Journal of Cancer and Tumor International

11(1): 35-44, 2021; Article no.JCTI.65668
ISSN: 2454-7360

Induction Chemotherapy Followed by Concurrent Chemo-Radiotherapy for Locally Advanced Gastro-Esophageal and Gastric Carcinoma

Nora Shaband[1*], Niveen Abo-Touk[1], Mohamed Elawadi[1] and Saleh Ta-Ema[1]

[1]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author NS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NAT and STE managed the analyses of the study. Author ME managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2021/v11i130143
Editor(s):
(1) Dr. William CS Cho, Queen Elizabeth Hospital, Hong Kong.
Reviewers:
(1) Veronica Martinez Marignac, UADER | Facultad de Ciencias de la Vida y la Salud (FCVyS) (Facultad de Ciencias de la Vida y la Salud (FCVyS) - UADER), Argentina.
(2) Nero M. Paderes, Abra State Institute of Sciences and Technology, Philippines.
(3) Yuki Wada, Akita University Graduate School of Medicine, Japan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65668

Original Research Article

Received 10 December 2020
Accepted 19 February 2021
Published 08 March 2021

ABSTRACT

Aims: To assess the safety and efficacy of chemo-radiotherapy before radical surgery in locally advanced gastric and gastroesophageal adenocarcinoma.
Study Design: This was a prospective phase Ⅱ single arm study.
Place and Duration of Study: Department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital, Mansoura, Egypt, between May 2017 and June 2019.
Methodology: Patients with pathologically proven gastric or gastroesophageal junction adenocarcinoma are included. They received one cycle of induction chemotherapy paclitaxel-carboplatin, [paclitaxel dose of 175 mg/m^2, carboplatin dose of (AUC: 5)], followed by CCRT [RT 45 Gy over 25 fractions over 5 weeks concurrent with weekly paclitaxel at a dose of 50 mg/m^2, carboplatin at a dose of (AUC: 2)], followed by surgery and 2 cycles of paclitaxel-carboplatin for responders.
Results: The study included 24 patients. Most of the patients were diagnosed at stage III (83.3%).

**Corresponding author: Email: nora_shbend@mans.edu.eg;*

There were no major side effects of the induction chemotherapy cycle. There were no reported grade 3 or 4 toxicities for the CCRT. Only two patients suffered from late radiation toxicities (distal esophageal stenosis). Pathological complete response was achieved in seven patients (31.8%). Twenty-two patients had surgical resection with a 95% resection margin zero. The median follow-up time was 22.5 months. The median progression-free survival (PFS) and overall survival (OS) were 23, 23.5 months, respectively.

Conclusion: The preliminary data suggested good efficacy of the studied treatment design with acceptable adverse-event rates, however a larger multicentric phase 3 trial with a longer follow-up duration is recommended.

Keywords: Adenocarcinoma; concurrent chemo-radiotherapy; gastroesophageal junction; gastric carcinoma.

1. INTRODUCTION

Gastric cancer (GC) represents the fifth-most common tumor and the third-leading cause of cancer-related death worldwide, showing similar trends in Europe [1]. Although surgery is the primary modality that can cure patients, most patients with locally advanced tumors with deeper invasion or nodal involvement present with recurrences leading to death within two years after resection [2].

The updated meta-Analysis of randomized controlled trials assessing the effect of neoadjuvant chemotherapy in advanced gastric cancer which compared a variety of preoperative chemotherapy regimens with surgery alone concluded that neoadjuvant chemotherapy was associated with a statistically significant benefit in terms of both overall and progression-free survivals [3]. Preoperative chemo-radiotherapy (CRT) appeared to improve survival even more than chemotherapy in adenocarcinoma of the esophagus, but at the cost of increased operative mortality [4]. Our study addresses the benefit of preoperative chemo-radiotherapy for gastric and gastro-esophageal adenocarcinoma using taxanes- platinum combination.

2. PATIENTS AND METHODS

A phase II prospective study included patients with locally advanced non-metastatic gastro-esophageal or gastric adenocarcinoma who presented to the Clinical Oncology& Nuclear Medicine Department, Mansoura University Hospital during the period from the start of January 2018 to the end of May 2019.

