World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i17.4307

World J Gastroenterol 2016 May 7; 22(17): 4307-4320
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Recent developments and innovations in gastric cancer

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Author contributions: Mihmanli M and Ilhan E contributed equally to this work, generated the figures and wrote the manuscript; Idiz UO, Alemdar A, Demir U contributed to the writing of the manuscript; Mihmanli M designed the aim of the editorial and wrote the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Received: January 26, 2016
Peer-review started: January 28, 2016
First decision: March 7, 2016
Revised: March 14, 2016
Accepted: March 30, 2016
Article in press: March 30, 2016
Published online: May 7, 2016

Abstract

Gastric cancer has an important place in the worldwide incidence of cancer and cancer-related deaths. It can metastasize to the lymph nodes in the early stages, and lymph node metastasis is an important prognostic factor. Surgery is a very important part of gastric cancer treatment. A D2 lymphadenectomy is the standard surgical treatment for cT1N+ and T2-T4 cancers, which are potentially curable. Recently, the TNM classification system was reorganized, and the margins for gastrectomy and lymphadenectomy were revised. Endoscopic, laparoscopic and robotic treatments of gastric cancer have progressed rapidly with development of surgical instruments and techniques, especially in Eastern countries. Different endoscopic resection techniques have been identified, and these can be divided into two main categories: endoscopic mucosal resection and endoscopic submucosal dissection. Minimally invasive surgery has been reported to be safe and effective for early gastric cancer, and it can be successfully applied to advanced gastric cancer with increasing experience. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were developed as a combined treatment modality from the results of experimental and clinical studies. Also, hyperthermia increases the antitumor activity and penetration of chemotherapeutics. Trastuzumab which is a monoclonal antibody interacts with human epidermal growth factor (HER) 2 and is related to gastric carcinoma. The anti-tumor mechanism of trastuzumab is not clearly known, but mechanisms such as interruption of the HER2-mediated cell signaling pathways and cell cycle progression have been reported previously. *H. pylori* is involved in 90% of all gastric malignancies and Japanese guidelines strongly recommend that all *H. pylori* infections should be eradicated regardless of the associated disease. In this review, we present innovations discussed in recent studies.

Key words: Gastric; Cancer; Endoscopic mucosal resection; Endoscopic submucosal resection; Minimally invasive surgery; Neoadjuvant chemotherapy; Human epidermal growth factor receptor 2

Core tip: Gastric cancers are distinguished from other cancers by their high mortality and morbidity. Many studies have been conducted to improve the quality of life and extend the survival rates of patients, and some of these studies are ongoing. Although promising developments have been made in recent years, the obtained results have limited reliability and benefits. We believe that significant improvements in the treatment of gastric cancer will be developed according to the long-term results of ongoing randomized clinical trials.

Mihmanli M, Ilhan E, Idiz UO, Alemdar A, Demir U. Recent developments and innovations in gastric cancer. *World J Gastroenterol* 2016; 22(17): 4307-4320 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i17/4307.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i17.4307

INTRODUCTION

Gastric cancer is in the fifth most common cancer worldwide but it has the third highest incidence of death[1]. Gastric cancer usually does not metastasize to the distant organs until the third stage, but it can metastasize to the lymph nodes during the early stages, which is an important prognostic factor. Metastatic lymph nodes are correlated with the depth (T level) of the cancer. The recurrence observed after a D2- lymph node dissection (LND) is different from the recurrence observed after limited surgery, and locoregional recurrence can occur in most patients who undergo limited surgery. In addition, a minority of patients without perigastric lymph node metastasis can skip metastasis to distant lymph nodes[2,3]. The CA19-9 value is associated with the number of metastatic lymph nodes, and elevated CA19-9 values are significantly correlated (P = 0.008) with the number of metastatic lymph nodes. This could be useful for selecting advanced gastric cancer[4]. Curative surgery for gastric cancer consists of the excision of the mesogastrium, which contains lymph nodes and the omentum, with adequate surgical margins. The Japanese Research Society for the Study of Gastric Cancer (JRSGC) standardized the lymph node dissection for gastric cancer.

According to the JRSGC, a gastrectomy without D2-LND can only provide palliation. D2-LND was used to extend the lymphadenectomy in the 1960's in Japan. Currently, a para-aortic lymphadenectomy is defined as an extended lymphadenectomy. However, a D2-LND is known as an extended lymphadenectomy in Western countries[5,6]. Innovations of gastric cancer therapies include revising the gastrectomy and lymphadenectomy margins; reorganization of the TNM classification; developments in the endoscopic, laparoscopic and robotic treatment of gastric cancer; and innovations in cytoreductive, neoadjuvant and targeted therapies.

REVISIONS FOR GASTRECTOMY AND LYMPHADENECTOMY FOR GASTRIC CANCER

The classifications of lymph nodes have been upgraded intermittently since their first publication in 1962. Lymph node groups were classified as N1-N2-N3-N4, according to cancer location, in the first English edition[7]. The groups were formed based on the incidence of lymph node metastasis and according to the cancer location and the survival rate. The lymph nodes in the "N" groups were upgraded periodically. For example lymph node "7" was originally located in the "N2" group. However, in the third English edition, it was included in the "N1" group. The lymph nodes were grouped into 4 main groups (N1-3 and M1) in the second English edition[8]. This classification was misunderstood such that "N1 and N2" lymph node dissections were thought to be equal to "D1 and D2" lymph node dissections in countries outside of Japan[9]. This definition did not fully coincide with the Japanese classification system determined according to tumor location. For example, if the cancer was located in the proximal part of the stomach, the left paracardial lymph node (No. 2) was defined as N1; if the cancer was located in the corpus of the stomach, the left paracardial lymph node (No. 2) was defined as N3, and if the cancer was located in the distal part of the stomach, the left paracardial lymph node (No. 2) was defined as M (metastatic). This confusion is based on the difficulty of defining the classification. This complex classification system changed in 2010[10]. "D" dissection types (D0, D1, D1+, D2) are defined according to the type of total or subtotal gastrectomy instead of the old classification system[11] (Table 1). This classification system was more practical and easier to understand than the others.

D0 dissection is performed less often than D1 dissection. D1 dissection is preferred for T1a cancers that are not suitable for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). In addition, cT1bN0, well differentiated, $\leqslant$ 1.5 cm cancers are suitable for D1 dissection. D1+ dissection includes cT1N0 tumors that are not suitable for D1 dissection (> 1.5 cm, poorly differentiated cancers). D2 dissection is suitable for the gastric cancers consisting of potentially curable T2-T4 and/or cT1N+ tumors. D2+ dissection involves removing the para-aortic lymph nodes in addition to the D2 lymph nodes.

Mesenteric vein lymph node dissection (No. 14v) is described as a part of the D2 dissection for distal gastric cancers in the previous edition of the guidelines. However, in the current edition, these lymph nodes are removed from the classification. Furthermore, removing the No.14v lymph nodes can be useful if apparent metastasis to the subpyloric lymph nodes (No. 6) occurs, and this dissection is called D2+No.14v. According to the latest guidelines, lymph nodes behind

Table 1 Lymph node dissections according to gastrectomy type for gastric cancer

Type of gastrectomy	Type of disection	Retrieved lymph node stations
Total	D0	Less than D1
	D1	No. 1-7
	D1+	D1 + No. 8a, 9, 11p[1]
	D2	D1 + No. 8a, 9, 10, 11p, 11d, 12a[1]
Distal subtotal	D0	Less than D1
	D1	No. 1, 3, 4sb, 4d, 5, 6, 7
	D1+	D1 + No. 8a, 9
	D2	D1 + No. 8a, 9, 11p, 12a
Pylor preserving	D0	Less than D1
	D1	No. 1, 3, 4sb, 4d, 6, 7
	D1+	D1+ No. 8a, 9
Proximal	D0	Less than D1
	D1	No. 1, 2, 3a, 4sa, 4sb, 7
	D1+	D1 + No. 8a, 9,11p[2]

[1]If the cancer has invaded the esophagus, the No. 110 lymph node must be removed in addition to D1+ dissection, and the No. 19, 20, 110 and 111 lymph nodes must be removed in addition to D2 dissection; [2]The No. 110 lymph node must be removed in addition to D1+ dissection.

the pancreatic head (No.13) must be dissected if the cancer has invaded the duodenum, and this dissection is defined as D2+ No.13. A prophylactic para-aortic lymphadenectomy is not recommended due to the increased number of postoperative complications and the reduced survival, according to a Japanese randomized clinical trial (RCT) (JCOG 9501)[12]. In the absence of direct invasion of the spleen and macroscopic splenic hilar lymph node metastasis, a splenectomy for dissection the splenic hilum (No. 10) and splenic artery (No. 11) lymph nodes is controversial. The results of RCT JCOG 0110 will provide guidance[13] on this matter.

DEVELOPMENTS IN THE TNM STAGING SYSTEM FOR GASTRIC CANCER

The TNM staging system is the gold standard for staging of all types of cancers. The depth of the cancer and number of the metastatic lymph nodes are the most important prognostic factors for curative gastric cancer surgery. Two major staging systems exist for gastric cancer. The first system is the Japanese Gastric Carcinoma Classification (JGCC) which is based on the location of the metastatic lymph node, and the second is the Union Internationale Contre le Cancer/American Joint Committee Cancer (UICC/AJCC) TNM staging system, which is based on the number of metastatic lymph nodes[14].

