World Cancer Research Journal WCRJ 2014; 1 (4): e395

GASTRIC CANCER: PROGNOSTIC ASPECTS, PREDICTIVE FACTORS TO THERAPY RESPONSE AND REAL IMPACT ON TREATMENT APPROACH

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Abstract: *Gastric cancer (GC) is the third leading cause of cancer death in both sexes worldwide, with the highest estimated mortality rates in Eastern Asia and the lowest in Northern America. However the availability of modern treatment have improved the survival the prognosis is often poor due to biological characteristics of disease. Here we summarized the most clinical and prognostic aspects in GC in the "Era" of target treatment.*

INTRODUCTION

Gastric cancer (GC) is the third leading cause of cancer death in both sexes worldwide (8.8% of the total), with the highest estimated mortality rates in Eastern Asia and the lowest in Northern America. High mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America[1-6].

Gastric cancer used to be the leading cause of cancer deaths in the world until the 1980s when it was overtaken by lung cancer. The worldwide incidence of GC has declined rapidly over the recent few decades. Part of the decline may be due to the recognition of certain risk factors such as H. pylori and other dietary and environmental risks[7-10]. However, the decline clearly began before the discovery of *H. pylori*. The decline first took place in countries with low GC incidence such as the United States (beginning in the 1930s), while the decline in countries with high incidence like Japan was slower[11]. In the United Kingdom, there was a consistent decline in incidence of GC, with a reduction in RR from 1.14 in 1971 to 1975 to 0.84 in 1996 to 2000 in men, and 1.18 in 1971 to 1975 to 0.81 in 1996 to 2000 in women[12,13]. In the United States, risk factors for noncardia GC include male gender, non-white race, and older age. Between 1977 and 2006, the incidence rate for non-cardia GC in the United States declined among all race and age groups except for whites aged 29 to 39 years for whom it increased[14-16]. The rise in incidence of non-cardia gastric cancer among those at 25 to 39 years is noteworthy since this may signal the introduction of new environmental factors. In other parts of the world, it continues to pose a major challenge for health care professionals. Environmental risk factors include smoking, high salt intake and other dietary factors. In a recent meta-analysis, there was no appreciable association between moderate alcohol drinking and GC-risk; however, there was a positive association with heavy alcohol drinking, particularly for non-cardia GC[17].

An interesting hypothesis is that the popularization of refrigerators marks a pivotal point for the decline. Refrigerators improved the storage of food, thereby reducing salt-based preservation of food and preventing bacterial and fungal contamination. Refrigeration also allowed for fresh food

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and vegetables to be more readily available, which may be a valuable source of antioxidants important for cancer prevention[18,19].

The purpose of this review is to the summarise existing data on prognostic aspects and predictive factors to response to therapy in GC.

CLINICAL PROGNOSTIC FACTORS

Despite the recent progress in the development of new therapeutic strategies and in early diagnosis, the prognosis of GC continues to be poor, with < 20% of patients surviving at 5 years[20-22].

Within this framework, identifying factors helping to predict survival and response to treatment is a crucial issue and may support an appropriate strategy among the available therapeutic options.

Two major classifications are currently used. The Japanese classification is more elaborate and is based on anatomic involvement, particularly the lymph node station[23]. The other staging system developed jointly by the AJCC and the Union for International Cancer Control (UICC), is the system used in countries in the Western Hemisphere[24]. The TNM stage is one of the most important prognostic tool for GC.

The prognosis of patients with GC is related to tumour extent and includes both nodal involvement and direct tumour extension beyond the gastric wall. Tumour grade may also provide some prognostic information[25,26].

In localized distal GC, more than 50% of patients can be cured. However, early-stage disease accounts for only 10% to 20% of all cases diagnosed in the United States. The remaining patients present with metastatic disease in either regional or distant sites. The overall survival rate in these patients at 5 years ranges from almost no survival for patients with disseminated disease to almost 50% survival for patients with localized distal GCs confined to resectable regional disease. Even with apparent localized disease, the 5-year survival rate of patients with proximal GC is only 10% to 15%. Although the treatment of patients with disseminated GC may result in palliation of symptoms and some prolongation of survival, long remissions are uncommon.

Recurrence following surgery is a major problem, and is often the ultimate cause of death. Residual tumor after gastric resection with curative intent is categorized by a system known as R classification and indicates the amount of residual disease left after tumour resection: R0 indicates no gross or microscopic residual tumour, R1 indicates microscopic residual tumour, and R2 shows macroscopic residual disease. This obvious and important prognostic factor was not always reported in the past, making interpretation of survival results difficult[27].

Two prognostic factors are standard on a type C basis: the degree of penetration of the tumour through the gastric wall, and the presence of lymph node involvement. These two factors also form the basis for all staging systems developed for this disease. The relationship between T stage and survival is well defined. Several reports from Japan, Europe, and the United States have demonstrated the significant prognostic importance of advanced T stage[26]. In the past, the N stage classification was based on the anatomical location of lymph nodes. Although the prognostic significance of such a classification may be relevant, it is very complicated for practice. In 1997, the AJCC/UICC N stage was changed and became based on the number of positive lymph nodes[28].

A minimum of 15 examined lymph nodes is recommended for adequate staging. Data from a jeer database show that the number of lymph nodes examined correlated with overall survival (OS) after gastrectomy. A trend for superior survival based on none lymph nodes examined was confirmed across all stage subgroups[29].

Apart from TNM classification and R0 resection, many other factors have been considered for prognostic purposes.

Most multivariate analyses have shown no effect on prognosis of the tumour histological classification proposed by the WHO, independent of stage, with the exception of the rare small cell carcinoma of the stomach, which has an unfavourable prognosis[30]. Other histological prognostic factors were considered the Laurén classification (intestinal or diffuse type), or the Ming classification (expanding or infiltrating type). For all stage groupings, grading correlates with outcome[31,32]. The Lauren's classification differentiates GC into two major types: intestinal or diffuse. This classification, based on tumour histology, characterizes two varieties of gastric adenocarcinomas, which have different pathology, epidemiology, aetiologies, and behaviour. The intestinal type consists of a differentiated cancer with a tendency to form glands. By contrast, the diffuse form exhibits low cell cohesion and tends to replace the gastric mucosa by signet-ring cells. About 16% of cases will be unclassifiable or of mixed type. Ming proposed a classification favourable expanding type, and the poor prognosis infiltrating type[33,34].

Macroscopic tumour configuration types as described by Borrmann has been shown to have prognostic significance in several large studies; I and II Borrmann types (polypoid and ulcerating cancers) seem to have a better prognosis than III

and IV Borrmann types (infiltrating cancers). However, the prognostic value of tumour configuration has not been confirmed in other studies. Studies in Asia have questioned the dictum that signet ring cell carcinoma (SRC) has a worse prognosis than other forms of GC[35]. In a study, Sharven Taghavi et al[36] determined differences in presentation and outcomes between SRC and gastric adenocarcinoma (AC) in the United States. They reviewed 10,246 cases of patients with GC, including 2,666 of SRC and 7,580 of AC.

SRC presented in younger patients and less often in men. SRC patients were more frequently black, Asian, American Indian/Alaska Native, or Hispanic. SRC was more likely to be stage T3-4 (45.8% *v* 33.3%), have lymph node spread (59.7% *v* 51.8%), and distant metastases (40.2% *v* 37.6%). SRC was more likely to be found in the lower (30.7% *v* 24.2%) and middle stomach (30.6% *v* 20.7%). Median survival was not different between the two (AC, 14.0 months *v* SRC, 13.0 months; p =.073). Multivariable analyses demonstrated SRC was not associated with mortality (hazard ratio [HR], 1.05; 95% CI, 0.96 to 1.11; p = .150). Mortality was associated with age (HR, 1.01; 95% CI, 1.01 to 1.02; p = .001), black race (HR, 1.10; 95% CI, 1.01 to 1.20; p = .026), and tumour grade. Variables associated with lower mortality risk included Asian race (HR, 0.83; 95% CI, 0.77 to 0.91; p =.001) and surgery (HR, 0.37; 95% CI, 0.34 to 0.39; p = .001). In the United States, SRC significantly differs from AC in extent of disease at presentation. However, when adjusted for stage, SRC does not portend a worse prognosis.

The adverse prognostic factor of tumour size is controversial. Tumour site has been shown to be an independent prognostic factor in GC, with proximal carcinomas (i.e., tumours of the upper third of the stomach, including the gastric cardia and gastroesophageal junction) having a poorer prognosis than distal cancers[36].

Lymphatic, venous, or perineural invasion have been shown to be adverse prognostic factors[37]. Several studies have reported a positive surgical resection margin associated with a significant decrease in overall survival[38-41]. The ratio of lymph nodes metastases (number of metastatic lymph nodes to the total number of dissected lymph nodes) appears to be an important prognostic factor and the best classification factor for lymph node metastasis[42]. Different survival rates have been reported between patients having undergone surgical intervention for the treatment of gastric carcinoma in Japan and Western countries. However, when using a similar staging classification and similar prognostic characteristics, the prognosis for GC in Japan and Germany may be the same[43]. Tumour volume, measured from serial tissue sections of GC by using a computer graphics analysis, seems to be of prognostic significance. In a recent report by Maehara et al[44], multivariate analysis revealed that the 10 factors of depth of invasion, lymph node metastasis, lymph node dissection, tumour size, liver metastasis, peritoneal dissemination, lymphatic invasion, vascular invasion, lesion in the whole stomach, and lesion in the middle stomach were independent factors for determining the prognosis. However many studies confirmed that tumour size, perineural or lymph vascular invasion, and the nodal status have been shower to be stronger predictors of survival.

