**Name of Journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 26606**

**Manuscript Type: Review**

**Regional but fatal: intraperitoneal metastasis in gastric cancer**

Wei J *et al.* Intraperitoneal metastasis in gastric cancer

Jia Wei, Nan-Die Wu, Bao-Rui Liu

**Jia Wei, Nan-Die Wu, Bao-Rui Liu,** Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, Nanjing 210008, Jiangsu Province, China

**Author contributions:** Wei J and Wu Nd contributed to this paper withliterature review; Liu BR revised the review and final approval of the final version.

**Supported by** National Natural Science Foundation of China, No. 81220108023, No. 81370064 and No. 81572329; Fundamental Research Funds for the Central Universities, No. 20620140729; Jiangsu Provincial Program of Medical Science, No. BL2012001; and Distinguished Young Investigator Project of Nanjing, No. JQX12002.

**Conflict-of-interest statement:** the authors have no conflict of interest related to the manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Bao-rui Liu, MD, PhD,** Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, 321 Zhongshan Road, Nanjing 210008, Jiangsu Province, China. [baoruiliu@nju.edu.cn](mailto:baoruiliu@nju.edu.cn)

**Telephone:** +86-25-83107081

**Fax:** +86-25-83317016

**Received:** April 18, 2016

**Peer-review started:** April 19, 2016

**First decision:** May 12, 2016

**Revised:** May 15, 2016

**Accepted:** June 15, 2016

**Article in press:**

**Published online:**

**Abstract**

Peritoneal carcinomatosisappears to be the most common pattern of metastasis or recurrence and is associated with poor prognosis in gastric cancer patients. Many efforts have been dedicated to improve the survival in patients with peritoneal metastasis. Until now, hyperthermic intraperitoneal chemotherapy is widely accepted strategy in the treatment of peritoneal dissemination. Several phase II-III studies confirmed the combination of cytoreducitve surgery and hyperthermic intraperitoneal chemotherapy obtained prolonger survival in patients with peritoneal carcinomatosis. In addition, proper selection and effective regional treatment in patients with high risk of peritoneal recurrence after resection will further improve prognosis in local advanced gastric cancer patients.

**Key words:** Gastric cancer; Intraperitoneal metastasis; Regional metastasis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The recurrence rate of gastric cancer patients after surgery within 2 years remains 79%. Gastric cancer patients with peritoneal metastases have the median survival time of only 3.1 mo. Understanding the influence of peritoneal metastasis on survival in gastric cancer patients, the potential molecular mechanism of peritoneal metastasis, and individualized treatment of patients that have high risk of peritoneal metastasis will be essential to select effective treatment strategies in advanced gastric cancer patients. In this review, we summarized translational and clinical researches on peritoneal carcinomatosis, providing comprehensive information to better understand the fatal role of peritoneal metastasis in gastric cancer.

Wei J, Wu ND, Liu BR. Regional but fatal: intraperitoneal metastasis in gastric cancer. *World J Gastroenterol* 2016; In press

Gastric adenocarcinoma is the fourth most common cancer and the second leading cause of cancer death worldwide[[1](#_ENREF_1)]. Apart from countries with national screening programs such as Japan and South Korea, most gastric cancer patients present with advanced disease because early-stage tumors are usually asymptomaticand often develop metastatic recurrences even after curative resection. Despite improvements in the surgical treatment of gastric adenocarcinoma, a high recurrence rate persists, with a 5-year overall survival rate for all diagnosed patients of only 24.5% in Europe[[2](#_ENREF_2)] and 40%–60% in Asia[[3](#_ENREF_3),[4](#_ENREF_4)].The most frequent cause of treatment failure following surgery for gastric cancer is peritoneal dissemination, mainly caused by the seeding of free cancer cells from the primary gastric cancer, which is the most common type of spread. Gastric cancer patients with evidence of macroscopic peritoneal carcinomatosis have very poor prognoses, with a median overall survival of 3–6 mo[[5](#_ENREF_5),[6](#_ENREF_6)].

In this review, we aim to summarize the influence of peritoneal metastasis on survival in gastric cancer patients, the potential molecular mechanism of peritoneal metastasis, and individualized treatment of patients that have high risk of peritoneal metastasis.

**Peritoneal metastasis is the most important factor for prognosis in gastric cancer**

The recurrence rate remains high particularly in patients with advanced stage disease. Among patients receiving R0 resection, 79% have documented recurrences within 2 years, and the median time to death from the time of recurrence is6 months[[7](#_ENREF_7)]. Many patients,especiallythose with stage III disease,developlocoreginal recurrence, peritoneal recurrence, or distant metastasis[[8](#_ENREF_8)].Many investigators have analyzed recurrence patterns of gastric cancer patients after curative surgery, but the data have shown variable incidences of these patterns. Schwarz *et al*[[9](#_ENREF_9)] found that the most common pattern was distant metastasis while Eom *et al*[[10](#_ENREF_10)] found hematogenous metastasis to bemost common among patients with early recurrence and locoregional and peritoneal recurrence among patients with late recurrence using acutoff time of 1year after curative resection for patient subgroups. This disagreement was attributed to differences in patient cohorts undergoing evaluation, the cutoffat which recurrence was determined, and the methods for determining recurrence patterns. In addition, autopsy studies revealed only end-stage disease, but not early recurrence patterns, and re-operation series probably reflect early locoregional and peritoneal recurrence. Laparoscopy and peritoneal cytology have beenshown to detect occult metastatic disease not seen onconventional imaging[[11](#_ENREF_11)].

A recent study of1178 patients with metastatic or recurrent gastric cancer showed that about 46% of patients had peritoneal metastases and about 30% had liver metastases[[12](#_ENREF_12)]. Several other clinical studies have reportedrecurrence patterns in a population ofpatientswith early stage to advanced disease[[7](#_ENREF_7),[9](#_ENREF_9),[13-15](#_ENREF_13)], showing that 30%–54% of patients had peritoneal recurrence alone or in combination.

