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乳腺癌相关淋巴水肿防治的研究进展

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摘要: 乳腺癌(BC)是女性常见的恶性肿瘤之一,乳腺癌相关淋巴水肿(BCRL)是BC患者术后的严重并发症之一,可引起上肢疼痛、肿胀及皮肤萎缩等一系列症状,严重影响患者术后的身心健康及生活质量,因此有效预防BCRL并采取合理治疗措施具有重要意义。本文就近年来BCRL的相关防治措施进行综述,为降低BC患者的BCRL发病率、改善BCRL治疗效果提供临床参考。

关键词: 乳腺癌; 淋巴水肿; 非手术治疗; 手术治疗

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Research Progress in the Prevention and Treatment of Breast Cancer-Related Lymphedema

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Abstract Breast cancer (BC) is one of the common malignant tumors in women, and breast cancer-related lymphedema (BCRL) is one of the serious complications to BC, which can cause a series of symptoms such as upper limb pain, swelling and skin atrophy, affecting the physical and mental health as well as life quality of patients after surgery seriously. Therefore, effective prevention of BCRL and reasonable treatment measures are of great significance. This article reviews the prevention and treatment measures of BCRL in recent years to provide clinical reference for reducing the incidence of BCRL in BC patients and improving the therapeutic effect of BCRL.

Keywords breast cancer(BC); lymphedema; non-surgical treatment; surgical treatment

乳腺癌(breast cancer, BC)是全世界最常见的癌症之一,也是导致女性癌症死亡的主要原因^[1]。2020年全球BC统计报告显示,BC约占所有女性癌症患者的24.5%,占癌症死亡的15.5%,已跃升成为全球癌症发病谱和全球女性癌症死亡谱首位^[2]。BC治疗多采用包括手术、放疗、全身治疗和靶向治疗等多学科的综合治疗方式^[3],以期根治癌症并降低复发风险,延长BC患者的总体生存率。然而接受BC治疗的患者可能会发生一些副作用,这些副作用可能在治疗完成后数月甚至数年发生,乳腺癌相关淋巴水肿

(breast cancer-related lymphedema, BCRL)就是其中之一^[4]。

1 乳腺癌相关淋巴水肿

淋巴水肿是一种由于先天性淋巴系统发育不良或继发性淋巴循环系统受损,引起淋巴液回流障碍^[5],导致富含大量高蛋白和细胞代谢产物的淋巴液淤积在组织间隙形成的高蛋白水肿,是一种严重的慢性疾病,致残率高,且难以治愈。淋巴水肿可分为原

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发性和继发性两种形式,大多数淋巴水肿是继发性的。BCRL为临床上一种常见的继发性淋巴水肿,其定义为在手术切除病灶、腋窝淋巴结清扫及接受放疗后,由于淋巴管通道中断,导致淋巴液的产生与回流不平衡,淋巴液积存在组织间隙,引起患侧上肢水肿^[6]。目前对于BCRL的发病机制尚不清楚,传统观点如淋巴管梗阻不足以解释淋巴水肿的产生。现有淋巴衰竭的假设、插页式假说及血流动力学三种相互关联的新假设^[7]。

2 乳腺癌相关淋巴水肿的分期和临床表现

国际淋巴学会将肢体淋巴水肿分为4期:0期亚临床或潜伏期,无明显的容量增加和肿胀,但初始淋巴网络受损;I期轻度淋巴水肿,伴一过性肢体肿胀和容量增加,但可能随着肢体抬高而减轻;II期不可复位淋巴水肿,伴凹陷性水肿,肢体抬高后几乎没有反应,常作为组织变化的指标;III期明显的淋巴水肿伴有组织变化,如脂肪和组织纤维化,肥厚性增厚皮肤和肢体畸形,直至出现淋巴细胞静止性象皮病^[8]。

BCRL的最早阶段,患者的手臂或手的表面发生轻微变化,伴有肢体沉重、不适或两者兼而有之的感觉。在中度至晚期阶段,受累区域变大,且随着水肿加重,局部皮肤角质增厚并出现纤维化,易发生溃疡、复发性蜂窝织炎及血管肉瘤等^[7]。BCRL不仅会影响患者形象,同时还易使患者出现焦虑、担忧等负性心理症状^[9],严重影响患者日常生活,降低生活质量^[10]。因此,在临床症状明显之前及早发现BCRL对于预防不可逆的淋巴水肿至关重要。

