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Gastric Cancer Historic Profile in an Emerging Country: 126 Tunisian Cases

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Abstract

Background: Management of gastric cancer is based on multidisciplinary approach and guidelines. Emerging countries face different issues in the oncologic pathologies and need a deep acknowledge of their epidemiology and prognostic factors. The aim of this study was to describe the clinical and therapeutic features of gastric cancer in Tunisian patients treated in the gastroenterology's department in "RABTA" academic hospital of Tunis.

Methods: We retrospectively analyzed the files of 144 gastric adenocarcinoma diagnosed and treated since 2001-2011. Population was divided into 2 Groups according to whether patients were treated before 2006 (Group I) or after (Group II).

Results: We included only 126 cases: 73 patients in Group I *vs.* 53 in Group II. The median age was 60 years in Group I *vs.* 57.5 years in Group II. Sex-ratio was 2.84 and 1.3 respectively. Malnutrition was reported in 38% *vs.* 24% of cases respectively in the Group I and II (p=0.02). Group II had significantly more locally advanced stages such as T4 in 6.8% *vs.* 18.8% (p=0.04). A total of 46 patients' *vs.* 29 had surgical removal: for curative intent in 38% *vs.* 30% of cases (p=0.34) and for palliative intent in 12.3% *vs.* 11.3% of cases (p=0.86) respectively in Group I and II. The perioperative treatment was performed in only 2.7% *vs.* 5.6% of cases (p=0.23); adjuvant chemotherapy in 9.3% *vs.* 33% (p=0.01) and adjuvant radio-chemotherapy in 9.3% *vs.* 26.6% (p=0.07). Palliative chemotherapy in metastatic forms was used more frequently after 2006 (52% *vs.* 92%; p=0.38). After a mean follow-up of 13 months, overall survival at 5 years was 15 *vs.* 18% respectively in Group 1 and 2 (p=0.9).

Conclusion: In our series, the management of these patients has evolved overtime in terms of preoperative staging and adjuvant treatment. There are still efforts to be made to better introduce the perioperative and neo adjuvant therapy in the treatment of Tunisian patients.

Keywords: Gastric cancer; Prognosis; Surgery; Chemotherapy, Radiotherapy; Survival

Introduction

Gastric cancer (GC) is the fifth most common cancer and the second leading cause of death for cancer worldwide (952,000 new cases/year), despite a decreasing global incidence and mortality [1]. In Tunisia, GC is the 2nd digestive cancer in men and the 3rd one in women [2]. GC is a heterogeneous disease many environmental, genetic factors and *H. pylori* are well-established causes of GC. Gastric adenocarcinoma (ADC) accounts for more than 90% of GC cases. In Tunisia, ADC with signet ring cells accounts approximately for 34% of cases [3]. Preoperative staging was improved recently by introducing endoscopic ultrasonography and multi-Barrett scans. This allowed a better evaluation of loco regional and distant extension and a better adapted management. Surgical resection with an adequate lymphadenectomy according to Japanese recommendations remains the cornerstone of curative treatment for resectable forms. However, about half of gastric cancers are not suitable for curative surgery, and even when it is possible, the recurrence rate remains high and the survival rate low [4]. Overall survival at 5 years is still poor, less than 30% as most patients present with advanced, inoperable disease. Even in those who undergo potentially curative resection about 50% patients survive 5 years [1,4]. In emerging countries, such as Tunisia, more issues face the oncologist mainly the availability of workup tools and new drugs.

Objectives

The aim of this study was to compare the clinico-epidemiological and therapeutic features of gastric ADC in two Tunisian population's overtime, treated before and after 2006.

Material and Methods

The study population enrolled consecutive patients with a histologically confirmed diagnosis of primary gastric adenocarcinoma, treated between 2001 and 2011 at the gastroenterology's department in Rabta's hospital in Tunisia. We excluded all patients lacking data concerning the loco regional or distant extension and treatment modalities. We detailed demographic and clinic-pathological parameters. Tumor-node-metastasis (TNM) staging was performed according to the 7th edition of American Joint Committee on Cancer. Tumors were considered as clinically locally advanced if we recorded a peri-gastric fat invasion, peri-gastric lymph nodes involvement and/or invasion of adjacent organs. We divided the population into 2 arms

according to whether patients were treated before 2006 (Group I) or after (Group II).