Although most reports[45] have suggested a dismal prognosis for young patients with GC, one study has suggested that young patients (≤39 years) do not have a worse prognosis than older patients. Women appeared to have a better prognosis than men in one study[46], but this was not confirmed in other reports[47].

According to some studies[48], older patients have been reported to have a poorer prognosis than do to younger patients, because they have more advanced disease stage at the time of diagnosis and a lower rate of curative resection. Also, other causes such cardiovascular disease, diabetics, other gerontological medical problems, alterations in the immune system, malnutrition have been suggested to reflect the increased operative mortality and shortened long term survival in older patients.

PROGNOSTIC SERUM MARKERS

Due to their low sensitivity and specificity in detecting early primary tumours, classic biomarkers have shown little benefit as a method for screening in the general population. However these markers may be used clinically for the monitoring of tumour recurrence or may be used as prognostic factors because higher levels have been normally observed in advanced disease. Introduction of new techniques as polymerase chain reaction (PCR) may increase the sensibility of detection of these markers respect common immunoassays.

CARCINOEMBRYONIC ANTIGEN (CEA)

Preoperative serum CEA levels have a predictive value in determining tumour stage and prognostic information for patients with potentially resectable GC during the preoperative period[49]. Curatively resected gastric cancer patients with higher preoperative plasma CEA levels have a poorer prognosis than those with lower levels, despite the adjust-

ment for the effects of major prognostic factors[50-52]. Others have found that higher CEA levels in peritoneal washings in GC patients at the time of laparotomy are prognostic of poor survival[53,54]. Chung et al[55] reported higher CEA serum levels in advanced GC of intestinal-type. Kodama et al[56] confirmed a low positive rate of CEA serum levels in early gastric cancers, similarly to Ca19.9 and Ca72.4. Ucar et al[57] demonstrated a correlation between CEA positivity and presence of liver metastases. Nakanishi et al[58] demonstrated a higher frequency of peritoneal metastases in patients with positive real time-PCR analysis for CEA transcripts in peritoneal washes of GC patients.

CARBOHYDRATE ANTIGEN (CA) 19-9

Kodama et al[56] showed a low positive rate for Ca19.9 in early GC. Ucar et al[57] showed a more frequent significant Ca19.9 serum positivity in patients with lymph nodes, peritoneal and serosal involvement.

CARBOHYDRATE ANTIGEN (CA) 72-4

The 72.4 carbohydrate epitope, contained in high-molecular weight mucin-type glycoprotein, called TAG-72, is detected by monoclonal antibodies CC49 and B72-3. Kodama et al[56] demonstrated a higher positive rate of serum expression for Ca 72.4 respect CEA and Ca19.9 in advanced GC, but not in early GC. Moreover a higher positive rate of expression was seen in the presence of peritoneal dissemination and a first elevation prior to other markers in the presence of recurrence. Mattar et al[59] confirmed increased serum positive expression of Ca 72.4 in advanced gastric disease. Ucar et al[57] showed a more frequent significant Ca 72.4 positivity in patients with lymph nodes, peritoneal and liver involvement and described Ca 72.4 as the only independent prognostic factor for survival among other markers such as CEA, Ca19.9, αFP. Fernandes et al[60] showed a significant correlation between high levels of Ca 72.4 in peritoneal washing and lymph nodes metastasis and serosa involvement by GC and also with more advanced stage of GC. The levels of Ca 72.4 in the blood correlates significantly with only lymph nodes involvement by GC.

CARBOHYDRATE ANTIGEN (CA) 125

The Carbohydrate antigen 125 (Ca 125) has been recently, by Food and Drug Administration (FDA) as test for ovarian cancer[61]. Recently Nacata et al[62], demonstrated the predictive role of Ca 125 for peritoneal metastasis from GC.

PROGNOSTIC TISSUE FACTORS

In the last decades, many studies have suggested the role that genetic alterations may have in the development and progression of gastric cancer[63]. Molecular pathology may be helpful not only to understand the disease pathogenesis, but also to give useful prognostic molecular markers.

Biological prognostic factors are often derived from the genetic process, which is thought to represent a crucial step to gastric cancer (HER2, E-cadherin, EGFR, DNA copy number changes, microsatellite instability, and changes in expression of several factors including thymidilate synthase, beta-catenin, mucin antigen, p53, COX-2, matrix metalloproteinases, and vascular endothelial growth factor receptor). Some of these potential prognostic factors can also be predictive of response to therapy as they are a molecular target either to chemotherapeutics or to biologic/targeted therapies, such as trastuzumab in HER2-positive tumours.

Overexpression of p53 as demonstrated by immunohistochemistry, has been reported in 17-91% of invasive tumours, whereas the reported incidence pf p53 mutations in invasive carcinomas range from 0 to 77%[64]. Assessment of the role of p53 in GC in relation to prognosis has produced conflicting result[65-69]. Published studies have reported conflicting and even contradictory results since they have involved immunohistochemical detection of the protein, which has been performed with different antibodies, detection techniques, or methods of interpretation. Other suggested biological prognostic factors were p21 expression, VEGF expression, overexpression of EGF-r, cyclin D2 overexpression, BAT-26 alterations, uPA (urokinase-type plasminogen activator) and PAI-1 (PA inhibitor), the serum level of soluble receptor for IL-2 (SolIL-2R), or some proliferation-related factors, such as Sphase fraction, Ki-67 or proliferating cell nuclear antigen (PCNA)[70]. Recent data on the correlation between molecular markers and response to chemotherapy are still controversial[71]. Using immunohistochemical p53 analysis of pretreatment endoscopical samples, two studies have reported a relationship between p53 staining and response to chemotherapy. Thymidylate synthase expression seemed to be related to response to chemotherapy[72-75].

A gene potentially involved in chemoresistance, ERCC-1 (excision repair cross-comple-

menting), has been shown to be more highly expressed in non-responsive GC patients than responsive patients. Thus, these data arise from retrospective studies, and well designed, prospective trial are warranted to further define the role of molecular markers in predicting response and survival of patients with GC.

The E-cadherins are a major class of adhesion molecules that play an important role in the homotypic cell-cell adhesion and, hence, cancer cell metastasis and invasion. E-cadherin is a member of the cadherin family and is expressed on all epithelial cells. The invasiveness of epithelial tumour cell lines could be inhibited in vitro by transfection with E-cadherin cDNA, and the invasiveness of these cell lines were induced again by exposure to anti-E-cadherin monoclonal antibodies. Underexpression of the E-cadherin molecule has been found in various malignancies, and it has the potential value of being a prognostic factor. In addition to its role in metastasis, E-cadherin is one of the most important candidate genes in gastric carcinogenesis. Somatic mutations of the E-cadherin gene have been identified in more than 50% of diffuse types of GC. According to Knudson's two-hits theory, somatic mutation of E-cadherin is the first of the two hits mechanisms for the silencing of the molecule, whereas methylation of E-cadherin has been shown recently to be the second hit. In fact, methylation of Ecadherin has recently been shown to be the second genetic hit in gastric carcinogenesis.

Serum soluble E-cadherin is the degradation product of the cellular E-cadherin molecule. It is found in the circulation of normal individuals but is particularly elevated in patients with malignancies. Gofuku et al showed that the concentration was significantly elevated in 67% of patients with GC. Chan et al found that high concentration of serum soluble E-cadherin was associated with inoperability/palliative treatment and lymph node metastasis[76-80]. They have also studied the correlation between serum level of soluble E-cadherin and the protein expression by immunohistochemical staining. They found that soluble E-cadherin is a potentially valuable pre-therapeutic factor in predicting long-term survival in patients with GC. By using a pre-therapeutic level of greater than 10,000, they were able to predict that 90% of patients would have a survival time of less than 3 years. Patients with pretherapeutic levels higher than this should perhaps receive more aggressive treatment, such as extended lymphadenectomy and adjuvant therapies. Further prospective study is required to investigate the value of soluble E-cadherin to predict recurrence.

PREDICTIVE TISSUE AND CLINICAL FACTORS

In gastric carcinomas (GCs), HER1 and HER2 overexpression is thought to be a prognostic factor and target of novel biologic agents.

The HER2 protein (p185, HER2/neu, ErbB-2) is a 185-kDa transmembrane tyrosine kinase (TK) receptor and a member of the epidermal growth factor receptors (EGFRs) family. This family is composed of four members: HER1 (also known as the EGFR), HER2, HER3 (also termed ErbB-3), and HER4 (also termed ErbB-4). These receptors share the same molecular structure with an extracellular ligand-binding domain, a short transmembrane domain, and an intracellular domain with TK activity (excepting the HER3). The binding of different ligands to the extracellular domain initiates a signal transduction cascade that can influence many aspects of tumour cell biology, including cell proliferation, apoptosis, adhesion, migration, and differentiation. Ligand binding induces EGFR homodimerization as well as heterodimerization with other types of HER proteins. HER2 does not bind to any known ligand, but it is the preferred heterodimerization partner for other members of the HER family. HER2 is encoded by a gene located on chromosome 17q21. The HER2 gene, located adjacent to the topoisomerase IIa genes, is related to the oncogene v-erbB of the avian erythroblastosis virus. In carcinomas, HER2 acts as an oncogene, mainly because high level amplification of the gene induces protein overexpression in the cellular membrane and subsequent acquisition of advantageous properties for a malignant cell.

