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Research Article

Evaluation of Clinicopathological Characteristics and Survival Outcomes of Young Gastric Cancer Patients, Single Center Experience

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Abstract

Objectives: We aimed to evaluate clinicopathological features and survival outcomes of young gastric cancer (YGC) patients.

Methods: We retrospectively evaluated data of gastric cancer (GC) patients (≤ 45 years old) who were followed-up in our center between 2008-2018.

Results: We included 130 patients (66 males, 64 females) with a median age of 38 years. Proportion of tumor node metastasis (TNM) stage IV was 50.8%. Seventy-nine patients underwent surgical resection. The most common sites of metastasis were peritoneum, distant lymph node, and liver. The median follow-up period was 19.6 months (range: 1.3 – 181.8 months). During the follow-up period, 26 (40.7%) patients had developed recurrence, and 92 (70.8%) patients had died. DFS rates at 1-, 3-, 5-years were 86%, 68%, 65%, respectively. Median overall survival (OS) was 19.6 months (95% Confidence Interval: 13.9 – 25.4) and OS rates at 1-, 3-, 5- years were 69%, 37%, 33%, respectively, regardless of TNM stage.

Conclusion: The study revealed nearly equal sex ratio, high frequency in diffuse type histology, undifferatiated tumor, proximal location, advanced stage and peritoneum metastasis in YGC patients. While DFS was similar, OS was relatively low compared to the literature. Our results emphasize the importance of early diagnosis in YGC patients.

Keywords: Gastric cancer, prognosis, young age

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Gastric cancer (GC) is the fifth most common cancer worldwide and causes significant morbidity and mortality.[1] GC occurs mainly in adults aged 50-70 years.[2–4] The incidence of young GC (YGC) has been reported as ~3-8% in the previous studies.[2,3,5,6] However, there are also studies revealed a higher incidence up to 19.8%.[7] The details of YGC have not been fully identified becouse of small number of patients and limited data. In a limited number of studies, YGC have been emphasized with distinct clinicopathological features, such as female predominance, diffuse type histology of Lauren classification, poor differantiation, peritoneal metastasis and advanced stage at diagnosis.[2,3,5,8,9] Although most of these features indicate the agressive behaviour, prognosis of YGC is not clear. There are controversial results on previous studies.[10–13] The conflicting results in the literature may be due to the differences

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in the patient inclusion criteria, heterogeneity in the treatment strategies and the definition of young age. Therefore, studies focused on YGC will serve for increasing in data and determining correct treatment and follow-up strategy in this special patient group.

In this study, we aimed to investigate the results of YGC patients comparing with the current literature.

Methods

We included GC patients who were ≤45 years of age and who were followed up between 2008-2018 at our center. We retrospectively reviewed the data from patients' files. We recorded baseline characteristics, performance status, tumor differantiation, Tumor Node Metastasis (TNM) stage, primary tumor location, sites of distant metastasis based on the time of diagnosis. We classified the upper and middle third of stomach as proximal, and lower third of the stomach as distal location. We defined TNM stage I/II/III as early, and TNM stage IV as advanced stage disease. We also recorded histopathological characteristics of patients underwent curative resection, and treatment approaches for curative and palliative intent. Her2/neu was evaluated according to American Society of Clinical Oncology (ASCO) guidelines. Scores 2+ and 3+ with immunohistochemistry (IHC) were evaluated with dual color fluorescence in situ hybridization (FISH), according to ASCO/CAP guidelines. The multidisciplinary tumor board decided adjuvant chemotherapy (CT) by evaluating the performance status, clinical and pathological stage of the patients. In patients underwent curative resection, we followed up the patients every three months in the first two years after surgery and every six months afterward. We evaluated chest computed tomography (CompT) and abdominal CompT every six months in the first three years and then once a year. In patients who have metastatic GC, we evaluated treatment responses at 8-12 week interval using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in conventional cross-sectional imaging. Disease free survival (DFS) described as time between surgery and disease recurrence, or last medical examination if patient was still recurrence-free follow-up. Overall survival (OS) described as time between the diagnosis of GC and death or last medical examination.

