·述评·

进展期胃癌围手术期治疗全程管理的若干要点

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【摘要】 进展期胃癌围手术期治疗全程管理的理念,主要针对进展期胃癌治疗过程中容易被疏忽或未得到充分重视的临床问题,提出并制定科学合理的诊疗计划,将诊断、治疗、康复等各环节有机整合,避免因多学科参与而缺乏有效衔接的状况。进展期胃癌的围手术期全程管理涉及多学科的专业工作,应始终围绕如何提高根治手术的效率、降低术后肿瘤复发、提高患者远期生存率为唯一目标。本文拟结合目前进展期胃癌患者围手术期诊疗中一些薄弱环节与问题,提出全程管理中应重视的若干要点,包括以下几个方面。(1)术前临床分期与评估:通过内镜与影像学诊断进行正确的术前分期,并制定合理的治疗计划,是实施患者围手术期治疗全程管理的必备条件。(2)腹腔镜探查的临床意义与指征:腹腔镜探查有助于发现腹腔内微小转移灶,避免不必要的剖腹探查,对于已浸润至浆膜或怀疑腹膜转移的进展期胃癌患者,应该常规施行术前腹腔镜探查。(3)应充分重视术前新辅助治疗:近年多项随机对照试验研究证实,术前新辅助化疗能使大多数进展期胃癌患者获益;因此,对于cTNM Ⅲ期与ⅣA期的进展期胃癌患者,应积极开展新辅助治疗。(4)有效预判新辅助化疗的疗效:内镜、多层螺旋CT扫描、PET-CT和液体活检等均有一定的预测价值,可以联合或分别应用以提高预测的准确性。(5)有效预防术后腹膜转移:术中腹腔内大量盥洗、新辅助腹腔内与全身联合化疗、腹腔内温热化疗、术后早期腹腔内化疗与常温腹腔内化疗等都被证实对于预防腹膜转移复发有一定疗效。(6)新辅助治疗患者术后病理评估与TNM再分期的重要性:关键的病理指标是肿瘤退缩程度(TRG)和ypTNM,特别是有无淋巴结转移和转移数量;对已接受新辅助化疗的进展期胃癌患者术后病理达到TRG 0级或ypN_0者,其预后常可与cTNM Ⅰ期患者相媲美。(7)重视术后辅助治疗:术后辅助化疗是进展期胃癌患者围手术期治疗全程管理的重要部分。近来若干研究证实,与单药口服相比,两药联合化疗方案能显著降低D_2胃癌根治术后肿瘤复发与死亡风险,特别是cTNM Ⅲ期患者。(8)强调围手术期营养支持治疗:进展期胃癌患者往往存在不同程度的营养不良,积极给予围手术期营养支持治疗不仅能减少手术并发症,同时也有助于患者完成必须的化疗疗程并最终改善预后。

【关键词】 胃肿瘤,进展期; 围手术期治疗; 全程管理

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Key points of perioperative whole-process management for patients with advanced gastric cancer

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【Abstract】 Perioperative whole-process management (WPM) for patients with advanced gastric cancer (AGC) mainly focuses on some clinical issues which are easily neglected or underappreciated. WPM is helpful in making a scientific and rational therapeutic plan, and avoiding inadequate communication in multi-disciplinary participation, so that the diagnosis, treatment and rehabilitation for AGC patients can be integrated organically. Based on the current clinical practice for AGC patients, eight key issues in WPM should be emphasized. (1) Preoperative clinical staging. An accurate preoperative staging by endoscopy and imaging technique is helpful in setting up a rational therapeutic plan, and is also a prerequisite to start WPM. (2) Indications and value of diagnostic laparoscopy. Laparoscopic exploration is beneficial to find intraperitoneal micro-metastases so as to avoid unnecessary laparotomy. For cases of AGC infiltrating serosal layer or suspected of peritoneal metastasis, preoperative laparoscopic exploration should be routinely performed. (3) Neoadjuvant therapy. Multiple RCT studies have shown that neoadjuvant chemotherapy can benefit

a majority of patients with AGC, improving prognosis and prolonging their overall survival. Therefore, neoadjuvant therapy should be considered first for stage III and IVA AGC patients. (4) Prediction of efficacy in neoadjuvant chemotherapy. Endoscopy, MDCT scan, PET - CT and liquid biopsy have certain predictive value individually, which can be used together or separately to improve the accuracy of prediction. (5) Effective prevention of postoperative peritoneal metastasis. Extensive intraoperative peritoneal lavage (EIPL), neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), and normothermic intraperitoneal chemotherapy (NIPEC) have been shown to be of various efficacy in preventing peritoneal metastases. (6) Prediction of postoperative prognosis of AGC patients. The key pathological indicators are tumor regression grade (TRG) and ypTNM staging, especially if there is lymph node metastasis. Usually for AGC patients who received neoajuvant chemotherapy with TRG 0 or ypN0, their prognosis was comparable to that of patients with cTNM stage I. (7) Postoperative adjuvant chemotherapy. Postoperative adjuvant therapy is always an important part of the WPM management of AGC patients. Several recent RCT studies have shown that duplet chemotherapy can significantly reduce the risk of death after D2 radical gastrectomy compared to singlet chemotherapy, especially for stage III patients. (8) Perioperative nutritional support. Due to different degrees of malnutrition in AGC patients, enhanced nutritional treatment in the perioperative period can not only reduce surgical complications, but also enable patients to complete necessary course of chemotherapy, and ultimately further improve their survival rate.

