世界华人消化杂志®
wcjd@wjgnet.com

世界华人消化杂志 2007年12月8日; 15(34): 3604-3610
ISSN 1009-3079 CN 14-1260/R

文献综述 REVIEW

胰腺肿瘤标志物的研究进展

王 伟, 张飞雄, 李兆申

■背景资料
胰腺癌是一种凶险的恶性肿瘤, 早期诊断困难, 预后差, 给患者及其家庭造成了巨大创伤. 胰腺肿瘤标志物在胰腺癌的诊断、治疗中发挥了重要作用. 本文就目前肿瘤标志物在胰腺癌的诊断、治疗中的研究进展作一综述.

王伟, 李兆申, 中国人民解放军第二军医大学附属长海医院消化内科 上海市 200433
张飞雄, 宁夏医学院附属医院消化内科 宁夏回族自治区银川市 750004
通讯作者: 李兆申, 200433, 上海市长海路174号, 中国人民解放军第二军医大学附属长海医院消化内科. zhsli@81890.net
电话: 021-25070552
收稿日期: 2007-06-30 修回日期: 2007-11-20

Progress in research of pancreatic tumor markers

Wei Wang, Fei-Xiong Zhang, Zhao-Shen Li

Wei Wang, Zhao-Shen Li, Department of Gastroenterology, Changhai Hospital Affiliated to the Second Military Medical University, Shanghai 200433, China
Fei-Xiong Zhang, Department of Gastroenterology, the Affiliated Hospital of Ningxia Medical College, Yinchuan 750004, Ningxia Hui zu Autonomous Region, China
Correspondence to: Zhao-Shen Li, Department of Gastroenterology, Changhai Hospital Affiliated to the Second Military Medical University, 174 Changhai Road, Shanghai 200433, China. zhsli@81890.net
Received: 2007-06-30 Revised: 2007-11-20

Abstract
Pancreatic carcinoma is an almost uniformly lethal disease of humans and is associated with the lowest survival rate for any solid cancer, with only 5% of patients surviving 5 years after the diagnosis of pancreatic cancer. However, few effective methods can detect this kind of cancer at its early stage. The term "tumor marker" has been defined as "a naturally occurring molecule that is measured in serum or plasma, or other body fluids or in tissue extracts or in paraffin-embedded tissue to identify the presence of cancer, to assess patient prognosis, or to monitor a patient's response to therapy with the overall goal of improving the clinical management of the patient." The greatest limitation of most studies of serum markers is that they fail to limit their analyses to patients with small, potentially curable pancreatic cancers. Therefore, it appears to be particularly urgent to explore new markers and establish novel diagnostic methods so as to achieve sufficient sensitivity and specificity. We discuss the advantages and disadvantages of different pancreatic tumor markers in improving the the diagnosis and treatment of pancreatic carcinoma.

Key Words: Pancreatic carcinama; Tumor marker

Wang W, Zhang FX, Li ZS. Progress in research of pancreatic tumor markers. Shijie Huaren Xiaohua Zazhi 2007; 15(34): 3604-3610

摘要
胰腺癌早期诊断困难, 预后差, 患者5年生存率小于5%. 新近研究报道, 早期发现并切除的胰腺癌患者5年生存率为15%-40%, 因此早期诊断胰腺癌能够有效挽救患者生命. 目前一些常用的肿瘤标志物在胰腺癌的诊断、治疗监测及预后评估中起到了重要作用, 但这些指标的特异性和敏感性尚不能满足临床的需要. 因此迫切需要寻找新的肿瘤标志物并建立联合诊断的方法来进一步提高胰腺癌的诊疗水平.

关键词: 胰腺炎; 肿瘤标志物

王伟, 张飞雄, 李兆申. 胰腺肿瘤标志物的研究进展. 世界华人消化杂志 2007; 15(34): 3604-3610
http://www.wjgnet.com/1009-3079/15/3604.asp

0 引言
肿瘤标志物(tumor markers, TM)是细胞在肿瘤发生、发展、浸润及转移过程中分泌产生的活性物质. 通过检测其在血清、血浆或其他体液、组织提取物以及石蜡切片中的存在或量变可以提示肿瘤的性质, 借以了解肿瘤的组织发生、细胞分化、细胞功能, 以帮助肿瘤的诊断、分类, 进而有效评估患者的预后或监测患者的治疗达到提高临床诊疗水平的总体目标[1]. 目前胰腺癌相关肿瘤标志物主要可以分为3类: A类: 已经进入临床应用并被广泛接受, 有确凿证据表明该标志物具有临床实用价值. B类: 有大量研究肯定其在肿瘤诊断中的作用, 但目前还没有明确的证据提示其临床实用价值. C类: 主要指已经公布的尚处于研究阶段, 仍需要进一步大规模对照研究才能确定其应用价值. 本

文就近年来胰腺癌肿瘤标志物的研究进展作一综述.

1 胰腺肿瘤标志物在临床诊疗中的应用价值

1.1 A类标志物

1.1.1 血清分子标志物: 主要包括肿瘤相关抗原CA19-9、CA50(34-40)、CA195[2], 胰岛淀粉样多肽(islet amyloid polypeptide, IAPP)[3], 肿瘤相关胰蛋白酶抑制剂(TATI)[4], 胰腺癌抗原(POA)[5]、YKL-40[6], 肿瘤型M2丙酮酸激酶(TUM2-PK)[7], HIP/PAP[8]. 诊断价值尚不确定的指标包括癌胚抗原(CEA)[9], CA72-4[10], DUPAN-2[11]和Span-1[12]. 这些指标将不再进一步讨论.

