

GASTRIC CANCER – NEW PERSPECTIVE

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Abstract: The article aims to update the approaches of gastric cancer in both epidemiology and biology of this cancer and the modern diagnostic modalities useful in order to choose the best therapeutic solution. Article highlights the particular experience of Chinese medicine school. This studies benefit of substantial study groups, which are best able to draw relevant conclusions.

Cuvinte cheie: cancer gastric, biologie, diagnostic, terapie

Rezumat: Articolul își propune să aducă la zi perspectivele asupra cancerului gastric atât din punct de vedere epidemiologic cât și cu privire la biologia acestui tip de cancer și asupra modalităților de diagnostic modern util în alegerea celor mai bune soluții terapeutice. Articolul evidențiază în special experiența școlii de medicină din China, studiile acesteia beneficiind de loturi de studiu substanțiale, acestea fiind cele mai în măsură pentru elaborarea unor concluzii pertinente.

SCIENTIFIC ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

Gastric cancer epidemiology

Gastric cancer incidence and mortality fell dramatically in the U.S. in recent decades. However, gastric cancer remains a major public health problem, being the 4th among the most common cancers and the second leading cause of cancer mortality (~800,000 per year) after lung cancer.

Demographic trends differ by tumor location and histology. While there has been a marked decline in distal, intestinal type gastric cancers, the incidence of proximal, diffuse type adenocarcinomas of the gastric cardia has been increasing, particularly in the Western countries.

Incidence by tumor sub-site also varies widely based on geographic location, race, and socioeconomic status. Distal gastric cancer predominates in developing countries, among blacks, and in lower socioeconomic groups, whereas proximal tumors are more common in developed countries, among whites, and in higher socio-economic classes. Diverging trends in the incidence of gastric cancer by tumor location suggest that they may represent two diseases with different etiologies.

The main risk factors for distal gastric cancer include *Helicobacter pylori* infection and dietary factors; whereas gastroesophageal reflux disease and obesity play important roles in the development of proximal stomach cancer. (1)

Scientists who have been following the health of more than 120,000 residents of the Netherlands for more than two decades have observed that smoking is linked to two forms of esophageal cancer as well as a form of stomach cancer, and that drinking alcohol is strongly associated with one form of esophageal cancer.

"The results of this study again confirm recommendations for a healthy lifestyle, namely not to smoke and to drink alcohol in moderation, but it also suggests that there must be other risk factors for EAC and GCA. Smoking is a risk factor for both cancers, but since a decreasing part of the population smokes, this cannot explain why the incidence is

rising so rapidly for both cancers in Western countries in recent decades." – Jessie Steevens, M.Sc., of the Department of Epidemiology at Maastricht University, in Maastricht.

Gastric hypoacidity and hypergastrinaemia are seen in several conditions associated with an increased risk of gastric malignancy. Studies using animal models can provide valuable information about risk factors and mechanisms in gastric cancer development as the models allow a high degree of intervention when introducing or eliminating factors possibly affecting carcinogenesis.

Animal models of gastric hypoacidity and hypergastrinaemia provide evidence hypergastrinaemia is a common causative factor in many otherwise diverse settings. In all species where sufficient hypoacidity and hypergastrinaemia have been induced, a proportion of the animals develop malignant lesions in the gastric oxyntic mucosa.

Gastric cancer like almost all other cancers has a molecular genetic basis which relies on disruption in normal cellular regulatory mechanisms regarding cell growth, apoptosis and cell division.

Growing evidence suggests that accumulation of multiple alterations such as activation of proto-oncogenes and inactivation of tumor suppressor genes is responsible for the development and progression of digestive system cancer. Genetic instability of oncogenes such as microsatellite instability (MSI) and loss of heterozygosity (LOH) is probably linked to mutations in genes responsible for tumor-genesis, and they play important roles in tumor clinical pathology. The studies of MSI and LOH of digestive system cancer have been focused on genetic instability of P53, P16 and FHIT, but few studies were seen in gene nm23H1.