Statistical analysis

The data were analyzed by SPSS 18.0 and MedCalc software. Quantitative values were compared by the Student's t test. Qualitative values by the chi 2 test or Fisher exact test. Overall survival (OS) was calculated from diagnosis until death from any cause or last follow-up alive. Disease-free survival (DFS) was calculated from diagnosis until occurrence of local or distant relapse or last follow-up alive without documented relapse. The OS and DFS at 5 years were chosen as long-term outcomes, and the Kaplane Meier method with the log-rank test was used to assess effect's variables on survival. All tests were two-sided and considered statistically significant at P<0.05.

Results

We enrolled one hundred-forty-four (144) patients with histologically confirmed gastric adenocarcinoma. Eighteen patients lacking data for the staging and treatment modalities were excluded. The remaining 126 patients were divided on two time period arms: 2001-2006 (Group I, n=73 patients) and 2006-2011(Group II, n=53 patients). The median age was 60 years (Group I) (26-90) *vs.* 57.5 years (Group II) (32-90). Sex ratio M/F was 2.84 *vs.* 1.3, respectively (p=0.04). The young population age d ≤ 40 accounted for 15.06% *vs.* 18.86% respectively in the Group I and II.

Clinical workup

Parameter	Group I	Group II	p
Median age (years)	60	57.5	0.23
Sex-ratio (M/F)	2.84	1.3	0.04
Medical history			
Diabetes (%)	2.7	13.2	0.02
Hypertension (%)	13.7	9.4	0.46
Gastrectomy	4	1.9	0.48
Family history of cancer (%)	6.8	1.9	0.19
Tobacco (PA)	18.7	13	0.2
Alcohol (%)	23.3	9.4	0.04
Symptoms (%)			
Weight loss	58	42	0.9
Epigastric pain	89	86	0.7
Vomiting	50	49	0.85
Dysphagia	8.2	11.3	0.55
Gastrointestinal bleeding	4.1	11.3	0.12
Anemia	8.2	5.7	0.58
Hepatomagaly	0	1.9	0.23
Clinical examination (%)			
Epigastric mass	4.1	7.5	0.32
Hepatomagaly	6.8	3.8	0.45
Ascites	1.4	3.8	0.38
Subclavicular nodes	2.7	1.9	0.75

Table 1: Demographic and clinical features.

The most frequent symptoms were weight loss and epigastric pain in both Groups (89% *vs.* 86.8; p=0.7). We noted significantly more alcohol consumers in Group I (before 2006) 23.3% *vs.* 9.4% (p=0.04). Demographic and clinical features are summarized in Table 1. Nutritional condition was evaluated by measuring body mass index (BMI) and the rate of albumin in serum.

Body mass index (BMI) was significantly higher in the Group II with an average of 19.78 Kg/m^2 (15-30) in Group I *vs.* 21.79 Kg/m^2 (12-37) in Group II (p=0.02). Clinical malnutrition (BMI<18.5 Kg/m^2) was recorded in 37.1% *vs.* 25% of cases respectively in Group I and II (p=0.16).

Biology

Serum albumin assay was comparable between the 2 Groups (an average of 31.47 g/l (12.9-49) *vs.* 31.8 g/l (17-46) p=0.08). Serum albumin levels <30 g/l was noted in 37% *vs.* 25.6% (p=0.21). The modified Glasgow score (mGPS), based on the rate of albumin and CRP levels, was equal to 0 in 9.6% *vs.* 13.8%, to 1 in 50% *vs.* 66% and to 2 in 40% *vs.* 19% (p=0.12).

CEA Serum Level was not significantly more frequently elevated (≥ 5 UI/l) in Group II (16.7% Group I *vs.* 37.4% Group II p=0.13) (Table 2).

Parameter	Group I	Group II
Serum Albumin	31%	81%
mGPS	71%	67%
CEA serum	32%	41.50%

Table 2: Biological features.

Endoscopy

All patients had diagnostic gastric endoscopy. Antrum and fundic are the common localizations in both Groups (72% *vs.* 79%; p=0.39) whereas cardia's localization only represented 19% *vs.* 13% (p=0.37). Endoscopic ulcerative budding was the common forming both Groups (56.8% *vs.* 43.2%; p=0.88). Isolated gastric ulcer form accounted for 22% *vs.* 17% (p=0.49) in respectively Group I and II.