Our unpublisheddata showed in a total number of 349 patients with stage III and IV gastric cancer, peritoneal metastasis was detected as any part of the metastasis/recurrence pattern in 62.8% of the patients. 81.1% of the patients developed metastasis in peritoneal cavity (peritoneal and liver) at the time of recurrence or diagnosis. Furthermore, peritoneal cancerinvolvement is associated with poor prognosis and qualityof life compared with metastasis to other organs. Our research showed stage IV patients with peritoneal metastasis had shorter survival (7.5 mo *vs* 14 mo) and a higher risk of mortality (HR = 2.026, *P* = 0.004).

**Molecular mechanisms of peritoneal metastasis**

Cancer cellsare thought to undergo the following sequential steps toform peritoneal metastases: (1) penetration of canceroustissues into the visceral serosa; (2) exfoliation of the cancercells from the primary tumor; (3) dissemination and survivalof the cancer cells within the abdominal cavity; (4) adhesionof cancer cells to the peritoneum; (5) invasion of cancer cellsthrough the peritoneal membrane; and (6) formation of theperitoneal metastasis[[16](#_ENREF_16)]. However, the mechanisms governing the formation of peritoneal metastasis remain poorly understood.A global expression profile of 21168 genes was analyzed in a gastric cancer cell line established from a primary main tumorand other cell lines established from the metastasis to the peritoneal cavity.They found out that 24 genes of cell adhesion, epithelial markers, drug metabolism and signal transduction were up-regulated and 17 genes of immune response, cell cycle and adhesion were down-regulated[[17](#_ENREF_17)] (Table 1). Loss of hypoxia inducible factor (HIF) -1α may accelerate the development of peritoneal dissemination *via* the upregulation of matrix metalloproteinases (MMP) -1 in gastric cancer cells was manifested in a mouse model[[18](#_ENREF_18)]. MMP-7-positive gastric cancer have significantly poorer overall survival and die more frequently of peritoneal recurrence than those patients with MMP-7-negative tumors in a Japanese cohort[[19](#_ENREF_19)]. Another compared analysis between the parental cell line GC9811 and its highly metastatic peritoneal counterpart, cell line GC9811-P revealed and confirmed that recombinant human S100 calcium binding protein A4 (S100A4) and cadherin-associated protein beta 1 (CTNNB1) were upregulated and phosphatase and tensin homolog deleted on chromosome ten (PTEN) was downregulated in GC9811-P cells. Identification of these differentially expressed genes could contribute to disclose the molecular mechanisms involved and provide new targets for therapeutic intervention to avoid peritoneal dissemination of gastric adenocarcinoma[[20](#_ENREF_20)]. A recent study revealed intraoperative hemorrhages were strongly correlated with peritoneal recurrence, probably due to an increased ability of cancer cells and mesothelial cells to adhere to each other in the presence of factors in plasma[[16](#_ENREF_16)]. Zinc protoporphyrin IX (ZnPPIX)[[21](#_ENREF_21)] androquoishomeobox protein 1 (IRX1)[[22](#_ENREF_22)] were also conformed to inhibit peritoneal metastasis *via* neovascularization.Identification of these differentially expressed genes could contribute to disclose the molecular mechanisms involved and provide new targets for therapeutic intervention to avoid peritoneal dissemination of gastric adenocarcinoma. At present, chemokinereceptor 5 (CCR5) antagonism can reduces the potential for gastric cancer cell dissemination[[23](#_ENREF_23)]. P38- mitogen-activated protein kinase (MAPK) inhibition by targeted small molecule inhibitor was demonstrated to be beneficial in preventing the peritoneal dissemination in poorly differentiated gastric cancer[[24](#_ENREF_24)]. Nevertheless, The molecular mechanisms of peritoneal dissemination need to be further clarifiedto supply more information for peritoneal dissemination therapy.

**Effective treatments for patients with peritoneal metastasis**

Patients with peritoneal carcinomatosis of gastric origin have an extremely bad prognosis. Systemic chemotherapy improves median survival in metastatic gastric cancer to 7–10 mo, but in patients with peritoneal carcinomatosis from gastric cancer the same improvement has not been reported[[25](#_ENREF_25)]. 20%–50% of patients treated with radical surgery will develop postoperatoryperitoneal recurrence[[26](#_ENREF_26)], and intraperitoneal spread of tumor cells is observed in 54% of patients who died of recurrence after surgery in advanced gastric cancer[[27](#_ENREF_27)].

At present, hyperthermic intraperitoneal chemotherapy(HIPEC) is the most widely accepted strategy among the treatment of peritoneal dissemination which is the most frequent metastatic pattern in gastric cancer[[28](#_ENREF_28)]. The theoreticaladvantage of the HIPEC is to add the direct cytotoxic effects of heat to high local concentration ofusedcytostatic drug[[29](#_ENREF_29),[30](#_ENREF_30)]. In additionto the mechanical washing effect, HIPECalso has the theoreticadvantage of delivering a higher anticancer drug concentration into abdominallavagewith reduced systemic toxicity. There are many molecular explanations for the effect of HIPEC. For example, induction of apoptosis, alterations of cell membraneproperty, changes in intracellular proteins and in their synthesis and heat inhibitionof DNA repair enhanced byinhibitors of the cellular heat-shockresponse[[31](#_ENREF_31),[32](#_ENREF_32)].

In gastric cancer patients with peritoneal carcinomatosis, surgical treatments directed at removing the primary lesion of peritoneal dissemination is palliative. The combination ofcytoreductive surgery (CRS) and HIPEC was first described in 1980 by Spratt *et al*[[33](#_ENREF_33)]. In the following years, Sugarbaker and his colleaguesappliedand spread this innovative technique for peritoneal carcinomatosis[[34](#_ENREF_34)]. Phase II-III studies revealed that patients who received CRS plus HIPEC obtained better survival resultsonly if completeness of cytoreduction (CCR-0) resection was achieved. However, the survival benefit of HIPEC remains extremelylow if cytoreductive surgery can not accomplish sufficient down-staging of the carcinomatosis burden[[35-37](#_ENREF_35)]. The largest experience published so far was a retrospective French study involving 159 patients which confirmed this combination advantage in selected CCR0 group of patients[[35](#_ENREF_35)]. The dismal effect of HIPEC in patients withextensive peritoneal carcinomatosis not amenable to downstaging toCCR-0 may be explained by limited drug penetration leading to no anti-tumor effect on the deeply invasive microfoci[[38](#_ENREF_38)]. Thus, drug delivery system with high permeability has the potential perspective role in the treatment of extensive peritoneal carcinomatosis cases[[39](#_ENREF_39)].

