

胰管内乳头状黏液性肿瘤的诊断与治疗进展

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■背景资料

胰管内乳头状黏液性肿瘤(intraductal papillary mucinous neoplasm, IPMN)是一种起源于主胰管及其导管分支上皮的罕见肿瘤, 无特异型临床症状, 有多种组织学形态, 可通过增生-腺瘤-癌的方式逐步进展为恶性肿瘤。若能早期诊断及及时治疗, 常能收到较好的预后效果。

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国家自然科学基金资助项目, Nos. 81170431, 81100314, 81101799

黑龙江省普通高等学校青年学术骨干支持计划基金资助项目, No.1155G35

黑龙江省青年科学基金资助项目, No. QC08C63

哈尔滨市科技创新人才研究专项基金资助项目, No. 2010RFQSQ059

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收稿日期: 2014-05-26 修回日期: 2014-07-16

接受日期: 2014-08-17 在线出版日期: 2014-10-08

Progress in diagnosis and treatment of intraductal papillary mucinous neoplasms

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Supported by: the National Natural Science Foundation of China, Nos. 81170431, 81100314, and 81101799; Heilongjiang Province Support Program Foundation for Youth Academic Backbone in Common Colleges and Universities, No.1155G35; Heilongjiang Province Science Foundation for Youths, No. QC08C63; the Harbin Special Research Fund for Talents Engaging in Scientific and Technological Innovations, No. 2010RFQSQ059

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Received: 2014-05-26 Revised: 2014-07-16

Accepted: 2014-08-17 Published online: 2014-10-08

Abstract

Intraductal papillary mucinous neoplasm (IPMN) is a rare form of exocrine pancreatic neoplasm arising from the ductal epithelium, which is difficult to diagnose in early stages owing to the lack of specific clinical symptoms. In most cases, IPMN is detected incidentally during medical examination. Some imaging studies such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography

(EUS) and computed tomography (CT) have been considered to be helpful to the preoperative diagnosis of IPMNs. Histologically, IPMNs may demonstrate a spectrum of cellular atypia, ranging from hyperplasia to invasive carcinoma. At present, IPMNs are classified into three types: main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN) and mixed type IPMN (MT-IPMN) according to the dominant location of the IPMN where the ductal dilatation occurs. Once diagnosed, all patients with MD-IPMN and MT-IPMN should undergo surgical resection as soon as possible regardless of size and symptoms due to the high risk of canceration. After surgical resection, the survival rate of IPMN patient is excellent. For patients with invasive IPMNs, the 5-year survival rate is 40%-60%, while for those with noninvasive IPMNs, the 5-year survival rate is 80%-100%. Therefore, early diagnosis and timely treatment are strongly recommended for all IPMN patients. The aim of this paper is to systematically review the diagnosis and treatment of IPMNs.

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Key Words: IPMN; Diagnosis; Treatment

Shao GD, Sun B, Bai XW. Progress in diagnosis and treatment of intraductal papillary mucinous neoplasms. *Shijie Huaren Xiaohua Zazhi* 2014; 22(28): 4270-4275
URL: <http://www.wjgnet.com/1009-3079/22/4270.asp>
DOI: <http://dx.doi.org/10.11569/wcjd.v22.i28.4270>

摘要

胰管内乳头状黏液性肿瘤(intraductal papillary mucinous neoplasm, IPMN)是一种起源于主胰管及其导管分支上皮的罕见肿瘤。IPMN无特异性临床症状, 早期诊断困难, 常于体检时发现, 磁共振胰胆管水成像、内镜超声及计算机断层扫描(computed tomography, CT)等影像学检查有助于术前诊断。IPMN生物学行为丰富多样, 可通过增生-腺瘤-癌的方式逐步进展为恶性肿瘤; 根据肿瘤在导管内发生的部位可将其分为主胰管型、分支胰管型和混

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合型. 主胰管型和混合型由于恶性几率高, 一经确诊, 无论大小、有无症状, 都应尽早手术. IPMN预后良好, 侵袭性IPMN术后5年生存率达40%-60%, 非侵袭性IPMN术后5年生存率更可达80%-100%. 因此, IPMN的早期诊断及治疗至关重要, 本文就此方面做一综述.