Recent studies indicate a role of HER2 in the development of numerous types of human cancer. HER2 overexpression and/or amplification have been detected in 10%-34% of invasive breast cancers and correlate with the clinical outcome, confer poor prognosis, and also constitute a predictive factor of poor response to chemotherapy and endocrine therapy (Table 1). HER2 overexpression and/or amplification have also been observed in colon, bladder, ovarian, endometrial, lung, uterine cervix, head and neck, esophageal, and GCs.

Trastuzumab is a monoclonal antibody which specifically targets HER2 protein by directly binding the extracellular domain of the receptor. Trastuzumab enhances survival rates in both primary and metastatic HER2-positive breast cancer patients. The efficacy of trastuzumab in breast cancer patients has led to investigate its antitumor activity in patients with HER2-positive cancers, including gastric adenocarcinomas.

However, in GC, the clinical significance of such overexpression is not yet fully clear, and not

TABLE 1. HER2 ESPRESSION AND CLINICOHISTOLOGIC CHARACTERISTICS.

Author	*n*	Histologic type				Localization			Method
		Intestinal (%)	Diffuse (%)	Mixed/ unknown	*p*	GEI (%)	Gastric (%)	*p*	
Tanner et al.39	231	21.5	2	5	0.005	24	12	–	CISH
Gravalos et al.28	166	16	7	14	0.27	25	9.5	0.01	IHC, FISH
Lordick et al.31	1527	34	6	20	–	32	18	–	IHC, FISH

all studies have shown an association between HER2 overexpression and poor prognosis. Although the effect of HER3 or HER4 expression in GC has not been clarified, HER3 expression is frequently observed in advanced gastric tumours with poor prognosis, and *HER4* gene expression seems to be higher in tumour tissue in comparison with adjacent gastric mucosa.

Some studies indicate that all members of the HER family are expressed in GC[81-90]. Furthermore, expression of HER2 and HER3 is a significant predictor of poor survival in GC and predictor of response to trastuzumab. Therefore, the development of HER-targeted agents and agents targeting downstream signaling pathways provides new possibilities in the treatment of GC.

There is increasing recognition of the existence of intratumoural heterogeneity of the human epidermal growth factor receptor (HER2), which affects interpretation of HER2 positivity in clinical practice and may have implications for patient prognosis and treatment.

The only targeted therapy approved in GC is trastuzumab. The Phase III ToGA trial[81-91] reported an increase in overall survival for patients with human EGF receptor HER2-positive GC treated with chemotherapy and trastuzumab compared to chemotherapy alone. HER2 overexpression is associated with a poor prognosis in GC, predicts sensitivity to trastuzumab.

In the ToGA database, HER2 was positive in 22% of tumours (34% of intestinal type vs 6% of diffuse type and 20% of mixed types). Furthermore, the highest rate was observed in 34% of GEJ tumours and 20% of GC samples. ToGA trial evaluated if trastuzumab added to cisplatin and a fluoropirymidine was able to improve the efficacy of chemotherapy in HER2-positive advanced GC patients. The HER2 overexpression was defined as immunohistochemistry (IHC) 3+ and/or fluorescent in situ hybridization (FISH) positivity and, therefore, the enrolment of patients was allowed with a FISH positivity but IHC 0 or 1+. The primary end point was OS. Secondary end points were PFS, time to progression (TTP), ORR, disease control, duration of response and QoL. Of 3807 patients screened, 810 were HER2-positive (IHC 3+ and/or FISH+) and 584 were randomized between chemotherapy alone (290) or chemotherapy plus trastuzumab (294). Trastuzumab improved the median OS when compared with chemotherapy alone (13.8 vs 11.1 months; hazard ratio (HR) 0.74; $p < 0.0046$); PFS (HR 0.71; $p < 0.0002$), TTP (HR 0.70; $p < 0.0003$), ORR (OR 1.70; $p < 0.0017$) and QoL were also improved in trastuzumab arm. The best OS improvement was observed in IHC 2+/FISH+ or IHC 3+ patients: 16 months in trastuzumab arm and 11.8 months in chemotherapy alone arm (HR 0.65).

The toxicity was very mild and no differences were recorded in the rate of cardiac adverse events between the two arms. Therefore, trastuzumab was approved in combination with cisplatin and fluoropirimidines for metastatic untreated HER2-positive GC. HER2 status should be assessed routinely by primary IHC: tumors with IHC 3+ score are eligible for trastuzumab. Samples with an equivocal IHC 2+ score should be retested using FISH: patients whose tumours score IHC2+/FISH+ are eligible for trastuzumab. According to these recommendations, ~16% of advanced GC patients are suitable for anti-HER2 therapy. This means that accurate HER2 testing in GC is necessary. Final data of ongoing trials with novel agents will be critical to further progress with this cancer. The role of HER2 as a prognostic factor in GC has been controversial because some of the initial studies failed to find an association with prognosis. Other authors, however, reported a direct correlation between HER2 expression and poorer survival. Therefore, there is mounting evidence of the role of HER2 overexpression in patients with GC, and it has been solidly correlated to poor outcomes and a more aggressive disease. Regarding patologic variables, a higher rate of HER2 expression in intestinal histologic type than in diffuse type has consistently been reported. GEJ cancer express HER2 with more frequency than GC do. Several clinical trials are exploring in different setting and with diverse designs the potential of anti HER2 therapies in GC patients.

A high interleukin-1_ (IL-1B) and interleukin-1 receptor antagonist (IL-RN) ratio underlies an unfavorable proinflammatory status. Also, it seems to be involved in the mechanisms of cancer cachexia and tumour angiogenesis and metastasis. Two single nucleotide polymorphisms in *IL-1B* gene (*IL-1B-511C/T*, *IL-1B-31T/C*) and a variable number of tandem repeat polymorphisms in *IL-RN* gene (*IL-1RNlong/2*) enhance the circulating levels of the two cytokines. Graziano et al[92] investigated he prognostic role of *IL-1B/IL-1RN* genotypes in patients with relapsed and metastatic gastric cancer treated with palliative chemotherapy. Before starting palliative chemotherapy, 123 prospectively enrolled patients supplied peripheral-blood samples for DNA extraction. Survival data were analyzed according to *IL-1RN/IL-1B* genotypes. Forty-two patients showed wild-type genotypes (*IL-1RN-long/long*, *IL-1B-511C/C*, and *IL-1B-31T/T*; group A). Forty-five patients showed the *IL-1RN2* polymorphism, with wild-type *IL-1B* genotypes in seven patients and with *IL-1B-511C/T* and/or *IL-1B-31T/C* polymorphisms in 38 patients (group B). The remaining 36 patients demonstrated wild-type *IL-1RN*, with *IL-1B-511C/T* and/or *IL-1B-31T/C* polymorphisms (group C). In group A and B patients, the median progression-free survival (PFS) was 25 and 26 weeks, respectively, and median overall survival (OS) was 42 and 43 weeks, respectively. Group C patients showed worse PFS (median, 16 weeks) and OS (median, 28 weeks) than group A ($P = .006$ for PFS; $p < .0001$ for OS) and group B patients ($p = .01$ for PFS; $p < .0001$ for OS). The *long/T/C* haplotype was overrepresented in patients with shortened PFS ($p < .001$) and OS ($p < .0005$).

Therefore in patients with advanced gastric cancer, *IL-1B* polymorphisms showed adverse prognostic influence when coupled with wild-type *IL-1RN* genotype. These findings deserve further

investigation for potential anticancer activity of recombinant *IL-RN*. Instead, according to other authors[93], the level of Interleukin seem to correlate with survival in advanced GC patients but is not an independent prognostic indicator.

After the results of trastuzumab in patients with *HER2*-positive GC, there is increasing interest in the development of targeted therapies in this lethal disease. However, the discovery and the optimal use of these selective treatments requires an adequate knowledge of the target and the potential clinical effects from its inhibition. A number of receptors and downstream pathways are known to be aberrantly activated in gastric cancer, and they may represent new treatment targets beyond *HER2* inhibition. HER2, MET and FGFR2 oncogenic driver alterations define distinct molecular segments for targeted therapies in GC[94]. Among them, the MET receptor and its hepatocyte growth factor (HGF) ligand have been found frequently expressed in GCs and are associated with a more aggressive phenotype. The activation of the MET/HGF pathway promotes proliferative and anti-apoptotic activities that are common to many growth factors, but specifically, *MET* activation demonstrated stimulation of cell-cell detachment, migration, and invasiveness.

Mutations in the kinase domain of the *MET* gene are almost lacking in GCs, and its activation has been mostly attributed to gene amplification. Also, Nakajima et al[95] and Tsugawa et al[96] found that survival rates of patients with gastric cancer with *MET* amplification are significantly lower than those of patients without amplification.

Graziano et al[97] investigated whether prognosis of patients with high-risk gastric cancer may depend on *MET* copy number gain (CNG) or an activating truncation within a deoxyadenosine tract element (DATE) in the promoter region of the *MET* ligand HGF.

A single-institution cohort of 230 patients with stage II/III gastric cancer was studied. Formalin-fixed paraffin-embedded tumor specimens were used for DNA extraction. Quantitative polymerase chain reaction (qPCR) for *MET* CNG and sequencing for *HGF* DATE truncation (25 deoxyadenosines instead of 30) were used. Results were analyzed for association with disease free survival (DFS) and overall survival (OS). To assess the reliability of the qPCR measurement, a random sample of cases was reanalyzed using an alternative assay (fluorescent in situ hybridization [FISH]) with calculation of the intra-correlation coefficient (ICC).

