

# Gastric Cancer Surgical Experience from a single expert Western center: case series results

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## Research

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# Abstract

**Background** Surgical treatment plays a key role in the cure of gastric cancer. Our aim was to analyze changes in epidemiology and outcome, 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 analysis 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 lymph nodes harvested changed significantly over the time ( $p < 0.05$ ).

**Conclusions** Our result showed an increasing trend in number of surgery for gastric adenocarcinoma in our center, probably due to the increasing in absolute number of cases in Italy and worldwide. We have also show that tumor location is shifting towards a distal location in the last period. Moreover in the last period there is also an improving trend in overall survival, probably due to a more aggressive surgery adopted and also due to an improved learning curve. 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.

## 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  $71,65 \pm 11,09$  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.

Variable	2004-2008 n=100	2009-2013 n=107	2014-2018 n=203	P
Age <sup>+</sup>	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:				
Adenocr	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:				
Open	97 (97%)	105 (98.1%)	159 (78.3%)	< 0.0001
Minimally Invasive	3 (3%)	2 (1.9%)	44 (21.7%)	
Tumor location:				
Proximal	45 (45%)	27 (25.2%)	54 (26.6%)	0.008
Distal	48 (48%)	63 (58.9%)	115 (56.5%)	
Other	7 (7%)	17 (15.9%)	29 (14.3%)	
Lauren Istotype**:				
Intestinal	52 (52%)	52 (48.6%)	108 (53.2%)	0.28
Diffuse	38 (38%)	33 (30.8%)	56 (27.6%)	
Mixed	5 (5%)	8 (7.5%)	22 (10.8%)	
pTNM stage***:				
I	26 (28,6%)	19 (24,7%)	44 (28.2%)	0.5
II	17 (18,7%)	19 (24,7%)	33(21,1%)	
III	31 (34,0%)	17 (22,1%)	43 (27,6%)	
IV	17 (18,7%)	22 (28.5%)	36 (23,1%)	
Lymphadenectomy***:				
D1	22 (24,1%)	16 (20,8%)	43 (27,6%%)	0.006
D2	66 (72,5%)	43 (55,8%)	79 (50.6%)	
D3	3 (3,4%)	18 (23,4%)	34(21,8%)	
Lymphonodes harvested <sup>*,***</sup>	22(4-58)	25 ( 8-61)	34 (7-135)	< 0.0001
Neoadjuvant chemotherapy***				
Yes				0.07
No	8 (8.8%)	16 (20,8%)	27 (17.3%)	
	83 (91,2%)	61 ( 79,2%)	129 (82,7%)	

**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).

### Statistical analysis

Descriptive data were expressed as means (+/-standard deviation) or medians (range) for quantitative variables and absolute numbers (and 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. A  $p < 0.05$  was considered statistically significant.

# 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. 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 in overall survival, however there is an interesting and clear trend in favor of the last surgical period included between 2014 and 2018 (Supplementary **Figure 2**,  $P=0.08$ ).

Lauren's istotype and stage 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 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**.

Five years overall survival and ten years overall survival of patient curatively treated were respectively: 44% and 34.7%; whereas 5 and 10Y-DFS were respectively 52% and 50%.

As previous, dividing the series into the three time periods, 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 years (Supplementary **Figure 3**).

Moreover also the type of lymphadenectomy and the number of lymphonodes harvested changed significantly over the time period analysis with a shift towards the standardization of D1 lymphadenectomy in early gastric cancer, elderly or not fit patients; a D2 lymphadenectomy was performed in locally advanced gastric cancer and in some selected cases a D3 lymphadenectomy was done (**Figure 3a**,  $p < 0.05$ ). Furthermore a greater number of lymphonodes 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].

The extent of systematic lymphadenectomy was defined as the Japanese guidelines (10) according to the type of gastrectomy conducted. In total gastrectomy D1 was defined when nodes No. 1–7 were retrieved; D2 was defined when nodes of D1 dissection plus nodes No. 8a, 9, 11p, 11d, 12a were dissected.

In Distal gastrectomy D1 was defined when nodes No. 1, 3, 4sb, 4d, 5, 6, 7 were retrieved and D2 was defined when nodes of D1 dissection plus nodes No. 8a, 9, 11p, 12a were dissected.

During the last two decades, centers have improved their learning curve for D2 lymphadenectomy. 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 lymphonodal stations; this approach seems to convey survival advantages in particular in locally advanced neoplasia with serosa or/and lymphonodal involvement, diffuse and proximal tumors, as the Italian Group of Gastric Cancer Research Group demonstrated [11].

