

## · 专家论坛 ·

## 乳腺癌保乳治疗的患者选择

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乳腺癌是女性常见恶性肿瘤,其发病率呈逐年上升趋势。2002 年全球乳腺癌新发病例超过 115 万<sup>[1]</sup>。据美国癌症协会估计,美国 2008 年确诊的乳腺癌新发病例超过 18.4 万,近 4.1 万乳腺癌患者死亡<sup>[2]</sup>。全国肿瘤登记中心统计的 1998 ~ 2002 年中国恶性肿瘤发病率显示,乳腺癌发病率较过去 5 年显著升高<sup>[3]</sup>。受益于乳腺癌的早期诊断和系统治疗的进展,乳腺癌死亡率呈下降趋势,患者的生存期延长<sup>[4]</sup>。

手术在乳腺癌治疗方案中占有重要地位,局部治疗的进步不仅在控制局部肿瘤的同时保留乳房的美观,而且减轻了患者的心理痛苦。近年来,多数学者已对保乳治疗能取得与全乳切除加腋窝淋巴结清扫相同的治疗效果形成共识<sup>[5-8]</sup>。国外约有 50% ~ 75% 的乳腺癌患者接受保乳治疗<sup>[9-11]</sup>,而在中国,接受保乳治疗的比例还不到 10%<sup>[12]</sup>。

NCCN 乳腺癌治疗指南中提出保乳治疗的绝对禁忌证包括:既往乳腺或胸壁接受过中等剂量或高剂量放射治疗;妊娠期间需要接受放射治疗的患者;乳腺摄像显示弥漫性可疑或恶性微小钙化灶;多中心病灶不能通过单一切口切除以达到切缘阴性且获得满意外观效果者;切缘阳性患者再次扩大切除仍不能获得阴性病理切缘者。保乳治疗的相对禁忌证包括:累及皮肤的活动性结缔组织疾病(尤其是硬皮病和系统性红斑狼疮);肿瘤大于 5 cm 和切缘病理检查呈局灶阳性;已知存在 BRCA1/2 突变的绝经前妇女;年龄  $\leq 35$  岁患者。现就以上问题做相关陈述,供参考。

## 1 保乳治疗的患者选择

## 1.1 年龄

欧、美国家进行过对照研究,将保乳手术的患者分为年龄  $\leq 35$  岁组和  $> 35$  岁组,局部复发率随诊结果是:美国宾夕法尼亚大学(UPenn)两组分别为

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24% 和 14% ~ 15%; 欧洲癌症治疗研究组织和丹麦乳腺癌协作组(EORTC 和 DBCG) 两组分别为 35% 和 9%, 荷兰 Leiden 大学两组分别为 28% 和 9%, 可见保乳手术后局部复发率在  $\leq 35$  岁组约是  $> 35$  岁组的 2 ~ 3 倍<sup>[13]</sup>。

年轻女性接受保乳治疗后有较高的局部复发率<sup>[14-16]</sup>, 早期研究结果显示<sup>[17]</sup>, 接受保乳治疗的 30 岁以下年轻女性其局部复发率显著高于 50 岁以上患者(35% 比 0%)。远期随访结果<sup>[18]</sup>也显示 32 岁以下年轻女性的 10 年局部复发率高于 55 岁以上患者(29% 比 3%)。Clark 等<sup>[14]</sup>报道, 40 岁以下患者的局部复发风险高于 40 岁以上患者 2.3 倍。Fisher 等<sup>[19]</sup>的研究结果也表明, 以 50 岁为界, 保乳治疗患者 9 年局部复发率分别为 38% 和 31%, 年轻女性的复发风险显著高于高龄患者。上述结果只能部分说明一种现象, 年轻女性保乳治疗后局部失败风险较高, 但是这一现象的深层次原因可能与年轻女性肿瘤的病理特征有关。单因素趋势分析显示<sup>[15,20]</sup>, 年轻女性乳腺癌倾向于腋窝淋巴结受侵、激素受体阴性、肿瘤细胞染色体 S 期比例高、p53 基因异常表达等。这些特征均提示年轻女性患者的肿瘤具有更高的侵袭性。多变量分析表明<sup>[15]</sup>无高危因素的年轻女性局部复发率为 3.1%, 而具备超过一个高危因素者复发率为 48%。此外, 广泛导管内成分(extensive intraductal component, EIC)也是年轻女性高局部复发风险的因素之一<sup>[21]</sup>。基于上述结果, 临床医师不能仅依据患者年龄而拒绝为年轻女性实施保乳治疗。在排除其他混杂因素后, 选择无高危因素的年轻女性患者接受保乳治疗可以获得与乳房切除相同的远期疗效<sup>[22]</sup>。