ADC diagnosis, confirmed by per-endoscopic biopsies in 97% of cases, was undifferentiated in 54% *vs.* 45% of cases (p=0.29), well differentiated in 4.1% *vs.* 7.5% (p=0.4). Signet ring cells were noted in 52% *vs.* 45% of cases (p=0.45).

Radiology

Before 2006, Tomo-Densitometry (CT) and endoscopic ultrasonography were less available. The radiological assessment was complete in 49% of patients treated before 2006 *vs.* 60% in Group II (p=0.21).

Group I: Barium meal was performed in 30% of cases, a chest X-ray and abdominal ultrasound in 37 patients (50%).

Group II: Endoscopic ultrasonography was performed only in 2 cases (0.03%), and a thoracic-abdominal pelvic scan in 32 patients (60% of cases).

Clinical staging

Unresectable forms accounted for 34% *vs.* 41% (p=0.4). We recorded significantly more locally advanced forms (T4 lesions 6.8% *vs.* 18.8%; p=0.04) and deep parietal invasion (36.9% *vs.* 67.9%; p=0.001) in Group II. Patients were metastatic at diagnosis in 31.5% *vs.* 24.5% of cases (p=0.39) with significantly more bone metastases before 2006 (5 cases *vs.* 0, p=0.05) (Table 3).

Parameter	Group I (%)	Group II (%)	p
Parietal thickness>10 mm	36.9	18.8	0.001
Peri-gastric nodes	35	39	0.32
Peri-gastric fat invasion	35	37	0.14
Stage T4	6.8	18.8	0.03
Metastasis	31.5	24.5	0.39

Table 3: Clinical staging.

Surgery

Seventy seven (61%) patients had surgical removal (46 (Group I) *vs.* 29 (Group II)): with a curative intent in 38% *vs.* 30% of cases (p=0.34) and a palliative intent in 12.3% *vs.* 11.3% of cases (p=0.86) respectively in Group I and II. In 13.5% of cases, exploratory laparotomy (12.3% *vs.* 13.2%; p=0.88) was done for intraoperative discovered unresectable tumor or metastases (Figures 1 and 2).

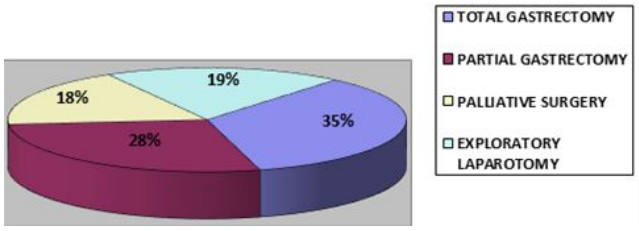

Figure 1: Type of surgery for whole population.

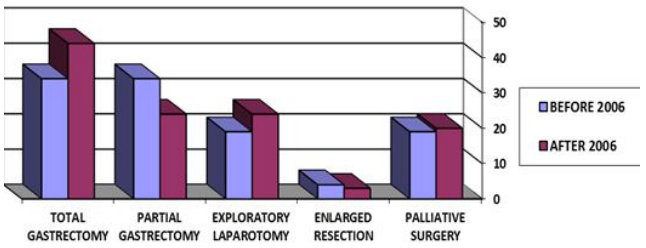

Figure 2: Type of surgery per group.

Pathologic staging

Tumors were classified at least pT3 in 32.6% *vs.* 41% (p=0.3) of cases and at least pN1 in 30% *vs.* 51% (p=0.13) respectively in Group I and II. Lymph node dissection brought an average of 12 nodes and 14 nodes respectively in Group I and II (p=0.42) with an average of 6.5 and 5.3 positive lymph nodes (p=0.62). Lymphadenectomy was insufficient (i.e. ≤ 15 nodes resected) in 46% *vs.* 31% respectively (Table 4).

Stages	Group I(n)	Group II(n)	p
pT1	4	0	0.3
pT2	9	6	
pT3	12	11	
pT4	3	1	
p N0	14	3	0.13
pN1	10	9	
pN2	3	4	
pN3	1	2	
Stage IA	4	0	0.27
Stage IB	6	2	
Stage IIA	6	5	
Stage IIb	7	4	
Stage IIIA	4	3	
Stage IIIB	1	2	
Stage IV	0	2	

Table 4: Pathologic staging.

