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妊娠哺乳期乳腺癌患者的预后情况及其影响因素分析*

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摘要 目的:分析妊娠哺乳期乳腺癌患者的预后情况及其影响因素。**方法:**将2010年1月至2012年12月期间贵州省贵阳市妇幼保健院、贵州省医科大学和贵州省肿瘤医院收治的妊娠哺乳期乳腺癌患者60例作为研究组,选择同期收治的非妊娠哺乳期乳腺癌患者60例作为对照组,比较两组5年生存率和临床病理特征,并应用单因素和多因素 Logistic 回归分析患者预后的影响因素。**结果:**研究组5年生存率为61.67%(37/60),5年无病生存率为46.67%(28/60),均低于对照组的81.67%(49/60),73.33%(44/60)($P<0.05$)。研究组肿瘤最大直径、腋淋巴结转移率、TNM分期为III期的比例、雌激素受体阳性率、Ki67细胞阳性率 $\geq 20\%$ 的比例均高于对照组($P<0.05$),两组孕激素受体阳性率比较无统计学差异($P>0.05$)。单因素分析显示妊娠哺乳期乳腺癌患者总生存期与肿瘤最大直径、TNM分期、Ki67细胞阳性率 $\geq 20\%$ 的比例、腋淋巴结转移率有关($P<0.05$)。多因素 Logistic 回归分析显示,TNM分期为III期、Ki67细胞阳性率 $\geq 20\%$ 、腋淋巴结转移是影响妊娠哺乳期乳腺癌患者预后的独立危险因素($P<0.05$)。**结论:**妊娠哺乳期乳腺癌患者的预后较差,TNM分期为III期、Ki67细胞阳性率 $\geq 20\%$ 、腋淋巴结转移是影响患者预后的危险因素,对于临床防治具有重要的启示作用。

关键词:乳腺癌;妊娠哺乳期;生存率;预后;影响因素

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Analysis of Prognosis and Influencing Factors in Breast Cancer during Pregnancy and Lactation*

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ABSTRACT Objective: To analyze the prognosis of breast cancer patients during pregnancy and lactation and its influencing factors. **Methods:** 60 cases of breast cancer in pregnant lactation period of Guiyang Maternal and Child Health-Care Hospital of Guizhou, Guizhou Medical University and Guizhou Cancer Hospital from January 2010 to December 2012 were selected as the study group. 60 cases of breast cancer without pregnancy and lactation were selected as control group. The 5 year survival rate and the clinicopathological features of the two groups were compared, and the single factor and multiple factor Logistic regression were used to analyzed the factors affecting the prognosis of patients. **Results:** The 5 year survival rate of the study group was 61.67% (37/60), and the 5 year disease-free survival rate was 46.67%(28/60), which were significantly lower than 81.67% (49/60), 73.33% (44/60) of the control group ($P<0.05$). The maximum diameter of the tumor, the rate of axillary lymph node metastasis, the ratio of TNM stage to III stage, the positive rate of estrogen receptor and the positive rate of Ki67 cells in the study group were higher than those of the control group ($P<0.05$). There was no significant difference in the positive rate of progesterone receptor between the two groups($P>0.05$). Single factor analysis showed that the total survival time of breast cancer patients in pregnancy lactation period was related to the maximum diameter of the tumor, TNM staging, the ratio of Ki67 cell positive rate more than 20%, and the axillary lymph node metastasis rate ($P<0.05$). Multiple factor Logistic regression analysis showed that TNM staging was III stage, Ki67 cell positive rate was more than 20%, axillary lymph node metastasis was an independent risk factor affecting the prognosis of breast cancer patients in pregnancy ($P<0.05$). **Conclusion:** The prognosis of breast cancer patients in pregnancy lactation period was poor, TNM stage is III stage, Ki67 cell positive rate is more than 20%, axillary lymph node metastasis is a risk factor affecting the prognosis of the patients, which has important implications for clinical prevention and treatment.