In 216 assessable patients, *MET* CNG five or more copies and homozygous *HGF*-truncated DATE occurred in 21 patients (10%) and 30 patients (13%), respectively. Patients with *MET* CNG five or more copies (*MET*-positive) showed significantly worse prognosis with multivariate hazard ratio (HR) of 3.02 (95% CI, 1.71 to 5.33; $p < .001$) for DFS and multivariate HR of 2.91 (95% CI, 1.65 to 5.11; $p < .001$) for OS. The agreement between qPCR and FISH was high, with ICC _ 0.9% (95% CI, 0.81% to 0.95%; the closer the ICC is to 1, the greater is the agreement). *HGF*-truncated DATE did not show relevant prognostic effect.

In this study, qPCR revealed approximately 10% of white patients with GC harbouring *MET* CNG of five or more copies. This marker was significantly associated with unfavourable prognosis. This information is relevant to the current clinical development of anti-*MET* compounds.

Rilotumumab is a fully human monoclonal antibody (IgG2) against human hepatocyte growth factor/scatter factor (HGF/SF) that blocks binding of HGF/SF to its receptor MET, inhibiting HGF/MET-driven activities in cells.

Phase two studies seem to indicate the overexpression of MET could be a predictor of response to therapy with rilotumumab.

SURGERY APPROACH

Surgery is the primary treatment for patients with early-stage gastric cancer. Completa resection with adequate margins (4 cm or greater) is widely considered as a standard goal, whereas the type of resection (subtotal vs. total gastrectomy) along with extent of lymph node dissection remains a subject of controversy. Clinical staging using computed tomography (CT) scan (chest, abdomen, and pelvis) with or wthout EUS should be performed before surgery to assess the extent of the disease. The primary goal of surgery is to accomplish a complete resection with negative margins (R0 resection). Only 50% of patients will end up with an R0 resection of their primary[98,99]. R1 indicates microscopic residual disease (positive margins) and R2 indicates gross (macroscopic) residual disease in the absence of distant metastasis[100].

Controversies surround the surgical management of GC. In 1999, Bozzetti et al[101] found no difference in survival between total and subtotal gastrectomies but that subtotal gastrectomy was associated with improved nutritional status and quality of life. With the advancement of laparoscopic techniques, laparoscopic gastrectomy was found to have similar outcomes but with fewer complications compared to open gastrectomy in meta-analyses and case-control studies[102-105]. Furthermore, a resection margin of 1 mm was found to be sufficient as long as the resection margins were free of tumor[104]. The depth of lymphadenectomy has been a topic of debate as well. A D1 dissection involves a gastrectomy and the removal of the greater and lesser omental lymph nodes. A D2 dissection involves the above plus the removal of all lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery. The D1 dissection was traditionally favored in the West, specifically in the United States, whereas D2 resection was preferred in the East[106] and Europe. This discrepancy was based on early randomized trials that failed to show a survival benefit with D2 lymphadenectomy[107,108]. Subsequent studies showed that D2 resection indeed offered a survival benefit, prompting a change in practice. Recently, Shrikhande et al[109] established the non-inferiority of perioperative gastrectomy with D2 lymphadenectomy for locally advanced resectable GC when combined with neaoadjuvant chemotherapy. More importantly, half of those patients who achieved a pathologic response were found to have lymph node involvements, arguing for the necessity of D2 gastrectomy[109]. A randomized trial comparing D1 and D2 dissections found that there was no difference in overall 5-year survival between the two practices. However, subgroup analyses suggest that D1 resection may be beneficial for those with pT1 disease while a trend towards improved survival was seen with D2 lymphadenectomy in patients with nodal involvement[110]. Based on some of these trials in addition to other clinical data, the National Comprehensive Cancer Network guidelines currently recommends a D1 or a modified D2 gastrectomy with at least 15 lymph nodes removed for examination in the United States, though noting that D2 lymphadenectomies should be performed at experienced centers[111].

ANTIBLASTIC TREATMENT APPROACH

The adjunctive therapy used for the treatment of localized Gc in addition to surgery depends on geographic location in the world. In Western Countries, results from the INT-0116[112] (the adjuvant chemoradiation treatment) and Medical Research Council Adjuvant Infusional Chemotherapy (MAGIC) (the neoadjuvant and adjuvant chemotherapy treatment) trials have established the standard of care[113]. In Asia, on the other hand adjuvant chemotherapy following a D2 resection is considered the gold standard[114,115].

This approach is based on the assumption that neo-adjuvant systemic therapy, can lead to tumor down-staging, leading to an improved R0 resection rate. This is particularly significant in Western patients in whom the tumors are usually bulky at diagnosis[116]. The question of the benefit of neoadjuvant chemotherapy was addressed as a part of the MAGIC trial, which has established Level 1 evidence for this approach[113]. The MAGIC trial enrolled 503 patients with gastric, gastroesophageal junction, and esophageal carcinoma[113]. These patients were randomized to receive three cycles of perioperative chemotherapy, consisting of epirubicin, cisplatin and 5-fluorouracil (5-FU) (ECF) followed by surgery, followed by three more cycles of ECF or to surgery followed by observation. In this trial, post-operative chemotherapy proved hard to deliver with only 34% of patients receiving

this treatment and only 68% of patients underwent a curative resection. Despite this, both progression free survival (PFS) and overall survival (OS) were improved in the group receiving ECF (HR for PFS hazard ratio for progression, 0.66; 95%CI: 0.53-0.81; $p < 0.001$, and HR for OS = 0.75; 95%CI: 0.60-0.93; $p = 0.009$). Five-year survival rates were 36.3% (95%CI: 29.5%-43.0%) among patients in the perioperative-chemotherapy group and 23.0% (95%CI: 16.6%-29.4%) among those in the surgery group[113]. Taken together this suggests that that majority of the benefit may in fact come from the preoperative portion of the chemotherapy.

A study by the European Organization for Research and Treatment of Cancer (EORTC) did not demonstrate a benefit from the addition of perioperative chemotherapy[117]. This trial showed a significantly increased R0 resection rate but failed to demonstrate a survival benefit for the addition of chemotherapy, however it was not sufficiently powered to demonstrate a difference given its premature termination due to poor accrual. An ongoing Japanese Clinical Oncology Group (JCOG0501) trial is attempting to answer the question of whether perioperative chemotherapy with cisplatin and S-1 adds anything to their standard of care which is surgery followed by adjuvant S-1 chemotherapy. The results of this trial are awaited; however, they are unlikely to be generalizable to the North American population because of different tumor biology.

The benefits of adjuvant chemotherapy after a D2 resection were initially demonstrated in Japan and the chemotherapy used was S1 (an oral fluoropyrimidine)[114]. The Adjuvant Chemotherapy Trial of S-1 for GC (ACTS-GC) trial randomized 1059 patients to 1 year of S-1 or observation. The primary analysis of follow-up data showed that the 3-year OS rate was 80.1% in the S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the S-1 group, as compared with the surgery-only group, was 0.68 (95%CI: 0.52-0.87; $p = 0.003$). This analysis was updated after five years of follow-up and demonstrated consistent results[118]. The OS rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (HR = 0.669; 95%CI: 0.540-0.828). The RFS rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-alone group (HR = 0.653; 95%CI: 0.537-0.793).

A second Asian study, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC trial) randomized 1035 patients who had undergone D2 gastrectomy to capecitabine plus oxaliplatin for 6 mo or observation[115]. The study demonstrated a benefit of capecitabine and oxaliplatin treated patients for the primary end point of disease-free survival (at 3 years; HR = 0.56, 95%CI: 0.44-0.72; $p < 0.0001$) at the prespecified interim analysis. After this analysis, the trial was stopped after a recommendation by the data monitoring committee. The mature OS data are awaited, however 3-year OS was 83% (95%CI: 79-87) in the chemotherapy group and 78% (74-83) in the surgery only group (HR = 0.72, 95%CI: 0.52-1.00; $p = 0.0493$). It is likely that an OS benefit will be found with longer follow-up.

A meta-analysis based on single patient-data from 3,838 patients and 17 randomized controlled trials showed a 7% improvement in OS (HR = 0.82; 95%CI: 0.76-0.90; $p < 0.001$) for fluorouracil-based postoperative chemotherapy when compared with surgery alone[119]. This meta-analysis was criticized because it combined studies from different time periods with differing eligibility criteria and therapeutic approaches, making it difficult to make a firm conclusion.

Based on the previously mentioned trials and meta-analysis, postoperative chemoradiotherapy (United States), pre-and post-operative chemotherapy (Europe), and adjuvant chemotherapy after a D2 resection (Asia) can all be regarded as standards of care in the localized gastric cancer management.

The medical treatment of metastatic gastric cancer is primarily palliative and confers a modest effect on OS. Multiple agents are active in the treatment of gastric cancer, including fluoropyrimidines (5-FU, capecitabine, and S1), anthracyclines, platinum agents, taxanes, irinotecan, and some targeted therapies such as trastuzumab for HER-2 overexpressing GCs. Combination regimens are associated with higher response rates, and according to one meta-analysis, are also associated with increased survival when compared with single-agent chemotherapies[120]. By and large the trials addressing the value of targeted therapies, for example EGFR and vascular endothelial growth factor (VEGF) were done in un-selected (not bio-marker enriched) populations and have not-surprisingly yielded disappointing results.

Only a minor amount of level 1 evidence exists for the treatment of GC in the first line setting. In fact, only docetaxel[121], cisplatin/oxaliplatin[122], and Trastuzumab[123] use is supported by high level of evidence.