Chemotherapy

Among 70 patients with locally advanced tumor, 7 underwent neoadjuvant chemotherapy (CT) (2.7% *vs.* 5.6% respectively in Group I and II, p=0.23). The common protocols used were TCF (Docetaxel +Cisplatin+5FU), ECF (Cisplatin+Epirubicin+5FU) in one case and Capecitabin-Cisplatin in another one.

Fourteen patients with stage II-III tumors had adjuvant CT (9.3% *vs.* 33% respectively in Group I and II, p=0.01). Twelve patients received concomitant radio-chemotherapy (RT-CT a modified Mac Donald protocol) 9.3% *vs.* 26.6%, respectively in Group I and II, p=0.07.

Twenty one patients received palliative CT (52% *vs.* 92% respectively in Group I and II; p=0.38). The common protocols used were ELF (Epirubicin, Cisplatin-5FU), TCF (docetaxel-cisplatin-5FU) and FAMTX (5FU-adriamycin-Methotrexate).

Survival

After a median follow-up of 13 months (1-108), 92 deaths had occurred. Overall survival at 5 years was 24% in the whole population and 15 *vs.* 18% respectively in Group I and II (p=0.9) (Figures 3 and 4).

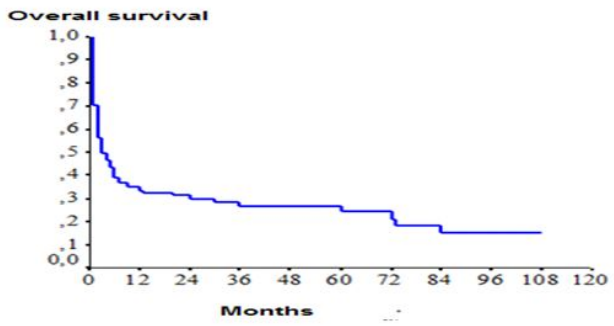

Figure 3: Overall survival for the whole population.

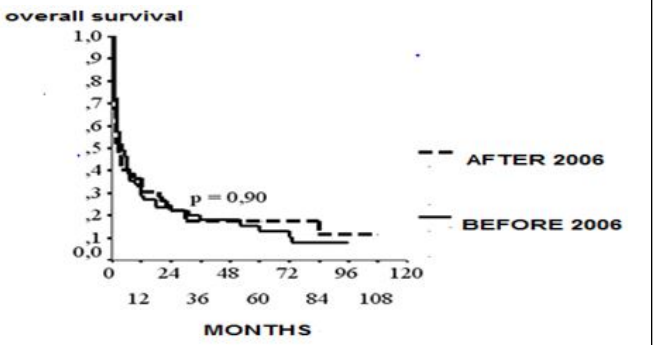

Figure 4: Overall survival in each group.

Discussion

Our study showed that gastric cancer was more frequently locally advanced and/or metastatic in Tunisia. Over the time, we noted the same clinical presentation with essentially weight loss and epigastric pain but malnutrition was less common in the second period of time (after 2006). Some gaps in the management of Gastric ADC in Tunisia were noted. Radiologic assessment was incomplete in 49% of cases before 2006 but it improved to 60% after 2006 (p=0.21) with the availability of CT scan. Neoadjuvant chemotherapy was rarely prescribed in both periods. Nevertheless, we noted an improvement in prescribing chemotherapy in the second period (neoadjuvant, adjuvant and palliative) with a statistical difference in adjuvant chemotherapy (9.3% *vs.* 33%, respectively in Group I and II, p=0.01). No statistical difference was noted in OS between the two Groups of time (15% *vs.* 18%; p=0.9).

Gastric ADC is the fifth cancer worldwide [1]. It has been most frequently observed in persons aged between 50 and 70 years [1]. In Tunisia, most of the series, as in our study, showed a mean age at diagnosis at the sixth decade [2]. As in the literature, we also recorded in our study a male predominance [1,2]. The incidence of gastric ADC in young population ≤ 40 years was rare and varies between 6 and 15% [3]. In our study, this population accounted for 15% and 18% of cases, which remains in line with western series but slightly higher than the Tunisian data (11%) [4].