The research team led by Prof. Li from Institute of Cell Biology, Zhejiang University used polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) to analyze MSI and LOH of nm23H1 gene, and immunohistochemistry was employed to check the expression of nm23H1 protein.

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Thus novel therapeutic approaches such as gene therapy promise to become the alternative choice of treatment in gastric cancer. In gene therapy, suicide genes, tumor suppressor genes and anti-angiogenesis genes among many others are introduced to cancer cells via vectors. Some of the vectors widely used in gene therapy are Adenoviral vectors.

In the article „FAT10 level in human gastric cancer and its relation with mutant p53 level, lymph node metastasis and TNM staging”(16) the role of FAT10 and mutant p53 in the pathogenesis, severity and prognosis of gastric cancer was revealed.

FAT10, mutant p53 mRNA and protein levels were measured by reverse transcription (RT)-PCR and immunohistochemistry in gastric cancer tissue (n = 62), tumor-adjacent tissue (n = 62) and normal gastric tissue (n = 62). Relation of FAT10 and mutant p53 expression with clinicopathological features and clinical outcomes of gastric cancer patients were analyzed. The FAT10, mutant p53 mRNA and protein levels were significantly higher in gastric cancer than in its adjacent and normal tissue. The FAT10 and mutant p53 levels in gastric cancer tissue were significantly correlated with lymph node metastasis and tumor, nodes, metastasis (TNM) staging. Moreover, the high FAT10 level was associated with the overall survival rate of patients. Multivariate Cox-proportional hazards model analysis showed that mRNA and protein levels of FAT10 and mutant p53, lymph node metastasis, distant metastasis and TNM stage were the independent prognostic factors for gastric cancer.

FAT10 may be involved in gastric carcinogenesis, and is a potential marker for the prognosis of gastric cancer patients.

„Influence of VEGF and Ki-67 expression on biological behavior of gastric cancer” (2) investigated the relationship between expression of vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen Ki-67 and the biological behavior of gastric cancer.

The Ki-67 labeling index (Ki-67-LI) and VEGF expression in tumors were analyzed by immunohistochemistry using specific antibodies. The relationship between each other and their prognostic significance were evaluated.

The Ki67-LI of VEGF positive group (562.8±118.3) was significantly higher than that of negative group (436.8±142.2)(P = 0.005). The prognosis of VEGF positive group was significantly worse than that of negative group. Ki67-LI was significantly correlated with lymph node metastasis (P = 0.027), tumor stage (P = 0.020) and prognosis (P = 0.036).

VEGF promotes tumor angiogenesis and development. High Ki67-LI reflects active proliferation of tumor cells. Both indicate an unfavorable prognosis.

The clinicopathological characteristics of patients with synchronous cancers and those of patients without synchronous cancers were compared in a retrospective study of the National Cancer Center, Korea from December 2000 to December 2004.

Multivariate analysis was performed to identify the risk factors for the presence of a synchronous cancer in gastric cancer patients.

111 of 3291 gastric cancer patients (3.4%) registered in the database had a synchronous cancer. Among these 111 patients, 109 had a single synchronous cancer and 2 patients had two synchronous cancers. The most common form of synchronous cancer was colorectal cancer (42 patients, 37.2%) followed by lung cancer (21 patients, 18.6%).

Multivariate analyses revealed that elderly patients with differentiated early gastric cancer have a higher probability of a synchronous cancer.

A study published in the World Journal of Gastroenterology in 21 May 2009 (Tsutomu Namikawa,

Kazuhiro Hanazaki, Department of Surgery, Kochi Medical School, Japonia) that investigated the clinicopathological features of early gastric cancer with duodenal invasion demonstrated that the incidence of early gastric cancer with duodenal invasion is extremely low, although advanced gastric cancer that arises in the antrum occasionally invades the duodenum. Tumors > 60 mm in size invaded the duodenum more extensively, and the distance of duodenal invasion from the pyloric ring was further in the elevated type than in the depressed type of tumor. There was no significant difference between the length of duodenal invasion and the histological type of the tumor.