The TNM classification system was adapted to the JGCC in 2009 and called the UICC/AJC TNM staging system in the 7th edition. This system can be effective for evaluating the clinical and pathological data and for minimizing the stage migration phenomenon. The main principles of pT and pN, according to this new staging system, are shown in Table 2.

Table 2 Comparison of the sixth and the seventh TNM staging systems for the pT and pN stages

Tumor localization	6th TNM staging system	7th TNM staging system
Lamina propria or muscularis mucosa	T1	T1a
Submukoza	T1	T1b
Muscularis propria	T2a	T2
Subseroza	T2b	T3
Serozal invasion	T3	T4a
Adjacent organ invasion	T4	T4b
1-2 lymp node metastasis	N1	N1
3-6 lymp node metastasis	N1	N2
7-15 lymp node metastasis	N2	N3a
⩾ 16 lymp node metastasis	N3	N3b

Another important difference between sixth and seventh TNM staging systems is that M0 patients could have been classified as stage Ⅳ in the sixth edition. However, in the seventh edition, only M1 patients (positive peritoneal fluid and liver, lung, bone, or brain metastasis) are classified as stage Ⅳ. In addition, a stage ⅢC sub-group has been added (T4aN3M0, T4bN2M0, and T4bN3M0). Esophagogastric cancers that have not invaded the esophagus and that are below the Z line are included in the gastric cancer TNM staging system. Esophagogastric cancers that are located in the proximal 5 cm area or that have invaded the esophagus are included in the esophageal cancer TNM staging system[1,15].

Some authors have suggested that the UICC/AJCC TNM staging system can cause stage migration phenomenon[16]. Patients with less than 15 lymph nodes removed were not included in the N3 classification in the sixth edition of the TNM staging system. Stage migration phenomenon can be prevented because the presence of 7 or more metastatic lymph nodes is classified as N3 in the seventh edition. However, this issue is still controversial. The reduction of the stage migration has not yet been shown in the seventh edition of the UICC/AJCC TNM staging system[17]. In clinical practice, especially when considering adjuvant treatment, the true staging of gastric cancer is very important[18]. Additionally, after removing an insufficient number of lymph nodes and staging the gastric cancer according to the UICC/AJCC TNM staging system of these lymph nodes, the prognosis of patient will be poorer than expected. A new classification system that is based on the ratio of metastatic lymph nodes to the total number of lymph nodes removed (N ratio) has been proposed for more accurate staging of gastric cancer and a more reliable prognostic assessment[19-21]. However, this classification system is in the hypothetical stage. Determining the cut-off value and the fact that this system is only useful for patients with less than 15 lymph nodes removed are the main problems for N ratio staging. The N ratio staging system requires further study.

ENDOSCOPIC INTERVENTIONS FOR EARLY GASTRIC CANCER

Surgical resection has long been the primary treatment for gastric cancers. Minimally invasive surgery and endoscopic treatment modalities have been used with increasing frequency to prevent the mortality and morbidity caused by conventional surgery. With these new interventions, less invasive and less costly treatment protocols that do not have any negative impact on oncologic outcomes, preserve physiological functions, and improve the quality of life after surgery have been developed.

Different endoscopic resection (ER) techniques have been identified, and these can be divided into two main categories: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[22-24].

Patients with very low risk for lymph node metastasis and local recurrence are ideal candidates for ER. Early gastric cancer (EGC) is a limited malignant lesion in the gastric mucosa and submucosa, regardless of lymph node metastasis, and has excellent survival rates with curative treatment[25]. However, despite the reported high long-term survival rate, 3% of mucosal cancers and 20% of submucosal cancers exhibit lymph node metastasis[26]. The first indications for ER (differentiated cancer, < 2 cm tumor, and lesions with no ulceration or lymphovascular invasion that are limited to the mucosa) were determined empirically[27]. The extended indications for ER are still being discussed.

Japanese and South Korean gastric cancer treatment guidelines recommend that extended indications for ER should not be used for routine clinical practice, only for clinical research, due to the lack of high level evidence regarding the curative effect of ER[11,28]. In addition, the guidelines also suggest that ER should be applied according to standard indications. However, some gastric cancer treatment guidelines [National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO)] have suggested that obtaining negative horizontal and vertical margins with ER is adequate for the treatment of gastric cancers that are < 2 cm, are well/moderately differentiated, have no lymphovascular invasion and are not located under the submucosa[29].

We can assess to the high level of evidence of the efficacy and safety of ER with the results of randomized clinical trials that compare gastrectomy and ER. However, no randomized clinical trials have compared ER and gastrectomy. The initial information generated by compiling data from 12 institutions in Japan indicates that if negative horizontal and vertical margins are present, EMR is an effective and safe treatment[30]. According to these results, EMR has a 75.8% *en bloc* resection rate, a 73.9% complete resection rate, a 1.9% recurrence rate after complete resection, and a 99% gastric cancer-specific survival rate. Recently, in a matched cohort study that compared EMR and gastrectomy, no difference was observed in the complication rates in terms of survival and recurrence between the groups. The risk of metachronous gastric cancer was higher in the EMR group, but shorter hospital stays and lower costs were reported as the benefits of the EMR procedure[31].

The use of ER increased when ESD was applied, and higher curative resection rates than those produced by EMR were obtained. Although different results from various clinical centers were obtained, rates of 65%-100% for unblocked resection, 68%-95% for complete resection, 94%-100% for 5-year recurrence-free survival and 95%-100% for 5-year survival have been reported for ESD[32,33]. According to a meta-analysis examining 3548 EGC cases and comparing EMR and ESD, ESD produced higher unblocked resection rates (odds ratio: 9.69; 95%CI: 7.74-12.13), higher complete resection rates (odds ratio: 5.66; 95%CI, 2.92-10.96) and lower recurrence rates (odds ratio: 0.10; 95%CI: 0.06-0.18)[34].

In another meta-analysis, standard ESD criteria were compared to the extended ESD criteria. No differences in the overall survival rates were found between the ESD and extended ESD groups. However, a higher rate of complications was observed in the extended ESD group[35]. In a retrospective study, ESD was compared to gastrectomy, and similar oncological results were obtained. However, lower complication rates were observed in the ESD group[36]. Although the ESD procedure is considered adequate for many EGC patients, histopathological examinations have shown that in 5%-20% patients, the procedure is non-curative[37]. Due to the risk of lymphatic metastasis and non-standard presentations (deep submucosal invasion and the presence of lymphovascular invasion), surgical resection with a lymphadenectomy should be performed. Surgery is suggested in the presence of positive lateral surgical margins; however, ER, endoscopic ablation therapy or close monitoring are also feasible[38,39]. The oncologic efficacy of ER has not been supported by a high level of evidence because most recent studies have consisted of retrospective comparisons of non-homogenous groups[36]. In addition, the clinical studies were performed mostly in the South Korea or Japan, which have a 50% rate of EGC. In Western countries, EGC is performed at lower rates; therefore, ER has been applied at lower rates than in Japan or South Korea. Due to these reasons, the applicability of ER by endoscopists is limited[40]. Detecting the early stages of gastric cancer and more widespread use of ER modalities for selected indications will be possible with the implementation of standardized training modules in Western countries[22,41].

MINIMALLY INVASIVE SURGERY FOR GASTRIC CANCER (LAPAROSCOPIC AND ROBOTIC SURGERY)

Laparoscopic surgery

Minimally invasive surgery (MIS) has been increasingly performed due to new surgical tools and the development of techniques for gastric cancer surgery. MIS has some short-term and long-term advantages. MIS has been reported to be safe and effective for EGC, and it can be successfully applied to advanced gastric cancer (AGC) with increasing experience[42-44]. T1 gastric cancer, which has clinically been shown to exhibit perigastric lymph node involvement, and gastric cancer, which has no serosal and lymph node involvement, are expanded indications for MIS[45]. The laparoscopic assisted distal gastrectomy (LADG) was described for EGC in 1991[46]. LADG for EGC has shown short-term benefits, such as reduced intraoperative blood loss and providing early postoperative mobilization, in a meta-analysis of RCTs[47]. The short-term results of laparoscopic gastrectomy (LG) are favorable, but the long-term results for gastric cancer are still controversial. Despite the increasing use of laparoscopic surgery for gastric cancer, a low level of evidence exists. Six RCTs have compared LG and open gastrectomy (OG)[48-53]. Recently, Chen *et al*[54] reported a meta-analysis that included 7336 patients and 23 studies. In this meta-analysis, the 5-year survival and death related to the gastric cancer rates were compared between the LG and OG groups. The 5-year overall survival, recurrence and gastric cancer-related death rates were comparable for LG and OG. The authors suggested that, based on current information at the end of the study, LG provided oncologic safety for early and advanced gastric cancer surgery. LADG has been compared with the open distal gastrectomy (ODG) in some studies, and no significant difference has been found in the 3-year survival rates[55-57]. Choi *et al*[58] reported no significant differences in the overall survival and disease free survival rates over a long period. Zhang *et al*[59] also found no significant differences in recurrence rates between LG and OG for EGCs. Tang *et al*[60] published a review consisting of 32 independent studies that compared LG and OG. They reported less intraoperative blood loss, less pain, earlier return to mobilization, earlier return of bowel sounds and shorter hospital stay as benefits of LG and found no difference in mortality between LG and OG. In addition, they stated that the increased operation time is the only disadvantage of LG, which can be solved by developing surgical techniques.