【Key words】 Gastric neoplasms, advanced; Perioperative treatment; Whole-process management

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进展期胃癌围手术期治疗全程管理的理念,主要针对进展期胃癌治疗过程中容易被疏忽或未得到充分重视的临床问题,提出并制定科学合理的诊疗计划,将诊断、治疗、康复等各环节有机整合,避免因多学科参与而缺乏有效衔接的状况。进展期胃癌的围手术期全程管理涉及多学科的专业工作,应始终围绕如何提高根治手术的效率,降低术后肿瘤复发,提高患者远期生存率为唯一目标。本文拟结合目前进展期胃癌患者围手术期诊疗中一些薄弱环节与问题,提出全程管理中应重视的若干要点。

一、术前临床分期与评估

胃癌诊疗全程化管理的重点在于,判断肿瘤能否获得根治性切除,筛选出新辅助治疗或转化治疗的合适对象,并为治疗后的再次评估准备基线对比资料。因此,做到正确的术前临床分期、从而制定相应的治疗方案,非常重要。进展期胃癌术前临床分期与评估主要通过术前内镜和超声内镜(endoscopic ultrasonograph, EUS)及影像学诊断结果,初步了解胃原发癌灶浸润深度、淋巴结转移范围和部位、有无远处转移等情况而进行术前临床TNM(cTNM)分期;其主要技术包括内镜+活检病理、EUS、增强多层螺旋(multidetector row computed tomography, MDCT)扫描等。我们早年在术前联合应用EUS与MDCT进行cTNM分期发现,对T、N、M分期及TNM分期判断的准确率分别为91.3%、85.4%、97.8%和83.7%[1]。我们发现,应用EUS鉴别早期胃癌与进展期胃癌的准确率可达95.1%,对早期胃癌淋巴结是否转移判断的准确率为90.9%,敏感性和特异性分别为66.7%和96.3%,表明EUS对早期胃癌术前分期具有较高的临床应用价值[2]。而应用MDCT判断T分期的准确率为73.8%~75.3%,判断淋巴结转移的准确率为78.6%~82.1%,判断肝转移及远处淋巴结转移的准确率为94.5%,由此再次印证,与其他方法相比,MDCT临床应用价值较高,应成为胃癌术前分期的首选手段[3-4]。此外,当其他检查提示可能存在远处淋巴结或血循转移时,可以作PET-CT检查以助确诊。

二、腹腔镜探查的临床意义与指征

鉴于上述诊断技术对腹膜转移判断的局限性,建议对浸润至浆膜或浆膜外的胃癌,应进行腹腔镜探查。开展术前诊断性腹腔镜探查的目的包括:(1)明确有无腹膜等远处转移,特别是常规影像学诊断难以鉴别的微小腹膜转移灶;(2)方便进行腹腔内游离癌细胞(free cancer cell, FCC)检测;(3)进一步明确施行根治性手术的可能性,避免盲目的剖腹探查。Leake等[5]报道,CT或PET-CT诊断胃癌腹腔内转移灶总准确率通常低于腹腔镜检查结果(分别为81.2%、88.2%比89.2%~100%);高达约60%的CT、PET-CT或MRI诊断为M_0的患者,再经腹腔镜探查证实存在不可治愈的远处转移灶;此外,根据腹腔镜诊断结果,有8.5%~59.6%的患者得以改变治疗方案,8.5%~43.8%的患者避免了不必要的剖腹探查(在T_{3-4}患者中该比例高达25%~54%)。李国新团

队通过回顾性分析582例术前均行腹腔镜探查的进展期胃癌($T_{2\sim3}$ 153例、T_4a 262例、T_4b 167例)发现,最终211例(36.3%)依据腹腔镜探查结果改变了原来治疗计划,71例(12.2%)避免了不必要的剖腹探查术[6]。他们同时发现,CT诊断胃癌远处转移的准确率为51.5%,而腹腔镜探查则可提高至86.8%;因而认为,术前腹腔镜探查有助于制定合理的治疗方案,并避免不必要的剖腹探查[6]。术前腹腔镜探查也获得了指南的推荐与认可。美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)强调,对进展期胃癌患者,应采用腹腔镜探查以发现腹腔内隐匿的微小转移灶,且认为其有利于进行腹腔内FCC的检测[7];中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)胃癌诊疗指南中提出,对具有腹膜转移高危倾向的或$cT_3\sim T_4aN_{1\sim3}M_0$的患者,应进行诊断性腹腔镜探查,并作为ⅠB证据予以推荐[8]。