## 1.2 肿瘤大小、部位和多中心癌

NCCN 治疗指南将肿瘤直径超过 5 cm 列为相对禁忌证, 而欧洲癌症研究所(European Institute of Oncology)2005 年保乳治疗共识<sup>[22]</sup>对肿瘤大小没有限制。Fitzal 等<sup>[23]</sup>发现局部晚期乳腺癌患者接受乳房切除与保乳治疗后局部复发、乳腺癌相关生存和总生存不受肿瘤大小影响。目前多数研究支持肿瘤大小与保乳治疗后局部控制率不相关<sup>[10,24-25]</sup>。肿瘤大小以 2B 类证据作为保乳治疗禁忌证这一事实表明学者们对此存在争议。很久以来大家普遍认为, 只要能够满足充分切除肿瘤, 获得阴性的病理切缘, 并且保证满意的美容效果, 肿瘤大小不再是保乳治疗的制约因素<sup>[26-27]</sup>。此外, 还可以通过转移肌皮瓣等技术重塑残留乳腺组织, 纠正轻度的乳房手术后畸形。对于乳房较大且下垂的患者, 由于术后照射剂量不均匀可能导致局部纤维化和萎缩, 进而影响美容效果, 在确定治疗方案时应充分考虑上述因素。

中央型乳腺癌患者接受保乳治疗后是否增加肿瘤复发风险? 肿瘤大小可能是这类乳腺癌保乳治疗局部失败的危险因素之一。Danoff 等<sup>[28]</sup>发现多数乳腺癌有沿乳管浸润的特征, 中央型乳腺癌实施保留乳头-乳晕复合体的术式可能增加局部复发风险<sup>[29-30]</sup>。对于这部分患者在实施部分乳房切除时应同时切除乳头、乳晕, 获得安全的病理切缘<sup>[31]</sup>, 术后可以通过移植物、转移皮瓣或肌皮瓣以及文身着色等方法重建乳头-乳晕<sup>[32]</sup>。因此, 中央型乳腺癌不是保乳治疗的禁忌证, 通过适当的重建方式仍可以获得满意的美容效果。

散在分布的多中心癌需要广泛切除并给予多部位加量放射治疗, 治疗后难以保证美容效果。并且这类患者保乳治疗的局部复发风险高达 25% ~ 40%<sup>[33-34]</sup>, 这样的结果对于患者和医师都不能接受。对于这部分患者, 乳房切除加再造才是合理的选择。病灶比较靠近的多中心癌, 如果能够通过一个切口完整切除并达到切缘阴性且获得良好的美容效果, 不作为保乳治疗禁忌<sup>[22]</sup>。

### 1.3 妊娠

尽管妊娠是放射治疗的绝对禁忌证, 但是放射治疗时间距离手术时间不超过 3 个月仍可获得满意疗效<sup>[22]</sup>。通过适当的提前分娩, 合理安排手术后放射治疗时间, 部分妊娠期乳腺癌患者可以接受保乳治疗。因此, 最初的保乳治疗禁忌证也仅限于妊娠的前 3 ~ 6 个月<sup>[35-36]</sup>。

### 1.4 胶原血管病

胶原血管病患者可因保乳手术和术后放射治疗导致小血管发生脉管炎或皮肤病变加重。这些患者对放射治疗的耐受性差<sup>[37-39]</sup>。若限制全乳放射治疗剂量不超过 45 Gy(25 次分割)、高能电子线剂量分布均匀并降低皮肤剂量, 部分患者仍可以接受保乳治疗<sup>[40]</sup>。因此, 胶原血管病只作为相对禁忌证被列入治疗指南。

### 1.5 既往放射治疗病史

乳腺区域既往接受过放射治疗是保乳治疗的禁忌证, 因为保乳手术后需进行患侧乳房放射治疗将导致原放射治疗过的部位总辐射剂量过高; 目前还不能准确判断这类患者治疗部位的远期总控制率和毒性反应<sup>[40-41]</sup>。由于还没有足够证据支持局部放射治疗和术中放射治疗能够替代保乳手术后常规放射治疗, 因此对这类既往有放射治疗史的患者应严格掌握适应证。