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 [12].

These Italian findings are confirmed by JCOG 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 [13].

In a recent paper Roviello et al. [14] concluded D3 lymphadenectomy could be further explored in specialized centers for curative surgery of advanced GC, providing that an acceptable morbidity and no increase in mortality can be offered.

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%).

No major complications were noted in patients who underwent D3 surgery. 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; however data also show that high volume specialized center s adequately trained surgeons are essential [15].

Our study also shows an increasing use of minimal-invasive approach in the time period 2014-2018 as compared to the previous ones; the explanation might be link 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 [10]. 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

Our result showed an increasing trend in number of surgery for gastric adenocarcinoma in our center, probably due to the increasing in absolute number of cases in Italy and worldwide. We have also show that tumor location is shifting towards a distal location in the last period a little bit in contrast with the scientific literature, in which, with the eradication of H. Pylori, this tumor seems to be decreasing.

In our results there was also an improving trend in overall survival; we associated this to a more aggressive surgery adopted and also to an improved surgical technique.

For this reason we do believe that gastric surgery must be done in experienced centers to obtain oncological outcomes; in selected cases an extended lymphadenectomy could give survival benefit to patients with locally advanced gastric cancer.

Gastric Cancer seems to be a very heterogeneous disease in which each cancer patient exhibits a distinct genetic and molecular profile [16] 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.

## Declarations

### **Ethics approval and consent to participate**

Data were retrospectively registered and extracted from a database; Ethical approval for anonymous usage of patients' data was obtained from the local ethical committee according to the Helsinki's declaration.

### **Consent for publication**

Consent for publication was also obtain into a consent form from all our patients

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

### **Competing interests**

The authors declare that they have no competing interests

## Funding

No funding were received for this paper

## Authors' contributions

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 retrieved all the data; LG and AD design the study; all authors read and approved the final manuscript

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## Figures

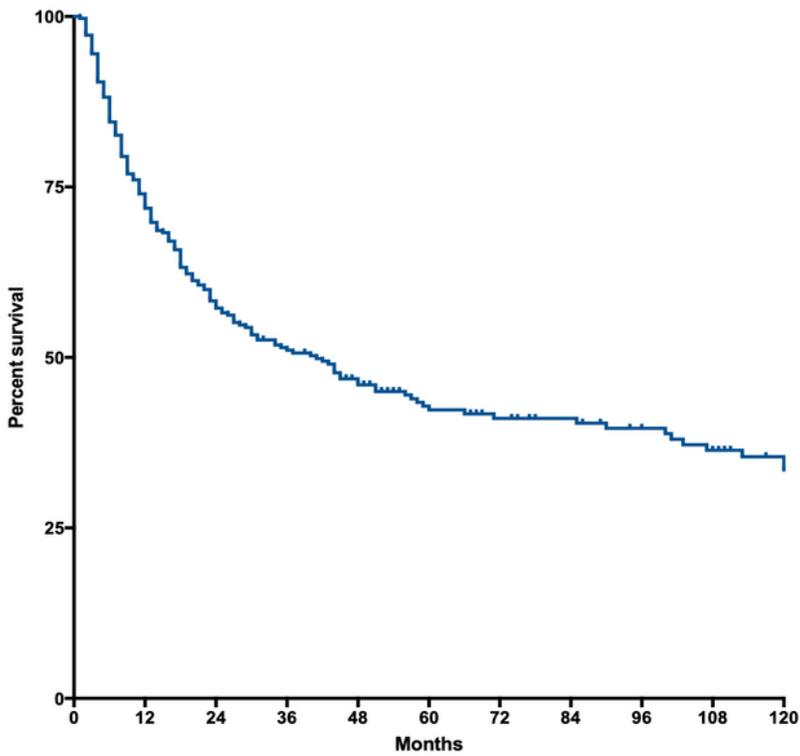
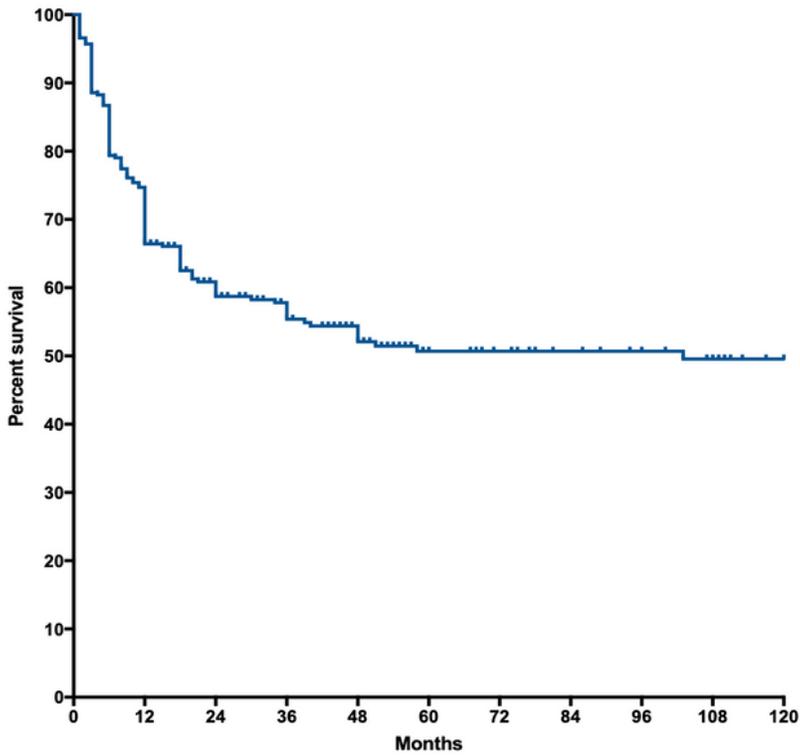