三、应充分重视术前新辅助治疗

新辅助治疗可使进展期胃癌患者临床获益,主要表现在:(1)使肿瘤原发灶与转移灶降期,提高R_0切除率;(2)术前患者对化疗(或放疗)的耐受性较好,多能完成有效的治疗剂量与疗程;(3)类似体内药敏试验,有助于了解个体肿瘤对化疗药物的敏感性,指导术后辅助化疗;(4)有助改善预后。近十余年来,欧美等国学者先后发表了胃癌或食管胃结合部癌肿经过术前化疗,有助于改善患者预后的随机对照试验(randomized controlled trial, RCT)报道,诸如MAGIC[9]、FNCLCC & FFCD[10]和FLOT[11]等临床研究;日本临床肿瘤学会(Japan Clinical Oncology Group, JCOG)则针对有转移淋巴结融合成团、腹主动脉旁淋巴结转移、肿瘤直径>7 cm的Borrmann Ⅲ~Ⅳ型胃癌进行了一系列术前化疗相关临床研究,其中JCOG0405[12]、JCOG1002[13]与JCOG0210[14]等研究结果都表明,对于转移淋巴结融合、腹主动脉旁淋巴结转移与皮革胃等胃癌患者,先行术前化疗再予以根治性手术,可使疗效有较大改善。

2019年,有3项针对局部进展期胃癌和食管胃结合部癌围手术期或新辅助化疗的前瞻性、随机化、多中心临床研究结果问世,引发了全球的关注。(1)FLOT研究[11,15]: Al-Batran团队分析了来自德国38家医院716例接受围手术期化疗的胃癌患者,其中356例接受FLOT方案(氟尿嘧啶+亚叶酸钙+奥沙利铂+多西他赛),360例接受ECF/ECX方案(表柔比星+顺铂+卡培他滨);结果发现,FLOT组的中位总生存期为50个月,高于ECF/ECX组(35个月);两组5年总生存率(overall survival, OS)分别为45%与36%;两组不良反应率均为27%;该研究肯定了FLOT方案的临床应用前景。(2)PRODIGY临床研究[16]:韩国学者针对局部进展期胃癌和食管胃结合部癌患者开展研究,其中238例接受术前3个疗程DOS方案[多西他赛+奥沙利铂+替吉奥(S-1)]新辅助化疗后施行D_2胃癌根治术,术后序贯8个疗程口服S-1辅助化疗(CSC组);另246例则直接行D_2胃癌根治术,术后予以8疗程S-1辅助治疗(SC组)。结果发现,CSC组3年疾病无进展生存期(progression-free survival, PFS)达66.3%,5年PFS为60.4%,高于SC组(分别为60.2%和55.6%),差异有统计学意义(P=0.023),提示对于可切除的局部进展期胃癌,DOS术前新辅助化疗序贯根治性手术与S-1辅助化疗可明显延长患者术后PFS。(3)RESOLVE临床研究[17]:季加孚团队的RESOLVE研究是我国第一个针对进展期胃癌围手术期化疗的大型多中心RCT研究,旨在探索新辅助治疗在局部进展期胃癌的价值,寻找最佳的治疗模式及方案。该研究将1 022例患者随机分为3组:A组345例,先行D_2根治术,序贯术后XELOX方案(奥沙利铂+卡培他滨)辅助化疗($D_2\rightarrow$XELOX);B组340例,同样行D_2根治术,但术后改为SOX方案(奥沙利铂+S-1)行辅助化疗($D_2\rightarrow$SOX);C组337例,先行SOX方案术前新辅助化疗,再行D_2根治术并序贯行SOX方案术后辅助化疗(SOX$\rightarrow D_2\rightarrow$SOX)。结果显示,A组3年DFS低于C组(54.78%比62.02%,95%CI:0.62~0.99,P=0.045),A组和B组的3年DFS分别为54.78%与60.29%,提示与术后XELOX方案相比,术前新辅助SOX可提高局部进展期胃癌患者DFS;术后辅助化疗中,SOX非劣于XELOX方案。

由此可见,术前新辅助治疗能提高DFS与中位总生存期,使大多数局部进展期胃癌患者获益。因此,在进展期胃癌治疗的全程管理中,应充分重视术前新辅助治疗。

四、有效预判新辅助化疗的疗效

胃癌属高度异质性肿瘤,生物学行为差异显著,故对新辅助化疗的反应也各异。若能在新辅助化疗初期即能预判治疗的效果,则可决定继续原方案化疗,还是改良给药方案,或提前转为手术,从而避免延误合理的治疗选项。目前,临床上预判新辅

助化疗效果的手段包括CT扫描、内镜检查、PET-CT扫描及检测血清肿瘤标志等技术。

长期以来,临床多依据治疗前后CT扫描所见肿瘤体积变化情况,按照RECIST标准来判断新辅助化疗的效果。虽然胃癌癌灶的不规则形态难以精准测量、或者化疗后癌灶内出现纤维化改变使得瘤体体积变化不明显等因素,都可能影响CT扫描对化疗效果的正确评估,但是鉴于CT扫描的普及与方便易行,其迄今仍是临床最常用的评估手段。对比新辅助化疗前与2~3个疗程后CT扫描图像中癌灶的碘浓度变化或碘摄取值,可以较敏感地预判癌灶组织退缩的情况,并可与病理学检测结果高度吻合。上海交通大学医学院附属瑞金医院影像诊断团队对比治疗前后CT扫描癌灶内碘总浓度值发现,CT门脉相癌灶内碘值减少≥64%者,与病理学肿瘤退缩程度(tumor regression grading,TRG)达到很高的一致性,且获得较理想的PFS;反之,治疗前后碘测值差别不大者,预示TRG、PFS与预后均欠佳[18]。我国北京大学肿瘤医院与郑州大学第一附属医院的研究都获得类似研究结果[19-20]。

