

DOI: 10.16781/j.CN31-2187/R.20220506

· 综 述 ·

腹腔加压气溶胶化学治疗在结直肠癌腹膜转移治疗中的研究进展

金 路, 郝立强*

海军军医大学(第二军医大学)第一附属医院肛肠外科, 上海 200433

〔摘要〕 结直肠癌腹膜转移患者预后不佳, 首次确诊时往往已处于晚期。人们对结直肠癌腹膜转移的治疗理念已从姑息治疗转变为以系统化学治疗、肿瘤细胞减灭术联合腹腔热灌注化学治疗等的多学科综合疗法。腹腔加压气溶胶化学治疗(PIPAC)以一种新型腹腔内给药方式被用来治疗不可切除的腹膜转移癌患者, 较既往治疗手段具有微创、安全、药物分布均质及渗透肿瘤能力强等优点。基于这些优势, 其自 2011 年首次应用于人体以来, 已在世界多国使用。研究者还不断改进着 PIPAC 的技术模式, 研发出了多种新治疗模式。本文对 PIPAC 主要在结直肠癌腹膜转移治疗中的历史、技术规范、并发症、安全性及预后等进行综述。

〔关键词〕 结直肠肿瘤; 腹腔加压气溶胶化学治疗; 腹膜转移; 技术规范

〔中图分类号〕 R 735.34 〔文献标志码〕 A 〔文章编号〕 2097-1338(2023)04-0466-08

Pressurized intraperitoneal aerosol chemotherapy in the treatment of peritoneal metastasis from colorectal cancer: research progress

JIN Lu, HAO Li-qiang*

Department of Colorectal Surgery, The First Affiliated Hospital of Naval Medical University (Second Military Medical University), Shanghai 200433, China

〔Abstract〕 Patients with peritoneal metastasis from colorectal cancer have poor prognoses and are usually at advanced stage when first diagnosed. We have changed their treatment concepts for peritoneal metastasis of colorectal cancers from traditional palliative treatment to multidisciplinary treatments (including chemotherapy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is introduced as a novel intraperitoneal administration approach to treat unresectable peritoneal metastasis from colorectal cancers. Compared with previous treatments, it has the advantages of minimal invasion, good safety, a homogeneous intraperitoneal distribution and enhanced tumour penetration. Owing to these advantages, PIPAC has been used in many countries around the world since its first application in humans in 2011. With increasingly improved technical models of PIPAC, several new treatment models were developed. The article reviews the history, technical criteria, complications, safety and prognosis of PIPAC treatment for peritoneal metastasis from colorectal cancers.

〔Key words〕 colorectal neoplasms; pressurized intraperitoneal aerosol chemotherapy; peritoneal metastasis; technical criteria

[Acad J Naval Med Univ, 2023, 44(4): 466-473]

结直肠癌是常见的恶性肿瘤之一, 其发病率居全球第 3 位(10%), 死亡率居第 2 位(9.4%)^[1]。结直肠癌腹膜转移问题十分棘手, 曾一度被认为是一种不可治愈的终末状态。结直肠癌腹膜转移患者预后不佳, 中位总生存期(median overall survival, mOS)仅为 3.1 个月^[2]。目前的治疗手段主要有系统化学治疗、靶向治疗、肿瘤细胞减灭术联合腹腔热灌注化学治疗(cytoreductive surgery/hyperthermic intraperitoneal chemotherapy, CRS/HIPEC)等多学科综合疗法。随着人们对结直肠癌

腹膜转移发生机制认识的提高及新技术、新方法的出现, 接受治疗的患者已可实现长期生存。尽管如此, 这些传统治疗手段都有着不可避免的限制与不足。

腹腔加压气溶胶化学治疗(pressurized intraperitoneal aerosol chemotherapy, PIPAC)是一种新型治疗手段, 目前主要用作不可切除腹膜转移癌患者的姑息疗法。PIPAC 将化学治疗药物以气溶胶的形式释放入腹腔, 较以往液体灌注疗法具有药物分布均匀、毒性小、渗透能力强等优势^[3], 且在门诊

〔收稿日期〕 2022-06-15 〔接受日期〕 2022-11-14

〔作者简介〕 金 路, 硕士生. E-mail: sdsdsd92@163.com

*通信作者(Corresponding author). Tel: 021-31161607, E-mail: hao_liqiang@139.com

即可实施^[4]。德国最先在临床应用 PIPAC, 目前欧洲、美国、韩国、巴西、新加坡等多地均已有使用的案例报道^[5]。本文拟对 PIPAC 的历史、技术规范、并发症、安全性及预后等进行综述。

1 结直肠癌腹膜转移既往疗法的限制

对于结直肠癌腹膜转移患者, 目前的一线系统化学治疗方案主要是 FOLFOX 方案(5-氟尿嘧啶/亚叶酸钙+奥沙利铂)、FOLFIRI 方案(5-氟尿嘧啶/亚叶酸钙+伊立替康)及 FOLFOXIRI 方案(氟尿嘧啶/亚叶酸钙+奥沙利铂+伊立替康), 但疗效甚微, 治疗后患者的 mOS 仅为 16.3 个月^[6]; 若联合靶向治疗, mOS 可延长至 27.0 个月^[7]。疗效不佳的原因主要有 2 个, 一是腹膜的表面血管分布密度过低, 二是肿瘤组织间隙液压过高, 两者共同阻碍了药物的吸收^[8]。