**Optional agents for intraperitoneal treatment**

Even multimodal treatment strategieshave been used to improve the prognosis of gastric cancer patientswith peritoneal recurrence, the results remain unsatisfactory[[40](#_ENREF_40)]. The oral anticancer drug S1 is a fluoropyrimidinederivative, combining tegafur with two modulators. A recent meta-analysis showed the use of S1 monotherapywas associated with a significant survival benefit (HR = 0.48; 95%CI: 0.32–0.70; *p* = 0.0002)[[41](#_ENREF_41)]. The advantage of S1 over other chemotherapeuticagents is its ability to attain higher concentrations intraperitoneally, due to thehigher concentrations of 5-FU and CDHP achieved inperitoneal tumors than in plasma[[42](#_ENREF_42),[43](#_ENREF_43)].

In addition to S1, paclitaxel and docetaxel,which binds to tubulin, leading to microtubule stabilization, and mitotic arrest, also have high sensitivityagainst diffuse-type adenocarcinoma, which is a commontype of peritoneal tumor. And some of these compounds are transported into theperitoneal cavitywhen administered intravenously[[44](#_ENREF_44)].

There have been numerous studies evaluating intraperitoneal drug delivery in gastric cancer patients. Intraperitoneal administration of anticancer drugs enables anextremely high concentration of drugs to directly contact thetarget cancer lesions in the peritoneal cavity. However, intraperitoneal administration of mitomycin C or cisplatin yielded no apparenttherapeutic effects against peritoneal metastasis of gastriccancer due to immediate absorption through the peritoneum[[45](#_ENREF_45)]. In contrast to these drugs, Intraperitoneal administration of paclitaxel was developed to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of the drug in the peritoneal cavity over a long period, and its clinical effects have been verified by a number of convincing clinical trials in ovarian cancer with peritoneal metastasis.These superior results were due to the pharmacokineticadvantage of taxanes after regional delivery[[46](#_ENREF_46)]. Taxanes are absorbed through the openings of lymphaticsystem, such as the milky spots and the stomata which areimportant sites for the formation of peritoneal dissemination[[47](#_ENREF_47)], due to their large molecular weight and fat solubility[[48](#_ENREF_48)]. A phase I/II study of intraperitoneal docetaxel plus S1 for the gastric cancer patients with peritoneal carcinomatosis demonstrated a superior 1-year overall survival rate of 70%, and peritoneal cytology turned negative in 81 % of the patients[[49](#_ENREF_49)]. Fujiwara *et al*[[50](#_ENREF_50)] also reported a median survival of 24.6 mo ingastric cancer with peritoneal carcinomatosis treated with intraperitoneal docetaxel combined with S1.

Although intraperitoneal paclitaxel showed a profoundpharmacokinetic advantage 1000 times higher than systemicadministration, the main problem of intraperitoneal chemotherapy is the limited depth of penetrationof anticancer drugs directly into the tumor.Accordingly, optimum use of paclitaxel may consist ofintraperitoneal and intravenous administration,because intraperitoneal paclitaxel reaches the systemic circulation inonly a small amount[[51](#_ENREF_51)]. Actually, Ishigami *et al*[[48](#_ENREF_48)] established intraperitoneal paclitaxel with S1 plus intravenous paclitaxel assystemic chemotherapy. The phase II study showed an overall response rate of 56% of patients with target lesionsand decrease or disappear of malignant ascites in 62% of the patients.

Another recent phase II trial in serosa-positive gastric cancer patients showed a higher similar response rate of 71.4%, and the 3- and 5-year OS rates of 78.0% and 74.9%, respectively[[52](#_ENREF_52)].

In addition, The efficacy of intraperitoneal irinotecan has been demonstrated in several animal studies. The AUC ratio of SN-38 varied between 3.7 and 14.8 depending on the concentration of administered irinotecan[[53](#_ENREF_53)]. Moreover, pemetrexed has been proven to be an option when used by intraperitoneal in a phase I trial in ovarian cancer[[54](#_ENREF_54)].

Except for chemotherapeutic agents, catumaxomab, a rat-mouse hybrid monoclonal antibody, was registered for the treatmentof malignant ascites of various epithelial cell adhesion molecule (EpCAM) positive malignancies, including ovarian, gastric, breast and colorectal cancer. Two studies[[55](#_ENREF_55),[56](#_ENREF_56)] demonstrate that this drug seems to improve progression-free survival in patients with gastric cancer (median 71 d *vs* 44 d; 𝑃 = 0.03) and that it seems to improve the survival in gastrointestinal anti-EpCAM positive tumors in intraperitoneal use.

**Selected population for intraperitoneal chemotherapy**

Positive peritoneal cytology was classified as metastatic disease (M1) in the 7th edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system for gastric cancer[[57](#_ENREF_57)]. Intraperitoneal free cancer cells isolated during peritoneal washing in patients with gastric cancer have been demonstrated to be significantly and independently related to the prognosis, influencing both recurrence and survival. It is important to prevent peritoneal recurrence aftercurative surgery to improve the prognosis of gastric cancer patients. However, to applythis modality, selection of patients who are at high risk for peritonealrecurrence is crucial. And, the recent trend in treatment is the administration of adjuvant intraperitonealchemotherapy immediately after resection in patientswho are at high risk for peritoneal recurrence[[58](#_ENREF_58),[59](#_ENREF_59)].