Fewer lymph nodes were removed during the first applications of MIS than by OG[61]. However, the number of the lymph nodes removed became similar to that of OG as surgeons gained experience[62]. LG is defined as a safe, feasible procedure, especially for EGC, in many studies, and this statement is widely accepted[42,63]. The success of this method depends on factors such as the experience of the surgeon, surgeon's experience with laparoscopy, hospital volume and gastric cancer volume of the surgeon, and preoperative diagnosis. These factors have been found in many studies[42].

With the development of surgical instruments and the increasing experience of surgeons, efforts have been made to decrease the number of ports used for MIS and to develop a single incision technique[64]. However, carbon dioxide pneumoperitoneum, increased intra-abdominal pressure, prolonged operative time, less lymph node removal, port site metastases and technical issues are still problems for laparoscopic gastric cancer surgery[47,65]. MIS does not increase peritoneal spread and port site metastasis according to many studies[66,67].

The short-term results of MIS applications for AGC have been described in the literature[42,68]. Authors report that MIS is a viable option compared to OG for selected cases. Son *et al*[43] reported similar survival and recurrence rates for MIS and GC for T4a cancers. In a meta-analysis that compared OG with D2 dissection and LG with D2 dissection, similar overall survival and major complication rates were observed. However, less blood loss, less pain, reduced minor postoperative complications and shorter hospital stays were reported for the LG patients[69]. However, some experienced surgeons have suggested that current surgical instruments are not sufficient for D2 dissection during MIS for AGC, and they have published their oncological results[48,68,70]. Some ongoing RCTs (JOCG-0912, JLSSG-0901, KLASS-01, KLASS-02, and CLASS-01) are being performed to assess the feasibility of MIS in Korea, Japan and China[71-75].

Robotic surgery

Robotic technology has developed new tools for use in MIS during the past decade[42]. The first robot-assisted gastrectomy (RAG) was reported by Hashizume and Sugimachi in 2003[76]. RAG has been used for gastric cancer surgery to overcome the technical difficulties of LG[77]. RAG has potential technical advantages such as providing a three-dimensional image, articulated instruments, and allowing for precise movement. In addition, RAG has spread rapidly[42]. Compared to the LG, RAG provides better images and movements. RAG is more effective and safe than LG according to many experienced surgeons[78,79].

In a meta-analysis by Xiong *et al*[80], LG and RAG were compared regarding their effects on gastric cancer treatment. RAG produced less intraoperative blood loss and comparable mortality and morbidity rates. However, the operation time was significantly longer than that for LG and OG.

The potential advantages of RAG include facilitation of intra-corporeal anastomosis and allowing extended

Table 3 Ongoing multicentric studies of minimally invasive surgery

Country	Study	Subject
Japan	JCOG 0912 Phase Ⅲ	LG *vs* OG
South Korea	KLASS 01 Phase Ⅲ	LG *vs* OG
South Korea	KLASS 02-NCT01456598	LG *vs* OG (for AGC)
Japan	JLSSG0901 Phase Ⅱ-Ⅲ	LG *vs* OG (for AGC)
China	CLASS 01-NCT01609309	LG *vs* OG (for AGC)
South Korea	KLASS 03-NCT01584336 Phase Ⅱ	LG *vs* OG (for TG)
South Korea	NCT01309256	LG *vs* RAG

AGC: Advanced gastric cancer; LG: Laparoscopic gastrectomy; OG: Open gastrectomy; RAG: Robot asisted gastrectomy; TG: Total gastrectomy.

lymph node dissection. However, inconsistent results have been presented in the literature regarding this subject[42]. RAG would be useful for overcoming the challenges of traditional LG, but it has not provided the theoretical advantages of lymph node dissection[42]. RCTs involving RAG have not been reported, However, the recent meta-analyses are weak and include few patients[80,81].

The overall and major complication rates were similar to the short-term surgical results of the multicenter NCT01309256 study from Korea (11.9 *vs* 10.3 and 1.1% *vs* 1.1%, respectively). However, the operation costs (US $13432 *vs* US $8090, $P < 0.001$) and time (221 min *vs* 178 min, $P < 0.001$) were significantly higher for RAG[82].

ONGOING MULTICENTRIC STUDIES OF MINIMALLY INVASIVE SURGERY

The final results of the KLASS 01 Phase Ⅲ study for stage Ⅰ gastric cancer patients are expected to show the oncologic safety of the treatments. In the early results of this study, no significant differences were found between the LG and OG groups regarding mortality and morbidity. No significant difference between the MIS and OG groups regarding 3-year overall survival rates were observed according to the first results of the multicentric KLASS 02-NCT01456598 study. Phase Ⅱ and Ⅲ studies (JLSSG0901 trial; UMIN-000003420) are being conducted by the Japanese Laparoscopic Gastric Surgery Study (JLSSG) group to investigate the technical and oncologic safety of laparoscopic treatment. The feasibility and the oncological safety of laparoscopic treatment of AGC are being investigated by the Chinese Laparoscopic Gastrointestinal Surgical Study Group (CLASS) in the CLASS 01-NCT01609309 study. The ongoing phase 2 KLASS 03-NCT01584336 study is investigating the feasibility and safety of laparoscopic and open gastrectomy for stage 1 gastric cancer patients in Korea. In addition, the NCT01309256 study continues to compare RAG and LG (Table 3).

INTRAPERITONEAL CHEMOTHERAPY

Gastric cancer is a biologically aggressive tumor. The prognosis is poor even if curative surgery can be performed. For higher stages of stomach cancer, the most common form of invasion is peritoneal metastasis[83]. Almost all patients with positive peritoneal cytology progress to peritoneal carcinomatosis and die within the first two years of the disease[84]. The peritoneum is supported by the basal membrane of mesothelial cells and connective tissue. The blood- peritoneal barrier is located between the mesothelial cells and mesothelial capillaries. Few systemic chemotherapeutic agents can pass through this barrier. Additionally, intraperitoneal chemotherapy has less adverse effects and produces a higher dose in the intraperitoneal regions than systemic chemotherapy[85]. Intraperitoneal chemotherapy can be given preoperatively and during the early postoperative period (EPIC). Intraperitoneal chemotherapy, given preoperatively, is aimed to prevent micro metastasis, increase the chance of curative resection and perform a complete cytoreduction. EPIC is given as soon as the general condition of the patient has recovered after surgery. It is started during the period in which the minimal residual tumor load is present and before the residual cancer cells become hidden between fibrin deposits[86].

EXTENSIVE INTRAOPERATIVE PERITONEAL LAVAGES

Kuramoto *et al*[87] developed a treatment modality called "extensive intraoperative peritoneal lavage treatment" (EIPL), which aims to destroy the free cancer cells spreading into the peritoneum. After a curative resection is performed, the abdomen is washed with 1 liter of isotonic saline and aspirated. Then, this procedure is repeated 10 times. The aim of this method, which is called "Limiting dilution method", is to remove the free cancer cells in the peritoneum by washing with isotonic saline. A prospective randomized controlled study was performed that included 1522 patients with higher stage stomach cancer who had undergone curative resection (R0) and D2 dissection. Then, 88 patients with positive cytology and without peritoneal invasion (CY+/P-) were divided into 3 groups. Surgery alone was performed on for the first group. The second group was treated with intraperitoneal chemotherapy, and the third group was treated with EIPL+intraperitoneal chemotherapy. In the group given prophylactic intraperitoneal chemotherapy and intraoperative peritoneal lavage, the 5-year survival rate was markedly increased compared to the other group. The 5-year survival rates of each of the three groups were 0%, 4.6% and 43.8%, respectively. Standard prophylactic treatment against peritoneal metastasis has been reported as an effective treat-

ment modality. It is practical, can be performed in any situation, and does not extend the operation time. In the reported studies, prophylactic treatments used to prevent peritoneal metastasis in the early period has been shown to be promising[84,87-89].

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) were developed as a combined treatment modality from the results of experimental and clinical studies[90]. In the 1990's Sugarbaker described the surgical method in detail. Complete cytoreduction must be performed before HIPEC is administered. Hyperthermia increases the antitumor activity and penetration of chemotherapeutics[91].

A meta-analysis of the results of 13 randomized studies (1648 cases) examined the benefits of adjuvant intraperitoneal chemotherapy after curative gastric cancer resection. It reported that patients who received intraperitoneal chemotherapy exhibited better survival[92]. Yang *et al*[93] reported median survival times of 11 and 6.5 mo, respectively, in their prospective randomized phase Ⅲ clinic study that compared the effects of CRS + HIPEC and CRS alone on 68 patients with gastric peritoneal carcinomatosis.

The survival time was increased to 13.5 mo after complete macroscopic cytoreduction (CC-0/1). Gill *et al*[94] summarized the data of 10 studies (n = 445), including one prospective controlled study, 3 retrospective case reports and 6 prospective case series, in which they found a median survival time of 15 mo (9.5-43.4 mo) for CC-0/1 patients. Additionally, the study results of pioneering authors such as Fujimoto, Sugarbaker, Glehen and Yonemura showed that the median survival time ranged between 11 and 16 mo in patients who underwent HIPEC with partial or complete cytoreduction[91,95]. Systemic chemotherapy produces a very limited survival benefit for patients who undergo CRS and HIPEC, increasing the life expectancy by 30%. This shows that systemic chemotherapy and HIPEC are more beneficial for patients who have been surgically treated. Koga *et al*[96] investigated the benefits of HIPEC as an adjuvant therapy for the prevention of peritoneal recurrence in a limited number of patients with gastric cancer and serosal invasion in a randomized clinical study. They found 3-year survival rates of 67.3% and 83% in patients with surgery plus HIPEC and in the control group.