CA19-9仍是目前诊断胰腺癌的标准血清肿瘤标志物. 欧洲肿瘤标志物组织(EGTM)与美国胃肠病协会(AGA)[13-14]推荐将其用于胰腺癌的处理, 美国食品暨药物管理局(FDA)已批准CA19-9测定用于胰腺癌患者治疗监测. CA199在胰腺癌临床诊断、筛查、预后判断及治疗监测中的实用性价值如下.

诊断: 大量回顾性与前瞻性研究已对CA19-9在胰腺癌诊断中的应用进行了广泛的调查[15-16], 并评估了其最佳诊断临界值. 一项大样本研究检测了胰腺疾病患者160例(胰腺癌90例, 良性病变70例), 胆道疾病患者322例(胆道癌152例, 良性病变170例)和无症状对照志愿者20035例血清的CA19-9水平, 发现无症状人群CA19-9的血清浓度平均值在9.42+/-9.95 U/L, 37 U/L的临界值可准确区分胰腺癌和胰腺良性疾病(灵敏度和特异度值分别为77%和87%)[17]. 在胰腺癌可疑人群中CA19-9的诊断价值有所提高, 但仍只有适度的灵敏度. 在一项对261例胰腺癌可疑患者的研究中, 血清CA19-9的敏感度为70%, 特异度为87%, 阳性预测值为59%, 阴性预测值为92%[18]. 1994年一个Meta分析研究报道, 血清CA19-9的平均灵敏度为81%(范围69%-93%), 特异性度为91%(范围76%-99%), 诊断临界值采用37 U/L水平[15]. 有关研究报道, 采用100 U/L水平时CA19-9的诊断特异度为97%[19], 采用1000 U/L水平时其特异度接近100%[15,20]. 另外, CA19-9的抗原决定簇为唾液酸化的血型抗原Lewisa(Lea), 他只对分子的非还原端含唾液酸化的Lea结构起特异反应, 而Lewis红细胞表型Le(a-b-)者糖链的合成多停留在CA19-9的前体CA50的阶段. 缺乏这样的非还原端, 因而肿瘤患者中的Le(a-b-)血清会表现为CA19-9阴性而CA50阳性. Le(a-b-)的人群占白种人口的5%-10%左右, 而有关中国人Le(a-b-)型的比例报道较少, 约在5.9%-23.1%之间[21]. 在这类人群中可能产生CA19-9的假阴性, 但如果将Lewisa抗原因素考虑进去, CA19-9在有症状的胰腺癌患者中的整体诊断灵敏度可达92%[21]. 结合影像学检查(腹部超声和CT)可提高血清CA19-9的阳性预测值[19].

CA19-9在胰腺癌诊断中的局限性表现在以下方面. 首先, CA19-9的诊断性与患者胰腺癌的进展程度有关[9,15]. 对于直径<3 cm的胰腺肿瘤CA19-9的诊断灵敏度显著降低(约55%)[15]. 因此CA19-9不能满足对小的可治愈肿瘤的早期发现. 其次, CA19-9在其他非胰腺的胃肠道恶性肿瘤以及多种良性疾病中也可升高. 例如梗阻性黄疸, 胆囊炎, 胆管炎, 肝硬化, 急性和慢性胰腺炎等都是CA19-9升高的常见原因[15]. 鉴于上述原因美国临床生物化学学会(NACB)不主张血清CA19-9检测用于诊断胰腺癌, 欧洲肿瘤标志物组织(EGTM)认为CA19-9检测可以作为胰腺癌影像学诊断的补充手段[13-14].

筛查: 胰腺癌发病率低, 在无症状者人群中大规模使用高灵敏度的肿瘤标志物进行胰腺癌筛查, 将产生大量的假阳性反应. 最近的一份研究报告中, 70 940例无症状受试者接受CA19-9筛查, 筛选出4例胰腺癌患者的同时出现了1059例假阳性反应, CA19-9阳性预测值仅为0.9%[22]. 在高危人群筛查中, 许多影像学上发现癌前病灶的患者其血清CA19-9往往处于正常水平[23]. 例如, 在一项研究中, 14例高风险受检者影像学发现异常并进行全胰腺切除术, 病理提示不典型增生, 但其CA19-9浓度均在正常范围内[24]. 大量研究证明, 胰腺导管腺癌起源于癌前病变胰腺上皮内瘤变(pancreatic intraepithelial neoplasia, PanIN), 而影像学及血清肿瘤标志物都不能及时发现这种微小病变[25]. 但血清肿瘤标记检测对早期无症状的浸润性胰腺癌的诊断仍非常有价值.

预后判断: 血清CA19-9检测可作为胰腺癌手术选择[9,20]及预后判断[23]的独立预测指标. 在一项队列研究中(n = 347), 肿瘤分期相同的患者经手术治疗后, CA19-9正常组的中位生存期长于非正常组[21]. 另一项研究提示, 治疗前CA19-9水平是判断生存期一个独立的、显著的指标, 远优于治后的CA19-9反应值(P = 0497)[26]. 最近研究表明, 术前低CA19-9水平(测不出)预示胰腺癌患者术后较长的生存期. 因此潜在的可手术切除

■研发前沿
胰腺癌中存在许多蛋白质的差异表达. 目前, 基因表达谱分析, 以及液相质谱等新研究工具的出现, 为发掘新的胰腺肿瘤标志物开辟了广阔空间. 新的肿瘤标志物可能具有更高的灵敏度、特异度.

