

胆管癌浸润转移途径及其机制

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■背景资料

胆管癌(cholangiocarcinoma)一般指原发于左、右肝管至胆总管下端的肝外胆管癌,在远东和东南亚地区发病率较高,临床治愈率很低,近年来有发病率升高的趋势。胆管癌的浸润和转移具有其自身的特点,对胆管癌及其浸润转移途径与机制的研究具有重要的理论和临床意义。

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Advance in the study of invasion and metastasis of cholangiocarcinoma

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Abstract

Invasion and metastasis of cholangiocarcinoma have specific characteristics. Lymph node metastasis is one of the metastatic modes of cholangiocarcinoma, and local metastasis occurs more frequently than distal one. Due to the specific anatomic structure of bile duct and its close relation with peripheral nerves and various neuropeptides, perineural invasiveness and metastasis of cholangiocarcinoma are attracting more and more attention in recent years. Besides invasive metastasis, inoculation metastasis, lymphatic metastasis and vascular metastasis, perineural invasiveness and metastasis are important pathological features of cholangiocarcinoma. Study on the mechanism of interaction between nerve fiber and cholangiocarcinoma cells and the regulatory factors during invasion and metastasis of cholangiocarcinoma is one of the hot spots in recent years.

Key Words: Cholangiocarcinoma; Invasion; Metastasis

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摘要

胆管癌的浸润和转移具有其自身的特点,经淋巴转移是胆管癌的主要转移方式之一,以局部淋巴结转移为主,较少发生远处转移。由于胆管的解剖部位的特点以及其与周围神经、包括多种神经肽的密切关系,其神经周围浸润转移途径近年来越来越受到人们的重视。除浸润转移、种植转移、淋巴道及血道转移等途径之外,经神经周围浸润和转移是胆管癌的一种重要病理特征,对胆管癌细胞与神经纤维的相互作用机制以及胆管癌神经周围浸润转移过程的调控因子的研究是近年来的研究热点之一。

关键词: 胆管癌; 浸润; 转移

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0 引言

胆管癌(cholangiocarcinoma)一般指原发于左、右肝管至胆总管下端的肝外胆管癌,不包括肝内的胆管细胞癌、胆囊癌和壶腹部癌^[1]。根据肿瘤的位置,肝外胆管癌又分为上段胆管癌(肝门部胆管癌, perihilar cholangiocarcinoma)、中段胆管癌、下段胆管癌,其中,肝门部胆管癌最为常见,大约占60%-70%,位于胆总管者约占20%-30%^[2-3]。胆管癌在世界上大多数地区较为少见,在美国,胆管癌发病率为每10万人口1-2人,每年的新发病例数在2000-3000例之间^[4],但在远东和东南亚地区发病率较高^[5-6],发病率随年龄增加而增高,男性略多于女性^[7],大多数患者大于65岁^[8]。胆管癌出现症状时,通常已经进入进展期,治愈率很低,近年来临床上发病率升高的趋势^[9]。对胆管癌及其浸润转移途径与机制的研究具有重要的理论和临床意义。

1 胆管癌的临床病理及预后

胆管癌起源于胆道上皮细胞, 按其大体形态分为4型: 息肉型、结节型、硬化型、浸润型; 组织学上多表现为腺癌, 包括浸润性腺癌、黏液性腺癌及乳头状癌, 少数为鳞状腺癌及鳞癌、间质肿瘤等, 囊腺癌少见^[10]. 在局部, 胆管癌主要表现为沿胆管壁向上、下直接浸润, 而且因胆管壁薄, 故肿瘤易侵犯胆管周围组织, 常形成较坚实、增厚的灰白色纤维组织增生环, 压迫或包裹肝动脉、门静脉, 大多数胆管癌常与胆管周围结缔组织增生伴行, 很难辨认胆管癌的浸润范围, 使得根治性手术切除非常困难或不可能, 而癌组织残留是导致术后胆管癌很快复发的主要原因^[11-12].

肝门部胆管癌根据侵犯的程度分为5期(TNM分期), 0期: 原位癌; I期: 肿瘤浸润限于黏膜、肌层; II期: 局部侵犯, 可见肿瘤已侵出胆管壁; III期: 肝十二指肠淋巴结、邻近组织局部转移; IV期: 远处转移^[13]. 胆管癌在肿瘤发展上可有以下特点: (1)肿瘤体积很小, 但可以引起胆道梗阻, 沿胆管侵犯; (2)局部呈浸润性生长, 早期侵犯淋巴管、肝动脉; (3)早期侵犯肝实质; (4)生长缓慢, 远处转移较少; (5)易沿神经周围浸润转移.

