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宫颈癌肝转移的治疗研究进展

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摘要: 宫颈癌肝转移的发生率较低,常伴有其他部位的转移,预后差。针对宫颈癌肝转移的治疗需综合患者一般情况、病灶分布、初始治疗方式和预期生存目标等多种因素,制订个体化治疗方案,以达到延长患者生存时间、提高生存质量的目的。本文主要结合国内外研究探讨宫颈癌肝转移的临床特征、治疗现状以及预后情况。

关键词: 宫颈肿瘤; 肿瘤转移; 肝; 治疗学

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Research advances in the treatment of cervical cancer with liver metastasis

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Abstract: Though liver metastasis of cervical cancer has a relatively low incidence rate, it is often accompanied by metastasis in other sites and thus has a poor prognosis. For the patients with liver metastasis of cervical cancer, it is necessary to formulate individualized treatment regimens based on various factors such as general status, lesion distribution, initial treatment modality, and life expectancy, so as to prolong the overall survival of patients and improve their quality of life. With reference to related studies in China and globally, this article reviews the clinical features, treatment, and prognosis of cervical cancer with liver metastasis.

Key words: Uterine Cervical Neoplasms; Neoplasm Metastasis; Liver; Therapeutics

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当前,宫颈癌仍然是女性生殖道发病率最高的恶性肿瘤。2020年全球约有60万宫颈癌新发病例,34万死亡病例^[1]。肝脏是继肺和骨之后,宫颈癌最常见的血行转移部位^[2],有0.99%~2.23%的宫颈癌患者发生肝转移^[3-4]。目前关于宫颈癌肝转移的危险因素、治疗现状缺乏系统阐述。本文将重点讨论宫颈癌肝转移患者的临床特征和治疗现状。

1 宫颈癌肝转移的临床特征

1.1 宫颈癌肝转移的发生率、发生时间和转移方式 肝

脏是血运丰富的脏器,宫颈癌患者中肝脏的继发肿瘤,其恶性细胞容易通过血流扩散到其他脏器,因此肝转移患者常伴有肝外转移表现,极少数患者出现孤立的肝转移^[2-3,5]。有研究^[5]显示,宫颈癌确诊后发生肝转移的中位时间为39个月(0~133个月),在确诊5年后出现晚期肝转移的宫颈癌患者并不罕见(6/20,30%)。虽然淋巴扩散是盆腔外转移的主要方式,但是肿瘤细胞可通过门静脉循环途径发生肝转移^[6]。

1.2 宫颈癌发生肝转移的危险因素

研究^[4]表明,肿瘤分期、分化程度、病理类型和种族等是宫颈癌发生肝转移

的主要危险因素;临床分期晚和组织分化程度低的患者容易发生肝转移,但仍有约1.47%的早期宫颈癌患者在行宫颈癌根治术后发生肝转移^[7]。研究^[4]表明,包括腺癌在内的非鳞状细胞宫颈癌患者发生肝转移的风险显著高于鳞癌患者,这可能与体细胞突变、人乳头瘤病毒整合以及基因表达的分子改变有关^[8];伴随淋巴结转移或者组织学类型为小细胞癌的宫颈癌患者术后更容易发生肝转移^[3]。另外,也有研究^[9]显示非裔女性在包括宫颈癌在内的多种妇科恶性肿瘤中表现出更高的转移率,这种种族差异可能与非裔人口的社会经济地位和医疗水平相对较低及其导致的诊断和治疗延迟相关^[10]。

1.3 宫颈癌肝转移的临床症状 单纯的肝转移患者常无明显的临床症状,少数伴有肝周淋巴结转移的患者可表现为腰痛^[7]。若肝转移患者伴有肝外的多发转移,根据转移脏器不同,可伴有便血、恶心呕吐、纳差腹胀等不适症状^[3,7]。

2 宫颈癌肝转移的诊断

对于可疑肝转移的宫颈癌患者,经超声引导下穿刺活组织病理学检查是诊断的金标准。对于不宜行活检的可疑病变,主要根据影像学检查确诊,包括腹部CT、磁共振或PET-CT。

