

超声结合临床特征基于 166 例乳腺癌新辅助化疗后腋窝淋巴结评估中的预测价值分析

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摘要: [目的] 探讨超声结合临床特征在乳腺癌新辅助化疗(neoadjuvant chemotherapy, NAC)后腋窝淋巴结状态的预测价值。[方法] 回顾性总结 2020 年 6 月至 2021 年 10 月浙江省肿瘤医院 166 例初诊乳腺癌且有腋窝淋巴结转移病例, 使用 Logistic 回归模型对临床病理及超声特征与 NAC 后腋窝淋巴结病理完全缓解(pathological complete response, pCR)的关系进行单因素与多因素分析, 建立预测模型, 绘制受试者工作特征(receiver operating characteristic, ROC)曲线并得出曲线下面积(area under curve, AUC)。[结果] 166 例乳腺癌患者中, 61 例经 NAC 后实现腋窝淋巴结 pCR, 单因素与多因素分析发现 NAC 后腋窝淋巴结纵横比值 >2 、淋巴结皮质厚度 ≤ 3 mm, 乳腺癌分子分型为三阴性型与 HER2 阳性型、乳腺癌原发灶临床疗效达完全缓解和腋窝淋巴结 pCR 显著相关($P<0.05$)。与单独使用临床病理或超声特征的预测模型相比, 超声结合临床病理特征预测模型具有良好的识别性能 (AUC 为 0.88, 灵敏度为 78.7%, 特异度为 81.0%)。[结论] 超声结合临床病理特征对腋窝淋巴结 pCR 具有较好预测价值, 可为临床选择适合的手术方式, 减少腋窝淋巴结清扫提供参考。

关键词: 乳腺癌; 新辅助化疗; 腋窝淋巴结; 超声

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Predictive Value of Ultrasound Combined with Clinical Features in the Evaluation of Axillary Lymph Nodes After Neoadjuvant Chemotherapy Based on 166 Cases of Breast Cancer Patients

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Abstract: [Objective] To analyze the predictive value of ultrasound combined with clinical features for the axillary lymph node status after neoadjuvant chemotherapy(NAC) for breast cancer. [Methods] From June 2020 to October 2021, the clinicopathological data and ultrasound imaging features of 166 cases that newly diagnosed as breast cancer with axillary lymph node metastasis in Zhejiang Cancer Hospital were analyzed retrospectively. Logistic regression model was used to analyze the relationship between clinicopathological and ultrasound characteristics and the pathological complete response(pCR) of axillary lymph nodes after NAC for univariate and multivariate analysis. The prediction model was built, the receiver operating characteristic(ROC) curve was draw and the area under curve (AUC) was obtained. [Results] Among the 166 cases of breast cancer, 61 cases achieved pCR of axillary lymph nodes after NAC, and multivariate regression analysis showed that the axillary lymph node aspect ratio >2 , the cortical thickness ≤ 3 mm, the triple negative and the HER2 positive type, and the clinical efficacy of breast primary lesions leading to complete response were significantly associated with axillary lymph node pCR ($P<0.05$). Compared with the prediction models with clinicopathological or ultrasound features alone, ultrasound combined with clinicopathological data prediction model had better identification performance (AUC was 0.88, sensitivity was 78.7%, specificity was 81.0%). [Conclusion] Ultrasound combined with clinical features has prediction value of axillary lymph node pCR, which can provide a reference for reducing axillary lymph node dissection.

Subject words: breast cancer; neoadjuvant chemotherapy; axillary lymph nodes; ultrasound

乳腺癌是目前女性中发病率最高的癌症, 严重

威胁到女性的健康与生命。新辅助化疗(neoadjuvant chemotherapy, NAC) 是目前临床应用于治疗乳腺癌的重要手段, 其能够控制体内癌细胞的扩散, 缩小原发病灶, 促使原发肿瘤及淋巴结的降期, 使本应行全

