Long-term Follow-up of Adjuvant Chemoradiation of Gastric Carcinoma in South Egypt Cancer Institute patients (Single Center Retrospective Study)

Abdelaal WAA[1], Mahran TZ[2], Elnaggar MSM[2]

[1] Radiation Oncology Department, South Egypt Cancer Institute, Assiut University
[2] Clinical Oncology Department, Faculty of Medicine, Assiut university

Abstract:

Background: Adjuvant combined chemoradiation in patients with completely resected gastric adenocarcinoma plays an important role in the treatment of gastric carcinoma as it helps to improve local control and overall survival.

Aim: Determine the pattern of failure, disease free survival and overall survival rates in patients with completely resected gastric adenocarcinoma treated with adjuvant combined chemoradiation regimen and detection of possible prognostic factors and their correlation with outcome of patients treated with chemoradiation regimen.

Methods: The study was conducted in South Egypt Cancer Institute at radiation oncology department. Patients received one cycle of 5-FU and leucovorin or capecitabine followed by a combination of bolus 5-FU or capecitabine and RT. After the RT was completed, two additional cycles of 5-FU and leucovorin or capecitabine were given. The total dose of 45 Gy in 25 fractions of 1.8 Gy (five fractions Per week) by intensity-modulated RT techniques.

Results: We reviewed 100 patients from 2010 to 2020 with median follow-up duration of 48 months for the patients, (11%) developed metastasis only, (17%) locoregional recurrence only and (42%) developed both locoregional recurrence with metastasis. According to Kaplan-Meier analysis, the median DFS (months) was 47 months (95%CI 36.94 – 57.06). During follow-up, 72/100 patients (72.0%) died.

Conclusion: The principal benefit associated with postoperative concurrent chemoradiotherapy following curative resection of gastric adenocarcinoma was reduction of locoregional failure.

Keywords: gastric carcinoma, adjuvant chemoradiation.

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Authors Information:
Walaa Abdelshafy Ali Abdelaal
Radiation Oncology Department, South Egypt Cancer Institute, Assiut University
email: walaaabdelshafy45@gmail.com

Taha Zaki Mahran
Clinical Oncology Department, Faculty of Medicine, Assiut university
email: taha.mahran@med.au.edu.eg

Maha Salah Mohamed Elnaggar
Clinical Oncology Department, Faculty of Medicine, Assiut university
email: maha_elnaggar@aun.edu.eg

Corresponding Author:
Walaa Abdelshafy Ali Abdelaal
Radiation Oncology Department, South Egypt Cancer Institute, Assiut University
email: walaaabdelshafy45@gmail.com

Introduction:

Gastric cancer (GC) is the fifth common cancer and ranks fourth in mortality worldwide [1]. The overall five-year survival rate for stomach cancer in 2022 was 33.3%[2]. Several factors have been noted to have a significant impact on the increased risk of developing GC, like family history, diet, alcohol consumption, smoking, Helicobacter pylori and Epstein–Barr virus (EBV) infections[3].

Surgical resection is the principal therapy for gastric cancer, as it offers the only potential for cure. Neoadjuvant therapy has several potential advantages, including the opportunity to test a tumor's response to a particular therapeutic regimen and tailor adjuvant therapy based on this response. Neoadjuvant therapy also has the potential to improve R0 resection rates and to improve compliance with systemic therapy[4].

In USA, adjuvant chemoradiotherapy with 5-fluorouracil plus folinic acid is the standard treatment according to the national comprehensive cancer network (NCCN) guidelines [5]. However, considering the high toxicity of the original regimen associated with radiotherapy (5-day bolus of 5-FU/FA every 28 days), modifications based on oral capecitabine [6] or 5-FU according to the De Gramont schedule [7] are encouraged. In case of D2 dissection, adjuvant chemotherapy without radiotherapy can be considered.

The aim is to determine the pattern of failure, disease free survival and overall survival rates in patients with completely resected gastric adenocarcinoma treated with adjuvant combined chemoradiation regimen and detection of possible prognostic factors and their correlation with outcome of patients treated with chemoradiation regimen.

Patients and Methods:

The retrospective study analyzed the data of all patients diagnosed with gastric cancer and received adjuvant concurrent chemoradiation during the period from January 2010 and December 2020, at radiation oncology department, South Egypt Cancer Institute, Assiut university.

Pretreatment evaluation:

Full history and physical examination were conducted at the time of initial presentation. CT chest and pelviabdomen were requested to all patients as a baseline study. Histopathological examination of the tumor, stage and grade of the tumor. Metastatic work up by different imaging studies.

Evaluation the response of both treatment modalities by imaging studies and operative pathology.