Although the precise mechanism drivingperitoneal recurrence remains unclear, the presence of malignantcells in the peritoneum at the time of surgery can lead to peritoneal recurrence[[60](#_ENREF_60),[61](#_ENREF_61)]. Therefore, examination of peritoneal fluids hasemerged as an option for identifying patients who are at high riskfor peritoneal recurrence after curative resection.

Although conventional peritoneal cytology is the standardand reliable method for detecting free cancer cells in theperitoneal wash and for predicting peritoneal metastasis, in large studies approximately 4%-11% of patients will havecytology positive andtherefore that it is not practical or cost-effective to perform in all patients[[62](#_ENREF_62)]. Furthermore, it lacks sensitivity for the detection of residual cancercells and prediction of peritoneal spread[[63](#_ENREF_63),[64](#_ENREF_64)]. A recent prospective clinical study demonstrated conventional cytology is not beneficial for predicting peritoneal recurrence after curative surgery for gastric cancer, because peritoneal washing cytology was not able to predict peritoneal recurrence or survival in gastric cancer patients[[65](#_ENREF_65)].

A study including 655 patients indicated that intraoperatively assessed macroscopic serosalchanges confer a poor prognosis and increased peritoneal recurrence for patients with curatively resectedgastric cancer.Macroscopicserosal changes were defined as changes in color or nodulartexture of the serosal surface on inspection and palpation.Macroscopic assessment of serosalchangesmay be a useful indicator that allows better risk stratificationof patients with resected gastric cancer in terms ofprognosis and peritoneal recurrence[[66](#_ENREF_66)].

Recently, genetic detection using reverse transcriptasepolymerasechain reaction (RT-PCR) analysis has been observed more sensitive than conventionalcytology. Thetarget genes of carcinoembryonic antigen (CEA), heparanase,matrix metalloproteinase-7, cytokeratin 20, telomerase, zinc‑finger E‑box binding homeobox 1 (ZEB1)andmelanoma-associated gene (MAGE) in single or in combination were used as potentmolecular markers[[67-69](#_ENREF_67)].

However, the amplified mRNA may bederived from dead cells or phagocytes that have engulfed tumor cells, and can be released from hematopoietic cellsin an inflammatory context[[70](#_ENREF_70)]. Therefore, the clinical issueof false-positive cases remains to be addressed. Using DNA methylation or flow cytometry to identifyintroperitoneal tumor cells is another valuable alteration for selecting patients who might have the high risk of peritoneal metastasis[[71](#_ENREF_71),[72](#_ENREF_72)].

**Conclusion**

Gastric cancer is the second leading cause of cancer death worldwide and more than half of the gastric cancer patients show disease progression and die of peritoneal carcinomatosis. Proper selection of intraperitoneal chemotherapy in patients with peritoneal metastasis or patients with potential risk of peritoneal recurrence may be a promising approach to improve the prognosis of advanced gastric cancer. Chemotherapeutic agents with maintaining high concentration and high permeability in the peritoneal cavity were ideal choice for intraperitoneal chemotherapy. Moreover, the study of potential biomarkers from peritoneal washing could provide valuable information for a better selection of subsequent treatment combinations.

**References**

1 **Leake PA**, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, Law C, Coburn NG. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer* 2012; **15** Suppl 1: S38-S47 [PMID: 21667136 DOI: 10.1007/s10120-011-0047-z]

2 **Sant M**, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; **45**: 931-991 [PMID: 19171476 DOI: 10.1016/j.ejca.2008.11.018]

3 **Zeng WJ**, Hu WQ, Wang LW, Yan SG, Li JD, Zhao HL, Peng CW, Yang GF, Li Y. Long term follow up and retrospective study on 533 gastric cancer cases. *BMC Surg* 2014; **14**: 29 [PMID: 24886548 DOI: 10.1186/1471-2482-14-29]

4 **Matsuda T**, Saika K. The 5-year relative survival rate of stomach cancer in the USA, Europe and Japan. *Jpn J Clin Oncol* 2013; **43**: 1157-1158 [PMID: 24186939 DOI: 10.1093/jjco/hyt166]

5 **Yonemura Y**, Endou Y, Sasaki T, Hirano M, Mizumoto A, Matsuda T, Takao N, Ichinose M, Miura M, Li Y. Surgical treatment for peritoneal carcinomatosis from gastric cancer. *Eur J Surg Oncol* 2010; **36**: 1131-1138 [PMID: 20933363 DOI: 10.1016/j.ejso.2010.09.006]

6 **Yonemura Y**, Elnemr A, Endou Y, Hirano M, Mizumoto A, Takao N, Ichinose M, Miura M, Li Y. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. *World J Gastrointest Oncol* 2010; **2**: 85-97 [PMID: 21160926 DOI: 10.4251/wjgo.v2.i2.85]

7 **D'Angelica M**, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004; **240**: 808-816 [PMID: 15492562]

8 **Chang JS**, Lim JS, Noh SH, Hyung WJ, An JY, Lee YC, Rha SY, Lee CG, Koom WS. Patterns of regional recurrence after curative D2 resection for stage III (N3) gastric cancer: implications for postoperative radiotherapy. *Radiother Oncol* 2012; **104**: 367-373 [PMID: 22981610 DOI: 10.1016/j.radonc.2012.08.017]

9 **Schwarz RE**, Zagala-Nevarez K. Recurrence patterns after radical gastrectomy for gastric cancer: prognostic factors and implications for postoperative adjuvant therapy. *Ann Surg Oncol* 2002; **9**: 394-400 [PMID: 11986192]

10 **Eom BW**, Yoon H, Ryu KW, Lee JH, Cho SJ, Lee JY, Kim CG, Choi IJ, Lee JS, Kook MC, Park SR, Nam BH, Kim YW. Predictors of timing and patterns of recurrence after curative resection for gastric cancer. *Dig Surg* 2010; **27**: 481-486 [PMID: 21063125 DOI: 10.1159/000320691]