最新研究显示接受 CRS/HIPEC 的患者 mOS 为 51 个月^[9], 尽管肿瘤学结局表现较好, 但不良事件发生率及死亡率较高; 且 HIPEC 应用的传统液体灌注疗法渗透能力差, 腹膜不能完全暴露于药物中^[10], 药物有效利用率低。此外, 近期 PRODIGE7 试验公布的结果也使人们对 HIPEC 的地位提出了质疑^[11]。以上均是目前 CRS/HIPEC 的局限与不足。

2 PIPAC 历史

2000 年, Reymond 等^[12]最先设想将药物以气雾剂的形式释放入腹腔。他们研发了一种微泵装置并以猪为实验动物进行了实验, 受当时技术水平限制, 当腹腔内相对湿度接近 100% 时, 微泵装置无法继续雾化, 导致气雾剂的稳定性较差。但之后的相关研究并未中断。2011 年, Solass 等^[13]将腹膜肿瘤组织放入一个充满 12 mmHg (1 mmHg=0.133 kPa) CO₂ 的盒子中用来模拟腹腔环境。实验使用了一种无毒性的药物 Dbait, 并设置气雾剂组和液体药物对照组。荧光显像结果显示实验组中 Dbait 侵入到肿瘤结节 1 mm 深度的位置, 而对照组无药物侵入肿瘤的迹象。Solaß 等^[14]分析了 2000 年初次实验表现不佳的原因, 研发了新的微泵装置。他们用新装置向猪的腹腔内释放亚甲蓝染色剂并与灌洗液对照组进行比较, 结果显示气雾剂组的染色面积更大。基于临床前实验的喜人结果, 2011 年, Solass 等^[15]首次对 3 例原发癌灶来源不同的晚期

腹膜癌患者实施了 PIPAC, 过程顺利且患者耐受良好, 自此 PIPAC 正式投入临床使用。2017 年, Khosrawipour 等^[16]进行的一项体外实验专门研究了 PIPAC 的治疗参数(药物剂量、压力、持续时间及温度)变化对疗效的影响。实验以人结直肠癌细胞系 HCT8 为对象, HCT8 细胞系转移特性强, 可被用来模拟腹膜转移癌的临床情形, 结果表明增加奥沙利铂剂量可显著提升其对野生型 HCT8 细胞系的杀伤作用($P<0.05$), 且在雾化形式下提升效果更明显($P<0.001$); 压力的升高也能提升杀伤作用; 而温度的升高及持续时间的延长则并无影响。

3 PIPAC 技术

3.1 PIPAC 的优势 PIPAC 具有以下优势: (1) 腹膜血浆屏障可阻挡药物进入血液, 既保证了腹腔内较高的药物浓度, 也减轻了药物毒性对身体的伤害^[17]; (2) 气溶胶是气体中的悬浮液滴, 较液体具有更好的均质分布特性; (3) 外部施加的压力可提高腹腔内流体静水压, 抵消较高的肿瘤组织间隙液压, 从而有利于药物的吸收; (4) 可根据需要调整环境参数(温度、酸碱度、电荷量等)^[10]。

3.2 操作流程 PIPAC 需在具备层流气流系统及远程控制系统的手术室进行, 操作体位取仰卧或分腿位, 麻醉方式采用全身麻醉^[18]。首先术者将 1 个 10~12 mm 的穿刺器插入腹腔, 通过穿刺器注入 CO₂, 建立一个充满 CO₂ 的腹腔内密闭空间 (12 mmHg, 37 °C), 而后在腹腔镜直视下插入第 2 个 5 mm 穿刺器, 若需进行其他手术, 还可再插入额外的穿刺器。之后术者探查腹腔, 若发现有腹水, 则取 150 mL 腹水样本送细胞学检查; 若无腹水, 则先注入 500 mL 生理盐水灌洗, 再取 150 mL 灌洗液样本送检^[19]; 为评估病变恶性程度, 探查时还需评估腹膜癌指数(peritoneal cancer index, PCI), 同时在 3~4 个有代表性的肿瘤位置取活检, 并用金属夹做好标记以便后续治疗定位^[20]。最后, 术者先将一个雾化微泵装置通过高压线与一个高压注射器连接, 后将其置于 10~12 mm 穿刺器内开始雾化治疗, 治疗通常持续 30 min, 气雾剂可通过配备有 2 个微粒滤过器的闭合气溶胶废物系统(closed aerosol waste system, CAWS)排出体外^[21]。2 次治疗的间隔通常为 6~8 周, 患者