Gastric cancer located adjacent to the pyloric ring, even if cancer invasion was confined to the mucosa or submucosa, was more likely to invade the duodenum, thus highlighting the importance of identification of duodenal invasion and emphasising that sufficient duodenal resection with a cancer-free distal surgical margin should be performed in cases of duodenal invasion.

The diagnosis of gastric cancer

In „Diagnostic role of serum interleukin-18 in gastric cancer patients” 68 patients were enrolled in a study at King Chulalongkorn Memorial Hospital during April 2003 to May 2005. Gastric cancer was histologically proven in 51 patients and gastric ulcer in 17 patients. Serum IL-6, IL-10, IL-12, and IL-18 levels were measured by enzyme-linked immunosorbent assay (ELISA). The findings of this study demonstrate that serum IL-6 and IL-18, but not IL-10 and IL-12 levels may be the useful biological markers of clinical correlation and prognostic factor in patients with gastric cancer. Moreover, IL-18 could serve as a diagnostic marker for gastric cancer with a high positive predictive value.

The study **Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer** (4) studied 41 patients with gastric cancer (12 early stage and 29 advanced stage) proved by esophagogastroduodenoscopy and biopsies, preoperatively evaluated with EUS according to TNM /UICC. Pentax EG-3630U/Hitachi EUB-525 echo endoscope with real-time ultrasound imaging linear scanning transducers (7.5 and 5.0 MHz) and Doppler information was used in the current study. EUS staging procedures for tumor depth of invasion (T stage) were performed according to the widely accepted five-layer structure of the gastric wall. All patients underwent surgery.

Diagnostic accuracy of EUS for TNM staging of gastric cancer was determined by comparing preoperative EUS with subsequent postoperative histopathologic findings and it was 68.3% (41/28) and 83.3% (12/10), 60% (20/12), 100% (5/5), 25% (4/1) for T1, T2, T3, and T4, respectively. The rates for overstaging and understaging were 24.4% (41/10), and 7.3% (41/3), respectively. EUS tended to overstage T criteria, and main reasons for overstaging were thickening of the gastric wall due to perifocal inflammatory change, and absence of serosal layer in certain areas of the stomach. The diagnostic accuracy of metastatic lymph node involvement or N staging of EUS was 100% (17/17) for N0 and 41.7% (24/10) for N+, respectively, and 66% (41/27) overall. EUS is a useful diagnostic method for preoperative staging of gastric cancer for T and N criteria. However, EUS evaluation of malignant lymph nodes is still unsatisfactory. The location and distribution of the tumour was predominately in the antrum (20 patients) and in the small curvature (17 patients). 3 cases were inoperable and were considered correctly diagnosed through EUS.

The treatment of gastric cancer

Surgery is currently the only potentially curative treatment for gastric cancer.

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Since the inception of the gastrectomy for cancer of the stomach, there has been debate over the bounds of surgical therapy, balancing potential long-term survival with perioperative morbidity and mortality.

Laparoscopy has emerged as an essential staging modality prior to gastric resection, identifying unresectable disease in a significant number of patients deemed resectable by current radiographic and endoscopic modalities. The diagnostic given by laparoscopy has been improved by the addition of laparoscopic ultrasound and peritoneal cytology. Endoscopic mucosal resection (EMR) has been established as one of the treatment options for early gastric cancer (EGC). In Korea the gastric cancer represents the most frequent malignant affection and the second cause of death through cancer.

Early gastric cancer (EGC) is defined as gastric carcinoma confined to the mucosa or submucosa regardless of the presence of regional lymph node metastases. The detection rate of EGC has been steadily increasing because of technical advances and awareness of benefit from early diagnosis, especially in eastern countries. Patients who undergo resection for EGC have an excellent prognosis, with a 5-year survival rate of over 90%. However, the quality of life after conventional surgical resection of gastric cancer is substantially impaired. Therefore, less invasive treatment options for EGC have been developed.