胆管癌发病原因不明, 在日本, 慢性胆管炎、胆石病患者大约有10%发展为胆管癌^[14]. 其他危险因素还有: 原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)^[15-16], 先天性胆总管囊肿(Caroli病)^[17], 胆管腺瘤、多发性乳头状瘤病、肝吸虫感染^[18-19], 乙肝、丙肝病毒感染^[20-21], 生活习惯如烟草、饮酒等^[22-23]. 性激素也可能影响胆管癌的发病过程^[24-25]. 近年的研究发现, k-ras, c-myc, c-neu, cerb-b2, fas, c-met, p53, bcl-2等多种基因参与了胆管癌的发生、发展过程^[26-32].

胆管癌预后不良, 目前的实验室检查对胆道系统恶性肿瘤早期诊断帮助不大. 胆汁细胞学或肿瘤组织学检查可明确病变的性质, 但阳性率不高; 影像学检查也难以发现早期肿瘤, 但可帮助明确病变的部位、大小、浸润范围及有无淋巴结和远处转移^[33]. 手术切除是唯一有效的治疗方法^[34-37], 根据手术部位的不同, 胆管癌的手术切除率从32%到51%不等, 根治性手术后3 a存活率为40%-60%^[38], 5 a生存率低于20%^[39-42]. 绝大多数胆管癌手术切除后易于复发, 资料显示, 肝门区转移者临床切除后1 a复发率73.9%, 3 a复发率100%, 平均复发时间术后

9.6 mo; 未见转移者切除术后1 a复发率13.3%, 3 a复发率71.4%, 平均复发时间术后17.5 mo, 复发的主要原因为肝及肝门区转移^[12]. 扩大手术切除和淋巴结清扫范围的治疗作用尚未能确定^[43]. 未经切除者, 只能通过PTCD或经内镜置管引流等手段缓解其临床症状, 生存期在6-12 mo之间^[44]. 胆管癌对放疗、化疗不敏感, 目前尚未有标准的治疗方案^[45].

2 肝外胆道的血管、神经及淋巴管分布

Stapleton *et al*^[46]发现, 左右肝管被来自左右肝动脉、肝段动脉、胃十二指肠动脉和副肝动脉供应的血管丛包绕, 这些血管丛与供应尾状叶的动脉关系密切, 而且联系左右叶肝脏的血液供应; 第4肝段和左肝管中部的血供常来自肝右动脉系统. Chen *et al*^[47]认为, 胆管的血液由至少7条动脉供应, 其中主要的动脉是胆囊动脉、胰十二指肠后上动脉、肝右动脉、门静脉后动脉; 动脉在胆管壁上形成3种吻合方式, 分别是形成血管网、沿着管壁纵向吻合和形成动脉环. 胆管旁的静脉系统起源于胰十二指肠上后静脉和幽门十二指肠静脉的几个小支, 在门静脉的前方沿胆总管和肝动脉向上走行, 在肝十二指肠韧带内及肝门附近形成静脉网, 并发出小支分布于肝门附近的肝段. Vellar *et al*^[48]发现肝内和肝外胆道表面均有静脉丛覆盖, 在肝总管和十二指肠上段的胆总管表面, 静脉丛引流到所谓的3点和9点边缘静脉; 较低边缘静脉和胆管静脉丛与胰十二指肠静脉丛汇合, 接着汇入胰十二指肠后上静脉. 较高位的边缘静脉分成数支, 一些与静脉丛和门静脉相邻的分支随着左右肝管进入肝脏, 而其他分支有的直接进入或通过肝门静脉丛进入第4段肝内或尾状叶内. 在肝总管分叉以上的静脉引流直接进入尾状叶和第4段肝内.

肝十二指肠韧带内的神经丛, 分为肝前、后丛, 均发支到肝外胆道系统, 神经纤维多数随肝动脉入肝. 肝前丛的交感神经来自左腹腔神经节, 其节前纤维来自左侧交感神经干上第7-10胸神经节, 而副交感神经则直接由左迷走神经发出. 肝后丛的交感神经来自右腹腔神经节, 节前纤维来源于右侧交感神经干上第7-10胸神经节, 而副交感神经由右迷走神经发出, 穿出右腹腔神经节, 分布至肝后丛^[49-50]. 肝外胆道的淋巴通过网膜孔淋巴结, 进而引流至胰十二指肠上淋巴结^[51].

■同行评价

本文对胆管癌的浸润转移进行了详细的叙述, 阅读文献较多, 材料比较丰富, 对胆管癌的研究有一定的帮助作用.

