



· 综述 ·

早期乳腺癌前哨淋巴结活检的前沿进展

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[摘要] 医学影像技术的飞速发展提高了早期乳腺癌腋窝淋巴结影像学诊断的能力, 能够检测到腋窝淋巴结更早、更小的转移灶, 通过影像学引导下穿刺活检明确淋巴结的转移状况, 从而为患者提供更完善的术前腋窝分期。对于术前超声影像学检查为腋窝淋巴结阴性的患者是否可以避免术中腋窝前哨淋巴结活检, 目前有两项大型临床试验正在进行中。山东大学附属山东省肿瘤医院乳腺病中心通过微泡超声造影显像技术引导腋窝前哨淋巴结术前穿刺活检, 正在探索一种高效、准确和超微创的腋窝前哨淋巴结活检技术。术前影像学检查大大提高了临床腋窝淋巴结阳性患者的检出率, 但也让一部分患者失去了通过腋窝前哨淋巴结活检替代腋窝淋巴结清扫的机会, 对临床查体淋巴结阴性但超声发现可疑淋巴结并通过穿刺活检确诊转移的患者是否适合前哨淋巴结活检, 本文也进行了相关的探讨和研究。另外, 对内乳前哨淋巴结活检的相关研究结果进行了汇总。

[关键词] 乳腺癌; 腋窝前哨淋巴结活检; 影像学检查; 前沿进展

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[Abstract] With the rapid development of medical imaging techniques, the diagnosis of axillary lymph node metastases is improved in early stage breast cancer. The smaller and earlier metastatic lesion can be detected and identified by fine needle aspiration cytology or core needle biopsy, which may provide the entire axillary staging for patient. There are two prospective, multicenter, international randomized trials to compare axillary sentinel lymph node biopsy with no surgical staging for patients with negative axillary ultrasound imaging. Our center used contrast-enhanced ultrasonography with microbubbles to identify the location of sentinel lymph node and guide its biopsy, which aimed to find an ultra-minimally invasive sentinel lymph node biopsy technique. The pre-operation imaging detection increased the detection rate of clinically positive axillary lymph node. However, it led some patients to lose the chance that they could receive axillary sentinel lymph node biopsy instead of axillary lymph node dissection. We also discussed whether sentinel lymph node biopsy suited cT₁₋₂N₀ patients who had 1-2 abnormal axillary lymph nodes detected by imaging technique and confirmed by fine needle aspiration cytology or core needle biopsy. Furthermore, the studies about internal mammary sentinel lymph node biopsy were reviewed.

[Key words] Breast cancer; Sentinel lymph node biopsy; Imaging detection; Recent advances

随着乳腺影像学技术的进步和乳腺癌局部控制的改善,我们正面临着一个可以对乳腺癌前哨淋巴结活检(sentinel lymph node biopsy, SLNB)进行“降阶梯”和“升阶梯”处理的新时代。ACOSOG Z0011临床试验已经公布了10年随访结果,进一步证实腋窝SLNB确诊1~2枚腋窝前哨淋巴结(sentinel lymph node, SLN)阳性的保乳术后患者可以避免腋窝淋巴结清扫(axillary lymph nodes dissection, ALND),这是Z0011时代SLNB“降阶梯”处理的最好佐证。虽然,Mamounas等^[1]在最新的综述中详细阐述了早期乳腺癌腋窝淋巴结(axillary lymph node, ALN)的处理策略,但是在SLNB方面仍存在许多值得探讨的问题。本文就SLNB的“加法”和“减法”处理策略进行详细的汇总分析,并探讨早期乳腺癌SLNB的一些新理念。

