·专题论坛·

早发性胃癌临床诊治难点与研究进展

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【摘要】 胃癌总体发病率有所下降,而早发性胃癌的发生率有所增加。目前,早发性胃癌的定义尚无定论。其分期较晚、分化较差的特征和针对性综合治疗的缺乏,使得早发性胃癌的诊治成为临床挑战之一。相关研究对早发性胃癌的遗传特征进行了解析,并初步揭示了其与幽门螺杆菌感染和分子分型之间的关系,有助于早发性胃癌的防治及个体化治疗。未来有待基于更大规模的循证证据,进一步确定诊断标准,阐明发生发展机制,制定有针对性的诊疗策略。

【关键词】 胃肿瘤,早发性; 诊断; 治疗; 临床特征; 分子特征
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Diagnostics and treatment challenges and research progress in early-onset gastric cancer

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【Abstract】 The incidence of gastric cancer has decreased, while the occurrence of early-onset gastric cancer has increased. There is no consensus on the definition of early-onset gastric cancer currently. The characteristics of tumor staging and differentiation, coupled with the lack of targeted comprehensive treatment, present a significant clinical challenge in managing early-onset gastric cancer. Relevant studies have analyzed the genetic characteristics of early-onset gastric cancer and have preliminarily revealed its relationship with *Helicobacter pylori* infection and molecular subtypes. These findings have the potential to contribute to the prevention and personalized treatment of early-onset gastric cancer. In the future, larger-scale evidence-based data are needed to establish diagnostic criteria, elucidate the mechanisms, and develop targeted diagnostic and therapeutic strategies of early-onset gastric cancer.

【Key words】 Stomach neoplasms, early-onset; Diagnostics; Treatment; Clinical characteristics; Molecular characteristics
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胃癌是常见的恶性肿瘤之一,世界范围内的发病率和死亡率分别高居第5位和第4位,我国均位列第3位,严重威胁人类健康[1-3]。胃癌常见于50~70岁的患者[4]。虽然总体发病率呈下降趋势,但是发生于年轻人中的胃癌即早发性胃癌(early-onset gastric cancer,EOGC)却有所增加[5-6]。EOGC特有的临床病理特征为其诊断和治疗带来了一定的挑战,也因此受到了很多学者的关注及深入研

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究。本文基于EOGC的特征，对其临床诊治难点进行总结，并综述相关研究前沿进展。

一、EOGC临床诊治的难点

1. EOGC的定义：EOGC通常用于描述年轻人群发生的胃癌，其确切的定义包括研究的年龄范畴和诊断标准等目前尚无定论。相关研究中年龄上限的设置有所不同，目前逐渐形成了较为常见的界定范围，包括<40岁、<45岁和<50岁等[7-9]；亦有研究主要关注30岁以下的年轻胃癌患者[10-11]。统一定义的缺乏，会影响不同研究之间的结果；而诊断标准的差异一方面影响EOGC高风险人群的预防和筛查策略，另一方面可能影响EOGC患者个体化治疗策略的制定。但定义EOGC又需要综合考虑人口学信息、临床分子病理特征、治疗反应以及预后等因素，为提出统一定义增加了困难。因此，在目前缺乏定论的现状下，应充分理解同类研究间的异质性，结合研究对象的特点对研究结果进行解读和参考。

2.EOGC的临床特征：多项研究表明，EOGC具有独特的分期较晚和分化较差的临床病理特征[12-20]。我国进行的基于大规模人群的回顾性研究结果显示，EOGC以女性为主，低分化或未分化比例占53.7%~93.9%，Lauren分型弥漫型占比40.4%~60.2%，远处转移即M1期占比7.1%~22.1%，均显著高于非EOGC[12-14]。来自欧美及亚洲其他国家的研究也在EOGC的性别构成、分化程度及肿瘤分期等方面得到类似结果[15-18]。Lauren分型为弥漫型肿瘤，其分化差、pTNM分期晚，是肿瘤组织退缩的不利因素[19-20]。