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关键词: 胰管内乳头状黏液性肿瘤; 诊断; 治疗

核心提示: 胰管内乳头状黏液性肿瘤(intraductal papillary mucinous neoplasm, IPMN)无特异性临床症状, 其诊治依赖于良好的多学科协作和规范化的诊疗流程, 而目前手术切除是治疗IPMN的首选, 而对于那些不能耐受手术或拒绝手术的患者, 可行经内镜逆行性胆胰管造影(endoscopic retrgrade cholangio pancreatograph)胰管支架引流术等非手术治疗.

邵光东, 孙备, 白雪巍. 胰管内乳头状黏液性肿瘤的诊断与治疗进展. 世界华人消化杂志 2014; 22(28): 4270-4275 URL: <http://www.wjgnet.com/1009-3079/22/4270.asp> DOI: <http://dx.doi.org/10.11569/wjcd.v22.i28.4270>

0 引言

胰管内乳头状黏液性肿瘤(intraductal papillary mucinous neoplasm, IPMN)是一种起源于主胰管及其导管分支上皮的罕见肿瘤, 常见于胰头或钩突部, 与胰管相通^[1]. 曾被命名为乳头状腺瘤、乳头状肿瘤、黏液性乳头状癌、黏液性胰腺导管扩张和胰腺分泌黏液的肿瘤等, 1996年世界卫生组织(World Health Organization, WHO)将其正式命名为IPMN^[2-6]. Distler等^[7]统计显示, IPMN占胰腺囊性肿瘤(cystic neoplasms of the pancreas, PCN)的21%-33%, 好发于60-70岁的老年男性, 男女比例约为2:1. 现已公认IPMN是胰腺癌的一种癌前病变, 可通过类似结肠息肉癌变的方式(增生-腺瘤-癌)逐步进展为恶性肿瘤, 因此, 早期诊断及治疗尤为重要^[8,9]. 鉴于此种情况, 本文着重从诊断和治疗入手, 对其作一综述.

1 诊断

与其他消化系肿瘤一样, IPMN的诊断依赖于良好的多学科协作和规范化的诊疗流程. 鉴于IPMN无特异性的临床症状, 偶表现为腹痛、恶心、呕吐, 可伴有体质量减轻、黄疸或糖尿病等, 使得该病的早期诊断较困难, 多数病例为体

检时发现^[10-12]. 目前临床上主要依靠影像学检查结合囊液实验室检查、组织病理学检查对其做出诊断.

1.1 影像学检查 影像学检查对IPMN的初始诊断和后期病情监测极为重要, 目前临床上常用的影像学检查主要有超声、内镜超声(endoscopic ultrasonography, EUS)、计算机断层扫描(computed tomography, CT)、磁共振胰胆管水成像(magnetic resonance cholangio pancreatography, MRCP)、经内镜逆行性胆胰管造影(endoscopic retrgrade cholangio pancreatograph, ERCP)等.

EUS能清楚地提供包括肿瘤大小、管壁厚度、壁结节以及肿块的毗邻在内的许多细节性图像, 精确地评价主胰管的扩张和恶性肿瘤的进展^[13]. 若EUS见到以下征象, 则高度提示IPMN恶变: (1)主胰管型, 主胰管直径>10 mm; (2)分支胰管型, 病变直径>4 cm伴不规则分隔; (3)混合型, 壁结节直径>10 mm^[14-16]. 同时, 超声内镜引导下细针穿刺活检(endoscopic ultrasonography guided fine needle biopsy, EUS-FNAB)可以通过对IPMN导管内黏液、导管内黏膜上皮细胞紧密连接簇、病变组织基质炎性浸润、是否存在坏死等情况进行分析, 评估IPMN的异型程度^[17].

CT不但能显示主胰管或囊性病变内所有3 mm以上的乳头状肿瘤、囊性肿块的内部结构(主胰管的钙化或壁结节等)、突出的大乳头、囊性肿块和主胰管的交通, 而且在评估恶性IPMN周围浸润方面也有很高的价值, 如血管浸润、淋巴结转移和种植播散等^[3,18,19]. CT血管造影(CT angiography, CTA)可以观察胰管及血管的侵犯程度, 评估肿瘤的可切除性.