Additionally, Hamazoe *et al*[97] found an increased survival rate in patients who underwent prophylactic HIPEC with high dose mitomycin C compared to the control group (64.2% *vs* 52.5% respectively). However, a randomized clinical study by Fujimoto, Fujimura and Yonemura showed that adjuvant HIPEC treatment decreased peritoneal recurrence and increased the survival rates of AGC patients[98-100]. Only one prospective randomized study showed that adjuvant HIPEC treatment produces no survival advantage[101]. The SRC and HIPEC multimodal combined treatment can only produce survival benefits for patients with gastric peritoneal carcinomatosis with well-defined boundaries. However, more detailed clinical studies are needed to determine the role of modern systemic chemotherapy[90].

NEO-ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER

Pre- and post-operative chemotherapy are accepted as the standard treatments for curable gastric cancers, except for the stage 1 gastric cancers, in Europe and England[102]. These results were concluded from the results of the Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) study[103]. In the USA and some Latin American countries, post-operative chemotherapy is the gold standard because it has narrower boundaries than D2 surgery in most patients. This result was concluded from the results of the Inter group 0116 study[104]. Adjuvant chemotherapy is used as the gold standard treatment in East Asian countries that typically perform standard D2 surgery[105-108]. Neo-adjuvant chemotherapy (NAC) indications are limited in these countries, and this method is accepted as an experimental treatment for most curable patients. NAC is typically only administered to patients with borderline resectable gastric cancer or a poor prognosis after R0 resection, even though evidence supported by phase 3 studies is lacking.

In a randomized controlled study of a large population in Europe, perioperative chemotherapy, including epirubicin cisplatin and 5-FU (ECF), significantly increased overall survival and cancer free survival compared to the surgery group alone (HR: 0.75, 95%CI: 0.60-0.93, P = 0.009)[103]. Other prospective studies of this procedure include the FFCD 9703 study and the EORCT 40954 study, which had relatively fewer participants. Less than 250 cases were reported in both studies, and they were ended before reaching the planned sample size[109,110]. The EORCT 40954 study does not include post-operative chemotherapy; therefore it only determines the effect of NAC compared to surgery alone. Though the FFCD 9703 study had completed data on 224 patients (the planned sample size had been 250), it was statically shown that NAC is significantly more beneficial than surgery alone (HR: 0.69, 95%CI: 0.50-0.95, P = 0.02). The EORCT study was ended due to a low enrollment rate after having recorded only 114 cases. No survival advantage was shown in this study. In the MAGIC study, the ECF regimen was used; in the FFCD 9703

study, a cisplatin regimen and 5-FU (CF) were used; in the EORCT study, cisplatin, leucovorin (FLC) and 5-FU (CF) regimens were used.

Recently, much attention has been focused on linitis plastica, which has a worse prognosis than other diseases that involve extensive lymph node invasion (either large sized lymph nodes surrounding the first branch of the celiac artery or para-aortic lymph node metastasis)[111,112]. Three phase Ⅱ clinical studies have reported a 5-year survival rate of 10% for diseases with extensive lymph node invasion. Most of these diseases have been classified as unresectable, and they are treated with palliative chemotherapy in Western countries. The survival rates were reported only in the first two studies[112,113]. Another area of focus is linitis plastica, which is accepted as inoperable by some surgeons[114].

Regarding ongoing studies, a Korean study is comparing S1 monotherapy following D2 lymphadenectomy to NAC with Docetaxel, S-1 and Oxaliplatin (PRODIGY study: NCT01515748). The RESONANCE study in China (NCT01583361) is testing the effectiveness of postoperative SOX treatment after D2 lymphadenectomy in addition to NAC with S1 and Oxaliplatin[102].

HER 2 IN GASTRIC CANCER AND TARGETED TREATMENT

Trastuzumab is a monoclonal antibody that interacts with human epidermal growth factor (HER) 2 and is related to gastric carcinoma[115]. The gene amplification and protein expression of HER2 were first reported in 1986[116,117]. Herceptin (trastuzumab) blocks HER2 function, and HER2 is a treatment option fort he breast cancer patients[118]. The anti-tumor mechanism of trastuzumab is not clearly known, but mechanisms such as blocking the cycle progression of the cell and cell signaling pathways; initiating the cell mediated cytotoxicity with antibodies; induction of anti-angiogenesis effects and increasing receptor turnover by endocytosis have been reported previously. Gene amplification of HER2 using fluorescence in situ hybridization (FISH) and protein overexpression with immunohistochemistry (IHC) have reported HER2 levels of 16%-27.1% and 8.2%-54%, respectively[119]. The trastuzumab for gastric cancer (ToGA) phase Ⅲ international multicenter RCT compared the clinical effect and safety of trastuzumab with that of standard chemotherapy (capecitabine or intravenous 5-fluorouracil and cisplatin). Survival after treatment with trastuzumab was significantly longer than that with only standard chemotherapy (13.8 mo *vs* 11.1 mo, respectively, $P = 0.0046$). Additionally, comparable toxicity and improvement of the time of progression and progression free survival were observed in the trastuzumab+ standard chemotherapy group[120]. Treatment with trastuzumab is standard for the HER2 (+) patients (IHC score +3 and/or FISH-) in the USA and Japan. Trastuzumab is recommended for patients with an IHC score of 2+/positive FISH or an IHC score of 3+ with high HER2 protein expression, according to the ToGA study in Europe. Evaluation of HER2 is essential for trastuzumab treatment[120]. The effect of trastuzumab on patients with low HER2 expression (IHC score 0/FISH positive or IHC score 1/FISH positive) is not clear according to the ToGA study. Interestingly, HER2 expression was higher in patients with gastroesophageal cancers than in those with other gastric cancers in this study (33.2% *vs* 20.9%, respectively, $P < 0.001$)[121].

In a observational, prospective, cohort, multicenter, study by Matsusaka *et al*[122], HER 2 expression and gene amplification were assessed, and the relationship between HER2 status and clinicopathological findings in Japanese gastric cancer patients with metastasis or recurrence was investigated. A total of 1461 patients in 157 centers were included in the study, and 1427 of 1461 patients were evaluated. The overall HER2 (+) patient rate was 21.2%. The rate of patients with high levels of HER2(+) (IHC score of 2+/FISH positive or IHC score of 3+) was 15.6%, and the rate of patients with low HER2 (+) levels was 7.0%. Multiple logistic regression analysis showed that an intestinal type of cancer, the absence of peritoneal metastasis and hepatic metastases are significant independent factors associated with the expression of HER2 positivity. An intestinal cancer type was associated with low HER2 expression. Factors such as the type specimen fixation, total fixation time, pH of the fixative and the time before the fixation affected the HER2 status according to this study. Additionally, the authors reported that HER2 has intratumoral heterogeneity and this rate is up to %70 in the HER2 (+) cancers. Because of that gastric biopsies can cause false negative or false positive results[122]. Therefore, endoscopists should consider conducting multiple biopsies. As a result, the intestinal type of gastric cancer is an independent factor for HER2 positivity and low HER2 expression.

The association between the HER2 gene amplification and protein expression and the clinicopathological findings of resectable gastric cancer patients were investigated in another study by He *et al*[119] A total of 197 patients who underwent curative resection were included in the study, and the survival rates were noted. The amount of HER2 gene amplification was 17.7% according to Hoffman's gastric cancer HER2 scoring system. Additionally, the HER2 (3+), HER2 (2+) and HER2 (0/1+) rates in all patients were 9.64%, 12.69% and 77.66%, respectively. The positivity of HER2 was higher in the intestinal type of cancer and well differentiated cancers than in the diffuse type and poorly differentiated cancers (28.57% *vs* 13.43%, $P = 0.0103$ and 37.25% *vs* 11.64%, $P < 0.0001$). The authors reported that gastric cancers that were well differentiated, of the intestinal type, and poorly differentiated with no metastasis to the lymph nodes

were suitable for the targeted therapy with Herceptin.

An ongoing RCT is examining the effect of trastuzumab on the HER2(+) gastric cancer patients who have undergone an extended lymphadenectomy. The results of this study will provide detailed information[123].

An accurate and standardized scoring system of HER2 is important for the Herceptin therapy and useful for the selection of gastric cancer patients.

HELICOBACTER PYLORI IN GASTRIC CANCER

Helicobacter pylori (*H. pylori*) which is involved in 90% of all gastric malignancies, infects nearly 50% of the world's population and it is the most crucial etiologic agent for gastric adenocarcinoma[124-126]. *H. pylori* infection causes some clinical manifestations such as; chronic gastritis, duodenal ulcer, gastric ulcer/adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma (MALToma). The most important *H. pylori* releated predisposed factors for gastric carcinoma are bacterial virulence factors [cagA (cytotoxin-associated gene A) and its pathogenicity island (cag PAI) and vacA (vacuolating cytotoxin A)], host genetic factors (IL-1 gene cluster polymorphism, TNF-α and IL-10 gene polymorphism) and environmental factors (salt, smoking)[127]. *H. pylori* eradication can prevent the recurrence of peptic ulcers and MALToma of the stomach. Also recurrence rates after endoscopic resection of early gastric cancer is lower after *H. pylori* eradication. However, it is not clear that the eradication of *H. pylori* reduces the risk of gastric cancer directly. A randomized controlled trial concluded that the eradication of *H. Pylori* provided decline of gastric cancer risk significantly after 15 years of follow-up[128]. The well-known indications for *H. pylori* eradication are peptic ulcer, MALToma, and endoscopic treatment of early gastric cancer. However, Japanese guidelines strongly recommend that all *H. pylori* infections should be eradicated regardless of the associated disease[129].

