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Microarray analysis in gastric cancer: A review

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Core tip: Gastric cancer remains one of the most common malignancies worldwide and has a poor prognosis. Early diagnosis is a key factor in improving the survival rate. No reliable diagnostic biomarker exists for gastric cancer. DNA microarray analysis is one of the new technologies able to measure the expression levels of a large number of genes simultaneously. Specific genes (differently up- or down-regulated) play an important role in the development and progression of gastric cancer. Another recent application of microarray analysis in gastric cancer is the possible tailoring of personalized chemotherapy.

Abstract

Gastric cancer is one of the most common tumors worldwide. Although several treatment options have been developed, the mortality rate is increasing. Lymph node involvement is considered the most reliable prognostic indicator in gastric cancer. Early diagnosis improves the survival rate of patients and increases the likelihood of successful treatment. The most reliable diagnostic method is endoscopic examination, however, it is expensive and not feasible in poorer countries. Therefore, many innovative techniques have been studied to develop a new non-invasive screening test and to identify specific serum biomarkers. DNA microarray analysis is one of the new technologies able to measure the expression levels of a large number of genes simultaneously. It is possible to define the gene expression profile of the tumor and to correlate it with the prognosis and metastasis formation. Several studies in the literature have been published on the role of microarray analysis in gastric cancer and the mechanisms of proliferation and metastasis formation. The aim of this review is to analyze the importance of microarray analysis and its clinical applications to better define the genetic characteristics of gastric cancer and its possible implications in a more decisive treatment.

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DEFINITION AND EPIDEMIOLOGY

Gastric cancer is one of the most common tumors worldwide, although there is a consistent decreasing trend in Europe secondary to diffuse *Helicobacter pylori* (*H. pylori*) eradication therapy^[1]. It is more common in men and in developing countries, with nearly one million new cases diagnosed each year^[2,3].

In the United States, gastric cancer represents approximately 2% of all new tumor cases annually, but is more common in countries such as South Korea where it is the most frequent cancer type, representing 20.8% of all neoplasms. The survival rate at six months is strictly related to the stage at diagnosis, and is around 65% in those diagnosed early and less than 15% in those diagnosed in advanced stages. Metastatic invasion occurs in 80%-90% of patients.

Although several treatment options have been developed, the incidence and mortality rates are increasing^[4].

RISK FACTORS

Risk factors for gastric cancer include^[5]: Age (> 60 years), lifestyle (smoking, alcohol consumption, ingestion of nitrate or nitrite-rich food)^[6], *H. pylori* infection^[7], gastric diseases (Menetrier's disease, autoimmune atrophic gastritis, pernicious anemia, and intestinal metaplasia), genetic factors, personal or familiar history of gastric cancer^[8].

Among these, *H. pylori* infection is considered the main risk factor, and a possible trigger in 65%-80% of gastric cancer cases^[9]. The CagA virulence factor could potentially induce cancer by causing chronic inflammation^[10].

In contrast, antioxidants, such as vitamin A and C, contained in fresh fruits and vegetables, typical of the Mediterranean diet, and green tea are considered protective factors, as they have been linked with a reduction in the prevalence of gastric cancer.

Estrogen is considered a protective factor for gastric cancer, justifying the higher incidence in males compared with females (3:1).

SYMPTOMS

Unfortunately, stomach cancer occurs with very general and non-specific symptoms such as nausea, difficulty in digestion, lack of appetite or difficulty in eating large amounts of food, pain in the upper abdomen, and these symptoms can easily be confused with those of gastritis or gastric ulcer.

Moreover, these symptoms are often wrongly treated with antacids or proton pump inhibitors with an initial improvement in symptoms.

More specific symptoms such as persistent pain, weight loss, anemia, loss of appetite, and iron-deficiency anemia appear in the advanced stages and this often delays the diagnosis.

DIAGNOSIS

Early detection of cancer can reduce the probability of disease progression, advanced cancer, and death, and increase the probability of successful treatment^[11].

Unfortunately, no reliable diagnostic biomarker exists for gastric cancer. Screening for gastric cancer is routinely performed in Eastern countries, where the incidence is much higher than in Western countries.

Diagnosis should be made by gastroscopy or surgical biopsy, reviewed by an experienced pathologist, and should be reported according to the World Health Organization criteria.

Ninety percent of gastric cancers are adenocarcinomas, and according to the Lauren classification are divided into diffuse and intestinal^[12].