With technical advances of EMR, the size of a lesion which can be resected en bloc is becoming larger. One must be careful because EMR has a very important limitation that lymph nodes cannot be dissected. Data from Korea and Japan have shown that the incidence of lymph node metastasis in intramucosal EGC is about 2%-3% and the risks increase up to 20% when submucosal invasions are present. Because results of long-term controlled trials are not available, the current indications of EMR are based on the detailed analysis of pathology results from surgically resected gastric cancers. The ideal candidates for EMR are EGC patients who have no risk of lymph node metastasis. The problem is that there is no method that can definitely evaluate the status of lymph node without surgical dissection. Ideally, endoscopic ultrasound (EUS) should be useful for selecting patients without lymph node metastasis. However, clinical studies evaluating the role of EUS before EMR for EGC have shown unsatisfactory results. The current accepted indications of EMR for the treatment of EGC are as follows: (1) differentiated (well- and/or moderately differentiated adenocarcinoma and/or papillary carcinoma) type confined to the mucosa; (2) smaller than 2 cm for superficially elevated type lesions; (3) smaller than 1 cm for the flat and depressed type lesions; (4) without ulcer or ulcer scar; and (5) without venous or lymphatic involvement.

Recently, based on some clinical observation and surgical data, expanded criteria for EMR have been proposed. One report in which EMR indications included EGC lesions as large as 3 cm showed the disease free survival rates of 98% during a median follow-up of 38 mo when complete resections were performed. Recent large surgical data from Gotoda *et al* also provided supporting evidence for expanded criteria.

The list of EMR methods is quite long, but the basic steps are in common: (1) delineation of the lateral margin with or without chromoendoscopy, (2) marking using brief burst of electrocautery or argon plasma coagulation, (3) submucosal injection to lift the lesion, and (4) resection of the lesion.

The complications of EMR include pain, bleeding, perforation, and EMR-induced ulcer. Pain after resection is typically mild and dull in nature. Pain can be controlled using a standard dose of proton pump inhibitor (PPI) twice a day with or without analgesics. Bleeding is the most common complication and most bleeding occurs during the procedure or within 24 h

Bleeding can be successfully treated in most cases through coagulation of the bleeding vessels, or placement of metallic clips. EMR-induced ulcer is reported to heal faster and to recur less often than noniatrogenic gastric ulcer and usually treated with antisecretory agents. Earlier experiences of EMR for EGC from 12 major institutions in Japan were reported by Kojima *et al* in 1998. En bloc resection rate was 75.8%, and complete resection rate was 73.9%. The follow-up period was from 4 mo to 11 years. Recurrence rate after histopathologically documented eradication was 1.9% and recurred lesions were treated with endoscopic retreatment or surgery. The disease-specific survival rate was 99.1%.

In the study „Endoscopic mucosal resection of early gastric cancer: Experiences in Korea” (5) 283 patients with EGC have been treated by EMR from January 2000 to June 2005. The median age of the patients was 64 (range 26-85) years. The male to female ratio was 3.2:1. The median duration of follow-up was 21 (range 3-66) months from January 2000 to December 2002. The mean size of cancerous lesion was 1.38 cm. The overall rate of curative resection was 72.1%. The rate of curative resection was highest with ESD (80.2%), followed by EMR-P (70.3%). Submucosal invasion was found in 44 cases (15.5%). In patients with curative resection, local recurrence at EMR site was found in only one case (0.5%). In 51 cases who underwent surgical resection due to non-curative or non-evaluable resection, residual cancer was found in 13 cases (25.0%). Among 28 patients, who were followed up without surgery after non-curative or non-evaluable results, there were 13 recurrences (12 local recurrences and 1 hepatic metastasis) after a median follow-up of 7 mo. Five patients died during the follow-up period, but there was no death related to gastric cancer.

