Prognosis and outcomes of management of gastric adenocarcinoma at or below the age of 40 years; NCI experience

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Abstract

Background: Gastric cancer has long been assumed to be more advanced and has a worse prognosis in younger people than in older ones. This assumption, however, has never been validated, most likely attributable to the lack of patient numbers for a stage-by-stage survival comparison.

Objectives: To present NCI, Cairo University experience in managing young patients ($\leq$ 40 years) with gastric adenocarcinoma

Patients and methods: Retrospective cohort study included all cases diagnosed in NCI with gastric adenocarcinoma at or below the age of 40 years in the period from 2010 to 2021. The data included demographic attributes, clinical presentation, investigations and results, adopted treatment modalities, and prognosis of these cases.

Results: During the period of the study, 30 cases of gastric adenocarcinoma with ages of around 40 years or less have been diagnosed and managed in NCI. Most cases presented in an advanced stage as stage 4 represented 46.7% (14 cases). Seventeen cases (56.7%) underwent surgical exploration, where chemotherapy was taken for twenty-six cases (86.7%).
The overall survival showed that patients presented with advanced stage, had omental deposits or ascites had a worse prognosis (P-value = 0.001, <0.001, <0.001 respectively). Additionally, cases who underwent surgery or received chemotherapy had better overall survival than those who did not have (P-value = 0.001, <0.001, respectively).

Conclusion: Gastric Cancer is aggressive in young age and presents mainly in advanced stage. In terms of overall survival, patients benefit significantly from combined treatment modalities (chemotherapy and surgical resection) compared to receiving only one treatment option.

Keywords: Gastric cancer; Adenocarcinoma; Young; Poor prognosis

Introduction

Regarding cancer-related deaths worldwide, gastric adenocarcinoma ranks third and is the fifth most prevalent cancer to be diagnosed **(Bray et al., 2018).** In the United States, the average age of onset is 68 years. It exhibits significant age variation and is typically diagnosed more commonly in elderly patients; more than 95% of all new cases are identified in people over the age of 40 **(De et al., 2018)**.

Although the prevalence of Gastric cancer (GC) has sharply decreased recently, young individuals seem to have a steady or even slightly rising trend **(Merchant et al., 2017)**. Consequently, there has been intense interest in exploring Gastric cancer in young people (GCYA). Young persons are less likely to get GC; however, earlier studies have revealed that 5.0% of GC patients were diagnosed before the age of 40 **(Al-Refaie et al., 2011)**.

Due to its aggressive growth pattern and the advanced stage upon diagnosis, GC in young individuals is typically challenging to cure. Additionally, several unresolved questions remain regarding carcinogenesis, the best treatment modality, prognosis, and prevention. Therefore, several oncologists have recommended managing GCYA as a distinct clinical entity **(Al-Refaie et al., 2011)**.This study aimed to analyze the relative frequency, severity, treatments outcome and prognosis of Gastric adenocarcinoma in patients aged 40 years and below treated in National Cancer Institute, Cairo University.

Patients and Methods

Retrospective cohort study included all patients aged 40 years or less diagnosed with Gastric adenocarcinoma at the NCI, Cairo University in the period between 2010 and 2021. Clinical features of all patients were extracted from the medical records, including demographics, presenting symptoms, endoscopic findings, pathological types and grades, and metastatic workup. All treatment modalities were recorded. Surgery was defined as any surgical intervention done to the patient. Also, chemotherapy protocols were described as either neoadjuvant or adjuvant or definitive.

Due to high toxicity of FLOT protocol (FluroUracil, Leucovorin, Oxaliplatin and Docetaxel) in relation to improper performance status of patients, (due to that gastric cancer presented in young age in advanced status which has negative effects on patient nutritional status and performance ; and also that NCI is tertiary referral cancer center and so most of cancer patients with poor performance status are refered to it from others hospitals), 2 drugs protocol were preferred.