A phase III trial involving 445 patients with metastatic cancer randomized patients to receive, cisplatin and 5-FU or Cisplatin, 5-FU and docetaxel. They found that the addition of docetaxel was superior in terms of response rate (37% *vs* 25%; $p = 0.01$), time-to-tumor progression (5.6 mo *vs* 3.7 mo; $p < 0.001$), and OS (9.2 mo *vs* 8.6 mo; $p = 0.02$)[121]. One could question the clinical significance of a less than one month absolute im-

provement in OS particularly in the context of significant toxicities, most notably, a high rate of febrile neutropenia (30%). Importantly, this regimen should not be used in patients who have a reduced performance status.

Trastuzumab was the first targeted agent with documented clinical activity in the advanced gastric and gastroesophageal setting cancer setting. This treatment is useful in the HER2 enriched population. However, approximately 20% of GCs and 30% of gastroesopageal cancers overexpress HER2 so that a relatively small proportion of patients benefits from the treatment. The trastuzumab in GC (ToGA) trial randomized 584 patients whose tumors overexpressed HER2 by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) to receive a fluoropyrimidine (5-FU or capecitabine) plus cisplatin with or without trastuzumab. The chemotherapy was administered every 3 wk for six cycles and trastuzumab was administered every 3 wk until disease progression[123]. They found that the addition of trastuzumab to chemotherapy increased OS from 11.1 mo to 13.8 mo (HR = 0.74, 95%CI: 0.60-0.91; $p = 0.0046$). The secondary endpoints of PFS (6.7 mo *vs* 5.5 mo; $p = 0.0002$) and response rate (47.3% *vs* 34.5%; $p = 0.0017$) were also improved. On extended follow-up the HR of OS for the addition of trastuzumab has decreased to 0.80[41], indicating that although real the response to trastuzumab may be short lived. The difference in median OS was reduced from 2.7 mo to merely 1.4 mo, representing an approximate 50% decrease in the effect of trastuzumab, which suggests that only a few patients benefit. Based on this trial the combination of Trastuzumab to chemotherapy has become the standard of care in patients whose tumors overexpress HER2. In contrast to the encouraging results with trastuzumab in HER2 overexpressing cancers, Bevacizumab failed to demonstrate an OS benefit when it was added to a combination of cisplatin and fluoropyrimidine in patients with advanced gastric and gastroesophageal junction adenocarcinoma[124]. Recently the safety and efficacy of trastuzumab in the treatment of patients with peritoneal carcinomatosis by GC with HER2 3+ has been reported. The treatment obtained a control of local disease with good safety[125]. FDA has been recently improved the use of Ramucirumab in combination with Paclitaxel for advanced gastric or gastroesophageal junction adenocarcinoma[126].

RADIOTHERAPY APPROACH

Because many patients present with locally advanced at the time of diagnosis, and this results in poor outcomes after surgery, with a significant number of patients having local relapse of the disease, there has been interest in treating patients with radiotherapy with or without chemotherapy. Gunderson, clearly, demonstrated that locoregional relapse occurred in 67% of resected patients and 23% of these patients failed only in the locoregional areas, without any other documented site of failure[127]. Despite improved and standardized surgical techniques, in the Dutch randomized study locoregional recurrence occurred in 35% of patients[107]. Clinical controlled trials of radiotherapy as a single adjuvant in the post surgical setting have shown conflicting results[128-130]. Although locoregional failure was substantially reduced with radiotherapy in all studies, no overall survival benefit was seen. To obtain an increased disease control adjuvant combined radiotherapy and chemotherapy was studied. There were several randomized clinical trials, however the results are inconclusive or conflicting because of the relatively small samples. A large study, the Intergroup Study INT-0116, concluded that postoperative radiochemotherapy significantly improves survival compared to surgery alone[112]. In all studies, adding chemotherapy to radiotherapy enhances radiation response (radio sensitizer), increasing the benefit in locoregional control.

Two meta-analysis were performed, both demonstrated beneft of adjuvant postoperative radiochemotherapy for GC[132,133]. However, an increased severe or life-threatening toxicities and risk of death from causes unrelated to GC. Fewer patients need to be treated by radiochemotherapy to benefit from the treatment long term than need to be treated to be harmed post surgery, therefore this benefit may outweigh the risks for patients at high local and distant recurrence rates, where as the risks outweigh the benefits for patients with low probability of local and distant failure.

Neoadjuvant radiotherapy is treatment given before an anticipated definitive surgery. Delivering radiotherapy preoperatively could enhance the rate of curative surgery and offer the theoretical advantage of treating a tumor with intact vascularization, without fibrotic remodeling of the tumor bed following surgical tumor removal. For these hypotheses, preoperative approach has become the focus of interest in an effort to prolong survival and reduce recurrence rates in gastric cancer patients. Several studies were carried out, however the results remain inconsistent, and the overall assessment of the treatment effect difficult to assess. Meta-analysis[132] demonstrated an improved overall survival in patients receiving preoperative radiotherapy without evidence of life-threatening toxicities.

Radiotherapy was studied intraoperatively, most notably the work by Abe et al and Sindelar et

al. Both investigators demonstrated decreased local recurrence rates and Abe suggested a survival advantage[134,135].

Furthermore, radiotherapy is an effective palliative modality of cancer symptoms. Symptomatic relief is achieved in 65-80% of patients[136,137]. Several series have documented a long-term survival in patients with low-volume locally unresectable GC – in the range of 5-10% – with a combination of radiotherapy and chemotherapy.

CLINICAL FOLLOW UP

All patients should be followed up systematically. Follow-up should include a complete history and physical examination every 3 to 6 months for 1 to 2 years, every 6 to 12 months for 3 to 5 years and annually thereafter. Chemistry profile, imaging studies (CT-Scan, CT-PET), or endoscopy should be done if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B12 and iron deficiency.

Although there is broad agreement in the staging, classification, and surgery for GC, there is no consensus regarding follow-up after gastrectomy. Follow-up varies from investigations on clinical suspicion of relapse to intensive investigations to detect recurrences early, assuming that this improves survival and quality of life. Advanced GC recur mainly by locoregional recurrence or distant metastasis[138,139].

Peritoneum followed by liver metastases are the most frequent distant sites of relapse [138-140]. Local recurrences detected at endoscopy or on CT-Scan are invariably incurable. For early GC, endoscopy can detect new primaries, but the incidence of these tumors is low, and many thousands of procedures are required to detect each operable case. CT-Scan is much better at detecting liver metastasis and, although these are usually multiple and unresectable, there are several reports of good survival following liver resection for isolated metastasis.

Tumor markers have been used with some success to detect subclinical recurrences and could be used to target more invasive or expensive procedures.

There are many investigations that may be used to detect recurrent GC, and these can broadly be divided into endoscopy, imaging, and blood tests. Endoscopy has the ability to detect intraluminal recurrences with a high degree of accuracy and it also has the ability to detect new cancers at a treatable stage.

The use of tumor markers has become more commonplace. CEA and CA 19-9 levels are easily determined by a simple blood test and have reported sensitivities of between 16% and 65% for individual markers, increasing to up to 85% if both were used. Increases in markers are commonly seen prior to the clinical detection of recurrences, and in a prospective study, both tumour markers were useful indicators of recurrence, even in patients whose original tumours did not express them. Other tumour markers, such CA 125, have been investigated, but sensitivities are significantly lower than those for CEA and CA19-.9.

Reports on the use of imaging in detecting recurrent GC are few, and are often limited. The ability to detect hepatic metastases is probably also overestimated, and has been examined in a recent meta-analysis of trials comparing the accuracy of several imaging methods. When the required specificity was set at greater than 85%, the most sensitive method was 18F-fluorodeoxyglucose positron emission tomography (PET) with a sensitivity of 90%, followed by magnetic resonance imaging (MRI; 76%), CT (72%), and ultrasonography (US; 55%)[141-144]. In GC, the great majority of patients under follow-up will not have hepatic metastases, and even with high specificities, there are likely to be many false-positive results. The ability of CT-Scan to primarily diagnose a primary carcinoma of the stomach is not as good as its ability to stage a known cancer, and there is a direct trade off between sensitivity and specificity.

Therefore, the imaging in the search for asymptomatic recurrence is fraught with difficulties, missing many recurrences and producing a number of false-positive results. Imaging is perhaps more useful when a clinical recurrence is suspected, such as in the face of rising tumour markers. In this role, PET can be especially useful in cases where conventional imaging results are equivocal, as it can confirm or refute the presence of recurrence in most cases.

CONCLUSIONS

The purpose of this review is to focus the most important prognostic factors and predicitve response to therapy in patients with GC, especially in metatstatic GC patients.

To date GC represent a challenge for the oncologists and typical example of cancer disease where the multidisciplinary approach represent the right way to approach this disease[145].

Probably the support of genetic tests (pharmacogenomics) in patients under treatment will represent in the next future the only way to approach these patients with “tailored” treatment, obtaining the good results, a significantly reduction of treatment related toxicities and finally the cost saving of the drugs[146-153].