Patients initiated adjuvant treatment within 8 weeks of surgery, patients received one cycle of 5-FU and leucovorin or capecitabine followed by a combination of bolus 5-FU (300mg/m2/day) or capecitabine (1650 mg/m2/day split BID) and RT. After the RT was completed, two additional cycles of 5-FU and leucovorin or capecitabine were given. total dose of 45 Gy in 25 fractions of 1.8 Gy (five fractions per week) by intensity- modulated RT techniques.

Inclusive Criteria:

Our study included all patients with pathologically proven gastric adenocarcinoma, aged between 18 to 70 years, WHO performance status 0-2, Haemoglobin at least 10g/dl, White blood cells at least 3000/mm3, Platelets count at least 100000/mm3, Bilirubin concentration no more than 25% higher than upper limit of normal (ULN), SGOT/SGPT no greater than 2.5 times ULN, Alkaline phosphatase no greater than 2 times ULN, Creatinine concentration no more than 25% higher than the ULN, who received adjuvant concurrent chemoradiation.

Exclusive criteria:

Patients with second malignancy, prior abdominal irradiation, pregnant or nursing female, or patient files with incomplete data.

Statistical methods:

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data was statistically described in terms of mean ± SD and median (range) when not normally distributed. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. Kaplan-Meier's method with log rank test was used for overall and disease free survival analysis. Hazard ratio (HR) with 95% Confidence Interval (CI) and COX regression analysis was calculated to determine significant factors associated with mortality. P-value is always 2 tailed set significant at 0.05 level.

Results:

This study analyzed the data of all patients diagnosed with gastric cancer and received adjuvant concurrent chemoradiation during the period from January 2010 and December 2020, at radiation oncology department, South Egypt Cancer Institute, Assiut university.

Table 1: Baseline characteristics of the studied participants (n=100)

Patients' characteristics	**N=100**	
Age (years)		
• Mean ± SD	57.44 ± 7.38	
• Median (range)	58.5 (40 – 69)	
Sex		
• Male	65	(65%)
• Female	35	(35%)
PS		
• 0	13	(13%)
• 1	57	(57%)
• 2	30	(30%)

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage).

Table 2: Tumor characteristics among the studied participants (n=100)

Tumor characteristics	N	(%)
Tumor site		
• Upper third & cardia	12	(12%)
• Middle third	30	(30%)
• Lower third	50	(50%)
• Diffuse infiltration	8	(8%)
Histopathology		
• Adenocarcinoma diffuse type	71	(71%)
• Adenocarcinoma intestinal type	15	(15%)
• Adenocarcinoma mixed type	14	(14%)
Tumor grade		
• Grade 1	12	(12%)
• Grade 2	22	(22%)
• Grade 3	66	(66%)
T staging		
• T2	30	(30%)
• T3	60	(60%)
• T4	10	(10%)
Nodal metastasis		
• N0	25	(25%)
• N1	53	(53%)
• N2	22	(22%)
Tumor stage		
• I	25	(25%)
• II A	5	(5%)
• III	70	(70%)

Qualitative data are presented as number (percentage).

Table 3: Treatment protocol received by the studied participants (n=100)

Treatment protocol	N	(%)
Surgery		
● Radical distal gastrectomy	50	(50%)
● Radical total gastrectomy without splenectomy	36	(36%)
● Radical total gastrectomy + splenectomy	7	(7%)
● Radical proximal gastrectomy	7	(7%)
Radiotherapy dose		
● 45 GY	100	(100%)
Chemotherapy		
● 5FU/Leucovorin	62	(62%)
● Capecitabine	38	(38%)

Qualitative data are presented as number (percentage).

Table 4: Incidence of early treatment related toxicity among the studied participants (n=100)

Early toxicity	N	(%)
Anemia		
● No	86	(86%)
● Grade 2	3	(3%)
● Grade 3	11	(11%)
Thrombothytopenia		
● No	97	(97%)
● Grade 2	3	(3%)
Nausea		
● No	66	(66%)
● Grade 1	34	(34%)
Vomiting		
● No	84	(84%)
● Grade 2	1	(1%)
● Grade 3	15	(15%)
Diarrhea		
● No	77	(77%)
● Grade 2	15	(15%)
● Grade 3	8	(8%)
Weight loss		
● No	68	(68%)
● Grade 1	32	(32%)
Anorexia		
● No	97	(97%)
● Grade 1	3	(3%)
Stomatitis		
● No	81	(81%)
● Grade 2	6	(6%)
● Grade 3	13	(13%)
Abdominal pain		
● No	86	(86%)
● Grade 2	14	(14%)

Qualitative data are presented as number (percentage).