Recognizing malnutrition condition is mandatory for the management of gastric ADC. Indeed, numbers of recent studies have indicated that hypoalbuminemia significantly affect survival, postoperative death and response to the RT-CT in patient with GC [5-7]. In our series, malnourished patients (i.e. with BMI <18.5 Kg/m^2 and a rate of albumin <30 g/l) were significantly more recognized before 2006 (p=0.02). This difference could be explained by progress in term of early diagnosis, treatment delay and improved nursing care. Similarly, some studies have shown that the modified Glasgow Score (mGPS) (based on of rate albumin and CRP), improved the pre-therapeutic staging and was an independent prognostic factor for curative surgery [8]. In our series, the mGPS could be calculated in 71% and 67% of cases respectively in Group I and II. The mGPS was >1 respectively in 63.8% *vs.* 59% of cases.

Recently, we noticed a reduced incidence of gastric ADC in distal location while tumors arising from the esophago-gastric junction (OGJ) are increasing related to more gastro-esophageal reflux and obesity occurrence [9]. According to Tunisian data, the proportion of antral and fundic tumors remains the most frequent and accounts for 50-55% of all ADC (72% and 79% in our series) [4].

Gastric endoscopy associated with multiple biopsies allows a diagnosis confirmation in 95% of cases. However, in case of superficial cancers or gastric linitis, biopsies may be negative in up to 50% of the cases [10]. In our study, the preoperative per-endoscopic biopsies were negative in 4 patients (3% of cases). Postoperative histological examination showed undifferentiated forms in both cases. According to the 7th edition of TNM classification, these tumors were classified pT1N0M0 in one case and pT3N1/N2 in the other three cases.

Gastric linitis is a specific form of gastric ADC, deemed to have a worse prognosis and represents 3-19% of cases in Western series [11] and 34% in Tunisian series [4]. In our series, 52% and 45% of patients had ADC with signet ring cells. This can be explained by the higher prevalence of young patients in our series in which gastric linitis are more common.

The computed tomography (CT) is the gold standard for radiological assessment in gastric ADC. It allows an accurate assessment of loco regional invasion and resectability. Endoscopic ultrasonography (EUS) is considered to be the most precise method for loco regional staging especially for accurate T and N staging [12] and is strongly recommended in gastric linitis, superficial tumors and in the evaluation of the proximal and distal invasion. In our series, the staging differs by year of diagnosis: prior to 2006 CT and EUS were less available. In our series, we noted significantly more invasion of adjacent organs (p=0.04) and gastric wall thickening >10 mm (p=0.001) in the Group of patients treated after 2006. This may be explained by a more accurate radiological assessment allowing better staging.

Gastric resection associated with D2 lymphadenectomy without splenopancreatectomy is the gold standard of curative treatment for gastric ADC [12,13]. In our series, only one third of our patients underwent curative surgery. In fact, 10% of tumors considered resectable could not have curative surgery because of a PS>2 or severe comorbidities. We insist on the value of nutritional assessment as an important part of the therapeutic management. The benefice of palliative surgery in GC remains debated in terms of OS and PFS [14]. In our series, 12.7% of patients had a palliative surgery mainly indicated for emergency as stenosis and/or uncontrolled symptoms. Exploratory laparotomy was reported in 13.5% of patients, probably

due to a lack of accuracy in preoperative staging (unavailability of EUS).

Since the MAGIC and FFCD 9703 trials results, perioperative chemotherapy became the standard for tumors classified >cT2 N stage or >IB stage [13,15-17]. In our series, neoadjuvant chemotherapy (NACT) was performed in only 10% of the 70 tumors considered as locally advanced (2.7% Group I *vs.* 5.6% Group II; p=0.23). Nevertheless, at that period NACT had recently been introduced in the common practice for the management of the gastric ADC.

In the absence of NACT, current recommendations of the NCCN 2015 indicate adjuvant RT-CT after R0 resection in case of T2N0 tumors with high risk of recurrence (undifferentiated form, high-grade, vascular emboli and age <50 years) and for locally advanced tumors (T3-T4 and/or N+) as well as for incomplete resections (R1-R2). In our study, adjuvant CT was performed in 50% of stage II-III tumors. Adjuvant chemotherapy was significantly more commonly used among patients treated after 2006 (9.3% *vs.* Group I *vs.* 33% Group II; p=0.01). Twelve patients received concomitant radio-chemotherapy (RT-CT a modified Mac Donald protocol): 9.3% *vs.* 26.6%, respectively in Group I and II, p=0.07. The tumors were classified: N ≥ 1 in 5 cases and pT2 or pT3 in 5 cases.

