



· 论 著 ·

56例隐匿性乳腺癌临床病理特征分析及 诊疗策略探讨

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[摘要] **背景与目的:** 隐匿性乳腺癌发病隐匿, 诊断困难, 治疗策略不确定, 是乳腺癌领域的难点和热点。本研究探讨了隐匿性乳腺癌的临床病理特征及诊疗策略。**方法:** 对56例隐匿性乳腺癌患者在术前采用乳腺彩超、钼靶、磁共振及PET/CT检查, 对比不同检查方法对隐匿性乳腺癌可疑原发灶检出率及病理符合率的差异。治疗方案采用新辅助化疗、乳腺癌改良根治术、保乳+腋窝淋巴结清扫术、腋窝淋巴结清扫术, 术后行化疗+放疗。**结果:** 乳腺超声、X线、MRI、PET/CT对乳腺可疑原发灶的检出率分别为7.14% (4/56)、29.41% (15/51)、37.50% (18/48)和16.28% (7/43); 结合术后病理学检查发现其病理符合率分别为66.67% (2/3)、50.00% (7/14)、50.00% (9/18)和50.00% (3/6); 26例患者乳腺超声、X线及MRI均未发现可疑原发灶, 其中21例接受病理学检查, 阳性率为14.29% (3/21); 对39例乳腺癌改良根治术标本行乳腺病理切片检查, 检出原发灶15例, 检出率38.46%。根据St. Gallen指南分子分型标准, Luminal A型、Luminal B型、HER-2阳性型和三阴性型比例分别为7.14%、46.43%、12.50%和33.93%。术后随访52例, 随访时间10~104个月, 中位时间35个月, 复发转移4例, 死亡0例。检出原发灶的15例患者中, 复发或转移2例; 未检出原发灶的24例患者中, 无复发或转移; 行新辅助化疗17例, 达病理学完全缓解 (pathological complete response, PCR) 2例, 复发或转移2例; 行乳腺癌改良根治术39例, 复发或转移2例; 行保乳+腋窝清扫8例, 复发或转移2例; 腋窝清扫9例, 无复发或转移。**结论:** 乳腺MRI检查在隐匿性乳腺癌的排除性诊断中有重要价值; 乳腺超声、X线及MRI均未发现可疑原发灶的患者其乳腺病理原发灶检出率较低; 隐匿性乳腺癌的治疗策略可选择新辅助化疗、乳腺癌改良根治术、保乳+腋窝清扫术、腋窝清扫术; 乳腺病理学未检出原发灶的患者复发转移率低于检出原发灶者。

[关键词] 隐匿性乳腺癌; 腋窝淋巴结转移; 磁共振成像; 新辅助化疗

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The exploration of clinical pathological characteristics and the diagnosis and treatment strategy of 56 patients with occult breast cancer SHEN Haoyuan^{1,2}, HU Chaohua¹, HAN Yuntao¹, PENG Dongjie¹, YU Youlin¹, XU Yuanbing¹, PENG Pai¹, LIU Chenhao¹, HOU Yifeng² (1. Thyroid and Breast Disease Center, Xiaogan Hospital Affiliated to Wuhan University of Science and Technology, Xiaogan 432100, Hubei Province, China; 2. Department of Breast Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)

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[Abstract] **Background and purpose:** Occult breast cancer is a difficult and hot spot in the field of breast cancer because of its occult onset, diagnostic difficulties, and unclear therapeutic strategies. In this study, we discussed the clinical pathological characteristics and the diagnosis and treatment strategy of occult breast cancer. **Methods:** Fifty-six cases of occult breast cancer received the preoperative examinations of ultrasonography, mammography, magnetic