Outcome analysis

The median follow-up duration of the studied 100 gastric cancer patients was 48 months (range, 19 to 130 months). During follow-up, 72/100 patients (72.0%) died. According to Kaplan-Meier analysis, the median overall survival (the length of time from either the date of diagnosis or the start of treatment for a disease that patients diagnosed with the disease are still alive) was 56 months (95%CI 52.58 – 59.42). A total of 70/100 patients (70.0%) developed either local disease recurrence and/or metastasis. The median time to local disease recurrence or distant metastasis was 47 months (range, 6 to 122 months). According to Kaplan-Meier analysis, the median DFS (the length of time after primary treatment for a cancer ends that the patients survive without any signs or symptoms of that cancer) was 47 months (95%CI 36.94 – 57.06).

During the median follow-up duration of 48 months for the patients, (11%) developed metastasis only, (17%) locoregional recurrence only and (42%) developed both locoregional recurrence with metastasis. According to Response evaluation criteria in solid tumors (RECIST) 70% of cases were developing progressive disease (PD).

Table 5: Outcome among the studied cases (n=100)

Outcome (144 months)	N	(%)
Recurrence		
● No recurrence	41	(41%)
● Recurrence	59	(59%)
Metastasis		
● No	47	(47%)
● Yes	53	(53%)
Site of metastasis		
● Peritoneal deposit	31	(58.5%)
● Liver	24	(45.3%)
● Lung	4	(7.5%)
● Bone	5	(9.4%)
Outcome		
● Alive	28	(28%)
● Died	72	(72%)

Qualitative data are presented as number (percentage).

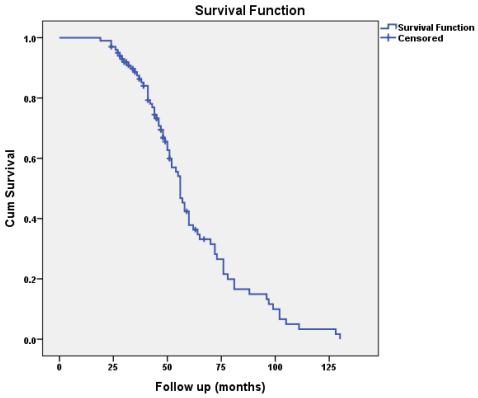


Figure 1: Overall survival curve of the studied gastric cancer cases

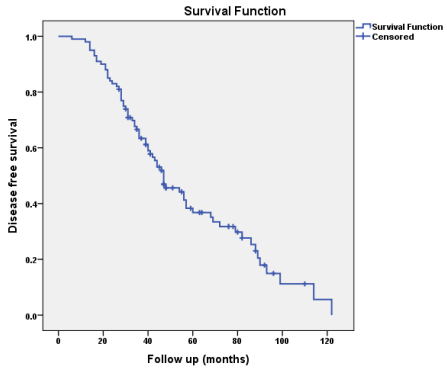
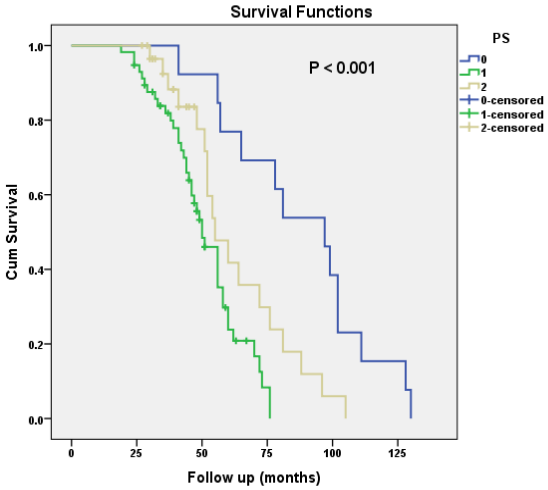


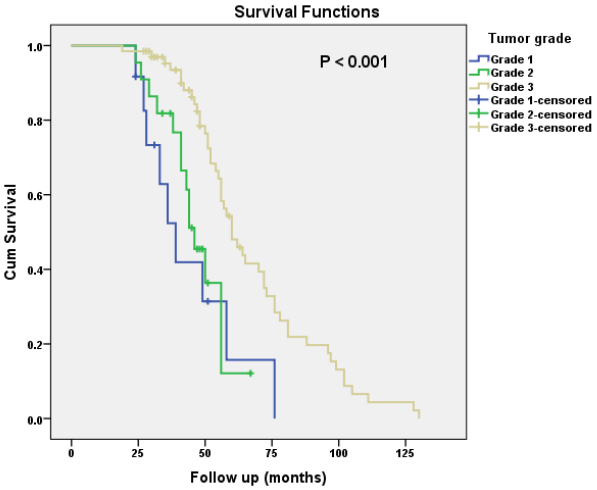
Figure 2: Disease free survival curve of the studied gastric cancer cases

