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胃癌 HER2 异质性的研究进展

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[摘 要] 胃癌的发病率和病死率较高，目前治疗多以外科手术辅助化疗为主。近年来，以人类表皮生长因子受体2(human epidermal growth factor receptor-2，HER2)为靶点的靶向治疗改善了胃癌患者的生存期，但由于胃癌HER2存在较大的异质性，使得HER2的测定产生一定的假阴性，因此可能使部分能够从中获益的胃癌患者失去靶向治疗的机会。

[关键词] 胃癌；人类表皮生长因子受体2；异质性；预后

Research progress of HER2 heterogeneity in gastric cancer

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Abstract The morbidity and mortality of gastric cancer are high. At present, the majority of treatments are mainly surgical adjuvant chemotherapy. In recent years, targeted therapy targeting human epidermal growth factor receptor 2 (HER2) has improved the survival of patients with gastric cancer, but due to the heterogeneity of HER2 in gastric cancer, the HER2 result assay produces a certain false negative, which may result in some of the gastric cancer patients who are able to benefit from it losing the opportunity for targeted therapy.

Keywords gastric cancer; human epidermal growth factor receptor 2 ; heterogeneity; prognosis

胃癌是最常见的消化道恶性肿瘤之一，据2018版全球癌症统计报告[1]显示：胃癌病死率(即占癌症总死亡人数的比率)为8.2%，仅次于肺癌(18.4%)和结直肠癌(10.2%)。现有的治疗主要为内镜下切除、手术和辅助化疗，在一定程度上延长了部分患者的生存期[2-5]。然而，不能手术或转移性胃癌的预后仍然很差，整体中位生存期<1年[6-7]。人类表皮生长因子受体2(human epidermal growth factor receptor 2，HER2)在乳腺癌中的作用自上世纪80年代后期被广泛研究[8]，并且在胃癌中的应用取得一定进展。但由于胃癌存在很大的异质性，使得HER2的测定结果差异较大，从而影响到HER2靶向药物的应用，引起了临床和病理医师的广泛关注。

1 胃癌 HER2 异质性

肿瘤异质性是指来源于同一个克隆的肿瘤细胞群，在其生长过程中形成在侵袭力、生长速度、对激素反应、对治疗药物敏感性等方面有所

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不同的亚克隆。目前胃癌中HER2异质性主要表现为组织异质性、空间异质性、时间异质性等，这使得一部分患者的胃癌HER2出现假阴性，从而遗漏掉可能从曲妥珠单抗的靶向治疗中获益的人群；另外，由于HER2异质性使得部分胃癌组织细胞表达HER2，而另一部分不表达HER2，靶向药物只能选择性的杀死一部分HER2阳性的肿瘤细胞，而HER2阴性肿瘤细胞对靶向药物产生耐药性，使得胃癌患者对于靶向药物的反应性和有效性降低。

