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ORIGINAL ARTICLE

Operative, Peri-Operative and Long-Term Oncological Benefits of Performing Open and Laparoscopic Gastrectomy for Management of Gastric Cancer Patients: A Comparative Study

Walid A. Mawla^{1*}, Taha A. Baiomy¹, Mohamed I Abdelhamid¹, Shady E. Shaker² Ahmed M. Elsayed³, Rehab Hameda⁴, Ibrahim Heggy¹

1. General Surgery department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

2. Internal Medicine department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

3. Tropical Medicine, Faculty of Medicine department, Zagazig University, Zagazig, Egypt

4. Clinical Oncology and Nuclear Medicine department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

*Corresponding Author:

Walid A. Mawla

General Surgery Department,
Zagazig University (MD),
Zagazig, Egypt.

E-mail:

walidabdelmawla@gmail.com

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ABSTRACT

Background: Laparoscopic assisted gastric resection (Laparoscopic gastrectomy LG) has become increasingly done, as there is marked improvement in equipment and experiences of surgeons regarding such minimally invasive procedures to the degree that many centers now performed LG as a routine resection method of the stomach in locally advanced gastric cancer.

The aim: is to compare between open gastrectomy and LG as management procedures for cancer stomach regarding operative, perioperative and detailed long-term, patients follow-up oncologic outcomes and survival benefits.

Methods: We performed this prospective study on 30 patients with confirmed gastric cancer. We divided patients into 2 equal groups, performed open gastrectomy for the first group and LG for the second group followed our patients for 5 years. We compared between groups regarding; operative, perioperative, postoperative parameters, recurrence and survival rates.

Results: Our results showed that the LG group has longer operating time, less amount of blood loss ($p < 0.001$), time of starting liquid diet ($P = 0.049$), and shorter period of postoperative hospital stay ($P = 0.043$). Wound and abdominal wall complications were significantly lower in the LG group ($p = 0.008$). The 5-year overall survival (OS), disease-free survival rates and recurrence of cancer are similar in both groups ($P > 0.05$).

Conclusions: We found that LG is an effective and safe surgical modality that is better than open approach in management of gastric cancer regarding; early recovery and less peri-operative morbidity, wound infection and respiratory complications.

Keywords: Gastric cancer, Laparoscopic gastrectomy, Open gastrectomy; Outcomes

INTRODUCTION

Cancer stomach ranked as the 4th cancer related death cause [1]. Although there is a major advancement in its management due to the introduction of novel chemotherapeutic regimens but surgery is still the only curative therapy. There is marked improvement which has occurred in this particular field with introduction of minimally invasive laparoscopic surgery. The most important

parameter of success of such procedure is adequate lymphadenectomy in addition to negative resection of the resected margin that needs to be near open procedure, as if laparoscopic surgery could not offer similar quality to their open counterpart, surgeons would not be encouraged to perform such procedure [2]. Laparoscopic assisted gastric resection (Laparoscopic gastrectomy LG) has become increasingly done since it has been described by

Kitano et al. in 1994 [3]. Since then there is marked improvement in techniques, equipment and experiences of surgeons regarding such minimally invasive procedures to the degree that many centers now performed LG as a routine resection method of the stomach in locally advanced gastric cancer due to its safety, feasibility and encouraging short term perioperative outcome [4, 5]. As most previous studies were retrospective which studied only short term oncologic outcome, but the operative, perioperative and detailed long-term and follow-up oncologic outcomes of performing LG as a management procedure for cancer stomach have not been detailed yet.

The aim of current study is to compare between open gastrectomy and LG as management procedures for cancer stomach regarding operative, perioperative and detailed long-term, patients follow-up oncologic outcomes and survival benefits.

METHODS

We collected information prospectively from our included 30 patients with confirmed resected gastric cancer. Divided patients into 2 equal group; first group underwent open gastrectomy with lymphadenectomy and the other group underwent LG with lymphadenectomy in the period between March 2015 and April 2020. The study was approved by the local ethics committee of Faculty of Medicine, Zagazig University.