一般于术后1~2 d或当天出院^[19]。

3.3 药物 一般来说,对于结直肠癌来源的腹膜转移病灶,PIPAC使用的药物是含92 mg/m²奥沙利铂的150 mL葡萄糖溶液(PIPAC-OX方案),参数通常设置为流速30 mL/min、压力200 psi(1 psi=6 894.8 Pa)^[22]。目前的药物剂量源自临床经验,尚未形成标准。为了探索最大耐受剂量(maximal tolerated dose, MTD),研究者们开展了多项剂量递增试验。新加坡的PIPAC-OX试验纳入的16例胃肠道肿瘤腹膜转移患者被分为45、60、90、120 mg/m²奥沙利铂4个剂量组,结果显示120 mg/m²组的3例患者耐受良好,无不良事件发生,研究者遂将后续Ⅱ期试验的药物剂量定为120 mg/m²^[23]。法国学者Dumont等^[24]报道,90 mg/m²奥沙利铂的剂量没有引发剂量限制毒性(dose-limiting toxicity, DLT)事件,而140 mg/m²奥沙利铂的剂量则引发了2例DLT事件,他们遂将MTD定为90 mg/m²。Robella等^[25]则发现患者在135 mg/m²奥沙利铂剂量下接受单次治疗时耐受良好。2022年,一项PIPAC治疗方案专家共识推荐的使用剂量为120 mg/m²奥沙利铂(对于身体状况不佳的患者推荐90 mg/m²)^[26],该共识还推荐PIPAC-OX同时联合5-氟尿嘧啶化学治疗,因为5-氟尿嘧啶可增强奥沙利铂的吸收^[27]。

3.4 适应证和禁忌证 现有报道中PIPAC的适应证包括:(1)系统化学治疗后转移灶仍不可切除;(2)患者对化学治疗方案表现出耐药性;(3)患者不适宜接受CRS/HIPEC;(4)作为CRS/HIPEC前的新辅助治疗^[28]。禁忌证包括:(1)预期寿命短于3个月;(2)肠梗阻;(3)完全肠外营养;(4)失代偿性腹水;(5)胃肠段切除减瘤术;(6)对治疗药物有过敏史。相对禁忌证包括:(1)腹膜外转移;(2)东部肿瘤协作组评分(eastern cooperative oncology group performance, ECOG) > 2;(3)门静脉血栓^[29]。PIPAC往往需要多周期治疗,为使多次治疗过程顺利完成,术者需挑选出适合接受治疗的患者,Balmer等^[30]报道治疗前无肠梗阻病史($P=0.037$)及接受过多种模式的治疗方案($P<0.001$)是顺利完成多次PIPAC的独立预测因素。

3.5 技术改进 PIPAC技术模式应用至今已有过多次改进,并衍生出多种新模式。静电腹腔加压气溶胶化学治疗(electrostatic pressurized

intraperitoneal aerosol chemotherapy, ePIPAC)就是其中一种。ePIPAC利用了静电加速原理^[31],具体操作概括如下:首先术者向腹腔内插入一根不锈钢电极刷,电极刷产生的高电压可促发电晕放电现象并释放负离子电荷^[19],接着负电荷会吸附于腹腔内的药剂微粒上,最后微粒与带正电荷的腹腔内组织接触,这样便可增强气雾剂的渗透性。在一项动物实验中,ePIPAC组的气雾剂清除时间较PIPAC组更短(15 s vs 30 min),且检测到的追踪剂组织浓度较PIPAC组更高($P=0.06$)^[32]。ePIPAC自2016年首次应用于人体以来,已在多项试验中表现出良好的安全性,但其肿瘤学功效仍有待进一步确证^[33-34]。除ePIPAC外,还有诸如旋转式腹腔加压气溶胶化学疗法(rotational intraperitoneal pressurized aerosol chemotherapy, RIPAC)、腹腔加压气溶胶病毒疗法(pressurized intraperitoneal aerosolised virotherapy, PIPAV)等其他改进模式^[35-36]。

4 PIPAC应用

4.1 PIPAC单独治疗 PIPAC已被证实可实现肿瘤的退缩。Ellebæk等^[37]分析了2项前瞻性试验PIPAC-OP1及PIPAC-OP2中24例结直肠癌腹膜转移患者的资料。结果显示首次PIPAC后,68%的患者实现肿瘤退缩,21%保持疾病稳定;第2次PIPAC后,67%的患者实现肿瘤退缩,27%维持疾病稳定;完成治疗后,21%的患者实现肿瘤完全退缩,患者的mOS为20.5个月,这一结果充分表明PIPAC可以很好地实现肿瘤退缩。一项前瞻性Ⅱ期试验CRC-PIPAC纳入了20例患者(13例原发癌灶位于结肠,7例位于阑尾),在59次单独PIPAC-OX方案治疗后,50%的患者腹膜退缩分级(peritoneal regression grading score, PRGS)有改善,56%的腹水症状缓解,67%的癌胚抗原值下降,但影像学检查结果及PCI评分未见明显改善。患者mOS仅为8个月,术后患者普遍发生了轻微不良事件(97%),15%的患者发生了显著不良事件,1例患者死亡,死因可能是不明原因的脓毒症^[38]。因为PIPAC的疗效在该试验中并不显著,且病例数较少,因此研究者未对PIPAC单独治疗的疗效作出定论,但观察到的部分缓解结果对推动后续试验的开展具有重要意义。

