世界华人消化杂志 2013年5月18日; 21(14): 1292-1296
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

辅助治疗与新辅助治疗在胰腺癌治疗中的作用

黄 鹏, 钟翔宇, 徐 艺, 崔云甫

■背景资料
胰腺癌近几年来发病率有所增加, 而手术后患者5年生存率较低, 所以胰腺癌的辅助治疗与新辅助治疗成为近年来研究的热点问题.

黄鹏, 钟翔宇, 徐艺, 崔云甫, 哈尔滨医科大学附属第二医院普外一科 黑龙江省哈尔滨市 150086
黄鹏, 硕士, 主要从事肝胆胰腺外科的临床研究.
黑龙江省科技厅攻关项目, No. GC12C304-1
作者贡献分布: 本文主要由黄鹏完成; 钟翔宇与徐艺收集文献; 崔云甫审校.
通讯作者: 崔云甫, 教授, 主任医师, 博士生导师, 150086, 黑龙江省哈尔滨市南岗区学府路246号, 哈尔滨医科大学附属第二医院普外一科. yfcui777@hotmail.com
收稿日期: 2013-03-04 修回日期: 2013-03-18
接受日期: 2013-03-29 在线出版日期: 2013-05-18

Role of neoadjuvant therapy and adjuvant therapy in treatment of pancreatic cancer

Peng Huang, Xiang-Yu Zhong, Yi Xu, Yun-Fu Cui

Peng Huang, Xiang-Yu Zhong, Yi Xu, Yun-Fu Cui, Department of General Surgery (Division I), the Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang Province, China
Supported by: Department of Science Research Project in Heilongjiang Province, No. GC12C304-1
Correspondence to: Yun-Fu Cui, Professor, Chief Physician, Department of General Surgery (Division I), the Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Nangang District, Harbin 150086, Heilongjiang Province, China. yfcui777@hotmail.com
Received: 2013-03-04 Revised: 2013-03-18
Accepted: 2013-03-29 Published online: 2013-05-18

Abstract

Pancreatic cancer is a highly malignant tumor that has a low resection rate. In Western countries, pancreatic cancer is the fourth cause of death in malignant tumors. Combined therapy is particularly important for the treatment of pancreatic cancer. Preoperative neoadjuvant therapy and postoperative adjuvant therapy are important parts of combined treatment for pancreatic cancer. Adjuvant therapy can improve survival and quality of life of patients with pancreatic cancer, and neoadjuvant therapy can reduce the primary lesion and lymph node metastasis, provide patients with the possibility of surgery to improve radical resection, decrease intraoperative bleeding and postoperative complications, and improve postoperative survival and life quality of patients. This article reviews the role of adjuvant therapy and neoadjuvant therapy in the management of pancreatic cancer.

■同行评议者
肖恩华, 教授, 中南大学湘雅二医院放射教研室

Key Words: Pancreatic cancer; Neoadjuvant therapy; Adjuvant therapy; Gemcitabine; 5-Fluorouracil; Folfirinox; Erlotinib

Huang P, Zhong XY, Xu Y, Cui YF. Role of neoadjuvant therapy and adjuvant therapy in treatment of pancreatic cancer. Shijie Huaren Xiaohua Zazhi 2013; 21(14): 1292-1296
URL: http://www.wjgnet.com/1009-3079/21/1292.asp
DOI: http://dx.doi.org/10.11569/wcjd.v21.i14.1292

摘要

胰腺癌是一种高度恶性的肿瘤. 在西方国家中, 胰腺癌是恶性肿瘤中的第4位死亡原因, 而且胰腺癌的手术切除率低. 所以胰腺癌的综合治疗显得尤为重要. 胰腺癌的术前的新辅助治疗与术后的辅助治疗是治疗胰腺癌的重要组成部分. 通过胰腺癌的辅助治疗, 可以提高胰腺癌患者的生存时间与生活质量. 而胰腺癌的新辅助治疗则可以降低胰腺癌临床病期缩小原发病灶及转移的淋巴结, 为无手术条件的患者提供手术的可能, 提高根治性手术的切除率. 减少术中出血和术后并发症. 提高患者的术后生存率与生活质量. 本文简要介绍了胰腺癌辅助治疗与新辅助治疗的方法.