Cases were admitted and surgically operated in General Surgery department, Oncology Unit, Zagazig University Hospitals. After endoscopic gastric biopsy which is taken in Hepatology and Gastroenterology unit in Internal Medicine Department, Faculty of Medicine, Zagazig University. All samples are sent to Pathology Department, Faculty of Medicine, Zagazig University for processing, diagnosis, grading and staging.

Pathologic staging made according to the American Joint Committee on Cancer (AJCC) staging system of cancer stomach 8th edition [6].

The inclusion criteria were as follow; Histopathologically confirmed adenocarcinoma of the stomach of variable stages and grades. Patients' age ranged from 18 to 65 years. Patients with no distant organ metastasis. No history of previous administration of chemotherapeutic agents or previous surgical management of gastric malignancy.

The exclusion criteria were as followed; Cases with cancer of other histopathological subtypes as, squamous cell carcinoma and gastrointestinal stromal tumors. Cases underwent conversion of approach from LG to OG. We have evaluated patients in the preoperative period by performing; upper gastrointestinal endoscopy, complete blood count, renal and liver-function tests and electrocardiogram. Preoperative radiological evaluation included CT-scan of the thorax, abdomen and pelvis.

Our patients were randomizedly arranged into two groups based on computer system (open or laparoscopic gastrectomy)

We performed total or partial gastrectomy according to tumor site. The dissection of lymph was performed in both included patients groups according to the Japanese guidelines [7].

We have assessed all patients' demographic, clinical and pathological parameters as age, sex, resection extent, tumor grade, size, histopathological subtype, number and extent of lymph nodes spread and pTNM stage.

Written informed consent was obtained from all participants. The study was done according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Surgical procedure

Laparoscopic surgical technique [8] :Detailed procedure: we have established a pneumoperitoneum with CO₂ at 15 mmHg and we have utilized 6 laparoscopic ports and a 30° scope. We divided the esophagus, the stomach and the duodenum by a 60 mm linear stapler. We extracted the resected surgical specimens through a suprapubic incision of about 4 cm. We performed a mechanical intra-corporeal gastro-jejunostomy after distal subtotal gastrectomy, and performed an oesophago-jejunostomy (EJ) with a Roux-en-Y reconstruction.

Open surgical technique [9]: We used epidural analgesia and utilized a mid-line laparotomy. We divided the esophagus, the stomach and the duodenum by a 60 mm linear stapler used a similar vessel-sealing device in open surgery to LG. We have sectioned the esophagus and prepared it for esophago-gastric anastomosis.

Immediate extubation was favored in postoperative period, physical and respiratory therapy has been begun for operated patients at the earliest. We have maintained epidural analgesia for 3 days in open

gastrectomy, keep the nasogastric tube in its place for about 4 days after subtotal gastrectomy and performed an oral contrast study about 3-7 days after a total gastrectomy. Finally we discharged the patients after they become able to tolerate a soft diet for about 24 h.

Any abnormal changes that were different from the usual postoperative period of elective gastrectomy during hospital stay or up to thirty days would be considered postoperative complications. We considered readmission for up to sixty days after operation. We monitored all operative data as operative time and amount of intra-operative blood loss.

Postoperative assessment and follow-up: In the postoperative follow-up period we performed a full physical examination, laboratory blood tests, upper gastrointestinal endoscopy, and ultrasonography or computed tomography.

We monitored postoperative complications which have been occurred within thirty days after surgery. We followed our patients every three months during the 1st two 2 years after operation and then every six months from two to 5 years to detect recurrence and survival rates.

We give post-operative adjuvant chemotherapy to all patients with stage II and II [4].

STATISTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analysed using Microsoft Excel software. Data were then imported

into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis.