结合上述EOGC的特征，预示EOGC的临床治疗难度可能较大。但尽管如此，与非EOGC患者相比，EOGC患者整体预后并未显示出显著劣势，相关研究结果尚存在争议。Wen和Shen[21]基于美国国立癌症研究所“监测、流行病学和最终结果”(Surveillance，Epidemiology，and End Results，SEER)数据库分析发现，EOGC比非EOGC具有更低的全因死亡风险，风险比(hazard ratio，HR)为0.87；然而，胃癌特异死亡风险又较高(HR=1.11)。Niu等[14]基于我国国家癌症中心胃癌数据库研究发现，病理分期为Ⅲ期的EOGC，其总生存劣于非EOGC，Ⅰ期则较优；Ⅱ期和Ⅳ期患者中，EOGC与非EOGC的总生存比较，差异无统计学意义。样本量较小的类似研究亦得到EOGC和非EOGC的总生存相当的结果[15, 22]。由于生存预后相关分析的混杂因素较多，加之分组年龄标准及样本量有所差异，开展针对EOGC患者的预后研究受限，也会影响对临床治疗的指导。目前，已有学者初步建立了EOGC的预后预测模型，筛选出人种、肿瘤部位、肿瘤大小、分化程度、N分期、M分期、手术治疗以及化疗等危险因素纳入模型中，以预测EOGC的生存，其外部验证集的受试者工作特征曲线下面积可达0.6~0.8以上[23-24]。

3.EOGC的综合治疗：目前尚无针对EOGC的综合治疗策略，其治疗方案与非EOGC基本相同，主要包括手术治疗、化疗、靶向治疗以及免疫治疗等[25]。LaPelusa等[26]统计了EOGC患者的治疗模式，结果显示，接受手术治疗和化疗患者的占比分别为50.3%和63.8%，而45~70岁患者中的上述比例为53.5%和58.2%。Kist等[27]比较了接受围手术期化疗的患者比例，结果显示，EOGC患者仅45.7%接受了根治性手术，低于非EOGC患者(49.1%)；接受围手术期化疗(新辅助化疗或术后辅助化疗)的患者占比14.9%，非EOGC患者中仅为10.1%。Rompen等[28]研究发现，相较于非EOGC，更多的EOGC患者接受了新辅助化疗及扩大手术切除。

上述结果提示，EOGC更多接受化疗的倾向。一方面，EOGC患者分期相对偏晚，可能更多地失去了根治性手术机会；另一方面，患者的年龄小，体力状态较好，对围手术期化疗有更高的耐受性。然而，有研究表明，仅接受手术治疗的EOGC患者比接受手术联合化疗和(或)放疗的患者预后更好；以分期、肿瘤大小、组织学类型分层后，接受联合放化疗的患者相比于仅接受手术或仅接受化疗的患者也并未显示出生存优势[13, 29]。此外，通过对比以紫杉醇或奥沙利铂为基础的一线化疗方案，结果发现，应用含有紫杉醇方案的EOGC患者总生存具有较高的趋势，说明EOGC患者的治疗反应可能与特定的化疗药物有关[13]。由此可见，EOGC的治疗尚存局限，治疗策略需要更具有针对性和合理性，放疗及化疗等辅助治疗的应用需要更加精准化，否则可能在增加患者负担的同时，却又无法得到满意的预后改善。

二、EOGC的研究进展

1.EOGC的基因特征与遗传特征：胃癌的发生与遗传因素有关，而EOGC的发生与遗传因素关系可能更为密切[25]。早在1976年，即有学者报道

了EOGC的家族聚集现象[30]。近年来，经统计发现，约有10%的EOGC具有家族史[13,31]。这种现象提示，EOGC可能具有独特的基因特征或与遗传因素相关。

*CDH1*基因突变是遗传性弥漫型胃癌的典型特征[32]。近年来的多项研究表明，*CDH1*基因的失活突变或缺失也是EOGC相关的遗传因素[33-34]。在EOGC患者中，*CDH1*基因突变携带者的比例为4.5%~22.9%，其平均年龄为41~50岁[35]。Hakkaart等[36]的研究表明，*CDH1*基因突变携带者发病的平均年龄小于非携带者；并且，与非EOGC相比，EOGC患者携带*CDH1*基因突变的比例更高。此外，通过蛋白质基因组学研究发现，EOGC中还存在*TP53*、*BANP*、*MUC5B*、*RHOA*和*ARID1A*等具有意义的突变基因。在弥漫型胃癌中，与非EOGC相比，EOGC中*CDH1*、*BANP*和*MUC5B*的突变率显著较高，而*TP53*的突变率则较低。其中，突变基因所表达的蛋白CDH1、ARID1A和RHOA的磷酸化水平显著增加，富集分析显示，这些蛋白在细胞黏附和迁移过程以及EGFR、ERBB、PI3K-AKT、mTOR、WNT、MAPK、FOXO以及Hippo等与肿瘤发生和发展相关的信号通路中显著富集[37]。亦有研究通过对比发现，在非EOGC患者中突变率较高的基因包括*LRP1B*、*GNAS*、*APC*、*KMT2D*，它们在肿瘤的发生发展过程中起到不同程度的作用[14]。在基因表达量方面，EOGC的细胞质内CHEK2蛋白水平、细胞核内磷酸化的CHEK2蛋白水平以及P53蛋白水平均较低[38]；而一些DNA损伤标志物基因如*RAD51C*、*γH2AX*基因的表达则显著较高[39]。

