

The 7th National Gastric Cancer Academic Conference: focus on translational research in gastric cancer

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Introduction

Gastric cancer is a heterogeneous disease with large variations across geographical regions (1). Although the global incidence of gastric cancer is declining, it remains highly prevalent in Asia as compared to the West (2,3). China is one of the countries with the highest incidence of gastric cancer, and accounts for over 40% of all new gastric cancer cases in the world (4,5). Gastric cancer is the third leading cause of cancer mortality in China (6,7). The 7th National Gastric Cancer Academic Conference (NGCAC) was held in Beijing from June 22 to June 24 with approximately 1,200 attendees, which was organized by Gastric Cancer Committee, Chinese Anti-Cancer Association (CACA) (Figure 1). The theme of this conference was specification, integration, and transformation. Dr. Jiafu Ji, MD, FACS, the chairman of the conference, the president of Gastric Cancer Committee, CACA, pointed out that the conference was aimed at standardizing the diagnosis and treatment of gastric cancer, integrating the information platform, and transferring current research achievements (Figure 1). It has been about thirteen years since last National gastric cancer academic conference, which was held in Nanjing in 1999. In this conference, nine pioneer experts (Drs Yan-Zhen Lin, Ji-Fu Wang, Guang-Wei Xu, Jun-Qing Chen, Wen-Fan Zhang, Yin-Chang Zhang, Mao-Lin Jin, Xiang-Fu Zhang, and Xi-Shan Hao) were awarded Lifetime Achievement Award by Gastric Cancer Committee, CACA. There were ten sessions and more than two hundred papers or abstracts submitted, the proceeding was published in *Translational*

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Symposium on evidence-based medicine for gastric cancer

Aimed at better interpretation of gastric cancer's diagnosis and treatment standards and assistance provision for the organization committee to reach consensus before the conference, an entirely new sort of meeting exclusively titled by Covidien Ltd, 'the symposium on development outline of evidence-based medicine for gastric cancer's standardized diagnosis and treatment', was held in Wuzhou Crowne Plaza Hotel on the afternoon of June 22nd, 2012. The conference teed off with a splendid speech by the chairman Prof. Jiafu Ji, based on the mainline of 'standardized diagnosis and treatment of gastric cancer', leading experts Profs. Jae-Moon Bae and Young-Kyu Park from Korea and Profs. Lin Chen and Lin Shen from China introduced and shared the experiences and development of the standardized treatment of gastric cancer (Figure 2).

Nearly forty renowned Chinese experts participated in this conference, airing their own views and speaking their minds in the quiz and discussions on hot spot issues interspersed between the lectures, exchanging their questions and opinions with each other, probing into current situations and looking forward to the future, pushing the symposium to one climax after another, and the whole conference room was permeated with an enthusiastic and active atmosphere.

Senior Director of Surgical Division of Covidien China,



Figure 1 The 7th National Gastric Cancer Academic Conference (A and B); Professor Jiafu Ji, MD, FACS, the chairman of the conference (C)



Figure 2 A. Symposium on evidence-based medicine for gastric cancer; B. Professor Jiafu Ji, MD, FACS, the chairman of the symposium; C. Professor Lin Chen; D. Professor Lin Shen; E. Mr. Min Ma, Director of the surgical product division of Covidien China; F. The experts are interested in the unique achievement of intelligent anastomosis technique Tri-Staple™

Mr. Min Ma, gave an inspiring introduction about Covidien, making perfection more perfect for this symposium. Covidien has been bringing new medical solutions to the clinics and patients by its outstanding research and product development capability, and has become the credible partner of medical workers. In his speech, Director Ma shared with the experts the unique achievement of intelligent anastomosis technique Tri-Staple™, a breakthrough product of Covidien Ltd that will launch in China, described in detail every matchless advantage of Tri-Staple™, and explained that this product can minimize the effect of

human factors and properly solve three contradictions in traditional anastomosis. These revolutionary changes can steer mechanical anastomosis technique towards truly entering the age of intelligence, which arouses the experts' interest and gains their approval. Covidien cooperated with those outstanding Chinese experts going in for the gastric cancer's professional diagnosis and treatment in this high-level symposium, coagulated group strength to promote the standardized diagnosis and treatment of gastric cancer. The successful organization of this symposium prepared for the conference on the next day.