The eradication of *H. pylori* varies by region. Recent Korean and Japanese guidelines still recommend Standard triple therapy (PPI + amoxicillin + clarithromycin or PPI + metronidazole + clarithromycin) as a first-line treatment[129-131]. However, recent European guidelines recommend that first-line treatment should be adjusted to clarithromycin resistance[132]. Standard triple therapy is recommended as a first-line treatment for the low-resistance (< 20%) regions, but bismuth quadruple therapy or sequential/concomitant therapy is recommended for the high-resistance (> 20%) regions[132].

Some authors suggested that, the process of *H. pylori*-related carcinogenesis is being inhibited by aspirin, NSAIDs, and COX-2 inhibitors and these can prevent the development of gastric cancer[133]. Vitamin C and antioxidants have also protective effects against *H. pylori*-induced gastric carcinogenesis[134]. In a recent meta-analysis which is including 45 randomized controlled trials, increased *H. pylori* eradication was associated with using of probiotics with standard triple therapy[135].

On the other hand, preoperative *H. pylori* infection is associated with increased survival after resection of gastric adenocarcinoma. In a multicenter retrospective study, *H. pylori* positivity was associated with longer overall survival (84.3 mo *vs* 44.2 mo, P = 0.008) for the 559 patients who had gastrectomy because of gastric cancer. *H. pylori* was not associated with recurrence free survival or disease spesific survival in all patients. Also, *H. pylori* infection showed no association with overall survival in stage 1 or stage 2 patients. But in the stage 3 patients, *H. pylori* was associated with longer overall survival (44.5 mo *vs* 24.7 mo, P = 0.018), longer recurrence free survival (31.4 mo *vs* 21.6 mo, P = 0.232), and longer disease spesific survival (44.8 mo *vs* 27.2 mo, P = 0.034)[136].

CONCLUSION

Gastric cancers are distinguished from other cancers by their high morbidity and mortality. Many studies have been conducted to improve the quality of life and extend the survival rates of patients, and some of these studies are ongoing. Although promising developments have been made in recent years, the obtained results have limited reliability and benefits. We believe that significant improvements in the treatment of gastric cancer will be developed according to the long-term results of ongoing randomized clinical trials.

REFERENCES

1 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2 **Sasako M**. Surgical management of gastric cancer: the Japanese experience. In: Daly JM, Hennesy TPH, Reynolds JV, editors. Management of Upper Gastrointestinal Cancer. London: W. B. Saunders, 1999: 107-122

3 **Maruyama K**, Gunvén P, Okabayashi K, Sasako M, Kinoshita T. Lymph node metastases of gastric cancer. General pattern in 1931 patients. *Ann Surg* 1989; **210**: 596-602 [PMID: 2818028 DOI: 10.1007/BF02468883]

4 **Mihmanli M**, Dilege E, Demir U, Coskun H, Eroglu T, Uysalol MD. The use of tumor markers as predictors of prognosis in gastric cancer. *Hepatogastroenterology* 2004; **51**: 1544-1547 [PMID: 15362797]

5 **Kajitani T**. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. *Jpn J Surg* 1981; **11**: 127-139 [PMID: 7300058]

6 **Sano T**, Katai H, Sasako M, Maruyama K. One thousand consecutive gastrectomies without operative mortality. *Br J Surg* 2002; **89**: 123 [PMID: 11851682]

7 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 1st English Edition. Tokyo: Kanehara, 1995

8 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition - *Gastric Cancer* 1998; **1**: 10-24 [PMID: 11957040]
9 **Sano T**. Surgery for cancer of the stomach. In: Griffin SM, Raimes SA, Shenfine J, editors. Oesophagogastric Surgery 5th Ed. Oxford: Elsevier, 2014: 118-145
10 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
11 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]
12 **Sasako M**, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; **359**: 453-462 [PMID: 18669424 DOI: 10.1056/NEJMoa0707035]
13 **Sano T**, Yamamoto S, Sasako M. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan clinical oncology group study JCOG 0110-MF. *Jpn J Clin Oncol* 2002; **32**: 363-364 [PMID: 12417603]
14 **Sobin LH**, Gospodarowicz MK. International Union Against Cancer (UICC) TNM Classification of Malignant Tumours. 7th ed. Oxford: Wiley-Blackwell, 2009: 73-77
15 **Edge SB**, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. American Joint Committee on Cancer (AJCC) Cancer Staging Handbook. 7th ed. New York: Spriger-Verlag, 2010: 117-127
16 **Jung H**, Lee HH, Song KY, Jeon HM, Park CH. Validation of the seventh edition of the American Joint Committee on Cancer TNM staging system for gastric cancer. *Cancer* 2011; **117**: 2371-2378 [PMID: 24048784 DOI: 10.1002/cncr.25778]
17 **Kim CY**, Yang DH. Adjustment of N stages of gastric cancer by the ratio between the metastatic and examined lymph nodes. *Ann Surg Oncol* 2009; **16**: 1868-1874 [PMID: 19434459 DOI: 10.1245/s10434-009-0430-8]
18 **Bunt AM**, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995; **13**: 19-25 [PMID: 7799019]
19 **Ilhan E**, Zengel B, Simsek H, Canpolat S, Yildirim M. Can the Ratio of Metastatic to Examined Lymph Nodes (N Ratio) be used as an Independent Prognostic Factor in Patients with Gastric Cancer? Is Hypothetical TRM (tumor-ratio-metastasis) Staging System an Alternative to TNM (tumor-node-metastasis) Staging System? *PRZ Gastroenterol* 2013; **8**: 247-256 [DOI: 10.5114/pg.2013.37488]
20 **Wang W**, Xu DZ, Li YF, Guan YX, Sun XW, Chen YB, Kesari R, Huang CY, Li W, Zhan YQ, Zhou ZW. Tumor-ratio-metastasis staging system as an alternative to the 7th edition UICC TNM system in gastric cancer after D2 resection--results of a single-institution study of 1343 Chinese patients. *Ann Oncol* 2011; **22**: 2049-2056 [PMID: 21310759 DOI: 10.1093/annonc/mdq716]
21 **Xiao LB**, Yu JX, Wu WH, Xu FF, Yang SB. Superiority of metastatic lymph node ratio to the 7th edition UICC N staging in gastric cancer. *World J Gastroenterol* 2011; **17**: 5123-5130 [PMID: 22171148 DOI: 10.3748/wjg.v17.i46.5123]
22 **Güner A**. Erken Mide Kanserinde Endoskopik Mukozal Rezeksiyon ve Endoskopik Submukozal Diseksiyon'un Yeri ve Tekniği. In: Mihmanlı M, İlhan E, Alemdar A. Mihmanlı'nın Mide Kanseri ve Cerrahi Tedavisi. 3th ed. Istanbul: Tıbbi Yayınlar Merkezi, 2016: 215-221
23 **Güner A**, Hyung WJ. Minimally invasive surgery for gastric cancer. *Ulus Cerrahi Derg* 2014; **30**: 1-9 [PMID: 25931879 DOI: 10.5152/UCD.2014.2607]
24 **Asano M**. Endoscopic submucosal dissection and surgical treatment for gastrointestinal cancer. *World J Gastrointest Endosc* 2012; **4**: 438-447 [PMID: 23189214 DOI: 10.4253/wjge.v4.i10.438]
25 **Wang J**, Yu JC, Kang WM, Ma ZQ. Treatment strategy for early gastric cancer. *Surg Oncol* 2012; **21**: 119-123 [PMID: 21256735]
26 **Kim YI**, Lee JH, Kook MC, Lee JY, Kim CG, Ryu KW, Kim YW, Choi IJ. Lymph node metastasis risk according to the depth of invasion in early gastric cancers confined to the mucosal layer. *Gastric Cancer* 2015; Epub ahead of print [PMID: 26304170]
27 **Ahn JY**, Jung HY, Choi KD, Choi JY, Kim MY, Lee JH, Choi KS, Kim do H, Song HJ, Lee GH, Kim JH, Park YS. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. *Gastrointest Endosc* 2011; **74**: 485-493 [PMID: 21741645 DOI: 10.1016/j.gie.2011.04.038]
28 **Lee JH**, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, Kim JM, Kim YI, Ryu KW, Kong SH, Kim HI, Jung HY, Kim YS, Zang DY, Cho JY, Park JO, Lim do H, Jung ES, Ahn HS, Kim HJ. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. *J Gastric Cancer* 2014; **14**: 87-104 [PMID: 25061536 DOI: 10.5230/jgc.2014.14.2.87]
29 **Ajani JA**, Bentrem DJ, Besh S, D'Amico TA, Das P, Denlinger C, Fakih MG, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hofstetter WL, Ilson DH, Keswani RN, Kleinberg LR, Korn WM, Lockhart AC, Meredith K, Mulcahy MF, Orringer MB, Posey JA, Sasson AR, Scott WJ, Strong VE, Varghese TK, Warren G, Washington MK, Willett C, Wright CD, McMillian NR, Sundar H. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2013; **11**: 531-546 [PMID: 23667204]
30 **Kojima T**, Parra-Blanco A, Takahashi H, Fujita R. Outcome of endoscopic mucosal resection for early gastric cancer: review of the Japanese literature. *Gastrointest Endosc* 1998; **48**: 550-554; discussion 554-555 [PMID: 9831855]
31 **Choi KS**, Jung HY, Choi KD, Lee GH, Song HJ, Kim do H, Lee JH, Kim MY, Kim BS, Oh ST, Yook JH, Jang SJ, Yun SC, Kim SO, Kim JH. EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. *Gastrointest Endosc* 2011; **73**: 942-948 [PMID: 21392757 DOI: 10.1016/j.gie.2010.12.032]
32 **Kim MY**, Cho JH, Cho JY. Ever-changing endoscopic treatment for early gastric cancer: yesterday-today-tomorrow. *World J Gastroenterol* 2014; **20**: 13273-13283 [PMID: 25309064 DOI: 10.3748/wjg.v20.i37.13273]
33 **Repici A**, Zullo A, Hassan C, Spaggiari P, Strangio G, Vitetta E, Ferrara E, Malesci A. Endoscopic submucosal dissection of early gastric neoplastic lesions: a western series. *Eur J Gastroenterol Hepatol* 2013; **25**: 1261-1264 [PMID: 23925276 DOI: 10.1097/MEG.0b013e328364b492]
34 **Facciorusso A**, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest Endosc* 2014; **6**: 555-563 [PMID: 25400870 DOI: 10.4253/wjge.v6.i11.555]
35 **Peng LJ**, Tian SN, Lu L, Chen H, Ouyang YY, Wu YJ. Outcome of endoscopic submucosal dissection for early gastric cancer of conventional and expanded indications: systematic review and meta-analysis. *J Dig Dis* 2015; **16**: 67-74 [PMID: 25421172 DOI: 10.1111/1751-2980.12217]
36 **Chiu PW**, Teoh AY, To KF, Wong SK, Liu SY, Lam CC, Yung MY, Chan FK, Lau JY, Ng EK. Endoscopic submucosal dissection (ESD) compared with gastrectomy for treatment of early gastric neoplasia: a retrospective cohort study. *Surg Endosc* 2012; **26**: 3584-3591 [PMID: 22678176 DOI: 10.1007/s00464-012-2371-8]
37 **Bang CS**, Baik GH, Shin IS, Kim JB, Suk KT, Yoon JH, Kim YS, Kim DJ, Shin WG, Kim KH, Kim HY, Lim H, Kang HS, Kim JH, Kim JB, Jung SW, Kae SH, Jang HJ, Choi MH. Endoscopic submucosal dissection for early gastric cancer with undifferentiated-type histology: A meta-analysis. *World J Gastroenterol* 2015; **21**: 6032-6043 [PMID: 26019470 DOI: 10.3748/wjg.v21.i19.6032]
38 **Lee JH**, Lee JH, Kim KM, Kang KJ, Min BH, Kim JJ. Clinicopathological factors of multiple lateral margin involvement after endoscopic submucosal dissection for early gastric cancer. *Surg Endosc* 2015; **29**: 3460-3468 [PMID: 25673346 DOI: 10.1007/s00464-015-4095-z]
39 **Han JP**, Hong SJ, Kim HK, Lee YN, Lee TH, Ko BM, Cho JY. Risk stratification and management of non-curative resection after endoscopic submucosal dissection for early gastric cancer. *Surg Endosc* 2016; **30**: 184-189 [PMID: 25829067 DOI: 10.1007/