Key words: Breast cancer; Pregnancy and lactation; Survival rate; Prognosis; Influencing factors

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前言

妊娠哺乳期乳腺癌是指在妊娠期间、女性妊娠结束 1 年以内及哺乳期内发生的原发性乳腺癌, 约占全部乳腺癌的 0.18~3.76%^[1,2]。近年来随着我国女性生育年龄的推迟及乳腺癌发病的年轻化的趋势,我国妊娠哺乳期乳腺癌发病率呈升高趋势。虽然妊娠哺乳期乳腺癌发病率不高,但妊娠和哺乳期的特殊性增加疾病诊治难度,国内外专业对于妊娠哺乳期乳腺癌的治疗方案也存在争议^[3-5]。从以往病例报道来看,妊娠哺乳期乳腺癌病理类型多为浸润性导管癌,免疫组织化学染色多为非激素依赖型^[6,7]。但目前缺乏关于妊娠哺乳期乳腺癌的系统研究,对研究妊娠哺乳期乳腺癌的预后及影响因素仍未完全明确。笔者对我院收治的妊娠哺乳期乳腺癌患者和非妊娠哺乳期乳腺癌患者进行了病例对照研究,现报道如下。

1 资料与方法

1.1 临床资料

选择 2010 年 1 月至 2012 年 12 月期间贵州省贵阳市妇幼保健院、贵州省医科大学和贵州省肿瘤医院收治的妊娠哺乳期乳腺癌患者 60 例作为研究组,纳入标准:(1)所有患者均符合 2017 版《中国抗癌协会乳腺癌诊治指南与规范》诊断标准^[8],并经医院病理科确诊为原发性乳腺癌;(2)患者病历资料真实完整,自愿参加本研究;(3)患者初次发病,具有完整的随访记录,无失访者。排除标准:(1)手术前进行内分泌治疗者;(2)外院进行手术的患者;(3)TNM 分期 IV 期者;(4)治疗期间死亡者。患者年龄 25~42 岁,平均(33.12±3.37)岁;发现病变至就诊时间 4~18 个月,平均(9.12±3.05)个月,治疗时间 1~8 个月,平均(2.86±1.32)个月。选择同期收治的非妊娠哺乳期乳腺癌患者 60 例作为对照组,患者年龄 26~45 岁,平均(34.01±3.45)岁;发现病变至就诊时间 4~16 个月,平均(8.85±3.14)个月,治疗时间 1~7 个月,平均(2.76±1.18)个月。两组年龄、发病至就诊时间、治疗时间比较无统计学差异($P>0.05$),具有可比性。本研究经我院伦理委员会同意。

1.2 方法

1.2.1 治疗方式 所有患者均进行手术治疗。其中研究组 12 例确诊后选择终止妊娠,10 例妊娠后期确诊,分娩后进行治疗,其余 38 例患者应用药物退乳后进行治疗。改良根治术 45 例、保留乳房手术 15 例。术后辅助化疗 15 例,新辅助化疗 7 例,放疗 4 例。对照组改良根治术 41 例、保留乳房手术 19 例。术后辅助化疗 14 例,新辅助化疗 6 例,放疗 5 例。

1.2.2 随访时间及方法 所有患者均通过电话和门诊复查进行随访,随访时间不少于 5 年,5 年内死亡患者随访时间至死亡为止,随访内容包括无病生存时间、总生存期、肿瘤有无复发、转移等。无病生存时间为确诊疾病至疾病复发或转移的时间;总生存期为确诊疾病至死亡或末次随访(生存时间超过 5 年者)的时间。

1.2.3 雌激素受体、孕激素受体和 Ki67 细胞阳性检验 术后将患者癌组织标本置于 4%甲醛溶液中固定 48 h,常规脱水后使用石蜡进行包埋和切片,采用免疫组化 SP 法检测组织中雌激素受体、孕激素受体和 Ki67 细胞阳性表达情况,若细胞呈棕褐色或棕黄色则判定为阳性^[9]。

1.3 统计学方法

使用 SPSS25.0 软件进行统计学分析,计量资料以($\bar{x} \pm s$)表示,两组比较实施 t 检验,计数资料以率或百分比表示,实施卡方检验,并应用单因素和多因素 Logistic 回归分析患者预后的影响因素, $P<0.05$ 记作差异有统计学意义。

2 结果

2.1 两组预后情况比较

研究组 5 年生存率为 61.67%(37/60),5 年无病生存率为 46.67%(28/60),均低于对照组的 81.67%(49/60),73.33%(44/60)($\chi^2=5.910, 8.889, P=0.015, 0.003$)。

2.2 两组临床病理特征比较

研究组肿瘤最大直径、腋淋巴结转移率、TNM 分期为 III 期的比例、雌激素受体阳性率、Ki67 细胞阳性率 $\geq 20\%$ 的比例均高于对照组($P<0.05$),两组孕激素受体阳性率比较无统计学差异($P>0.05$)。见表 1。