In palliative intent, many chemotherapy regimens are available but none of them seems to be superior to another. However, the toxicity profiles are different. It is therefore important to evaluate the benefit/risk balance before any therapeutic decision. In our series only 21 patients (16.6% of the whole population and 25.6% of the patients in palliative setting) received palliative CT (52% 1 *vs.* 92% respectively in Group I and II; p=0.38). The PS score was the main decisive factor to initiate palliative chemotherapy or not. In metastatic forms, palliative chemotherapy was significantly more frequently used in patients treated after 2006 although the difference was not significant (Group I 52% *vs.* 92% Group II; p=0.38).

Adding trastuzumab in the amplified Her2neu forms has improved OS to 16 months if amplified Her2neu+++ [17]. Unfortunately, none of our patients had access to this targeted therapy that has no marketing authorization for this indication in our country.

Conclusion

Gastric ADC has a poor prognosis due to its late diagnosis and its potential to spread locoregionnally and at distance. Its management in Tunisia, an emerging country with low income, did not change significantly in 10 years except a better preoperative classification thanks to a more accurate radiological assessment. Until the late 2000s the diagnosis remained late with a low use of chemotherapy and radiotherapy in perioperative or palliative intent. Since, multidisciplinary staffs have been established with the hope of improving the treatment of gastric ADC in Tunisia.

References

1. World Health Organisation (2012) GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012.
2. Registre des cancers Nord Tunisie. Données 1999-2003, Evolution 1994-2003, Projections à l'horizon 2024 (2003) Le Cancer de l'estomac, pp: 43-46.
3. Hsieh FJ, Wang YC, Hsu JT, Liu KH, Yeh CN (2012) Clinicopathological features and prognostic factors of gastric cancer patients aged 40 years or younger. J Surg Oncol 105: 304-309.
4. Ksantini R, Hmila F (2012) Monograph of the Tunisian Association of Surgery. The gastric adenocarcinoma. Report presented at the XXXIII Tunisian Congress of Surgery.
5. Kath R, Fiehler J, Schneider P, Hoffken K (2000) Gastric cancer in young adults: apropos four patients and a review of the littérature. J Cancer Res Clin Oncol 126: 233-237.
6. Aparicio T, Yacoub M, Cohen PK, René E (2004) Gastric adenocarcinoma: basic notions, diagnosis and treatment. Encycl Med Chir 1: 47-66.
7. Fiore F, Lecleire S, Pop D, Rigal O, Hamidou H, et al. (2007) Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. Am J Gastroenterol 102: 2557-2563.
8. Jiang X, Hiki N, Nunobe S, KumagaiK, Kubota T, et al. (2012) Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer. Br J Cancer 107: 275-279.
9. Andriulli A, Recchia S, De Angelis C, Mazzucco D, Berti E, et al. (1990) Endoscopic evaluation of patients with biopsy negative gastric linitis plastica. Gastrointest Endosc 36: 611-615.
10. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statics. CA Cancer J Clin 61: 69-90.
11. Topart P, Lozac'h P (1998) Cancer on gastric stump. In: Lozach P, Meyer C, editors. Monograph of the French Association of Surgery Report of the 100th congress. Paris, pp. 185-192.
12. SNFGE (2013) Thesaurus of digestive cancer. Stomach cancer.
13. Ajani JA, Bentrem DJ, Besh S, Amico TA, Das P, et al. (2013) Gastric cancer version 2.2013: Featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 11: 531-546.
14. Li C, Yan M, Chen J, Xiang M, Zhu ZG, et al. (2010) Survival benefit of non-curative gastrectomy for gastric cancer patients with synchronous distant metastasis. J Gastrointest Surg 14: 282–288.
15. D'Avanzo B, La Vecchia C, Franceschi S (1994) Alcohol consumption and the risk of gastric cancer. Nutr Cancer 22: 57–64.
16. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, et al. (2007) A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 165: 1424-1433.
17. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, et al. (2013) Gastric cancer: ESMO-ESSO-ESTRO Clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 24: 57-63.
18. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, et al. (2010) 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 376: 687-697.