Figure 3 A. Professor Huimian Xu; B. Professor Wanqing Chen

Keynote lecture series

In the main session, Dr. Junqing Chen, from Chinese Medical University, gave a lecture entitled “The past, present, and future of gastric cancer in China”, and concluded that the keys to improve outcomes of gastric cancer management were to seek more attention from the government, to reduce the incidence, and to take more measures on early diagnosis and treatment. Dr Jiafu Ji, addressed the importance of translational medicine in bridging the gap between basic and clinical science, with three examples regarding surgical management, chemotherapy improvement, and staging criteria. The Director of US National Institutes of Health (NIH), Dr. Francis Collins, proposed a new initiative of five thematic areas in 2010, and “Translating Basic Science Discoveries into New and Better Treatments” was one of those five thematic areas. Furthermore, NIH created its newest National Center for Advancing Translational Sciences (NCATS) on December 23, 2011. There is no doubt that advancing translational sciences have become an important mission of NIH. By leveraging findings from basic research, innovative methods and technologies as well as new targets can be developed for potential clinical applications of diagnostics and therapeutics in various diseases (8-13). Dr Sasako Mitsuru from Hyogo College of Medicine, Japan, gave a lecture on the current situation of gastric cancer management in Japan. Dr Huimian Xu from Chinese Medical University interpreted the guidelines of diagnosis and management of gastric cancer promulgated by Ministry of Public Health (Figure 3A). Dr Wanqing Chen, from

National Cancer Prevention and Control Office, for the first time, released the epidemical data of gastric cancer in China (Figure 3B). According to the 2010 annual report of Cancer Registry Data in China, the incidences of gastric cancer were 49.53 and 28.28 per 100,000 people in rural and urban areas, ranking the first and the third respectively. And the mortalities were 41.29 and 22.64 per 100,000 people in rural and urban areas in China.

Staging of gastric cancer

Reasonable staging is the first step in the multidisciplinary management of gastric cancer, a significant link for the choice of treatment programs and determination of the efficacy and prognosis. Since its first edition in 1977, the TNM staging system has been used as a basis for the clinical staging of gastric cancer and a standard staging method in each update of the clinical diagnosis and treatment guidelines of gastric cancer. Staging of gastric cancer typically makes use of a variety of imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasounds (EUS), and combined positron tomography (PET-CT), as well as laparoscopic staging and cytogenetic analysis of peritoneal fluid in appropriate patients (14). However, the gastric cancer staging is in continuous evolution in order to provide more delicate accurate prognosis prediction. Shan *et al.* performed a retrospective analysis of 922 gastric cancer patients with complete clinical data who underwent treatment in Beijing Cancer Hospital from Sep. 1995 to Dec. 2007. The prognostic differences between the 6th edition of gastric

cancer staging AJCC and the 7th edition were analyzed, and it was concluded that T and N staging of 7th edition showed better performance, but the 7th TNM staging had not been proven to be superior to the 6th edition in general.

Kang *et al.* proposed a new subclassification of pT4 gastric cancers according to the magnitude of serosal changes [narrow serosal changes (nSE) and wide serosal changes (wSE)]. Seven hundred and eighty-one pT4a/pT4b stage patients who underwent curative surgery for gastric cancer between January 1997 to December 2007 were investigated in terms of prognostic performance. When the cutoff value on serosa infiltration was 60 mm, there was significant difference in most of the clinicopathologic features between nSE and wSE cancers, but wSE was similar to SI (15). Dr Liu from Tianjin Cancer Hospital found that for patients with gastric cancer when the numbers of lymph nodes were retrieved no less than 15 in operation, the ratio of positive lymph nodes (rN) classification was more suitable than N and Log odds (LODDS) classifications for prognostic assessment (16). One study demonstrated that type IV gastric cancer was an independent predictor of poor prognosis and the dominant recurrence pattern was peritoneal recurrence.

Prognostic markers for gastric cancer

An accumulation of genetic and molecular abnormalities occurs during gastric carcinogenesis, including activation of oncogenes, overexpression of growth factors/receptors, inactivation of tumor suppression genes, DNA repair genes and cell adhesion molecules, loss of heterogeneity and point mutations of tumor suppressor genes, and silencing of tumor suppressors by CpG island methylation. The revelation and understanding of the molecular events and pathways have led to the application of molecular pathology in the prevention, early diagnosis, tumor classification and therapeutic intervention. The applications of molecular testing such as the testing of CDH1 gene for hereditary diffuse gastric carcinoma (HDGC) and of HER2 expression in gastric cancers have had significant impact on medical practice, and become standard patient care (17,18). Wu *et al.* analyzed 372 proximal gastric cancer patients compared with distal gastric cancer cases and it is concluded that lymph node metastasis ratio (LMR), lymphovascular invasion (LVI), and Lauren's classification were independent prognostic factors for proximal gastric cancer (19). Xing *et al.* identified that PLA2G2A, the secreted phospholipase A2 type IIA gene may predict survival and might be a potential biomarker for

early detection and individualized therapy. PLA2G2A was elevated significantly in well-differentiated carcinoma and seemed a positive biomarker of good survival (20).