3 预防乳腺癌相关淋巴水肿

了解BCRL的危险因素,从而采取针对性预防措施,对于避免或减缓淋巴水肿的进展至关重要。BCRL的危险因素已被广泛研究,其中淋巴结切除术是接受手术治疗的BC患者发生BCRL的主要危险因素。一项关于单侧BC患者BCRL发病率的研究发现^[11],接受腋窝淋巴结清扫(axillary lymph node dissection, ALND)的患者淋巴水肿发病率是接受前哨淋巴结活检术患者的4倍。此外,淋巴结清扫数量越多,BCRL发生风险越高。Kilbreath等^[12]研究发现,切除 ≥ 5 个腋窝淋巴结的患者BCRL的发病率为18.2%,而切除 < 3 个淋巴结的患者则为3.5%。与

接受全乳房切除术或改良根治性乳房切除术的患者相比,接受乳房肿瘤切除术的患者的BCRL率显著降低。此外,术后放疗可能导致淋巴管破裂,是BCRL进展的主要危险因素之一^[4]。

BCRL的非治疗相关独立危险因素包括年龄^[13]、体重指数(BMI > 25)^[14]、遗传因素、术后感染^[15]、蜂窝织炎^[16]及亚临床水肿^[17]等,这些都可能增加BCRL的发生风险。此外,若缺乏对BCRL的认识,会导致诊断延迟并加重BCRL的疾病进展。

3.1 非手术预防方法

早期监测并及时干预可降低BCRL的发病率并减轻其严重程度^[18],较晚开始进行生物阻抗谱(bio-impedance spectroscopy, BIS)监测的BC队列^[19]中被诊断患有BCRL的明显增多,同时严重程度也更高。事实上,BCRL预防效果可能取决于所采用的评估方法。在最近的一项研究中,BIS与磁带测量相比,能更精确地识别出从早期加压干预中获益的患者^[20]。另外,BCRL真皮回流通常在手臂肿胀前几个月出现,可帮助早期识别淋巴系统功能障碍,从而进行早期治疗。

患者教育也是BCRL预防的重要组成部分,BC患者应了解早期BCRL治疗的益处,要知道若出现手臂症状可能是BCRL的前驱症状^[21]。最近发表的关于BCRL预防性干预的国际共识指出,对患者进行有关淋巴水肿的充分教育至关重要,要确保患者理解信息并采取积极的预防措施^[22]。

前瞻性监测模型(prospective surveillance model, PSM)是BC患者生存医疗保健的综合方法^[23],提供了从诊断到长期生存的评估和教育时间点,强调BCRL的识别和促进健康行为管理。PSM在实际临床实践中预防BCRL的可行性已经得到证实^[24]。

3.2 手术预防方法

3.2.1 腋窝反向映射

腋窝反向映射(axillary reverse mapping, ARM)已被用于引流四肢的淋巴管,可用于保护接受ALND或前哨淋巴结活检术(sentinel lymph node biopsy, SLNB)患者的淋巴引流功能,旨在最大限度地降低淋巴水肿风险^[25]。采用蓝色或荧光染料可以直观地区分手臂淋巴管和染料标记的乳腺淋巴管,从而有效避免淋巴管在手术过程中被损伤。

3.2.2 淋巴显微外科预防性愈合

淋巴显微外科预防性愈合(lymphatic microsurgical preventing healing approach, LYMPHA)包含淋巴管静脉吻合术(lymphatic venous anastomosis, LVA),其绕过近端梗阻将淋巴液转移到静脉系统,

可用于BC术后手臂淋巴水肿的一级预防^[26]。虽然LYMPHA的应用前景较好,但需要显微外科方面的专业知识、乳腺和整形外科医生之间的协调^[27]。研究发现^[28],不需要显微手术的简化版LYMPHA可以将BCRL的发病率从32%降至16%。

4 乳腺癌相关淋巴水肿的治疗

4.1 非手术治疗方法

4.1.1 减压充血淋巴疗法

根据国际淋巴学会的建议,淋巴水肿需要用减压充血淋巴疗法进行治疗,包括强化阶段和维持阶段^[29]。强化阶段的目标是尽可能促进淋巴回流并改善受影响区域的组织水肿,包括锻炼和手动淋巴引流(manual lymphatic drainage, MLD)等。MLD是根据淋巴通路的解剖方向使用手动按摩来增加血液和淋巴循环,并减轻多余的组织液^[30]。它包括三个步骤:打开淋巴通路,软化疤痕组织和刺激淋巴引流。研究表明^[31],MLD作为综合消肿疗法(complete decongestive therapy, CDT)的组成部分之一,在临床上得到了广泛的应用。

