was no statistical difference in HER2 expression before and after chemotherapy (x^2=0.522, P=0.945). Among the 176 breast cancer patients, 104 were Ki67 positive before neoadjuvant chemotherapy, 95 were Ki67 positive after neoadjuvant chemotherapy, 72 were Ki67 negative before neoadjuvant chemotherapy, and 81 were Ki67 negative after neoadjuvant chemotherapy. Status changed before and after neoadjuvant chemotherapy, 109 patients (61.93%), 54 cases of neoadjuvant chemotherapy before Ki67 negative into Ki67 positive, 55 cases of neoadjuvant chemotherapy before Ki67 positive into Ki67 negative after neoadjuvant chemotherapy, Ki67 expression changes of the patients before and after chemotherapy was statistically difference (chi-square = 2.936, P=0.048), after neoadjuvant chemotherapy, Ki67 appear raised to express the highest, at 23.86%, is also a cut to express the highest, 38.07%. The expression of HER2 remained the highest at 98.30%. **Conclusion:** Neoadjuvant chemotherapy can affect the expression of ER, PR, HER2 and Ki67 in breast cancer patients, especially HER2.

Key words: Breast cancer; Neoadjuvant chemotherapy; Immunohistochemistry; Clinical study

Chinese Library Classification(CLC): R737.9 Document code: A

Article ID: 1673-6273(2020)10-1997-04

前言

乳腺癌是女性发生率居首位的恶性肿瘤，占女性恶性肿瘤发病率的23%[1]。2015年，我国乳腺癌新发病例为26.9万人，严重威胁女性生命安全[2]，手术切除仍然是乳腺癌主要的治疗手段，放化疗作为重要的辅助治疗手段一直被临床所重视。

新辅助化疗是以使不可切除或者不易切除的肿瘤在进行化疗后能切除为目的治疗方法，具有使乳腺癌的分期降级、提高保乳率、评估化疗药物敏感性的作用[3]。但是研究显示乳腺癌患者在进行过新辅助化疗后，乳腺癌标记物的表达可能会随之改变，甚至影响肿瘤的分期分级。ER、PR、HER2、Ki67是公认与乳腺癌关系最为密切的因子，其中ER、PR的表达状态可以用来指导内分泌治疗的选择，且还是评估乳腺癌预后的重要指标；HER2是判断乳腺癌预后的重要指标；Ki67是与细胞有丝分裂密切相关的核抗原，可以反映肿瘤的增殖活性，各指标水平的改变能够反映出肿瘤进展情况、化疗的疗效，是肿瘤治疗过程中的重要参考依据。

1 资料与方法

1.1 一般资料

选择2012年1月-2017年12月我院收治的患者176例，患者年龄28-64岁，平均年龄(46.22± 15.33)岁。绝经患者106例，未绝经患者70例。肿瘤位置：左侧乳腺91例，右侧乳腺85例，AJCC乳腺癌临床分期IIA期24例，IIB期50例，IIIA期43例，IIIB期32例，IIIC期27例。

纳入标准[4]：(1)年龄>18岁；(2)经术前病理检查确诊为乳腺癌，免疫组化：ER或PR阳性，HER-2阴性的患者；(3)病灶为单侧；(4)KFS评分≥ 60分；(5)心、肝、肾等脏器功能正常，能够耐受化疗；(6)非远处转移。排除标准[5]：(1)新辅助化疗期间肿瘤发生远处转移的患者；(2)既往有其他恶性肿瘤病史的患者；(3)既往有内分泌治疗、靶向治疗、放疗史的患者。

1.2 方法

1.2.1 研究方法 所有患者化疗前行经B超引导下核芯针穿刺取病理活检，并于术后行病理检查。所有病理标本行免疫组化检测。

设备和试剂：兔抗人HIF-1α单克隆抗体、兔抗人BCL-2单克隆抗体、SP试剂盒、DAB显色试剂盒均购自北京中杉金桥公司。SABC免疫组化试剂盒购自北京中山生物技术有限公司。

方法：采集到的患者病理组织常规制成蜡块，组织切片，在68℃下烤片12h，常规行二甲苯脱蜡，梯度酒精脱水，放置于98℃的EDTA缓冲液中煮沸3 min，自然冷却20 min，冷水冲洗高压锅至室温，PBS冲洗3次，每次2 min，以修复抗原。阻断灭活内源性过氧化物酶，滴加一抗，室温放置3 h，使用PBS冲洗3次，每次2 min，滴加二抗，37℃孵育30 min，PBS冲洗3次，每次2 min，给予DAB反应染色，常规脱水，透明、干燥、封片。由两名经验丰富的病理医师进行阅片，并协商判定免疫组化结果。所有操作均由本院病理科完成。