2.1 Selection of Patients

Pathological evidence of adenocarcinoma of the stomach or gastro-esophageal junction, radiological evidence of locally advanced gastric or gastro-esophageal cancer (T3 or T4) with or without radiologically evident positive lymph nodes, Eastern Collaborative Oncology Group (ECOG) performance status ≤ 2, age > 18 years, adequate bone marrow (hemoglobin ≥ 10gm/dl, platelet ≥ 100,000/mcl, WBCs ≥ 3000/mcl provided that absolute neutrophilic count (ANC) ≥ 1500/mcl), and adequate renal and hepatic function (creatinine clearance > 50 ml/min and bilirubin ≤ 1.5 mg/ml). Patient exclusion criteria: patients with active concurrent or previous malignancies, local recurrence, metastatic disease, and or severe active comorbidity will be excluded from the study.

2.2 Patients Assessment

History was taken from all patients. Physical examination was done including weight, height, and surface area. Performance status was assessed according to ECOG performance status scale [5]. Investigations included upper gastro-intestinal tract (GIT) endoscopy with or without endoscopic ultrasound (EUS), biopsy with a pathological examination, and baseline computed tomography chest, abdomen, and pelvis.

2.3 Treatment Details

Thirty patients were fulfilled the inclusion criteria; however, six patients had been excluded. One patient died from severe uncontrolled hematemesis and melena before starting treatment protocol. Three patients refused to receive chemoradiotherapy protocol and were shifted to the standard perioperative chemotherapy. Two patients had lost follow up after the first cycle of induction chemotherapy. The patients received one cycle of induction chemotherapy of paclitaxel, carboplatin; 22 patients received the paclitaxel at a dose of 175

mg/m^2, carboplatin at a dose of (AUC: 5), 2 patients who had a performance status of ECOG 2 received 3 weeks of paclitaxel at a dose of 80 mg/m^2, carboplatin at a dose of (AUC: 2). The interval between day 1 of the induction chemotherapy cycle and the first day of chemo-radiotherapy ranged from 21 to 30 days. Twenty-four patients had received phase one of conformal three dimensional (3D) planned radiotherapy at a dose of 45 Gy over 25 fractions over 5 weeks concurrent with weekly paclitaxel at a dose of 50 mg/m^2, given intravenous over 1 hour, followed by carboplatin at a dose of (AUC: 2) given IV over 30 minutes, on days 1, 8, 15, 22, 29 of the conformal radiotherapy. The response was assessed by CT chest, abdomen, and pelvis, the interval between the end of CCRT and surgery ranged from 6 to 10 weeks. The non-metastatic surgically fit patients (22 patients) had radical surgery according to the surgeon's decision. The only one non-metastatic surgically unfit patient (due to persistent thrombocytopenia) had an additional tumor boost 50.4 Gy. The responders had then additional 2 adjuvant chemotherapy cycles of the same dose of the induction cycle (20 patients as post-operative chemotherapy and one patient who received a boost dose of CCRT).

2.4 Toxicity Measurement

Patients were evaluated each cycle during chemotherapy treatment, and five times during chemo-radiation to assess acute toxicity. Toxicities were assessed and recorded according to the Common Terminology Criteria for Adverse Event (CTCAE) v4.0.

2.5 Follow up

Clinical examination was performed at each follow-up visit, CT chest, abdomen, and pelvis was done after completing neoadjuvant treatment, post-surgical intervention, and then every 3 months or when clinically indicated. Patients who developed a progressive or metastatic disease were shifted to second-line chemotherapy and were followed for at least 6 months or till death.

2.6 Study End Points

The primary endpoints were to evaluate toxicity profiles and radiological response. The secondary endpoints included evaluation of progression-free survival (PFS) which defined as the time from diagnosis until first evidence of tumor progression, or death, and overall survival (OS) which is defined as the time from diagnosis to death from any cause.

2.7 Statistical Analysis and Data Interpretation

Data were analyzed using IBM SPSS software package version 22.0. Qualitative data were tabulated using number and percent. After testing normality using the Kolmogrov-Smirnov test, quantitative data were described using median (minimum and maximum) for non-parametric data and mean, the standard deviation for parametric data. Significance was judged at the (0.05) level.

Kaplan-Meier used to calculate overall survival and progression free survival times. Univariate analysis was done using log-rank test to calculate the effect of pathologic types and treatment response on median survival times.