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乳根治术改为侵袭性较小的乳房手术,从而使乳腺癌得以被有效控制。以往主要行腋窝淋巴结清扫术(axillary lymph node dissection, ALND),术后淋巴水肿使得上肢活动受限,影响生活质量,因此评估NAC对腋窝淋巴结转移患者的疗效,判断淋巴结良恶性,避免淋巴结清扫成为研究的热点。在临床腋窝淋巴结阴性的乳腺癌中,前哨淋巴结活检(sentinel lymph node biopsy, SLNB)是标准方案^[1],但初诊腋窝淋巴结阳性乳腺癌患者行NAC后,SLNB的假阴性率高,因此如何评估腋窝淋巴结状态,选择哪种手术方式是临床亟待解决的问题。本研究旨在分析超声结合临床资料对初诊腋窝淋巴结阳性乳腺癌患者经NAC后腋窝淋巴结病理完全缓解(pathological complete response, pCR),建立预测模型从而为选择适合的腋窝淋巴结手术方式提供信息。

1 资料与方法

1.1 研究对象

回顾性分析2020年6月至2021年10月期间在浙江省肿瘤医院行NAC的女性乳腺癌患者166例,在NAC前均经穿刺病理证实腋窝淋巴结转移,经NAC治疗后实施乳腺及腋窝淋巴结清扫手术。入组标准:原发灶和腋窝淋巴结病理确诊恶性;NAC后均行ALND完善病理结果;NAC前及术后均完善超声检查;所有检查均未发现远处脏器的转移灶;既往未有过放、化疗病史。排除标准:在治疗期间发现远处脏器转移;未完成NAC周期;超声或临床病理特征资料纳入不全者。入组患者术前均签署知情同意书。本文研究内容经过医院伦理委员会审批。

1.2 治疗方案

NAC治疗参照中国抗癌协会乳腺癌诊治指南与规范,以及中国临床肿瘤学会乳腺癌诊疗指南规定实施。

1.3 仪器与方法

超声图像由两位3年以上资历的超声医生进行提取整理,意见不同时经过协商达成一致。使用Philips IU22型超声仪和GE LOGIQ E9型超声仪,频率为5~12 MHz的L12-5高频线阵探头,患者仰卧位,充分暴露乳房及腋窝,以乳头为中心实施扇形扫查,然后侧卧位腋窝部位扫查。收集化疗后腋窝淋巴结皮质厚度、淋巴结纵横比值、淋巴门结构是否存在、乳腺残余肿瘤最大直径的超声信息。淋巴结皮

质厚度参考美国外科医师学会肿瘤组Z1071试验结果^[2],以3 mm为截断值。

收集的临床病理特征包括:患者年龄、肿瘤组织学分级、临床T分期、乳腺原发灶临床疗效、乳腺癌分子分型。根据是否存在淋巴结转移分为腋窝pCR组和未达pCR组。乳腺原发灶临床疗效评估依据实体瘤疗效评价标准(RECIST)1.1版,分为完全缓解(complete response, CR)、部分缓解(partial response, PR)、疾病稳定(stable disease, SD)、疾病进展(progressive disease, PD)。治疗方案及剂量依据中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)乳腺癌诊疗指南规定。组织病理学信息来自空芯针穿刺活检后的免疫组织化学染色,根据细胞核染色情况判定孕激素受体(progesterone receptor, PR)、雌激素受体(estrogen receptor, ER)及细胞核抗原-67(Ki-67)性质,并根据细胞膜染色判断人类表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)性质,HER2状态不明确者再行荧光原位杂交(fluorescence in situ hybridization, FISH)检测。最后依据中国抗癌协会2021版乳腺癌诊疗指南与规范判定Luminal A型、Luminal B型、HER2阳性型及三阴性型4种乳腺癌分型。

1.4 统计学处理

用SPSS 25.0软件进行统计分析。计量资料检验其是否符合正态性,符合者以均数±标准差表示,行 t 检验;以频数(百分比)表示计数资料,用卡方检验或Fisher确切概率法进行比较。单因素分析纳入年龄、临床T分期、乳腺癌分子分型、组织学分级、残余肿瘤最大直径、乳腺癌原发灶临床疗效、腋窝淋巴结皮质厚度、淋巴结纵横比值、淋巴门结构是否存在进行分析,筛选具有统计学意义的因素作为与腋窝pCR相关变量纳入多因素Logistic回归中(LR向后逐步法)进行分析获得独立预测因素,得出预测概率值纳入到检验变量中绘制受试者工作特征(receiver operating characteristic, ROC)曲线,并得出曲线下面积(area under curve, AUC),采用Hosmer-Lemeshow拟合优度检验模型拟合度。所有分析均为双侧检验,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 腋窝淋巴结pCR相关因素