MRCP能清楚地建立胰管系统的形态、显示扩张的胰管以及肿瘤的范围^[20]. 而ERCP则可以清楚地观察到胰管的扩张程度及黏液栓塞所致的胰管内充盈缺损情况, 在直视下看到肿大的十二指肠乳头及自十二指肠乳头开口流出的黏液, 并可获取黏液进行分析(黏液的外观性质、黏蛋白、CEA、CA19-9)和细胞学检查^[18,21,22]. 二者相比, MRCP不受稠厚黏液的影响, 能更好的显示囊状扩张的分支胰管的数目; 而ERCP显示正常大小的分支胰管比MRCP敏感, 并可以提供关于肿瘤的病理学信息^[23]. 但随着高分辨MRCP诊断技术不断提高, 现已不推荐ERCP作为辨别囊性病变更是否与胰管交通的首选^[24-26].

此外, 胰管镜(peroral pancreatoscope, POPS)

■ 研发前沿

IPMN术前缺乏有效的评估方法, 过度、过早的治疗会给良性的IPMN患者带来不必要的痛苦, 如何准确、及时的判断IPMN的进程, 尤为重要.

■ 相关报道

Tanaka等指出, 手术切除是治疗IPMN的首选, 其具体手术指征可概括为: (1)胰头部囊性病变更伴梗阻性黄疸; (2)囊腔内有强化壁结节; (3)主胰管≥10 mm.

■创新盘点

本文较全面的介绍了IPMN的相关知识及当下的诊断和治疗方法。

和胰管内超声也逐步成为诊断IPMN的方法,POPS更是目前唯一能体外直接观察胰管内病变和鉴别良恶性IPMN最有效的方法^[27,28]。Hara等^[28]调查显示,结合两种检查方法,鉴别IPMN良恶性的灵敏性和特异性可分别达到91%和82%。

1.2 实验室检查 目前,尚未发现一种特异性的肿瘤标志物可用于IPMN的诊断,其中,部分IPMN患者中可见CA19-9或CEA值升高,且多发生于恶性者^[29]。Jones等^[30]报道,CA19-9升高的IPMN患者因其潜在恶性,均应手术切除。此外,血清中胰腺癌相关抗原(Span-1抗原)水平及外周血Foxp3/CD25/CD4 T淋巴细胞数目可用于鉴别良恶性IPMN^[31]。

1.3 病理学检查 IPMN的生物学行为丰富多样,根据肿瘤在导管内发生的部位可将其分为主胰管型(main duct IPMN, MD-IPMN)、分支胰管型(branch duct IPMN, BD-IPMN)和混合型(mixed type IPMN, MT-IPMN)^[32]。根据上皮细胞的异型性可分为腺瘤、交界性肿瘤和非浸润性癌,非浸润性癌又可分为高、中、低度异型性;而日本学者将其更进一步细分为非侵袭性癌、微小侵袭癌和侵袭癌^[33-35]。根据被覆上皮的形态及免疫组织化学,可分为胃型、肠型、胰胆管细胞型和嗜酸性细胞型,各类型可同时出现,都有黏蛋白-5AC(mucin-5AC, MUC-5AC)(+)^[36,37]。

2 治疗

IPMN的治疗方法包括手术治疗、内镜治疗、辅助化疗和放疗等,但目前尚无完善的治疗标准,现行的IPMN治疗指南是2012年修订的《仙台指南》^[24]。

2.1 手术治疗 《仙台指南》指出,手术切除是治疗IPMN的首选。MD-IPMN和MT-IPMN由于恶性几率高,一经确诊,无论大小、有无症状,都应尽早手术;而BD-IPMN,由于其相对良性的生物学行为,目前认为,在无高风险症状、直径<3 cm的情况下可密切随访观察。其具体手术指征包括:(1)胰头部囊性病伴梗阻性黄疸;(2)囊腔内有强化壁结节;(3)主胰管≥10 mm^[24]。但IPMN具体的切除范围尚存争议,目前推荐的手术方式包括:(1)良性IPMN,倾向于保留胰腺和胃肠功能的手术方式,如保留十二指肠的胰头切除术(Beger术)、胰腺肿瘤局部剝除术、胰腺节段性切除术、保留脾脏的胰体尾切除术、保留幽门的胰十二指肠切除术等;(2)恶性IPMN,需行扩大根治术加淋巴结清扫;(3)交界性IPMN,