近些年来，胃癌HER2异质性越来越受到人们的关注,其发生机制不清，Seol等[9]报道HER2异质性是由染色体不稳定引起的，肿瘤内异质性中的小细胞亚群可以促进肿瘤的生长，并导致治疗抗药性。影响胃癌HER2异质性结果判断的主要有以下因素：1)评判标准。以往研究[10-16]采用30%~100%的截断值，判定胃癌的HER2异质性为39.0%~75.4%，影响HER2状态评估的准确性。一些专家[17-18]建议当HER2免疫组织化学法强染色肿瘤细胞<10%时接受原位杂交(in situ hybridization，ISH)检测，若检测到扩增则应视为HER2阳性。这项建议已被一些国际准则采纳。未来胃癌HER2阳性的定义可能会倾向于乳腺癌HER 2检测标准，将其最小截定面积从30%改为10%。2)组织样本类型。以往研究[15,19-23]采用外科标本、活检标本和组织微阵列(tissue microarrays，TMA)等多种组织样本来测定HER2，结果显示胃癌活检和配对手术的HER2符合率为45.5%~94%。Ahn等[15]的研究显示：仅12.3%的活检标本与配对标本的结果不一致，其中阴转率和阳转率分别为66.3%和33.7%，这表明活检标本中的异质性很可能预示着手术标本的异质性。TMA由于其大规模、高通量、标准化等优点被广泛用于大量研究中。Gasljevic等[24]的研究显示胃癌TMA与全切片的HER2蛋白表达符合率为84.9%。但另一些研究[17,25-27]认为：由于胃癌HER2异质性较大，即使增加多个芯片组织，TMA也很容易遗漏掉HER2阳性组织。3)活检组织块数。研究[28-31]显示：单个活检组织块侧测定HER2的假阴性率为7%~10%，而多块分析可以提高胃癌灵敏度和准确性。其中一些研究[15,31]证明：利用4~5块活检组织测定时，HER2阳性率明显增加，此时HER2异质性最小；而Rüschoff等[17]指出，至少需要6~8个肿瘤组织块才能对活检进行充分的评估。总之，多块评估可减少胃癌HER2测定的异质性。4)检测方法、抗体类型及检测过程中的条件控制。目前《胃癌HER2检测指南》中规定检测胃癌中HER2状态的主要有免疫组织化学法(immunohistochemistry，IHC)(首选筛查性手段)、荧光原位杂交(fluorescence in situ hybridization，FISH)(金标准)。当不考虑异质性较高的HER2 IHC 2+病例时，IHC检测HER2蛋白过表达与ISH检测HER2基因扩增的一致性为87%~98%[14,32]。胃癌HER2的表型异质性(蛋白表达异质性)明显高于基因异质性(基因扩增异质性)[13,33-34]，发生率分别为68.8%~79.3%和44.0%~57.6%，且IHC 2+的HER2异质性远高于IHC 3+(100%和42.9%)。此外，研究[35-38]表明：银染原位杂交(silver in situ hybridization，SISH)和FISH之间的一致性94.5%~98.3%，显色原位杂交(chromogenic in situ hybridization，CISH)和SISH之间的一致性为91%~100%，由于CISH和SISH能够评价组织学形态(如选择肠型腺癌区域)，可能成为未来的首选检测方法[17]。少数研究通过新一代基因测序技术(next generation sequencing，NGS)[39]和微滴式数字PCR(droplet digital polymerase chain reaction，DdPCR)[40]测定胃癌患者血浆中循环肿瘤DNA(circulating tumor DNA，ctDNA)状态来反映HER2基因扩增，并与IHC和双色原位杂交(dual-color in situ hybridization，DISH)的结果比较，符合率分别为91.43%和73.3%。有研究[41]表明血浆HER2扩增患者对曲妥珠单抗治疗有效，所以检测血浆ctDNA可能会成为检测HER2状态的新方法。不同的HER2抗体也会影响胃癌中HER2状态的测定，目前美国FDA批准应用于乳腺癌和胃癌检测的抗体有HercepTest，4B5，CB 11和SP3等。以往研究[42-44]显示：4B5和SP3抗体敏感性要高于HercepTest，因此认为这两种抗体可能比HercepTest更适用于临床应用。另外，检测过程中的条件控制也会影响HER2状态的评判，从活检/手术到固定的时间必须尽量减少(特别是对于迅速脱水的活检)[45-46]；固定应使用10%中性缓冲甲醛，固定时间应为8~48 h；长期固定也可能导致不可靠的HER2结果[47]。

2 胃癌中 HER2 的组织异质性

HER2组织异质性是同一胃癌个体内，不同组织类型的HER2状态不一致。胃癌按Lauren分型分为肠型、弥漫型和混合型，在不同组织类型的

胃癌中，HER2表达的状态不同。近年来许多研究[29,48-50]表明：肠型胃癌的HER2过表达率显著高于弥漫性/混合型胃癌，分化较好的胃癌HER2过表达率显著高于分化较差的胃癌。根据ToGA试验及后续的探索性研究[14,35]分析发现：胃食管结合部腺癌HER2阳性率(33%)明显高于胃癌(21%)，这可能与胃食管结合部腺癌多为肠型腺癌有关[51]。Phan等[34]和Lee等[52]的研究均表明：弥漫型胃癌HER2表达的异质性高于肠型或混合型胃癌。所以在评估胃癌组织内HER2状态时，应选择肠型区域较多的样本。

3 胃癌中 HER2 的空间异质性

胃癌中HER2的空间异质性研究多为胃癌原发灶的不同区域的组织中HER2状态的不同。目前研究[44,53]结果多显示贲门部胃癌的HER2阳性率高于胃体和幽门。Tominaga等[54]将两个或两个以上的肿瘤区域的HER2阳性肿瘤细胞比例有显著差异定义为HER2表达的异质性，通过比较同一个体的不同活检区域(分别为近口腔端肿瘤区域、中心肿瘤区域和远肛门端区域)、不同深度(浅层和深层)、活检标本与外科切除标本之间的肿瘤组织中HER2的状态，结果显示不同部位的活检标本中HER2阳性肿瘤细胞的中位百分比有显著差异，在近口腔区域最高(34.5%)，在近肛门区最低(0%)；HER2在胃壁浅层的阳性率明显高于深层(阳性中位百分比分别为60.3%和21.7%)；取样自近端肿瘤组织的活检标本HER2阳性细胞百分率与整个手术切除标本的符合率最高(79%)，取样自远端肿瘤组织的活检标本HER2阳性细胞百分率与手术切除标本的符合率最低(63%)。这可能是首次比较同一个体中胃癌的不同区域的HER2状态来评估其异质性。