关键词: 胰腺癌; 辅助治疗; 新辅助治疗; 吉西他滨; 5-氟尿嘧啶; Folfirinox方案; 埃罗替尼

核心提示: 对于胰腺癌来说, 任何单一手段对于胰腺癌的治疗效果都非常有限. 因此需要各个科室间的密切合作. 通过手术、辅助治疗及新辅助治疗等方法, 从根本上提高胰腺癌的治疗水平, 延长患者的生存期, 改善患者的生活质量.

黄鹏, 钟翔宇, 徐艺, 崔云甫. 辅助治疗与新辅助治疗在胰腺癌治疗中的作用. 世界华人消化杂志 2013; 21(14): 1292-1296
URL: http://www.wjgnet.com/1009-3079/21/1292.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i14.1292

0 引言

胰腺癌是一种高度恶性的肿瘤. 在西方国家中,

胰腺癌是恶性肿瘤中的第4位死亡原因[1], 而且患者的5年的生存率低于5%[1-3]. 胰腺癌缺乏特异的症状, 造成了胰腺癌早期诊断与治疗的困难[3,4]. 只有大约10%-20%的患者可早期行根治性手术[1,5], 而且胰腺癌的复发率高. 因此为提高患者的生存时间与生活质量, 胰腺癌的辅助与新辅助治疗显得尤为重要.

1 辅助治疗

为了提高手术后胰腺癌患者的生存时间与生活质量, 系统的放化疗与联合治疗是必不可少的.

1.1 化疗 最早进行胰腺癌术后辅助治疗的是胃肠肿瘤研究组, 他们用5-氟尿嘧啶(5-fluorouracil, 5-Fu)联合放疗来治疗胰腺癌术后的患者, 通过双盲对比试验, 他们得出进行辅助治疗的患者的生存时间与生活质量均比未进行辅助治疗的患者有明显的提高[6].

5-Fu是最早用于进行胰腺癌辅助治疗的药物, 近几年的研究证明胰腺癌术后接受5-Fu治疗的患者, 中位生存时间是19.7 mo, 明显高于未接受治疗患者(14 mo), 而且有其统计学意义[7-11].

吉西他滨的发现被认为是胰腺癌治疗方面的一项重要发现. 吉西他滨在治疗胰腺癌, 尤其是针对已发生转移的胰腺癌患者, 其治疗效果优于5-Fu, 而且使用吉西他滨有较小的不良反应[12-14]. 一项III期临床试验已证明, 单独使用吉西他滨的患者的中位生存时间与1年的生存率均明显高于单独使用5-Fu的患者[15]. 近几年来, 以吉西他滨为主的联合治疗方案逐渐增多, 许多学者认为联合治疗可以提高胰腺癌患者的治疗效果[16-19]. 通过临床试验证明, 使用吉西他滨联合希罗达, 可以明显延长患者生存时间[20,21]. Cunningham等[21]、Herrmann等[20]通过临床试验与Meta分析的结果得出吉西他滨联合希罗达的方案是进展期胰腺癌患者的首选方案.

1.2 联合治疗 对于转移性胰腺癌的患者来说, Folfirinox方案(奥沙利铂+伊立替康+叶酸+氟尿嘧啶)为治疗的首选方案. 其治疗效果优于单用吉西他滨. 在2011年Conroy等[22]所做的临床对比试验证实了这一点. 他们选出342例晚期胰腺癌患者, 并随机分为两组, 一组给予Folfirinox方案进行治疗(奥沙利铂85 mg/m^2、伊立替康180 mg/m^2、叶酸400 mg/m^2、氟尿嘧啶400 mg/m^2, 2 wk/次), 另一组给予吉西他滨1000 mg/m^2, 1次/wk. 使用Folfirinox方案进行治疗的患者的中位生存时间是11.1 mo, 中位无进展生存期为6.4 mo, 而使用吉西他滨的患者的中位生存时间是6.8 mo, 中位无进展生存期为3.3 mo.