### 1.6 家族性乳腺癌和遗传性乳腺癌

家族性乳腺癌是指超过一位 I 级亲属(母亲、姐妹或女儿)或 II 级亲属

(祖母、姨妈、姑妈或表亲等)患有乳腺癌<sup>[42]</sup>, 占有所有乳腺癌的 20% ~ 25%。患者有乳腺癌家族史不是保乳治疗禁忌证。研究发现<sup>[43]</sup>, 如果 I、II 级亲属患有乳腺癌, 其局部复发率不高于无家族史的患者。遗传性乳腺癌是家族性乳腺癌的一个亚型。这种类型的乳腺癌与常染色体高度外显的癌易感性相关, 占有所有乳腺癌的 5% ~ 10%, 表现为发病早、包括卵巢癌在内的多位原发癌和双侧乳腺癌<sup>[44-46]</sup>。目前对这类患者采取何种治疗方案尚存争议。NCCN 治疗指南将携带 BRCA1/2 基因突变的绝经前女性列为保乳治疗相对禁忌证, 原因在于这部分患者保乳术后有较高的同侧乳腺癌复发或发生对侧乳腺癌的风险, 在欧美国家可考虑行预防性乳房切除以降低风险。遗传性乳腺癌在汉族妇女中所占比例低于欧美的白人妇女, 因此可以考虑对这类患者进行严密随访, 而慎用预防性对侧乳房切除。关于有保乳要求的遗传性乳腺癌患者可考虑行乳房切除加即刻再造<sup>[47-48]</sup>。

### 1.7 影像学检查和 EIC

实施保乳手术前进行双侧乳腺摄像非常重要。如果发现弥漫散在分布的钙化灶, 应慎行保乳手术<sup>[49]</sup>。通过乳腺摄像检查, 医师能越来越多地发现以钙化灶和微小病灶为特征的不可触及肿块的乳腺癌, 并给予保乳治疗。影像检查在保乳术前的重要作用日益受到重视<sup>[50]</sup>。随着技术的进步, 乳腺摄像发现钙化灶的能力日益增强, 但是随之而来的是特异性的降低。如何解决上述问题是外科医师在制定治疗方案过程中遇到的难题。磁共振成像(MRI)为这一问题提供了有益的帮助。MRI 诊断乳腺癌灵敏度和特异度分别达到 87.5% 和 50%<sup>[51]</sup>, 与乳腺摄像(48.5%)和超声(34.2%)相比, MRI 术前诊断 EIC 的准确率达 68%<sup>[52]</sup>。由此可见, MRI 对保乳治疗方案的选择具有重要意义。

EIC 是指原发性浸润癌中含有超过 25% 的导管原位癌(DCIS)成分, 并且在癌周乳腺组织中也同时含有 DCIS 成分<sup>[53]</sup>。伴有 EIC 的乳腺癌倾向于在乳房内沿乳管浸润, 因此难以达到切缘“干净”。除此之外, 浸润癌伴 EIC 倾向于多中心发生<sup>[54-55]</sup>。EIC 是保乳术后患侧局部复发的危险因素<sup>[56-57]</sup>。含有 EIC 的乳腺癌接受保乳治疗后 10 年局部复发风险高达 22% ~ 32%<sup>[58-59]</sup>。进一步分析发现, 只有 EIC 且距切缘不足 1 mm 者局部复发率升高, 对这部分患者应再次扩大切除<sup>[60-61]</sup>。EIC 不是保乳治疗的禁忌证, 但在术前诊断和术中切缘检测过程中应加以重视, EIC 导致放弃保乳手术的主要原因是广泛切除后不能满足美容需求<sup>[53, 62]</sup>。

## 1.8 新辅助化疗后的保乳治疗

超过 80% 接受新辅助化疗的局部晚期乳腺癌可获得缓解率,进展率仅为 2% ~ 3%<sup>[63]</sup>。新辅助化疗可以显著改善获得病理完全缓解 (pathological complete response, pCR) 者的预后<sup>[64]</sup>。与术后化疗相比,新辅助化疗不仅可获得相同的无病生存率、局部复发率和总生存率,而且显著提高了这部分患者的保乳率<sup>[65]</sup>。尽管 NSABP B-18 试验观察到新辅助化疗后降期患者在保乳术后局部复发率高于化疗前符合保乳指征的患者,但是 EORTC 10902 试验的长期随访结果显示这两组患者的总生存率和局部复发率没有差异<sup>[66-68]</sup>。上述两项 III 期临床试验结果不一致提示在评价新辅助化疗后降期患者是否适合接受保乳治疗方面尚须有更多有价值的证据加以评价。尽管如此,新辅助化疗因其显著的疗效而被推荐为乳腺癌系统治疗中的组成部分<sup>[65,69-70]</sup>。

## 2 结语

综上所述,乳腺癌患者采用保乳治疗日渐增多,患者选择应考虑多方面因素,概括起来包括以下四个方面:(1)患者的病史与体检结果;(2)细致的乳房影像学评价;(3)切除标本和切缘的组织学评价;(4)对患者保乳愿望的评价。

【关键词】 乳腺癌; 保乳治疗

【中图法分类号】 R737.9 【文献标识码】 A

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