Figure 1

Overall survival (OS) and Disease free survival (DSF) of the entire cohort of patients

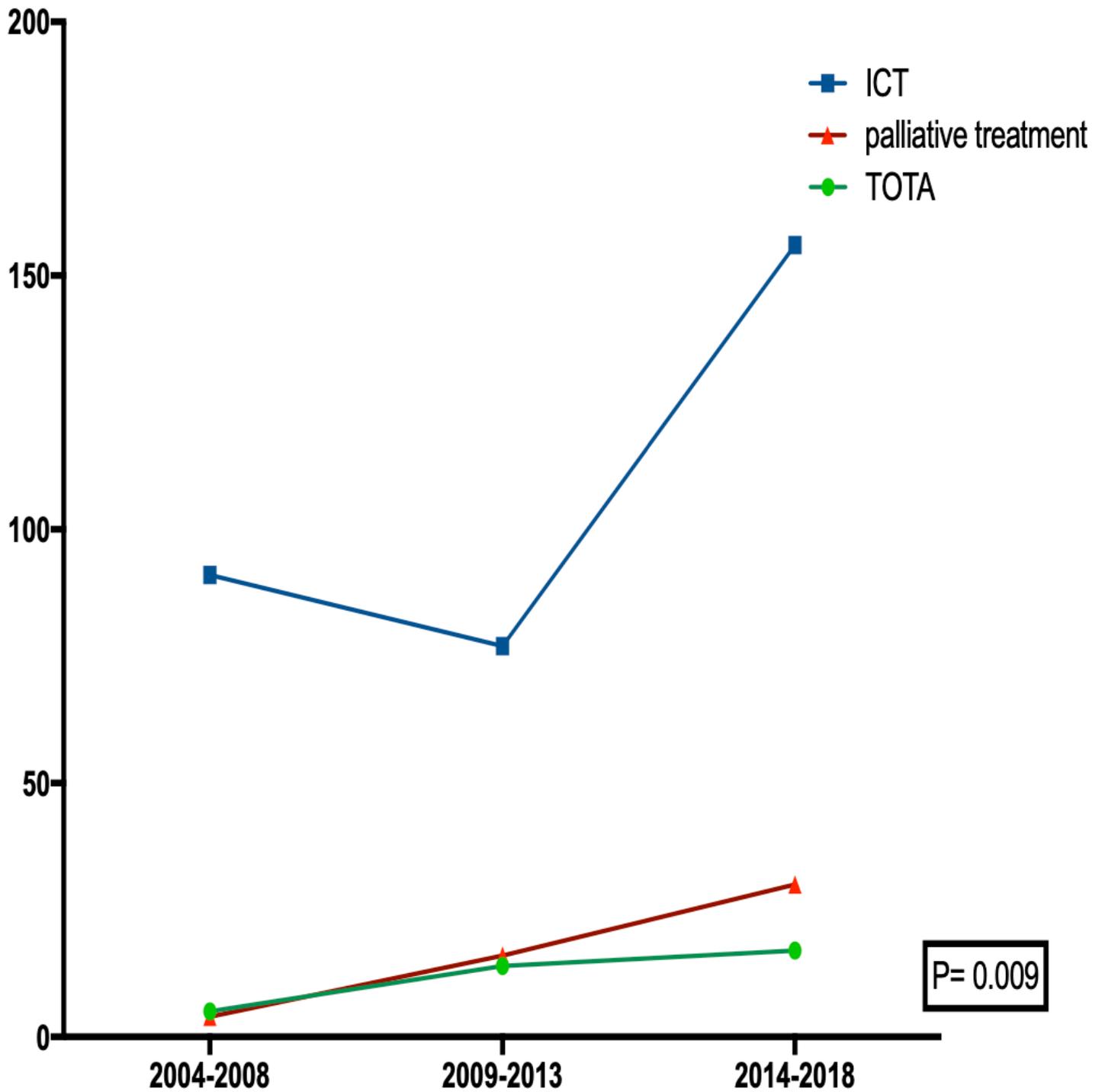


Figure 2

trend according to surgery strategy over the entire time period;(ICT: intention to cure treatment; TOTA: tumor other than adenocarcinoma),  $p < 0.05$ .