resonance imaging (MRI) and PET/CT. The different detection rates and pathological coincidence rates in suspicious primary lesions of occult breast cancer were compared. Treatment options included the neoadjuvant chemotherapy, modified radical mastectomy, breast-conserving surgery with axillary lymph node dissection and axillary lymph node dissection. All patients received postoperative chemotherapy with radiotherapy. **Results:** The detection rates of ultrasonography, mammography, MRI and PET/CT for the suspicious breast primary tumors were 7.14% (4/56), 29.41% (15/51), 37.50% (18/48) and 16.28% (7/43). Combined with the postoperative pathological examination, we found that the pathological coincidence rates were 66.67%, 50.00%, 50.00% and 50.00%. Twenty-six cases examined with ultrasonography, mammography and MRI did not have suspicious primary tumors, 21 patients underwent breast pathology examination with a positive rate of 14.29% (3/21). Thirty-nine patients received pathology examination, and the breast primary tumors were detected in 15 patients. The detection rate by pathology examination was 38.46%. According to the St.Gallen molecular classification standards, the ratio of Luminal A, Luminal B, HER-2 positive and triple-negative breast cancer was 7.14%, 46.43%, 12.50% and 33.93%, respectively. There were 52 cases with postoperative follow-up, the median follow-up period was 35 months (10-104 months), recurrence or metastasis occurred in 4 cases, and there was no death. Among the 15 patients with primary tumors, 2 cases eventually had recurrence or metastasis; 24 patients without the primary tumors did not have recurrence or metastasis; 17 patients received neoadjuvant chemotherapy, of whom 2 patients achieved pathologic complete response (PCR) and 2 patients had recurrence or metastasis. Modified radical mastectomy was performed on 39 cases, and recurrence or metastasis occurred in 2 cases. Breast-conserving surgery with axillary lymph node dissection was performed on 8 cases, and recurrence or metastasis occurred in 2 cases. Axillary lymph node dissection with radiotherapy was performed on 9 cases, and there was no recurrence or metastasis. **Conclusion:** MRI examination has important value in excluding the occult breast cancer. Breast pathology of primary tumors has lower detection rate in the patients without suspicious primary tumors on ultrasonography, mammography and MRI. The treatment options for occult breast cancer include the neoadjuvant chemotherapy, modified radical mastectomy, breast-conserving surgery with axillary lymph node dissection and axillary lymph node dissection. Patients who did not have primary tumors examined by breast pathology had a lower recurrence or metastasis rate than patients with the primary tumors.

[**Key words**] Occult breast cancer; Axillary lymph node metastasis; Magnetic resonance imaging; Neoadjuvant chemotherapy

隐匿性乳腺癌(occult breast cancer)一般是指以腋窝淋巴结或锁骨上淋巴结转移为首发症状,而临床体检乳房未能触及肿块且影像学检查(包括乳腺彩超、乳腺钼靶等检查)也不能确定的乳腺癌,同时全身其他部位检查亦未发现原发病灶。然而随着影像学技术的进步,特别是乳腺MRI的应用,使隐匿性乳腺癌的定义发生了变化。目前多数学者认为,隐匿性乳腺癌是指以腋窝淋巴结或锁骨上淋巴结转移为首发症状,而乳腺影像学(包括乳腺超声、乳腺X线、MRI等)及病理学检查均没有发现原发灶的患者,其发病少见,文献报道隐匿性乳腺癌占新发乳腺癌患者的0.3%~3.0%^[1-2],自Halsted^[3]在1907年首先报道了3例仅表现为腋窝淋巴结肿大的隐匿性乳腺癌,1907年Cameron又报道了3例类似患者,此后隐匿性乳腺癌逐渐引起人们的注意,由于术前找不到乳腺的原发肿瘤病灶,隐匿性乳腺癌的处理有一定的特殊性,是目前公认的乳腺癌诊断治疗的难点。很多外科医师及肿瘤内

科医师缺乏对隐匿性乳腺癌的认识及规范诊疗措施。因此,本研究通过对56例隐匿性乳腺癌的临床病理特征分析及治疗策略探讨,同时复习国内外文献,希望能加深对隐匿性乳腺癌诊断、治疗策略、生物学特征及预后的认识。

1 资料和方法

1.1 一般资料

回顾性分析复旦大学附属肿瘤医院2007年1月—2017年6月56例隐匿性乳腺癌患者的临床资料,患者均为女性,占同期乳腺癌住院患者的0.17%(56/33 258),年龄27~81岁,中位年龄55.5岁,绝经前15例,绝经后41例,均以单侧腋窝肿块为首发症状,左侧27例,右侧29例,腋窝肿块直径1.00~6.00 cm,平均3.53 cm,有乳腺癌或卵巢癌家族史2例,占3.57%(表1)。