Table 6: Ten years overall survival and disease free survival according to clinic-pathological details of the studied gastric cancer cases (n=100)

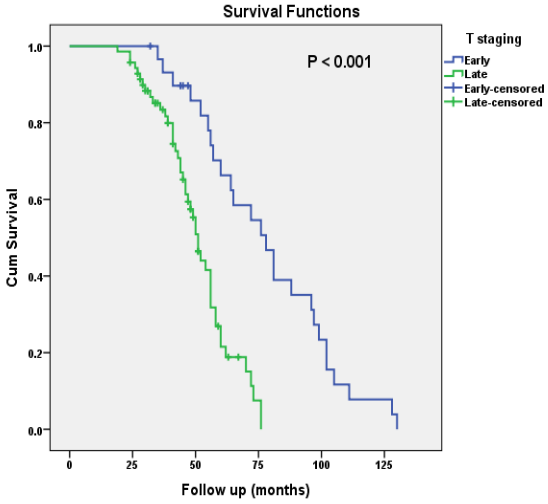
	OS (10 years)		**DFS (10 years)**	
	Estimate ± SE	**P value**	**Estimate ± SE**	**P value**
Age groups		0.570		0.443
• < 50 years	52.0 ± 5.47		47.0 ± 8.43	
• ≥ 50 years	56.0 ± 1.54		47.0 ± 5.49	
Sex		0.509		0.555
• Male	55.0 ± 2.77		44.0 ± 3.47	
• Female	58.0 ± 4.79		54.0 ± 5.25	
PS		**<0.001**		**0.014**
• 0	97.0 ± 12.58		79.0 ± 7.79	
• 1	50.0 ± 2.82		36.0 ± 3.27	
• 2	55.0 ± 5.30		57.0 ± 16.37	
Tumor site		0.073		0.834
• Upper third & cardia	49.0 ± 8.57		40.0 ± 6.35	
• Middle third	52.0 ± 2.21		44.0 ± 2.32	
• Lower third	60.0 ± 5.29		47.0 ± 8.60	
• Diffuse infiltration	70.0 ± 36.70		60.0 ± 0.0	
Tumor grade		**<0.001**		**<0.001**
• Grade 1	39.0 ± 4.49		22.0 ± 6.06	
• Grade 2	46.0 ± 3.16		33.0 ± 4.69	
• Grade 3	60.0 ± 3.92		68.0 ± 9.53	
T stage		**<0.001**		**0.005**
• Early (T2)	78.0 ± 8.04		82.0 ± 9.12	
• Advanced (T3 + T4)	51.0 ± 1.84		40.0 ± 4.03	
Nodal metastasis		**<0.001**		**0.019**
• Negative	78.0 ± 5.62		82.0 ± 9.29	
• Positive	51.0 ± 1.79		42.0 ± 3.71	
Tumor stage		**<0.001**		**<0.001**
• Early (stage 1 + 2)	60.0 ± 3.06		57.0 ± 7.65	
• Advanced (stage 3)	43.0 ± 2.36		27.0 ± 3.06	



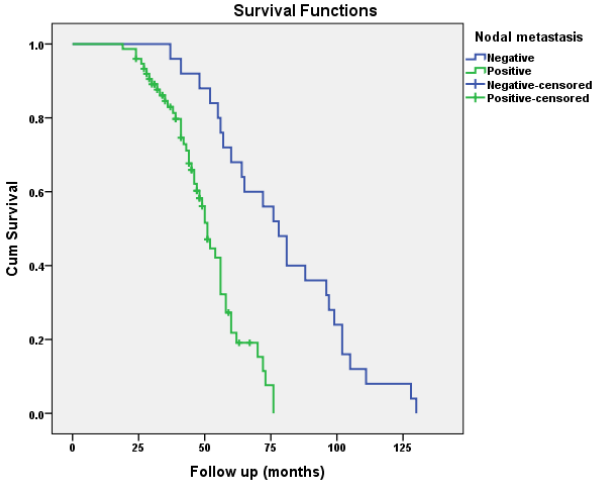
Overall survival according to performance status



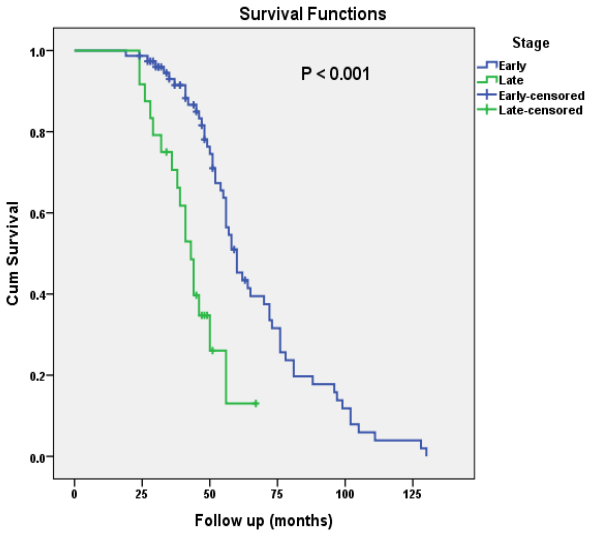
Overall survival according to tumor grade