表 1 两组临床病理特征比较

Table 1 Comparison of clinicopathological features between the two groups

Clinicopathological features		Study group (n=60)	Control group (n=60)	t/ χ^2	P
Maximum diameter of tumor(cm)		7.48±2.12	5.02±1.72	5.132	0.017
Axillary lymph node metastasis[n(%)]	Yes	37(61.67)	19(31.67)	10.848	0.001
	No	23(38.33)	41(68.33)		
TNMstage[n(%)]	I-IIstage	25(41.67)	37(61.67)	4.805	0.023
	IIIstage	35(58.33)	23(38.33)		
Estrogen receptor[n(%)]	Positive	20(33.33)	8(13.33)	6.708	0.010
	Negative	40(66.67)	52(86.67)		
Progesterone receptor[n(%)]	Positive	22(36.67)	20(33.33)	0.147	0.702
	Negative	38(63.33)	40(66.67)		
Ki67 Cell positive rate[n(%)]	<20%	38(63.33)	50(83.33)	6.136	0.013
	$\geq 20\%$	22(36.67)	10(16.67)		

2.3 妊娠哺乳期乳腺癌患者预后的单因素分析

研究组中位总生存期为 3.8 年(总生存期超过随访时间者按 5 年计算),单因素分析显示妊娠哺乳期乳腺癌患者总生存

期与肿瘤最大直径、TNM 分期、Ki67 细胞阳性率 $\geq 20\%$ 的比例、腋淋巴结转移率有关($P<0.05$),而与雌激素受体和孕激素受体阳性率无关($P>0.05$),见表 2。

表2 妊娠哺乳期乳腺癌患者预后的单因素分析

Table 2 Single factor analysis of prognosis in breast cancer patients during pregnancy and lactation

Clinicopathological features		<3.8 years of total survival(n=26)	≥ 3.8 years of total survival(n=34)	t/ χ^2	P
Maximum diameter of tumor(cm)		8.48 $\pm$ 1.55	6.71 $\pm$ 1.22	5.857	0.011
Axillary lymph node metastasis[n(%)]	Yes	21(80.77)	16(47.06)	7.083	0.008
	No	5(19.23)	18(52.94)		
TNM stage[n(%)]	I-IIstage	6(23.08)	19(55.88)	6.524	0.011
	IIIstage	20(76.92)	15(44.12)		
Estrogen receptor[n(%)]	Positive	8(30.77)	12(35.29)	0.136	0.713
	Negative	18(69.23)	22(64.71)		
Progesterone receptor[n(%)]	Positive	10(38.46)	12(35.29)	0.064	0.801
	Negative	16(61.54)	22(64.71)		
Ki67 Cell positive rate[n(%)]	<20%	12(46.15)	26(76.47)	5.831	0.016
	$\geq 20\%$	14(53.85)	8(23.53)		

2.4 妊娠哺乳期乳腺癌患者预后的多因素 Logistic 回归分析

以总生存期 <3.8 年为自变量,以肿瘤最大直径、TNM 分期、Ki67 细胞阳性率 $\geq 20\%$ 的比例、腋淋巴结转移为因变量进

行多因素 Logistic 回归分析,结果显示,TNM 分期为 III 期、Ki67 细胞阳性率 $\geq 20\%$ 、腋淋巴结转移是影响妊娠哺乳期乳腺癌患者预后的独立危险因素($P<0.05$),见表 3。

表 3 妊娠哺乳期乳腺癌患者预后的多因素 Logistic 回归分析

Table 3 Multivariate Logistic regression analysis of prognosis in breast cancer patients during pregnancy and lactation

Influence factor	β	SE	Wald χ^2	P	OR	95%CI
Maximum diameter of tumor	0.641	0.172	2.124	0.128	0.886	0.433-1.356
TNM stage III phase	0.665	0.241	11.254	0.001	2.782	1.432-5.736
Ki67 Cell positive rate	0.732	0.382	5.123	0.000	2.927	2.202-5.973
Axillary lymph node metastasis	0.726	0.166	6.294	0.000	2.783	1.662-3.395