可行胰腺部分切除术,如胰十二指肠切除术、胰中段切除术、胰体尾切除术等^[38,39]。此外,因MD-IPMN具有潜在的多中心病变且恶性几率高,有学者提倡施行全胰腺切除术;但此种术式手术风险大,并发症多,术后胰腺内、外分泌功能完全丧失,故术前应慎重权衡利弊^[24,40-43]。

需要注意的是,胰腺切缘情况与术后复发及预后的关系尚不明确,但IPMN起源于主胰管及其导管分支上皮,可沿胰管连续生长,甚至呈多中心分布,所以胰腺切缘阳性病例并不少见,Nagai等^[44]报道其切缘阳性率为7%-30%。因此,对于胰腺切缘阳性病例的处理还需个体化,预期寿命较长的患者,应扩大切除范围直到切缘阴性,以期获得长期无病生存;反之不强求达到切缘阴性。

2.2 非手术治疗 由于IPMN进展缓慢,患者可长期带瘤生存,对不能耐受手术或拒绝手术的患者,为缓解症状,改善生活质量,延长生存时间,可考虑行内镜治疗。临床上,主要通过结合患者的实际情况行胰管内黏蛋白栓取出术、胰管内支架引流术,同时行胰管镜下肿物烧灼或胆管支架引流术等,其中以放置胰管支架或同时放置胆管支架为最常用^[45]。至于IPMN辅助化疗及放疗的作用还需进一步研究证实^[46]。

此外,Topazian等^[47]还报道了一例内镜下光动力学治疗IPMN的案例,报道中指出,光动力学治疗可缓解患者的症状,使肿瘤缩小,但远期效果如何,尚缺乏大宗病例的临床证据。

3 预后

IPMN预后良好,Poultides等^[48]报道,浸润性IPMN患者,术后5年生存率达40%-60%;非侵袭性IPMN患者,术后5年生存率更可达到80%-100%。Salvia等^[49]、D'Angelica等^[50]及Wada等^[51]认为,影响IPMN患者术后生存的因素主要包括:浸润性癌的成分及类型、血管侵犯、淋巴结转移、切缘状态及黄疸等。然而,良性的IPMN可进展为恶性或出现转移,切缘阴性的IPMN患者亦可能复发。因此,术后随访至关重要。

4 结论

IPMN无特异性临床症状,其诊治依赖于良好的多学科协作和规范化的诊疗流程。病理类型上,从良性的上皮异型增生到浸润性癌都有可能出现,并且,部分IPMN呈多中心性,同一病例中,可同时出现多种病理类型。目前手术切除是治

疗IPMN的首选,而对于那些不能耐受手术或拒绝手术的患者,可行ERCP胰管支架引流术等非手术治疗。IPMN患者预后良好,但存在一定的复发风险,故应密切随访和定期复查。

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■应用要点

IPMN首选的治疗方法是手术切除,但应准确、及时的判断其进程,以避免过度、过早的治疗。

■名词解释

黏蛋白:一类大分子量糖蛋白,在正常生理状态下,黏蛋白的表达具有明确的组织特异性,其表达稳态容易受到损伤因子的破坏,其表达异常是许多炎症及肿瘤的显著特征。

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■同行评价

本文选题得当, 文献较全面, 可读性强, 对IPMN的诊断与治疗具有一定的指导意义。

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ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569 2014年版权归百世登出版集团有限公司所有

●消息●

《世界华人消化杂志》于 2012-12-26 获得 RCCSE 中国权威学术期刊 (A+) 称号

本刊讯 《世界华人消化杂志》在第三届中国学术期刊评价中被武汉大学中国科学评价研究中心(RCCSE)评为“RCCSE中国权威学术期刊(A+)”。本次共有6 448种中文学术期刊参与评价, 计算出各刊的最终得分, 并将期刊最终得分按照从高到低依次排列, 按照期刊在学科领域中的得分划分到A+、A、A-、B+、B、C级6个排名等级范围。其中A+(权威期刊)取前5%; A(核心期刊)取前5%-20%; A-(扩展核心期刊)取前20%-30%; B+(准核心期刊)取前30%-50%; B(一般期刊)取前50%-80%; C(较差期刊)为80%-100%。