11 **Leake PA**, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, Rowsell C, Coburn NG. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. *Gastric Cancer* 2012; **15** Suppl 1: S27-S37 [PMID: 21809111 DOI: 10.1007/s10120-011-0071-z]

12 **Jo JC**, Ryu MH, Koo DH, Ryoo BY, Kim HJ, Kim TW, Choi KD, Lee GH, Jung HY, Yook JH, Oh ST, Kim BS, Kim JH, Kang YK. Serum CA 19-9 as a prognostic factor in patients with metastatic gastric cancer. *Asia Pac J Clin Oncol* 2013; **9**: 324-330 [PMID: 23176400 DOI: 10.1111/ajco.12019]

13 **Deng J**, Liang H, Wang D, Sun D, Pan Y, Liu Y. Investigation of the recurrence patterns of gastric cancer following a curative resection. *Surg Today* 2011; **41**: 210-215 [PMID: 21264756 DOI: 10.1007/s00595-009-4251-y]

14 **Yoo CH**, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. *Br J Surg* 2000; **87**: 236-242 [PMID: 10671934 DOI: 10.1046/j.1365-2168.2000.01360.x]

15 **Youn HG**, An JY, Choi MG, Noh JH, Sohn TS, Kim S. Recurrence after curative resection of early gastric cancer. *Ann Surg Oncol* 2010; **17**: 448-454 [PMID: 19904573 DOI: 10.1245/s10434-009-0772-2]

16 **Arita T**, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Hiramoto H, Hamada J, Shoda K, Kawaguchi T, Hirajima S, Nagata H, Fujiwara H, Okamoto K, Otsuji E. Increase in peritoneal recurrence induced by intraoperative hemorrhage in gastrectomy. *Ann Surg Oncol* 2015; **22**: 758-764 [PMID: 25201501 DOI: 10.1245/s10434-014-4060-4]

17 **Sakakura C**, Hagiwara A, Nakanishi M, Shimomura K, Takagi T, Yasuoka R, Fujita Y, Abe T, Ichikawa Y, Takahashi S, Ishikawa T, Nishizuka I, Morita T, Shimada H, Okazaki Y, Hayashizaki Y, Yamagishi H. Differential gene expression profiles of gastric cancer cells established from primary tumour and malignant ascites. *Br J Cancer* 2002; **87**: 1153-1161 [PMID: 12402156 DOI: 10.1038/sj.bjc.6600580]

18 **Hiraki M**, Kitajima Y, Kai K, Nakamura J, Hashiguchi K, Noshiro H, Miyazaki K. Knockdown of hypoxia-inducible factor-1α accelerates peritoneal dissemination via the upregulation of MMP-1 expression in gastric cancer cell lines. *Exp Ther Med* 2012; **4**: 355-362 [PMID: 23181099 DOI: 10.3892/etm.2012.600]

19 **Yonemura Y**, Endou Y, Fujita H, Fushida S, Bandou E, Taniguchi K, Miwa K, Sugiyama K, Sasaki T. Role of MMP-7 in the formation of peritoneal dissemination in gastric cancer. *Gastric Cancer* 2000; **3**: 63-70 [PMID: 11984713]

20 **Bai FH**, Wang NJ, Wang J, Yang L, Zhang FM, Yin F, Liang J, Wu KC, Fan DM. Screening and identification of peritoneal metastasis-related genes of gastric adenocarcinoma using a cDNA microarray. *Genet Mol Res* 2012; **11**: 1682-1689 [PMID: 22782588 DOI: 10.4238/2012.June.25.1]

21 **Shang FT**, Hui LL, An XS, Zhang XC, Guo SG, Kui Z. ZnPPIX inhibits peritoneal metastasis of gastric cancer via its antiangiogenic activity. *Biomed Pharmacother* 2015; **71**: 240-246 [PMID: 25960243 DOI: 10.1016/j.biopha.2015.03.005]

22 **Jiang J**, Liu W, Guo X, Zhang R, Zhi Q, Ji J, Zhang J, Chen X, Li J, Zhang J, Gu Q, Liu B, Zhu Z, Yu Y. IRX1 influences peritoneal spreading and metastasis via inhibiting BDKRB2-dependent neovascularization on gastric cancer. *Oncogene* 2011; **30**: 4498-4508 [PMID: 21602894 DOI: 10.1038/onc.2011.154]

23 **Mencarelli A**, Graziosi L, Renga B, Cipriani S, D'Amore C, Francisci D, Bruno A, Baldelli F, Donini A, Fiorucci S. CCR5 Antagonism by Maraviroc Reduces the Potential for Gastric Cancer Cell Dissemination. *Transl Oncol* 2013; **6**: 784-793 [PMID: 24466382]

24 **Graziosi L**, Mencarelli A, Santorelli C, Renga B, Cipriani S, Cavazzoni E, Palladino G, Laufer S, Burnet M, Donini A, Fiorucci S. Mechanistic role of p38 MAPK in gastric cancer dissemination in a rodent model peritoneal metastasis. *Eur J Pharmacol* 2012; **674**: 143-152 [PMID: 22119383 DOI: 10.1016/j.ejphar.2011.11.015]

25 **Montori G**, Coccolini F, Ceresoli M, Catena F, Colaianni N, Poletti E, Ansaloni L. The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. *Int J Surg Oncol* 2014; **2014**: 912418 [PMID: 24693422 DOI: 10.1155/2014/912418]

26 **Roviello F**, Marrelli D, Neri A, Cerretani D, de Manzoni G, Pedrazzani C, Cioppa T, Nastri G, Giorgi G, Pinto E. Treatment of peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion (IHCP): postoperative outcome and risk factors for morbidity. *World J Surg* 2006; **30**: 2033-240; discussion 2033-240; [PMID: 17006608 DOI: 10.1007/s00268-006-0038-0]

27 **Fujimoto S**, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999; **85**: 529-534 [PMID: 10091726]