4.2 PIPAC联合治疗 一项回顾性研究纳入了

17例结直肠癌腹膜转移患者,他们共接受了48次PIPAC-OX方案治疗(有11例同时接受了系统化学治疗),其中14例患者完成了至少2次以上的PIPAC并接受评估,结果显示7例患者完全缓解、4例显著缓解、1例部分缓解、2例无缓解,客观肿瘤缓解率为71%,患者的mOS为15.7个月,出现的不良事件程度均较轻^[39]。这一初步试验结果表明PIPAC联合系统化学治疗可实现肿瘤退缩,安全性较好。此外,还有学者研究了联合靶向治疗的可行性。一项回顾性研究纳入了134例腹膜转移患者,26例患者(结直肠原癌来源18例)被设为PIPAC联合贝伐单抗组,对应的108例则被设为非贝伐单抗组,结果显示两组的30d及Ⅲ级以上不良事件发生率均无明显差别(14.8% vs 9.4%, $P=0.147$; 4.5% vs 3.2%, $P=0.521$),30d死亡率分别为0和5.5%,这说明PIPAC联合贝伐单抗治疗是可行、安全、可耐受的^[40],但该试验并无肿瘤学功效结果。CRC-PIPAC-II是一项前瞻性Ⅱ期试验,首次研究了PIPAC联合贝伐单抗治疗结直肠癌腹膜转移患者的有效性,试验结果尚未公布^[41]。

4.3 新辅助治疗与辅助治疗 CRS/HIPEC对结直肠癌腹膜转移患者至关重要,若临床医师以PIPAC作为新辅助治疗手段将不可切除的转移灶转至可切除状态,这将是患者的巨大福音。Girshally等^[42]报道,406例腹膜转移患者接受PIPAC后,21例原本无CRS/HIPEC计划的腹膜转移患者(占5.1%,且多数为结直肠癌来源)最终成功接受了该治疗,这表明PIPAC有作为新辅助治疗的可能。此外,为预防结直肠癌腹膜转移高危患者术后发生转移,PIPAC-OPC3试验探索了PIPAC作为辅助治疗的可行性,目前试验仍在进行中^[43]。

4.4 PIPAC联合手术 回顾性多中心研究PLUS试验纳入了196例腹膜转移患者,其中96例患者(结直肠癌来源15例)接受了额外的手术治疗(粘连松解术、网膜切除术、子宫附件切除术、胃切除术、肠段切除术等),被设为额外手术组。结果显示,额外手术组患者的中位手术时间和住院天数较未手术组更长($P<0.001$),额外手术组与未手术组的外科并发症发生率相似(5.2% vs 2%),尽管手术组的内科并发症发生率明显更高(30.2% vs 3%, $P<0.001$),但程度均不严重,这说明PIPAC治疗的同时追加手术是安全、可行的^[44]。

5 PIPAC安全性与生活质量

5.1 并发症 Lurvink等^[45]系统综述了3项研究,总结了21例结直肠癌腹膜转移患者接受PIPAC治疗后的并发症情况,结果显示,依据不良事件通用术语标准(common terminology criteria for adverse event, CTCAE),4例患者发生了3级腹痛不良事件(19%),无4、5级不良事件发生;1、2级不良事件有:疼痛(7例,33%)、恶心/呕吐(7例,33%)、感染(1例,5%)、腹泻(1例,5%)、发热(4例,19%)。炎症反应也是PIPAC的常见不良事件。一项回顾性研究结果显示,41例接受PIPAC的腹膜转移患者中,17例(41%)发生了不严重的一过性的炎症反应,研究者认为药物诱导的化学性腹膜炎可能是发生炎症反应的原因^[46]。

PIPAC还会引发一些罕见并发症。2018年,Siebert等^[47]首次报道,71例腹膜转移患者接受PIPAC-OX方案治疗后有2例(2.8%)出现了严重超敏反应,这是一种不常见但可致命的不良事件。2例患者均于治疗前接受过含奥沙利铂的系统化学治疗,这可能与该不良事件的发生有关。Ezanno等^[48]报道了1例左半结肠癌腹膜转移患者在接受治疗后发生了严重的奥沙利铂诱导综合征。Thibaudeau等^[49]则报道了1例左半结肠癌腹膜转移患者在接受治疗后发生了急性呼吸窘迫综合征,这可能是由化学性腹膜炎、肺部毒性或罕见的严重超敏反应引起的。

5.2 职业安全性 气雾化的给药形式可能会增加人员暴露于药物的风险,这是由于在实施PIPAC过程中,气溶胶的扩散难以控制,眼部、皮肤及呼吸道是常见的暴露部位^[50]。Willaert等^[51]检测了PIPAC后外科手套、过滤器、手术室地面和外科医师双手等擦拭样本中的铂类含量,结果显示样本中的铂类含量均未达到检出标准。Graversen等^[52]评估了手术环境的安全性,在2例患者接受PIPAC后,他们检测了术者和麻醉医师所在位置空气及术者血液中的药物微粒浓度,结果显示在整个治疗过程中,空气中的药物微粒浓度均很低,在术者的血液中也未检测到铂类药物。Ametsbichler等^[53]发现,实施PIPAC时手术室空气中的铂类浓度很低($<9\text{ pg/m}^3$),且地面、穿刺器、手套等表面的污染程度具有波动性($0.01\sim1\,733\text{ pg/cm}^2$,中位数值