The effectiveness of endoscopic submucosal dissection using an insulation-tipped diathermic knife (IT-ESD) for the treatment of patients with over 20 mm early gastric cancer (EGC) is certain. A total of 112 patients with over 10 mm EGC were treated with IT-ESD at Sumitomo Besshi Hospital and Shikoku Cancer Center in the 5 year period from January 2002 to December 2006, including 40 patients with over 20 mm EGC. We compared patient backgrounds, the one-piece resection rate, complete resection (CR) rate, operation time, bleeding rate, perforation rate between patients with over 20 mm EGC (over 20 mm group (21-40 mm)) and the remaining patients (under 20 mm group). No significant difference was found between the 2 groups.

The study proves that IT-ESD is a feasible treatment for patients with over 20 mm mucosal gastric cancer although the long-term outcome should be evaluated in the future. The extent of gastric resection for distal lesions had been debated, and the traditional view that total gastrectomy (TG) is required for all gastric lesions have been challenged. Gouzi *et al* conducted a multicenter randomized trial comparing TG (with Roux en-Y esophagojejunostomy) to subtotal gastrectomy (distal gastrectomy and Billroth II gastrojejunostomy) enrolling 169 patients with resectable lesions of the gastric antrum.

Patients with macroscopic lymph node involvement of the cardioesophageal or splenopancreatic region were excluded from the study. Both procedures included a total omentectomy, and lymph node dissection extended to the pyloric, left gastric, hepatic, and cardiac nodes. Splenectomy was not routinely performed; however, the TG group had an unspecified higher splenectomy rate than the SG group. The authors concluded that TG or SG could be performed with equal morbidity and mortality, but that TG offered no added survival benefit. In a larger trial, Bozzetti *et al* also performed a randomized trial comparing TG to SG in 618 patients with resectable tumors at least 6 cm from the cardia. The authors concluded that SG was

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the preferred operation for distal gastric cancer, provided that a proximal margin of at least 6 cm could be obtained, because it is technically less demanding, results in a lower splenectomy rate, and is associated with better quality of life.

The extent of resection needed to achieve cure in tumors of the gastroesophageal junctions has been a topic of much debate, Ito et al reviewed patients with Siewert type II (59) or III (23) carcinoma of the gastric cardia in an attempt to discern the optimal surgical approach.

The surgical approach varied, with 33% undergoing total esophagectomy, 29% undergoing extended gastrectomy with thoracotomy, and 38% undergoing extended gastrectomy without thoracotomy. There was no significant difference in post-operative mortality and survival rate; however, there was a higher post-operative morbidity associated with total esophagectomy as compared to extended gastrectomy with or without thoracotomy (33% vs 11%). There was a significantly higher incidence of microscopic residual disease at the proximal margin in the extended gastrectomy group with or without thoracotomy as compared to the total esophagectomy group (38% vs 7%).

Based on these results, showing R0 status and nodal status to be predictors of survival, the authors made the following recommendations: (1) A minimum proximal margin of 6 cm and distal margin of 4 cm should be obtained. (2) A minimum of 15 lymph nodes should be sampled. The type of surgical approach should be tailored to fit the individual patient with these goals in mind. TG is the traditional treatment for proximal gastric cancer; however, this has been recently challenged as well. Harrison et al reviewed 98 patients with proximal gastric cancer who underwent gastric resection via an abdominal approach, excluding all patients who underwent esophagogastrectomy of these 98 patients, 65 underwent proximal gastrectomy (PG), and 33 underwent TG. There was no difference in post-operative mortality, in time to recurrence or first site of recurrence and 5-year survival rate.

The article „**Distribution of solitary lymph nodes in primary gastric cancer: A retrospective study and clinical implications**” (6) investigated the distribution pathway of metastatic lymph nodes in gastric carcinoma as a foundation for rational lymphadenectomy. 173 cases with solitary or single station metastatic lymph nodes (LN) were investigated from among 2476 gastric carcinoma patients.

The location of metastatic LN, histological type and growth patterns were analyzed retrospectively.