■创新盘点
本文讨论内容充分, 肿瘤标志物涵盖范围广, 阐述深入, 从科研及临床应用等不同层面讨论了各自的应用价值.

的胰腺癌患者伴有低CA19-9水平(测不出)时, 不论分期应考虑手术治疗[27]. 欧洲肿瘤标志物组织(EGTM)提出, CA19-9具有评估胰腺癌预后的潜在价值, 但其临床实用价值还未被证实[14].

治疗监测: 大量研究表明, CA19-9可作为评估胰腺癌姑息化疗的监测指标. 最近的两项研究(n = 89, 2个研究合并)发现, 化疗8 wk(2个周期)后CA19-9跌幅>20%相对影像学能更好的反应化疗疗效[28]. 在其他化疗药物的姑息治疗研究中, 也将连续检测CA19-9水平作为判断预后的独立指标[29]. 相关研究中, 4例行胰腺全切的患者采用吉西他滨和顺铂治疗后得到完全缓解, 其CA19-9水平回降至正常范围; 而4例胰腺部分切除的患者达到部分缓解, 其CA199水平下降[30]. 连续检测CA19-9水平的变化相对单次检测具有更好的灵敏度和特异度. 有研究报道, 连续下降的CA19-9水平反应疗效的敏感度为67%, 预测病程进展的灵敏度为86%[30]. 另一项研究结果表明, 吉西他滨化疗期间CA19-9水平下降提示肿瘤进展停滞、治疗有效, 应继续治疗; 而CA19-9水平升高提示预后很差, 化疗效果不明显, 进一步化疗值得商榷[28]. 类似的研究也见于预测胰腺癌放射治疗的疗效反应[31]. 但由于放射治疗疗程短, 连续检测CA19-9水平不太可行. 当用于跟踪患者放化疗的预后时, 连续检测CA19-9预测疾病复发的灵敏度和特异度较高分别为100%和88%[31], 但现行准则不主张连续检测CA19-9作为胰腺癌疗效的监测指标. 美国临床生物化学学会(NACB)建议CA19-9连续检测结合影像学检查用于监测患者的治疗反应.

1.1.2 基因分子标志物: 个体遗传易感基因突变是进展为遗传性胰腺癌的高危因素, 常常表现为BRCA2、STK11p(Peutz-Jeghers综合征)、16基因(家族性非典型性多痣性黑色素瘤)、阳离子胰蛋白酶基因PRSSI(遗传性胰腺炎)、FANCC、FANCG以及DNA配修复基因等的缺陷(如遗传性非息肉性结肠癌)[32-34]. 约10%的家族性胰腺癌患者与BRCA2基因的生殖系突变(germ-line mutation)有关[35]. 因此, 许多专家建议对有较强胰腺癌家族史特别是其家族中胰腺癌患者存在BRCA2突变的成员要进行BRCA2的生殖系突变检测[35]. 这样不但可以预防乳腺癌和卵巢癌, 也可通过检测预防胰腺肿瘤的发生[36]. 有极少数的家族性胰腺癌以及家族性非典型性多痣性黑色素瘤的患者可能存在*P16*基因生殖系突变, 但目前尚没有足够证据支持对此类患者进行*P16*基因的检测[37].

1.1.3 组织分子标志物: 监测胰腺癌中异常表达的特异性分子标志物有助于胰腺癌的诊断. 如胰腺癌细胞均能表达细胞角蛋白cytokeratin(CK), 其中CK7、CK8、CK18、CK19可表达于70%-100%的胰腺癌组织[37]; 而CK17表达阳性率仅为50%-70%, CK20<20%[38]. 此外, 大部分腺瘤特别是高分化的内分泌腺瘤不表达CK7. 因此, CK表达谱可有助于胰腺肿瘤类型的诊断. 胰腺导管腺癌(PDAC)也表达上皮膜抗原(epithelial membrane antigen, EMA)和多种肿瘤抗原, 包括癌胚抗原(CEA)、癌抗原19-9(19-9)、CA125和DuPan2等[38-40]. 约30%的胰腺癌血清CEA升高, 故CEA可作为胰腺癌术后复发和转移的预测指标. 另外, 胰腺组织还表达几种黏蛋白(Mucins), 包括MUC1(相当于胰腺上皮膜抗原EMA), MUC3, MUC4和MUC5AC(胃小凹黏蛋白)[41]. 1/4的胰腺癌还表达MUC6(幽门腺黏蛋白), 少于10%的胰腺癌表达MUC2. 黏蛋白表达谱有助于区分胰腺导管腺癌和其他类型的胰腺肿瘤. 比如, 导管内乳头状黏液性肿瘤(IPMNs)表达MUC2而不表达MUC1[41-42]. MUC4表达目前正处于研究中, 他在胰腺上皮内瘤变PanIN中随瘤变级别的升高而增强[43], 可有助于鉴别胰腺癌和慢性胰腺炎组织[44]. 抑癌基因DPC4基因失活可见于55%的胰腺癌而少见于其他肿瘤. Smad4的异常表达提示胰腺癌预后较差[45-46].