3 宫颈癌肝转移的治疗

由于肝转移属于晚期宫颈癌,治疗效果差,因此针对该临床阶段的晚期肿瘤患者,其治疗的主要目的是控制疾病进展、延长生存时间、提高生存质量。治疗原则主要参照复发/转移宫颈癌的治疗指南,以系统治疗为主,包括化疗、靶向治疗及免疫治疗等方案。局部治疗根据转移病灶的大小、数目、位置、是否伴有其他部位转移以及患者身体状况、经济条件等,可以选择手术治疗、介入治疗和放疗等方案。

3.1 系统治疗

3.1.1 化疗 化疗是晚期及复发性宫颈癌的主要治疗手段,对于具有广泛持续性/复发性且无法达到治愈的转移性宫颈癌患者,化疗的主要目的是尽可能延长生命,同时提高生活质量^[11]。顺铂、卡铂、紫杉醇是宫颈癌治疗的经典化疗药物,多项临床研究^[12-13]显示,以顺铂为基础的联合化疗方案疗效显著优于顺铂单药。以顺铂为基础的联合化疗,已成为复发或转移性宫颈癌的标准化疗方案,常用的一线化疗方案包括顺铂或卡铂/紫杉醇/贝伐珠单抗、顺铂联合紫杉醇、顺铂联合托泊替康、紫

杉醇联合托泊替康等^[14]。二线化疗主要采用非铂类单药治疗,包括紫杉醇类药物、拓扑替康、长春瑞滨、吉西他滨、培美曲塞、氟尿嘧啶等,但总体而言肿瘤对单药化疗的应答反应不高,其客观缓解率(objective response rate, ORR)大多不超过20%,中位无进展生存期(median progression-free survival, mPFS)为2~3个月,中位总生存期(median overall survival, mOS)为6~9个月^[14]。李盼盼等^[3]报道了4例接受全身化疗的肝转移宫颈癌患者(包括3例伴肝外多发转移和1例单纯肝转移),其mOS为7个月(3~8个月),而5例伴肝外多发转移并放弃治疗的患者mOS仅为4个月(3~4个月)。Kim等^[5]研究结果显示,接受化疗的肝转移宫颈癌患者的预后优于期待治疗的患者(mOS:11个月 vs 5个月)。因此,对于体力状态尚可的宫颈癌肝转移患者,可考虑给予积极的系统治疗(如化疗),相对最佳支持治疗或放弃抗肿瘤治疗,仍可取得一定的生存获益。

3.1.2 靶向治疗 近年来,许多分子靶向药物逐步应用于晚期宫颈癌的治疗,包括靶向血管内皮生长因子及其受体的大分子单克隆抗体、抗血管生成小分子酪氨酸激酶抑制剂等。贝伐珠单抗是宫颈癌治疗中最常用的抗血管生成药物,GOG-227C研究^[15]显示贝伐珠单抗药物治疗复发性宫颈癌(接受≤2线治疗)的ORR为10.9%,mPFS和mOS分别为3.4个月和7.2个月。GOG-240(NCT00803062)研究^[16]进一步证实,在复发、转移和晚期宫颈癌的一线治疗中,化疗联合贝伐珠单抗较单纯化疗显著降低了患者复发和死亡风险(mPFS:8.2个月 vs 6.0个月;mOS:16.8个月 vs 13.3个月)。