3. RESULTS

3.1 Patients and Tumor Characteristics

The baseline characteristics of the 24 patients and their tumors are summarized in (Table 1). Age ranged from 36 to 67 years. The median is 57 years old. Males predominated; there were 17 males (70.8%) and 7 females (29.2%). Most of the patients were ECOG 1 (91.6%). The most commonly involved primary site was the proximal part of the stomach (gastroesophageal junction and cardia), found in 21 patients (87.5%). The pathological differentiation was variable with 14 patients had moderately differentiated adenocarcinoma (AC), 9 patients had poorly differentiated AC and only one patient had poorly differentiated AC with signet ring formation.

According to AJCC prognostic staging groups (8th ed., 2017) [6], twenty patients (83.3%) were presented to us at stage III and three patients were at stage IVA (12.5%), only one patient was at stage IIB. This radiological staging was performed mainly via CT. T3 was the predominant presentation (79.2%, 19 patients). Radiological LN staging presentation was variable with 8 patients presented with N2 disease, while another 8 patients had N1, 5 patients were N0 and only three patients were diagnosed as N3. Pre-neoadjuvant endoscopic US was performed only in four patients. However, the limitation to perform EUS with

biopsy on the first presentation was essentially financial. Three of them had T3 and one diagnosed as T4, the LN staging among those patients were two patients had N1 and two patients had N2 disease.

3.2 Clinical Tumor Response, Surgical Findings, and Pathology

Clinical tumor response was assessed by CT chest, abdomen, pelvis between second to third weeks after finishing CCRT, twenty-two (91.6%) patients had clinical downstaging, one patient had stable disease (4.1%) and another patient had clinical progression in the form of distant metastasis, although locally he had got a partial response. Clinical and pathological tumor response is summarized in Table 2. Post CCRT radiological staging was variable with 37.5% of the patients had downstaged to stage I, while 41.6% had stage II (20.8% stage IIA, 20.8% stage IIB). Four patients (16.7%) were stage III. Only one patient was progressed to stage IVB. According to post-CCRT radiological T staging, T2 was the predominant finding (75%, 18 patients). Radiological CT LN staging was variable with 14 patients (58.3%) downstaged to N0 disease, while 5 patients had N1 disease; another 5 patients were diagnosed with N2 disease. One patient showed systemic progression and distant metastatic disease in the form of peritoneal nodules (Table 2).

Twenty- two patients had surgical excision. The median interval between ending CCRT treatment and surgical intervention was nine weeks, ranged from 6 to 10 weeks. Twenty patients had proximal subtotal gastrectomy with LN dissection, while two patients had total gastrectomy with LN dissection. The median

Table 1. Baseline patients and tumor characteristics

Characteristic	No. of Patients (N=24)	%
Age, years		
Median	57	
Range	36:67	
Sex		
Male	17	70.8%
Female	7	29.2%
PS		
ECOG 1	22	91.7%
ECOG 2	2	8.3%
Primary sites		
Proximal	21	87.5%
Distal	3	12.5%
Pathology differentiation		
Moderate differentiated AC	14	58.3%
Poorly differentiated AC	9	37.5%
Poorly differentiated AC with signet ring	1	4.2%
Clinical radiological staging		
IIB	1	4.2%
III	20	83.3%
IVA	3	12.5%
Radiological tumor (T) staging		
T2	2	8.3%
T3	19	79.2%
T4a	3	12.5%
Radiological LN (N) staging		
N0	5	20.8%
N1	8	33.3%
N2	8	33.3%
N3	3	12.5%
Endoscopic ultrasound assessment		
Not done	20	83.3%
Done	4	16.7%

PS: performance status. ECOG: Eastern Collaborative Oncology Group, AC: adenocarcinoma

Table 2. Radiological and pathological tumor response after receiving CCRT

Characteristic	No. of patients (N=24)	%
Radiological staging		
I	9	37.5%
IIA	5	20.8%
IIB	5	20.8%
III	4	16.7%
IVB	1	4.2%
Radiological tumor (T) staging		
T1	2	8.3%
T2	18	75%
T3	4	16.7%
Radiological lymph node (N) staging		
N0	14	58.3%
N1	5	20.8%
N2	5	20.8%
Radiological M staging		
M0	23	95.8%
M1	1	4.2%
Type of surgery No. of patients (N=22)		
Proximal subtotal gastrectomy	20	90.9%
Total gastrectomy	2	9.1%
Number of lymph nodes excised		
Median number	15	
10-15	13	59.09%
>15	9	40.9%
Surgical margin		
R0	21	95.5%
R2	1	4.5%
Pathological response		
Complete pathological response	7	31.8%
Partial pathological response	14	63.6%
Stable disease	1	4.5%
Post-surgical pathological T staging		
T0	7	31.8%
T2	11	50%
T3	4	18.2%
Post-surgical pathological LN staging		
N0	10	45.5%
N1	9	40.9%
N2	2	9.1%
N3	1	4.5%

R0: complete surgical resection, R2: macroscopic gross residual.

number of excised LN was 15 with nine patients had 15 LN excision. Twenty-one patients had R0 resection margin and only one patient had R2 resection margin (residual non-resected bulky LN).