3 胆管癌的浸润、转移途径

胆管癌存在多种转移方式,经淋巴转移是胆管癌的主要转移方式之一,以局部淋巴结转移为主,较少发生远处转移.淋巴转移的方式在上段与中段相似,而下段有所不同.中、上段胆管癌的主要淋巴转移方式是沿肝总动脉、门静脉周围及胰头上方的淋巴结转移,而下段胆管癌的淋巴转移主要位于胰头周围.淋巴结转移的方式决定于胆管癌原发部位,这种淋巴结转移方式是根治性手术中进行适当淋巴清除的重要前提.胆管癌的血管浸润常见,病理学研究发现,胆管癌标本中其周围发现血管浸润者达58.3%-77.5%^[52-53],这与胆管的解剖位置密切相关.

除直接浸润转移、种植转移、淋巴道及血道转移等途径之外,神经周围组织间隙作为一个独立的肿瘤细胞转移途径在胆管癌的转移中起着重要作用.经神经周围浸润(perineural invasiveness, PNI)和转移是胆管癌的一种重要病理特征,指肿瘤沿神经浸润指肿瘤细胞包绕神经纤维,并进入神经束膜内沿其扩展的局部浸润转移现象,胆管癌细胞可通过胆管周围的神经周围间隙向近端或远端方向转移.除常见于胆管癌外,也见于胰腺癌、前列腺癌、直肠癌和头颈部鳞癌等肿瘤.对40例患者的病理学观察发现,肿瘤附近淋巴管受侵29例(72.5%),肿瘤组织内血管受侵31例(77.5%),神经周围间隙受侵33例(82.5%)^[52]. Nagakawa *et al*^[53]也在40例胆管癌病例中发现有34例神经周围浸润. Bhuiya *et al*^[54]对70例胆管癌手术标本分析发现,有81.4%的标本发现有神经周围浸润,与胆管癌的部位、肿瘤大小、有无淋巴结转移无关,其5 a生存率明显为低,有神经周围受侵犯者根治术后5 a生存率为32%,未受侵犯者为67%.神经周围浸润的方向是横向明显高于纵向浸润(52.2% *vs* 34.8%),他有别于淋巴浸润,即肝脏侧大于十二指肠侧(52.2% *vs* 39.1%),血管浸润方向与此相似(13.0% *vs* 0)^[55].神经周围间隙细胞浸润与十二指肠韧带内结缔组织转移明显相关,提示肝十二指肠韧带结缔组织的癌转移可能是通过神经周围间隙癌细胞扩散而实现^[56].研究还发现,胆管癌神经周围浸润在结节浸润型(10/10)和浸润型(24/24)胆管癌中的发生率明显高于乳头状癌(6/14)和结节状癌(17/22),常见于浸润至浆膜下层或超出浆膜下层的肿瘤,而未见于局限于黏膜层的肿瘤,神经浸润发生的频率与肿瘤

浸润的深度呈明显的相关性^[57].

4 胆管癌的浸润转移机制

一般认为肿瘤的浸润转移过程包括以下几个环节:(1)原发部位的肿瘤的生长,对周围血管、淋巴管及其他邻近组织的浸润破坏,肿瘤细胞表面表达黏附分子降低,细胞之间黏附性减小,使肿瘤细胞容易脱落,某些具有较强转移能力的肿瘤细胞逃逸;(2)肿瘤细胞进入组织间隙、血液或/和淋巴系统内转移;(3)经过与邻近组织、血液和淋巴循环中的某些免疫细胞、细胞分子相互作用,部分的肿瘤细胞生存下来;(4)得以生存的肿瘤细胞在特异的部位附着于邻近组织、血管或淋巴管的内皮细胞或基底膜;(5)突破基底膜,游出血管或淋巴管;(6)转移部位的肿瘤细胞休眠或继续生长.实际上,肿瘤细胞的浸润转移过程是十分复杂,这一过程包括了一系列的肿瘤细胞与肿瘤细胞、肿瘤细胞与宿主细胞、肿瘤细胞与细胞外基质(extracellular matrix, ECM)间的相互作用,尤其是多种细胞因子的参与调节,才使某些肿瘤细胞能够发生成功的转移^[58].胆管癌的神经周围浸润和转移也具有类似的过程,对胆管癌及周围组织病理标本的三维模式立体重建图像显示,肿瘤细胞可首先浸润小血管、淋巴管、在神经纤维周围形成“卫星”灶,继而浸润神经周围.研究发现,在神经周围间隙、血管、淋巴管中,肿瘤组织与原发灶并无结构上的连续性,肿瘤细胞在脱离原发灶后可独立存活下来,形成新的克隆^[59].提示神经周围组织间隙是一个独立的肿瘤细胞转移途径.研究还发现,人胆管癌细胞能够穿过人工基质黏附并浸润神经纤维,形成包绕神经纤维的细胞团,显示人胆管癌细胞对神经纤维具有亲嗜性^[60].