1.04 pg/cm²),地面铂类浓度最低而穿刺器表面浓度最高。Larroque等^[54]检测了参与PIPAC-OX方案治疗的相关人员的血液及尿液样本,检测结果表明这些人员均无暴露于奥沙利铂的风险。尽管多项试验结果均显示了PIPAC的职业安全性,但相关人员仍要严格恪守安全守则,强化个人及环境保护措施,并在现场配备应急处置包^[55]。PIPAC术者也必须在专业的培训中心接受培训,学习操作流程及安全方案^[56]。

5.3 生活质量 (quality of life, QoL) 腹膜转移肿瘤本身及相应的治疗均会对患者的QoL产生影响,因此患者QoL的评估也是决定治疗方式是否可行的重要影响因素。一项回顾性研究纳入了42例结直肠癌腹膜转移患者,在接受92次PIPAC后,患者的QoL无显著变化($P=0.388$),但消化道癌来源患者的QoL评分倾向更低^[57]。一项系统综述纳入了2013年至2020年10项研究的186例患者,这些患者共接受了959次PIPAC,该10项研究均采用欧洲癌症研究与治疗组织生活质量测定量表评估了患者的QoL,结果显示6项研究中的患者身体功能领域评分保持稳定,2项研究有改善表现;所有接受重复PIPAC患者的身体、情绪、认知、角色、社会5项功能领域评分无进一步恶化;各研究量表的胃肠道症状领域评分保持稳定,2项研究评分有改善^[58]。就现有临床证据看,PIPAC不会对患者QoL产生明显影响。

6 PIPAC 预后

一项前瞻性研究纳入了51例接受PIPAC的腹膜转移患者(结直肠癌来源19例),多因素分析结果表明只有预后营养指数 <36.5 是总生存期的独立预测因素($P=0.034$)^[59]。另一项研究的单因素分析结果表明PRGS评分可预测总生存期的趋势($P=0.08$),而多因素分析结果则表明双向化疗($P=0.04$)、PCI评分($P=0.009$)、Karnofsky评分($P=0.003$)及患者已接受的化学治疗线数($P=0.001$)对预后有预测价值^[60]。目前有关PIPAC预后因素的研究相当匮乏,没有专门针对结直肠癌腹膜转移患者的研究。

7 小 结

结直肠癌腹膜转移患者预后差,系统化学治疗

及靶向治疗疗效不佳、毒性大,而传统腹腔内液体热灌注疗法限制和争议多。PIPAC是一种新型治疗手段,能有效实现腹膜肿瘤的退缩,安全性及可耐受性好。目前工作的重点是形成药物剂量及技术方案的标准。PIPAC作为新辅助治疗、辅助治疗的价值也有待进一步确认。尽管国内目前尚无PIPAC治疗患者的案例报道,但相信在不久的将来会实现零的突破。

[参考文献]

- [1] SUNG H, FERLAY J, SIEGEL R L, LAVERSANNE M, SOERJOMATARAM I, JEMAL A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71: 209-249.
- [2] ROTH L, RUSSO L, ULUGOEL S, FREIRE DOS SANTOS R, BREUER E, GUPTA A, et al. Peritoneal metastasis: current status and treatment options[J/OL]. Cancers (Basel), 2021, 14: 60. DOI: 10.3390/cancers14010060.
- [3] LURVINK R J, VAN DER SPEETEN K, ROVERS K P, DE HINGH I H J T. The emergence of pressurized intraperitoneal aerosol chemotherapy as a palliative treatment option for patients with diffuse peritoneal metastases: a narrative review[J]. J Gastrointest Oncol, 2021, 12(Suppl 1): S259-S270.
- [4] GRAVERSEN M, LUNDELL L, FRISTRUP C, PFEIFFER P, MORTENSEN M B. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as an outpatient procedure[J/OL]. Pleura Peritoneum, 2018, 3: 20180128. DOI: 10.1515/pp-2018-0128.
- [5] MARTELOTTO S, MAILLOT C, VILLENEUVE L, EVENO C, SGARBURA O, POCARD M. Restricted access to innovative surgical technique related to a specific training, is it ethical? Example of the PIPAC procedure. A systematic review and an experts survey[J]. Int J Surg, 2020, 83: 235-245.
- [6] NADIRADZE G, HORVATH P, SAUTKIN Y, ARCHID R, WEINREICH F J, KÖNIGSRÄINER A, et al. Overcoming drug resistance by taking advantage of physical principles: pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J/OL]. Cancers (Basel), 2019, 12: 34. DOI: 10.3390/cancers12010034.
- [7] FRANKO J, SHI Q, MEYERS J P, MAUGHAN T S, ADAMS R A, SEYMOUR M T, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive

- System (ARCAD) database[J]. *Lancet Oncol*, 2016, 17: 1709-1719.
- [8] CEELEN W, VAN NIEUWENHOVE Y, VANDE PUTTE D, PATTYN P. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and hyperthermic intraperitoneal chemoperfusion (HIPEC) for colorectal carcinomatosis[J]. *Ann Surg Oncol*, 2014, 21: 3023-3028.
- [9] BREUER E, HEBEISEN M, SCHNEIDER M A, ROTH L, PAULI C, FRISCHER-ORDU K, et al. Site of recurrence and survival after surgery for colorectal peritoneal metastasis[J]. *J Natl Cancer Inst*, 2021, 113: 1027-1035.
- [10] FLESSNER M F. Pharmacokinetic problems in peritoneal drug administration: an update after 20 years[J]. *Pleura Peritoneum*, 2016, 1: 183-191.
- [11] QUÉNET F, ELIAS D, ROCA L, GOÉRE D, GHOUTI L, POCARD M, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial[J]. *Lancet Oncol*, 2021, 22: 256-266.
- [12] REYMOND M A, HU B, GARCIA A, RECK T, KÖCKERLING F, HESS J, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator[J]. *Surg Endosc*, 2000, 14: 51-55.
- [13] SOLASS W, HERBETTE A, SCHWARZ T, HETZEL A, SUN J S, DUTREIX M, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept[J]. *Surg Endosc*, 2012, 26: 847-852.
- [14] SOLAß W, HETZEL A, NADIRADZE G, SAGYNALIEV E, REYMOND M A. Description of a novel approach for intraperitoneal drug delivery and the related device[J]. *Surg Endosc*, 2012, 26: 1849-1855.
- [15] SOLASS W, KERB R, MÜRDTER T, GIGER-PABST U, STRUMBERG D, TEMPFER C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy[J]. *Ann Surg Oncol*, 2014, 21: 553-559.
- [16] KHOSRAWIPOUR V, DIAZ-CARBALLO D, ALI-HAYDAR A, KHOSRAWIPOUR T, FALKENSTEIN T A, WU D, et al. Cytotoxic effect of different treatment parameters in pressurized intraperitoneal aerosol chemotherapy (PIPAC) on the *in vitro* proliferation of human colonic cancer cells[J/OL]. *World J Surg Onc*, 2017, 15: 43. DOI: 10.1186/s12957-017-1109-4.
- [17] DE BREE E, MICHELAKIS D, STAMATIOU D, ROMANOS J, ZORAS O. Pharmacological principles of intraperitoneal and bidirectional chemotherapy[J]. *Pleura Peritoneum*, 2017, 2: 47-62.
- [18] NOWACKI M, ALYAMI M, VILLENEUVE L, MERCIER F, HUBNER M, WILLAERT W, et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: an international survey study[J]. *Eur J Surg Oncol*, 2018, 44: 991-996.
- [19] WINKLER C S, SANDHU J, PETTKE E, MERCHEA A, FONG Y, KUMARA H M C S, et al. Pressurized intraperitoneal aerosol chemotherapy, a palliative treatment approach for patients with peritoneal carcinomatosis: description of method and systematic review of literature[J]. *Dis Colon Rectum*, 2020, 63: 242-255.
- [20] HÜBNER M, GRASS F, TEIXEIRA-FARINHA H, PACHE B, MATHEVET P, DEMARTINES N. Pressurized intraperitoneal aerosol chemotherapy—practical aspects[J]. *Eur J Surg Oncol*, 2017, 43: 1102-1109.
- [21] RAHIMI-GORJI M, VAN DE SANDE L, DEBBAUT C, GHORBANIASL G, BRAET H, COSYNS S, et al. Intraperitoneal aerosolized drug delivery: technology, recent developments, and future outlook[J]. *Adv Drug Deliv Rev*, 2020, 160: 105-114.
- [22] KIM G, TAN H L, CHEN E, TEO S C, JANG C J M, HO J, et al. Study protocol: phase I dose escalating study of pressurized intra-peritoneal aerosol chemotherapy (PIPAC) with oxaliplatin in peritoneal metastasis[J/OL]. *Pleura Peritoneum*, 2018, 3: 20180118. DOI: 10.1515/pp-2018-0118.
- [23] KIM G, TAN H L, SUNDAR R, LIESKE B, CHEE C E, HO J, et al. PIPAC-OX: a phase I study of oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy in patients with peritoneal metastases[J]. *Clin Cancer Res*, 2021, 27: 1875-1881.
- [24] DUMONT F, PASSOT C, RAOUL J L, KEPENEKIAN V, LELIÈVRE B, BOISDRON-CELLE M, et al. A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic approach using pressurised intraperitoneal aerosol chemotherapy for advanced peritoneal metastases of gastrointestinal tract cancers[J]. *Eur J Cancer*, 2020, 140: 37-44.
- [25] ROBELLA M, DE SIMONE M, BERCHIALLA P, ARGENZIANO M, BORSANO A, ANSARI S, et al. A phase I dose escalation study of oxaliplatin, cisplatin and doxorubicin applied as PIPAC in patients with peritoneal carcinomatosis[J/OL]. *Cancers (Basel)*, 2021, 13: 1060. DOI: 10.3390/cancers13051060.