Fan *et al.* investigated the role of S100A9 in gastric cancer and found that it was specifically expressed by inflammatory cells infiltrating cancer and gastritis. High S100A9 cell count was negatively correlated with lymph node metastasis ($P=0.009$) and tumor invasion ($P=0.011$). S100A9 was an independent prognostic predictor ($P=0.04$)⁽²¹⁾. Xue *et al.* conducted an experimental study on the effects of VEGF and EGF on biological properties of gastric cancer cells. The expression of VEGF and EGF had close relationship with intra-abdominal exfoliation of cancer cells, and was also correlated with the properties of migration, adhesion, invasion of gastric cancer cells *in vitro* which decreased survival rate. Therefore specific inhibition of VEGF and EGF may impair the abilities of proliferation, migration, adhesion and invasion of gastric cancer cells *in vitro*. Targeting VEGF and EGF may be a potential therapeutic strategy for inhibiting peritoneal metastasis of gastric cancer (22).

Wang *et al.* found that S100A6 was overexpressed in gastric cancer and histone H3 acetylation may regulate the S100A6 overexpression in gastric cancer (23). Dr Xue aimed to identify proteins associated with lymph node metastasis by potential of lymph node metastasis, and study their relationship with lymph node metastasis and clinical significance. Gastric cancer tissues from 12 patients with great potential of lymph node metastasis and 12 patients with poor potential of lymph node metastasis were collected. Finally the researchers found that 14-3-3 β and profilin-1 may be useful markers for lymph node metastasis of gastric cancer, and 14-3-3 β could serve as a predictive marker for the prognosis (24). Wang *et al.* conducted a prospective study focusing on the relationship between chemosensitivity of taxanes and beta-tubulin III expression in gastric cancer, and found there was no correlation between beta-tubulin III expression and clinical characteristics, such as age, gender, primary tumor location, and pathological type. However, the beta-tubulin III expression level in gastric cancer tissue may be a good predictor of taxane sensitivity (25). The same group also identified five-miRNA signature for GC diagnosis by genome-wide serum miRNA expression profiling. Expression levels of this serum miRNA-based biomarker also indicated tumor progression stages (26).

Several studies reported their advances in the cancer stem cells and tumor immunology. Liu *et al.* explored the expressions and clinical significances of cancer stem cell

marker CD133, EpCAM, ABCG2, Oct4 in primary lesion and lymphatic metastatic lesions of gastric carcinoma. Expressions of CD133, EpCAM, ABCG2 and Oct4 in gastric carcinoma tissues were significantly higher than that of adjacent tissue ($P < 0.05$). Expressions of CD133 were significantly higher in subgroups with severer invasion depth ($P = 0.029$), severer lymph node metastasis ($P = 0.020$) and later TNM stage ($P = 0.001$). Expressions of EpCAM were significantly higher in subgroups with severer invasion depth ($P = 0.022$). Expressions of ABCG2 were significantly higher in subgroups with lower differentiation of tumor ($P = 0.042$), severer invasion depth ($P = 0.020$) and later TNM stage ($P = 0.035$). Expressive rates of CD133, EpCAM and ABCG2 in lymphatic metastatic lesions were 28%, 60% and 44% respectively, lower than that in primary lesion ($P < 0.05$). Expression of EpCAM in lymphatic metastatic lesions was significantly higher in subgroups with higher primary lesion expression ($P = 0.040$). The authors concluded that CD133, EpCAM, ABCG2 and Oct4 maybe regarded as markers of gastric carcinoma. Higher expressive level of CD133 and EpCAM was relevant to severer advanced gastric cancer. Higher expressive level of ABCG2 was related to lower differentiation of tumor and severer advanced gastric cancer. These four markers expressed in lymphatic metastatic lesions of gastric carcinoma. Higher expressive level of EpCAM in lymphatic metastatic lesions was associated to higher primary lesion expression (27). Liu *et al.* reported the mechanism induced by the Fas/FasL system. The study suggested that there was indeed a possible mechanism to assist cancer cells to evade host immune attack, and this mechanism depended on the dynamic state of Fas/FasL expression (28). The role of biomarkers, e.g., BMP-7, promoter CCAAT enhancer binding protein (CEBPB), lumican, tissue factor and Her-2, chemotactic factors, CMTM3, were also reported by different centers from China (29-31).