表 1 56例隐匿性乳腺癌患者临床病理特征及治疗情况

Tab. 1 Clinical and pathological characteristics and treatment methods of 56 occult breast cancer patients

Characteristics	Case <i>n</i>
Age/year	
≤50	16
>50	40
Location	
Left	27
Right	29
Menstrual status	
Premenopausal	15
Postmenopausal	41
Axillary staging	
N ₁	34
N ₂	9
N ₃	13
Histologic classification	
I	0
II	5
III	17
Ki-67	
≤20%	14
20%-50%	14
>50%	9
Family history	
Yes	2
No	54
Axillary lump size <i>l</i> /cm	
≤3	25
>3	31
Neoadjuvant chemotherapy	
Yes	17
No	39
Molecular classification	
Luminal A	4
Luminal B	26
HER-2 positive	7
Triple-negative breast cancer	19
Operation method	
Modified radical mastectomy	39
Breast-conserving surgery with axillary lymph node dissection	8
Axillary lymph node dissection	9
The pathologic types of primary foci	
Infiltrating ductal carcinoma	8
DCIS	4
DCIS with micro infiltration	3

DCIS: Ductal carcinoma *in situ*

1.2 诊断

入组标准：全组患者均对切除的腋窝淋巴结行病理学检查证实为转移性癌，并行免疫组织化学分析推定乳腺来源，同时对乳腺行体格检查、超声诊断和X线检查，全身行CT、彩超及PET/CT检查，均未发现明显原发灶。排除标准为乳腺超声、X线检查发现的乳腺BI-RADS4a类以上患者。

1.3 治疗

结合患者分子分型、乳房原发灶情况、腋窝淋巴结转移情况分别采用新辅助化疗、乳腺癌改良根治术、保乳+腋窝淋巴结清扫术、腋窝淋巴结清扫，术后行辅助化疗+放疗。新辅助化疗方案包括：PC方案4个周期（多西他赛+卡铂）、PC方案4个周期序贯EC方案4个周期（多西他赛+卡铂序贯表柔比星+环磷酰胺）、CEF方案3个周期序贯T方案3个周期（环磷酰胺+表柔比星+氟尿嘧啶序贯多西他赛）、NE方案4个周期（长春瑞滨+表柔比星）、TE方案4个周期（多西他赛+表柔比星）、FEC方案6个周期（氟尿嘧啶+表柔比星+环磷酰胺）、新辅助内分泌治疗（来曲唑+卡培他滨）；术后辅助化疗方案包括：EC方案4个周期序贯T方案4个周期（表柔比星+环磷酰胺序贯多西他赛）、FEC方案3个周期序贯T方案3个周期（氟尿嘧啶+表柔比星+环磷酰胺序贯多西他赛）、PC方案6个周期（多西他赛+卡铂）、TC方案4个周期（多西他赛+环磷酰胺），放疗含乳腺、锁骨上区和内乳区。雌激素受体（estrogen receptor, ER）和（或）孕激素受体（progesterone receptor, PR）阳性者给予内分泌治疗。

2 结 果

2.1 不同检查方法对隐匿性乳腺癌可疑原发灶的检出率及病理符合率

56例患者接受乳腺超声检查，发现可疑原发灶4例，均为BI-RADS 0类，检出率7.14%（4/56），其中3例行乳腺病理学检查，病理阳性2例，病理符合率66.67%（2/3）；51例行

乳腺X线检查, 发现可疑原发灶15例, 均为BI-RADS 0类, 检出率29.41% (15/51), 其中14例行乳腺病理学检查, 病理阳性7例, 病理符合率50% (7/14); 48例行乳腺MRI检查, 发现可疑原发灶18例, BI-RADS 0类6例, BI-RADS 4a类12例 (MRI发现的局灶性强化灶或局灶性结构紊乱), 检出率37.50% (18/48), 其中18例行乳腺病理学检查, 病理阳性9例, 病理符合率50% (9/18); 43例行PET/CT检查, 发现可疑原发灶7例 (PET/CT发现的FDG代谢增高结节或