The pathological response was reported in twenty-one patients (95.5%), with seven patients (31.8%) who had got a complete pathological response (pathCR) which defined as an absence of carcinoma cells in the primary site, and fourteen patients (63.6%) had a partial pathological response (pathPR) which defined as less than 10% of residual cancer cells in the primary site. Only one patient showed no tumor response with stable disease.

The post-surgical pathological staging according to AJCC TNM staging classification (8th ed., 2017) 6, was variable with seven patients had ypT0, while eleven patients were ypT2, and only four patients had ypT3. The post neoadjuvant pathological LN staging was variable with ten patients were staged as ypN0 disease, nine

patients were ypN1, and two patients had ypN2 disease. One patient had ypN3 disease.

3.3 Progression, Mode of Progression, and Death

Twenty-two patients had completed our study protocol. Two patients died from post-surgical complications while 8 patients died from the disease. Nine patients (37.5%) had progression during the follow-up period. The most common site of relapse was peritoneal metastases (4 patients, 44.4%). Two patients (22.2%) showed liver metastases. One patient showed lung metastasis and another patient showed regional LN recurrence, one patient had presented left supraclavicular LN metastasis.

3.4 Survival Results

At a median follow-up period of 90 weeks (22.5 months) (range 33: 123 weeks), the median overall survival was 23.5 months. (94 weeks, 95% confidence interval (CI), 75.45-112.56), while the median PFS was 23 months, (92.13 weeks, 95% CI., 76.85-106.33) (Figs. 1 & 2), Table 3.

Progression was more in patients with the pathology of poorly differentiated adenocarcinoma with a non-significant *P*-value of .092. However, progression decreased significantly in patients who had a complete pathological response (*P*=.029).

A number of deaths was significantly affected by pathological differentiation (*P*=.003), and pathological response type *(P*=.015). The radiological response did not reflect the number of progressions or, the number of deaths with *P*-value of .162, and .217, respectively.

Univariate analysis was done to study factors affecting PFS time, and OS time. Regarding the PFS time, there was a significant correlation with post-CCRT radiological downstaging. Although the patients with a complete pathological response and a pathology of moderately differentiated adenocarcinoma tended to have higher PFS, they did not reach the significant difference with *P* value of .06, .05, respectively.

Among the studied factors for OS time, there was a significant correlation between OS time with the pathological differentiation, and post CCRT radiological response with a significant *P*-value of .015, and .009, respectively. However, survival was not reached in the patients who had a complete pathological response, their OS time tended to be higher with a non-statistically significant *P*-value of .09.

3.5 Toxicities of Chemotherapy and CCRT

Details of acute induction chemotherapy and CCRT-induced toxicities are listed in Table 4. Induction chemotherapy-induced toxicities were only grade one toxicities except one patient who showed grade 2 anemia. For CCRT induced complications many patients had grade 2 toxicities. No reported grade 3 or 4 toxicities. There were only two patients who suffered from late radiation toxicities in the form of distal esophageal stenosis. Twenty-one patients had received the post CCRT chemotherapy. There were no reported grade 4 toxicities. Two cases only suffered from G3 anemia, leukopenia, and one case had developed G3 neuropathy.

3.6 Surgical Complication

Surgical complications (all grades) that had occurred within 30 days from operation were reported, with a median hospital stay of two weeks. The most common complications were cardiac complications followed by pulmonary complications. Two patients had died from post-operative complications, the first patient had anastomotic leakage and uncontrolled mediastinitis, the 2nd one died from respiratory complications (he was smoker with chronic obstructive pulmonary disease).

4. DISCUSSION

In Egypt gastric cancer represents the 14th most common cancer, accounting for 18% of cases in both sexes [7]. According to cancer registry report in Mansoura university hospital, during 2015, Cancer stomach represents only 1.8% of frequencies of all the cancer sites [8]. Thus, explaining the limited number of patients in our study.