一项Ⅱ期、单臂、前瞻性研究^[17]显示,安罗替尼(多靶点酪氨酸激酶抑制剂)单药治疗既往接受二线及以上复发或转移宫颈癌的ORR为24.4%,疾病控制率为58.5%,mPFS为3.2个月,mOS为9.9个月。一项多中心单臂前瞻性Ⅱ期临床研究^[18]显示,安罗替尼联合信迪利单抗[细胞程序性死亡受体-1(programmed cell death 1 ligand 1, PD-1)抑制剂]治疗接受二线及以上程序性死亡受体配体-1(programmed cell death 1 ligand 1, PD-L1)阳性的复发或晚期宫颈癌患者的ORR为59.0%,疾病控制率为94.9%,mPFS为9.4个月(95%CI:8.0~14.6个月)。另一项多中心开放标签单臂Ⅱ期临床研究^[19]显示,阿帕替尼(多靶点酪氨酸激酶抑制剂)联合卡瑞利珠单抗(PD-1抑制剂)治疗晚期宫颈癌的ORR为55.6%,mPFS为8.8个月。基于以上研究,我国专家共识^[20]推荐安罗替尼联合PD-1抑制剂如信迪利单抗等(2A类)、阿帕替尼联合抗

PD-1 抑制剂如卡瑞利珠单抗等(2A类)或安罗替尼单药(2B类)用于晚期复发/转移宫颈癌的治疗。

此外,抗体偶联药物在宫颈癌治疗中的地位也日益显现,例如靶向组织因子抗体和微管抑制剂的抗体偶联药物替索单抗(Tivdak)在宫颈癌中的研究正在开展,其药物安全性和有效性的初步结果为抗体偶联药物在晚期宫颈癌中的应用前景带来了希望^[21]。

3.1.3 免疫治疗 随着免疫检查点抑制剂在多个实体瘤中的广泛应用,其在宫颈癌治疗领域也积累了较多的临床证据和经验。KEYNOTE158^[22]、CHECKMATE 358^[23]、GOG-3016^[24]、KEYNOTE-826^[25]、NCT03852251^[26]等多项临床研究均证明了免疫检查点抑制剂对宫颈癌的抗肿瘤效果。基于上述临床研究,我国专家共识^[27]推荐帕博利珠单抗用于肿瘤突变负荷高(TMB-H)、PD-L1 阳性、微卫星不稳定性高(MSI-H)/DNA 错配修复缺陷(dMMR)复发、转移性子宫颈癌二线及以上治疗;纳武利尤单抗用于PD-L1 阳性既往治疗失败的复发、转移性宫颈癌治疗;西米普利单抗用于既往治疗失败的复发、转移性宫颈癌治疗;帕博利珠单抗联合铂类/紫杉醇±贝伐珠单抗用于PD-L1 联合阳性指数(combined positive score, CPS)≥1 或dMMR 或TMB-H 的复发、转移性宫颈癌的一线治疗;推荐卡度尼利单抗用于既往治疗失败的复发、转移性宫颈癌治疗。Nance 等^[28]报道了1例Ib期肝转移宫颈腺癌患者,经过化疗及经导管动脉化疗栓塞术(transcatheter arterial chemoembolization, TACE)治疗进展后,采用钇-90 放射栓塞联合帕博利珠单抗治疗,获得完全缓解的时间至少8个月。宋耕^[29]报道了2例宫颈癌肝转移患者在二线化疗后使用卡瑞利珠单抗治疗2个周期,分别获得3个月和8个月的缓解持续时间,PFS至少为6个月和10个月,疗效较既往化疗药物有显著提升。由此可见,免疫检查点抑制剂治疗宫颈癌肝转移患者呈现较好的临床获益趋势。

3.2 局部治疗

3.2.1 肝部分切除手术 在患者自身状况允许的情况下,部分肝转移宫颈癌患者可通过肝部分切除延长生存时间。Bacalbasa 等^[30]报道了13例确诊宫颈癌半年后发现肝转移的患者,接受肝部分切除手术后,mOS为18个月,其中不伴肝外转移的患者获益明显。Kaseki 等^[31]报道了1例呈孤立病灶的肝转移宫颈癌患者,行肝叶切除术后1年10个月,无复发迹象。值得注意的是,多数肝转移患者在多线治疗后难以耐受肝切除手术,而且绝大多数肝转移宫颈癌患者同时伴有肝外转移,因此不适合接受单纯肝切除手术^[5,32]。