Overall survival according to T staging

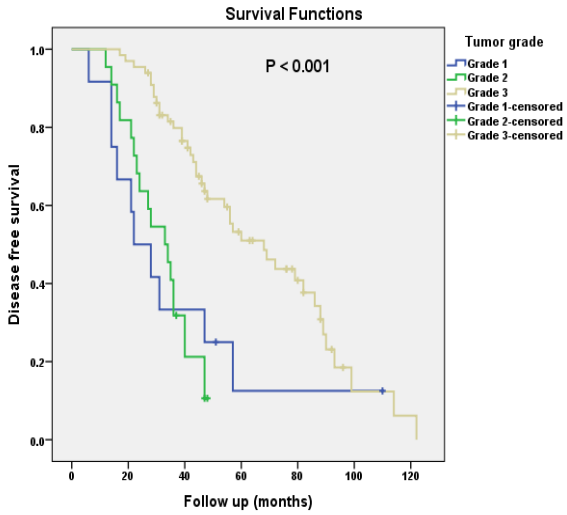


Overall survival according to nodal metastasis

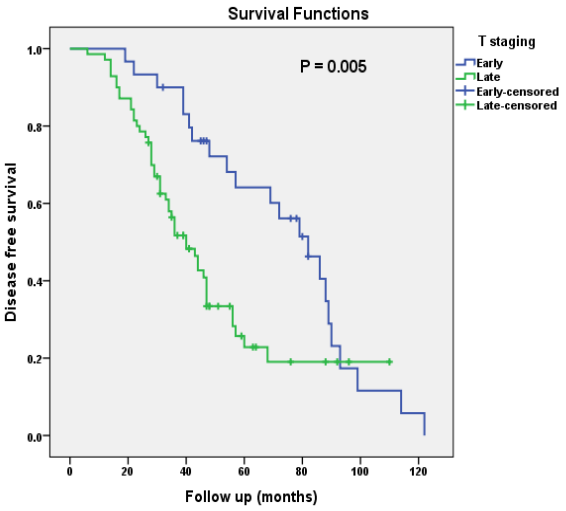


Overall survival according to tumor stage

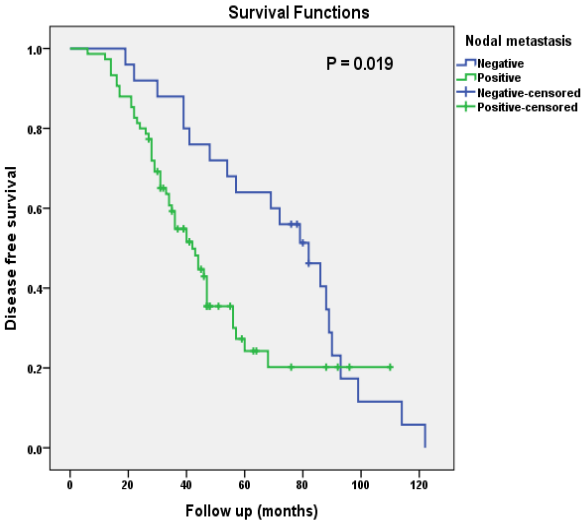
Figure 3: Overall survival curve of the studied gastric cancer cases according to the performance status, tumor grade, T staging, nodal metastasis, and tumor stage.



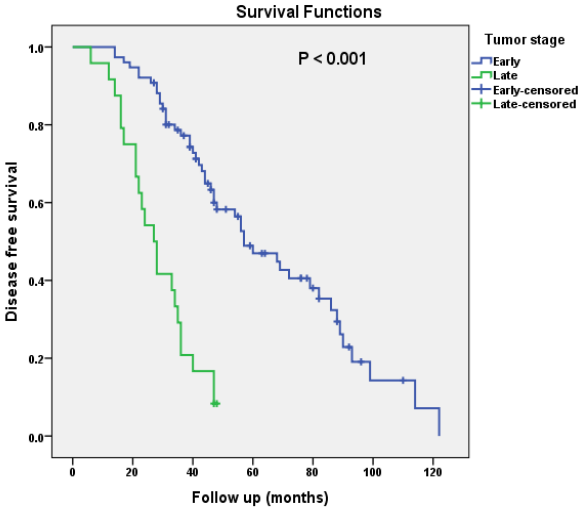
Disease free survival curve of the studied gastric cancer cases according to the tumor grade.