Table 3. Median survival time among studied cases

	Median times (weeks)	Median times (months)	95% CI
PFS	92.13	23	76.85-106.33
OS	94.0	23.5	75.45-112.56

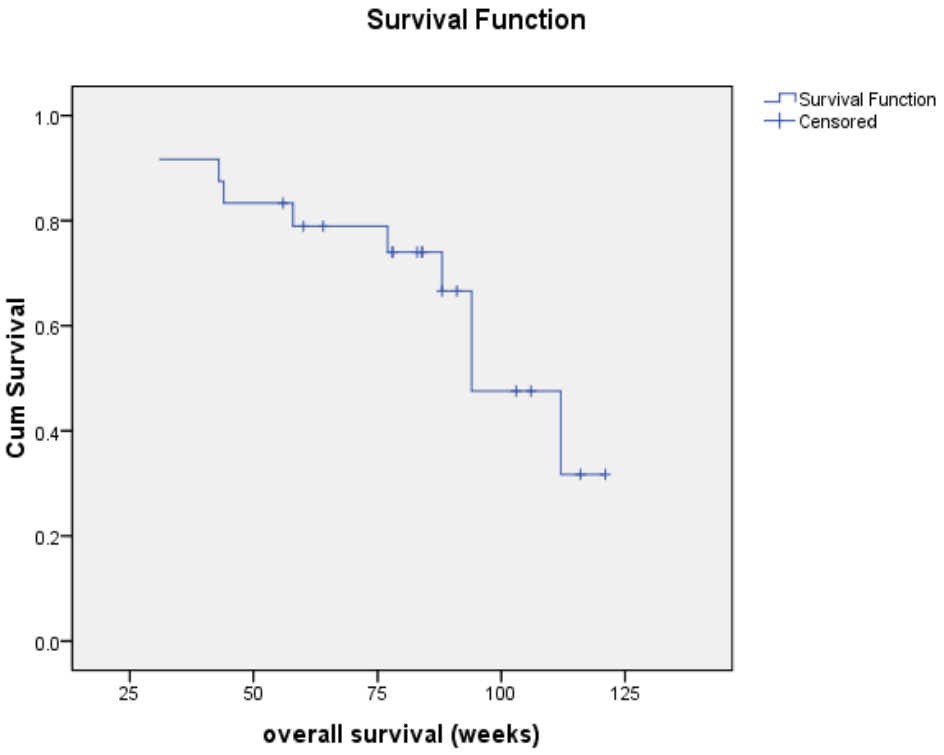

Fig. 1. Kaplan Meier curve showing overall survival in weeks among studied cases

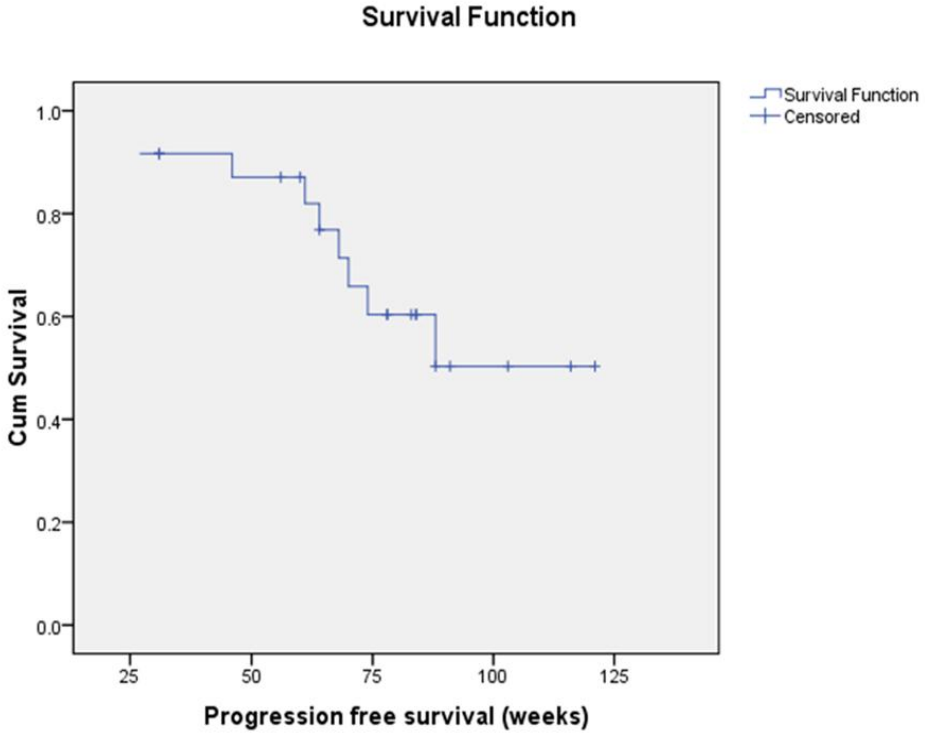

Fig. 2. Kaplan Meier curve showing progression-free survival in weeks among studied cases