EOGC与家族史相关。有研究表明，父母患胃癌的EOGC患者，诊断胃癌的年龄显著小于父母无胃癌病史的患者[40]。因此，如具有相应家族史，胃癌筛查应尽早进行。此外，EOGC与已知的多种遗传综合征包括遗传性弥漫型胃癌、林奇综合征、青少年息肉病综合征、Peutz-Jeghers综合征和家族性腺瘤性息肉病等相关。上述疾病患者发生胃癌的年龄相对较小。其中遗传性弥漫型胃癌的平均诊断年龄为37岁；而患有林奇综合征的患者发生胃癌的风险为1%~13%，且出现的年龄也更小[41]。因此，EOGC的遗传特性可能决定了其独有的临床病理特征，对基因特征的理解也将有助于EOGC的筛查和治疗。

2. 幽门螺杆菌（*Helicobacter pylori*，*Hp*）感染与EOGC：*Hp*感染作为引起胃癌的重要病因之一，在EOGC的发生发展中可能也起到了特殊的作用。有研究纳入了30或40岁以下的年轻胃癌患者，结果发现，*Hp*感染是年轻患者胃癌的重要风险因素之一[42-43]；EOGC中*Hp*感染的比例也高于非EOGC[44]。然而，亦有研究结果显示，EOGC的*Hp*感染率与非EOGC患者之间差异无统计学意义[13-14]。因此，基于目前研究的结果，尚无有力证据证实*Hp*感染是EOGC的特异性致病因素。但通过进一步病理学评估，EOGC患者慢性炎性浸润较非EOGC更显著，而肠化生则在非EOGC中更突出，据此可推测，*Hp*感染引起EOGC发生可能存在独特的机制[44]。由此可见，在全人群中进行更为广泛的*Hp*筛查可能更具有意义，同时对*Hp*感染导致胃癌发生的更加深入地探索、理解，有助于更好地解析EOGC的本质特征。

3. 分子分型与EOGC：2016年，癌症基因组图谱（the cancer genome atlas，TCGA）基于肿瘤的基因组、转录组和蛋白质组等多方面信息，提出了胃癌的TCGA分子分型，将胃癌分为以下4种亚型：EB病毒（Epstein-Barr virus，EBV）阳性型、微卫星不稳定型（microsatellite instability，MSI）、基因组稳定型（genomically stable，GS）和染色体不稳定型（chromosomal instability，CIN）[45]。MSI主要出现于老年胃癌患者中，占比约15%，而年轻胃癌患者中则缺乏MSI的表现[46]。基于EOGC具有诊断年龄较低、Lauren分型以弥漫型为主、缺乏MSI等特征，可以推测其与GS型最为相似[12]。Bergquist等[47]对EOGC与非EOGC的TCGA分型进行比较发现，EOGC中EBV阳性型及GS型相对更多，而非EOGC则是MSI型更多。EBV阳性型中约有80%的患者存在*PIK3CA*基因突变，远高于其他亚型[48]；且PD-L1在其肿瘤细胞和免疫细胞的表达比例也较高[49]。因此，PI3K抑制剂及免疫治疗可能对EBV阳性型的患者产生较好的疗效。GS型则对免疫治疗和靶向治疗不敏感[12]；这可能是EOGC肿瘤退缩不良以及预后差的原因之一。

三、结语与展望

在胃癌总体发病率下降的背景下，EOGC的发生却有所增加。其在分期、分化程度、预后、基因特征、发病机制以及分子分型等方面均具有特点。随着胃癌筛查防治与个体化治疗的迅猛发展，希望在未来能够逐渐定准EOGC的人群范围，理解其特征背后的

根本原因，取得更高级别的循证证据，使EOGC的诊治水平得到实质性提升。

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