1.3 靶向治疗 基于胰腺癌的特殊的生物学行为, 许多研究小组已对胰腺癌的靶向治疗进行了研究. 常见的生物靶点有表皮生长因子受体[23,24]、人类表皮生长因子受体II型[25-29]、血管内皮生长因子[30-32]等. 这些因子在胰腺癌的发生与发展中起着相关作用.

对于表皮生长因子受体而言, 目前已被证明在治疗胰腺癌方面有疗效的是埃罗替尼. 2007年加拿大国家临床试验组运用埃罗替尼联合吉西他滨对569例晚期胰腺癌患者的随机双盲的III期临床试验表明, 埃罗替尼联合吉西他滨相对于安慰剂联合吉西他滨组能明显提高晚期胰腺癌患者的生存率, 不良反应发生率较低, 加拿大国家临床试验组给出的推荐剂量为100 mg/d[33].

2 新辅助治疗

新辅助治疗是指在恶性肿瘤局部实施手术前应用的全身性治疗. 目前鉴于乳腺癌和结直肠癌的新辅助治疗方面所取得了很好的效果, 使得胰腺外科医生对胰腺癌的新辅助治疗有很大的期望.

2.1 新辅助治疗的优势 胰腺癌新辅助治疗的优势有如下几点: (1)有效的术前化疗在减轻多种恶性肿瘤伴随症状的同时也减轻了患者的精神和心理上的不适反应; (2)降低临床(TNM)病期缩小原发病灶及转移的淋巴结, 为无手术条件的患者提供手术的可能, 提高根治性手术的切除率, 由于瘤体缩小可使手术范围相对缩小, 有利于手术中最大限度的保留正常组织; (3)新辅助化疗使手术时肿瘤细胞活力降低, 不易播散入血, 减少手术中转移, 术后并发症的发生, 有利于患者术后恢复; (4)及早预防远处转移的发生, 提高长期生存率; (5)新辅助化疗方案与术后化疗一样, 但效果优于术后化疗等[34-40].

2.2 新辅助治疗的方法 在早期胰腺癌新辅助研究中, Hoffman等[41]对34例患者进行了新辅助治疗. 患者术前先接受50.4 Gy放疗, 并且在放疗第2-5天和第29-32天给予静脉持续滴注5-Fu[1000 mg/(m^2 • d)]的治疗, 在放疗第2天加用丝裂霉素[10 mg/(m^2 • d)]. 新辅助治疗后34例患者中9例患者未接受手术治疗, 25名患者接受了剖腹探查术, 其中11例行根治性胰腺癌切除术切除(包括whipple术和胰体尾切除). 接受新辅助治疗与手术的患者的中位生存时间为45 mo(从明确诊断时算起), 中位无病存活时间为27 mo.

■创新盘点

本文综合阐述了胰腺癌的辅助治疗与新辅助治疗方法, 而非单一的介绍某种治疗方法, 可以指导临床医生对治疗方案的选择, 有助于拓宽临床医生的诊疗思路.

■应用要点
本文通过介绍不同药物(方案)在胰腺癌治疗方面所产生的作用, 使临床医生对胰腺癌的非手术治疗有了初步的认知.

Evans等[38]所用的以吉他西滨为主的治疗方案对胰腺癌有很好的疗效. 在他们所选取的86例患者中, 给予连续7 wk的吉他西滨静注(400 mg/m^2), 并且外加2 wk的放疗(30 Gy). 在进行完新辅助治疗4-6 wk后接受手术治疗. 86例患者中, 有64例接受了胰头十二指肠切除术. 86例患者的中位生存时间是22.7 mo, 5年生存率是27%. 其中接受胰头十二指肠切除术的64例患者的中位生存时间是34 mo, 5年生存率是36%.