REFERENCES

1. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available: http://globocan.iarc.fr/Pages/fact_sheets cancer.aspx. Accessed 2014 February 12.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11.
3. Parkin DM. Epidemiology of cancer: global patterns and trends. Toxicol Lett 1998; 102-103: 227.
4. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer 1993; 55: 891.
5. Haenszel W. Variation in incidence of and mortality from stomach cancer, with particular reference to the United States. J Natl Cancer Inst 1958; 21: 213.
6. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev Oncol Hematol 2009; 71(2): 127-164.
7. Zhu AL, Sonnenberg A. Is gastric cancer again rising? J Clin Gastroenterol 2012; 46: 804.
8. Wynder EL, Kmet J, Dungal N, Segi M. An epidemiological investigation of gastric cancer. Cancer 1963; 16: 1461.
9. Correa P, Haenszel W, Tannenbaum S. Epidemiology of gastric carcinoma: review and future. Natl Cancer Inst Monogr 1982; 62: 129-134.
10. Scheiman JM, Cutler AF. Helicobacter pylori and gastric cancer. Am J Med 106 (2): 222-6, 1999. Natl Cancer Inst Monogr 1982; 62: 129.
11. Hirayama T. Epidemiology of cancer of the stomach with special reference to its recent decrease in Japan. Cancer Res 1975; 35: 3460.
12. OPCS (Office of Population, Census and Surveys). 1994 Cancer statistics: Registrations in England and Wales (Series MB No. 21). HMSO, London 1978.
13. Fitzsimmons D, Osmond C, George S, Johnson CD. Trends in stomach and pancreatic cancer incidence and mortality in England and Wales, 1951-2000. Br J Surg 2007; 94: 1162.
14. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. CA Cancer J Clin 2006; 56: 106-130.
15. Schlansky B, Sonnenberg A. Epidemiology of non-cardia gastric adenocarcinoma in the United States. Am J Gastroenterol 2011; 106: 1978.
16. Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA 2010; 303: 1723.
17. Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, Corrao G, La Vecchia C, Boffetta P. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012; 23: 28-36.
18. Coggon D, Barker DJ, Cole RB, Nelson M. Stomach cancer and food storage. J Natl Cancer Inst 1989; 81: 1178.
19. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk. Br J Cancer 1990; 62: 136.
20. Allum WH, Powell DJ, McConkey CC, Fielding JW. Gastric cancer: a 25-year review. Br J Surg 1989; 76: 535-540.
21. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg 1993; 218: 583-592.
22. Akoh JA, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. Br J Surg 1992; 79: 293-299.
23. Japanese Research Society for Gastric cancer. The general rules for the gastric cancer study in surgery and pathology (ed 12): Tokyo Kanahara Shuppan, 1993.
24. Roder JD, Böttcher K, Busch R, Wittekind C, Hermanek P, Siewert JR. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. Cancer 1998; 82: 621-631.
25. Kurtz RC, Sherlock P. The diagnosis of gastric cancer. Semin Oncol 1985; 12: 11-18.
26. Alexander HR, Kelsen D, Tepper JC. Cancer of the stomach. In: De Vita V, Hellman S, Rosenberg S, editors. Cancer: principles and practice of oncology. 5th edition Philadelphia: JB Lippincott, 1997; pp. 1021-1054.
27. Hermanek P, Maruyama K, Sobin LH. Gastric cancer. In: Hermanek, Gospodarowicz MK, Henson DE, Hutter RVP, Sobin LH, editors. Prognostic factors in cancer. Geneve: International Union Against Cancer (UICC), 1995.
28. Alexander HR, Kelsen D, Tepper JC. Cancer of the stomach. In: De Vita V, Hellman S, Rosenberg S, editors. Cancer: principles and practice of oncology. 5th edition Philadelphia: JB Lippincott, 1997; pp. 1021-1054.
29. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005; 23: 7114-7124.
30. UICC (International Union Against Cancer). In: Sobin LH,Wittekind CH, editors. TNM classification of malignant tumours. 5th edition New York, Chichester, Weinheim, Brisbane, Singapore, Toronto: Wiley-Liss, 1997.
31. van Krieken JH, Sasako M, van de velde CJ. Gastric cancer. In: Gospodarowicz MK, Henson DE, Hutter RVP, O'Sullivan B, Sobin LH, Wittekind C, editors. Prognostic factors in cancer. New York: Wiley-Liss, 2001; pp. 251-265.
32. Rohde H, Gebbensleben B, Bauer P, Stutzer H, Zieschang J. Has there been any improvement in the staging of gastric cancer? Findings from the German Gastric Cancer TNM Study Group. Cancer 1989; 64: 2465-2481.
33. Carriaga MT, Henson DE. The histologic grading of cancer. Cancer 1995; 75: 406-421.
34. Lauren P. The two histological main types of Gastric Carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31.
35. Ikeda Y, Mori M, Kamakura T, Haraguchi Y, Saku M, Sugimachi K. Improvements in diagnosis have changed the incidence of histological types in advanced gastric cancer. Br J Cancer 1995; 72: 424-426.
36. Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. J Clin Oncol 2012; 30: 3493-3498.
37. Bunt AM, Hogendoorn PC, van de Velde CJ, Bruijn JA, Hermans J. Lymph node staging standards in gastric cancer. J Clin Oncol 1995; 13: 2309-2316.
38. Hartgrink HH, Bonenkamp HJ, van de Velde CJ. Influence of surgery on outcomes in gastric cancer. Surg Oncol Clin N Am 2000; 9: 91-117.
39. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg 1998; 228: 449-461.
40. British Stomach Cancer Group. Resection line disease in stomach cancer. Br Med J (Clin Res Ed) 1984; 289: 601-603.
41. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T, Ohkubo H. Clinicopathologic characteristics of gastric cancer patients with cancer infiltration at surgical margin at gastrectomy. Anticancer Res 1997; 17: 689-694.

42. Takagane A, Terashima M, Abe K, Araya M, Irinoda T, Yonezawa H, Nakaya T, Inaba T, Oyama K, Fujiwara H, Saito K. Evaluation of the ratio of lymph node metastasis as a prognostic factor in patients with gastric cancer. Gastric Cancer 1999; 2: 122-128.
43. Bollschweiler E, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, Siewert JR. Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer 1993; 71: 2918-2925.
44. Maehara Y, Kakeji Y, Oda S, Takahashi I, Akazawa K, Sugimachi K. Time trends of surgical treatment and the prognosis for Japanese patients with gastric cancer. Br J Cancer 2000; 83: 986-991.
45. Moriguchi S, Maehara Y, Korenaga D, Sugimachi K, Nose Y. Relationship between age and the time of surgery and prognosis after gastrectomy for gastric cancer. J Surg Oncol 1993; 52: 119-123.
46. Maguire A, Porta M, Sanz-Anquela JM, Ruano I, Malats N, Piñol JL. Sex as a prognostic factor in gastric cancer. Eur J Cancer 1996; 32A: 1303-1309.
47. Maehara Y, Watanabe A, Kakeji Y, Emi Y, Moriguchi S, Anai H, Sugimachi K. Prognosis for surgically treated gastric cancer patients is poorer for women than men in all patients under age 50. Br J Cancer 1992; 65: 417-420.
48. Rabuñal RR, Pita SF, Rigueiro MT, Casariego EV, Pértega SD, García-Rodeja E, Abraira V. Presentation and prognosis of gastric cancer in patients aged 80 years and older. World J Surg 2004; 28: 155-159.
49. Tachibana M, Takemoto Y, Nakashima Y, Kinugasa S, Kotoh T, Dhar DK, Kohno H, Nagasue N. Serum carcinoembryonic antigen as a prognostic factor in resectable gastric cancer. J Am Coll Surg 1998; 187: 64-68.
50. Nakane Y, Okamura S, Akehira K, Boku T, Okusa T, Tanaka K, Hioki K. Correlation of preoperative carcinoembryonic antigen levels and prognosis of gastric cancer patients. Cancer 1994; 73: 2703-2708.
51. Sakamoto J, Nakazato H, Teramukai S, Ohashi Y, Takahashi Y, Mai M, Toge T, Okura H, Kodaira S, Maetani S, Okajima K, Nomoto K, Hattori T, Inokuchi K. Association between preoperative plasma CEA levels and the prognosis of gastric cancer following curative resection. Tumor Marker Committee, Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan. Surg Oncol 1996; 5: 133-139.
52. Maehara Y, Kusumoto T, Takahashi I, Kakeji Y, Baba H, Akazawa K, Sugimachi K. Predictive value of preoperative carcinoembryonic antigen levels for the prognosis of patients with well-differentiated gastric cancer. A multivariate analysis. Oncology 1994; 51: 234-237.
53. Irinoda T, Terashima M, Takagane A, Sasaki N, Abe K, Araya M, Nishizuka S, Yonezawa H, Nakaya T, Shimooki O, Oyama K, Ikeda K, Saito K. Carcinoembryonic antigen level in peritoneal washing is a prognostic factor in patients with gastric cancer. Oncol Rep 1998; 5: 661-666.
54. Nishiyama M, Takashima I, Tanaka T, Yoshida K, Toge T, Nagata N, Iwamori S, Tamura Y. Carcinoembryonic antigen levels in the peritoneal cavity: useful guide to peritoneal recurrence and prognosis for gastric cancer. World J Surg 1995; 19: 133-137.
55. Chung HW, Kim JW, Lee JH, Song SY, Chung JB, Kwon OH, Lim JB. Comparison of the validity of three biomarkers for gastric cancer screening: carcinoembryonic antigen, pepsinogens, and high sensitive C-reactive protein. J Clin Gastroenterol 2009; 43: 19-26.
56. Kodama I, Koufuji K, Kawabata S, Tetsu S, Tsuji Y, Takeda J, Kakegawa T. The clinical efficacy of CA 72-4 as serum marker for gastric cancer in comparison with CA19-9 and CEA. Int Surg 1995; 80: 45-48.
57. Ucar E, Semerci E, Ustun H, Yetim T, Huzmeli C, Gullu M. Prognostic value of preoperative CEA, CA 19-9, CA 72-4, and AFP levels in gastric cancer. Adv Ther 2008; 25: 1075-1084.
58. Nakanishi H, Kodera Y, Yamamura Y, Ito S, Kato T, Ezaki T, Tatematsu M. Rapid quantitative detection of carcinoembryonic antigen-expressing free tumor cells in the peritoneal cavity of gastric-cancer patients with real-time RT-PCR on the lightcycler. Int J Cancer 2000; 89: 411-417.
59. Mattar R, Alves de Andrade CR, DiFavero GM, Gama-Rodrigues JJ, Laudanna AA. Preoperative serum levels of CA 72-4, CEA, CA 19-9, and alpha-fetoprotein in patients with gastric cancer. Rev Hosp Clin Fac Med Sao Paulo 2002; 57: 89-92.
60. Fernandes LL, Martins LC, Nagashima CA, Nagae AC, Waisberg DR, Waisberg J. CA72-4 antigen levels in serum and peritoneal washing in gastric cancer. Correlation with morphological aspects of neoplasia, Arq Gastroenterol 2007; 44: 235-239.
61. Leung F, Diamandis EP, Kulasingam V. Ovarian cancer biomarkers: current state and future implications from high-throughput technologies. Adv Clin Chem 2014; 66: 25-77.
62. Nakata B, Hirakawa-YS Chung K, Kato Y, Yamashita Y, Maeda K, Onoda N, Sawada T, Sowa M. Serum CA 125 level as a predictor of peritoneal dissemination in patients with gastric carcinoma. Cancer 1998; 83: 2488-2492.
63. Becker KF, Keller G, Hoefler H. The use of molecular biology in diagnosis and prognosis of gastric cancer. Surg Oncol 2000; 9: 5-11.
64. Fenoglio-Preiser CM, Wang J, Stemmermann GN, Noffsinger A. TP53 and gastric carcinoma: a review. Hum Mutat 2003; 21: 258-270.
65. Tahara E, Semba S, Tahara H. Molecular biological observations in gastric cancer. Semin Oncol 1996; 23: 307-315.
66. Kubicka S, Claas C, Staab S, Kühnel F, Zender L, Trautwein C, Wagner S, Rudolph KL, Manns M. p53 mutation pattern and expression of c-erbB2 and c-met in gastric cancer: relation to histological subtypes, helicobacter pylori infection, and prognosis. Dig Dis Sci 2002; 47: 114-121.
67. Maeda K, Kang SM, Onoda N, Ogawa M, Sawada T, Nakata B, Kato Y, Chung YS, Sowa M. Expression of p53 and vascular endothelial growth factor associated with tumor angiogenesis and prognosis in gastric cancer. Oncology 1998; 55: 594-599.
68. Fonseca L, Yonemura Y, De Aretxabala X, Yamaguchi A, Miwa K, Miyazaki I. p53 detection as a prognostic factor in early gastric cancer. Oncology 1994; 51: 485-490.
69. Victorzon M, Nordling S, Haglund C, Lundin J, Roberts PJ. Expression of p53 protein as a prognostic factor in patients with gastric cancer. Eur J Cancer 1996; 32A: 215-220.
70. Xiangming C, Hokita S, Natsugoe S, Tanabe G, Baba M, Takao S, Kuroshima K, Aikou T. p21 expression is a prognostic factor in patients with p53-negative gastric cancer. Cancer Lett 2000; 148: 181-188.
71. Catalano V, Baldelli AM, Giordani P, Cascinu S. Molecular markers predictive of response to chemotherapy in gastrointestinal tumors. Crit Rev Oncol Hematol 2001; 38: 93-104.
72. Cascinu S, Graziano F, Del Ferro E, Staccioli MP, Ligi M, Carnevali A, Muretto P, Catalano G. Expression of p53 protein protein and resistance to preoperative chemotherapy in locally advanced gastric carcinoma. Cancer 1998; 83: 1917-1922.
73. Nakata B, Chung KH, Ogawa M, Ogawa Y, Yanagawa K, Muguruma K, Inoue T, Yamashita Y, Onoda N, Maeda K, Sawada T, Sowa M. p53 protein overexpression as a predictor of the response to chemotherapy in gastric cancer. Surg Today 1998; 28: 595-598.