Disease free survival curve of the studied gastric cancer cases according to T staging.



Disease free survival curve of the studied gastric cancer cases according to the nodal metastasis.



Disease free survival curve of the studied gastric cancer cases according to tumor stage.

Figure 4: Disease free survival curve of the studied gastric cancer cases according to the tumor grade, T staging, nodal metastasis, and tumor stage.

Table 7: Results of COX regression analysis for predicting likelihood of death according to clinic-pathological characteristics of the studied participants (n=100)

Variable name	n	B	S.E.	P value	HR	95% C.I. for HR
PS						
● 0	13				ref	
● 1	57	1.815	0.428	<0.001	6.142	2.65 – 14.22
● 2	30	1.105	0.416	0.008	3.018	1.34 – 6.82
Tumor grade						
● Grade 1	12				ref	
● Grade 2	22	-0.125	0.435	0.773	0.882	0.376 – 2.068
● Grade 3	66	-1.161	0.376	0.002	0.313	0.150 – 0.654
T stage						
● Early (T2)	30				ref	
● Advanced (T3 + T4)	70	1.431	0.334	<0.001	4.181	2.175 – 8.039
Nodal metastasis						
● Negative	25				ref	
● Positive	75	1.489	0.346	<0.001	4.431	2.249 – 8.728
Tumor stage						
● Early (stage 1 + 2)	30				ref	
● Advanced (stage 3)	70	1.272	0.314	<0.001	3.569	1.930 – 6.599

B = regression coefficient, SE = standard error, HR= hazard ratio, CI =confidence interval, p value is significant ≤0.05

Discussion:

Gastric cancer represents the fifth most common malignancy and despite a steady decline remains the third leading cause of cancer mortality with widely varying incidence worldwide [8].

In this study the age of the patients ranged between 40-69 years with median age of 58.5 years. The male patients were representing (65%) of total number.

In González-Domingo et al. (2020) the median age was 62 years but wider range of ages between 23-85 years due to larger number in their study and males were represent 72% of study population. [9].

In Barad et al, (2014) the peak incidence of gastric cancer was in age group older than 60 years old (42.4%). Also male predominance was noted with male to female ratio of 2.16:1, which are comparable with other studies [10].

The younger age reported in the present study, result in higher proportion of patients to have better performance status (57% had performance status of 1) which reflect in their tolerability to chemoradiation.

Non-cardia gastric cancer, which is more common in East Asia and Latin America, represents 80% of gastric tumors globally and has been associated with Helicobacter pylori (H. pylori) infection, alcohol use, high salt intake and low consumption of fruit and vegetables.

Proximal (cardia) gastric cancer is associated with obesity and gastro-esophageal reflux and is more common in North America and Western Europe [11].

Similar results in our study were obtained as the most common site was distal third (50%), followed by middle third (30%), then proximal third and cardia (12%) while least one was the diffuse type (8%).

In Barad et al, (2014) study the most common site of gastric cancer was antrum (50.6%) followed by cardia (17.1%), body (13.9%), pylorus (13.3%) and fundus (2.5%). In their study the most common site of tumor in both males and females was antrum, 57.4% and 36% respectively. The second most common site was cardia (17.6%) in males and body of the stomach (22%) in females [10].

According to Laurén histopathological classification the diffuse type was the commonest type in our study (71%) followed by intestinal type (15%) then the mixed type (14%).

In Korean patients Similar results in Park et al, (2014) as the predominance was for diffuse type cancers (81.0 %) [12].

In Taiwan the result was different gastric cancer patients, there are 1423 intestinal type (46.3 %), 1000 diffuse type (32.6 %) and 648 mixed type (21.1 %) gastric cancer.

In present study the most common tumor grade is grade III (66%) followed by grade II (22%) then grade I (12%)

In Shi et al, (2022) most of the patients were poorly differentiated (74.4%), both moderately and moderately to poorly differentiated (7.4%) and (17.7%) consecutively, while the well differentiated is (0.5%) [14].

As regard staging, we found in the present study that most cases presented in T3 (60%), then followed by T2 (30%) and the least presentation T4 (10%), (53%) of cases are N1, (22%) are N2, while (25%) are N0.

This was different than Shi et al, (2022) as T4 cases was the common presentation (58.6%), followed by T3

(38.1%) while both T1 and T2 (3.3%), N3 patients were representing (79.1%), while N0-N2 were (20.9%) [14].

In González-Domingo et al. (2020) T4 cases were (62.6%), T3 cases were (20.5%), T 2 cases (11.2%) and T1 cases (5.6%), N1 patients were (20.5%), while N2 (31.3%), N3 (33.1%) and N0 patients were (14.9%) [9].