166例乳腺癌患者NAC后有61例实现了腋窝

淋巴结 pCR (Table 1)。单因素分析显示：乳腺癌分子分型、乳腺癌原发灶临床疗效、残余肿瘤最大直径、腋窝淋巴结结构存在、淋巴结皮质厚度、淋巴结纵横比值与 pCR 显著相关 ($P<0.05$)。二元 Logistic 多因素回归分析提示,腋窝淋巴结皮质厚度 ≤ 3 mm、淋巴结纵横比值 >2 ,乳腺癌原发灶临床 CR、乳腺癌分子分型为 HER2 阳性型与三阴性型更易达到腋窝淋巴结 pCR ($P<0.05$) (Table 2)。

2.2 构建预测模型

根据 Logistic 回归逐步分析法得到预测概率值,单独临床特征预测模型 AUC 为 0.81 (95%CI:0.78~0.88),单独超声因素预测模型 AUC 为 0.73 (95%CI:0.66~0.81),超声与临床特征预测模型 AUC 为 0.88 (95%CI:0.83~0.94),灵敏度为 78.7%,特异度为 81.0%,相比超声或临床特征单独预测,联合预测模型更优 (Figure 1)。Hosmer-Lemeshow 拟合优度检验显示模型拟合度较好 ($\chi^2=7.265$, $P=0.297$)。

3 讨论

目前世界范围内乳腺癌是女性发病率最高的恶性肿瘤^[3],NAC 的出现改善了乳腺癌的预后,尤其随着不同化疗方案和靶向药物治疗的联合应用,大大提高了乳腺和腋窝淋巴结 pCR 率,也增加了保乳和

Table 1 Clinical and ultrasound characteristics of breast cancer patients with or without axillary pCR [n(%)]

Characteristic	Patients without axillary pCR (n=105)	Patients with axillary pCR (n=61)	χ^2/t	P
Age ($\bar{x}\pm s$) (years old)	51.6 $\pm$ 10.8	49.4 $\pm$ 9.8	1.275	0.204
Clinical T stage				
T ₁	20 (19.05)	15 (24.59)	4.421	0.221
T ₂	56 (53.33)	37 (60.66)		
T ₃	18 (17.14)	4 (6.56)		
T ₄	11 (10.48)	5 (8.20)		
Histological grading				
I ~ II	77 (73.33)	38 (62.30)	2.209	0.137
III	28 (26.67)	23 (37.70)		
Clinical primary tumor response				
CR	11 (10.48)	28 (45.90)	26.940	<0.001
PR+SD+PD	94 (89.52)	33 (54.10)		
Molecular subtype				
Luminal A	38 (36.19)	5 (8.20)	34.442	<0.001
Luminal B	32 (30.48)	9 (14.75)		
Triple negative	17 (16.19)	13 (21.31)		
HER2	18 (17.14)	34 (55.74)		
Residual tumor diameter (mm)				
≥ 15	68 (64.76)	15 (24.59)	24.906	<0.001
<15	37 (35.24)	46 (75.41)		
Lymph node aspect ratio				
>2	60 (57.14)	57 (93.44)	24.437	<0.001
<2	45 (42.86)	4 (6.56)		
Lymph node cortical thickness (mm)				
≤ 3	61 (58.10)	57 (93.44)	23.454	<0.001
>3	44 (41.90)	4 (6.56)		
Lymph node portal structure				
Clear	88 (83.81)	58 (95.08)	4.627	0.031
Not clear	17 (16.19)	3 (4.92)		

Notes: pCR: pathological complete response; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

Table 2 Results of multivariate Logistic regression analysis

Characteristic	B	SE	Wald	OR (95%CI)	P
Lymph node cortical thickness ≤ 3 mm	1.821	0.673	7.322	6.178 (1.652~23.104)	0.007
Lymph node aspect ratio >2	1.711	0.652	6.890	5.533 (1.542~19.847)	0.009
Lymph node portal structure clear	-0.498	1.118	0.198	1.645 (0.184~14.720)	0.656
Molecular subtype					
Luminal A			23.303	1.000	<0.001
Luminal B	1.127	0.678	2.797	3.087 (0.824~11.569)	0.094
Triple negative	2.024	0.687	8.690	7.571 (1.971~29.086)	0.003
HER2	2.895	0.637	20.656	18.087 (5.189~63.036)	<0.001
CR of the primary lesion	1.428	0.507	7.952	4.172 (1.546~11.259)	0.005
Residual tumor diameter < 15 mm	0.772	0.489	2.494	2.165 (0.830~5.645)	0.114
Constant	-5.425	0.965	31.591		