We recorded descriptive data as frequencies and percentages. We presented continuous variables as median values with interquartile ranges (IQRs). Survival was estimated with Kaplan-Meier method and log-rank test. We performed all statistical analyses using SPSS version 22.0 (IBM Corp., NY, USA).

Results

The study included 130 patients (66 males and 64 females) with a median age of 38 years (IQR, 32 - 41). Table 1 summarizes the baseline characteristics of patients. All patients had adenocarcinoma histology. Most common subtypes of adenocarcinoma were diffuse, and signet ring cell according to Lauren and World Health Organization (WHO) classifications, respectively. At the time of diagnosis, 64 (49.2%) patients had early stage (TNM stage I/II/III), 66 (50.8%) patients had stage IV disease. The most common sites of metastasis were peritoneum, distant lymph nodes, and liver, respectively. Sixteen (24%) patients had peritonitis carcinomatosa at diagnosis. Peritonitis carcinomatosa was detected during surgical resection in nine patients. Twelve (9.2%) patients had linitis plastica. The signet ring cell component could be evaluated in 105 patients, and 61 (58.1%) were positive.

A total of 79 (60.8%) patients underwent surgical resection, 72 were curative and seven were palliative. Median tumor size was 5 cm (range: 1 cm – 12 cm). While 10 (13.9%) of the patients whom underwent surgery for curative intent had R1 resection, all patients whom underwent surgery for palliative intent had R0 resection. Table 2 summarizes the histopathological features of patients underwent curative surgery, and Table 3 shows curative and palliative treatments for early and advanced stage disease.

The median follow-up period was 19.6 months (range: 1.3 – 181.8 months). During the follow-up period, 26 (40.7%) patients developed recurrence [one was local recurrence and 25 were distant metastasis], and 92 (70.8%) patients died. While DFS did not reach median value, DFS rates at 1-, 3-, and 5- years were 86%, 68%, 65%, respectively. Median OS was 19.6 months (95% CI: 13.9 – 25.4) regardless of disease stage. OS rates at 1-, 3-, 5- years were 69%, 37%, 33%, respectively, in all study population. While median OS of patients with early stage disease did not reach median value, OS rates at 1-, 3-, 5- years were 91%, 73%, 67%, respectively. Median OS of patients with metastatic disease at diagnosis was 11.7 months (95% CI: 9.1 – 14.4), and OS rates at 1-, 3- years were 48%, 2%, respectively. Table 4 summarizes the survival outcomes of study population. Figure 1 and Figure 2 show Kaplan meier curve for DFS and OS, respectively.

Discussion

The study aimed to evaluate the clinicopathological characteristics and prognosis of YGC patients and compare with the literature.

YGC is a distinct subgroup of GC in terms of baseline characteristics and histopatological features. The most of previous studies emphasized female gender predominance in

Table 1. Baseline Patient Characteristics

Median age (IQR)	38 (32-41)
Gender, n (%)	
Female	64 (49.2)
Male	66 (50.8)
Family history of cancer, n (%)	
+	35 (26.9)
-	95 (73.1)
Family history of gastric cancer, n (%)	
+	13 (10.0)
-	117 (90.0)
Smoking History, n (%)	
+	52 (40.0)
-	78 (60.0)
ECOG-PS, n (%)	
0-1	119 (91.5)
2-3	11 (8.5)
Linitis Plastica, n (%)	
+	12 (9.2)
-	118 (90.8)
Primary tumor location, n (%)	
GEJ	6 (4.6)
Cardia	17 (13.1)
Fundus	2 (1.5)
Corpus	46 (35.4)
Antrum	53 (40.8)
Prepyloric	6 (4.6)
Primary tumor location_group, n (%)	
Proximal	71 (54.7)
Distal	59 (45.3)
Grade, n(%)	
1	5 (3.8)
2	13 (10.0)
3	91 (70.0)
Unknown	21 (16.2)
Her2-IHC, n (%)	
0/1+/2+	90 (69.2)
3+	11 (8.5)
Unknown	29 (22.3)
Signet Ring Cell Component, n (%)	
+	61 (46.9)
-	44 (33.8)
Unknown	25 (19.2)
TNM Stage at Diagnosis, n (%)	
I	6 (4.6)
II	20 (15.4)
III	38 (29.2)
IV	66 (50.8)
Sites of Distant Metastasis*, n (%)	
Liver	17 (25.8)
Lung	2 (3.0)
Peritonium	33 (50.0)
Lymph Node	22 (33.3)
Bone	7 (10.6)
Over	10 (15.2)
Peritonitis Carcinomatosa	16 (24.2)
Bone Marrow	1 (1.5)