Cases received chemotherapy according to the protocols:

- Neoadjuvant and adjuvant protocol: Capecitabine or 5 Fluorouracil + Oxaliplatin.
- Definitive chemotherapy protocol: Capecitabine or 5 Fluorouracil + Oxaliplatin. Carboplatin and Paclitaxel were used as a second line

Ethical approval: This study was approved by Institutional Review Board (IRB) of National Cancer Institute, Cairo University with approval No: 2211-510-020

Statistical analysis

Data was analyzed using SPSS statistical package version 24. Numerical data was expressed as median and range. Frequency and percentage were used to represent qualitative data. In order to estimate overall and disease-free survival, the Kaplan-Meire method was applied. The log rank

test was used to relate prognostic factors to survival. To assess independent prognostic factors influencing survival, Cox regression analysis was used. Every test had two sides. P values under 0.05 were regarded as significant.

Results:

During the period of the study, 702 cases of gastric adenocarcinoma were diagnosed and managed in NCI; form them, Only 30 patients (4.27%) aged 40 years or less. No gender predilection was found in the cohort, and ages ranged between 21-38 years, with a median of 32 years. The most common site was the body of the stomach (9 cases [30%]).

Most cases were presented in an advanced stage with high-grade pathology, where stage 4 tumours represent 46.7% (14 cases) of the cohort, and grade 3 tumours account for most of the cases (19 cases [63.4%]). Omentum was the most common site of distant metastasis (10 cases [33.3%]).

Patients' characteristics, Tumours' characteristics, and metastatic workout results were summarised in **Table 1, Table 2, and Table 3**, respectively.

Table 1. Patients' Characteristics

Variables	Frequency (n)	Percent (%)
Gender		
• Female	16	53.3%
• Male	14	46.7%
Age (years)		
• ≤ 32	16	53.3%
• > 32	14	46.7%
Main presenting symptom		
• Epigastric Pain	11	36.7%
• Abdomianl distension	1	3.3%
• Vomiting	10	33.3%
• Haematemisis	6	20%
• Melena	1	3.3%
• Dysphagia	1	3.3%

Table 2. Tumours' Characteristics

Variables	Frequency (n)	Percent (%)
Endoscopy site		
• Antrum	6	20.0%
• Body	9	30.0%
• Cardia	1	3.3%
• Fundus	3	10.0%
• Pylorus	5	16.7%
• Whole	6	20.0%

Endoscopy morphology		
• Diffuse	11	36.7%
• Polypoid	9	30.0%
• Ulcer	10	33.3%
Pathological type		
• Adenocarcinoma (NOS)	22	73.3%
• Signet Ring	6	20%
• Mucinous Adenocarcinoma	2	6.7%
Pathological grade		
• 2	10	33.3%
• 3	19	63.4%
• unknown	1	3.3%

Table 3. Metastatic workup results

Variables	Frequency (n)	Percent (%)
Stage		
• 2	9	30.0%
• 3	7	23.3%
• 4	14	46.7%
LNs metastasis		
• Yes	14	46.7%
• No	16	53.3%
Liver Mets		
• Yes	4	13.3%
• No	26	86.7%
Lung metastasis		
• Yes	2	6.7%
• No	28	93.3%
Omental metastasis		
• Yes	10	33.3%
• No	20	66.7%
Krukenberg		
• Yes	4	25%
• No	12	75%
Ascites [a]		
• Yes	12	40.0%
• No	18	60.0%

Surgery: Seventeen cases (56.7%) underwent surgical exploration. From them, 2 cases were inoperable as they had amalgamated celiac LNs while the other 15 cases underwent resections. 2 cases underwent total gastrectomy, 12 cases subtotal gastrectomy while the other case underwent partial Gastro-oesophagectomy. Regarding the morbidity of the operations, Two cases were complicated by leakage from gastro-jejunal anastomosis and managed conservatively.