3.2.2 经皮射频消融术 对于无法手术切除的肝转移患者,经皮射频消融具有良好的安全性^[33],可长期控制结直肠癌肝转移^[34]。2015年,王勤等^[35]报道了1例宫颈癌肝转移患者经射频消融治疗后达到临床完全缓解。

3.2.3 放疗 立体定向体部放射治疗(stereotactic body radiotherapy, SBRT)作为一种精确的外照射方法,将高剂量辐射聚焦于目标靶区上,对肿瘤细胞造成最大程度杀伤的同时保护肿瘤周围正常组织,可实现较高的治疗效益比。已有多项临床试验将SBRT应用于肝转移肿瘤患者,并证实了该治疗模式的有效性和安全性。对于放疗靶区剂量覆盖理想的实体瘤患者而言,SBRT治疗后1~2年肝转移灶局部控制率为70%~100%,2年总生存率为30%~38%。该技术通常用于肿瘤最大直径≤6 cm,病灶<3个、无肝外转移的患者^[36-37]。乳腺癌伴肝转移患者因副作用停止化疗后,选择SBRT进行治疗,SBRT后24个月未发现再生或复发^[38]。另外,8例伴有转移的子宫内膜癌患者接受了肝脏部位的SBRT,结果显示3例(37.5%)患者的预后得到改善^[39]。然而,SBRT能否进一步改善肝转移患者的PFS,仍然需要开展更多研究予以验证。目前针对SBRT应用于宫颈癌肝转移的临床研究较少。李盼盼等^[3]报道了2例仅伴肝周淋巴结转移的宫颈癌患者行SBRT局部放疗后,生存时间分别达到29个月和32个月。SBRT技术在宫颈癌肝转移中的治疗价值还需要进一步探索。

3.2.4 化疗 TACE是将导管选择性插入至肿瘤供血靶动脉后,注入适量的栓塞剂,使靶动脉闭塞引起肿瘤组织缺血坏死。李盼盼等^[3]报道了2例单纯宫颈癌肝转移患者行TACE介入治疗后,生存时间分别达到24个月和25个月。李继兵等^[40]报道了6例肝转移宫颈癌患者接受TACE介入治疗(顺铂+紫杉醇+盐酸吡柔比星)后,5例患者部分缓解,有效率达83.3%。

4 预后

研究^[41]显示,远处转移的宫颈癌患者中,肝转移患者的预后较无肝转移患者差。宫颈癌患者一旦出现肝转移,预后极差,mOS为10个月^[5]。仅发生肝转移的宫颈癌患者mOS为8(6.11~9.89)个月,同时合并骨转移的肝转移患者mOS为6(4.71~7.29)个月,若同时出现肺、骨和肝转移,患者mOS仅为4(2.04~5.96)个月^[41]。此外,有研究^[4]显示合并肺转移、未接受放疗和化疗的患者预后较差,放化疗是改善宫颈癌肝转移患者总生存率的重要治疗因素。值得注意的是,病灶大小、转移病灶数量和转移灶在肝脏内的分布情况与预后无关,这可

能是由于肝转移常伴盆腔广泛累及或盆腔广泛转移,因此肝脏受累程度本身对存活率的影响微乎其微^[5]。宫颈癌肝转移患者的主要死亡原因是尿毒症、盆腔脓肿、大出血等^[5]。

5 小结

宫颈癌肝转移的发生率低,多伴随盆腔广泛累及或者盆腔外多发转移,肿瘤分期、分化程度和病理类型等因素与宫颈癌肝转移发生风险相关。单纯的肝转移患者临床症状轻,预后相对较好,可选择肝部分切除、经皮射频消融术等局部治疗的同时辅以全身治疗。合并肝外转移的宫颈癌患者临床症状重,预后极差,多基于综合治疗以延长患者总体生存时间。目前,免疫治疗在宫颈癌肝转移方面的研究较少,未来可探索免疫治疗药物与常用的化疗药物联合用于宫颈癌肝转移的疗效。宫颈癌肝转移强调基于多学科会诊制订个体化综合治疗方案,以达到控制疾病进展、延长生存时间、提高生存质量的目的。

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