1 SLNB的“减法”

临床上影像学检查设备的不断更新以及超声检查医师诊断技术的不断进步,依据腋窝超声影像情况能够有效地发现可能转移的ALN并可以确定可疑转移淋巴结的个数^[2],通过术前腋窝超声引导的可疑转移ALN穿刺活检是明确腋窝分期的有效手段^[3],超声引导下对可疑ALN细针穿刺细胞学检查或粗针穿刺活检(fine needle aspiration cytology or core-needle biopsy, FNAC/CNB)确诊淋巴结转移的特异度可达100%^[4],然而该技术的灵敏度只有79.6%。正在进行的SOUND研究(NCT02167490)和INSEMA研究(NCT02466737)是为了探索早期乳腺癌患者腋窝超声影像检查阴性是否能避免SLNB,这两项研究将超声确诊为临床影像学腋窝阴性的患者随机分为SLNB组和无SLNB组^[5],这两项研究结果的公布可能会改变目前的临床实践,但是该技术仍在很大程度上受限于常规超声诊断难以达到较高灵敏度的问题。

多项研究结果均证实,微泡超声造影显像技术(contrast-enhanced ultrasonography, CEUS)是术前确定乳腺癌腋窝SLN的可行手段,该技术术前SLN确诊率为96%~98%^[5-8]。Server等^[9-11]的系列研究显示,术前将微泡造影剂注

射于乳晕周围皮下通过CEUS可以确定腋窝SLN的位置,该方法确定的SLN与联合法(核素与染料)SLNB的结果进行对比,发现该技术术前能够有效地确定腋窝SLN的位置,通过该技术引导SLN FNAC/CNB能够提高术前腋窝分期的准确性。Xie等^[7]将微泡CEUS导丝定位SLN与染料法SLNB的结果进行对比,发现微泡CEUS是术前确定腋窝SLN的有效方法,CEUS造影显像特点可能有助于发现转移的SLN。Cox等^[12-14]的系列研究显示,术前微泡CEUS定位SLN并进行淋巴结穿刺活检能够有效减少患者要求ALND的发生率,缩短患者的麻醉时间。Shimazu等^[6]的研究中,通过微泡CEUS检出的SLN平均值为1.52,核素与染料联合检出的SLN平均值为2.19。Omoto等^[15]的研究中,通过微泡CEUS检出的SLN平均值为1.1,核素与染料联合检出的SLN平均值为1.8。虽然通过微泡CEUS确定的SLN数目比常规核素与染料联合法的要少,但是在SLN确诊转移的患者中至少存在1枚阳性SLN是通过微泡CEUS方法确定的。然而,微泡CEUS定位SLN的相关研究仍存在一些缺点,例如,微泡CEUS发现了SLN但未进行定位,通过体表标记和穿刺针道定位将会导致结果不准确,通过金属导丝定位给患者带来了很大不便(与放射性粒子¹²⁵I定位对比),未进行显像SLN的术前穿刺活检(表1)。目前,我们需要更加注重提高乳腺癌临床ALN阴性患者术前微泡CEUS引导定位腋窝SLNB的灵敏度。

在山东大学附属山东省肿瘤医院乳腺病中心,术前将超声微泡造影剂注射于患侧乳腺乳晕区皮下,通过CEUS实时观察微泡造影剂的引流情况,确定腋窝SLN的位置并进行FNAC/CNB明确其转移情况,随后在该淋巴结处放置放射性粒子¹²⁵I对其进行定位并于术中通过 γ 探测仪检测其位置,术中常规应用核素与染料联合法进行SLNB,对检出的SLN进行常规病理检测,从而明确微泡CEUS定位的SLN的转移状况是否与联合法定位的SLN相一致,并确定微泡CEUS引导SLN穿刺活检的灵敏度。该研究旨在探索一种准确、超微创的腋窝SLNB技术,该技术可以在术