s00464-015-4180-3]
40 **Spiliotis J**, Ziogas D, Baltogiannis G. Outweighing the benefits and weakness of endoscopic submucosal dissection for early gastric cancer in the west. *Surg Endosc* 2010; **24**: 1507-1509 [PMID: 20044771 DOI: 10.1007/s00464-009-0789-4]
41 **Coman RM**, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; **5**: 369-378 [PMID: 23951392 DOI: 10.4253/wjge.v5.i8.369]
42 **Desiderio J**, Jiang ZW, Nguyen NT, Zhang S, Reim D, Alimoglu O, Azagra JS, Yu PW, Coburn NG, Qi F, Jackson PG, Zang L, Brower ST, Kurokawa Y, Facy O, Tsujimoto H, Coratti A, Annecchiarico M, Bazzocchi F, Avanzolini A, Gagniere J, Pezet D, Cianchi F, Badii B, Novotny A, Eren T, Leblebici M, Goergen M, Zhang B, Zhao YL, Liu T, Al-Refaie W, Ma J, Takiguchi S, Lequeu JB, Trastulli S, Parisi A. Robotic, laparoscopic and open surgery for gastric cancer compared on surgical, clinical and oncological outcomes: a multi-institutional chart review. A study protocol of the International study group on Minimally Invasive surgery for GASTRIc Cancer-IMIGASTRIC. *BMJ Open* 2015; **5**: e008198 [PMID: 26482769 DOI: 10.1136/bmjopen-2015-008198]
43 **Son T**, Kwon IG, Hyung WJ. Minimally invasive surgery for gastric cancer treatment: current status and future perspectives. *Gut Liver* 2014; **8**: 229-236 [PMID: 24827617 DOI: 10.5009/gnl.2014.8.3.229]
44 **Uyama I**, Suda K, Satoh S. Laparoscopic surgery for advanced gastric cancer: current status and future perspectives. *J Gastric Cancer* 2013; **13**: 19-25 [PMID: 23610715 DOI: 10.5230/jgc.2013.13.1.19]
45 **An JY**, Heo GU, Cheong JH, Hyung WJ, Choi SH, Noh SH. Assessment of open versus laparoscopy-assisted gastrectomy in lymph node-positive early gastric cancer: a retrospective cohort analysis. *J Surg Oncol* 2010; **102**: 77-81 [PMID: 20578083 DOI: 10.1002/jso.21554]
46 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]
47 **Chen XZ**, Hu JK, Yang K, Wang L, Lu QC. Short-term evaluation of laparoscopy-assisted distal gastrectomy for predictive early gastric cancer: a meta-analysis of randomized controlled trials. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 277-284 [PMID: 19692873 DOI: 10.1097/SLE.0b013e3181b080d3]
48 **Hayashi H**, Ochiai T, Shimada H, Gunji Y. Prospective randomized study of open versus laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer. *Surg Endosc* 2005; **19**: 1172-1176 [PMID: 16132323]
49 **Huscher CG**, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A, Ponzano C. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg* 2005; **241**: 232-237 [PMID: 15650632]
50 **Kim HH**, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, Lee HJ, Song KY. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report--a phase III multicenter, prospective, randomized Trial (KLASS Trial). *Ann Surg* 2010; **251**: 417-420 [PMID: 20160637 DOI: 10.1097/SLA.0b013e3181cc8f6b]
51 **Kim YW**, Baik YH, Yun YH, Nam BH, Kim DH, Choi IJ, Bae JM. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. *Ann Surg* 2008; **248**: 721-727 [PMID: 18948798 DOI: 10.1097/SLA.0b013e318185e62e]
52 **Kitano S**, Shiraishi N, Fujii K, Yasuda K, Inomata M, Adachi Y. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. *Surgery* 2002; **131**: S306-S311 [PMID: 11821829]
53 **Lee JH**, Han HS, Lee JH. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. *Surg Endosc* 2005; **19**: 168-173 [PMID: 15580441]
54 **Chen XZ**, Wen L, Rui YY, Liu CX, Zhao QC, Zhou ZG, Hu JK. Long-term survival outcomes of laparoscopic versus open gastrectomy for gastric cancer: a systematic review and meta-analysis. *Medicine* (Baltimore) 2015; **94**: e454 [PMID: 25634185 DOI: 10.1097/MD.0000000000000454]
55 **Qiu J**, Pankaj P, Jiang H, Zeng Y, Wu H. Laparoscopy versus open distal gastrectomy for advanced gastric cancer: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 1-7 [PMID: 23386142 DOI: 10.1097/SLE.0b013e3182747af7]
56 **Chen K**, Xu XW, Zhang RC, Pan Y, Wu D, Mou YP. Systematic review and meta-analysis of laparoscopy-assisted and open total gastrectomy for gastric cancer. *World J Gastroenterol* 2013; **19**: 5365-5376 [PMID: 23983442 DOI: 10.3748/wjg.v19.i32.5365]
57 **Sun J**, Li J, Wang J, Pan T, Zhou J, Fu X, Zhang S. Meta-analysis of randomized controlled trials on laparoscopic gastrectomy vs. open gastrectomy for distal gastric cancer. *Hepatogastroenterology* 2012; **59**: 1699-1705 [PMID: 22626787 DOI: 10.5754/hge12259]
58 **Choi YY**, Bae JM, An JY, Hyung WJ, Noh SH. Laparoscopic gastrectomy for advanced gastric cancer: are the long-term results comparable with conventional open gastrectomy? A systematic review and meta-analysis. *J Surg Oncol* 2013; **108**: 550-556 [PMID: 24115104 DOI: 10.1002/jso.23438]
59 **Zhang CD**, Chen SC, Feng ZF, Zhao ZM, Wang JN, Dai DQ. Laparoscopic versus open gastrectomy for early gastric cancer in Asia: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 365-377 [PMID: 23917592 DOI: 10.1097/SLE.0b013e31828e3e6e]
60 **Tang HN**, Hu JH. A comparison of surgical procedures and postoperative cares for minimally invasive laparoscopic gastrectomy and open gastrectomy in gastric cancer. *Int J Clin Exp Med* 2015; **8**: 10321-10329 [PMID: 26379823]
61 **Memon MA**, Khan S, Yunus RM, Barr R, Memon B. Meta-analysis of laparoscopic and open distal gastrectomy for gastric carcinoma. *Surg Endosc* 2008; **22**: 1781-1789 [PMID: 18437472 DOI: 10.1007/s00464-008-9925-9]
62 **Tokunaga M**, Hiki N, Fukunaga T, Nohara K, Katayama H, Akashi Y, Ohyama S, Yamaguchi T. Laparoscopy-assisted distal gastrectomy with D2 lymph node dissection following standardization--a preliminary study. *J Gastrointest Surg* 2009; **13**: 1058-1063 [PMID: 19267164 DOI: 10.1007/s11605-009-0840-8]
63 **Kitano S**, Shiraishi N. Current status of laparoscopic gastrectomy for cancer in Japan. *Surg Endosc* 2004; **18**: 182-185 [PMID: 14691704]
64 **Kunisaki C**, Ono HA, Oshima T, Makino H, Akiyama H, Endo I. Relevance of reduced-port laparoscopic distal gastrectomy for gastric cancer: a pilot study. *Dig Surg* 2012; **29**: 261-268 [PMID: 22907557 DOI: 10.1159/000341677]
65 **Fujiwara M**, Kodera Y, Misawa K, Kinoshita M, Kinoshita T, Miura S, Ohashi N, Nakayama G, Koike M, Nakao A. Longterm outcomes of early-stage gastric carcinoma patients treated with laparoscopy-assisted surgery. *J Am Coll Surg* 2008; **206**: 138-143 [PMID: 18155579]
66 **Son T**, Hyung WJ, Lee JH, Kim YM, Noh SH. Minimally invasive surgery for serosa-positive gastric cancer (pT4a) in patients with preoperative diagnosis of cancer without serosal invasion. *Surg Endosc* 2014; **28**: 866-874 [PMID: 24149848 DOI: 10.1007/s00464-013-3236-5]
67 **Oh SY**, Kwon S, Lee KG, Suh YS, Choe HN, Kong SH, Lee HJ, Kim WH, Yang HK. Outcomes of minimally invasive surgery for early gastric cancer are comparable with those for open surgery: analysis of 1,013 minimally invasive surgeries at a single institution. *Surg Endosc* 2014; **28**: 789-795 [PMID: 24263458 DOI: 10.1007/s00464-013-3256-1]
68 **Gordon AC**, Kojima K, Inokuchi M, Kato K, Sugihara K. Long-term comparison of laparoscopy-assisted distal gastrectomy and open distal gastrectomy in advanced gastric cancer. *Surg Endosc* 2013; **27**: 462-470 [PMID: 22890478 DOI: 10.1007/s00464-012-2459-1]
69 **Wei HB**, Wei B, Qi CL, Chen TF, Huang Y, Zheng ZH, Huang JL, Fang JF. Laparoscopic versus open gastrectomy with D2 lymph node dissection for gastric cancer: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2011; **21**: 383-390 [PMID: 22146158 DOI: 10.1097/SLE.0b013e31822d02dc]
70 **Pugliese R**, Maggioni D, Sansonna F, Costanzi A, Ferrari GC, Di Lernia S, Magistro C, De Martini P, Pugliese F. Subtotal gastrectomy with D2 dissection by minimally invasive surgery for distal