Regarding tumor staging, according to the American Joint Committee on Cancer (AJCC) staging system 8th edition, in this study (5%) of cases are stage II, (25%) are stage I while (70%) are stage III [9].

Our results were consistent with other studies. Yang Li et al, (2020) stage III was the presentation of the most of the patient (62.9%), and stage II patients were (32.3%) only [14].

The same was for González-Domingo et al, (2020) as stage III patients were (69.2%) and total number of stage II patients (30.8%) [9].

In Stumpf et al, (2017), as (53.1%) of the patients were presented in stage II while (29.0%) of patients were classified as stage I, and (17.9%) as stage III [16].

Toxicity is an important item when we are talking about adjuvant chemotherapy.

One of the concerns on the application of adjuvant chemoradiotherapy as a standard treatment for gastric cancer is its significant toxicity. In the INT 0116 study, there was 73% grade 3 toxicity or above and 1.1% toxic death Macdonald et al., (2001) [17].

In the present study 85% of patients completed the whole course of chemoradiation without any interruption. Grade 3 early toxicity, according to RTOG, occurred in 47% of patients.

This relative low percentage of toxicity profile most probably due to there is (70%) of the patients has performance status zero and one and younger age of our patients which allowed them to tolerate chemoradiation.

These results comparable with Cats et al, (2018) as (41%) of the patients developed grade III toxicity, and (4%) grade IV toxicity [18].

Several factors may contribute to locoregional and peritoneal recurrence, including inadequate lymphadenectomy or possibly direct peritoneal seeding from surgery itself.

Studies have also demonstrated evidence of direct peritoneal seeding during surgery. For example, one study from Japan found that over 60 percent of patients with negative peritoneal washings pre-gastrectomy subsequently converted to positive washings post-gastrectomy based on mRNA biomarkers. Furthermore, a subset of these patients had viable cancer cells in their peritoneal fluid that could be grown in cell culture and form tumors in mice [19].

In this study locoregional recurrence occurred in (59%) of cases, this mostly due to relative long duration of the study time sample.

In Shi et al, (2022) local and regional recurrence was (39.5%) of cases [14].

In MacDonald et al, (2001) locoregional recurrence was (19%) of cases [17].

Regarding Metastasis (53%) of cases in the present study developed distant metastasis.

Most common site for metastasis is the peritoneum by (31%) of cases.

Several trials were then conducted to assess whether the addition of adjuvant chemoradiotherapy to postoperative or perioperative chemotherapy could further improve survival outcomes. patients with node-positive disease seemed to benefit from the addition of adjuvant chemoradiotherapy[20].

Only 27% of newly diagnosed gastric cancers are localized with a 5-year overall survival (OS) rate of 30.4%, which remains stable over the last 30–40 years.

Overall survival in the current study representing (28%) of cases.

It is mostly due to longevity of the study duration.

González-Domingo et al, (2020) showed in their study that the overall survival at 3 and 5 years for the entire group of the patients was 54.9% and 40.85%, respectively [9].

In Shi et al, (2022) before the PSM, the 5-year recurrence-free survival (RFS) rates were 57.7% and 47% in the CRT group and CT group, respectively ($P = 0.024$). The 5-year overall survival (OS) rate in the CRT group was significantly higher than that in the CT group (62.8% vs. 49.4%, $P = 0.002$). After the PSM, the 5-year OS rate was still higher in the CRT group compared with that in the CT group (62.8% vs. 45.7%, $P = 0.004$), while there was a trend to improve the 5-year RFS rate in the CRT group (57.7% vs. 46.3%, $P = 0.06$) [14].

According to Muller et al, (2009) and Norero et al, (2016) the published experience comes exclusively from experiences with adjuvant radiochemotherapy from different reference cancer centers, with global 5-year survival rates varying between 37.5% and 54% [21, 22].

In González-Domingo et al, (2020) the univariate analysis, of the factors explored, showed that those with a poor prognosis that significantly affected survival were the number of lymph nodes involved ($p = 0.000$), aged > 65 years ($p = 0.001$) and tumour stage ($p = 0.022$) [9].

Their study demonstrated overall 5-year survival according to nodal stage was 61.2% in N0, 54.5% in pN1, 37.3% in pN2, 26% in pN3a and 28% in pN3b patients ($p = 0.00$). Overall 5-year survival was 50% for patients aged <65 years and 29.9% for those aged ≥65 years. Overall 5-year survival according to stage was 58% for pT1, 45.8% for pT2, 50% for pT3 and 35.3% for pT4a [9].