- [26] SGARBURA O, EVENO C, ALYAMI M, BAKRIN N, GUIRAL D C, CEELLEN W, et al. Consensus statement for treatment protocols in pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J]. *Pleura Peritoneum*, 2022, 7: 1-7.
- [27] BADRUDIN D, SIDERIS L, LEBLOND F A, PICHETTE V, CLOUTIER A S, DROLET P, et al. Rationale for the administration of systemic 5-FU in combination with heated intraperitoneal oxaliplatin[J]. *Surg Oncol*, 2018, 27: 275-279.
- [28] RODOLFINO E, MARCO M D, ILOTA, IEZZI R, GUI B, AVESANI G, et al. Radiologist checklist for selecting patients to undergo PIPAC (pressurized intraperitoneal aerosol chemotherapy)[J/OL]. *Life (Basel)*, 2021, 11: 941. DOI: 10.3390/life11090941.
- [29] ALYAMI M, HÜBNER M, GRASS F, BAKRIN N, VILLENEUVE L, LAPLACE N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications[J/OL]. *Lancet Oncol*, 2019, 20: e368-e377. DOI: 10.1016/S1470-2045(19)30318-3.
- [30] BALMER A, CLERC D, TOUSSAINT L, SGARBURA O, TAÏBI A, HÜBNER M, et al. Selection criteria for pressurized intraperitoneal aerosol chemotherapy (PIPAC) treatment in patients with peritoneal metastases[J/OL]. *Cancers (Basel)*, 2022, 14: 2557. DOI: 10.3390/cancers14102557.
- [31] ANSELL J, WARREN N, WALL P, COCKS K, GODDARD S, WHISTON R, et al. Electrostatic precipitation is a novel way of maintaining visual field clarity during laparoscopic surgery: a prospective double-blind randomized controlled pilot study[J]. *Surg Endosc*, 2014, 28: 2057-2065.
- [32] KAKCHEKEEVA T, DEMTRÖDER C, HERATH N I, GRIFFITHS D, TORKINGTON J, SOLAB W, et al. *In vivo* feasibility of electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy (ePIPAC)[J]. *Ann Surg Oncol*, 2016, 23: 592-598.
- [33] GRAVERSEN M, DETLEFSEN S, ELLEBAEK S B, FRISTRUP C, PFEIFFER P, MORTENSEN M B. Pressurized intraperitoneal aerosol chemotherapy with one minute of electrostatic precipitation (ePIPAC) is feasible, but the histological tumor response in peritoneal metastasis is insufficient[J]. *Eur J Surg Oncol*, 2020, 46: 155-159.
- [34] TAÏBI A, FARINHA H T, FONTANIER S D, SAYEDALAMIN Z, HÜBNER M, SGARBURA O. Pressurized intraperitoneal aerosol chemotherapy enhanced by electrostatic precipitation (ePIPAC) for patients with peritoneal metastases[J]. *Ann Surg Oncol*, 2021, 28: 3852-3860.
- [35] PARK S J, LEE E J, LEE H S, KIM J, PARK S, HAM J, et al. Development of rotational intraperitoneal pressurized aerosol chemotherapy to enhance drug delivery into the peritoneum[J]. *Drug Deliv*, 2021, 28: 1179-1187.
- [36] TATE S J, VAN DE SANDE L, CEELLEN W P, TORKINGTON J, PARKER A L. The feasibility of pressurised intraperitoneal aerosolised virotherapy (PIPAV) to administer oncolytic adenoviruses[J/OL]. *Pharmaceutics*, 2021, 13: 2043. DOI: 10.3390/pharmaceutics13122043.
- [37] ELLEBÆK S B, GRAVERSEN M, DETLEFSEN S, LUNDELL L, FRISTRUP C W, PFEIFFER P, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC)-directed treatment of peritoneal metastasis in end-stage colorectal cancer patients[J/OL]. *Pleura Peritoneum*, 2020, 5: 20200109. DOI: 10.1515/pp-2020-0109.
- [38] ROVERS K P, WASSENAAR E C E, LURVINK R J, CREEMERS G J M, BURGER J W A, LOS M, et al. Pressurized intraperitoneal aerosol chemotherapy (oxaliplatin) for unresectable colorectal peritoneal metastases: a multicenter, single-arm, phase II trial (CRC-PIPAC)[J]. *Ann Surg Oncol*, 2021, 28: 5311-5326.
- [39] DEMTRÖDER C, SOLASS W, ZIEREN J, STRUMBERG D, GIGER-PABST U, REYMOND M A. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis[J]. *Colorectal Dis*, 2016, 18: 364-371.
- [40] SIEBERT M, ALYAMI M, MERCIER F, GALLICE C, VILLENEUVE L, LAPLACE N, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in association with systemic chemotherapy and bevacizumab, evaluation of safety and feasibility. A single center comparative study[J]. *Eur J Surg Oncol*, 2021, 47: 139-142.
- [41] LURVINK R J, RAUWERDINK P, ROVERS K P, WASSENAAR E C E, DEENEN M J, NEDEREND J, et al. First-line palliative systemic therapy alternated with electrostatic pressurised intraperitoneal aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases: protocol of a multicentre, single-arm, phase II study (CRC-PIPAC- II)[J/OL]. *BMJ Open*, 2021, 11: e044811. DOI: 10.1136/bmjopen-2020-044811.
- [42] GIRSHALLY R, DEMTRÖDER C, ALBAYRAK N, ZIEREN J, TEMPFER C, REYMOND M A. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy[J/OL].