1.2 B类标志物

1.2.1 CA242: CA242是一种唾液酸化的糖脂类抗原, CA242抗原决定簇在唾液酸化的路易氏抗原的Sialy lewis(sLea)黏蛋白上表达. 正常人体胆管细胞、胰管细胞中含少量CA242. CA242主要存在于胰腺和结肠的恶性肿瘤细胞中, 胰腺肿瘤细胞CA242免疫荧光明显强于邻近正常胰腺细胞. 总之, 其在胰腺癌中的诊断价值与CA19-9相似[47-48]. 有研究报道, CA242检测诊断胰腺癌的敏感度为41%-75%, 特异度为85-95%[47,49]. 一项对42例胰腺癌患者的研究中, CA19-9(诊断临界值为37 kU/L)和CA242(诊断临界值为20 kU/L)表现出相似的性能, CA242具有更高的特异度(>90%), 而CA19-9具有更好的敏感度(>70%)[50]. CA242水平检测还可判断预后. 在一项研究中, 排除手术方式和CA19-9水平两个因素后发现, 术前CA242<25 kU/L的患者术后疗效优于术前CA242高水平患者[51]. CA242与CA19-9相比, 其

优势在于CA242表达不受Lewis抗原和胆汁分泌的影响. 总之, CA242已被证明具有类似但不优于CA19-9的诊断性能. 在某些情况下如易出现CA19-9假阴性的Le(a-b-)肿瘤患者可采用CA242.

1.2.2 CAM 17.1: CAM 17.1是最近研制的一种IgM抗体, 他是一种黏液型标志物, 对胰液中的黏液糖蛋白有很高的特异性. 相关研究报道, CAM17.1诊断胰腺癌的敏感度为67%-78%, 特异度为76%-91%, 其诊断灵敏度与CA19-9相似但可能有较高的特异性(未得到证实)[52-53]. 另一项大型的前瞻性研究(n = 250)发现, CAM 17.1诊断胰腺癌的敏感度和特异度分别为86%和91%, 在无黄疸的患者中其敏感度和特异度分别为89%和94%[54], 结合腹部超声其敏感度可进一步增加至94%. 还发现高水平CAM17.1, 提示肿瘤晚期而不能手术切除, 因CAM17.1的表达受Lewisa抗原的影响[55], 与CA19-9相似, 但其在7%-10% Le(a-b-)肿瘤患者中的作用受限.

1.2.3 组织多肽特异性抗原: 组织多肽特异性抗原(tissue polypeptide specific antigen, TPS)是细胞角蛋白18片段上的M3抗原决定簇. 血清中TPS含量的高低是衡量肿瘤细胞分裂和增殖活性的1个较为特异的指标. 研究表明, TPS在肿瘤的早期诊断、预示复发和转移和评价预后方面有独特的价值. 有两项回顾性队列研究探讨了TPS在晚期胰腺癌姑息治疗中的作用. 其中一项研究显示, TPS相比CA19-9具有更高的敏感性[56], 但其样本例数较少. 另一项研究检测122例怀疑胰腺肿瘤或慢性胰腺炎的患者血清TPS、CA19-9的水平, 发现46例胰癌患者100%(46/46)TPS升高(>100 U/L), 而70% (32/46) CA19-9升高(>37 kU/L). 74例慢性胰腺炎患者中TPS和CA19-9升高, 阳性率分别为22%和19%. 如果TPS采用200 U/L的临界值, 其在鉴别胰腺癌和慢性胰腺炎时的敏感性为97%, 特异性为98%[57]. 这些数据表明, TPS可能在检测早期胰腺癌和监测治疗反应中发挥作用, 但需进一步研究加以明确.

1.3 C类标志物

1.3.1 巨噬细胞抑制因子1: 巨噬细胞抑制因子1(MIC-1)可在胰腺癌、大肠癌、前列腺癌等肿瘤中过度表达. 血清MIC-1水平检测可反映大肠癌的进展及预后[58]. 最近, 一项研究采用ELISA方法检测326例患者(可切除的胰腺癌患者80例, 可切除的壶腹与胆管癌患者30例, 其他胰腺肿瘤患者42例, 慢性胰腺炎77例和正常对照97例)血清标本中MIC-1、CA19-9水平, 发现MIC-1在胰腺肿瘤诊断中的敏感度为71%, 特异度为78%(诊断临界值为1070 ng/L), 而CA19-9有相似的性能(受试者工作特征曲线, ROC; ROC曲线下的面积, AUC: MIC-1为0.81, CA19-9为0.77). 结合MIC-1和CA19-9可显著提高诊断的准确性(ROC为0.87). 改良后的MIC-1与CA19-9及其他指标相比较, MIC-1升高在可切除的胰腺癌患者中阳性率为96%, 在慢性胰腺炎患者中为42%. ROC曲线分析其诊断的准确性显著优于CA19-9(Koopmann *et al*, 未发表).