近年,治疗前后经内镜检查评估正日益受到重视。内镜评估主要依据对胃内原发癌灶的最大径、溃疡深浅变化等肉眼观察结果判断化疗的效果,其敏感性和准确性与CT扫描相当甚至更优。Tahara等[21]分别采用内镜与CT扫描对进展期胃癌新辅助治疗前后的情况进行评估,结果显示,CT扫描与内镜评估的有效率分别为29%和47%;与CT扫描结果相比较,内镜评估的新辅助化疗有效性与OS及PFS的正相关性更强;同时,内镜评估新辅助化疗无效者的OS很差,且往往伴有远处淋巴结或腹膜转移。同样地,Sugawara等[22]将新辅助治疗前后,内镜下所见胃原发癌灶变化分为肿瘤完全消退、肿瘤部分消退、肿瘤稳定和肿瘤进展4类,发现内镜下肉眼所见癌灶的变化与TRG有高度相关性,提示新辅助化疗后内镜评估达到肿瘤完全消退或部分消退者预后良好。王芳和年亮[23]回顾性分析180例接受新辅助化疗的胃癌患者,发现内镜评估有效者OS和PFS显著高于CT评估有效者,且多因素生存分析结果显示,内镜无效者为不良预后的独立危险因素,因此认为,内镜评估可有效预测胃癌化疗患者预后,有效性高于单纯CT扫描的判断。

作为分子影像学诊断的重要手段,应用PET-CT检测肿瘤细胞的代谢变化对预测胃癌新辅助治疗效果也有一定的价值。Song等[24]对144例局部进展期胃癌治疗前进行氟脱氧葡萄糖(fluorodeoxy glucose,FDG) PET-CT检测,结果发现,癌灶总糖酵解率(total lesion glycolysis,TLG)是影响患者预后的重要因素,高TLG值患者的3年PFS和OS分别为30%和38%,低于低TLG值者(分别为38%和47%;$P<0.05$)。Schneider等[25]则发现,FDG标准摄取值(standardized uptake value, SUV)减少≥35%者,原发癌灶中病理TRG残存肿瘤细胞≤10%的反应率达50%;而SUV值减少<35%者反应率仅为10%;作者还发现,通过新辅助化疗1~2疗程后复查PET-CT,预判疗效的敏感性为90.0%,特异性为47.3%,阳性预测值为50%,阴性预测值为90%,准确率为63.3%;由此特别强调,对于PET-CT复查提示对化疗不敏感者,应即转为手术或调整其他治疗方案。液体活检可以动态观察对肿瘤治疗的效果,主要观察的内容有各类血清肿瘤标志物、循环肿瘤细胞、循环肿瘤DNA和外泌素等,特别经二代测序获得的检测结果可在不同程度上反应药物的敏感性、治疗的效果与判断预后等,临床上已证实可用于预判胃癌新辅助化疗的效果[26-28]。

五、有效预防术后腹膜转移

有10%~20%的进展期胃癌患者,在实行根治性手术时已存在腹膜的微小转移灶,特别当肿瘤已浸润至浆膜或浆膜外时,肉眼难以发现的腹膜转移灶或腹腔内FCC发生率更高;40%~60%的进展期胃癌患者,腹膜是其术后癌肿首先复发的部位;50%~70%的胃癌患者,腹膜转移是导致死亡的主要因素。因此,采取有效措施预防进展期胃癌术后腹膜转移复发是改善患者预后的关键之一。目前,临床上较为行之有效的措施包括术中广泛腹腔内灌洗(extensive intraoperative peritoneal lavage, EIPL)、新辅助腹腔内与全身联合化疗(neoadjuvant intraperitoneal and systemic chemotherapy NIPS)、腹腔内温热化疗(hyperthermic intraperitoneal chemotherapy, HIPEC)、术后早期腹腔内化疗(early postoperative intraperitoneal chemotherapy, EPIC)和常温腹腔内化疗(normothermic intraperitoneal chemotherapy, NIPEC)等[29-30]。笔者团队曾对96例进展期胃癌患者进行胃癌根治术+术中HIPEC(治疗组42例)与单纯胃癌根治术(对照组54例)对照研究,术后随访6年发现,治疗组术后腹膜复发率明显低于对照组(19%比47%),且逐年生存率也有显著