The criteria used for patient inclusion was:

- (1) D2 lymph node dissections had been performed;
- (2) There were greater than 15 lymph nodes analyzed pathologically;
- (3) Patients with pT4 and M1 stage were excluded;
- (4) Patients' medical records were complete

Among the 173 cases, 88 had solitary lymph metastasis and 85 involved a single station lymph node. Sixty-four of the 88 patients were male and 24 female. The average age of the patients in this group was 57.6 ± 7.2 years (range 30-80). With respect to tumor location, the tumor was found in the upper third stomach area (U) in 8 cases, in the middle third (M) in 28, and in the lower third (L) in 52. With respect to tumor location, the tumor was found in the upper third stomach area (U) in 8 cases, in the middle third (M) in 28, and in the lower third (L) in 52. Amongst the patients with single station node metastasis, 60 were male and 25 female. The average age of the patients in this group was 58.2 ± 8.3 years (range 32-76). In respect of tumor location; the tumor was in the U in 23 cases, in the M in 12, and in the L stomach areas in 50. Among the 88 patients with a solitary metastatic lymph node, in 65 (73.9%) the lymph nodes involved were within N1, and 23 (26.1%) were

over N1. In this study, transversal and skipping metastasis were found to be notable. Nodal metastases occur in a random and multidirectional process in gastric cancer and that not every first metastatic node is located in the perigastric region near the primary tumor. The rate of “jumping metastasis” in gastric cancer is much higher than expected, which suggests that the blind examination of the nodal area close to the primary tumor can not be a reliable method to detect the SLN and that an extended lymph node dissection (ELND) should be performed if the preoperative examination indicates submucosal invasion. (7). D1 resection consisted of the removal of all lymph nodes within 3 cm of the tumor and D2 resection consisted of the standard resection of the omental bursa, the hepatoduodenal nodes for antral lesions and the splenic artery, splenic hilar, and retropancreatic nodes by distal pancreatectomy for middle and upper third lesions.

D2 curative resection, which includes gastrectomy and D2 lymphadenectomy, required dissection of all the Group 1 and Group 2 nodes classified by anatomical location. However, with the development of D2 lymphadenectomy, larger lymph nodes dissected may enable to find larger metastatic lymph nodes, which induces a migration in the staging system.

The ratio of the number of metastatic lymph nodes over the total number of resected lymph nodes is introduced to prognosis evaluation.

It was reported that metastatic lymph node ratio (MLR) can minimize the stage migration effect caused by increasing total dissected lymph nodes, also can help refine the current TNM stage system.

Though many studies on the prognostic significance of MLR in gastric cancer have been carried out, relevant researches on advanced gastric cancer from the cardia and fundus are still rare. Therefore, the aim of the retrospective study „**Prognostic impact of metastatic lymph node ratio in advanced gastric cancer from cardia and fundus**” (8) was to discuss the clinical impact of MLR in patients with gastric cancer from the cardia and fundus, and provide further evidence for rational lymphadenectomy.

Two hundred and thirty-six cases, diagnosed as primary gastric cancer from the cardia and fundus were treated with curative resection D2.

The correlations between MLR and the total lymph nodes, positive nodes and the total lymph nodes were analyzed respectively. The survival time of patients was influenced by MLR.

The MLR did not correlate with the total lymph nodes resected ($r = -0.093$, $P = 0.057$). The 5-year overall survival rate of the whole cohort was 37.5%.

Kaplan-Meier survival analysis identified that the following eight factors influenced the survival time of the patients postoperatively: gender ($\chi^2 = 4.26$, $P = 0.0389$), tumor size ($\chi^2 = 18.48$, $P < 0.001$), Borrmann type ($\chi^2 = 7.41$, $P = 0.0065$), histological grade ($\chi^2 = 5.07$, $P = 0.0243$), pT category ($\chi^2 = 49.42$, $P < 0.001$), pN category ($\chi^2 = 87.7$, $P < 0.001$), total number of retrieved lymph nodes ($\chi^2 = 8.22$, $P = 0.0042$) and MLR ($\chi^2 = 34.3$, $P < 0.001$).