28 **Di Vita M**, Cappellani A, Piccolo G, Zanghì A, Cavallaro A, Bertola G, Bolognese A, Facchini G, D'Aniello C, Di Francia R, Cardì F, Berretta M. The role of HIPEC in the treatment of peritoneal carcinomatosis from gastric cancer: between lights and shadows. *Anticancer Drugs* 2015; **26**: 123-138 [PMID: 25406023 DOI: 10.1097/CAD.0000000000000179]

29 **Desai AD**, Hawksworth GM. Cryopreservation of rat hepatocytes with high attachment efficiency and mixed function oxidase activity post thawing. *Biochem Soc Trans* 1990; **18**: 1214 [PMID: 2088875]

30 **Brücher BL**, Piso P, Verwaal V, Esquivel J, Derraco M, Yonemura Y, Gonzalez-Moreno S, Pelz J, Königsrainer A, Ströhlein M, Levine EA, Morris D, Bartlett D, Glehen O, Garofalo A, Nissan A. Peritoneal carcinomatosis: cytoreductive surgery and HIPEC--overview and basics. *Cancer Invest* 2012; **30**: 209-224 [PMID: 22360361 DOI: 10.3109/07357907.2012.654871]

31 **Hildebrandt B**, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, Felix R, Riess H. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002; **43**: 33-56 [PMID: 12098606]

32 **Eppink B**, Krawczyk PM, Stap J, Kanaar R. Hyperthermia-induced DNA repair deficiency suggests novel therapeutic anti-cancer strategies. *Int J Hyperthermia* 2012; **28**: 509-517 [PMID: 22834701 DOI: 10.3109/02656736.2012.695427]

33 **Spratt JS**, Adcock RA, Sherrill W, Travathen S. Hyperthermic peritoneal perfusion system in canines. *Cancer Res* 1980; **40**: 253-255 [PMID: 7356508]

34 **Sugarbaker PH**, Stuart OA, Yoo D. Strategies for management of the peritoneal surface component of cancer: cytoreductive surgery plus perioperative intraperitoneal chemotherapy. *J Oncol Pharm Pract* 2005; **11**: 111-119 [PMID: 16390599 DOI: 10.1191/1078155205jp157oa]

35 **Glehen O**, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010; **17**: 2370-2377 [PMID: 20336386 DOI: 10.1245/s10434-010-1039-7]

36 **Bozzetti F**, Yu W, Baratti D, Kusamura S, Deraco M. Locoregional treatment of peritoneal carcinomatosis from gastric cancer. *J Surg Oncol* 2008; **98**: 273-276 [PMID: 18726891 DOI: 10.1002/jso.21052]

37 **Graziosi L**, Marino E, Donini A. Role of CRS plus HIPEC in gastric cancer peritoneal carcinomatosis. *J Surg Oncol* 2015; **111**: 248 [PMID: 25279726 DOI: 10.1002/jso.23789]

38 **Fujimoto S**, Takahashi M, Kobayashi K, Kure M, Mutou T, Masaoka H, Ohkubo H. Relation between clinical and histologic outcome of intraperitoneal hyperthermic perfusion for patients with gastric cancer and peritoneal metastasis. *Oncology* 1993; **50**: 338-343 [PMID: 8378028]

39 **Sha H**, Zou Z, Xin K, Bian X, Cai X, Lu W, Chen J, Chen G, Huang L, Blair AM, Cao P, Liu B. Tumor-penetrating peptide fused EGFR single-domain antibody enhances cancer drug penetration into 3D multicellular spheroids and facilitates effective gastric cancer therapy. *J Control Release* 2015; **200**: 188-200 [PMID: 25553823 DOI: 10.1016/j.jconrel.2014.12.039]

40 **Glockzin G**, Piso P. Current status and future directions in gastric cancer with peritoneal dissemination. *Surg Oncol Clin N Am* 2012; **21**: 625-633 [PMID: 23021720 DOI: 10.1016/j.soc.2012.07.002]

41 **Cabalag CS**, Chan ST, Kaneko Y, Duong CP. A systematic review and meta-analysis of gastric cancer treatment in patients with positive peritoneal cytology. *Gastric Cancer* 2015; **18**: 11-22 [PMID: 24890254 DOI: 10.1007/s10120-014-0388-5]

42 **Shitara K**, Mizota A, Matsuo K, Sato Y, Kondo C, Takahari D, Ura T, Tajika M, Muro K. Fluoropyrimidine plus cisplatin for patients with advanced or recurrent gastric cancer with peritoneal metastasis. *Gastric Cancer* 2013; **16**: 48-55 [PMID: 22362376 DOI: 10.1007/s10120-012-0143-8]

43 **Oshima T**, Yamada R, Hatori S, Kunisaki C, Imada T. Pharmacokinetics of S-1 in patients with peritoneal dissemination of gastric cancer. *Oncol Rep* 2006; **16**: 361-366 [PMID: 16820916]

44 **Naitoh H**, Kawaguch A, Yamamoto H, Mekata E, Tan T, Morii H, Chiba M. [Measurement of docetaxel concentration in blood and ascites after drip infusion into each vessel and intraperitoneal cavity of gastric cancer]. *Gan To Kagaku Ryoho* 2004; **31**: 2031-2034 [PMID: 15570934]

45 **Sautner T**, Hofbauer F, Depisch D, Schiessel R, Jakesz R. Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. *J Clin Oncol* 1994; **12**: 970-974 [PMID: 8164049]

46 **Morgan RJ**, Doroshow JH, Synold T, Lim D, Shibata S, Margolin K, Schwarz R, Leong L, Somlo G, Twardowski P, Yen Y, Chow W, Lin P, Paz B, Chu D, Frankel P, Stalter S. Phase I trial of intraperitoneal docetaxel in the treatment of advanced malignancies primarily confined to the peritoneal cavity: dose-limiting toxicity and pharmacokinetics. *Clin Cancer Res* 2003; **9**: 5896-5901 [PMID: 14676112]