钙化), 检出率16.28% (7/43), 其中6例行乳腺病理学检查, 病理阳性3例, 病理符合率50% (3/6); 26例患者乳腺超声、X线、MRI均未发现可疑原发灶, 其中21例行乳腺病理学检查, 病理阳性3例, 阳性率14.29% (3/21); 30例乳腺MRI检查阴性的患者中, 24例行乳腺病理学检查, 病理阳性4例, 阳性率16.67% (4/24); 39例乳腺癌改良根治术标本行乳腺病理切片检查, 检出原发灶15例, 检出率38.46% (表2)。

表2 不同检查隐匿性乳腺癌方法的准确率与病理检查一致性对比

Tab. 2 The coincidence of different detection rates and pathological analysis of occult breast cancer

Primary focal check method	Case <i>n</i>	Suspicious lesions <i>n</i>	The detection rate/%	Breast biopsy <i>n</i>	Pathological positive <i>n</i>	Pathological coincidence rate/%
Ultrasonography	56	4	7.14	3	2	66.67
Mammography	51	15	29.41	14	7	50.00
MRI	48	18	37.50	18	9	50.00
PET/CT	43	7	16.28	6	3	50.00

2.2 隐匿性乳腺癌分子分型及组织学分级

56例行免疫组织化学检测ER、PR和HER-2阳性率分别为54.55%、36.36%和33.96%, 根据St.Gallen指南分子分型标准, Luminal A型、Luminal B型、HER-2阳性型、三阴性型比例分别为7.14% (4/56)、46.43% (26/56)、12.50% (7/56)和33.93% (19/56)。37例行Ki-67检测: ≤20%、20%~50%、>50%分别占37.84% (14/37)、37.84% (14/37)和24.32% (9/37)。22例行组织学分级: I级0例, II级5例 (22.73%), III级17例 (77.27%)。具体结果见表1。

2.3 隐匿性乳腺癌新辅助化疗选择

行新辅助化疗的17例患者中, 三阴性乳腺癌8例, HER-2阳性8例, Luminal B型1例; 其中PC方案4个周期 (多西他赛+卡铂) 11例, 疗效评估10例达部分缓解 (partial response, PR), 1例稳定 (stable disease, SD); PC方案4个周期序贯EC方案4个周期 (多西他赛+卡铂序贯表柔比星+环磷酰胺) 1例, 达PCR; CEF方案3个周期序贯T方方案3个周期 (环磷酰胺+表柔比星+氟尿嘧啶序

贯多西他赛) 1例, 达PR; NE方案4个周期 (长春瑞滨+表柔比星) 1例, 达PCR, TE方案4个周期 (多西他赛+表柔比星) 1例, 达SD; FEC方案6个周期 (氟尿嘧啶+表柔比星+环磷酰胺) 1例, 达PR; 新辅助内分泌治疗 (来曲唑)+卡培他滨1例, 达PR (表3)。

2.4 隐匿性乳腺癌手术方式选择

56例患者中, 行乳腺癌改良根治术39例, 复发或转移2例; 行保乳+腋窝清扫8例, 复发或转移2例; 腋窝清扫9例, 无复发或转移 (表4)。

2.5 原发灶的检出对预后的影响

39例乳腺癌改良根治术标本行乳腺病理切片检查, 检出原发灶15例, 其中复发或转移2例; 未检出原发灶的24例患者中, 无复发或转移。

2.6 随访

术后随访52例, 随访时间10~104个月, 中位时间35个月, 失访7例, 随访率88.14% (52/59), 出现复发转移4例, 死亡0例。4例复发转移的患者中, 2例行乳房切除+腋窝淋巴结清扫术, 2例行保乳+腋窝淋巴结清扫术 (表3)。

表3 不同新辅助化疗方案的疗效评估

Tab. 3 The curative effect evaluation of different neoadjuvant chemotherapy scheme