Cox proportional hazard model showed that tumor size ($\chi^2 = 7.985$, $P = 0.018$), pT ($\chi^2 = 30.82$, $P < 0.001$) and MLR ($\chi^2 = 69.39$, $P < 0.001$) independently influenced the prognosis. A linear correlation between MLR and the 5-year survival was statistically significant based on the multiple linear regression ($\beta = -0.63$, $P < 0.001$). Hypothetically, the 5-year survival would surpass 50% when MLR was lower than 10%. The MLR is an independent prognostic factor for patients with advanced gastric cancer from the cardia and fundus. The decrease of MLR due to adequate number of total resected lymph nodes can improve the survival. The best known trial to

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evaluate lymphadenectomy was from the Dutch Gastric Cancer Group. Bonenkamp et al published the results from a randomized controlled trial comparing D1 and D2 gastrectomy in 80 Dutch hospitals over 5 years. D1 resection was defined as containing only the N1 (perigastric) nodes. D2 resection was defined as encompassing the N2 nodes. These authors reported statistically significant differences in post-operative mortality (4% vs 10%) and complication rate (25% vs 43%) for D1 vs D2 resection. The 5-year survival rate and the 5-year risk of relapse were not statistically significant. D2 lymphadenectomy was associated with a higher morbidity and mortality without offering a long-term survival benefit, and thus it was not recommended. A modified D2 lymphadenectomy, sparing the spleen and pancreas when possible, can be performed safely and may offer the best chance for long-term survival. To improve the long-term survival of patients with advanced gastric cancer located in the cardia and fundus, removing at least 20 LNs for stage II, 25 LNs for stage III, and 30 LNs for stage IV patients during D2 radical dissection is recommended. (9)

The following recommendations are made:

- Segmental/subtotal gastrectomy plus D1/D1+ No.7 should be performed for carcinoma (≤ 1.0 cm in diameter, protruded type and mucosa invasion).
- Subtotal gastrectomy plus D2 or D1 + No.7, 8a, 9 is the most rational operation, whereas No.11p, 12a, 14v lymphadenectomy should not be recommended routinely for poorly differentiated and depressed type of submucosa carcinoma (> 3.0 cm in diameter).

Total gastrectomy should not be performed in proximal, so does combined resection or D2+/D3 lymphadenectomy. (10)

Resection of adjacent organs in conjunction with gastrectomy can increase survival with minimal additional morbidity in a highly selected patient population.

Judicious use of en bloc PD and gastrectomy and strictly preventing postoperative complications may improve the long-term survival for advanced gastric cancer patients with pancreaticoduodenal region involvement. Well-differentiated histology and negative resection margin are the most important predictors of long survival. (11) **"Pancreaticoduodenectomy for advanced gastric cancer with pancreaticoduodenal region involvement"**

Given the very poor prognosis associated with positive margins, re-laparotomy may be justified in those patients with node-negative disease. A positive margin is more of an indication of advanced disease in patients with gastric adenocarcinoma of the cardia rather than an independent prognostic factor for survival. (12) **"Influence of a microscopic positive proximal margin in the treatment of gastric adenocarcinoma of the cardia"**

Since palliative gastrectomies are associated with significant perioperative morbidity and mortality, the authors recommend deliberate palliative resection only in carefully selected patients with severe symptoms.