表 1 微泡CEUS定位腋窝SLN的相关研究汇总

Tab. 1 Studies summary of CEUS with microbubbles to localize SLN in axilla

First author	Enrolling years	Cases	Localized method	Pre-operative SLN FNAC/CNB	Intra-operative SLNB method	Sensitivity	Specificity	False negative rate	Positive predictive value	Negative predictive value
Sever ^[11]	2008-2009	80	Guidewires	No	Radioisotope+ blue dye	89%	100%	-	-	-
Cox ^[12]	2009-2011	371	Biopsy tract	Yes	Radioisotope+ blue dye	61%	100%	39%	-	-
Sever ^[10]	2009-2010	136	Biopsy tract	Yes	Radioisotope+ blue dye	65%	100%	8.3%	100%	92%
Xie ^[7]	2013-2014	101	Titanium clip	No	Blue dye	81.8%	86.2%	3%	75%	90.3%
Esfehani ^[8]	2013-2014	50	Guidewires	No	Radioisotope+ blue dye	96%	100%	-	-	-
Shimazu ^[6]	2014-2015	100	Skin marked	Yes	Radioisotope+ blue dye	33.3%	99.2%	-	-	-

前有效地评估腋窝SLN的转移状况,完善腋窝的术前分期情况,指导腋窝是否需要ALND,同时最大程度地减少患者的组织损伤。

2 SLNB的“加法”

随着腋窝超声影像引导淋巴结穿刺活检技术假阴性率的改善,一部分临床查体腋窝阴性患者的分期被提升($cN_0 \rightarrow cN_1$)并直接进行了ALND。然而,EORTC 10981-22023 AMAROS^[16]和ACOSOG Z0011^[17]临床试验纳入的是临床查体腋窝阴性的患者,入组患者均未接受常规的腋窝影像学检查,即使影像学发现可疑转移淋巴结也不进行淋巴结穿刺活检明确诊断,这意味着入组患者中将会包含临床查体腋窝阴性但影像学发现可疑转移淋巴结并穿刺活检确诊阳性的患者。Lloyd等^[18]回顾性分析了141例超声引导FNAC/CNB确诊阳性并接受ALND患者的临床资料,发现其中40.3%的患者只有1~2枚ALN转移。Pilewskie等^[19]的回顾性分析也显示,临床查体腋窝阴性但超声发现可疑淋巴结、FNAC/CNB确诊阳性并实施ALND的患者中,按照Z0011患者入组标准,只有45%符合ALND的要求,其余55%可以考虑不进行ALND。有研究证实,术前影像学引导ALN FNAC/CNB发现ALN阳性并不能准确预测临床查体ALN阴性患者是否需要ALND,因为47%的患者接受ALND后确诊只有1~2枚ALN转移^[20]。因此,临床查体腋窝

阴性但超声发现可疑淋巴结且FNAC/CNB确诊阳性的一部分患者可能接受了过度ALND的治疗。

那么,在Z0011临床试验数据公布后,对临床查体腋窝阴性但超声发现可疑ALN并通过FNAC/CNB确诊转移的患者,SLNB是否适合?山东大学附属山东省肿瘤医院乳腺病中心为明确临床查体腋窝阴性但超声发现可疑ALN并通过FNAC/CNB确诊1~2枚转移的患者是否仍适合SLNB,首先回顾性分析了临床ALN阳性接受ALND的患者资料,发现在术前超声检测到1~2枚可疑淋巴结并经FNAC确诊转移的患者中,ALND后发现42.9%(42/98)的患者存在1枚ALN转移,15.3%(15/98)存在2枚ALN转移,41.8%(41/98)存在2枚以上ALN转移;其中,40例患者接受了腋窝SLNB,SLNB的假阴性率为0%,2例患者确诊3枚SLN转移,38例确诊为1~2枚SLN转移,1~2枚SLN转移的患者中,63.2%(24/38)确诊无非前哨淋巴结(non-SLN)转移,7.9%(3/38)发现1枚non-SLN转移,2.6%(1/38)发现2枚non-SLN转移,5.3%(2/38)发现3枚non-SLN转移,21.1%(8/38)发现3枚以上non-SLN转移。然而,由于超声检查人员的诊断技术和操作经验不同,可能会将多枚融合肿大淋巴结误判为1枚可疑淋巴结,从而导致ALND后发现2枚以上淋巴结转移的比例增加,这也会影响我们回顾性分析的结果。值得注意的是,