74. Lenz HJ, Leichman CG, Danenberg KD, Danenberg PV, Groshen S, Cohen H, Laine L, Crookes P, Silberman H, Baranda J, Garcia Y, Li J, Leichman L. Thymidylate synthase mRNA level in adenocarcinoma of the stomach: a predictor for primary tumor response and overall survival. J Clin Oncol 1996; 14: 176-182.
75. Yeh KH, Shun CT, Chen CL, Lin JT, Lee WJ, Lee PH, Chen YC, Cheng AL. High expression of thymidylate synthase is associated with the drug resistance of gastric carcinoma to high dose 5-fluorouracil-based systemic chemotherapy. Cancer 1998; 82: 1626-1631.
76. Metzger R, Leichman CG, Danenberg KD, Danenberg PV, Lenz HJ, Hayashi K, Groshen S, Salonga D, Cohen H, Laine L, Crookes P, Silberman H, Baranda J, Konda B, Leichman L. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. J Clin Oncol 1998; 16: 309-316.
77. Chan AO, Chu KM, Lam SK, Wong BC, Kwok KF, Law S, Ko S, Hui WM, Yueng YH, Wong J. Soluble E-Cadherin is an Independent Pretherapeutic Factor for Long-Term Survival in Gastric Cancer. J Clin Oncol 2003; 21: 2288-2293.
78. Frixen UH, Behrens J, Sachs M, Eberle G, Voss B, Warda A, Löchner D, Birchmeier W. E-cadherin-mediated cell-cell adhesion prevents invasiveness of human carcinoma cells. J Cell Biol 1991; 113: 173-185.
79. Vleminckx K, Vakaet L Jr, Mareel M, Fiers W, van Roy F. Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell 1991; 66: 107-119.
80. Takeichi M. Cadherins in cancer: Implications for invasion and metastasis. Curr Opin Cell Biol 1993; 5: 806-801.
81. 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; ToGA Trial Investigators. 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(9742): 687-697.
82. Tateishi M, Toda T, Minamisono Y, Nagasaki S. Clinicopathological significance of c-erbB-2 protein expression in human gastric carcinoma. J Surg Oncol 1992; 49: 209-212.
83. Sasano H, Date F, Imatani A, Asaki S, Nagura H. Double immunostaining for c-erbB-2 and p53 in human stomach cancer cells. Hum Pathol 1993; 24: 584-589.
84. Uchino S, Tsuda H, Maruyama K, Kinoshita T, Sasako M, Saito T, Kobayashi M, Hirohashi S. Over expression of c-erbB-2 protein in gastric cancer. Its correlation with long-term survival of patients. Cancer 1993; 72: 3179-3184;
85. Mizutani T, Onda M, Tokunaga A, Yamanaka N, Sugisaki Y. Relationship of c-erbB-2 protein expression and gene amplification to invasion and metastasis in human gastric cancer. Cancer 1993; 72: 2083-2088.
86. García I, Vizoso F, Martín A, Sanz L, Abdel-Lah O, Raigoso P, García-Muñiz JL. Clinical significance of the epidermal growth factor receptor and HER2 receptor in resectable gastric cancer. Ann Surg Oncol 2003; 10: 234-241.
87. Tanner M, Hollmén M, Junttila TT, Kapanen AI, Tommola S, Soini Y, Helin H, Salo J, Joensuu H, Sihvo E, Elenius K, Isola J. Amplification of HER-2 in gastric carcinoma: association with topoisomerase IIa gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005; 16: 273-278.
87. Takehana T, Kunitomo K, Kono K, Kitahara F, Iizuka H, Matsumoto Y, Fujino MA, Ooi A. Status of c-erbB-2 in gastric adenocarcinoma: a comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. Int J Cancer 2002; 98: 833-837.
89. Lin JT, Wu MS, Shun CT, Lee WJ, Sheu JC, Wang TH. Occurrence of microsatellite instability in gastric carcinoma is associated with enhanced expression of erbB-2 oncoprotein. Cancer Res 1995; 55: 1428-1430.
90. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008; 19: 1523-1529.
91. 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; ToGA Trial Investigators. 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(9742): 687-697. doi: 10.1016/S0140-6736(10)61121-X. Epub 2010 Aug 19. Lancet 2010; 376(9749): 1302.
92. Graziano F, Ruzzo A, Santini D, Humar B, Tonini G, Catalano V, Berardi R, Pizzagalli F, Arduini F, Bearzi I, Scartozzi M, Cascinu S, Testa E, Ficarelli R, Magnani M. Prognostic Role of Interleukin-1Gene and Interleukin-1 Receptor Antagonist Gene Polymorphisms in Patients With Advanced Gastric Cancer. J Clin Oncol 2005; 23: 2339-2345.
93. De Vita F, Romano C, Orditura M, Galizia G, Martinelli E, Lieto E, Catalano G. Interleukin-6 serum level correlates with survival in advanced gastrointestinal cancer patients but is not an independent prognostic indicator. J Interferon Cytokine Res 2001; 21: 45-52.
94. Liu YJ, Shen D, Yin X, Gavine P, Zhang T, Su X, Zhan P, Xu Y, Lv J, Qian J, Liu C, Sun Y, Qian Z, Zhang J, Gu Y, Ni X. HER2, MET and FGFR2 oncogenic driver alterations define distinct molecular segments for targeted therapies in gastric carcinoma. Br J Cancer 2014; 110: 1169-1178.
95. Nakajima M, Sawada H, Yamada Y, Watanabe A, Tatsumi M, Yamashita J, Matsuda M, Sakaguchi T, Hirao T, Nakano H. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. Cancer 1999; 85: 1894-1902.
96. Tsugawa K, Yonemura Y, Hirono Y, Fushida S, Kaji M, Miwa K, Miyazaki I, Yamamoto H. Amplification of the c-met, c-erbB-2 and epidermal growth factor receptor gene in human gastric cancers: correlation to clinical features, Oncology 1998; 55: 475-481.
97. Graziano F, Galluccio N, Lorenzini P, Ruzzo A, Canestrari E, D'Emidio S, Catalano V, Sisti V, Ligorio C, Andreoni F, Rulli E, Di Oto E, Fiorentini G, Zingaretti C, De Nictolis M, Cappuzzo F, Magnani M. Genetic Activation of the MET Pathway and Prognosis of Patients With High-Risk, Radically Resected Gastric Cancer. J Clin Oncol 2011; 29: 4789-4795.
98. Ajani JA, Mayer RJ, Ota DM, Steele GD, Evans D, Roh M, Sugarbaker DJ, Dumas P, Gray C, Vena DA. Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. J Natl Cancer Inst 1993; 85: 1839-1844.
99. Leichman L, Silberman H, Leichman CG, Spears CP, Ray M, Muggia FM, Kiyabu M, Radin R, Laine L, Stain S. Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: a University of Southern California pilot program. J Clin Oncol 1992; 10: 1933-1942.