- World J Surg Oncol, 2016, 14: 253. DOI: 10.1186/s12957-016-1008-0.
- [43] GRAVERSEN M, DETLEFSEN S, FRISTRUP C, PFEIFFER P, MORTENSEN M B. Adjuvant pressurized intraperitoneal aerosol chemotherapy (PIPAC) in resected high-risk colon cancer patients—study protocol for the PIPAC-OPC3 Trial. A prospective, controlled phase 2 study[J/OL]. Pleura Peritoneum, 2018, 3: 20180107. DOI: 10.1515/pp-2018-0107.
- [44] ROBELLA M, HUBNER M, SGARBURA O, REYMOND M, KHOMIAKOV V, DI GIORGIO A, et al. Feasibility and safety of PIPAC combined with additional surgical procedures: PLUS study[J]. Eur J Surg Oncol, 2022, 48: 2212-2217.
- [45] LURVINK R J, ROVERS K P, NIENHUIJS S W, CREEMERS G J, BURGER J W A, DE HINGH I H J. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) in patients with colorectal peritoneal metastases—a systematic review[J]. J Gastrointest Oncol, 2021, 12(Suppl 1): S242-S258.
- [46] TEIXEIRA FARINHA H, GRASS F, LABGAA I, PACHE B, DEMARTINES N, HÜBNER M. Inflammatory response and toxicity after pressurized intraperitoneal aerosol chemotherapy[J]. J Cancer, 2018, 9: 13-20.
- [47] SIEBERT M, ALYAMI M, MERCIER F, GALLICE C, VILLENEUVE L, BÉRARD F, et al. Severe hypersensitivity reactions to platinum compounds post-pressurized intraperitoneal aerosol chemotherapy (PIPAC): first literature report[J]. Cancer Chemother Pharmacol, 2019, 83: 425-430.
- [48] EZANNO A C, MALGRAS B, AOUN O, DELARGE A, DOREILLE A, POCARD M. A severe oxaliplatin immune-induced syndrome after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J]. Pleura Peritoneum, 2022, 7: 35-38.
- [49] THIBAudeau E, BRIANCHON C, RAOUL J L, DUMONT F. Acute respiratory distress syndrome (ARDS) after pressurized intraperitoneal aerosol chemotherapy with oxaliplatin: a case report[J]. Pleura Peritoneum, 2021, 6: 167-170.
- [50] SOLAß W, GIGER-PABST U, ZIEREN J, REYMOND M A. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects[J]. Ann Surg Oncol, 2013, 20: 3504-3511.
- [51] WILLAERT W, SESSINK P, CEELEN W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J]. Pleura Peritoneum, 2017, 2: 121-128.
- [52] GRAVERSEN M, PEDERSEN P B, MORTENSEN M B. Environmental safety during the administration of pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J]. Pleura Peritoneum, 2016, 1: 203-208.
- [53] AMETSBICHLER P, BÖHLANDT A, NOWAK D, SCHIERL R. Occupational exposure to cisplatin/oxaliplatin during pressurized intraperitoneal aerosol chemotherapy (PIPAC)?[J]. Eur J Surg Oncol, 2018, 44: 1793-1799.
- [54] LARROQUE M, ARNAUDGUILHEM C, BOUYSSIERE B, QUENET F, BOUAZZA N, JARLIER M, et al. Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy[J/OL]. Toxicol Appl Pharmacol, 2021, 429: 115694. DOI: 10.1016/j.taap.2021.115694.
- [55] GIRARDOT-MIGLIERINA A, CLERC D, ALYAMI M, VILLENEUVE L, SGARBURA O, REYMOND M A, et al. Consensus statement on safety measures for pressurized intraperitoneal aerosol chemotherapy[J]. Pleura Peritoneum, 2021, 6: 139-149.
- [56] ALYAMI M, SGARBURA O, KHOMYAKOV V, HORVATH P, VIZZIELLI G, SO J, et al. Standardizing training for pressurized intraperitoneal aerosol chemotherapy[J]. Eur J Surg Oncol, 2020, 46: 2270-2275.
- [57] TAIBI A, GEYL S, SALLE H, SALLE L, MATHONNET M, USSEGLIO J, et al. Systematic review of patient reported outcomes (PROs) and quality of life measures after pressurized intraperitoneal aerosol chemotherapy (PIPAC)[J]. Surg Oncol, 2020, 35: 97-105.
- [58] TEIXEIRA FARINHA H, GRASS F, KEFLEYESUS A, ACHTARI C, ROMAIN B, MONTEMURRO M, et al. Impact of pressurized intraperitoneal aerosol chemotherapy on quality of life and symptoms in patients with peritoneal carcinomatosis: a retrospective cohort study[J/OL]. Gastroenterol Res Pract, 2017, 2017: 4596176. DOI: 10.1155/2017/4596176.
- [59] ROTOLO S, GIORGIO A D, CINTONI M, RINNINELLA E, PALOMBARO M, PULCINI G, et al. Body composition and immunonutritional status in patients treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) for gastrointestinal peritoneal metastases: a prospective single-center analysis[J]. Pleura Peritoneum, 2022, 7: 9-17.
- [60] SOLASS W, KURTZ F, STRULLER F, STAEBLER A, BÖSMÜLLER H, KÖNIGSRAINER A, et al. Prognostic value of peritoneal grading regression score (PRGS) in peritoneal metastasis: an exploratory analysis on registry data[J/OL]. Pleura Peritoneum, 2018, 3(s1): A27. DOI: 10.1515/pp-2018-7007.