IQR: Interquartile Range, ECOG-PS: Eastern Cooperative Oncology Group – Performance Status, GEJ: Gastroesophageal Junction, TG: Total Gastrectomy, PSG: Proximal Subtotal Gastrectomy, DSG: Distal Subtotal Gastrectomy, '+' refers the existence of variable, '-' refers the absence of variable, IHC: Immunohistochemistry, *: Refers patients who have stage IV disease at diagnosis

YGC.[3,8,9,11,14,15] However, there are conflicting results in the literature. Liu W et al. and Yu JI et al. found equality in sex ratio similar to our study.[12,13] Additionally, Kono Y et al. demonstrated nearly egual sex ratio in YGC patients.[16]. Due to the male predominance of GC in the general population, the female-to-male ratio equality in our study contributed to the female gender predominance data in YGC patients. In previous series, the primary tumor mostly located in upper and middle third of stomach in YGC patients.[14,16,17] In contrast, in the series of Liu W et al. and Ramos MFKP et al., the primary tumor commonly located in lower third of stomach.[11,12] In our current study, the primary tumor mostly located in the proximal stomach, which defined upper and middle third of stomach, consistent with the literature. Nearly all studies emphasized diffuse type of Lauren classification and undifferantiated histology of YGC patients.[5,7,9,11,13,14] Diffuse type of Lauren classification has been reported up to 80%. In our study, diffuse type histology was

Table 2. Histopathological Characteristics of Patients Underwent Curative Resection

pT, n (%)	
1	2 (2.8)
2	12 (16.7)
3	24 (33.3)
4	34 (47.2)
pN, n (%)	
0	12 (16.7)
1	20 (27.8)
2	12 (16.7)
3	28 (38.9)
Lauren classification, n (%)	
Intestinal	22 (30.6)
Diffuse	35 (48.6)
Mixt	5 (6.9)
Unknown	10 (13.9)
WHO classification, n (%)	
Tubular	14 (19.4)
Papillary	10 (13.9)
Mucinous	2 (2.8)
Signet ring cell	29 (40.3)
Poorly cohesive	11 (15.3)
Mixt	6 (8.3)
Lymphatic invasion, n (%)	
+	58 (80.6)
-	14 (19.4)
Vascular invasion, n (%)	
+	41 (56.9)
-	31 (43.1)
Perineural invasion, n (%)	
+	46 (63.9)
-	26 (36.1)
R1 resection, n (%)	
+	10 (13.9)
-	62 (86.1)

WHO: World Health Organization, '+' refers the existence of variable, '-' refers the absence of variable.

Table 3. Curative and Palliative Treatments

Surgery, n (%)	
+	79 (60.8)
-	51 (39.2)
Surgical technique, n (%)	
TG	27 (34.2)
PSG	15 (19.0)
DSG	30 (38.0)
Palliative	7 (8.9)
Adjuvant CT, n (%)	
+	59 (92.2)
-	5 (7.8)
Adjuvant RT, n (%)	
+	31 (48.4)
-	33 (51.6)
Adjuvant CT regimens, n (%)	
FOLFOX/XELOX	35 (59.3)
ECF	12 (20.3)
DCF	7 (11.9)
Other	5 (8.5)
Metastatic Setting*, n (%)	
No Treatment	9 (9.9)
1 line	30 (33.0)
2 lines	29 (31.8)
≥3 lines	23 (25.3)

CT: Chemotherapy, RT: Radiotherapy, TG: Total gastrectomy, PSG: Proximal subtotal gastrectomy, DSG: Distal subtotal gastrectomy, FOLFOX: Flourouracil+Folinic acid+Oxaliplatin, XELOX: Capecitabine+Oxaliplatin, ECF: Epirubicin+Cisplatin+Flourouracil, DCF: Docetaksel+Cisplatin+Flourouracil, '+' refers the existence of variable, '-' refers the absence of variable, *: At any time during follow-up.