100. Hermanek P, Wittekind C. Residual tumor (R) classification and prognosis. Semin Surg Oncol 1994; 10: 12-20.
101. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg 1999; 230: 170-178.
102. Chen K, Xu XW, Mou YP, Pan Y, Zhou YC, Zhang RC, Wu D. Systematic review and meta-analysis of laparoscopic and open gastrectomy for advanced gastric cancer. World J Surg Oncol 2013; 11: 182.
103. Fang C, Hua J, Li J, Zhen J, Wang F, Zhao Q, Shuang J, Du J. Comparison of long-term results between laparoscopyassisted gastrectomy and open gastrectomy with D2 lymphadenectomy for advanced gastric cancer. Am J Surg 2014; 208: 391-396.
104. Kim BS, Oh ST, Yook JH, Kim HS, Lee IS, Kim BS. Appropriate gastrectomy resection margins for early gastric carcinoma. J Surg Oncol 2014; 109: 198-201.
105. Wang W, Li Z, Tang J, Wang M, Wang B, Xu Z. Laparoscopic versus open total gastrectomy with D2 dissection for gastric cancer: a meta-analysis. J Cancer Res Clin Oncol 2013; 139: 1721-1734.
106. Fujitani K. Overview of adjuvant and neoadjuvant therapy for resectable gastric cancer in the East. Dig Surg 2013; 30: 119-129.
107. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the ran-domized Dutch gastric cancer group trial. J Clin Oncol 2004; 22: 2069-2077.
108. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79: 1522-1530.
109. Shrikhande SV, Barreto SG, Talole SD, Vinchurkar K, Annaiah S, Suradkar K, Mehta S, Goel M. D2 lymphadenectomy is not only safe but necessary in the era of neoadjuvant chemotherapy. World J Surg Oncol 2013; 11: 31.
110. Degiuli M, Sasako M, Ponti A, Vendrame A, Tomatis M, Mazza C, Borasi A, Capussotti L, Fronda G, Morino M; Italian Gastric Cancer Study Group. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg 2014; 101: 23-31.
111. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines): Gastric Cancer. Version: Jan 2014
112. 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.
113. 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, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.
114. 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; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357: 1810-1820.
115. 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; CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315-321.
116. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v50-v54.
117. 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.
118. 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.
119. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010; 303: 1729-1737.
120. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006; 24: 2903-2909.
121. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991-4997.
122. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36-46.
123. 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; ToGA Trial Investigators. 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.
124. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29: 3968-3976.
125. Berretta M, Fisichella R, Borsatti E, Lleshi A, Ioffredo S, Meneguzzo N, Canzonieri V, Di Grazia A, Cannizzaro R, Tirelli U, Berretta S. Feasibility of intraperitoneal Trastuzumab treatment in a patient with peritoneal carcinomatosis from gastric cancer. Eur Rev Med Pharmacol Sci 2014; 18: 689-692.

126. FDA approves Ramucirumab in combination with Paclitaxel for advanced gastric or gastroesophageal junction adenocarcinoma. By The ASCO Post. Posted: 11/05/2014.
127. Gunderson LL. Gastric cancer--patterns of relapse after surgical resection. Semin Radiat Oncol 2002; 12: 150-161.
128. Regine WF, Mohiuddin M. Impact of adjuvant therapy on locally advanced adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 1992; 24: 921-927.
129. Guzel Z, Gajl D, Grzegorzewski J. Postoperative radiotherapy in gastric cancer. J Surg Oncol 1995; 58: 35-39.
130. Caudry M, Escarmant P, Maire JP, Demeaux H, Guichard F, Azaloux H. Radiotherapy of gastric cancer with a three field combination: feasibility, tolerance, and survival. Int J Radiat Oncol Biol Phys 1987; 13: 1821-1827.
131. Hallissey MT, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 1994; 343(8909): 1309-1312.
132. Fiorica F, Cartei F, Enea M, Licata A, Cabibbo G, Carau B, Liboni A, Ursino S, Cammà C. The impact of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis of literature data. Cancer Treat Rev 2007; 33: 729-740.
133. Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, D'Angelo E, Dinapoli N, Nicolotti N, Valentini C, La Torre G. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. Radiother Oncol 2009; 92: 176-183.
134. Abe M, Shibamoto Y, Ono K, Takahashi M. Intraoperative radiation therapy for carcinoma of the stomach and pancreas. Front Radiat Ther Oncol 1991; 25: 258-269; discussion 330-333.
135. Sindelar WF, Kinsella TJ, Tepper JE, DeLaney TF, Maher MM, Smith R, Rosenberg SA, Glatstein E. Randomized trial of intraoperative radiotherapy in carcinoma of the stomach. Am J Surg 1993; 165: 178-186; discussion 186-187.
136. Kim MM, Rana V, Janjan NA, Das P, Phan AT, Delclos ME, Mansfield PF, Ajani JA, Crane CH, Krishnan S. Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol 2008; 47: 421-427.
137. Hashimoto K, Mayahara H, Takashima A, Nakajima TE, Kato K, Hamaguchi T, Ito Y, Yamada Y, Kagami Y, Itami J, Shimada Y. Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience. J Cancer Res Clin Oncol 2009; 135: 1117-1123.
138. Wu CW, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, Lin HJ, Li AF, Lui WY. Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. World J Surg 2003; 27: 153-158.
139. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma, Univariate and multivariate analyses. Cancer 2000; 89: 255-261.
140. Landry J, Tepper JE, Wood WC, Moulton EO, Koerner F, Sullinger J. Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys 1990; 19: 1357-1362.
141. MaBkowski B, Staniuk T, Srutek E, Gorycki T, Zegarski W, Studniarek M. (18)F-FLT PET/CT in Patients with Gastric Carcinoma. Gastroenterol Res Pract. 2013; 2013: 696423.
142. Lacueva FJ, Calpena R, Medrano J, Compañ AF, Andrada E, Moltó M, Ferrer R, Diego M. Follow-up of patients resected for gastric cancer. J Surg Oncol. 1995 Nov;60(3):174-179.
143. Huguier M, Houry S, Lacaine F. Is the follow-up of patients operated on for gastric carcinoma of benefit to the patient? Hepatogastroenterology 1992; 39: 14-16.
144. Bohner H, Zimmer T, Hopfenmuller W, Berger G, Buhr HJ. Detection and prognosis of recurrent gastric cancer–is routine follow-up after gastrectomy worthwhile? Hepatogastroenterology 2000; 47: 1489-1494.
145. Berretta M, Di Francia R, Tirelli U, Editorial – The new oncologic challenges in the 3RD millennium WCRJ 2014; 1: e133.
146. Di Francia R, Catapano O, Pezone A, Lus G, Berretta M, Del Pup L, Tommaselli P, A. De Lucia D. Molecular diagnostics in the clinical practice – "Research Centre CETAC" Caserta (Italy) the 23/24 May 2014. WCRJ 2014; 1: e220.
147. De Monaco A, Faioli D, Di Paolo M, Catapano O, D'Orta A, Del Buono M, Del Buono R, Di Francia R. Pharmacogenomics markers for prediction response and toxicity in cancer therapy WCRJ 2014; 1: e276.
148. Catapano O, Barletta O, Di Paolo M, Faioli D, Di Francia R. Impact of DPYD variants in Fluoropyrimidine based-therapy: the state of the art WCRJ 2014; 1: e279.
149. Di Francia R, Siesto RS, Valente D, Spartà D, Berretta M. Pharmacogenomics panel test for prevention toxicity in patient who receive Fluoropirimidine/Oxaliplatin-based therapy. Eur Rev Med Pharmacol Sci 2012; 16: 1211-1217.
150. Di Francia R, Valente D, Catapano O, Rupolo M, Tirelli U, Berretta M. Knowledge and skills needs for health professions about pharmacogenomics testing field. Eur Rev Med Pharmacol Sci 2012; 16: 781-788.
151. Di Francia R, Berretta M, Catapano O, Canzoniero LM, Formisano L. Molecular diagnostics for harmacogenomic testing of fluoropyrimidine based-therapy: costs, methods and applications. Clin Chem Lab Med 2011; 49: 1105-1111.
152. De Monaco A, Berretta M, Pugliese S, Valente D, Ciaffarafa S, Di Francia R. Evaluation of genotyping methods and the relative cost of pharmacogenomics. Eur Rev Med Pharmacol Sci 2014; 18: 2084-2087.