4.1.2 加压治疗

BCRL会影响上腹部或手臂组织水肿,加压治疗可以有效解决这一问题,具体措施包括加压绷带、压缩服装、梯度加压装置或气动加压装置,对早期淋巴水肿的体积减小和防止其进展有效^[32]。在MLD治疗后立即将加压绷带应用于肢体或上腹,并在CDT的维护阶段,患者需要穿上压缩服,以保持最初实现的体积减少。压缩服装是可用于防止液体再积聚,但必须由经验丰富的物理治疗师安装并每6个月更换一次,常用于早期BCRL患者。此外,作为CDT辅助手段的另一种加压方法,间歇气动压缩泵是一种类似长袜的装置,在手臂上间歇性充气,可以每天使用。

4.1.3 运动锻炼

在淋巴水肿的维护阶段,建议进行中等水平的运动,结合有氧运动和阻力运动^[33],从低阻力开始,逐渐增加重复次数和阻力水平,患者在运动期间应适当按压BCRL局部组织。在适当按压的同时运动可以减少水肿体积,减缓BCRL进展^[34]。

4.1.4 综合消肿疗法

CDT可有效促进淋巴回流、减轻组织水肿,从而缓解患者的疼痛强度和手臂沉重感,提高生活质量并降低蜂窝织炎的发病率^[35]。CDT被认为是BCRL治疗的基石。一项关于淋巴水肿研究的系统评价发现,CDT可有效减少组织淋巴水肿,且证据等级为中

等强度^[36]。

4.1.5 光生物调节

光生物调节(photobiomodulation, PBM),也称为低水平激光治疗,使用波长在650~1000 nm的光以低辐照度传递到靶位点^[37]。PBM已被证明可减轻炎症,促进淋巴活动性和再生,有效缓解BCRL^[38]。

4.1.6 干细胞疗法

干细胞疗法包括移植来自脂肪组织、肌肉和骨髓的自体间充质基质细胞以缓解组织淋巴水肿,这为BCRL患者提供了新的治疗方法。研究发现^[39],将脂肪来源的自体间充质基质细胞注射到腋窝区域,淋巴水肿得到缓解。该方法耐受性好,肿胀肢体无反弹。

4.2 手术治疗

手术治疗BCRL通常分为生理功能重建和消融手术两类^[40]。生理功能重建,通过重建正常淋巴流动或替代途径来减轻淋巴负担,从而解决淋巴水肿,这包括LVA和血管化淋巴结转移术(vascularized lymph node transfer, VLNT)。消融手术(如吸脂术)可以帮助缓解症状,但不能从根本上解决淋巴水肿。

4.2.1 血管化淋巴结转移术

VLNT不是通过绕过现有淋巴结引流中的梗阻,而是通过显微手术采集远处供体部位的自体淋巴结瓣移植到靶区,并通过移植物中的动脉和静脉吻合到受体部位的血管来保证淋巴引流。供体部位包括肠系膜、腹股沟、胸外侧、网膜和颈下^[41]。虽然恢复淋巴流动的机制尚不完全清楚,但研究已经证明VLNT能显著改善淋巴转运。另外,VLNT可以有效减轻肢围、减少压缩衣使用,并能降低蜂窝织炎发生率和改善患者生活质量^[42]。但其可能存在供体部位淋巴水肿、淋巴囊膨出和感染等风险。

4.2.2 消融性手术

因长期非凹陷性淋巴水肿患者皮下新形成的脂肪组织没有被切除,显微外科手术通常无法完全缩小肢体水肿,这可以通过吸脂来解决^[43]。吸脂术可有效去除大容量的慢性非凹陷性肢体的淋巴水肿,且很少有并发症的报道。此外,吸脂术可改善淋巴流动及流向皮肤的血流量,并且不会损伤受影响肢体内的现有淋巴管,显著降低了丹毒和蜂窝织炎的发生率^[44]。

5 小结

BCRL是BC患者面临的一种严重并发症,虽不足以危及生命,但通常是无法治愈的,会严重影响生活质量、身体机能和日常活动,需要终身管理。BCRL

筛查和高危患者的教育势在必行,建议采用个性化的治疗措施以提高依从性。ARM 和 LYMPHA 等方法已被证明可有效预防 BCRL 的发生,BCRL 手术治疗的目的是恢复淋巴水肿患者的正常淋巴流动,但需要专门的显微外科或超显微外科专业知识及不断使用压缩服装来保持治疗效果。迄今为止,BCRL 尚无确切的根治方法,其治疗仍是临床医师需要面对的问题和挑战。

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