Before undergoing surgery it is also necessary to assess possible distant spread of the tumor with either computed tomography scan or ultrasound, and in some

cases endoscopic ultrasonography may also be useful to assess the degree of stomach wall infiltration.

PROGNOSIS

The prognosis of gastric cancer is closely linked to the diffusion stage at diagnosis; 5-year survival is approximately 90% if gastric cancer is detected early, and is less than 10% in patients with advanced stage cancer^[13].

Staging is based on three parameters: parietal infiltration (T), lymph node involvement (N) and the presence of distant metastases (M).

It is well known that correct staging is essential in order to select patients with locally advanced cancer who can be treated peri-operatively and those with early-stage disease who are candidates for immediate surgery or treatment which will result in organ preservation.

Lymph node involvement is considered the most reliable prognostic indicator in gastric cancer, but its detection by all currently available imaging techniques is unreliable^[14].

High mortality is secondary to the low rate of curative resections in locally advanced cancers, which occur in approximately 2/3 of cases at diagnosis, and lead to unsatisfactory results following adjuvant postoperative treatment.

IMPORTANCE OF BIOMARKERS

Early diagnosis is a key factor in the approach to gastric cancer detection in patients who are asymptomatic, as it improves survival rate and increases the likelihood of treatment success. Available treatments include surgery or endoscopic mucosal resection, which may be preceded or followed by radiation and chemotherapy.

The most reliable diagnostic method is endoscopic examination, however, it is not considered a good screening test as it is invasive, expensive and not practicable in poorer countries^[15].

Therefore, many innovative techniques have been studied to develop a new non-invasive screening test and to identify a serum biomarker, which is unfortunately as yet unavailable^[16-18].

A biomarker of gastric cancer could also be useful in helping to clarify cancer-related mechanisms, to identify a new target therapy and monitor treatment response.

Ideal biomarkers for early cancer detection should be expressed in a high percentage of patients with high levels in tumor tissues. Biomarker expression should be constantly elevated during the whole neoplastic process and absent in normal tissue. Moreover, the detection method should be easily performed.

The evolution of proteomic technologies has contributed to the discovery and development of diagnostic tools in the management of cancer through the identification of protein expression in different conditions.

Many target proteins have been proposed as diagnostic biomarkers in different cancer types, such as carcinoembryonic antigen (CEA) for colon cancer, CA-125 for ovarian cancer, alpha-fetoprotein for liver cancer, and

CA-19.9 for prostate and pancreatic cancer. Unfortunately, the specificity and sensitivity (20%-30%) of these biomarkers such as CEA, CA 19-9, and Ca72-4 are not acceptable for gastric cancer^[19].

MICROARRAY

DNA microarray analysis is one of the new technologies in the field of cancer genetics research and can measure the expression levels of large numbers of genes simultaneously.

It is characterized by a collection of microscopic DNA spots attached to a solid surface.

The method comprises several phases: samples are extracted and processed for total RNA extraction, then labeled, hybridized, stained, and scanned using the chip for the human genome. Finally, microarray image data are analyzed by special software. This technique has helped scientists identify which genes are active and which are inactive in different cell types and to understand how these cells function normally and how they are affected when various genes do not function properly. The production of RNA is directly proportional to the activity of the analyzed gene and generates a very bright fluorescent area. Conversely, the less active genes produce less RNA and lower fluorescence. One of the most frequent uses of this technique is to evaluate gene activity at different times such as before and after therapy or to compare two biological conditions, such as disease state *vs* normal state. Clearly there may be higher expression of specific genes in neoplastic tissue compared to normal (up-regulated genes in neoplastic cells) or vice versa (down-regulated genes in neoplastic cells).

The results help to better understand the mechanisms of disease, to identify disease subphenotypes and to predict possible progression. Moreover, this technique could help to assign functions to previously annotated genes, to frame group genes into functional pathways, and to predict the activities of new compounds^[20].

CDNA MICROARRAY IN GASTRIC CANCER

In recent decades, many studies have suggested that genetic alterations play an important role in the development and progression of gastric cancer^[21]. Metastatic dissemination is the culmination of a complex process that matures over a long period, and which involves up- and down-regulation of genes and proteins.

This interaction between genes is thus responsible for tissue invasion, angiogenesis, cell circulation, colonization in secondary organs, and not least, the evasion of host defenses^[22].