RESULTS

The study included 30 patients with gastric cancer. All patients included 22 (73.3%) males and 20 (66.7%) patients were >60 years old and 15 (50%) patients have associated comorbidities. The age and sex of patients, comorbidities, histopathological subtype, size, site, grade and stage of the tumor and extent of gastrectomy or degree of dissection of lymph nodes have not significantly differed between both surgical groups (Table 1).

Short-term intra and post-operative surgical findings: Detailed data about both intraoperative and post-operative results of the two studied groups was revealed in (Table 2). The LG group has longer operative time, less blood loss (p<0.001), shorter duration of starting liquid diet (P=0.049), and shorter period of postoperative hospital stay (P=0.043).

The overall rate of postoperative complication rate (leakage, bleeding, stricture, pneumonia or pulmonary embolism) tended to be lower in the LG group, but this difference was not significant. Wound and abdominal wall complications were significantly lower in the LG group (p=0.008).

Follow-up and Long-term patients' survival : After a median follow-up of 37 months, the 5-year overall survival (OS), Disease-free survival rates and recurrence of cancer (Table 3) are similar in both groups (P > 0.05).

Table (1) Comparison between the studied surgical techniques regarding demographic, pathological, operative data:

Variables	Total N=30 (%)	Surgical techniques		Test	
		Open gastrectomy N=15 (%)	Laparoscopic gastrectomy N=15 (%)	X ² /t	P
		Age groups:			
<60 years old	10 (33.3)	6 (60)	4 (40)	0.6 [∞]	0.439
>60 years old	20 (66.7)	9 (45)	11 (55)		
Gender:					
Male	22 (73.3)	11 (50)	11 (50)	0 [∞]	1
Female	8 (26.7)	4 (50)	4 (50)		
Comorbid condition:					
Absent	15 (50)	10 (66.7)	5 (33.3)	3.333 [∞]	0.068
Present	15 (50)	5 (33.3)	10 (66.7)		
Size of ulcer (cm):					
< 5 cm	9 (30)	5 (55.6)	4 (44.4)	1.026 [∞]	0.311
≥ 5 - 10 cm	21 (70)	10 (47.6)	11 (52.4)		
Histopathological type:					

Variables	Total	Surgical techniques		Test	
		Open gastrectomy	Laparoscopic gastrectomy	X ² /t	P
		N=30 (%)	N=15 (%)	N=15 (%)	
Intestinal	21 (70)	12 (57.1)	9 (42.9)	1.429 [∞]	0.232
Diffuse	9 (30)	3 (33.3)	6 (66.7)		
Initial site:				0.889 [∞]	0.641
Proximal	6 (20)	4 (66.7)	2 (33.3)		
Distal diffuse	18 (60)	8 (44.4)	10 (55.6)		
Grade:				1.51 [∞]	0.47
Poor	11 (36.7)	4 (36.4)	7 (63.6)		
Moderate	13 (43.3)	8 (61.5)	5 (38.5)		
Well	6 (20)	3 (50)	3 (50)		
T stage:				0.286 [∞]	0.991
T1a	7 (23.3)	3 (42.9)	4 (57.1)		
T2	4 (13.4)	2 (50)	2 (50)		
T3	6 (20)	3 (50)	3 (50)		
T4a	7 (23.3)	4 (57.1)	3 (42.9)		
T4b	6 (20)	3 (50)	3 (50)		
N stage:				0.311 [∞]	0.958
N0	10 (33.3)	5 (50)	5 (50)		
N1	6 (20)	3 (50)	3 (50)		
N2	5 (16.7)	2 (40)	3 (60)		
N3	9 (30)	5 (55.6)	4 (44.4)		
Stage:				3.111 [∞]	0.795
IA	4 (13.3)	2 (50)	2 (50)		
IB	4 (13.3)	1 (25)	3 (75)		
IIA	4 (13.3)	3(75)	1 (25)		
IIB	6 (20)	3 (50)	3 (50)		
IIIA	1 (3.3)	0 (0)	1 (100)		
IIIB	2 (6.7)	1 (50)	1 (50)		
IIIC	9 (30)	5 (55.6)	4 (44.4)		
Number of retrieved lymph node:				0.556 [∞]	0.757
1-14	9 (30)	4 (44.4)	5 (55.6)		
15 – 25	9 (30)	4 (44.4)	5 (55.6)		
>25	12 (40)	7 (58.3)	5 (41.7)		
Margin status:				Fisher	1
Free	16 (86.7)	13 (50)	13 (50)		
Invaded	4 (13.3)	2 (50)	2 (50)		
Type of gastrectomy:				0.952 [∞]	0.621
Total	14 (46.7)	6 (42.9)	8 (57.1)		
Distal	10 (33.3)	5 (50)	5 (50)		
Proximal	6 (20)	4 (66.7)	2 (33.3)		
Operation time:				-5.961 [#]	<0.001**
Mean ± SD	198.33±52.68	159.6±42.81	237.07 ± 26.47		
Range	20 – 300	20 -200	200 - 300		
Estimated blood loss (ml)				3.95 [#]	<0.001**
	193.83±51.41	224.07 ± 41.4	163.06 ± 42.45		