In multivariate analysis in González-Domingo et al, (2020), the factor with a poor prognosis for overall survival was the number of lymph nodes involved, with a HR of 1.40 for each increased N stage ($p = 0.00$), with a HR of 1.78 for those aged 65 years ($p = 0.00$) and a HR of 1.35 for those with more advanced tumour stages ($p = 0.01$) [9].

In Shi et al, (2022) the five variables which included age, T stage, N stage, TNM stage, and whether they received CRT were shown related to the overall survival in the univariate analysis. In the multivariate analysis, five variables were included in the Cox regression. The multivariate analysis showed that advanced TNM stage ($P < 0.001$) and not being able to

receive the chemoradiotherapy treatment were the significant risk factors for OS[14].

The prognostic factors affecting this study are performance status, grade, T staging, nodal metastasis and tumor staging.

Conclusion:

The principal benefit associated with postoperative 5- FU/Leucovorin, and radiotherapy following curative resection of gastric adenocarcinoma was reduction of locoregional failure.

References:

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-249.
2. Colleen D. Stomach Cancer Survival Rate and Prognosis. https://wwwverywellhealthcom/stomach-cancer-prognosis-and-recovery-4154216. 2022;28 Sep.
3. Machlowska J, Baj J, Sitarz M, et al. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci. 2020 Jun 4;21(11):4012.
4. Ahmad MU, Javadi C, Poultsides GA. Neoadjuvant Treatment Strategies for Resectable Proximal Gastric, Gastroesophageal Junction and Distal Esophageal Cancer. Cancers (Basel). 2022 Mar 30;14(7):1755.
5. National Comprehensive Cancer Network. Gastric Cancer (Version 2.2022). Available online: https://wwwnccnorg/ professionals/physician_gls/pdf/gastricpdf (accessed on 27 December 2022). 2022.
6. Jansen EP, Boot H, Saunders MP, et al. A phase I–II study of postoperative capecitabine-based chemoradiotherapy in gastric cancer. Int J Radiat Oncol Biol Phys. 2007 Dec 1;69(5):1424-8.
7. de Gramont A, Bosset J-F, Milan C, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol. 1997 Feb;15(2):808-15.
8. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.
9. González-Domingo M, Ulloa C, Olivares J, et al. Adjuvant radiochemotherapy in locally advanced gastric cancer: from evidence to daily clinical practice in a single institution. Ecancermedicalscience. 2020 Nov 5;14:1137.
10. Barad AK, Mandal SK, Harsha HS, et al. Gastric cancer—a clinicopathological study in a tertiary care centre of North-eastern India. J Gastrointest Oncol. 2014 Apr;5(2):142-7..
11. Colquhoun A, Arnold M, Ferlay J, et al. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015 Dec;64(12):1881-8.
12. Park HJ, Ahn JY, Jung H-Y, et al. Clinical characteristics and outcomes for gastric cancer patients aged 18–30 years. Gastric Cancer. 2014 Oct;17(4):649-60.
13. Chen YC, Fang WL, Wang RF, et al. Clinicopathological variation of Lauren classification in gastric cancer. Pathol Oncol Res. 2016 Jan;22(1):197-202.
14. Shi J, Kang W, Tang Y, Li N, et al. Adjuvant Chemoradiotherapy Versus Adjuvant Chemotherapy for Stage III Gastric or Gastroesophageal Junction Cancer After D2/R0 Resection. Front Oncol. 2022 Jul 12;12:916937.
15. Li Y, Zhu Z, Ma F, et al. Improving survival of stage II-III primary gastric signet ring cell carcinoma by adjuvant chemoradiotherapy. Cancer Med. 2020 Sep;9(18):6617-6628.
16. Stumpf PK, Amini A, Jones BL, et al. Adjuvant radiotherapy improves overall survival in patients with resected gastric adenocarcinoma: A National Cancer Data Base analysis. Cancer. 2017 Sep 1;123(17):3402-3409.
17. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001 Sep 6;345(10):725-30.
18. Cats A, Jansen EP, van Grieken NC, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):616-628.
19. Takebayashi K, Murata S, Yamamoto H, et al. Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer. Ann Surg Oncol. 2014 Jun;21(6):1991-7.
20. Li GZ, Wang J. The evolution of treatment for resectable gastric cancer. Clin Surg Oncol. 2023; 2(1):100008.
21. Müller B, Balbontín P, Cárcamoa M, et al. Results of adjuvant chemoradiation after curative surgery for gastric cancer. A retrospective study. Rev Med Chil. 2009 May;137(5):649-56.
22. Norero E, Bustos M, Herrera M, et al. Postoperative adjuvant treatment for gastric cancer improves long-term survival after curative resection and D2 lymphadenectomy. Results from a Latin American Center. Eur J Surg Oncol. 2016 Jan;42(1):94-102.