48% and lower than the literature. However, Lauren classification has not been evaluated in some of the patients. In addition, the frequency of undifferentiated histology was quite high at 70.0% and was consistent with the literature.

YGC patients are expected to have more advanced stage than older patients at diagnosis, due to delay in hospital admission and diagnosis. However, there is a wide range for the initial disease stage in the literature. Kono Y et al. demonstrated very high frequency of stage 1 disease.[16] The proportion of the TNM stage I,II,III,IV was 44.4%, 11.1%, 8.3%, 36.1%, respectively.[16] Ławniczak M et al. reported a 79.3% rate for advanced stage disease in YGC patients.[14] However, in the same study, the frequency of

Table 4. Survival Outcomes of Patients

	1-, 3-, 5- years DFS	1-, 3-, 5- years OS	Median DFS (95% CI)	Median OS (95% CI)
All	-	69%, 37%, 33%	-	19.6 mos (13.9-25.4)
Stage I/II/III	86%, 68%, 65%	91%, 73%, 67%	NR (NR-NR)	NR (NR-NR)
Stage IV	-	48%, 2%, 0%	-	11.7 mos (9.1-14.4)

DFS: Disease free survival; OS: Overall survival; CI: Confidence interval; mos: Months; NR: Not reached.

advanced stage disease was quite high in also the control group which consisting of patients were >40 years old. High frequencies may be due to the definition of advanced stage. Ramos MFKP et al. demonstrated the proportion of the TNM stage I, II, III, IV was 21.4%, 13.1%, 33.3%, 32.1%, respectively.[11] In our study, early stage disease was lower and advanced stage disease was relatively higher compared to previous studies. This finding may have occurred due to late presentation of young patients and delay in diagnosis. Additionally, in our study, 9.9% of patients could not received systemic therapy, 33.0% could receive only one line of therapy, for metastatic disease. This finding supports delay in presentation and diagnosis.

Peritoneal metastasis is a distinct feature of YGC patients. In the review of Rijken A et al., although definition of young age was quite different between the evaluated studies, young age was found as a risk factor for peritoneal metastasis in GC patients.[18] In our study, we detected peritoneum metastasis in half proportion of the patients who have metastatic disease, and it was consistent with the literature. Additionally, the relationship between signet ring cell histology and peritoneal metastasis has been reported in several studies.[19] The fact that both peritoneum metastasis and signet ring cell histology were quite high in our study supported this finding.

Studies evaluating YGC, mostly included patients underwent curative resection. Liu W et al. evaluated GC patients who ≤ 45 years of age and underwent curative resection.[12] They reported DFS rates at 1-, 3-, 5- years 83.9%, 68.2%, 64.7%, respectively; and OS rates at 1-, 3-, 5- years as 93.0%, 70.3%, 65.3%, respectively. The study design, stage III disease frequency was similar with our study, and survival outcomes were almost same. Liu S et al. reported a 5-year OS of 62.8% in YGC patients undergoing curative resection, similar to our study.[3] In the series of Ramos MFKP et al., the median DFS was 12.9 months in patients who ≤ 45 years of age and underwent curative resection.[11] In our study, DFS did not reach the median value at 19.6 months