改善[31-32]。荟萃分析也发现,针对进展期胃癌患者预防性应用HIPEC能取得较理想的疗效,腹膜复发率更低(7%~27%比14%~45%),总生存期更长(32~35个月比22~28个月),5年OS更高(39%~87%比17%~61%)[33]。由此认为,预防性应用HIPEC是一项行之有效的措施,应该在临床积极开展与普及。此外,EIPL、NIPS、EPIC与NIPEC等方法在预防胃癌术后腹膜转移复发均取得了较好的成绩。韩国研究者发现,接受胃癌根治术+EPIC治疗的进展期胃癌患者5年OS和胃癌相关生存率均优于单纯手术者(分别为47.4%比26.75%, 53.1%比29.7%, P=0.012),EPIC组术后腹膜复发率低于非EPIC组(18.5%比32.2%, P=0.038)[34]。

六、新辅助治疗患者术后病理评估与TNM再分期的重要性

对接受新辅助治疗患者手术后病理学的评估,关系到制定术后合理的辅助治疗方案、随访观察以及对预后判断等。迄今,病理学对TRG分级有不同的标准,但没有实质性的差异[35-36]。依据TRG分级可以对胃癌新辅助治疗后的手术标本进行TNM再分期(ypTNM),两者结合应用是目前评价胃癌新辅助治疗效果的金标准[37]。多项临床研究发现,CT对新辅助疗效的评判结果与患者的OS或PFS并非完全一致,而TRG评判结果对术后OS或PFS则呈现显著的相关性[38-40]。除了胃原发癌灶TRG改变外,有无淋巴结转移或转移数量对患者的预后也至关重要。研究发现,无论治疗前淋巴结有无转移,若新辅助化疗后其淋巴结转移变为阴性(ypN_0),则其预后可与无淋巴结转移者相媲美,因此,应将ypN_0视为评判新辅助治疗疗效最关键的标志,其重要性甚至超过TRG[40-42]。Coimbra等[43]分析239例经新辅助化疗后手术的进展期胃癌患者发现,病理完全缓解者与ypTNM为Ⅰ期者预后相似,5年生存率均达90%;Ikoma等[37]比较354例进展期胃癌患者cTNM分期与ypTNM分期对预后的影响,发现cTNM分期Ⅰ~Ⅳ各期间的生存率相差较小,而ypTNM各分期的逐年生存率则呈现出明显的差异,ypT_0N_0与ypⅠ期患者生存率相近,再次表明,对新辅助治疗的胃癌患者,依据TRG与ypTNM分期评估其预后的重要性。

七、重视术后辅助治疗

术后辅助治疗始终是进展期胃癌患者治疗全程管理中的重要组成部分,是预防肿瘤复发不可缺少的治疗环节。NCCN和CSCO都指出了术后辅助治疗的重要性。针对进展期胃癌患者术后辅助化疗方案较多,单药、两药、甚至三药方案均有。但长期以来,对进展期胃癌患者术后生存率并不令人满意。在2018年美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)会议上,日本学者Yoshida等[44-45]报道了对Ⅲ期进展期胃癌患者根治术后辅助化疗效果的研究,显示,S-1联合多西他赛的3年无复发生存率(relapse-free survival, RFS)达到65.9%,优于对照组的S-1单药口服,且也未增加化疗的不良反应。因此,对实行D_2根治手术后的Ⅲ期胃癌,S-1与多西他赛作为新的辅助化疗方案正获得普遍接受。

同样地,韩国学者Kim等[46]对来自29个医疗中心共计1 898例进展期胃癌患者进行了D_2胃癌根治术后S-1单药口服(S-1组)与卡培他滨+奥沙利铂两药方案(XELOX组)的对比研究,结果发现,在Ⅱa、Ⅱb与Ⅲa期患者中,两组3年DFS相近(均P>0.05);但在Ⅲb与Ⅲc组患者中,S-1组的3年DFS均明显低于XELOX组(分别为65.8%比68.6%, P=0.019;48.4%比66.7%, P=0.002);提示对施行D_2根治术后的Ⅲb与Ⅲc期胃癌,XELOX两药辅助化疗效果优于S-1单药。荟萃分析比较胃癌根治术后辅助治疗化疗联合方案与化疗单药方案的随机三期临床研究显示,普遍认为联合化疗较单药显著降低胃癌D_2根治术后死亡风险(P=0.02)[47]。

八、强调围手术期营养支持治疗

胃癌患者发生营养不良的原因及机制错综复杂,与肿瘤生物学特性及抗肿瘤治疗不良反应均有关。其主要因素包括:(1)进展期胃癌患者存在不同程度消化调节中枢功能障碍,尤其当肿瘤浸润胃壁达到一定范围后所产生的进食疼痛不适,甚至恶心呕吐等,都影响营养摄入;(2)围手术期放化疗的不良反应等引起患者厌食、消化不良、恶性呕吐或腹泻等导致食欲减退,营养摄入和利用度下降,体质量减轻;(3)手术后、尤其是全胃切除后患者,胃的容量减少或丧失,消化道功能紊乱,影响营养物质的吸收与利用。晚期胃癌患者一旦出现消化道梗阻、腹水,则全身营养状况进一步恶化,不但影响治疗效果,且进一步危及生命[48-49]。进展期胃癌患者营养不良可增加手术并发症与病死率。Guo等[50]采用欧洲营养风险筛查标准(Nutritional Risk Screening 2002, NRS 2002)对314例进展期胃癌患者进行前瞻性研究,发现NRS 2002≥3分者手术并发

