Gastric Cancer Surgical Experience from a single expert western center: case series results
Luigina Graziosi, MD, Phd; Elisabetta Marino, MD; Stefano Avenia, MD; Maria Cristina Vannoni, MD; Annibale Donini, MD.

aGeneral and Emergency Surgery, Santa Maria della Misericordia Hospital, University of Perugia, Via G.Dottori, 06132, Perugia, Italy

Corresponding author:
Elisabetta Marino,
General and Emergency Surgery, University of Perugia
Via G.Dottori, 06132, Perugia, Italy
Email: elisabetta.marino1986@gmail.com
Abstract

Background

Surgical treatment plays a key role in the cure of gastric cancer. Our aim was to analyzed changes both in outcomes and in the epidemiology, over a time period of 15 years.

Methods

410 patients operated between January 2004 and December 2018 were enrolled. Patients were subdivided into 3 groups. The entire cohort was evaluated, and a more detailed analysys was made in patients that underwent a curative surgery. Survival outcomes and oncological surgical outcomes have been described and correlated with Overall Survival.

Results

Results showed an increase trend in gastric cancer operation over the time period analyzed ( p< 0.05).Overall and disease free survival did not vary in the different time periods.

In patients treated with the intent to cure: 5- and 10-Year survivals were respectively: 44% and 34.7%; 5- and 10 years disease free survival were 50.7 and 49.4%. Type of lymphadenectomy and number of lymphondal harvested changed significantly over the time (p < 0.05).

Conclusions

Gastric surgery must be done in an experienced center to obtain oncological outcomes; in selected cases an extended lymphadenectomy could give survival benefit to patients with locally advanced gastric cancer.

Key words: gastric surgery; lymphadenectomy; minimally invasive.
Background

According to GLOBOCAN 2018 data, gastric cancer (GC) is the third leading cause of cancer deaths worldwide [1].

Despite the continuing advancements in chemotherapy and the advent of new biological chemotherapies, GC mortality rate did not vary during the last three decades. [2] Surgery remains the main treatment playing a key role in the cure of this tumor [3;4].

Timing of the surgical approach as respect to chemotherapy administration, extension of lymphadenectomy, surgeon learning curves and consequently high volume centers versus low volume centers are some of the main debated issues in the world health policy; both in Eastern and Western countries.

Morover many controversies exist about indications for minimally invasive surgical approach in treating locally advanced tumors; the main concerns are the possibility of reaching correct oncological results, and feasibility of extended adequate lymphadenectomy (5).

In our region, in particular in the so-called “Alta Valle del Tevere” Area, the incidence of GC is similar to that reported in eastern countries probably for similar eating habits. The 5 years overall survival rate is too low (about 30%) and it is quite stable in the last years [6].

Our surgical department can be defined as a “center of excellence” for the management of GC on the basis of the annual number of GC surgical procedures performed in our department.

The aim of our study was to retrospectively analyze a single surgical center experience in order to evaluate oncological outcomes over a time period of 15 years.
Methods

All consecutive gastrectomies for gastric cancer performed between January 2004 and December 2018, were retrospectively registered and extracted from a database to evaluate surgical and oncologic outcomes that were examined according to three distinct time periods.

A written consent to anonymously collect and retrieved data was obtained from all the patients, according to our hospital regulation.

A total of 410 patients were enrolled in the study; average age of the entire population was 71,65 ± 11,09 and the female to male ratio was 153/257.

Patients were subdivided into 3 groups on the basis of the period during which they were operated upon obtaining three groups of 5 years each (2004-2008, 2009-2013; 2014-2018).

The entire cohort was firstly evaluated, and then a more detailed analysis was made only in patients that underwent curative surgery for gastric adenocarcinoma, excluding palliative surgical treatments.

Clinical pathological characteristics of the studied population are represented in Table 1. Overall survival and disease free survival were globally analyzed and a univariate analysis was done in order to identify statistically significant prognostic factors of survival.