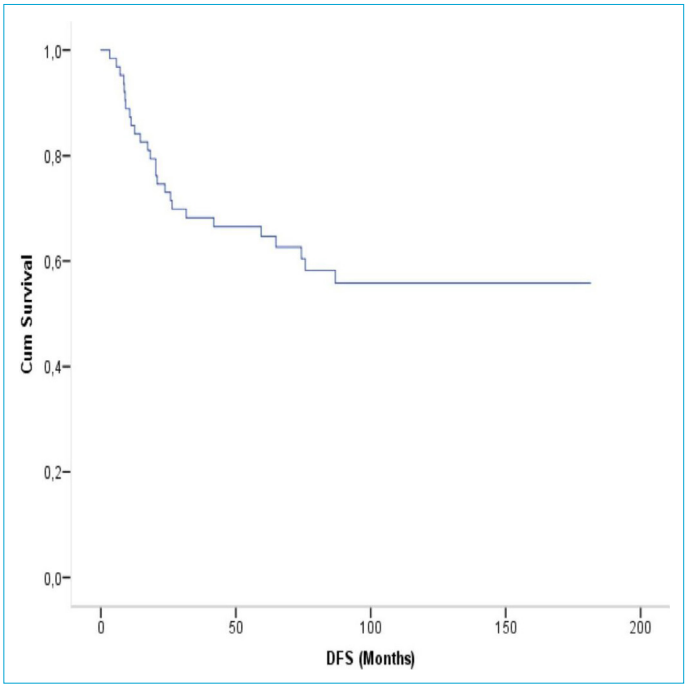

Figure 1. Kaplan Meier Curve for DFS.

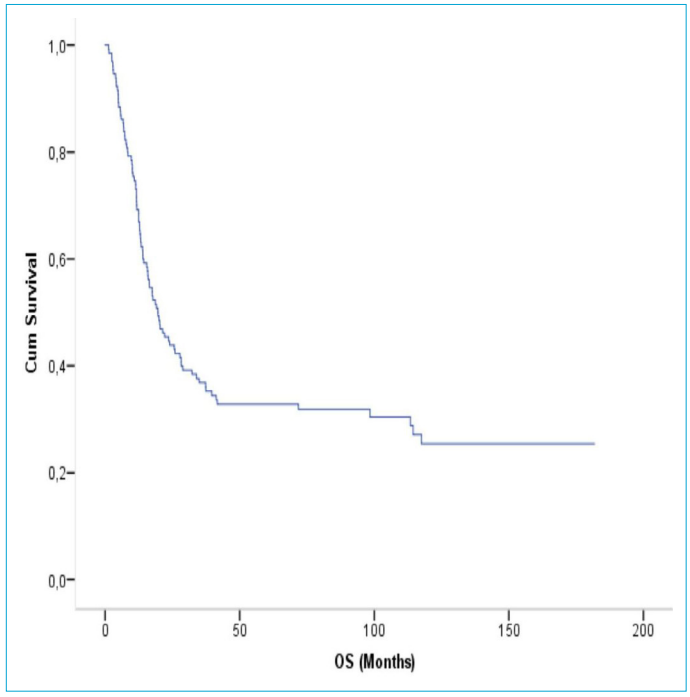

Figure 2. Kaplan Meier Curve for OS.

of follow-up. There are few studies including YGC patients regardless of TNM stage. Ramos MFKP et al. found longer median OS (33.3 months) compare to our study in YGC patients regardless of TNM stage. This difference finding may be due to lower proportion of stage IV disease compared to our study.[11] Nakayama I et al. included only young patients with relapsed or stage IV GC. They found relatively higher median OS (13.2 months) compared to our study (11.7 months).[8] It is difficult to interpret the results in the literature because of the retrospective design of previous studies, differences in inclusion criteria and treatment strategies.

The study has some major limitations, primarily due to its retrospective nature and small sample size. Some histopathological features such as Lauren classification and tumor differentiation have not been evaluated in some patients. R0 resection could not be performed in some patients underwent curative resection. These conditions made confusion in the results.

Conclusion

The study revealed nearly equal sex ratio, high frequency in diffuse type histology, undifferatiated tumor, proximal location, advanced stage and peritoneum metastasis in YGC patients. OS was relatively low and DFS was similar compared to previous studies. These results may be due to high rate of advanced stage disease. The fact that DFS did not reach median value emphasizes the importance of early diagnosis. Because of the aggressive behaviour of advanced stage disease in YGC patients, symptoms should not be ignored for early diagnosis.

Disclosures

Ethics Committee Approval: Local Ethics Committee of our center approved the study protocol in compliance with Helsinki Declaration, approval number [09.2023.863].

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – R.A., T.A.T.; Design – R.A.; Supervision – O.E., I.V.B.; Data collection &/or processing – R.A., S.I.; Analysis and/or interpretation – R.A., O.K.; Literature search – M.S.; Writing – R.A.; Critical review – I.V.B.

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