3 讨论

妊娠哺乳期乳腺癌是一种发生于女性特殊生理阶段的恶性肿瘤,是乳腺癌的特殊类型。尽管妊娠哺乳期乳腺癌发生率仅占妊娠女性 0.03%,但疾病临床治疗较为复杂^[10,11]。以往有文献报道,妊娠哺乳期乳腺癌发病的平均年龄为 33 岁^[12],本研究中妊娠哺乳期乳腺癌患者平均年龄(33.12 $\pm$ 3.37)岁,与以往报道相符。从妊娠哺乳期乳腺癌患者预后情况来看,妊娠哺乳期乳腺癌患者 5 年生存率为 61.67%,5 年无病生存率为 51.67%均显著低于非妊娠哺乳期乳腺癌患者的 81.67%,73.33%。有研究报道^[13],与非妊娠哺乳期乳腺癌患者相比,妊娠哺乳期乳腺癌患者体内雌二醇、雌三醇、孕酮和肾上腺皮质激素明显升高,而乳腺癌的发生、发展与激素水平有密切关系,因此妊娠哺乳期乳腺存在特殊的临床特点。Parker S 等研究报道,妊娠哺乳期乳腺癌患者雌激素和孕激素水平升高,导致肿瘤生长加快,患者预后不佳^[14]。但本研究结果中雌激素和孕激素的阳性表达率并不会影响患者的总生存期,这可能与选择的病例及研究范围有关。

本研究通过对我院收治的妊娠哺乳期乳腺癌患者和非妊

娠哺乳期乳腺癌患者进行了病例对照研究发现,妊娠哺乳期乳腺癌患者肿瘤最大直径更大,腋淋巴结转移率更高,同时 TNM 分期为 III 期的比例、雌激素受体阳性率更高,患者预后更差。笔者认为这可能与以下几方面原因有关:(1)妊娠哺乳期乳房增大、乳腺血流量增加导致肿瘤增殖加快,利于肿瘤细胞转移^[15,16];(2)妊娠哺乳期乳腺癌患者体内雌激素水平升高,导致肿瘤生长加快,雌激素受体阳性率升高^[17,18];(3)妊娠哺乳期乳腺癌患者顾忌胎儿和婴儿喂养,忽略疾病治疗^[19,20]。而 Ki67 可以反映肿瘤增殖情况,是反映乳腺癌患者预后的重要指标,Ki67 越高表明肿瘤增殖能力越强,恶性程度越高^[21,22]。本研究中研究组 Ki67 细胞阳性率 $\geq 20\%$ 的比例显著高于对照组,提示妊娠哺乳期乳腺癌肿瘤增殖能力更强,并可能影响患者预后。而两组孕激素受体阳性率比较无统计学差异可能与本研究病例较少有关。此外,单因素分析显示妊娠哺乳期乳腺癌患者总生存期与肿瘤最大直径、TNM 分期、Ki67 细胞阳性率 $\geq 20\%$ 的比例、腋淋巴结转移率有关,多因素 Logistic 回归分析显示,TNM 分期为 III 期、Ki67 细胞阳性率 $\geq 20\%$ 、腋淋巴结转移是影响妊娠哺乳期乳腺癌患者预后的独立危险因素。其中肿瘤 TNM 分期是影响肿瘤预后的重要指标,TNM 分期越高表明肿瘤的恶

性程度越高,患者治疗后肿瘤更易复发,预后更差^[23,24]。而 Ki67 细胞阳性率 $\geq 20\%$ 反映肿瘤增殖能力更强,恶性程度更高,预后也较差^[25,26]。腋淋巴结是乳腺癌常见的转移部位,临床研究发现存在腋淋巴结转移的患者术后肿瘤复发率更高,患者生存期缩短。本研究结果与 Yu HH 等研究相符^[27],证实腋淋巴结转移是影响妊娠哺乳期乳腺癌患者预后的独立危险因素。而临床上应对肿瘤 TNM 分期较高、Ki67 细胞阳性率较高及存在腋淋巴结转移患者给予重点防治,提高妊娠哺乳期乳腺癌患者预后^[28-30]。本研究中也存在一定的不足,如选择病例少、范围小等,同时对其他影响因素并未进行全面分析,可能限制结果的准确性,后期需要增加病例和研究内容,从而证实研究结果的可靠性。

综上所述,妊娠哺乳期乳腺癌预后较差,应对 TNM 分期偏高、Ki67 细胞阳性率偏高及腋淋巴结转移的患者进行重点防治,可改善患者的预后效果,临床意义较高。

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