adenocarcinoma of the stomach: results and 5-year survival. *Surg Endosc* 2010; **24**: 2594-2602 [PMID: 20414682 DOI: 10.1007/s00464-010-1014-1]

71 **Nakamura K**, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashima M, Ito S, Takagi M, Takagane A, Ninomiya M, Fukushima N, Sasako M. A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric Cancer (JCOG0912). *Jpn J Clin Oncol* 2013; **43**: 324-327 [PMID: 23275644 DOI: 10.1093/jjco/hys220]

72 **Etoh T**, Japanese Laparoscopic Surgery Study Group (JLSSG). Randomized controlled trial to evaluate laparoscopic versus open surgery for advanced gastric cancer (JLSSG0901: Adv.GC-LAP/OPEN, P II/III). Unique trial number: UMIN000003420. (cited 2015-09-18). Available from: URL: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000004144&language=E

73 **Kim HH**, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park do J, Song KY, Lee SI, Ryu SY, Lee JH. Prospective randomized controlled trial (phase III) to comparing laparoscopic distal gastrectomy with open distal gastrectomy for gastric adenocarcinoma (KLASS 01). *J Korean Surg Soc* 2013; **84**: 123-130 [PMID: 23396494 DOI: 10.4174/jkss.2013.84.2.123]

74 **Han SU**, Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group. Efficacy of laparoscopic subtotal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer (KLASS-02-RCT). (cited 2015-01-13). Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01456598

75 **Li G**, Chinese Laparoscopic Gastrointestinal Surgical Study (CLASS) Group. Multicenter study on laparoscopic distal subtotal gastrectomy for advanced gastric cancer (CLASS-01). (cited 2015-01-13). Available from: URL: http://clinicaltrials.gov/show/NCT01609309

76 **Hashizume M**, Sugimachi K. Robot-assisted gastric surgery. *Surg Clin North Am* 2003; **83**: 1429-1444 [PMID: 14712877]

77 **Marano A**, Choi YY, Hyung WJ, Kim YM, Kim J, Noh SH. Robotic versus Laparoscopic versus Open Gastrectomy: A Meta-Analysis. *J Gastric Cancer* 2013; **13**: 136-148 [PMID: 24156033 DOI: 10.5230/jgc.2013.13.3.136]

78 **Kim MC**, Heo GU, Jung GJ. Robotic gastrectomy for gastric cancer: surgical techniques and clinical merits. *Surg Endosc* 2010; **24**: 610-615 [PMID: 19688399 DOI: 10.1007/s00464-009-0618-9]

79 **Yoon HM**, Kim YW, Lee JH, Ryu KW, Eom BW, Park JY, Choi IJ, Kim CG, Lee JY, Cho SJ, Rho JY. Robot-assisted total gastrectomy is comparable with laparoscopically assisted total gastrectomy for early gastric cancer. *Surg Endosc* 2012; **26**: 1377-1381 [PMID: 22083338 DOI: 10.1007/s00464-011-2043-0]

80 **Xiong B**, Ma L, Zhang C. Robotic versus laparoscopic gastrectomy for gastric cancer: a meta-analysis of short outcomes. *Surg Oncol* 2012; **21**: 274-280 [PMID: 22789391 DOI: 10.1016/j.suronc.2012.05.004]

81 **Shen WS**, Xi HQ, Chen L, Wei B. A meta-analysis of robotic versus laparoscopic gastrectomy for gastric cancer. *Surg Endosc* 2014; **28**: 2795-2802 [PMID: 24789136 DOI: 10.1007/s00464-014-3547-1]

82 **Kim HI**, Han SU, Yang HK, Kim YW, Lee HJ, Ryu KW, Park JM, An JY, Kim MC, Park S, Song KY, Oh SJ, Kong SH, Suh BJ, Yang DH, Ha TK, Kim YN, Hyung WJ. Multicenter Prospective Comparative Study of Robotic Versus Laparoscopic Gastrectomy for Gastric Adenocarcinoma. *Ann Surg* 2016; **263**: 103-109 [PMID: 26020107 DOI: 10.1097/SLA.0000000000001249]

83 **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]

84 **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]

85 **Sugarbaker PH**, Mora JT, Carmignani P, Stuart OA, Yoo D. Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. *Oncologist* 2005; **10**: 112-122 [PMID: 15709213]

86 **Van der Speeten K**, Stuart OA, Sugarbaker PH. Pharmacology of perioperative intraperitoneal and intravenous chemotherapy in patients with peritoneal surface malignancy. *Surg Oncol Clin N Am* 2012; **21**: 577-597 [PMID: 23021717 DOI: 10.1016/j.soc.2012.07.013]

87 **Kuramoto M**, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, Yonemura Y, Baba H. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. *Ann Surg* 2009; **250**: 242-246 [PMID: 19638909 DOI: 10.1097/SLA.0b013e3181b0c80e]

88 **Misawa K**, Mochizuki Y, Ohashi N, Matsui T, Nakayama H, Tsuboi K, Sakai M, Ito S, Morita S, Kodera Y. A randomized phase III trial exploring the prognostic value of extensive intraoperative peritoneal lavage in addition to standard treatment for resectable advanced gastric cancer: CCOG 1102 study. *Jpn J Clin Oncol* 2014; **44**: 101-103 [PMID: 24287077 DOI: 10.1093/jjco/hyt157]

89 **Kuramoto M**, Shimada S, Ikeshima S, Matsuo A, Kuhara H, Eto K, Baba H. A proposal of a practical and optimal prophylactic strategy for peritoneal recurrence. *J Oncol* 2012; **2012**: 340380 [PMID: 22481921 DOI: 10.1155/2012/340380]

90 **Sökmen S**. Mide Kanserinde Sitoredüktif Cerrahi ve Hipertermik İntraperitoneal Kemoterapi (HIPEC) Uygulaması. In: Mihmanlı M, İlhan E, Alemdar A. Mihmanlı'nın Mide Kanseri ve Cerrahi Tedavisi. 3th ed. İstanbul: Tıbbi Yayınlar Merkezi, 2016: 381-390