Statistical analysis

Descriptive data were expressed as means (+/-standard deviation) or medians (range or IC 95%) for quantitative variables and numbers (percentages) for qualitative variables. The continuous variables were converted into binary categories and compared using Ki-square test or Fisher test when appropriate. The probabilities of survival were calculated
according the Kaplan-Meier method. The comparison of the survival curves was carried out by the Log Rank test. The significance threshold was retained for $p < 0.05$. 
Results

From January 2004 to December 2018 a total of 410 gastric surgical procedures were performed.

Between 2004-2008, 100 procedures were performed in our center; of these: 5% of them were done for tumours other than adenocarcinoma and 4% consisted in palliative treatments. 3% of all the procedures were approached in a minimally invasive way.

Between 2009-2013, 107 procedures were performed; of these 13.1% were done for tumours other than adenocarcinoma and 14.9% were palliative surgical procedures. In this period 1.9% of all the procedures were minimally invasive approached.

Between 2014-2018, 203 procedures were performed; of these 8.4% were done for tumors other than adenocarcinoma and 14.8% were palliative treatment. A percentage of 21.7% of all the procedures were minimally invasive approached.

These results showed an increased trend in the number of GC surgical procedures over the time period analyzed (p< 0.05) as shown in Supplementary Figure 1.

5 and 10 Year survival (5Y-OS, 10Y-OS) of all the series were respectively: 40 and 32%, whereas 5 and 10 Years disease free survival (5Y-DFS, 10Y-DFS) were both 50 % (Figure 1). Dividing the entire cohort according to the three time periods, did not shown any statistical differences, however there is an interesting and clear trend in favour of the last surgical period included between 2014 and 2018 (Supplementary Figure 2, P=0.08).

Lauren’s istotype and stages distribution did not differ between the three periods, whereas tumor location changed over the considered time period in a statistical significant way (P= 0.008) showing a higher incidence of distal location in the last period.

Secondly, we performed our analysis only in patients treated with the intent to cure, excluding thus palliative treatments (PT) and patients affected by tumor other than
adenocarcinomas (TOTA). The trend for palliative treatment seems to increase over the time as shown by Figure 2.

5 and 10Y-OS were respectively: 44% and 34.7%; 5 and 10Y-DFS were 52 and 50%. As previous, dividing the series into the three time period, survival outcomes did not changed in a statistically significance way.

Tumor location changes remained the same observed above reporting an evident and statistically significant increasing of distal tumor location over the three decades of years (Supplementary Figure 3).

Moreover also the type of lymphadenectomy and the number of lymphonodal harvested changed significantly over the time period analysis with a shift towards the standardization of D1 lymphadenectomy in early gastric cancer, elderlies or not fit patients; D2 lymphadenectomy in locally advanced gastric cancer performing in some selected cases a D3 lymphadenectomy (Figure 3a, p < 0.05). Furthermore a greater number of lymphonodal were harvested over the time periods (Figure 3b, p < 0.05) according to the median value.

Observing the last period and the extension of lymphadenectomy in function of the “T” and “N” parameter, it’s clear the increasing of D3 lymphadenectomy especially in T3/T4a and N3 patients (figure 4).

Analyzing overall survival according to the lymphadenectomy approach, there was a statistically significant difference only in the last time period (2014-2018), showing a better prognosis in patients that underwent D2 or D3 lymphadenectomy (Figure 5).

Over the time period analyzed there was an increase of the neoadjuvant treatments, but significant survival advantage difference was not seen in our results.
Discussion

Overtime, surgery remained the main choice to cure locally advanced GC patients; since 1980, Eastern surgeons have adopted a D2 lymphadenectomy as the oncologically correct surgical approach [7;8]. Since then, slowly all the major European centers have adopted this surgical behavior of treatment except in the USA where, NCCN guidelines too, are currently recommending a D1+ or a modified D2 lymph node dissection for the management of a locally advanced disease [9]. During the last two decades, centers that experienced D2 lymphadenectomy have increased improving their learning curve and becoming expert institutions where to treat GC patients. This has caused an increasing of the total number of the removed lymphonodes, a better staging of the tumor and a survival benefit.