EORTC 10981-22023 AMAROS研究的入组条件为临床体格检查腋窝阴性的患者，在腋窝SLN阳性接受ALND的患者中，32.8%的患者存在non-SLN转移^[14]；Z0011研究同样入组的是临床体格检查腋窝阴性的患者，其中，27.3%的患者存在non-SLN转移^[17]。本回顾性研究的结果提示，对术前超声发现1~2枚可疑淋巴结并穿刺活检确诊转移的患者，SLNB可能也是准确的，其中，超过65%的患者未发现non-SLN转移。然而，由于本回顾性研究分析的这些患者与AMAROS和Z0011研究入组的患者相比，存在更高的non-SLN转移率和肿瘤负荷，因此需要更完备的放疗和全身治疗计划加强局部控制。但仍需要更大的队列分析和前瞻性临床试验验证临床查体淋巴结阴性但超声发现可疑淋巴结并通过穿刺活检确诊转移的患者仍适合SLNB。同时，需要依据肿瘤大小、组织学分级、分子分型及脉管浸润等相关因素建立预测ALN肿瘤负荷的列线图，从而有效地预测SLN的转移情况，并指导腋窝淋巴结的进一步处理。

为解决Z0011研究放疗射野存在的争议，Morrow等^[21]针对放疗射野对患者局部控制的影响进行了前瞻性验证研究，对比了全乳放疗±腋窝放疗不同治疗组患者腋窝局部复发的情况，发现对符合Z0011入组条件的患者，即使不进行腋窝影像学评估和常规淋巴结放疗，5年累积淋巴结复发率也仅为1%，且与ALN放疗组差异无统计学意义（ $P=0.544$ ）。因此，对临床查体腋窝阴性T₁₋₂接受保乳手术确诊1~2枚SLN转移进行全乳放疗和全身治疗的患者，避免ALND是尤为重要的。

随着放疗设备和技术的不断革新，腋窝放疗对局部控制的作用越来越显著，正在进行的有关SLNB的研究涉及多项对比ALND与腋窝放疗的临床试验。POSNO研究（NCT02401685）是在乳房切除发现1~2枚SLN宏转移的患者中，对比腋窝无处理、ALND或放疗在局部控制方面的作用^[22]；Alliance 11202研究（NCT01901094）是将新辅助化疗后SLN阳性的患者进行ALND与腋窝放疗对比，明确两组间乳腺癌复发率

的差异^[23]；NSABP-B51/RTOG 1304研究（NCT01872975）是为明确新辅助化疗腋窝淋巴结降期（cN₁→pN₀）的患者，局部放疗是否能够改善乳腺癌无复发间期^[24]。这些临床试验的研究结果有望改变当前的临床实践，所以非常值得期待。

在内乳SLNB方面，内乳SLNB是进行内乳区淋巴结分期的微创技术，能够指导个体化的内乳区放疗。我们已经开始通过内乳淋巴结清扫验证内乳前哨淋巴结准确性的相关研究（NCT03024463）^[25]，初步结果显示，腋窝淋巴结阳性的患者中内乳SLNB假阴性率为0%，前哨淋巴结转移率为57.1%，其中non-SLN转移率为80%。因此，对确诊内乳前哨淋巴结阳性的患者，仍会存在其他内乳淋巴结的转移，这部分患者是需要进行术后内乳区放疗的。

3 总结

综上所述，对早期乳腺癌腋窝SLNB仍是有效的腋窝处理策略，但是随着多项临床试验结果的公布，在不久的将来可能会确定豁免SLNB的指征，以及证实超微创腋窝SLNB的准确性，并且SLNB可能扩展应用于影像学发现可疑淋巴结并通过穿刺活检确诊转移的患者中。另外，内乳SLNB将会得到临床推广并提供有利的内乳区放疗证据。

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