免疫组化结果判定：ER、PR在细胞核上出现棕黄色染色为阳性细胞，阳性细胞数量不足10%为(-)，10-25%为(+)，26-50%为(++)，超过50%为(+++)。HER2表达在细胞膜上出现黄色或者棕色染色的细胞为阳性细胞，阳性细胞数量不足10%为(-)，10-25%为(+)，26-50%为(++)，超过50%为(+++)。(-)、(+)型被认为阴性。HER2 (++)则性FISH检测确认阴性者入组。Ki67＜15%为低表达，Ki67>30%为高表达。

1.2.2 分析指标 观察患者在辅助化疗前后雌激素受体(ER)、孕激素受体(PR)、人类表皮生长因子受体2(HER2)、细胞增殖核抗原Ki67(Ki-67)的结果变化情况、变化趋势。

1.3 统计学分析

用SPSS19.0统计学数据处理软件处理研究中所有相关数据，计量资料用均数± 标准差($\bar{x}$± s)表示，组间比较采用t检验，计数资料以(n，%)表示，组间比较采用x^2检验，以P<0.05为差异有统计学意义。

2 结果

2.1 乳腺癌患者新辅助化疗前后 ER 表达的变化

176 例乳腺癌患者新辅助化疗前 ER 阳性为 57 例，新辅助化疗后 ER 阳性为 69 例，新辅助化疗前 ER 阴性为 119 例，新辅助化疗后 ER 阴性 107 例；新辅助化疗前后状态改变了 34 例(19.32%)，其中 12 例新辅助化疗前 ER 阴性转变为 ER 阳性，22 例新辅助化疗前 ER 阳性转变为新辅助化疗后 ER 阴性，化疗前后患者 ER 表达有统计学差异(P<0.05)，详见表 1。

表 1 乳腺癌患者在新辅助化疗前后 ER 变化情况比较(例)

Table 1 Comparison of Er changes in breast cancer patients before and after neoadjuvant chemotherapy (cases)

Time	-	+	++	+++
Before chemotherapy	53	66	39	18
After chemotherapy	61	46	42	27
x^2		8.044		
P		0.037		

2.2 乳腺癌患者新辅助化疗前后 PR 表达的变化

176 例乳腺癌患者新辅助化疗前 PR 阳性为 83 例，新辅助化疗后 PR 阳性为 89 例，新辅助化疗前 PR 阴性为 93 例，新辅助化疗后 PR 阴性 87 例；新辅助化疗前后状态改变了 82 例(46.59%)，其中 45 例新辅助化疗前 PR 阴性转变为 PR 阳性，37 例新辅助化疗前 PR 阳性转变为新辅助化疗后 PR 阴性，化疗前后患者 PR 表达变化有统计学差异(P<0.05)，详见表 2。

表 2 乳腺癌患者在新辅助化疗前后 PR 变化情况比较

Table 2 Comparison of PR changes in breast cancer patients before and after neoadjuvant chemotherapy

Time	-	+	++	+++
Before chemotherapy	42	51	57	26
After chemotherapy	44	43	51	38
x^2		6.311		
P		0.049		

2.3 乳腺癌患者新辅助化疗前后 HER2 表达的变化

176 例乳腺癌患者新辅助化疗前 HER2 阳性为 31 例，新辅助化疗后 HER2 阳性为 30 例，新辅助化疗前 HER2 阴性为 145 例，新辅助化疗后 HER2 阴性 146 例；新辅助化疗前后状态改变了 3 例(1.70%)，其中 1 例新辅助化疗前 HER2 阴性转变为 HER2 阳性，2 例新辅助化疗前 HER2 阳性转变为新辅助化疗后 HER2 阴性，化疗前后患者 HER2 表达变化无统计学差异(P>0.05)。

2.4 乳腺癌患者在新辅助化疗前后 Ki67 表达的变化

176 例乳腺癌患者新辅助化疗前 Ki67 阳性为 104 例，新辅助化疗后 Ki67 阳性为 95 例，新辅助化疗前 Ki67 阴性为 72 例，新辅助化疗后 Ki67 阴性 81 例；新辅助化疗前后状态改变了 109 例(61.93%)，其中 54 例新辅助化疗前 Ki67 阴性转变为 Ki67 阳性，55 例新辅助化疗前 Ki67 阳性转变为新辅助化疗后 Ki67 阴性。