The quality of life is a very hard to achieve goal. Comparing postoperative quality of life (QOL) in patients with gastric cancer treated by esophagogastronomy reconstruction after proximal gastrectomy was the aim of **"Improved quality of life in patients with gastric cancer after esophagogastronomy reconstruction"**(13). QOL assessments that included functional outcomes (a 24-item survey about treatment specific symptoms) and health perception (Spitzer QOL Index) were performed in 149 patients with gastric cancer in the upper third of the stomach, who had received proximal gastrectomy with additional esophagogastronomy. Fifty-four patients underwent reconstruction by esophagogastric anterior

wall end-to-side anastomosis combined with pyloroplasty (EA group); 45 patients had reconstruction by esophagogastric posterior wall end-to-side anastomosis (EP group); and 50 patients had reconstruction by esophagogastric end-to-end anastomosis (EE group). The EA group showed the best postoperative QOL, such as recovery of body weight, less discomfort after meals, and less heart burn or belching at 6 and 24 mo postoperatively. However, the survival rates, surgical results and Spitzer QOL index were similar among the three groups. Metastatic gastric cancer remains an incurable disease, with a relative 5-year survival rate of 7%-27%. Chemotherapy, which improves overall survival (OS) and quality of life, is the main treatment option. Metaanalysis has demonstrated that the best survival results obtained in earlier randomized studies were achieved with three-drug regimens containing a fluoropyrimidine, an anthracycline, and cisplatin (ECF). **"New perspectives in the treatment of advanced or metastatic gastric cancer"** (14)

A number of new combinations incorporating docetaxel, oxaliplatin, capecitabine, and S-1 have been explored in randomized trials. Some combinations, such as epirubicin-oxaliplatin-capecitabine, have been shown to be as effective as (or perhaps more effective than) ECF, and promising early data have been derived for S-1 in combination with cisplatin. One factor that might contribute to extending median OS is the advancement whenever possible to second-line cytotoxic treatments. However, the biggest hope for significant survival advances in the near future would be the combination of new targeted biological agents with existing chemotherapy first-line regimens. Preoperative intra-arterial infusion chemotherapy could increase the radical resection rate of advanced gastric cancer, but its effect on the long-term survival has not been assessed.

The article **"Clinical significance of preoperative regional intra-arterial infusion chemotherapy for advanced gastric cancer"** (15) illustrated the important role played by preoperative intra-arterial infusion chemotherapy in improving the prognosis of advanced gastric cancer. Clinicopathological data of 91 patients who underwent curative resection for advanced gastric cancer were collected. Among them, 37 patients undertaken preoperative intra-arterial infusion chemotherapy were used as the interventional chemotherapy group, and the remaining 54 patients as the control group. Eleven factors including clinicopathological variables, treatment procedures and molecular biological makers that might contribute to the long-term survival rate were analyzed using Cox multivariate regression analysis. The 5-year survival rate was 52.5% and 39.8%, respectively, for the interventional group and the control group ($P < 0.05$).

A Pilot study was conducted to evaluate the efficacy and toxicity of postoperative adjuvant chemoradiation for advanced gastric cancer: Adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. Thirty-one patients who had undergone a potentially curative resection for Stage III and IV (M0) gastric cancer were enrolled. Therapy consists of one cycle of FP (continuous infusion of 5-FU 1000 mg/m² on day 1 to 5 and cisplatin 60 mg/m² on day 1) followed by 4500 cGy (180 cGy/day) with capecitabine (1650 mg/m² daily throughout radiotherapy). Four weeks after completion of the radiotherapy, patients received three additional cycles of FP every three week. The median follow-up duration was 22.2 months. The 3-year disease free and overall survival in this study was 82.7% and 83.4%, respectively. Four patients (12.9%) showed relapse during follow-up. Eight patients did not complete all planned adjuvant therapy. Grade 3/4 toxicities included neutropenia in 50.2%, anemia in 12.9%, thrombocytopenia in 3.2% and

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nausea/vomiting in 3.2%. Neither grade 3/4 hand foot syndrome nor treatment related febrile neutropenia or death was observed.

These preliminary results suggest that this postoperative adjuvant chemoradiation regimen of FP before and after capecitabine and concurrent radiotherapy appears well tolerated and offers a comparable toxicity profile to the chemoradiation regimen utilized in INT-0116. This treatment modality allowed successful loco-regional control rate and 3-year overall survival.

In spite of the various therapeutical methods the prognostic of gastric cancer still remains a very poor one, being the second cause of cancer mortality worldwide.

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