Item	PCR	PR	SD	PD
PC scheme 4 cycles (n=11)	0	10	1	0
PC scheme 4 cycles followed EC scheme 4 cycles (n=1)	1	-	-	-
CEF scheme 3 cycles followed T scheme 3 cycles (n=1)	-	1	-	-
NE scheme 4 cycles (n=1)	1	-	-	-
TE scheme 4 cycles (n=1)	-	-	1	-
FEC scheme 6 cycles (n=1)	-	1	-	-
Letrozole+capecitabine (n=1)	-	1	-	-

表4 不同治疗方式对隐匿性乳腺癌局部复发率及远处转移率的影响

Tab. 4 The influence of the different treatment methods of occult breast cancer on the local recurrence rate and distant metastasis rate

Item	Modified radical mastectomy (N=39) n(%)	BCS+ALND (N=8) n(%)	ALND (N=9) n(%)	Neoadjuvant chemotherapy (N=17) n(%)
Local recurrence	2(5.13)	1(12.5)	0	1(5.88)
Distant metastases	0	1(12.5)	0	1(5.88)
Death	0	0	0	0

3 讨 论

隐匿性乳腺癌由于其发病率低、术前找不到乳腺原发病灶,同时对隐匿性乳腺癌的概念模糊及临床诊断困难等原因,导致临床医师对该病的定义、临床病理特征、术前诊断措施、化疗方案、手术方式的选择及预后等缺乏足够的认识,许多隐匿性乳腺癌患者并未得到正确的诊断及规范的治疗。

对临床以腋窝淋巴结肿大为首发症状的患者,应首先行腋窝肿块粗针穿刺活检或手术切除活检,经病理学检查证实为转移性腺癌,考虑来源于乳腺,而临床体检及乳腺彩超、钼靶均未见明显乳腺癌征象,则隐匿性乳腺癌的诊断可初步成立。其次是寻找乳腺原发病灶进一步排除隐匿性乳腺癌,目前常用的检查手段是乳腺超声及X

线检查,但乳腺超声及X线检查对隐匿性乳腺癌原发病灶检出率极低,本研究中乳腺超声及X线检查对可疑原发病灶检出率分别为7.14%和29.41%。郭丰丽等^[4]对62例隐匿性乳腺癌术前行乳腺超声及X线检查发现可疑原发病灶检出率分别为3.23% (2/62)、4.84% (3/62),因此乳腺超声及X线检查在隐匿性乳腺癌的排除性诊断中价值有限。而乳腺MRI对隐匿性乳腺癌原发病灶检出率则明显提高,本研究中乳腺MRI对可疑原发病灶检出率37.5% (18/48),明显高于乳腺超声及X线检查。Lu等^[5]对35例隐匿性乳腺癌行乳腺MRI检查发现乳腺原发病灶检出率为57% (20/35),且20例原发病灶在乳腺MRI上的表现为积聚性强化占55% (11/20),沿导管分布或段样强化占45% (9/20)。张俊杰等^[6]对34例隐匿性乳腺癌行MRI检查检出原发病灶17例,检出率50%,其中肿块型病变6例,直径0.6~1.2 cm (平均0.9 cm);非肿块样强化病变11例。进一步证实乳腺MRI在隐匿性乳腺癌的排除性诊断中的价值。本研究中乳腺MRI发现的乳腺4a类病灶13例,包括结节样或线样强化、结构紊乱。

本研究还发现,26例患者乳腺彩超、钼靶、MRI均未发现可疑原发病灶,其中21例行乳房病理学检查,病理阳性3例,阳性率14.29% (3/21),提示影像学检查均阴性的患者其病理学阳性率极低,乳腺彩超、钼靶、MRI均未发现可疑原发病灶的患者可选择保留乳房的手术。同时本研究还发现,30例乳腺MRI检查阴性的患者中,24例行乳房病理学检查,病理阳性4例,阳性率16.67% (4/24),提示乳腺MRI对隐匿性乳腺癌手术方式的选择也有重要意义,Olson等^[7]报道结果与本研究相似,因此认为对于MRI未发现原发病灶的患者可选择保留乳房的手术。而de Bresser等^[8]认为乳腺MRI对隐匿性乳腺癌原发病灶检出率敏感性高,但特异度较低,建议对乳腺MRI发现的病灶行MRI或超声引导下活检,待活检证实后再决定是否行保乳手术。本研究中,乳腺MRI对原发病灶检出的特异度为50%。PET/CT对隐匿性乳腺癌原发病灶检出率并不高,本研究43例患者行PET/CT检查,检出可疑原发病灶7例,检出率为16.28%。