3 讨论

乳腺并非维持人体生命活动的重要器官，因此原位乳腺癌并不致命，但是一旦发生病灶转移，则会危及生命[6,7]。对于肿瘤已经扩散的乳腺癌患者，直接切除效果差，转移病灶无法通过手术切除。近年来，临床给予新辅助化疗的临床应用为这部分患者的治疗提供了新的方案[8-10]。新辅助化疗是指在实施局手术等局部治疗方法前所进行的全身化疗，以缩小患者肿块，杀灭看不见的转移癌细胞，为后续的手术等治疗提供较好的治疗条件为目的，有利于乳腺癌的降级降期、提高保乳率，而且能够对化疗药物的敏感性进行评估，从而选择敏感的药物进行后续的化疗[11-12]。但研究显示 ER、PR、HER2、Ki67 等免疫组化标记物与乳腺癌的分型、预后密切相关，新辅助化疗有可能影响上述标记物的表达，从而改变肿瘤的分型，甚至影响到后续治疗方案的选择[13-15]。

有关新辅助化疗后乳腺癌患者的免疫组化标记物变化情况近年来一直是临床研究的热点，但是不同的研究所得到的结果差异很大，Taucher 的研究发现新辅助化疗前后患者 ER 和 PR 均会发生显著表达改变，也有研究发现改变的只有 PR 而无 ER，而且这种变化是由新辅助化疗所导致的，目前尚无定论[16-18]。

ER 是一种蛋白质分子，较多的存在于靶器官的细胞内，能够与激素发生特异性结合，形成激素 - 受体复合物，使激素能够发挥其生物学效应[19,20]。ER 可位于细胞膜、细胞止或者细胞核上，其蛋白质在翻译后短暂位于胞浆，扩散到细胞核的雌激素与其核受体结合后会引起基因调控机制出现，对下游的基因转录进行调控[21,22]。PR 是核受体超家族成员之一，是雌激素与雌激素受体结合诱导后所得到的产物，期合成必须以雌激素作为起到因子，而雌激素在体内一系列作用的最终产物之一既是 PR 蛋白。在介导与调节卵巢、子宫、乳腺等方面的功能和生殖

活动中具有重要的意义[23-25]。理论上妊娠 PR 阴性的细胞接受化疗后效果更好。HKi67 已经被证实为乳腺癌的独立预后因素,研究发现早期乳腺癌患者 Ki67 水平越高,则预后越差。

从本次研究来看,在新辅助化疗前后患者乳腺癌标志物发生了明显的改变。Ki67 是与细胞有丝分裂密切相关的核抗原,在细胞有丝分裂 G0 期以外的各期均可检测到 Ki67 的表达。Ki67 可以反映肿瘤的增殖活性,且本研究也发现 176 例乳腺癌新辅助化疗患者化疗后,34 例 ER 表达有变化,HER-2 有 3 例变为阳性,109 例 Ki67 表达有变化,上调表达最高,为 23.86%,同时也是下调表达最高,为 38.07%。影响新辅助化疗前后患者免疫组化标记物表达不一致的因素复杂,有研究认为在新辅助化疗后 HR 表达状态的改变可能与化疗杀灭敏感的癌细胞,但不敏感的癌细胞发生了增殖有关。在化疗过程中,药物起到杀灭肿瘤细胞的作用,但是不同肿瘤对药物的敏感性不同,敏感的细胞更容易被化疗药物杀死,但是不敏感细胞却进一步发生了增殖,从而导致化疗后免疫组化指标发生了变化。HER-2 变化考虑为肿瘤异质性所致。

术前所有患者均按预定方案完成化疗,然后行手术治疗,2015 年相关指南将 ER、PR 的阳性阈值定位≧1,此后治疗采用该标准,对于无论穿刺病理或术后病理 ER 或 PR 阳性者均给予内分泌治疗,考虑 KI-67 为乳腺癌预后的预测指标,对于新辅助化疗后 KI67>30%的患者强化内分泌治疗,绝经前患者给予戈舍瑞林皮下注射抑制卵巢功能。

综上所述,新辅助化疗会对乳腺癌患者 ER、PR、Ki67 的表达造成影响,其中对 Ki67 的影响最为显著。明确了新辅助化疗中 ER、PR、Ki-67 变化值对乳腺癌患者预后的指导意义,为预测新辅助化疗后乳腺癌患者的预后提供依据,为乳腺癌新辅助化疗临床工作提供帮助。

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