In selected patients, oncological surgeons are now recommending an extended D3 lymphadenectomy that includes posterior lymphonal stations; this approach seems to convey survival advantages in particular in locally advanced neoplasia with serosa or/and lymphonal involvement, diffuse and proximal tumors, as the Italian Group of Gastric Cancer Research Group demonstrated [10].

Without an adequate screening program, similar to the one adopted in the East, patients in our region typically show at the diagnosis symptoms related to the disease and they are often affected by an advanced disease that could not benefit by an endoscopic treatment as opposed to what it happening in a high percentage of the Eastern patients.

Thus, we usually approach these patients in a multimodal manner integrating neoadjuvant treatments to surgery accompanied by an extended lymphadenectomy in selected cases.
Bencivenga M. recently demonstrated that a D3 lymphadenectomy could be addressed in T3 patients improving in a statistically way survival outcomes. This could be explained by the fact that the costs of a super-extended lymphadenectomy exceed the benefits in less advanced cancers as pT2-N0 stages but also in pT4b when cancer cells have already invaded the surrounding organs and a more aggressive nodal dissection is not sufficient to obtain a local control of the disease [11].

These Italian findings are confirmed by JOCG trial that also shows that a D3 lymphadenectomy might be associated with better survival in patients with tumors with subserosal invasion and not in early or more advanced disease [12].

Considering our center, D3 lymphadenectomy has increased over the years in particular in the last five years period and in T3/T4a patients, these changes can be see also in others Western and Eastern surgical centers. Although a longer follow-up is needed, D3 seems to convey an exciting 5y-OS in patients who underwent an extended lymphadenectomy compared to D1/D2 patients (90% vs 48% vs 51%).

Performing this procedure does not implicate in our patients major complications. Certainly we know that a D3 dissection is indisputably a more technically complicated and time consuming surgical procedure compared to D1 or D2. As a matter of fact, it requires dissection around large important vessels that are located in deep retroperitoneal space causing a major surgical stress and injury. Available data suggest that D3 can be safely performed only if done in high expert volume specialized centers and by adequately trained surgeons [13].

In addition our study shows an evident increasing of mini-invasive procedures in the last five year thanks to an improved learning curve and to the introduction of robotic approach that makes easier and more feasible sovrapancreatic lymphadenectomy.
According to Italian and Japanese guidelines we approach only early disease in a mini invasive way. Laparoscopic surgery can be considered as an option to treat exclusively cStage I cancer that are resectable by distal gastrectomy as it is well underlined in the last published Japanese guidelines [14]. As for more advanced cancer, there is currently no scientific evidence to address them with laparoscopic approach, since randomized trials to look at safety and long-term outcome are currently ongoing (JLSSG0901 AND KLASS02) and since their data are not clearly published.

**Conclusions**

Gastric Cancer seems to be a very heterogeneous disease in which each cancer patient probably exhibits a distinct genetic and molecular profile [15] and this might be the reason why we do not assist to an implementation of the prognosis as we are expecting. The molecular pathway, together with the implementation of the surgical technique and the selection of the patients will probably lead our future in this pathology both in the diagnosis and in the treatment.
1. Ferlay J, Colombet M and Bray F. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. Available from: http://ci5.iarc.fr.

2. Thomassen, I.; van Gestel, Y.R.; van Ramshorst, B.; Luyer, M.D.; Bosscha, K.; Nienhuijs, S.W.; Lemmens, V.E.; de Hingh, I.H. Peritoneal Carcinomatosis of Gastric Origin: A Population-Based Study on Incidence, Survival and Risk Factors. Int. J. Cancer 2014, 134, 622–628.