Multidisciplinary approach for the treatment of gastric cancer

The management of gastric cancer has been evolving over the past two decades. Complete surgical resection remains the corner stone for the cure of localized gastric cancer. Issues investigated and debated over the past 20 years have focused on the extent of lymphadenectomy (D1 *vs.* D2 dissection) with the goal of delivering an optimal cancer operation while limiting morbidity. Although D2 dissection has been the standard practice in Japan and most Asian

countries, major Western studies, the “Dutch trial” (32,33) by Bonenkamp *et al.* and The British MRC ST01 trial (34), failed to show survival benefit of D2 dissection. These trials were criticized by poor quality control of participating surgeons. Despite these negative large randomized studies, most physicians consider that D2 dissection is advantageous due to more precise staging. Adjuvant chemoradiation with 5-fluoracil (5-FU) and leucovorin has been the standard practice in the United States for the past twenty years. Postoperative radiotherapy is not commonly practiced in Japan and other Asian countries. Preoperative chemoradiation and perioperative chemotherapy provide benefit to down-stage the primary tumor and eliminate micrometastasis early on. In addition, the preoperative therapy is generally better tolerated. The most compelling evidence for perioperative chemotherapy is the phase III UK Medical Research Council Adjuvant Gastric (MAGIC) trial (35). Li *et al.* reported a prospective non-randomized study comparing peri-operative FOLFOX versus adjuvant FOLFOX in patients with resectable locally advanced gastric cancer. Complete and partial response was observed in 2 (6%) and 21 (64%) patients respectively. Four-year overall survival (OS) in the neoadjuvant arm was 78% versus 51% in the adjuvant arm ($P = 0.031$). Subgroup analysis found R0 resection (86% *vs.* 55%, $P = 0.011$) and patients with proximal cancers (87% *vs.* 14%, $P < 0.001$) to have improved OS. And the regimen administered preoperatively was not associated with increased postoperative morbidity (36).

Shan *et al.* presented the results of efficacy and toxicity of oxaliplatin and S-1 combination chemotherapy. A total of 13 (65.0%) out of 20 patients showed downstaging, 3 patients (15.0%) complete response and 9 (45.0%) partial response, the overall response rate is 60.0% (95% CI, 38.5-81.5%) (37). Zhou *et al.* examined the micrometastasis of para-aortic lymph node and found that the positive rate was 20.97%, much higher than 14.52% detected by routine staining. The micrometastasis of para-aortic lymph nodes was associated with metastasis of No. 13, and then No. 12, as well as No. 2, 3, 6, 7, 8, 9, 10, 11, and 14. It also accompanied with a poorer prognosis compared with no micrometastasis (0% *vs.* 53.06%).

One meta-analysis conducted by Huang *et al.* evaluated the role and safety of intra-peritoneal chemotherapy for patients with gastric cancer. The meta-analysis consisted of 13 studies, including 9 high-quality papers, 4 low-quality papers, and a total of 1,466 patients. The results of the meta-analysis demonstrated that hyperthermic intraoperative intra-peritoneal chemotherapy (HIIC) and

hyperthermic intraoperative intra-peritoneal chemotherapy combined with postoperative intra-peritoneal chemotherapy (HIIC combined with PIC) could significantly lower the mortality rate (HIIC group: OR=0.54, 95% CI, 0.39 to 0.75, P=0.0002; HIIC combined with PIC group OR=0.35, 95% CI, 0.19 to 0.65, P=0.0009). Normothermic intraoperative intra-peritoneal chemotherapy (NIIC) and normothermic postoperative intra-peritoneal chemotherapy (NPIC) also showed mortality reductions, but the results were not as good as HIIC or HIIC combined with PIC. Further analysis showed that PIC remarkably decreased the rate of postoperative hepatic metastasis in gastric cancer patients by 72% (OR=0.28, 95% CI, 0.12 to 0.67, P=0.004) and played a weak role in preventing postoperative peritoneal relapse (OR=0.61, 95% CI, 0.39 to 0.96, P=0.03). Intra-peritoneal chemotherapy was also found to be associated with high risks of marrow depression (OR=3.81, 95% CI, 1.67 to 8.70, P=0.002), fever (OR=3.66, 95% CI, 1.34 to 9.94, P=0.01) and intra-abdominal abscess (OR=3.57, 95% CI, 1.49 to 8.57, P=0.004) (38).

In conclusion, gastric cancer in Chinese patients is different from that occurring in the West, and is a significant health burden. Moreover, there is currently no internationally accepted standard treatment regimen and clinical practice varies widely across countries. With the development of medical technology and wide application of more and more novel technologies, evidence-based approaches in combination with the strengths of various treatments will be the key to multidisciplinary management of gastric cancer for ultimately improving the outcomes and quality of life of these patients.

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