1.3.2 骨桥蛋白: 骨桥蛋白(osteopontin, OPN)是一种具有多种生物学活性的分泌型磷酸化糖蛋白, 分子量为41.5 kDa. OPN基因的表达具有组织细胞特异性并且受多种激素、生长因子、原癌基因表达产物的调控. 骨桥蛋白可以促进肿瘤细胞的趋化、黏附和迁移. 近年来, 大量研究发现OPN在肿瘤的复发与转移过程中起重要作用, 被认为是肿瘤早期诊断、复发和预后判断的1个新指标[59]. 骨桥蛋白在肺癌、乳腺癌、前列腺癌、胃癌、食道癌和卵巢癌中高表达[60]. 基因表达谱芯片技术发现胰腺癌中OPN基因在mRNA水平高表达[61]. 作为分泌型蛋白, ELISA可检测患者血清中OPN蛋白. 一项针对50例胰腺癌和22例正常对照的研究发现, OPN蛋白对胰腺癌的诊断作用优于CA19-9, 敏感度为80%, 特异度为97%(临界值为334 μg/L).

1.3.3 金属蛋白酶抑制剂-1: 血浆1型组织基质金属蛋白酶抑制剂(TIMP-1)在胰腺癌组织中过度表达, 被认为是胰腺癌的潜在分子标志物[62]. 血浆TIMP-1水平升高在判断大肠癌和乳腺癌患者预后上有重要作用. ELISA检测胰腺癌患者(n = 85)和正常人(n = 98)血清TIMP-1水平发现, TIMP-1的诊断性能并不优于CA19-9. 相关研究联合检测血清TIMP-1、CA19-9和CEA水平发现, TIMP-1诊断特异度为100%时其敏感度仅为60%(特异性优化临界值), 特异度为95%时的敏感度为81%(灵敏度优化临界值), 提示TIMP-1为潜在的联合检测指标[62]. TIMP-1在不同体液中的检测(血浆与血清)及其在胰腺癌诊断中的价值仍需进一步研究.

2 胰腺肿瘤标志物的研究现状

胰腺癌中存在许多蛋白质的差异表达. 如间皮素(mesothelin)在将近100%胰腺癌中表达, 被证明是一个有效的肿瘤抗原[63]. 其他在胰腺癌

■应用要点
本文以相关研究为基础, 评价了不同类型肿瘤标志物在胰腺癌及胰腺炎临床实际应用的价值, 对临床实际工作具有较好的参考价值.

■同行评价
本文选题新颖, 内容丰富, 条理清楚, 思路清晰, 分析全面, 有一定的科学性和较强的可读性.

中过表达的蛋白包括前列腺干细胞抗原PSCA, Fascin蛋白(95%), Claudin-4蛋白, 14-3-3σ蛋白, 谷氨酰胺转移酶2(transglutaminase), CDC25B, ADAM9, cdc2/p34, 热休克蛋白HSP47, 三叶因子2(trefoil factor 2, TFF2)[64]和DNA拓扑异构酶Ⅱalpha(TopoⅡα) (95%)[65]. 若干S100蛋白家族成员[66-67]和有丝分裂激酶Aurora家族成员以及2个kallikreins基因家族成员KLK6和KLK10在胰腺癌中的表达均大幅上调[68]. 这些指标的临床实用性还没有得到证实. 目前, 基因表达谱分析已成为发掘判断胰腺癌预后指标的工具, 但由于胰腺癌预后极差, 并没有被广泛研究. 有些标志物可以用于预测, 如术前检测Claudin-4蛋白, S100A4, Mesothelin可以预测IPMN的良恶性[68], 有助于手术方式的选择. COX-2是Hegdgehog通路的调节分子, 在大多胰腺癌中过表达, 已被认为胰腺癌治疗的潜在靶标[67-68].

确定新的分子靶标来建立胰腺癌诊疗的新方法日趋重要. 例如, 研究发现范科尼贫血通路中的基因在一小部分胰腺癌细胞中失活, 而这些细胞对特定的化疗药物, 如丝裂霉素高敏感, 这也许可以解释临床上丝裂霉素治疗的间断反应[69]. 预计随着更多治疗方案的出现, 我门需要发掘更加准确的分子标志物来评估不同信号通路的状态, 进而帮助确定某一特定疗法是否适合胰腺癌的个体化治疗.

总之, 虽然CA19-9仍是目前最常用的胰腺肿瘤标志物, 但多个新的指标正处于研究中. 这些标志物将不仅方便胰腺癌的早期诊断而且还有助于诊断胰腺癌的癌前病变. 随着我们对胰腺肿瘤发病机制认识的逐渐深入, 发掘新的分子标志物并结合影像学检查定能帮助我们突破胰腺癌的诊治难关.