Variables	Total	Surgical techniques		Test	
		Open gastrectomy	Laparoscopic gastrectomy	X ² /t	P
		N=30 (%)	N=15 (%)	N=15 (%)	
Mean ± SD	20 – 300	130 – 300	20 - 200		
Range					

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant

∞ Chi square test #Independent sample t test

Table (2) Comparison between the studied surgical techniques regarding postoperative complications and patient outcome (recurrence and death):

Variables	Total	Surgical techniques		Test	
		Open gastrectomy	Laparoscopic gastrectomy	X ² /Z	P
		N=30 (%)	N=15 (%)	N=15 (%)	
Postoperative complication:					
Absent				Fisher	0.651
Present	24 (80)	11 (45.8)	13 (54.2)		
	6 (20)	4 (66.7)	2 (33.3)		
Postoperative wound infection:					
Absent	18 (60)	5 (27.8)	13 (72.2)	Fisher	0.008*
Present	12 (40)	10 (83.3)	2 (16.7)		
Recurrence:					
Absent	10 (33.3)	5 (50)	5 (50)		
Present	20 (66.7)	10 (50)	10 (50)	0 [∞]	1
Death:					
No	16 (53.3)	8 (50)	8 (50)		
Yes	14 (46.7)	7 (50)	14 (50)	0 [∞]	1
Time to start liquid diet(hours):					
Mean ± SD	2.87 ± 0.5	3.01 ± 0.54	2.73 ± 0.43	1.619	0.049
Range	2 – 4	2 – 4	2 – 3		
Time of first flatus:					
Mean ± SD	2.87 ± 0.5	3.01 ± 0.54	2.73 ± 0.43	1.619 [#]	0.049
Range	2 – 4	2 – 4	2 – 3		
Postop hospital stay (days):					
Mean ± SD				1.086 [#]	0.043
Range	7.37 ± 1.54	7.07 ± 1.84	7.07 ± 1.84		
	5 – 11	5 – 9	5 – 11		
Recurrence free survival:					
Median	28.53 ±	28.2 ± 15.46	28.87 ± 15.32	-0.249 [¥]	0.769
Range	15.12	7 – 58	5 – 15		
	7- 58				
Overall survival:					
Median	30.2 ±13.91	30.2± 14.15	8	0 [¥]	1
Range	11 – 58	11 – 58	11- 58		