3. Liao et al; Learning curve and short-term outcomes of modularized LADG for advanced gastric cancer A retrospective study; Medicine (2019) 98:10.

4. Prashanth Rawla, Adam Barsouk; Epidemiology of gastric cancer: global trends, risk factors and prevention; Gastroenterology Rev 2019; 14 (1): 26–38.

5. Priego et al; Outcomes of the Learning Curve in Our First 100 Consecutive Laparoscopic Gastrectomies; Surg Laparosc Endosc Percutan Tech. 2019 Apr;29(2):126-132.

6. Registro tumori Umbria, https://gecortup.ict4life.com/Statistiche.

7. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. J Clin Oncol. 1998;16:1490–3.

8. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al.
Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi57–63.

9. Ajani JA, Bentrem DJ, Besh S, D'Amico TA, Das P, Denlinger C, et al. Gastric cancer, version 2.2013: featured update to the NCCN Guidelines. J Natl Compr Canc Netw. 2013;11:531–46.

10. Roviello F¹, Pedrazzani C, Marrelli D, Di Leo A, Caruso S, Giacopuzzi S, Corso G, de Manzoni G; Super-extended (D3) lymphadenectomy in advanced gastric cancer. Eur J Surg Oncol. 2010 May;36(5):439-46. doi: 10.1016/j.ejso.2010.03.008. Epub 2010 Apr 13.

11. Bencivenga M, Verlato G, Mengardo V, Scorsone L, Sacco M, Torroni L, Giacopuzzi S, de Manzoni G; Is There Any Role for Super-Extended Limphadenectomy in Advanced Gastric Cancer? Results of an Observational Study from a Western High Volume Center. J Clin Med. 2019 Oct 27;8(11). pii: E1799. doi: 10.3390/jcm8111799.

12. Sasako, M.; Sano, T.; Yamamoto, S.; Kurokawa, Y.; Nashimoto, A.; Kurita, A.; Hiratsuka, M.; Tsujinaka, T.; Kinoshita, T.; Arai, K.; et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N. Engl. J. Med. 2008, 359, 453–462.

13. Gerassimos N. Douridas and Stefanos K. Pierrakakis; is There Any Role for D3 Lymphadenectomy in Gastric Cancer? Front Surg. 2018 Mar 22;5:27. doi: 10.3389/fsurg.2018.00027. eCollection 2018.

14. Japanese Gastric Cancer Association; Japanese gastric cancer treatment guidelines 2018 (5th edition); Gastric Cancer https://doi.org/10.1007/s10120-020-
15. Tasuku Matsuoka and Masakazu Yashiro Biomarkers of gastric cancer: Current topics and future perspective; World J Gastroenterol. 2018 Jul 14; 24(26): 2818–2832. Published online 2018 Jul 14. doi: 10.3748/wjg.v24.i26.2818.
Declarations

• Data were retrospectively registered and extracted from a database; Ethical approval for anonymous usage of patients’ data was obtain from the local ethical committee according to the Declaration of Helsinki
• Consent for publication was also obtain into a consent form from all our patients
• The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request
• The authors declare that they have no competing interests
• No founding were received for this paper
• Authors’ contributions: EM and MCV analyzed and interpreted the patient data; EM, LG and AD were a major contributors in writing the manuscript; MCV and SV retrived all the data; LG and AD design the study; all authors read and approved the final manuscript
• Acknowledgements: not applicable
Figures:

![Overall survival (OS) and Disease free survival (DSF) of the entire cohort of patients.](image)