Proteolysis, motility and cell adhesion are conventionally considered the local triad of functions necessary for tumor cells to metastasize. These functions are the basis of the transport of tumor cells through tissue barriers. They are regulated by the interaction of a number of proteins inside the cell that send signals to the surface and to cellular and extracellular compartments of the

host. A cascade of cytokines, receptors, enzymes, enzyme inhibitors, and adhesion molecules, simultaneously regulate the cross-talk between the mechanisms of signals at the invasive front.

The metastatic process begins with the detachment of cells from the primary tumor, as the loss of cohesiveness results in cells being easily detached from the primary tumor. Intracellular adhesion molecules (ICAM), vascular cell adhesion molecules, and neural cell adhesion molecules are implicated in this process^[23]. Polymorphism of ICAM has been used as a biomarker for gastric cancer and has been associated with disease progression^[23].

Proteolysis of the extracellular matrix is an essential component of neoplastic invasion: the matrix metalloproteinases (MMP), the activator of plasminogen and plasmin, the cathepsins and eparanase are all involved in this process^[24]. Numerous studies have evaluated the expression of certain metalloproteinases and their correlation with disease progression in gastric cancer using microarray analysis^[24].

Koskensalo *et al*^[25] detected an overexpression of MMP-7 in gastric cancer and suggested that it may be an independent prognostic marker. Zheng *et al*^[26] analyzed over 200 patients with gastric cancer in Japan, and found that the expressions of MMP-2, MMP-9 and VEGF were positively correlated with increased local and distant invasion.

Tumor cells are capable of active movements through the tissues in which they are located as single cells or as small aggregates. The signals that regulate tumor cell motility are mediated by components of the extracellular matrix, typically by integrins, or by factors secreted by the host or by the tumor itself and are recognized by specific receptors expressed on the tumor cell.

It is believed that tumor growth requires the formation of new blood vessels, a process called angiogenesis, and these new blood vessels are derived from pre-existing capillaries and veins. Recently, it was discovered that the proliferation of lymphatic vessels is controlled, at least in part, by two members of the family of vascular endothelial growth factors^[27].

Using microarray techniques which allowed the analysis of gene expression on a large scale it was shown that the genetic profile of metastasis in an individual is similar to the corresponding primary tumor. It was also possible to define the gene expression profile (gene expression signature) of the tumor at diagnosis which was shown to correlate with prognosis and metastasis formation.

Genetic alterations are divided into two classes of genes: oncogenes, whose actions are dominant, and suppressor genes which require that both alleles are inactivated.

Some studies based on the comparison of tumor tissue *vs* normal tissue, have often revealed up-regulation of genes involved in cell proliferation and down-regulation of genes concerned with cell differentiation and homeostasis.

Hippo *et al*^[28] compared, through gene expression analysis using oligonucleotide microarrays, 22 primary human advanced gastric cancer tissues and 8 non-cancerous gastric tissues and identified around 150 genes dif-

ferentially expressed. In particular, genes associated with lymph node metastasis belonged to cell adhesion proteins such as Cadherin and transcription factors such as Oct-2.

A large study which compared gastric adenocarcinoma and non-neoplastic gastric mucosa using cDNA microarray, showed a larger group of genes associated with cell cycle progression in tumors than in non-neoplastic tissues^[29].

Our group recently published a paper on cDNA-microarray analysis as a new tool to predict lymph node metastasis in gastric cancer. In particular we identify gene expression patterns associated with the presence or absence of lymph node metastases in gastric adenocarcinoma. We found seven genes exclusively expressed in N+ and five genes exclusively expressed in N0 patients. The up-regulated genes in cancer specimens belong to cell proliferation and control, transcription and neo-angiogenesis, meanwhile the down-regulated genes were involved in the mechanism of apoptosis and cell differentiation^[30]. Another small study which compared 9 xenograft and 2 primary gastric cancer samples with normal gastric epithelial tissues using cDNA array, found an overexpression of several genes involved in cell cycle control in cancer samples^[31], confirming our results.

More recently, another study evaluated the association between the expression of the trefoil factor family (TFF1-TFF3) involved in mucosal protection, and the clinicopathological characteristics of gastric adenocarcinoma. Interestingly, they observed normal expression of TFF1 in healthy gastric tissue and a reduction in half of the gastric cancer samples. On the other hand, TFF3 was not expressed in normal tissue and highly expressed in tumor samples. They found a correlation between high levels of TFF3 and metastatization, poor prognosis and patient survival^[32]. The authors indicated that an imbalance in the expression of the two genes with a reduction in TFF1 and increased expression of TFF3 play a role in gastric carcinogenesis.