3 参考文献

1 Fleisher M, A.M. D, Sturgeon CM, Lamerz R, Witliff JL. Tumor markers: Physiology, Pathobiology, Technology and Clinical Applications. Chicago: AACC press; 2002. 32
2 Hyoty M, Hyoty H, Aaran RK, Airo I, Nordback I. Tumour antigens CA 195 and CA 19-9 in pancreatic juice and serum for the diagnosis of pancreatic carcinoma. *Eur J Surg* 1992; 158: 173-179
3 Chari ST, Klee GG, Miller LJ, Raimondo M, DiMagno EP. Islet amyloid polypeptide is not a satisfactory marker for detecting pancreatic cancer. *Gastroenterology* 2001; 121: 640-645
4 Pasanen PA, Eskelinen M, Partanen K, Pikkarainen P, Penttila I, Alhava E. Tumour-associated trypsin inhibitor in the diagnosis of pancreatic carcinoma. *J Cancer Res Clin Oncol* 1994; 120: 494-497
5 Shahangian S, Fritsche HA Jr, Hughes JI, Gelder FB. Pancreatic oncofetal antigen and carbohydrate antigen 19-9 in sera of patients with cancer of the pancreas. *Clin Chem* 1989; 35: 405-408
6 Fukushima N, Koopmann J, Sato N, Prasad N, Carvalho R, Leach SD, Hruban RH, Goggins M. Gene expression alterations in the non-neoplastic parenchyma adjacent to infiltrating pancreatic ductal adenocarcinoma. *Mod Pathol* 2005; 18: 779-787
7 Schneider J, Schulze G. Comparison of tumor M2-pyruvate kinase (tumor M2-PK), carcinoembryonic antigen (CEA), carbohydrate antigens CA 19-9 and CA 72-4 in the diagnosis of gastrointestinal cancer. *Anticancer Res* 2003; 23: 5089-5093
8 Rosty C, Christa L, Kuzdzal S, Baldwin WM, Zahurak ML, Carnot F, Chan DW, Canto M, Lillemoe KD, Cameron JL, Yeo CJ, Hruban RH, Goggins M. Identification of hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I as a biomarker for pancreatic ductal adenocarcinoma by protein biochip technology. *Cancer Res* 2002; 62: 1868-1875
9 Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. *Arch Surg* 2003; 138: 951-955; discussion 955-956
10 Carpelan-Holmstrom M, Louhimo J, Stenman UH, Alfthan H, Haglund C. CEA, CA 19-9 and CA 72-4 improve the diagnostic accuracy in gastrointestinal cancers. *Anticancer Res* 2002; 22: 2311-2316
11 Kawa S, Oguchi H, Kobayashi T, Tokoo M, Furuta S, Kanai M, Homma T. Elevated serum levels of Dupan-2 in pancreatic cancer patients negative for Lewis blood group phenotype. *Br J Cancer* 1991; 64: 899-902
12 Frena A. SPan-1 and exocrine pancreatic carcinoma. The clinical role of a new tumor marker. *Int J Biol Markers* 2001; 16: 189-197
13 DiMagno EP, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. American Gastroenterological Association. *Gastroenterology* 1999; 117: 1464-1484
14 Tumour markers in gastrointestinal cancers--EGTM recommendations. European Group on Tumour Markers. *Anticancer Res* 1999; 19: 2811-2815
15 Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. *Am J Gastroenterol* 1990; 85: 350-355
16 Sawabu N, Watanabe H, Yamaguchi Y, Ohtsubo K, Motoo Y. Serum tumor markers and molecular biological diagnosis in pancreatic cancer. *Pancreas* 2004; 28: 263-267
17 Kim HJ, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, Seo DW, Lee SK, Min YI. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. *Am J Gastroenterol* 1999; 94: 1941-1946
18 Pleskow DK, Berger HJ, Gyves J, Allen E, McLean A, Podolsky DK. Evaluation of a serologic marker, CA19-9, in the diagnosis of pancreatic cancer. *Ann Intern Med* 1989; 110: 704-709
19 Ritts RE Jr, Nagorney DM, Jacobsen DJ, Talbot RW, Zurawski VR Jr. Comparison of preoperative serum CA19-9 levels with results of diagnostic imaging modalities in patients undergoing laparotomy for suspected pancreatic or gallbladder disease.