症和手术病死率均明显高于NRS 2002≤3患者(26.2%比13.8%,2.4%比0)。此外,手术后体质量下降将使得辅助化疗疗程难以完成。Aoyama等[51]认为,患者体质量下降是影响术后化疗疗效非常重要的独立因素,因而强调胃癌根治术后化疗期间必须维持患者的营养与体质量。进展期胃癌患者因营养不良出现的肌少症(主要指骨骼肌丢失),同样被认为是影响预后的重要指标。Nishigori等[52]对177例进展期胃癌患者以骨骼肌指数(skeletal muscle index, SMI)来比较肌少症与预后的关系,发现35例肌少症患者的5年RFS与OS分别为41%和45%,而无肌少症的48例患者则分别为67%和70%,强烈提示进展期胃癌患者有否肌少症是决定其预后的敏感且关键的指标。据此,临床上应对进展期胃癌患者的营养状况给予高度重视,应将给予患者营养支持治疗与维持良好营养状态视为整体治疗的重要组成部分。

综上所述,胃癌围手术全程管理涉及的问题较多,要正确认识并妥善处理好相关问题,在临床工作中不断探索与完善,以进一步提高胃癌综合治疗的效果。

参 考 文 献

[1] 朱正纲,严超,陈克敏,等.内镜超声检查与多层螺旋CT对胃癌术前分期的对比研究[J].中华胃肠外科杂志, 2002,5(2):99-103. DOI:10.3760/cma.j.issn.1671-0274.2002.02.005.

[2] 严超,朱正纲,诸琦,等.内镜超声检查在早期胃癌术前分期的应用[J].中华肿瘤杂志, 2003,25(4):390-393. DOI:10.3760/j.issn.0253-3766.2003.04.023.

[3] Yan C, Zhu ZG, Yan M, et al. Value of multidetector-row computed tomography in the preoperative T and N staging of gastric carcinoma: a large-scale Chinese study[J]. J Surg Oncol, 2009,100(3):205-214. DOI:10.1002/jso.21316.

[4] 严超,朱正纲,燕敏,等.多排CT对胃癌术前分期的单中心大宗病例研究[J].外科理论与实践, 2013,18(4):335-339.

[5] Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer[J]. Gastric Cancer, 2012,15 Suppl 1:S38-S47. DOI:10.1007/s10120-011-0047-z.

[6] Hu YF, Deng ZW, Liu H, et al. Staging laparoscopy improves treatment decision-making for advanced gastric cancer[J]. World J Gastroenterol, 2016,22(5):1859-1868. DOI:10.3748/wjg.v22.i5.1859.

[7] Ajani JA, D'Amico, TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology[J]. JNCCN, 2016, 14(10): 1286-1312. DOI: 10.6004/jnccn.2016.0137.

[8] Wang FH, Shen L, Li J, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer[J]. Cancer Commun (Lond), 2019, 39(1):10. DOI:10.1186/s40880-019-0349-9.

[9] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer[J]. N Engl J Med, 2006,355(1):11-20. DOI:10.1056/NEJMoa055531.

[10] Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial[J]. J Clin Oncol, 2011,29(13):1715-1721. DOI:10.1200/JCO.2010.33.0597.

[11] Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial[J]. Lancet Oncol, 2016, 17(12): 1697-1708. DOI:10.1016/S1470-2045(16)30531-9.

[12] Tsuburaya A, Mizusawa J, Tanaka Y, et al. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis[J]. Br J Surg, 2014, 101(6): 653-660. DOI:10.1002/bjs.9484.

[13] Ito S, Sano T, Mizusawa J, et al. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002[J]. Gastric Cancer, 2017, 20(2): 322-331. DOI:10.1007/s10120-016-0619-z.

[14] Iwasaki Y, Sasako M, Yamamoto S, et al. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210)[J]. J Surg Oncol, 2013, 107(7): 741-745. DOI:10.1002/jso.23301.

[15] Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial[J]. Lancet, 2019,393(10184):1948-1957. DOI:10.1016/S0140-6736(18)32557-1.

[16] Kang YK, Yook JH, Park YK, et al. A phase III open label randomized study of neoadjuvant chemotherapy with docetaxel, oxaliplatin and S-1(DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1 for resectable advanced gastric cancer (PRODIGY study)[J]. Ann Oncol, 2019, 30 Suppl 5: S851-S934.

DOI:10.1093/annonc/mdz394.

[17] Ji J, Shen L, Li Z, et al. LBA42 Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: a randomized phase III trial (RESOLVE trial) [J]. Ann Oncol, 2019,26 Suppl 4:S29-S30. DOI:10.1093/annonc/mdv233.106.