4 胃癌中 HER2 的时间异质性

胃癌中HER2的时间异质性主要体现在胃癌患者同一个体的早期与进展期、化疗前与化疗后以及原发灶与转移灶中HER2状态的不一致。有多项研究[55-58]表明：HER2过表达/扩增率从胃黏膜低级别上皮内瘤变、高级别上皮内瘤变和进展期胃癌显著增加，早期胃癌比进展期胃癌的HER2异质性更高。这提示HER2阳性可能与早期胃癌的肿瘤进展有关。有研究[59-61]显示：24%~35%的HER2阳性胃癌患者在接受曲妥珠单抗治疗后，HER2状态转为阴性。Pietrantonio等[59]的研究结果显示：HER2 IHC 2+患者在接受曲妥珠单抗治疗后的转阴率明显高于IHC 3+的患者。而Seo等[62]的研究显示：原结果为IHC 2+和IHC 3+的患者在HER2转阴方面无显著性差异，并且HER2的遗传异质性从治疗前的2.9%上升到治疗后的21.9%。大多数研究[63-65]报道胃癌原发灶和转移灶之间的HER2状态不一致率为1%~14%。Park等[19]的研究显示：与原发灶相比，转移灶内HER2阳性率增加6%；远处转移至肝的患者，在重复活检中HER2阳性的可能性是在其他转移部位的5.88倍，因此认为对于初次评估为HER2阴性的晚期胃癌/胃食管结合部腺癌患者，建议在复发部位重复进行HER2评估。原发肿瘤阳转(原发肿瘤阴性，转移阳性)和阴转(原发肿瘤阳性，转移阴性)差异的可能解释是肿瘤进展过程中的HER2基因漂移或克隆选择，或HER2肿瘤内异质性的结果[63]。但Kumarasinghe等[66]的研究结果显示HER2在转移部位的阳性率(13.2%)与总阳性率(13.9%)相当，提示原发部位和转移部位同样适合检测。

5 胃癌 HER2 异质性对预后及曲妥珠单抗治疗的影响

肿瘤内异质性一直被认为是一种潜在的恶性特征[67]。多项研究[9,68-69]证实：与存在HER2异质性的乳腺癌相比，无HER2异质性的乳腺癌患者在基于曲妥珠单抗的治疗中可有更大的获益，并且有更高的生存期。近年来有部分研究HER2异质性对于胃癌的预后影响，但结果并不一致。多数研究[16,20,70]认为：无异质性的HER2阳性组胃癌患者预后明显差于有异质性的HER2阳性组患者，这可能是因为无异质性的胃癌组织中HER2阳性细胞成分更多；无异质性的HER2阳性胃癌患者对于靶向药物的反应性优于有HER2异质性组。研究[71-72]表明：无异质性的胃癌HER2阳性组的中位生存期明显长于存在异质性的HER2阳性组。研究[11,73]则显示HER2异质性对胃癌患者的生存期无影响。还有研究[74-75]表明：HER2状态结合Lauren分类是胃癌无进展生存期(progress-free survival，PFS)的独立预后因素，HER2阴性/肠型胃癌组患者预后最好，HER2阳性/弥漫型组患者生存最差；在HER2阳性的胃癌中，HER2同质阳性/非肠型的预后最差。Seo等[62]证实：在基于曲妥珠单抗的化疗后HER2转阴是二线HER2靶向治疗反应的潜在预测因子，因此在开始二线HER2靶向治疗之前，需要

重新检查HER2的状态。

6 结语

明确HER2状态对于能够获益于HER2靶向治疗的胃癌患者十分重要，最近建立的HER2评分指南[75]虽然详细描述了胃癌活检和手术标本中HER2阳性的定义，但并未明确活检标本的数量、位置及每个活检标本的肿瘤含量；另外，该指南也未考虑到HER2阳性与组织学亚型、分化程度之间的关系，所以需建立更完善的HER2检测体系。以往研究[15,19,31,34,48-54,59-62]提示在检测胃癌中HER2状态时，应多选择近口腔侧区域、肠型成分多的肿瘤组织，避免在溃疡中心取材；至少应取4个活检组织块；无论首次检测HER2状态如何，在肿瘤复发转移后和行二线HER2靶向治疗前需重复检测HER2状态，减少异质性带来的假阴性，尽可能筛选出所有可能从靶向治疗中获益的人群；另外，一些检测HER2状态的方法如CISH，SISH，DISH，NGS等方法各有优势，但研究较少，它们是否可以成为更有效的HER2检测技术，仍需更多的临床研究去验证。

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