Gillen等[42]于2010年做的一项Meta分析表明, 对于早期可切除肿瘤的胰腺癌患者来说, 新辅助治疗对其总体的治疗效果影响不大, 但对于那些早期不可切除肿瘤的胰腺癌患者来说, 其中的33.3%的患者可通过新辅助治疗后进行手术治疗, 而且其术后生存率与早期可切除肿瘤的胰腺癌患者相同, 所以对于早期不可切除肿瘤的胰腺癌患者来说, 新辅助治疗是很有必要的.

2.3 *新辅助治疗的展望* 目前来看, 新辅助治疗在胰腺癌的治疗中作用在日益提高, 并且确实大大改善了胰腺癌的预后效果. 并且对于中晚期患者提高生存时间和对生活质量的改善有很大的益处. 但是, 并非所有的胰腺癌患者都能从新辅助治疗中取得良好的治疗效果, 而且术前的辅助治疗有时会延误病情. 由于新辅助治疗可能诱导大量纤维组织增生, 造成对病情判断的失误、或者增加了手术的难度等的一系列问题. 这些问题亟待我们去解决[43].

3 结论

任何单一手段对于胰腺癌的治疗效果都非常有限. 因此需要各个科室间的密切合作. 通过手术、辅助治疗及新辅助治疗等方法, 从根本上提高胰腺癌的治疗水平, 延长患者的生存期, 改善患者的生活质量[44-48].

4 参考文献

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59: 225-249 [PMID: 19474385 DOI: 10.3322/caac.20006]

2 Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; 8: 82 [PMID: 18373843 DOI: 10.1186/1471-2407-8-82]

3 Sultana A, Tudur Smith C, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: results of secondary end points analyses. *Br J Cancer* 2008; 99: 6-13 [PMID: 18577990 DOI: 10.1038/sj.bjc.6604436]

4 Stathis A, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. *Nat Rev Clin Oncol* 2010; 7: 163-172 [PMID: 20101258 DOI: 10.1038/nrclinonc.2009.236]

5 Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. *Ann Surg* 2007; 246: 173-180 [PMID: 17667493 DOI: 10.1097/SLA.0b013e3180691579]

6 Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985; 120: 899-903 [PMID: 4015380 DOI: 10.1001/archsurg.1985.01390320023003]

7 Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; 358: 1576-1585 [PMID: 11716884 DOI: 10.1016/S0140-6736(01)06651-X]

8 Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]

9 Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Büchler MW. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 2009; 100: 246-250 [PMID: 19127260 DOI: 10.1038/sj.bjc.6604838]

10 Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; 25: 2607-2615 [PMID: 17577041 DOI: 10.1200/JCO.2006.09.2551]

11 Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. *JAMA* 1985; 253: 2061-2067 [PMID: 2579257 DOI: 10.1001/jama.1985.03350380077025]

12 Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, Grindey GB. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). *Cancer Res* 1990; 50: 4417-4422 [PMID: 2364394]

13 Huang P, Chubb S, Hertel LW, Grindey GB, Plunkett W. Action of 2',2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991; 51: 6110-6117 [PMID: 1718594]

14 Carmichael J, Fink U, Russell RC, Spittle MF, Harris AL, Spiessi G, Blatter J. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 1996; 73: 101-105 [PMID: 8554969 DOI: 10.1038/bjc.1996.18]