Table 4. Induction chemotherapy and CCRT induced toxicities

Toxicity	Induction chemotherapy-induced toxicity grade (N=24)		CCRT induced toxicities grade (N=24)	
	G1 (N&%)	G1 (N&%)	G1 (N&%)	G2(N&%)
Hematological complication				
Anemia	23 (95.8%)	1 (4.2%)	18 (75%)	6 (25%)
Leucopenia	0	0	15 (62.5%)	2 (8.3%)
Thrombocytopenia	2 (8.3%)	0	0	0
Non-hematological complication grading				
Abdominal pain	2 (8.3%)	0	7 (29.2%)	6 (25%)
Diarrhea	0	0	3 (12.5%)	1 (4.2%)
Dysphagia	0	0	14 (70%)	2 (10%)
Vomiting	2 (8.3%)	0	13 (65%)	3 (15%)
Dyspepsia	0	0	6 (25%)	7 (29.2%)
Cough	0	0	10 (41.7%)	3 (12.5%)
Dyspnea	0	0	7 (29.2%)	1 (4.2%)
Fatigue	0	0	15 (62.5%)	9 (37.5%)
Neuropathy	1 (4.2%)	0	4 (16.7%)	2 (8.6%)

**G: grade of toxicity N: number of cases*

Many phase II trials studied the induction chemotherapy followed by CCRT: the multi-institutional trial of preoperative chemoradio-therapy, the RTOG 9904 trial, and the phase II Australian trial. They used 5FU-leucovorin-cisplatine as induction chemotherapy, followed 5FU-potentiated CCRT. Many grades (G) 3 and 4 hematological and non-hemato-logical toxicities were reported during the neoadjuvant treatment except the Australian trial which reported no G4 toxicities [9-11]. However, our patients did not suffer from any G3 or 4 toxicities during neoadjuvant treatment. G3 toxicities were reported only during adjuvant chemotherapy treatment, with no reported grade 4 toxicity. That may denote the tolerability of CCRT with paclitaxel- carboplatin, which was studied in the large CROSS-Phase III trial. The study reported G3 hematologic toxicities of only 7%, and G4 toxicities had occurred in one patient. All other major nonhematologic toxic effects of grade 3 or higher occurred in less than 13% of patients [12].

Regarding treatment response in our study, surgery resulted in R0 margin of 95.5%, ypT0 of 31.8%, and ypN0 of 45.5%. The pathCR was 31.8%, while the pathPR was 63.6% inconsistent with trials that had tested the 5FU based CCRT; the multi-institutional trial of preoperative chemoradiotherapy showed that 85% of the patients (28 patients out of 33 included patients) had undergone surgical resection with R0 resection rate of only 70%. The ypT0 was diagnosed in 10 (36%) of 28 patients undergoing surgery, there were no nodal metastases in 17 patients. Pathological complete response (pathCR) was found in 30%, while 24% had partial pathological response (pathPR) [9]. The phase II Australian trial, the R0 was reported in 84.6% in the CCRT arm, while five patients (13%) had ypT0NOM0, and 6 patients (16%) had N0. The pathCR was 13%, while the major histological response rate (<10% viable cells) was 31% [11]. The phase III Swedish (NeoRes) trial had reported R0 of 74% patients in its CCRT arm with ypN0 of 65%. The pathCR was achieved in 22 patients (28%) [13]. The higher percent of ypT0 & ypN0 of the multi-institutional trial of preoperative chemoradiotherapy might probably be due to the discrepancy in the primary included stages, being 35% of their patients had pretreatment radiologically N0 disease. There were no included patients with T4 tumor [11]. The higher percent of ypN0 in the Swedish trial was mostly related to the percent of pre neoadjuvant treatment clinically negative LN of the included patients (37%) [13]. While the lower percent of pathCR and pathPR of the Australian trial might be referred to the lower dose of RT of only 35 Gy versus 45 Gy in other previously mentioned trials [11]. The CROSS-phase III trial, which studied the paclitaxel-carboplatin CCRT had reported R0 of 92% with 29% pathCR reflecting the efficacy of CCRT with paclitaxel-carboplatin in local control and tumor response [12]. However, this minor difference of the percent of R0 may be probably due to the large number of patients included in this trial (178 patients in the CCRT arm) versus only 24 patients in ours. This might be also due to our longer preoperative treatment of induction chemotherapy followed by CCRT.