Chemotherapy: Chemotherapy was taken for 26 cases (86.7%). From the 15 cases who experienced surgical resection; one case had received only Neoadjuvant chemotherapy, 8 cases received only adjuvant, and 4 cases received both neoadjuvant and adjuvant. The remaining 2 cases were lost to follow-up after surgery and died after 3 and 6 months from the date of the operation. 13 cases received definitive chemotherapy without surgical intervention.

Survival Analysis: The cases' follow-up period ranged from 1 to 75 months, with a median of 9.5 months. Of the seventeen cases that underwent surgical exploration, 15 cases underwent R0 resection. During the period of follow-up, 7 cases had developed recurrences. The Disease-free survival (DFS) of these cases and the governing factors are illustrated in **Table 4.** The median DFS was 27 months. In Univariate analysis regarding DFS, the patient who had leukopenia (TLC <4000 cell/mm^3) or neutrophilic count <2000 cells/ mm^3 before starting treatment and those who missed chemotherapy were found to have dismal prognosis (p-value 0.018, 0.005, and <0.001 respectively) **(Fig.1-3)**. In Multivariate analysis as illustrated in **Table 5**, leukopenia represented the only independent risk factor for DFS (p-value 0.04).

Table 4. DFS and its relation to different factors

Variables	Total N	Cumulative survival estimate at 1 year	Cumulative survival estimate at 3 years	Median survival time (months)	p value
	15	66 %	41.3 %	27.170	
Gender					
• Female	6	62.5 %	62.5 %	NR *	0.505
• Male	9	66.7 %	25 %	19.340	
Age (years)					
• < 32	10	50 %	500 %	5.660	0.409
• ≥ 32	5	75 %	37.5 %	27.170	
Pathology type					
• AdenoCarcinoma (NOS)	10	70 %	42 %	27.170	0.720
• Signet Ring	5	60 %	NR	NR	

Pathology grade					
• 2	8	75 %	40 %	27.170	0.723
• 3	7	57.1 %	57.1 %	NR	
Pathological T					
• 3	13	69.2 %	43.3 %	27.170	0.465
• 4	2	NR	NR	1.710	
Pathological N					
• N0	9	77.8 %	41.5 %	27.170	0.445
• N1,N2&N3	6	50 %	50 %	1.810	
Pathological margin					
• Negative	12	75 %	62.5 %	27.170	0.271
• Positive	3	NR	NR	5.660	
Chemotherapy intake					
• Yes	13	76.2 %	47.6 %	27.170	<0.001
• No	2	NR	NR	.720	
HB (gm/dl)					
• < 10	6	71.4 %	23.8 %	19.340	0.417
• ≥ 10	9	58.3 %	58.3 %	NR	
TLC (cells/mm^3)					
• < 4000	2	NR	NR	.720	0.018
• ≥ 4000	13	76.9 %	48.1 %	27.170	
Neutrophils count (cells/mm^3)					
• < 2000	3	NR	NR	1.810	0.005
• ≥ 2000	12	83.3 %	52.1 %	NR	
Lymphocytes count (cells/mm^3)					
< 2000	7	57.1 %	28.6 %	19.340	0.410
≥ 2000	8	75 %	50 %	27.170	

*NR: Not reached

Table 5.Multivariate analyses for factors affected the DFS

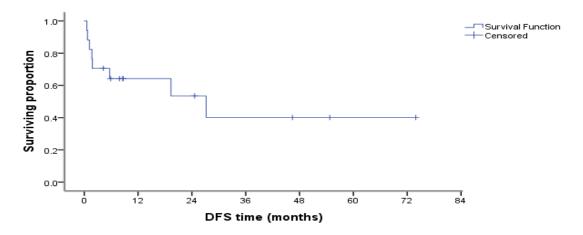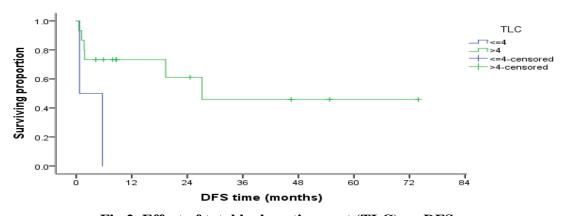| Independent prognostic factors	Beta coefficient	Standard error	P value	Hazard Ratio	95.0% CI for HR	
					Lower	Upper
TLC	1.893	.920	0.040	6.637	1.094	40.260