本研究发现隐匿性乳腺癌中三阴性乳腺癌占

33.93% (19/56), 而三阴性乳腺癌在全部乳腺癌中所占比例则更低, 一项2009年的统计数据显示^[9], 全球每年乳腺癌新发患者100万, 其中三阴性乳腺癌约17万, 占17%。我们曾统计2008—2012年212例乳腺癌, 其中三阴性乳腺癌36例, 占17.82%^[10]。张俊杰等^[6]对34例隐匿性乳腺癌行病理特征分析发现三阴性乳腺癌所占比例为30.4%, Lu等^[5]报道在隐匿性乳腺癌中, 三阴性乳腺癌所占比例为37.5% (12/32), 与本研究结果类似。

关于隐匿性乳腺癌手术方式的选择, 腋窝淋巴结清扫术是目前公认的腋窝处理方式, 而乳房的处理目前主要有4种方式: 乳房切除术、保乳术、乳房单纯放疗、乳房不处理。本研究56例患者中行乳腺癌改良根治术39例, 随访36例, 中位随访41个月, 复发或转移2例; 行保乳+腋窝淋巴结清扫8例, 中位随访21.5个月, 复发或转移2例; 腋窝淋巴结清扫联合放疗9例, 随访8例, 中位随访30个月, 无复发或转移。全组随访时间10~104个月, 中位时间35个月, 无死亡患者。复旦大学附属肿瘤医院^[11]对95例隐匿性乳腺癌进行的回顾性研究发现, 乳房切除联合腋窝淋巴结清扫术或腋窝淋巴结清扫术联合放疗较腋窝淋巴结清扫术能明显提高患者的无局部复发生存率 (locoregional recurrence-free survival, LRFS) 及无复发转移生存率 (recurrence/metastasis-free survival, RFS)。隐匿性乳腺癌的手术方式可选乳房切除联合腋窝淋巴结清扫术, 保乳手术联合腋窝淋巴结清扫术, 以及腋窝淋巴结清扫术联合放疗, 这三种手术方式疗效相似, 而单纯腋窝淋巴结清扫术因局部复发率高、总生存率低目前并不提倡。

郝晓蕊等^[2]对205例隐匿性乳腺癌行预后相关性分析发现有无新辅助化疗是影响隐匿性乳腺癌的独立预后因素。郭美琴等^[12]认为对T₀N₂₋₃M₀的隐匿性乳腺癌患者建议行新辅助化疗, 因N₂₋₃属于局部晚期病变。本研究中17例新辅助化疗患者中腋窝淋巴结平均直径为4.29 cm, 而未行新辅助化疗患者腋窝淋巴结平均直径为3.16 cm, 因新辅助化疗前难以获得准确的N分期, 可以考虑对于腋窝淋巴结直径大于4 cm者行新辅助化疗。同时本研究17例新辅助化疗患者中, 三阴性乳腺癌8例, HER-2阳性8例, Luminal型1例, 为此对三阴性或HER-2阳性的隐匿性乳腺癌建议行

新辅助化疗。但哪些隐匿性乳腺癌患者能从新辅助化疗中获益, 尚需更大样本的随机对照研究来证实。

隐匿性乳腺癌的预后与普通乳腺癌相似, 本研究中56例隐匿性乳腺癌术后随访52例, 随访时间10~104个月, 中位时间35个月, 失访7例, 随访率为88.14% (52/59), 出现复发转移4例, 死亡0例。本研究39例乳腺癌改良根治术标本行乳腺病理切片检查, 检出原发灶15例, 检出原发灶的15例患者中, 复发或转移2例, 未检出原发灶的24例患者中, 无复发或转移, 提示乳房病理未发现原发灶的患者预后好。在本研究基础上, 我们会继续累积资料, 为隐匿性乳腺癌的治疗提供更多的依据。

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