With our median follow up of 22.5 months, the median PFS, and OS were 23, and 23.5 months, respectively. Nine patients (40.9%) had relapse, all of them in the form of distant relapse except for one patient who had regional LN recurrence. This high relapse rate could be mostly due to the higher stage of our included patients with almost all patients had ≥ stage III disease. In agreement with phase II RTOG 9904 trial had similar short follow up period with a median of 21.5 months, its median OS was 23.2 months [10].

With longer follow up period ranging from 48 to 84 months, with a median of 50 months, the phase 2 trial of the multi-institutional trial of preoperative chemoradiotherapy median OS was 33.7 months, which magnify the importance of longer follow up is the assessment of OS [9]. The German POET trial had a median follow-up of 46 months with median OS of 33.1 months for the patients who received neoadjuvant chemo-therapy followed by CCRT (cisplatin-etoposide with 30 Gy over 15 treatments). The local and distant recurrence occurred in 9 and 10 patients, respectively which represent about 42.2% [14]. The low dose of radiotherapy might explain the higher local recurrence rate.

Finally, this study has several limitations, being non-comparative single-center design, with a small number of patients, with limited follow-up time. Further larger phase III comparative trial is needed for confirmation of the efficacy and standardization for the treatment protocol.

5. CONCLUSION

The preliminary data suggested a good efficacy of the treatment design with acceptable adverse-event rates which may encourage for larger multicentric phase 3 trial with long follow up period to investigate the same regimen before standardizing it.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed consent has been written before patients' enrolment in the trial.

ETHICAL APPROVAL

The study was approved by IRB unit at the faculty of medicine, Mansoura University.

ACKNOWLEDGEMENTS

Thanks for Mansoura University, prof. Dr. Saleh Mansour Ta-Ema, Prof. Dr. Niveen Ahmed Abo-Touk and Prof. Dr. Mohamed Mahmoud ELawadi for their great efforts in planning and application of this valuable clinical trial.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-2185.
2. Lagarde SM, Cense HA, Hulscher JB et al. Prospective analysis of patients with adenocarcinoma of the gastric cardia and lymph node metastasis in the proximal field of the chest. Br J Surg. 2005;92(11):1404-1408.
3. Xiong BH, Cheng Y, Ma L, Zhang C QJCi. An updated meta-analysis of randomized controlled trial assessing the effect of neoadjuvant chemotherapy in advanced gastric cancer. Cancer investigation 2014;32(6):272-284.
4. Stahl M, Walz MK, Stuschke M et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esopha-gogastric junction. J Clin Oncol. 2009;27 (6):851-856.
5. Schag CC, Heinrich RL, Ganz PAJJoCO. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2(3):187-193.
6. In H, Solsky I, Palis B et al. Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the national cancer database. Annals of Surgical Oncology. 2017;24(12):3683-3691.

7. Ibrahim AS, Khaled HM, Mikhail NN, et al. Cancer incidence in egypt: Results of the national population-based cancer registry program. J Cancer Epidemiol 2014;2014: 437971.
8. Abo-Touk NA. Cancer registry report in Mansoura University Hospital, Egypt in 2015. In Forum of Clinical Oncology. 2019; 10(2):26-33.
9. Ajani JA, Mansfield PF, Janjan N, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol. 2004;22(14):2774-2780.
10. Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. J Clin Oncol. 2006;24(24):3953-3958.
11. Burmeister BH, Thomas JM, Burmeister EA et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Best Practice & Research Clinical Gastroenterology. 2011;47(3):354-360.
12. Van Hagen P, Hulshof M, Van Lanschot J, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. New England Journal of Medicine. 2012;366 (22):2074-2084.
13. Klevebro F, Alexandersson von Dobeln G, Wang N et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-667.
14. Stahl M, Walz MK, Riera Knorrenschild J et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. European Journal of Cancer. 2017;81:183-190.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/65668