[18] Gao X, Zhang Y, Yuan F, et al. Locally advanced gastric cancer: total iodine uptake to predict the response of primary lesion to neoadjuvant chemotherapy [J]. J Cancer Res Clin Oncol, 2018,144(11):2207-2218. DOI:10.1007/s00432-018-2728-z.

[19] Liu W, Zhu Y, Zhu X, et al. CT-based renal volume measurements: correlation with renal function in patients with renal tumours[J]. Clin Radiol, 2015,70(12):1445-1450. DOI:10.1016/j.crad.2015.09.005.

[20] Li R, Li J, Wang X, et al. Detection of gastric cancer and its histological type based on iodine concentration in spectral CT[J]. Cancer Imaging, 2018,18(1):42. DOI:10.1186/s40644-018-0176-2.

[21] Tahara T, Shibata T, Okubo M, et al. Evaluations of primary lesions by endoscopy clearly distinguishes prognosis in patients with gastric cancer who receive chemotherapy [J]. PLoS One, 2017,12(3):e0173663. DOI:10.1371/journal.pone.0173663.

[22] Sugawara N, Ota K, Terazawa T, et al. Endoscopic evaluation of neoadjuvant chemotherapeutic efficacy in gastric cancer before gastrectomy might be as useful as histological assessment after gastrectomy[J]. Digestion, 2019:1-7. DOI:10.1159/000500907.

[23] 王芳,年亮. 内镜和CT评估病变程度在分析胃癌患者疗效中的价值[J]. 胃肠病学和肝病学杂志,2019,28(1):39-43,47. DOI:10.3969/j.issn.1006-5709.2019.01.010.

[24] Song J, Li Z, Chen P, et al. A 18FDG PET/CT-based volume parameter is a predictor of overall survival in patients with local advanced gastric cancer[J]. Chin J Cancer Res, 2019,31(4):632-640. DOI:10.21147/j.issn.1000-9604.2019.04.07.

[25] Schneider PM, Eshmuminov D, Rordorf T, et al. 18FDG-PET-CT identifies histopathological non-responders after neoadjuvant chemotherapy in locally advanced gastric and cardia cancer: cohort study[J]. BMC Cancer, 2018,18(1):548. DOI:10.1186/s12885-018-4477-4.

[26] Okabe H, Tsunoda S, Hosogi H, et al. Circulating tumor cells as an independent predictor of survival in advanced gastric cancer [J]. Ann Surg Oncol, 2015,22(12):3954-3961. DOI:10.1245/s10434-015-4483-6.

[27] Lee MW, Kim GH, Jeon HK, et al. Clinical application of circulating tumor cells in gastric cancer[J]. Gut Liver, 2019, 13(4):394-401. DOI:10.5009/gnl18484.

[28] Zhou J, Ma X, Bi F, et al. Clinical significance of circulating tumor cells in gastric cancer patients [J]. Oncotarget, 2017, 8(15):25713-25720. DOI:10.18632/oncotarget.14879.

[29] Sugarbaker PH. Intraperitoneal delivery of chemotherapeutic agents for the treatment of peritoneal metastases: current challenges and how to overcome them [J]. Expert Opin Drug Deliv, 2019,16(12):1393-1401. DOI:10.1080/17425247.2019.1693997.

[30] Macrì A, Morabito F. The use of intraperitoneal chemotherapy for gastric malignancies[J]. Expert Rev Anticancer Ther, 2019,19(10):879-888. DOI:10.1080/14737140.2019.1671189.

[31] Zhu ZG, Tang R, Yan M, et al. Efficacy and safety of intraoperative peritoneal hyperthermic chemotherapy for advanced gastric cancer patients with serosal invasion. A long-term follow-up study[J]. Dig Surg, 2006,23(1-2):93-102. DOI:10.1159/000093778.

[32] 朱正纲,汤睿,燕敏,等. 术中腹腔内温热化疗对进展期胃癌的临床疗效研究[J]. 中华胃肠外科杂志,2006,9(1):26-30. DOI:10.3760/cma.j.issn.1671-0274.2006.01.008.

[33] HJF B, Päeva M, van Hillegersberg R, et al. Prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric cancer-a systematic review[J]. J Clin Med, 2019,8(10):1685. DOI:10.3390/jcm8101685.

[34] Kwon OK, Chung HY, Yu W. Early postoperative intraperitoneal chemotherapy for macroscopically serosa-invading gastric cancer patients[J]. Cancer Res Treat, 2014,46(3):270-279. DOI:10.4143/crt.2014.46.3.270.

[35] 王鑫,盛伟琪. 胃癌新辅助治疗后的肿瘤退缩分级评价[J]. 外科理论与实践,2019,24(1):10-14. DOI:10.16139/j.1007-9610.2019.01.003。

[36] 马乾宸,袁菲. 胃癌术前治疗的病理学判效体系[J]. 中华胃肠外科杂志,2018,21(10):1121-1124. DOI:10.3760/cma.j.issn.1671-0274.2018.10.008.

[37] Ikoma N, Blum M, Estrella JS, et al. Evaluation of the American Joint Committee on Cancer 8th edition staging system for gastric cancer patients after preoperative therapy [J]. Gastric Cancer, 2018,21(1):74-83. DOI:10.1007/s10120-017-0743-4.