15 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson

R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403-2413 [PMID: 9196156]
16 Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002; 20: 3270-3275 [PMID: 12149301 DOI: 10.1200/JCO.2002.11.149]
17 Di Costanzo F, Carlini P, Doni L, Massidda B, Mattioli R, Iop A, Barletta E, Moscetti L, Recchia F, Tralongo P, Gasperoni S. Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). *Br J Cancer* 2005; 93: 185-189 [PMID: 15986036 DOI: 10.1038/sj.bjc.6602640]
18 Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006; 24: 3946-3952 [PMID: 16921047 DOI: 10.1200/JCO.2005.05.1490]
19 Jacobs AD, Otero H, Picozzi VJ, Aboulafia DM. Gemcitabine combined with docetaxel for the treatment of unresectable pancreatic carcinoma. *Cancer Invest* 2004; 22: 505-514 [PMID: 15565807 DOI: 10.1081/CNV-200026392]
20 Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, Saletti P, Bauer J, Figer A, Pestalozzi B, Köhne CH, Mingrone W, Stemmer SM, Tàmas K, Kornek GV, Koeberle D, Cina S, Bernhard J, Dietrich D, Scheithauer W. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007; 25: 2212-2217 [PMID: 17538165 DOI: 10.1200/JCO.2006.09.0886]
21 Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; 27: 5513-5518 [PMID: 19858379 DOI: 10.1200/JCO.2009.24.2446]
22 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; 364: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
23 Kullmann F, Hollerbach S, Dollinger MM, Harder J, Fuchs M, Messmann H, Trojan J, Gäbele E, Hinke A, Hollerbach C, Endlicher E. Cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in first-line metastatic pancreatic cancer: a multicentre phase II study. *Br J Cancer* 2009; 100: 1032-1036 [PMID: 19293797 DOI: 10.1038/sj.bjc.6604983]
24 Philip PA. Improving treatment of pancreatic cancer. *Lancet Oncol* 2008; 9: 7-8 [PMID: 18177814 DOI: 10.1016/S1470-2045(07)70391-1]
25 Novotný J, Petruzelka L, Vedralová J, Kleibl Z, Matous B, Juda L. Prognostic significance of c-erbB-2 gene expression in pancreatic cancer patients. *Neoplasma* 2001; 48: 188-191 [PMID: 11583287]
26 Safran H, Steinhoff M, Mangray S, Rathore R, King TC, Chai L, Berzein K, Moore T, Iannitti D, Reiss P, Pasquariello T, Akerman P, Quirk D, Mass R, Goldstein L, Tantravahi U. Overexpression of the HER-2/neu oncogene in pancreatic adenocarcinoma. *Am J Clin Oncol* 2001; 24: 496-499 [PMID: 11586103 DOI: 10.1097/00000421-200110000-00016]
27 Stoecklein NH, Luebke AM, Erbersdobler A, Knoefel WT, Schraut W, Verde PE, Stern F, Scheunemann P, Peiper M, Eisenberger CF, Izbicki JR, Klein CA, Hosch SB. Copy number of chromosome 17 but not HER2 amplification predicts clinical outcome of patients with pancreatic ductal adenocarcinoma. *J Clin Oncol* 2004; 22: 4737-4745 [PMID: 15570074 DOI: 10.1200/JCO.2004.05.142]
28 Saeki H, Yanoma S, Takemiya S, Sugimasa Y, Akaike M, Yukawa N, Rino Y, Imada T. Antitumor activity of a combination of trastuzumab (Herceptin) and oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2-overexpressing pancreatic cancer. *Oncol Rep* 2007; 18: 433-439 [PMID: 17611667]
29 Safran H, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, Hesketh P, Rathore R, Wolff R, Tantravahi U, Hughes TM, Maia C, Pasquariello T, Goldstein L, King T, Tsai JY, Kennedy T. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. *Cancer Invest* 2004; 22: 706-712 [PMID: 15581051 DOI: 10.1081/CNV-200032974]
30 Ko AH, Youssoufian H, Gurtler J, Dicke K, Kayaleh O, Lenz HJ, Keaton M, Katz T, Ballal S, Rowinsky EK. A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. *Invest New Drugs* 2012; 30: 1597-1606 [PMID: 21629990 DOI: 10.1007/s10637-011-9691-8]
31 Kindler HL, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, Springett GM, Wasan HS, Trask PC, Bycott P, Ricart AD, Kim S, Van Cutsem E. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011; 12: 256-262 [PMID: 21306953 DOI: 10.1016/S1470-2045(11)70004-3]
32 Spano JP, Chodkiewicz C, Maurel J, Wong R, Wasan H, Barone C, Létourneau R, Bajetta E, Pithavala Y, Bycott P, Trask P, Liau K, Ricart AD, Kim S, Rixe O. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet* 2008; 371: 2101-2108 [PMID: 18514303 DOI: 10.1016/S0140-6736(08)60661-3]
33 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA,

■同行评价
本文综述了辅助治疗与新辅助治疗在胰腺癌综合治疗中的作用, 对临床应用有一定参考价值.

Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]

34 Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Charnsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992; 127: 1335-1339 [PMID: 1359851 DOI: 10.1001/archsurg.1992.01420110083017]

35 Jessup JM, Steele G, Mayer RJ, Posner M, Busse P, Cady B, Stone M, Jenkins R, Osteen R. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. *Arch Surg* 1993; 128: 559-564 [PMID: 8098206 DOI: 10.1001/archsurg.1993.01420170093014]

36 Moutardier V, Magnin V, Turrini O, Viret F, Hennekinne-Mucci S, Gonçalves A, Pesenti C, Guiramand J, Lelong B, Giovannini M, Monges G, Houvenaeghel G, Delpero JR. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2004; 60: 437-443 [PMID: 15380577 DOI: 10.1016/j.ijrobp.2004.04.004]

37 Pisters PW, Hudec WA, Lee JE, Raijman I, Lahoti S, Janjan NA, Rich TA, Crane CH, Lenzi R, Wolff RA, Abbruzzese JL, Evans DB. Preoperative chemoradiation for patients with pancreatic cancer: toxicity of endobiliary stents. *J Clin Oncol* 2000; 18: 860-867 [PMID: 10673529]

38 Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerkel GA, Charnsangavej C, Lano EA, Ho L, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; 26: 3496-3502 [PMID: 18640930 DOI: 10.1200/JCO.2007.15.8634]

39 Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerkel GA, Lee JH, Ross WA, Tamm EP, Bhosale PR, Krishnan S, Das P, Ho L, Xiong H, Abbruzzese JL, Evans DB. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; 26: 3487-3495 [PMID: 18640929 DOI: 10.1200/JCO.2007.15.8642]

40 Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, Buckels JA, Bramhall SR. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol* 2007; 14: 2088-2096 [PMID: 17453298 DOI: 10.1245/s10434-007-9384-x]

41 Hoffman JP, Weese JL, Solin LJ, Engstrom P, Agarwal P, Barber LW, Guttmann MC, Litwin S, Salazar H, Eisenberg BL. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. *Am J Surg* 1995; 169: 71-77; discussion 77-78 [PMID: 7818001 DOI: 10.1016/S0002-9610(99)80112-3]

42 Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; 7: e1000267 [PMID: 20422030 DOI: 10.1371/journal]

43 赵玉沛, 徐徕, 丛林. 胰腺癌新辅助治疗的现状与展望. 中华普外科手术学杂志(电子版) 2011; 5: 1-6

44 Greer JB, Brand RE. New developments in pancreatic cancer. *Curr Gastroenterol Rep* 2011; 13: 131-139 [PMID: 21258973 DOI: 10.1007/s11894-011-0175-y]

45 Pisters PW, Wolff RA, Janjan NA, Cleary KR, Charnsangavej C, Crane CN, Lenzi R, Vauthey JN, Lee JE, Abbruzzese JL, Evans DB. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002; 20: 2537-2544 [PMID: 12011133 DOI: 10.1200/JCO.2002.11.064]

46 Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S, Raijman I, Evans DB. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001; 234: 47-55 [PMID: 11420482 DOI: 10.1097/00000658-200107000-00008]

47 Mullen JT, Lee JH, Gomez HF, Ross WA, Fukami N, Wolff RA, Abdalla EK, Vauthey JN, Lee JE, Pisters PW, Evans DB. Pancreaticoduodenectomy after placement of endobiliary metal stents. *J Gastrointest Surg* 2005; 9: 1094-1094; discussion 1104-1105 [PMID: 16269380]

48 赵玉沛, 戴梦华. 胰腺癌的免疫治疗. 中国实用外科杂志 2001; 21: 525-526

编辑 田滢 电编 闫晋利