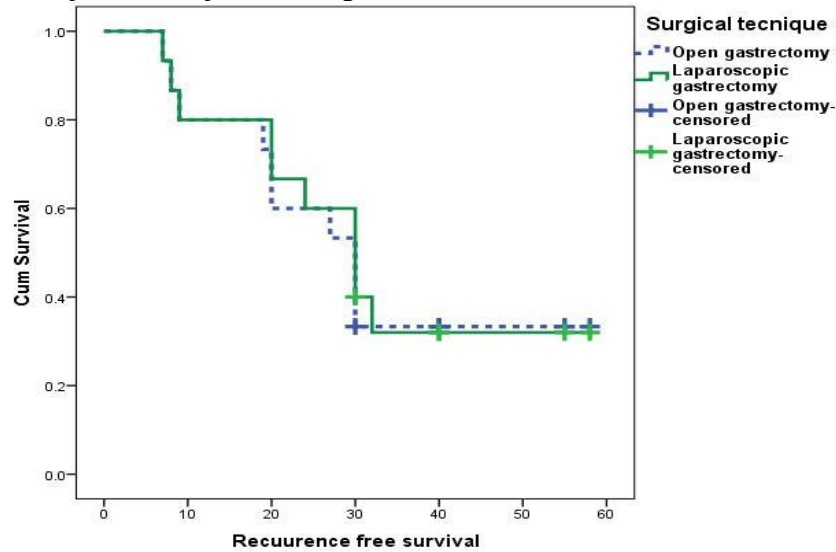
*p<0.05 is statistically significant **p≤0.001 is statistically highly significant

¥Mann Whitney test ∞ Chi square test #Independent sample t test

Table (3) Comparison between the studied groups regarding recurrence free survival and overall survival

Time	Initial Management techniques				Mantel cox test
	Open gastrectomy		Laparoscopic gastrectomy		
	Mean	SEM	Mean	SEM	P
RFS	32.67	4.99	32.99	4.92	0.868
OS	39.59	5.16	39.59	5.16	1

Figure (1-A) Kaplan Meier plot showing recurrence free survival (time to recurrence) among



patients underwent different surgical techniques (Mean RFS in open gastrectomy was 32.67 while mean RFS in laparoscopic gastrectomy was 32.99 with a statistically non-significant difference between them, $p > 0.05$)

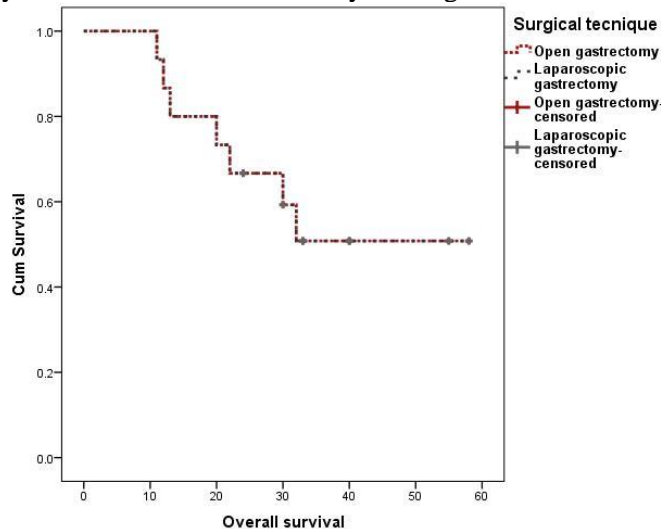


Figure (1-B) Kaplan Meier plot showing overall survival (time to death) among patients underwent different surgical techniques (both had equal mean OS which was 39.59)

DISCUSSION

The first LG was done more than twenty years ago, there is a controversy regarding the use of LG in

management of gastric cancer due to insufficient studies about its long-term oncologic outcomes [10]. Most previous studies which have compared

LG with open gastrectomy included only a small number of patients and just focused on the short-term and the perioperative outcomes, as intra-operative bleeding, operative time and postoperative complications [11]. In the present study we have showed that LG was better than open gastrectomy in treatment of gastric cancer regarding; operative, peri-operative, post-operative and long term outcomes as it is associated with less amount of intra-operative blood loss, early starting oral intake and shorter duration of postoperative hospital stay. So the advantages of the laparoscopic approach could be applied to gastric cancer patients. Our results are similar to many previous recent studies [4, 10-14].