胆管癌的神经周围浸润和转移机制目前尚不清楚,可能与下面的因素有关:(1)神经周围的潜在间隙有利于胆管癌细胞移动和扩散生长;(2)肿瘤细胞表面有噬神经的黏附分子存在;(3)自分泌或旁分泌激素的作用,胆管癌细胞可能通过分泌蛋白酶,降解神经束膜,侵入神经周围间隙,在某些自分泌或旁分泌激素的作用下,通过影响肿瘤细胞运动迁移能力导致肿瘤细胞嗜神经浸润(neurotropic tumor infiltration, NTI),胆管壁及其周围有丰富的内脏神经丝分布.这些神经纤维与肿瘤细胞密切接触.研究发现,与支配肿瘤起源组织的神经纤维相比,肿瘤中神经

纤维的化学性质发生明显改变^[61]. 肿瘤细胞与神经组织作用, 能够导致蛋白水解酶释放、某些化学趋化或促进因子释放以及细胞增殖^[62], 通过细胞黏附分子与神经纤维作用影响肿瘤细胞的神经周围浸润过程^[63-64]. 研究发现, 神经细胞黏附分子(NCAM)在神经周围组织有较高浓度, 能够介导细胞-细胞、细胞-基质黏附^[65-66], NCAM的表达与胆管癌的组织学分型有关, 随细胞恶性程度的增加NCAM阳性率增高^[67], 对24例胆管癌的观察发现, NCAM与胆管癌神经周围浸润显著相关^[68]. 提示当胆管癌突破生长屏障后, 癌细胞表面的NCAM可能诱导癌细胞向神经细胞移动、黏附, 在肿瘤浸润神经的过程中发挥“导航”和“停泊”作用.

肿瘤细胞与细胞外基质成分黏附的相互作用在肿瘤细胞的神经浸润和转移过程中也具有重要作用. 研究表明, 细胞外基质蛋白成分中, 如纤联蛋白(fibronectin)、层黏蛋白(laminin)、玻联蛋白(vitronectin)、血小板反应蛋白(thrombospondin)及多种胶原(collagen), 在体外直接促进肿瘤细胞的黏附与运动^[66]; 观察发现, 肿瘤细胞通过趋向作用直接向含该成分密度高的方向迁移, 且速率较对照组明显加快; 体内接近肿瘤细胞处的特异细胞外基质成分密度的局部变化同样会影响肿瘤细胞的迁移^[69-70]. 研究发现, 肿瘤细胞在与细胞外基质黏附相互作用的过程中, 能够产生并释放大蛋白水解酶, 如金属蛋白酶(metalloproteinase)、丝氨酸蛋白酶(serine protease)和半胱氨酸蛋白酶(cysteineprotease)等, 其含量随肿瘤细胞的恶性程度而增加^[71]. 通过破坏包括血管内皮、基底膜在内的各种细胞外基质结构, 肿瘤细胞得以进入血液或淋巴循环, 并到达特异部位继续生存. 一些实验结果显示, MMP-2, MMP-9表达与胆管癌发展、浸润和转移密切相关, 对该类酶的抑制可以阻断肿瘤细胞的浸润转移能力^[72]. 表皮生长因子能够通过NF- κ B路径激活MMP-9等蛋白水解酶增强胆管癌细胞的侵袭力^[73], 干扰NF- κ B的活性能够改变胆管癌细胞的生物学行为^[74]. 肿瘤细胞内不同亚群的共存或转移能力不同的细胞亚群混合, 使转移能力低的细胞也表现出较强的浸润转移能力, 其原因可能与不同亚群间的细胞外基质成分及降解酶的互补作用, 使其转移能力发生了改变有关^[75]. 胆管周围有丰富的内在及外在神经丝, 他们由分布于消化道的神经细胞(神经节)、连接神经节的神经纤维束以及众多由

神经节发出的支配肌肉、腺体和血管的神经纤维组成. 除肾上腺素能和胆碱能纤维外, 尚有丰富的含有多种消化道激素(神经肽)的肽能纤维, 研究表明, 许多胃肠肽类激素对肿瘤的生物学行为具有非常重要的调控作用, 他们通过自分泌、旁分泌及神经内分泌机制在多种消化道肿瘤的发生、发展中发挥重要作用^[76-77].

总之, 对胆管癌的浸润和转移机制的研究和深入了解是实现胆管癌早期诊断、提高其疗效的根本途径, 神经周围浸润转移途径近年来越来越受到人们的重视. 由于胆管的解剖部位的特点以及其与周围神经、包括CCK在内的神经肽的密切关系, 使包括CCK在内的神经肽与胆管癌的浸润转移的关系特别是其在胆管癌的神经周围浸润转移中的作用的研究具有重要的意义, 对于揭示胆管癌与神经纤维的相互作用机制以及胆管癌神经周围浸润转移过程的调控机制具有重要价值.

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