**Figure 1**: Overall survival (OS) and Disease free survival (DSF) of the entire cohort of patients;
Figure 2: trend according to surgery strategy over the entire time period;(ICT: intention to cure treatment; TOTA: tumor other than adenocarcinoma), p < 0.05.
Figure 3: (a) Lymphadenectomy trend, $p < 0.05$; (b) lymphonal harvested with median number according to the time period, $p<0.05$. 
Figure 4: extension of lymphadenectomy as a function of pathological T value, in different time periods;
Figure 5: Overall survival according to lymphadenectomy approach between 2014 and 2018.
Supplementary Figure 1: number of surgical procedure and trend in our center according to the time period, p <0.05.
Supplementary Figure 2: Overall survival and Disease free survival according to the time period.
Supplementary Figure 3: Tumor location trend in the curative subgroup, p < 0.05.
| Variable                          | 2004-2008 n=100 | 2009-2013 n=107 | 2014-2018 n=203 | P     |
|----------------------------------|-----------------|----------------|----------------|-------|
| **Age**                          | 70.50± 10.09    | 70.59± 12.2    | 72.77± 10.89   | 0.12  |
| **Gender:**                      |                 |                |                |       |
| Male                             | 67 (67%)        | 57 (53.3%)     | 133 (65.5%)    | 0.06  |
| Female                           | 33 (33%)        | 50 (46.7%)     | 70 (34.5%)     |       |
| **Tumor type:**                  |                 |                |                |       |
| Adenocar                       | 95 (95%)        | 93 (86.9%)     | 186 (91.6%)    | 0.11  |
| Other                           | 5 (5%)          | 14 (13.1%)     | 17 (8.4%)      |       |
| **Surgical goal:**              |                 |                |                |       |
| Curative                        | 91 (91%)        | 77 (72%)       | 156 (76.8%)    | 0.0096|
| Palliative                      | 4 (4%)          | 16 (15%)       | 30 (14.8%)     |       |
| **Surgical approach:**          |                 |                |                | < 0.0001|
| Open                            | 97 (97%)        | 105 (98.1%)    | 159 (78.3%)    |       |
| Minimally Invasive              | 3 (3%)          | 2 (1.9%)       | 44 (21.7%)     |       |
| **Tumor location:**             |                 |                |                | 0.008 |
| Proximal                        | 45 (45%)        | 27 (25.2%)     | 54 (26.6%)     |       |
| Distal                          | 48 (48%)        | 63 (58.9%)     | 115 (56.5%)    |       |
| Other                           | 7 (7%)          | 17 (15.9%)     | 29 (14.3%)     |       |
| **Lauren IStotype:**            |                 |                |                | 0.28  |
| Intestinal                      | 52 (52%)        | 52 (48.6%)     | 108 (53.2%)    |       |
| Diffuse                         | 38 (38%)        | 33 (30.8%)     | 56 (27.6%)     |       |
| Mixed                           | 5 (5%)          | 8 (7.5%)       | 22 (10.8%)     |       |
| **pTNM stage***:                |                 |                |                | 0.5   |
| I                               | 26 (26%)        | 19 (17.8%)     | 44             |       |
| II                              | 17 (17%)        | 19 (17.8%)     | 33             |       |
| III                             | 31 (31%)        | 17 (15.9%)     | 43             |       |
| IV                              | 17 (17%)        | 22 (20.5%)     | 36             |       |
| **Lymphoadenectomy***:          |                 |                |                | 0.006 |
| D1                              | 22 (22%)        | 16 (15%)       | 43             |       |
| D2                              | 65 (65%)        | 43 (40.2%)     | 79             |       |
| D3                              | 3 (3%)          | 18 (16.8%)     | 34             |       |
| **Lymphonodes harvested**       | 22(4-58)        | 25 (8-61)      | 34 (7-135)     | < 0.0001|
| **Neoadjuvant chemotherapy**    |                 |                |                | 0.07  |
| Yes                             | 8 (8%)          | 16 (15%)       | 27             |       |
| No                              | 83 (83%)        | 61 (57%)       | 129            |       |

Table 1: Clinical pathological characteristics of patients enrolled in the study expressed as absolute number and as percentage of the entire population; (+= mean and s.d value; *= median value and range; ** = only for adenocarcinomas; *** = only in curative setting).