We showed a lower incidence of abdominal wound infection and local complication, additionally we showed a lower incidence of respiratory complications in LG than in open gastrectomy due to early movement and shorter time of hospital stay. **NORERO et al.**, [10] **Kim et al.**, [15] and **Marrelli et al.** [16], showed similar results.

Many studies have showed the rate of postoperative complication in patients that underwent LG was less than those of patients that underwent open gastrectomy, that was near to our results [4, 5, 17].

We have showed that there were no significant differences between the two operated groups of patients regarding incidence of complications.

Regarding follow-up and survival results our results and results of **NORERO et al.** [10] study supports a similar rates of overall and disease-specific survival in both operated groups. The number of excised lymph nodes is considered an indicator of the success of complete lymph node dissection. **NORERO et al.** [10] study, and our study showed that number of dissected lymph nodes was similar in both LG and open gastrectomy groups, highlighting the success in doing a complete lymphadenectomy using the laparoscopic approach. Previously published studies showed different results are conflicting; Wada A et al, 2018 showed a lower number of excised lymph nodes. An important parameter of success of surgical excision of cancer stomach is the negative surgical margin (R0) and we showed that the rate of R0 resection was the same in both groups.

Another important indicator of success of the surgical technique is long term sequel and survival rates that we showed that they are similar in both groups.

So the three most important oncologic outcomes in our study; number of dissected lymph nodes, surgical resection margins, rates of overall and disease-specific survival, highlighting the oncologic similarity between laparoscopic assisted gastric resection and open gastrectomy for treatment of cancer stomach.

Previous studied have reported that the survival rates of patients underwent LG are similar with those who surgically managed by open gastrectomy [14, 19, 20]. Although their results were similar to our results but they were retrospective studies while our study is better as it is a prospective study. Regarding recurrence rate we showed that the rate and pattern of recurrence was not differed between the two included groups, so LG has not increased peritoneal recurrence rate in comparison to OG. Similarly, many studies showed that LG has not promoted peritoneal recurrence of gastric cancer [20, 21].

CONCLUSION

We found that LG is a safe and effective surgical modality that is better than open approach in management of gastric cancer regarding; early recovery and less peri-operative morbidity, wound infection and respiratory complications. Additionally LG provides nearly similar number of resected lymph nodes, resection margins R0 and similar survival and oncologic outcomes when compared to the open approach.

Conflict of interest: None

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REFERENCES

1. F. Bray, J. Ferlay, I. Soerjomataram et al., "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," CA: A Cancer J. for Clinic.2018; 68(6); 394–424.
2. Chevally M, Jung M, Berlth F et al. Laparoscopic Surgery for Gastric Cancer: The European Point of View J. Onc. 2019.
3. S.I.Y. Kitano, M. Moriyama, K. Sugimachi, Laparoscopy-assisted billroth I gastrectomy, Surg. Laparosc. Endosc. 1994;4; 146–148.
4. Li Z, Liu Y, Hao Y, Bai B, Yu D, Zhao Q. Surgical and long-term oncologic outcomes of laparoscopic and open gastrectomy for serosa-positive (pT4a) gastric cancer: A propensity score-matched analysis. Surg. Onc. 2019; 28: 167–3
5. Y.K. Park, H.M. Yoon, Y.W. Kim et al., Laparoscopy-Assisted versus open D2 distal gastrectomy for advanced gastric cancer: results from a randomized phase II multicenter clinical trial (COACT 1001), Ann. Surg. 2017;42: S98–S9.