Fig 1. Disease free survival

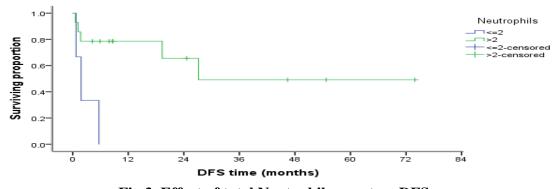**Fig 2. Effect of total leukocytic count (TLC) on DFS**

Fig 3. Effect of total Neutophils count on DFS

The median overall survival (OS) was only 14 months. Cases who underwent surgery had better overall survival, with one-year survival of 76% in comparison to only 30.8% who did not (P value = 0.001). Chemotherapy significantly impacted the overall survival, whereas the median survival of the cases who had received chemotherapy was 17.86 months compared to only 3.61 months for those who did not receive it (P-value <0.001). Factors that affected overall survival are illustrated in **Table 6.** In Univariate analysis; advanced stage (III or IV), the presence of omental deposits or ascites at the time of presentation had a dismal prognosis (p-value= 0.001, p-value <0.001, p-value <0.001 respectively) **(Fig.4-7)**. In Multivariate analysis as showed in **Table 7**, ascites represented the only independent prognostic factor on the OS (p-value <0.001).

Table 6. OS and its relation to different factors:

Variables	Total N	Cumulative survival estimate at 1 year	Cumulative survival estimate at 3 years	Median survival time (months)	p value
	30	55.7 %	29.5 %	14.145	-
Gender					
• Female	16	46.9 %	35.2 %	9.145	0.842
• Male	14	64.3 %	19.3 %	14.145	
Age (years)					
• < 32	16	49.2 %	32.8 %	9.145	0.760
• ≥ 32	14	63.5 %	21.8 %	20.132	
LNs enlargement					
• No	16	61.9 %	53 %	NR*	0.086
• Yes	14	48.2 %	NR	8.257	
Liver Metastasis					
• No	26	56.9 %	35.9 %	20.132	0.153
• Yes	4	50 %	NR	9.145	
Lung metastasis					
• No	28	56.5 %	33.1 %	14.145	0.690
• Yes	2	50 %	NR	9.145	
Omental metastasis					
• No	20	74 %	47.8 %	32.000	<0.001
• Yes	10	20 %	NR	4.000	
Ascites					
• No	18	77.4 %	48.8 %	32.000	<0.001
• Yes	12	22.2 %	NR	4.000	

Stage					
• II	9	88.9 %	71.1 %	NR	0.001
• III & IV	21	40.7 %	8.5 %	8.257	
Surgery					
• No	13	30.8 %	NR	4.375	0.001
• Yes	17	76.0 %	54.1 %	NR	
Chemotherapy intake					
• No	4	NR	NR	3.618	<0.001
• Yes	26	64.3 %	34.0 %	17.862	
HB (gm/dl)					
• < 10	10	70 %	36 %	14.145	0.833
• ≥ 10	17	51 %	40.8 %	20.132	
TLC (cells/mm^3)					
• < 4000	2	50%	50%	8.257	0.706
• ≥ 4000	25	59.2 %	34.9 %	14.145	
Neutrophils count (cells/mm^3)					
• < 2000	3	33.3 %	33.3 %	8.257	0.891
• ≥ 2000	24	61.9 %	36.5 %	17.862	
Lymphocytes count (cells/mm^3)					
• < 2000	19	47.4 %	27.1 %	9.145	0.054
• ≥ 2000	8	85.7 %	64.3 %	NR	