Jin *et al*^[33] analyzed the gene expression profiles of gastric cancer tissue samples and healthy controls using microarray analysis. They found that genes which were up-regulated were involved in cell proliferation, while down-regulated genes controlled the immune response and cellular homeostasis.

Another recent application of microarray analysis in gastric cancer is the possible tailoring of personalized therapy. In advanced and metastatic gastric cancer, conventional chemotherapy has shown limited efficacy. Numerous studies have been published on new treatments for gastric cancer, however, encouraging results have only been observed for trastuzumab and ramucirumab^[34,35].

Trastuzumab is a monoclonal antibody against epidermal growth factor receptor 2. A large study of over 500 patients with gastric cancer and overexpression of HERB2 showed an improved survival rate (greater than 10 mo) in the group treated with chemotherapy (capecitabine/fluorouracil plus cisplatin) in combination with trastuzumab compared to those treated with chemotherapy alone^[36].

Shah *et al*^[37] using cDNA array, analyzed 36 patients with gastric cancer and identified several pathways that were differentially regulated in each gastric cancer subtype

with a plausible biological difference and different behavior.

CONCLUSION

It is well known that patients with a diagnosis of gastric cancer, even if they have the same characteristics of local and distant diffusion, have different prognoses and treatment responses. Obtaining a “real identity card” for each tumor could revolutionize the treatment of cancers. The increased use of microarray analysis in clinical practice is accelerating the understanding of the complex structure and natural history of tumors. Furthermore, its role as a prognostic factor is emerging and it is believed that in the future it may be used in the clinical setting.

However, most of these data originate from a limited number of small studies, thus larger trials are needed in order to better define the role of microarray analysis in clinical practice and its prognostic value.

The use of microarray analysis in gastric cancer can help physicians understand the aggressiveness of different cancers and improve their management.

The possibility of studying the gene expression of a tumor and to correlate this with its clinical characteristics could significantly change therapeutic procedures. The big challenge will be the assessment of the real contribution of research on the clinical aspects of microarrays and molecular data provided by the studies. Therefore, it will be important to propose and develop analytical models able to integrate all the different aspect of tumors such as clinical data, molecular factors (gene expression and functional proteomics), traditional risk factors and parameters of response to current therapies^[38].

Based on various studies, a team of oncologists, surgeons, geneticists, pathologists, biologists, and bioinformaticians, will be necessary in order to realize personalized targeted cancer therapy^[38].

REFERENCES

- 1 **Arnold M**, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, Renahan AG, Forman D, Soerjomataram I. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. *Eur J Cancer* 2013 Oct 8; Epub ahead of print [PMID: 24120180 DOI: 10.1016/j.ejca.2013.09.002]
- 2 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]
- 3 **Ferlay J**, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49**: 1374-1403 [PMID: 23485231 DOI: 10.1016/j.ejca.2012.12.027]
- 4 **Paoletti X**, Oba K, Bang YJ, Bleiberg H, Boku N, Bouché O, Catalano P, Fuse N, Michiels S, Moehler M, Morita S, Ohashi Y, Ohtsu A, Roth A, Rougier P, Sakamoto J, Sargent D, Sasako M, Shitara K, Thuss-Patience P, Van Cutsem E, Burzykowski T, Buyse M. Progression-free survival as a surrogate for overall survival in advanced/recurrent gastric cancer trials: a meta-analysis. *J Natl Cancer Inst* 2013; **105**: 1667-1670 [PMID: 24108811 DOI: 10.1093/jnci/djt269]
- 5 **de Martel C**, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. *Gastroenterol Clin North Am* 2013; **42**: 219-240 [PMID: 23639638 DOI: 10.1016/j.gtc.2013.01.003]
- 6 **Forman D**, Burley VJ. Gastric cancer: global pattern of the

- disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol* 2006; **20**: 633-649 [PMID: 16997150 DOI: 10.1016/j.bpg.2006.04.008]
- 7 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelstein JH, Orentreich N, Sibley RK. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131 [PMID: 1891020]
 - 8 **Lo SS**, Wu CW, Hsieh MC, Kuo HS, Lui WY, P'Eng FK. Relationship between age and clinical characteristics of patients with gastric cancer. *J Gastroenterol Hepatol* 1996; **11**: 511-514 [PMID: 8792301 DOI: 10.1111/j.1440-1746.1996.tb01693.x]
 - 9 **Cid TP**, Fernández MC, Benito Martínez S, Jones NL. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2013; **18** Suppl 1: 12-17 [PMID: 24011239 DOI: 10.1111/hel.12076]
 - 10 **Cover TL**, Peek RM. Diet, microbial virulence, and Helicobacter pylori-induced gastric cancer. *Gut Microbes* 2013; **4**: 482-493 [PMID: 23989802 DOI: 10.4161/gmic.26262]
 - 11 **Etzioni R**, Urban N, Ramsey S, McIntosh M, Schwartz S, Reid B, Radich J, Anderson G, Hartwell L. The case for early detection. *Nat Rev Cancer* 2003; **3**: 243-252 [PMID: 12671663 DOI: 10.1038/nrc1041]
 - 12 **Turner ES**, Turner JR. Expanding the Lauren classification: a new gastric cancer subtype? *Gastroenterology* 2013; **145**: 505-508 [PMID: 23891604 DOI: 10.1053/j.gastro.2013.07.019]
 - 13 **Ohta H**, Noguchi Y, Takagi K, Nishi M, Kajitani T, Kato Y. Early gastric carcinoma with special reference to macroscopic classification. *Cancer* 1987; **60**: 1099-1106 [PMID: 3607727 DOI: 10.1002/1097-0142(19870901)60:5<1099::AID>]
 - 14 **Weber WA**, Ott K. Imaging of esophageal and gastric cancer. *Semin Oncol* 2004; **31**: 530-541 [PMID: 15297944 DOI: 10.1053/j.seminoncol.2004.04.016]
 - 15 **Genta RM**. Screening for gastric cancer: does it make sense? *Aliment Pharmacol Ther* 2004; **20** Suppl 2: 42-47 [PMID: 15335412 DOI: 10.1111/j.1365-2036.2004.02039.x]
 - 16 **Marrelli D**, Roviello F, De Stefano A, Farnetani M, Garosi L, Messano A, Pinto E. Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. *Oncology* 1999; **57**: 55-62 [PMID: 10394126]
 - 17 **Ishigami S**, Natsugoe S, Hokita S, Che X, Tokuda K, Nakajo A, Iwashige H, Tokushige M, Watanabe T, Takao S, Aikou T. Clinical importance of preoperative carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer. *J Clin Gastroenterol* 2001; **32**: 41-44 [PMID: 11154168 DOI: 10.1097/00004836-200101000-00010]
 - 18 **Gaspar MJ**, Arribas I, Coca MC, Díez-Alonso M. Prognostic value of carcinoembryonic antigen, CA 19-9 and CA 72-4 in gastric carcinoma. *Tumour Biol* 2001; **22**: 318-322 [PMID: 11553862 DOI: 10.1159/000050633]
 - 19 **Ebert MP**, Röcken C. Molecular screening of gastric cancer by proteome analysis. *Eur J Gastroenterol Hepatol* 2006; **18**: 847-853 [PMID: 16825900 DOI: 10.1097/00042737-200608000-00007]
 - 20 **DeRisi J**, Penland L, Brown PO, Bittner ML, Meltzer PS, Ray M, Chen Y, Su YA, Trent JM. Use of a cDNA microarray to analyse gene expression patterns in human cancer. *Nat Genet* 1996; **14**: 457-460 [PMID: 8944026]
 - 21 **Peddanna N**, Holt S, Verma RS. Genetics of gastric cancer. *Anticancer Res* 1995; **15**: 2055-2064 [PMID: 8572602]
 - 22 **Corso G**, Seruca R, Roviello F. Gastric cancer carcinogenesis and tumor progression. *Ann Ital Chir* 2012; **83**: 172-176 [PMID: 22595727]
 - 23 **Tian MM**, Sun Y, Li ZW, Wu Y, Zhao AL, Li JY. Polymorphisms of ICAM-1 are associated with gastric cancer risk and prognosis. *World J Gastroenterol* 2012; **18**: 368-374 [PMID: 22294843 DOI: 10.3748/wjg.v18.i4.368]