Pancreas 1994; 9: 707-716
20 Forsmark CE, Lambiase L, Vogel SB. Diagnosis of pancreatic cancer and prediction of unresectability using the tumor-associated antigen CA19-9. *Pancreas* 1994; 9: 731-734
21 Safi F, Schlosser W, Falkenreck S, Beger HG. CA 19-9 serum course and prognosis of pancreatic cancer. *Int J Pancreatol* 1996; 20: 155-161
22 Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *J Gastroenterol Hepatol* 2004; 19: 182-186
23 Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevoy SV, Kalloo AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006; 4: 766-781; quiz 665
24 Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med* 1999; 131: 247-255
25 Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, Biankin SA, Compton C, Fukushima N, Furukawa T, Goggins M, Kato Y, Kloppel G, Longnecker DS, Luttges J, Maitra A, Offerhaus GJ, Shimizu M, Yonezawa S. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2004; 28: 977-987
26 Saad ED, Machado MC, Wajsbrot D, Abramoff R, Hoff PM, Tabacof J, Katz A, Simon SD, Gansl RC. Pretreatment CA 19-9 level as a prognostic factor in patients with advanced pancreatic cancer treated with gemcitabine. *Int J Gastrointest Cancer* 2002; 32: 35-41
27 Berger AC, Meszoely IM, Ross EA, Watson JC, Hoffman JP. Undetectable preoperative levels of serum CA 19-9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. *Ann Surg Oncol* 2004; 11: 644-649
28 Ziske C, Schlie C, Gorschluter M, Glasmacher A, Mey U, Strehl J, Sauerbruch T, Schmidt-Wolf IG. Prognostic value of CA 19-9 levels in patients with inoperable adenocarcinoma of the pancreas treated with gemcitabine. *Br J Cancer* 2003; 89: 1413-1417
29 Stemmler J, Stieber P, Szymala AM, Schalhorn A, Schermuly MM, Wilkowski R, Helmberger T, Lamerz R, Stoffregen C, Niebler K, Garbrecht M, Heinemann V. Are serial CA 19-9 kinetics helpful in predicting survival in patients with advanced or metastatic pancreatic cancer treated with gemcitabine and cisplatin? *Onkologie* 2003; 26: 462-467
30 Heinemann V, Schermuly MM, Stieber P, Schulz L, Jungst D, Wilkowski R, Schalhorn A. CA19-9: a pedictor of response in pancreatic cancer treated with gemcitabine and cisplatin. *Anticancer Res* 1999; 19: 2433-2435
31 Micke O, Bruns F, Kurowski R, Horst E, deVries AF, Hausler JW, Willich N, Schafer U. Predictive value of carbohydrate antigen 19-9 in pancreatic cancer treated with radiochemotherapy. *Int J Radiat Oncol Biol Phys* 2003; 57: 90-97
32 Klein AP, Beaty TH, Bailey-Wilson JE, Brune KA, Hruban RH, Petersen GM. Evidence for a major gene influencing risk of pancreatic cancer. *Genet Epidemiol* 2002; 23: 133-149
33 van der Heijden MS, Yeo CJ, Hruban RH, Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. *Cancer Res* 2003; 63: 2585-2588
34 Petersen GM, Hruban RH. Familial pancreatic cancer: where are we in 2003? *J Natl Cancer Inst* 2003; 95: 180-181
35 Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, Gerdes B, Kress R, Ziegler A, Raeburn JA, Campra D, Grutzmann R, Rehder H, Rothmund M, Schmiegel W, Neoptolemos JP, Bartsch DK. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003; 95: 214-221
36 Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol* 2004; 2: 606-621
37 Rutter JL, Bromley CM, Goldstein AM, Elder DE, Holly EA, Guerry D 4th, Hartge P, Struewing JP, Hogg D, Halpern A, Sagebiel RW, Tucker MA. Heterogeneity of risk for melanoma and pancreatic and digestive malignancies: a melanoma case-control study. *Cancer* 2004; 101: 2809-2816
38 Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol* 2004; 2: 606-621
39 Balague C, Audie JP, Porchet N, Real FX. In situ hybridization shows distinct patterns of mucin gene expression in normal, benign, and malignant pancreas tissues. *Gastroenterology* 1995; 109: 953-964
40 Shimizu M, Saitoh Y, Ohyanagi H, Itoh H. Immunohistochemical staining of pancreatic cancer with CA19-9, KM01, unabsorbed CEA, and absorbed CEA. A comparison with normal pancreas and chronic pancreatitis. *Arch Pathol Lab Med* 1990; 114: 195-200
41 Luttges J, Zamboni G, Longnecker D, Kloppel G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am J Surg Pathol* 2001; 25: 942-948
42 Adsay NV, Merati K, Andea A, Sarkar F, Hruban RH, Wilentz RE, Goggins M, Iocobuzio-Donahue C, Longnecker DS, Klimstra DS. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. *Mod Pathol* 2002; 15: 1087-1095
43 Swartz MJ, Batra SK, Varshney GC, Hollingsworth MA, Yeo CJ, Cameron JL, Wilentz RE, Hruban RH, Argani P. MUC4 expression increases progressively in pancreatic intraepithelial neoplasia. *Am J Clin Pathol* 2002; 117: 791-796
44 Andrianifahanana M, Moniaux N, Schmied BM, Ringel J, Friess H, Hollingsworth MA, Buchler MW, Aubert JP, Batra SK. Mucin (MUC) gene expression in human pancreatic adenocarcinoma and chronic pancreatitis: a potential role of MUC4 as a tumor marker of diagnostic significance. *Clin Cancer Res*