*NR: Not reached

Table 7. Multivariate analyses for factors affected OS

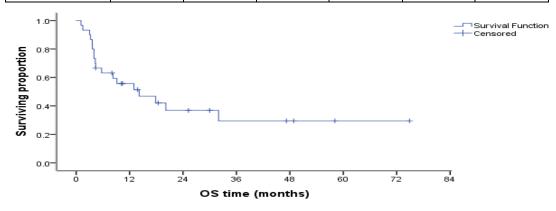| Independent prognostic factors	B	SE	P value	HR	95.0% CI for HR	
					Lower	Upper
Ascites (imaging)	2.170	0.613	<0.001	8.759	2.632	29.150

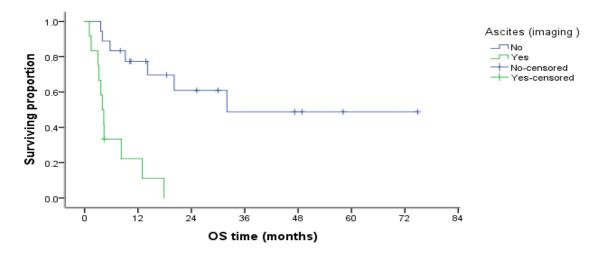**Fig 4. Overall survival (OS)**

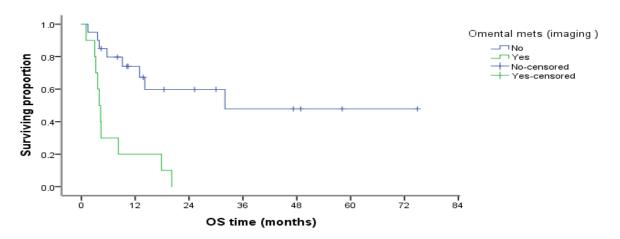**Fig 5. Effect of Ascited on OS**

Fig 6. Effect of Omental metastasis on OS

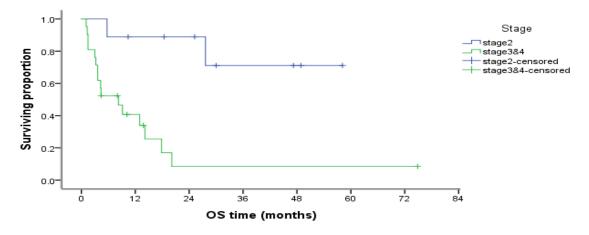**Fig 7. Effect of stage of tumors on OS**

Discussion

Most cases of gastric cancer are reported in elderly people, with incidence and mortality rates peaking in the Chinese population between the ages of 85 and 89. In the USA, more than 95% of gastric cancer cases were above 40 years **(Merchant et al., 2017)**. Gastric cancer among young individuals was often not suspected by physicians in comparison with old patients. Given the lengthy life expectancies of young patients and their contributions to the economy, the disease burden was disproportionately heavy among young patients. Therefore, reducing the prevalence and mortality in this vulnerable part of the community may promote society and economic development **(Smith and Stabile, 2009).**

It is widely assumed that the remarkable increase in early-stage stomach cancer detection in Japan in recent decades is primarily attributable to mass screening. However, this is not the case for individuals with ages below 40, as mass screening is not recommended for this age group. **(Mabe et al., 2022)**. In a Brazilian study comparing younger and older gastric cancer patients, 39 patients under the age of 40 were included. They discovered a higher frequency of diffuse-type gastric cancer and a higher incidence in females in the younger age group. They suggested that patients under this young age typically consume more red and processed meat than older patients, which were thought to be the risk factors for promoting stomach cancer **(de Souza Giusti et al., 2016)**.

In the current study, no evident gender predilection was found as males: females ratio was 1:1.15. The same results were also reported in the previous studies that addressed the demographic pattern of gastric cancer in young patients, where equal gender or mild female predilection was revealed in their cohorts **(Tekesin et al., 2019; Takatsu et al., 2016)**.