6. T. Sano, D.G. Coit, H.H. Kim et al., Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project, *Gastric Canc. Off. J. Int. Gastric Cancer Assoc.* 2017; 20: 217–25.
7. Association JGC. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer.* 2017; 20(1):1-19.
8. Norero E, Muñoz R, Ceroni M et al. Two- Layer Hand-Sewn Esophagojejunostomy in totally laparoscopic total gastrectomy for gastric cancer *J. Gastric Cancer.* 2017; 17(3):267-76.
9. Pereira MA, Ramos MFKP, Dias AR et al. Detection of occult lymph node tumor cells in node-negative gastric cancer patients. *Arq Bras Cir Dig.* 2017; 30(1):30-34.
10. Norero E, Vargas C, Achurra P et al., survival and perioperative morbidity of totally laparoscopic versus open gastrectomy for early gastric cancer: analysis from a single latin american centre. *Arq Bras Cir Dig.* 2019;32(1):e1413.
11. Honda M, Hiki N, Kinoshita T et al. Long term outcomes of laparoscopic versus open surgery for clinical stage I gastric cancer: The LOC-1 Study. *Ann Surg.* 2016; 264(2):214-22.
12. Brian YO Chan, Kelvin KW Yau, Canon KO Chan. Totally laparoscopic versus open gastrectomy for advanced gastric cancer: a matched retrospective cohort study *Hong Kong Med J* 2019; 25:30–7.
13. Beyer K, Baukloh AK, Kamphues C et al. Laparoscopic versus open gastrectomy for locally advanced gastric cancer: a systematic review and meta-analysis of randomized controlled studies. *World J. of Surg. Oncol.* 2019; 17:68
14. M. Inokuchi, M. Nakagawa, T. Tanioka et al. Long- and short-term outcomes of laparoscopic gastrectomy versus open gastrectomy in patients with clinically and pathological locally advanced gastric cancer: a propensity score matching analysis, *Surg. Endosc.* 2018; 32:735–742.
15. Kim YW, Yoon HM, Yun YH et al. Long-term outcomes of laparoscopy-assisted distal gastrectomy for early gastric cancer: result of a randomized controlled trial (COACT 0301). *Surg Endosc.* 2013; 27(11):4267-76.
16. Marrelli D, Morgagni P, de Manzoni G et al. Prognostic value of the 7th AJCC/UICC TNM classification of noncardia gastric cancer: analysis of a large series from specialized Western centers. *Ann Surg.* 2012; 255(3):486-91.
17. Y. Shi, X. Xu, Y. Zhao et al. Short-term surgical outcomes of a randomized controlled trial comparing laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer, *Surg. Endosc.* 2018; 32: 2427–2433.
18. Y. Quan, A. Huang, M. Ye et al. Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis, *Gastric Cancer: Off. J. Int. Gastric Cancer Assoc.* 2016;19: 939–950.
19. J.X. Lin, C.M. Huang, C.H. Zheng, et al. Is all advanced gastric cancer suitable for laparoscopy-assisted gastrectomy with extended lymphadenectomy? A case-control study using a propensity score method, *Ann. Surg. Oncol.* 2016; 23: 1252–1260.
20. T. Son, W.J. Hyung, J.H. Lee et al., Minimally invasive surgery for serosa-positive gastric cancer (pT4a) in patients with preoperative diagnosis of cancer without serosal invasion, *Surg. Endosc.* 2014; 28: 866–874.
21. T. Shinohara, S. Satoh, S. Kanaya et al., Laparoscopic versus open D2 gastrectomy for advanced gastric cancer: a retrospective cohort study, *Surg. Endosc.* 2013; 27: 286–294.

Mawla, W., Baiomy, T., Abdelhamid, M., Shaker, S., Elsayed, A., Hemeda, R., Heggy, I. Operative, peri-operative and long-term oncological benefits of performing open and laparoscopic gastrectomy for management of gastric cancer patients: A comparative study. *Zagazig University Medical Journal*, 2022; (720-727): -. doi: 10.21608/zumj.2020.29434.1841