Notes: CR: complete response; OR: odds ratio; CI: confidence interval

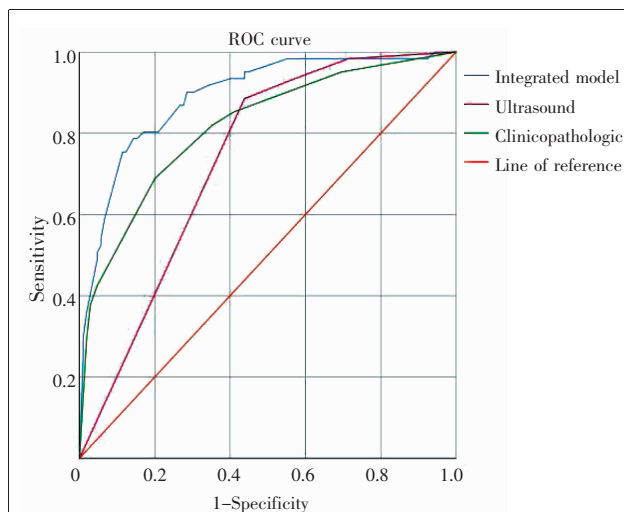


Figure 1 ROC curve for predictive performance of integrated, clinicopathological and ultrasound model

腋窝保守手术的可能性,减少了并发症的发生。SLNB是目前评估乳腺癌腋窝病理分期的活检技术,对于初诊乳腺癌腋窝淋巴结临床阴性,仅有1到2枚前哨淋巴结转移的情况下可以避免ALND^[4-5];而对于乳腺癌腋窝淋巴结阳性,且分期为cN₂期及以上的患者,NAC后SLNB假阴率高,所以SLNB作用并未得到一致认同^[6],但对于cN₁期病例,SLNB阴性患者更建议用影像学检查对腋窝淋巴结状态进行评估^[7-8]。本研究利用超声结合临床特征评估乳腺癌NAC后腋窝淋巴结pCR率,为临床选择NAC后侵入性较小的手术方式提供参考。

本研究发现乳腺癌分子分型、原发病灶临床疗效以及腋窝淋巴结超声表现与乳腺NAC后腋窝淋巴结pCR率有相关性。在达到腋窝淋巴结pCR的乳腺癌分型中,HER2阳性型占55.74%,与既往研究结果类似^[9-10]。Fayanju等^[11]的研究表明,NAC后实现乳腺癌原发灶pCR患者中86.2%实现了腋窝淋巴结pCR,本研究也得出了相似结果,乳腺癌原发灶临床CR较其他状态患者更容易达到腋窝淋巴结pCR。《乳腺癌新辅助化疗后的病理诊断专家共识》^[12]指出,转移淋巴结和原发灶经NAC后发生退变,被正常组织细胞和胶原化、纤维化的组织所替代,腋窝淋巴结的超声表现也会发生改变,包括淋巴结形态、皮质厚度、淋巴门结构等,Z1071试验研究^[2]也支持该结论。本研究将超声成像结果进一步细化至对淋巴结的具体描述,在对超声特征的单因素分析中,残余肿

瘤最大直径、腋窝淋巴结皮质厚度、淋巴结纵横比值、淋巴门结构是否存在与NAC后腋窝pCR相关,多因素分析显示淋巴结皮质厚度 ≤ 3 mm、淋巴结纵横比值 >2 是NAC后腋窝pCR的独立预测因素。本研究利用超声结合临床特征建立预测模型,AUC为0.88,灵敏度为78.7%,特异度为81.0%。相比单独临床或超声模型,超声和临床特征结合能增加诊断的灵敏度和特异度,与既往研究结果类似,如王贝等^[13]纳入淋巴结血流因素对腋窝状态建模,也有较好效果。

综上所述,超声影像是临床工作中评估乳腺癌NAC治疗效果的重要手段,通过结合临床病理资料,评估乳腺癌NAC后腋窝淋巴结状态,建立准确有效的预测模型,为临床提供客观的评估,能减少并发症,从而提高术后生存质量。由于该研究来源为单中心数据,会存在一定局限性,以后的研究中将纳入多中心病例及引入磁共振^[14]或PET/CT^[15]等多模态数据,形成多因素大样本统计分析,建立更加准确有效的预测模型。

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