 - 24 **Yang S**, Zhao Z, Wu R, Lu H, Zhang X, Huan C, Wang C, Wu X, Guan G. Expression and biological relationship of vascular endothelial growth factor-A and matrix metalloproteinase-9 in gastric carcinoma. *J Int Med Res* 2011; **39**: 2076-2085 [PMID: 22289522 DOI: 10.1177/147323001103900603]
 - 25 **Koskensalo S**, Mrena J, Wiksten JP, Nordling S, Kokkola A, Hagström J, Haglund C. MMP-7 overexpression is an independent prognostic marker in gastric cancer. *Tumour Biol* 2010; **31**: 149-155 [PMID: 20300917 DOI: 10.1007/s13277-010-0020-1]
 - 26 **Zheng H**, Takahashi H, Murai Y, Cui Z, Nomoto K, Niwa H, Tsuneyama K, Takano Y. Expressions of MMP-2, MMP-9 and VEGF are closely linked to growth, invasion, metastasis and angiogenesis of gastric carcinoma. *Anticancer Res* 2006; **26**: 3579-3583 [PMID: 17094486]
 - 27 **Huang SM**, Chen TS, Chiu CM, Chang LK, Liao KF, Tan HM, Yeh WL, Chang GR, Wang MY, Lu DY. GDNF increases cell motility in human colon cancer through VEGF-VEGFR1 interaction. *Endocr Relat Cancer* 2014; **21**: 73-84 [PMID: 24165321 DOI: 10.1530/ERC-13-0351]
 - 28 **Hippo Y**, Taniguchi H, Tsutsumi S, Machida N, Chong JM, Fukayama M, Kodama T, Aburatani H. Global gene expression analysis of gastric cancer by oligonucleotide microarrays. *Cancer Res* 2002; **62**: 233-240 [PMID: 11782383]
 - 29 **Chen X**, Leung SY, Yuen ST, Chu KM, Ji J, Li R, Chan AS, Law S, Troyanskaya OG, Wong J, So S, Botstein D, Brown PO. Variation in gene expression patterns in human gastric cancers. *Mol Biol Cell* 2003; **14**: 3208-3215 [PMID: 12925757 DOI: 10.1091/mbc.E02-12-0833]
 - 30 **Ojetti V**, Persiani R, Cananzi FC, Sensi C, Piscaglia AC, Saulnier N, Biondi A, Gasbarrini A, D'Ugo D. cDNA-microarray analysis as a new tool to predict lymph node metastasis in gastric cancer. *World J Surg* 2014; **38**: 2058-2064 [PMID: 24696059 DOI: 10.1007/s00268-014-2529-8]
 - 31 **El-Rifai W**, Frierson HF, Harper JC, Powell SM, Knuutila S. Expression profiling of gastric adenocarcinoma using cDNA array. *Int J Cancer* 2001; **92**: 832-838 [PMID: 11351303 DOI: 10.1002/ijc.1264]
 - 32 **Im S**, Yoo C, Jung JH, Choi HJ, Yoo J, Kang CS. Reduced expression of TFF1 and increased expression of TFF3 in gastric cancer: correlation with clinicopathological parameters and prognosis. *Int J Med Sci* 2013; **10**: 133-140 [PMID: 23329884 DOI: 10.7150/ijms.5500]
 - 33 **Jin Y**, Da W. Screening of key genes in gastric cancer with DNA microarray analysis. *Eur J Med Res* 2013; **18**: 37 [PMID: 24093889 DOI: 10.1186/2047-783X-18-37]
 - 34 **Sanford M**. Trastuzumab: a review of its use in HER2-positive advanced gastric cancer. *Drugs* 2013; **73**: 1605-1615 [PMID: 24057416 DOI: 10.1007/s40265-013-0119-y]
 - 35 **Meza-Junco J**, Sawyer MB. Metastatic gastric cancer - focus on targeted therapies. *Biologics* 2012; **6**: 137-146 [PMID: 22807624 DOI: 10.2147/BTT.S23917]
 - 36 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121]
 - 37 **Shah MA**, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H, Kelsen DP. Molecular classification of gastric cancer: a new paradigm. *Clin Cancer Res* 2011; **17**: 2693-2701 [PMID: 21430069 DOI: 10.1158/1078-0432.CCR-10-2203]
 - 38 **Cho JY**. Molecular diagnosis for personalized target therapy in gastric cancer. *J Gastric Cancer* 2013; **13**: 129-135 [PMID: 24156032]

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