The current study was conducted on young patients treated at NCI and revealed that most tumors were at the body and the antrum with a marked dominance for diffuse and ulceration morphology. **Sandeep et al. (2020)** reported a higher incidence of the location of gastric tumors in the distal third of the stomach in young patients in comparison with older patients

The most important prognostic factor for GC patients is the tumor stage, and there is a considerable variation in long-term survival across tumors of different stages **(Zhou et al., 2016)**.

Our findings regarding patients' presentations in this hospital-based analysis are consistent with past reports, including advanced clinical stage disease (stage 4 = 46.7%), high grade (G3 = 63.4%), and advanced nodal involvement (N+= 46.7%). There was a higher frequency of omental metastasis and ascites over lung and liver metastasis among our patients. This is in harmony with literature findings, as **Cheng et al. (2020)** indicated that young patients (below 49 years) with gastric cancer presented with higher stage, a higher percent of N3b positive LNs and more poorly differentiated carcinoma compared to patients with higher ages and this was translated to poorer outcome (5-year OS 62.4% vs. 70.8%, P = 0.019). Additionally, **Sandeep et al. (2020)** cohort demonstrated a higher percentage of T4 and undifferentiated pathology in young patients below 40 years in comparison with those with higher ages (p-value 0.049, <0.001 respectively).

Younger patients had a lower likelihood of not receiving chemotherapy for stage IV disease than older patients.

Younger patients may be believed to be more able to endure treatment because of their younger age and fewer comorbidities. So despite staging in gastric adenocarcinoma serving to guide treatment and prognosis, the age factor should be taken into consideration by oncologists when they choose therapies for patients (**Ajani et al., 2016**). In the literature, there were different results regarding the impact of age on the treatment results of stage IV gastric cancer. **Wang Z et al. (2016)** noted that the younger patients in stage IV had a superior 5-year survival rate compared to the older patients (26.9% vs. 10.3%, P-value = 0.003).

Conversely, **Kim et al. (2014)** indicated that the overall 5-year survival rates in younger and older groups were 84.3% and 89.6%, respectively (P-value =0.172). Additionally, **Park et al. (2009)** study demonstrated no significant differences in 5-year survival rates between younger (≤45 years) versus older (>45 years) GC patients (69.97% vs. 69.03%, P value =0.534).

The demonstrated effect of treatment in our study is consistent with other gastric cancer studies, which exhibited improved overall survival in the cases who underwent surgery (76%) in comparison to only (30.8%) who did not (P-value = 0.001). Also, our results were comparable with other studies' results as the MAGIC trial and the Inter-group study, which denote that perioperative chemotherapy had a good impact on overall survival. We noticed that the median survival of the cases who had received chemotherapy was 17.86 months compared to only 3.61 months in those who did not receive it (P-value <0.001).
In our study, the absence of omental metastasis or ascites has significantly affected the overall survival in comparison with the presence of either of them with a P-value (<0.001), also cases presented in early stage (II) had better survival than those with advanced stage (III, IV) (P-value = 0.001), and these results are compatible with other studies which recommended aggressive treatment in locally advanced cases in the absence of metastatic lesions and\or ascites.

This study had multiple limitations that should be mentioned. The patients' demographic data at our institute are limited; there may be confounders in the analysis that cannot be accounted for. The retrospective study design is a significant weakness of our study, where not every case has a comprehensive dataset to analyse. Also the small number of cases which was due to rarity of gastric cancer in this young age group. Nevertheless, the significance of this study is that it highlighted that most cases of gastric cancer in young patients presented in advanced stages with high-grade pathology and analysed their dismal overall survival and factors that affected it, especially those who have ascites or omental metastasis.

Conclusion

Gastric adenocarcinoma in young age is rare, but it presents in an advanced stage with high-grade pathology, and its DFS and OS are dismal with the current lines of treatment.

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