[38] Tahara T, Shibata T, Okubo M, et al. Histological evaluations of primary lesions are independently associated with prognosis in patients with gastric cancer who receive neoadjuvant chemotherapy[J]. Oncol Lett, 2017,13(6):4892-4896. DOI:10.3892/ol.2017.6040.

[39] Noble F, Lloyd MA, Turkington R, et al. Multicentre cohort study to define and validate pathological assessment of response to neoadjuvant therapy in oesophagogastric adenocarcinoma [J]. Br J Surg, 2017,104(13):1816-1828. DOI:10.1002/bjs.10627.

[40] Smyth EC, Fassan M, Cunningham D, et al. Effect of pathologic tumor response and nodal status on survival in the medical research council adjuvant gastric infusional chemotherapy trial [J]. J Clin Oncol, 2016,34(23):2721-2727. DOI:10.1200/JCO.2015.65.7692.

[41] Ikoma N, Estrella JS, Hofstetter W, et al. Nodal downstaging in gastric cancer patients: promising survival if ypN0 is achieved [J]. Ann Surg Oncol, 2018,25(7):2012-2017. DOI:10.1245/s10434-018-6471-0.

[42] Fujitani K, Mano M, Hirao M, et al. Posttherapy nodal status, not graded histologic response, predicts survival after neoadjuvant chemotherapy for advanced gastric cancer[J]. Ann Surg Oncol, 2012,19(6):1936-1943. DOI:10.1245/s10434-011-2165-6.

[43] Coimbra FJF, de Jesus VHF, Ribeiro HSC, et al. Impact of ypT, ypN, and adjuvant therapy on survival in gastric cancer patients treated with perioperative chemotherapy and radical surgery[J]. Ann Surg Oncol, 2019,26(11):3618-3626. DOI:10.1245/s10434-019-07454-0.

[44] Yoshida K, Kodera Y, Kochi M, et al. A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected Stage III gastric cancer (JACCRO GC-07 trial)[J]. J Clin OncoL, 36 Suppl 15:S4007. DOI:10.1200/JCO.2018.36.15_suppl.4007.

[45] Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage III gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial[J]. J Clin Oncol, 2019,37(15):1296-1304. DOI:10.1200/JCO.18.01138.

[46] Kim IH, Park SS, Lee CM, et al. Efficacy of adjuvant s-1 versus xelox chemotherapy for patients with gastric cancer after D2 lymph node dissection: a retrospective, multi-center observational study[J]. Ann Surg Oncol, 2018,25(5):1176-1183. DOI:10.1245/s10434-018-6375-z.

[47] Iacovelli R, Pietrantonio F, Maggi C, et al. Combination or single-agent chemotherapy as adjuvant treatment of gastric cancer: a systematic review and meta-analysis of published trials[J]. Crit Rev Oncol Hematol, 2016,98:24-28. DOI:10.1016/j.critrevonc.2015.09.002.

[48] Horstman AM, Sheffield-Moore M. Nutritional / metabolic response in older cancer patients[J]. Nutrition, 2015,31(4):605-607. DOI:10.1016/j.nut.2014.12.025.

[49] Musolino C, Allegra A, Pioggia G, et al. Immature myeloid-derived suppressor cells: A bridge between inflammation and cancer (Review)[J]. Oncol Rep, 2017,37(2):671-683. DOI:10.3892/or.2016.5291.

[50] Guo W, Ou G, Li X, et al. Screening of the nutritional risk of patients with gastric carcinoma before operation by NRS 2002 and its relationship with postoperative results[J]. J Gastroenterol Hepatol, 2010,25(4):800-803. DOI:10.1111/j.1440-1746.2009.06198.x.

[51] Aoyama T, Yoshikawa T, Shirai J, et al. Body weight loss after surgery is an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer[J]. Ann Surg Oncol, 2013,20(6):2000-2006. DOI:10.1245/s10434-012-2776-6.

[52] Nishigori T, Tsunoda S, Obama K, et al. Optimal cutoff values of skeletal muscle index to define sarcopenia for prediction of survival in patients with advanced gastric cancer[J]. Ann Surg Oncol, 2018,25(12):3596-3603. DOI:10.1245/s10434-018-6728-7.

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中华医学会系列杂志关于伦理委员会的审批以及知情同意的规范

在临床试验研究中涉及人体数据的研究时,应该在文中说明所采用的试验程序是否已经通过伦理审查委员会(单位或国家)的评估,并著录其审批文号;如果没有正式的伦理委员会,则应在文中描述该研究是否符合2013年修订的《赫尔辛基宣言》(www.wma.net/en/30publications/10policies/b3/index.html)的要求。通常情况下,涉及人的研究包括以下几种:

(1)针对个体采取干预措施,获得相关安全性和(或)有效性的信息:如药物、医疗器械、手术疗法、健康宣教等。

(2)与个体直接接触,通过采血或组织标本、访谈或调查问卷等形式收集个人信息。

(3)收集既往保存的个人信息,涉及隐私且可辨别个人身份。

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