47 **Tsujimoto H**, Hagiwara A, Shimotsuma M, Sakakura C, Osaki K, Sasaki S, Ohyama T, Ohgaki M, Imanishi T, Yamazaki J, Takahashi T. Role of milky spots as selective implantation sites for malignant cells in peritoneal dissemination in mice. *J Cancer Res Clin Oncol* 1996; **122**: 590-595 [PMID: 8879256]

48 **Ishigami H**, Kitayama J, Kaisaki S, Hidemura A, Kato M, Otani K, Kamei T, Soma D, Miyato H, Yamashita H, Nagawa H. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. *Ann Oncol* 2010; **21**: 67-70 [PMID: 19605503 DOI: 10.1093/annonc/mdp260]

49 **Fushida S**, Kinoshita J, Kaji M, Hirono Y, Goda F, Yagi Y, Oyama K, Sudo Y, Watanabe Y, Fujimura T. Phase I/II study of intraperitoneal docetaxel plus S-1 for the gastric cancer patients with peritoneal carcinomatosis. *Cancer Chemother Pharmacol* 2013; **71**: 1265-1272 [PMID: 23423490 DOI: 10.1007/s00280-013-2122-0]

50 **Fujiwara Y**, Takiguchi S, Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, Mori M, Doki Y. Intraperitoneal docetaxel combined with S-1 for advanced gastric cancer with peritoneal dissemination. *J Surg Oncol* 2012; **105**: 38-42 [PMID: 21882194 DOI: 10.1002/jso.22057]

51 **Markman M**. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol* 2003; **4**: 277-283 [PMID: 12732164]

52 **Peng YF**, Imano M, Itoh T, Satoh T, Chiba Y, Imamoto H, Tsubaki M, Nishida S, Yasuda T, Furukawa H. A phase II trial of perioperative chemotherapy involving a single intraperitoneal administration of paclitaxel followed by sequential S-1 plus intravenous paclitaxel for serosa-positive gastric cancer. *J Surg Oncol* 2015; **111**: 1041-1046 [PMID: 26060133 DOI: 10.1002/jso.23928]

53 **Turcotte S**, Sideris L, Younan R, Drolet P, Dubé P. Pharmacokinetics of intraperitoneal irinotecan in a pig model. *J Surg Oncol* 2010; **101**: 637-642 [PMID: 20461774 DOI: 10.1002/jso.21569]

54 **Chambers SK**, Chow HH, Janicek MF, Cragun JM, Hatch KD, Cui H, Laughren C, Clouser MC, Cohen JL, Wright HM, Abu Shahin N, Alberts DS. Phase I trial of intraperitoneal pemetrexed, cisplatin, and paclitaxel in optimally debulked ovarian cancer. *Clin Cancer Res* 2012; **18**: 2668-2678 [PMID: 22421191 DOI: 10.1158/1078-0432.CCR-12-0261]

55 **Heiss MM**, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, Dudnichenko AS, Aleknaviciene B, Razbadauskas A, Gore M, Ganea-Motan E, Ciuleanu T, Wimberger P, Schmittel A, Schmalfeldt B, Burges A, Bokemeyer C, Lindhofer H, Lahr A, Parsons SL. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: Results of a prospective randomized phase II/III trial. *Int J Cancer* 2010; **127**: 2209-2221 [PMID: 20473913 DOI: 10.1002/ijc.25423]

56 **Ströhlein MA**, Lordick F, Rüttinger D, Grützner KU, Schemanski OC, Jäger M, Lindhofer H, Hennig M, Jauch KW, Peschel C, Heiss MM. Immunotherapy of peritoneal carcinomatosis with the antibody catumaxomab in colon, gastric, or pancreatic cancer: an open-label, multicenter, phase I/II trial. *Onkologie* 2011; **34**: 101-108 [PMID: 21358214 DOI: 10.1159/000324667]

57 **Washington K**. 7th edition of the AJCC cancer staging manual: stomach. *Ann Surg Oncol* 2010; **17**: 3077-3079 [PMID: 20882416 DOI: 10.1245/s10434-010-1362-z]

58 **Matharu G**, Tucker O, Alderson D. Systematic review of intraperitoneal chemotherapy for gastric cancer. *Br J Surg* 2011; **98**: 1225-1235 [PMID: 21644239 DOI: 10.1002/bjs.7586]

59 **Yan TD**, Black D, Sugarbaker PH, Zhu J, Yonemura Y, Petrou G, Morris DL. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol* 2007; **14**: 2702-2713 [PMID: 17653801 DOI: 10.1245/s10434-007-9487-4]

60 **Kojima N**, Kunieda K, Matsui K, Kato H, Saji S. Evaluation of carcinoembryonic antigen mRNA in living, necrotic, and apoptotic gastric cancer cells by reverse transcriptase-polymerase chain reaction. *Surg Today* 2003; **33**: 839-846 [PMID: 14605956 DOI: 10.1007/s00595-003-2617-0]

61 **To EM**, Chan WY, Chow C, Ng EK, Chung SC. Gastric cancer cell detection in peritoneal washing: cytology versus RT-PCR for CEA transcripts. *Diagn Mol Pathol* 2003; **12**: 88-95 [PMID: 12766613]

62 **De Andrade JP**, Mezhir JJ. The critical role of peritoneal cytology in the staging of gastric cancer: an evidence-based review. *J Surg Oncol* 2014; **110**: 291-297 [PMID: 24850538 DOI: 10.1002/jso.23632]

63 **Bentrem D**, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol* 2005; **12**: 347-353 [PMID: 15915368 DOI: 10.1245/ASO.2005.03.065]

64 **Kodera Y**, Nakanishi H, Ito S, Mochizuki Y, Ohashi N, Yamamura Y, Fujiwara M, Koike M, Tatematsu M, Nakao A. Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: analysis of real time reverse transcriptase-polymerase chain reaction after 5 years of followup. *J Am Coll Surg* 2006; **202**: 231-236 [PMID: 16427547 DOI: 10.1016/j.jamcollsurg.2005.09.008]