2001; 7: 4033-4040
45 Tascilar M, Skinner HG, Rosty C, Sohn T, Wilentz RE, Offerhaus GJ, Adsay V, Abrams RA, Cameron JL, Kern SE, Yeo CJ, Hruban RH, Goggins M. The SMAD4 protein and prognosis of pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2001; 7: 4115-4121
46 Wilentz RE, Iacobuzio-Donahue CA, Argani P, McCarthy DM, Parsons JL, Yeo CJ, Kern SE, Hruban RH. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. *Cancer Res* 2000; 60: 2002-2006
47 Haglund C, Lundin J, Kuusela P, Roberts PJ. CA 242, a new tumour marker for pancreatic cancer: a comparison with CA 19-9, CA 50 and CEA. *Br J Cancer* 1994; 70: 487-492
48 Plebani M, Basso D, Navaglia F, D'Angeli F, Panozzo MP, Del Giudice G, Battistel M, Meggiato T, Del Favero G. Is CA242 really a new tumour marker for pancreatic adenocarcinoma? *Oncology* 1995; 52: 19-23
49 Ventrucci M, Ubalducci GM, Cipolla A, Panella MA, Ligabue A. Serum CA 242: the search for a valid marker of pancreatic cancer. *Clin Chem Lab Med* 1998; 36: 179-184
50 Banfi G, Bravi S, Ardemagni A, Zerbi A. CA 19.9, CA 242 and CEA in the diagnosis and follow-up of pancreatic cancer. *Int J Biol Markers* 1996; 11: 77-81
51 Lundin J, Roberts PJ, Kuusela P, Haglund C. Prognostic significance of serum CA 242 in pancreatic cancer. A comparison with CA 19-9. *Anticancer Res* 1995; 15: 2181-2186
52 Gansauge F, Gansauge S, Parker N, Beger MI, Poch B, Link KH, Safi F, Beger HG. CAM 17.1--a new diagnostic marker in pancreatic cancer. *Br J Cancer* 1996; 74: 1997-2002
53 Parker N, Makin CA, Ching CK, Eccleston D, Taylor OM, Milton JD, Rhodes JM. A new enzyme-linked lectin/mucin antibody sandwich assay (CAM 17.1/WGA) assessed in combination with CA 19-9 and peanut lectin binding assay for the diagnosis of pancreatic cancer. *Cancer* 1992; 70: 1062-1068
54 Yiannakou JY, Newland P, Calder F, Kingsnorth AN, Rhodes JM. Prospective study of CAM 17.1/WGA mucin assay for serological diagnosis of pancreatic cancer. *Lancet* 1997; 349: 389-392
55 Eccleston DW, Milton JD, Hoffman J, Bara J, Rhodes JM. Pancreatic tumour marker anti-mucin antibody CAM 17.1 reacts with a sialyl blood group antigen, probably I, which is expressed throughout the human gastrointestinal tract. *Digestion* 1998; 59: 665-670
56 Glimelius B, Hoffman K, Einarsson R, Pahlman L, Graf W. Monitoring palliative chemotherapy in advanced gastrointestinal cancer using serial tissue polypeptide specific antigen (TPS) measurements. *Acta Oncol* 1996; 35: 141-148
57 Slesak B, Harlozinska-Szmyrka A, Knast W, Sedlaczek P, van Dalen A, Einarsson R. Tissue polypeptide specific antigen (TPS), a marker for differentiation between pancreatic carcinoma and chronic pancreatitis. A comparative study with CA 19-9. *Cancer* 2000; 89: 83-88
58 Brown DA, Ward RL, Buckhaults P, Liu T, Romans KE, Hawkins NJ, Bauskin AR, Kinzler KW, Vogelstein B, Breit SN. MIC-1 serum level and genotype: associations with progress and prognosis of colorectal carcinoma. *Clin Cancer Res* 2003; 9: 2642-2650
59 Rittling SR, Chambers AF. Role of osteopontin in tumour progression. *Br J Cancer* 2004; 90: 1877-1881
60 Furger KA, Menon RK, Tuck AB, Bramwell VH, Chambers AF. The functional and clinical roles of osteopontin in cancer and metastasis. *Curr Mol Med* 2001; 1: 621-632
61 Iacobuzio-Donahue CA, Maitra A, Shen-Ong GL, van Heek T, Ashfaq R, Meyer R, Walter K, Berg K, Hollingsworth MA, Cameron JL, Yeo CJ, Kern SE, Goggins M, Hruban RH. Discovery of novel tumor markers of pancreatic cancer using global gene expression technology. *Am J Pathol* 2002; 160: 1239-1249
62 Zhou W, Sokoll LJ, Bruzek DJ, Zhang L, Velculescu VE, Goldin SB, Hruban RH, Kern SE, Hamilton SR, Chan DW, Vogelstein B, Kinzler KW. Identifying markers for pancreatic cancer by gene expression analysis. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 109-112
63 Thomas AM, Santarsiero LM, Lutz ER, Armstrong TD, Chen YC, Huang LQ, Laheru DA, Goggins M, Hruban RH, Jaffee EM. Mesothelin-specific CD8(+) T cell responses provide evidence of in vivo cross-priming by antigen-presenting cells in vaccinated pancreatic cancer patients. *J Exp Med* 2004; 200: 297-306
64 Terris B, Blaveri E, Crnogorac-Jurcevic T, Jones M, Missiaglia E, Ruszniewski P, Sauvanet A, Lemoine NR. Characterization of gene expression profiles in intraductal papillary-mucinous tumors of the pancreas. *Am J Pathol* 2002; 160: 1745-1754
65 Guo J, Kleeff J, Li J, Ding J, Hammer J, Zhao Y, Giese T, Korc M, Buchler MW, Friess H. Expression and functional significance of CDC25B in human pancreatic ductal adenocarcinoma. *Oncogene* 2004; 23: 71-81
66 Sato N, Fukushima N, Maitra A, Iacobuzio-Donahue CA, van Heek NT, Cameron JL, Yeo CJ, Hruban RH, Goggins M. Gene expression profiling identifies genes associated with invasive intraductal papillary mucinous neoplasms of the pancreas. *Am J Pathol* 2004; 164: 903-914
67 Maitra A, Ashfaq R, Gunn CR, Rahman A, Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Wilentz RE. Cyclooxygenase 2 expression in pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia: an immunohistochemical analysis with automated cellular imaging. *Am J Clin Pathol* 2002; 118: 194-201
68 Berman DM, Karhadkar SS, Maitra A, Montes De Oca R, Gerstenblith MR, Briggs K, Parker AR, Shimada Y, Eshleman JR, Watkins DN, Beachy PA. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. *Nature* 2003; 425: 846-851
69 van der Heijden MS, Brody JR, Gallmeier E, Cunningham SC, Dezentje DA, Shen D, Hruban RH, Kern SE. Functional defects in the fanconi anemia pathway in pancreatic cancer cells. *Am J Pathol* 2004; 165: 651-657

编辑 何燕 电编 郭海丽