91 **Yonemura Y**, Canbay E, Endou Y, Ishibashi H, Mizumoto A, Miura M, Li Y, Liu Y, Takeshita K, Ichinose M, Takao N, Hirano M, Sako S, Tsukiyama G. Peritoneal cancer treatment. *Expert Opin Pharmacother* 2014; **15**: 623-636 [PMID: 24617975 DOI: 10.1517/14656566.2014.879571]

92 **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]

93 **Yang XJ**, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011; **18**: 1575-1581 [PMID: 21431408 DOI: 10.1245/s10434-011-1631-5]

94 **Gill RS**, Al-Adra DP, Nagendran J, Campbell S, Shi X, Haase E, Schiller D. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. *J Surg Oncol* 2011; **104**: 692-698 [PMID: 21713780 DOI: 10.1002/jso.22017]

95 **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]

96 **Koga S**, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 1988; **61**: 232-237 [PMID: 3121165]

97 **Hamazoe R**, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994; **73**: 2048-2052 [PMID: 8156509]

98 **Fujimura T**, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, Ninomiya I, Matsumoto H, Tsugawa K, Nishimura G. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. *World J Surg* 1994; **18**: 150-155 [PMID: 8197772]

99 **Yonemura Y**, Ninomiya I, Kaji M, Sugiyama K, Fujimura K, Sawa T, Katayama K, Tanaka S, Hirono Y, Miwa K. Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. *World J Surg* 1995; **19**: 450-454; discussion 455 [PMID: 7639005]

100 **Yonemura Y**, de Aretxabala X, Fujimura T, Fushida S, Katayama

K, Bandou E, Sugiyama K, Kawamura T, Kinoshita K, Endou Y, Sasaki T. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001; **48**: 1776-1782 [PMID: 11813623]

101 **Ikeguchi M**, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. *Eur J Surg* 1995; **161**: 581-586 [PMID: 8519874]

102 **Sasako M**. Mide Kanserinde Neoadjuvan Kemoterapi. In: Mihmanlı M, İlhan E, Alemdar A. Mihmanlı'nın Mide Kanseri ve Cerrahi Tedavisi, 3th ed. Istanbul: Tıbbi Yayınlar Merkezi, 2016: 361-364

103 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992]

104 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741]

105 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289]

106 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]

107 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/S0140-6736(11)61873-4]

108 **Noh SH**, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1389-1396 [PMID: 25439693 DOI: 10.1016/S1470-2045(14)70473-5]

109 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.0597]

110 **Schuhmacher C**, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010; **28**: 5210-5218 [PMID: 21060024 DOI: 10.1200/JCO.2009.26.6114]

111 **Pedrazzani C**, Marrelli D, Pacelli F, Di Cosmo M, Mura G, Bettarini F, Rosa F, de Manzoni G, Roviello F. Gastric linitis plastica: which role for surgical resection? *Gastric Cancer* 2012; **15**: 56-60 [PMID: 21717092 DOI: 10.1007/s10120-011-0063-z]

112 **Tsuburaya A**, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014; **101**: 653-660 [PMID: 24668391 DOI: 10.1002/bjs.9484]

113 **Yoshikawa T**, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009; **96**: 1015-1022 [PMID: 19644974 DOI: 10.1002/bjs.6665]

114 **Aranha GV**, Georgen R. Gastric linitis plastica is not a surgical disease. *Surgery* 1989; **106**: 758-762; discussion 762-763 [PMID: 2552599]

115 **Cuello M**, Ettenberg SA, Clark AS, Keane MM, Posner RH, Nau MM, Dennis PA, Lipkowitz S. Down-regulation of the erbB-2 receptor by trastuzumab (herceptin) enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in breast and ovarian cancer cell lines that overexpress erbB-2. *Cancer Res* 2001; **61**: 4892-4900 [PMID: 11406568]

116 **Watson S**, Validire P, Cervera P, Zorkani N, Scriva A, Lemay F, Tournigand C, Perniceni T, Garcia ML, Bennamoun M, Paye F, Louvet C. Combined HER2 analysis of biopsies and surgical specimens to optimize detection of trastuzumab-eligible patients in eso-gastric adenocarcinoma: a GERCOR study. *Ann Oncol* 2013; **24**: 3035-3039 [PMID: 24114855 DOI: 10.1093/annonc/mdt393]

117 **Warneke VS**, Behrens HM, Böger C, Becker T, Lordick F, Ebert MP, Röcken C. Her2/neu testing in gastric cancer: evaluating the risk of sampling errors. *Ann Oncol* 2013; **24**: 725-733 [PMID: 23139264 DOI: 10.1093/annonc/mds528]

118 **Lee KE**, Lee HJ, Kim YH, Yu HJ, Yang HK, Kim WH, Lee KU, Choe KJ, Kim JP. Prognostic significance of p53, nm23, PCNA and c-erbB-2 in gastric cancer. *Jpn J Clin Oncol* 2003; **33**: 173-179 [PMID: 12810831]

119 **He C**, Bian XY, Ni XZ, Shen DP, Shen YY, Liu H, Shen ZY, Liu Q. Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer. *World J Gastroenterol* 2013; **19**: 2171-2178 [PMID: 23599643 DOI: 10.3748/wjg.v19.i14.2171]

120 **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-X]

121 **Meza-Junco J**, Au HJ, Sawyer MB. Trastuzumab for gastric cancer. *Expert Opin Biol Ther* 2009; **9**: 1543-1551 [PMID: 19916733 DOI: 10.1517/14712590903439702]

122 **Matsusaka S**, Nashimoto A, Nishikawa K, Miki A, Miwa H, Yamaguchi K, Yoshikawa T, Ochiai A, Morita S, Sano T, Kodera Y, Kakeji Y, Sakamoto J, Saji S, Yoshida K. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC44-1101). *Gastric Cancer* 2015; Epub ahead of print [PMID: 26265390]

123 **Kataoka K**, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, Tomita T, Nakamura K, Boku N, Sano T, Terashima M, Sasako M. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). *Jpn J Clin Oncol* 2015; **45**: 1082-1086 [PMID: 26355164 DOI: 10.1093/jjco/hyv134]

124 **Noto JM**, Peek RM. Helicobacter pylori: an overview. *Methods Mol Biol* 2012; **921**: 7-10 [PMID: 23015485]

125 **Suzuki H**, Iwasaki E, Hibi T. Helicobacter pylori and gastric cancer. *Gastric Cancer* 2009; **12**: 79-87 [PMID: 19562461 DOI: 10.1007/s10120-009-0507-x]

126 **Polk DB**, Peek RM. Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer* 2010; **10**: 403-414 [PMID: 20495574 DOI: 10.1038/nrc2857]

127 **Ahn HJ**, Lee DS. Helicobacter pylori in gastric carcinogenesis.

World J Gastrointest Oncol 2015; **7**: 455-465 [PMID: 26690981 DOI: 10.4251/wjgo.v7.i12.455]

128 **Ma JL**, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, Pee D, Blot WJ, Fraumeni JF, You WC, Gail MH. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 2012; **104**: 488-492 [PMID: 22271764 DOI: 10.1093/jnci/djs003]

129 **Lee SY**. Current progress toward eradicating Helicobacter pylori in East Asian countries: differences in the 2013 revised guidelines between China, Japan, and South Korea. *World J Gastroenterol* 2014; **20**: 1493-1502 [PMID: 24587624 DOI: 10.3748/wjg.v20.i6.1493]

130 **Kim SG**, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, Shin WG, Shin ES, Lee YC. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. *Korean J Gastroenterol* 2013; **62**: 3-26 [PMID: 23954956]

131 **Fock KM**, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, Lam SK, Xiao SD, Tan HJ, Wu CY, Jung HC, Hoang BH, Kachintorn U, Goh KL, Chiba T, Rani AA. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2009; **24**: 1587-1600 [PMID: 19788600 DOI: 10.1111/j.1440-1746.2009.05982.x]

132 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

133 **Tan VP**, Wong BC. Gastric cancer chemoprevention: the current evidence. *Gastroenterol Clin North Am* 2013; **42**: 299-316 [PMID: 23639642 DOI: 10.1016/j.gtc.2013.02.001]

134 **Park JY**, von Karsa L, Herrero R. Prevention strategies for gastric cancer: a global perspective. *Clin Endosc* 2014; **47**: 478-489 [PMID: 25505712 DOI: 10.5946/ce.2014.47.6.478]

135 **Zhang MM**, Qian W, Qin YY, He J, Zhou YH. Probiotics in Helicobacter pylori eradication therapy: a systematic review and meta-analysis. *World J Gastroenterol* 2015; **21**: 4345-4357 [PMID: 25892886 DOI: 10.3748/wjg.v21.i14.4345]

136 **Postlewait LM**, Squires MH, Kooby DA, Poultsides GA, Weber SM, Bloomston M, Fields RC, Pawlik TM, Votanopoulos KI, Schmidt CR, Ejaz A, Acher AW, Worhunsky DJ, Saunders N, Swords D, Jin LX, Cho CS, Winslow ER, Cardona K, Staley CA, Maithel SK. Preoperative Helicobacter pylori Infection is Associated with Increased Survival After Resection of Gastric Adenocarcinoma. *Ann Surg Oncol* 2016; **23**: 1225-1233 [PMID: 26553442 DOI: 10.1245/s10434-015-4953-x]

P- Reviewer: Gurkan A, Koc HO, Lee YC, Matsubara T
S- Editor: Yu J **L- Editor**: A **E- Editor**: Wang CH

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ISSN 1007-9327
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