65 **Kang KK**, Hur H, Byun CS, Kim YB, Han SU, Cho YK. Conventional cytology is not beneficial for predicting peritoneal recurrence after curative surgery for gastric cancer: results of a prospective clinical study. *J Gastric Cancer* 2014; **14**: 23-31 [PMID: 24765534 DOI: 10.5230/jgc.2014.14.1.23]

66 **Yoo C**, Ryu MH, Park YS, Yoo MW, Park SR, Ryoo BY, Jang SJ, Yook JH, Kim BS, Kang YK. Intraoperatively assessed macroscopic serosal changes in patients with curatively resected advanced gastric cancer: clinical implications for prognosis and peritoneal recurrence. *Ann Surg Oncol* 2015; **22**: 2940-2947 [PMID: 25605515 DOI: 10.1245/s10434-014-4352-8]

67 **Fujiwara Y**, Doki Y, Taniguchi H, Sohma I, Takiguchi S, Miyata H, Yamasaki M, Monden M. Genetic detection of free cancer cells in the peritoneal cavity of the patient with gastric cancer: present status and future perspectives. *Gastric Cancer* 2007; **10**: 197-204 [PMID: 18095074 DOI: 10.1007/s10120-007-0436-5]

68 **Yabusaki N**, Yamada S, Murai T, Kanda M, Kobayashi D, Tanaka C, Fujii T, Nakayama G, Sugimoto H, Koike M, Nomoto S, Fujiwara M, Kodera Y. Clinical significance of zinc-finger E-box binding homeobox 1 mRNA levels in peritoneal washing for gastric cancer. *Mol Clin Oncol* 2015; **3**: 435-441 [PMID: 25798282 DOI: 10.3892/mco.2014.462]

69 **Jeon CH**, Kim IH, Chae HD. Prognostic value of genetic detection using CEA and MAGE in peritoneal washes with gastric carcinoma after curative resection: result of a 3-year follow-up. *Medicine (Baltimore)* 2014; **93**: e83 [PMID: 25192488 DOI: 10.1097/MD.0000000000000083]

70 **Kowalewska M**, Chechlinska M, Nowak R. Carcinoembryonic antigen and cytokeratin 20 in peritoneal cells of cancer patients: are we aware of what we are detecting by mRNA examination? *Br J Cancer* 2008; **98**: 512-53; author reply 514 [PMID: 18195708 DOI: 10.1038/sj.bjc.6604189]

71 **Yu JL**, Lv P, Han J, Zhu X, Hong LL, Zhu WY, Wang XB, Wu YC, Li P, Ling ZQ. Methylated TIMP-3 DNA in body fluids is an independent prognostic factor for gastric cancer. *Arch Pathol Lab Med* 2014; **138**: 1466-1473 [PMID: 25357107 DOI: 10.5858/arpa.2013-0285-OA]

72 **Kitayama J**, Emoto S, Yamaguchi H, Ishigami H, Onoyama H, Yamashita H, Seto Y, Matsuzaki K, Watanabe T. Flow Cytometric Quantification of Intraperitoneal Free Tumor Cells is a Useful Biomarker in Gastric Cancer Patients with Peritoneal Metastasis. *Ann Surg Oncol* 2015; **22**: 2336-2342 [PMID: 25404476 DOI: 10.1245/s10434-014-4238-9]

**P-Reviewer:** Beltran MA, Caboclo JLF, Marrelli D, Nagahara H **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Twenty-four up-regulated and 17 down-regulated genes in gastric cancer cells from malignant ascites in comparison to those from primary lesion**

|  |  |  |
| --- | --- | --- |
| **Gene expression level** | **Gene name** | **Gene function** |
| Down-regulated |  |  |
|  | Nucleobinding 2 | Signalling (apoptosis) |
|  | Acyl-Coenzyme A dehydrogenase | Signalling |
|  | Chaperonin containing TCP1 | Signalling |
|  | FKBP54 | Signalling |
|  | Histone deacetylase 3 | Signalling |
|  | p27kip | Signalling |
|  | PAK-interacting exchange factor alpha | Signalling |
|  | CD4 | Immune response |
|  | IL4 stat | Immune response |
|  | L2 receptor gamma | Immune response |
|  | IGFBP2 | Growth and metabolism |
|  | RAD51 homologue C | Chromosome stability |
|  | Heterogenous nuclear ribonucleoprotein | Cell adhesion |
|  | Integrin β4 | Cell adhesion |
|  | Tubulin beta-1 chain | Cell adhesion |
|  | Death associated protein | Apoptosis |
|  | H2A histone family member L | Apoptosis |
| Up-regulated |  |  |
|  | Dopa decarboxylase | Signalling or progression |
|  | Caveolin-3 | Signalling (modification) |
|  | CD9 | Signalling |
|  | Dystroglycan1 | Signalling |
|  | Inositol triphosphate receptor | Signalling |
|  | LMO 7 | Signalling |
|  | Sodium/hydrogen exchanger, isoform 1 | Signalling |
|  | Cystein protease (legumain) | Invasion |
|  | Myosin 6 | Intracellular organelle transport |
|  | Destrin (actin depolymerising factor) | Interaction with extracellular matrix |
|  | Renal tumour antigen RAGE1 | Immune response |
|  | Aldehyde dehydrogenase | Drug metabolism |
|  | Aldo-keto reductase family 1 | Drug metabolism |
|  | Keratin 14 | Cell adhesion, invasion |
|  | Keratin 7 | Cell adhesion, invasion |
|  | Keratin 8 | Cell adhesion, invasion |
|  | CD44 | Cell adhesion |
|  | Desmoplakin (DPI, DPII) | Cell adhesion |
|  | Galectin 3 (lectin) | Cell adhesion |
|  | Integrin alpha3 | Cell adhesion |
|  | Occludin | Cell adhesion |
|  | S100 A10 (ligand of Annexin II) | Cell adhesion |
|  | Leukocyte elastase inhibitor | Apoptosis |
|  | TGFb-induced antiapoptotic factor | Apoptosis |