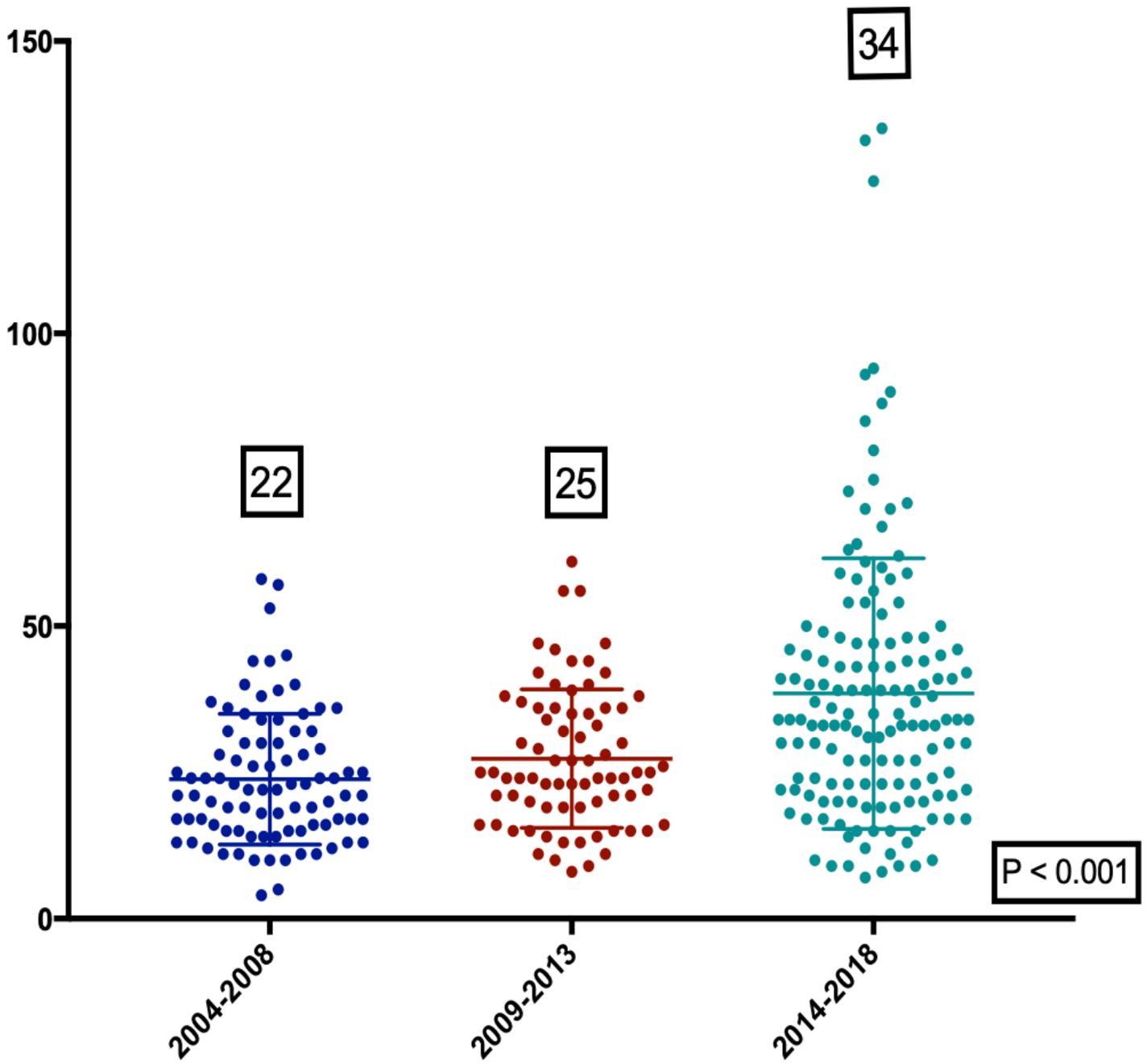
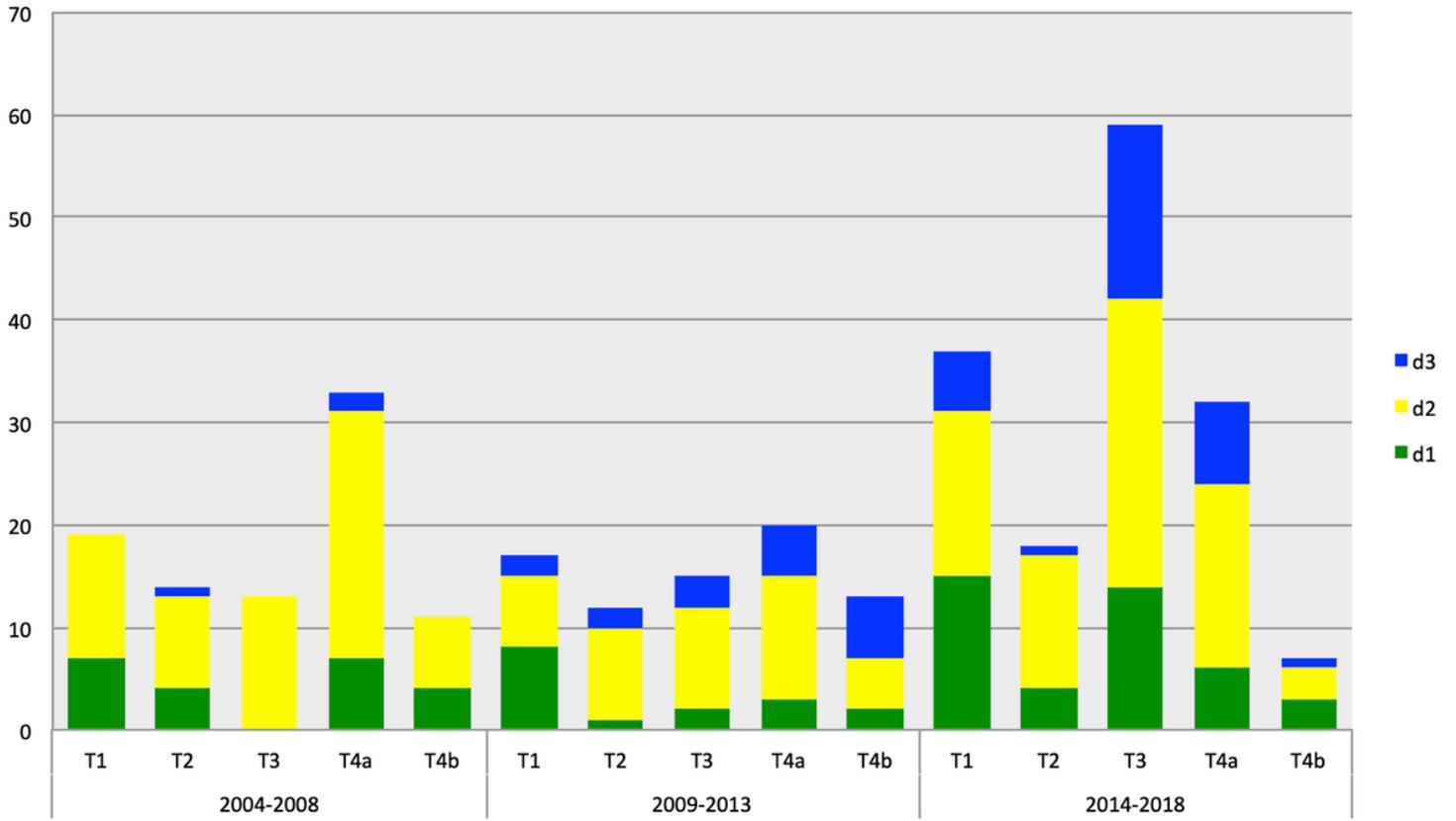


Figure 3

(a) Lymphadenectomy trend,  $p < 0.05$ ; (b) lymphodal 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;

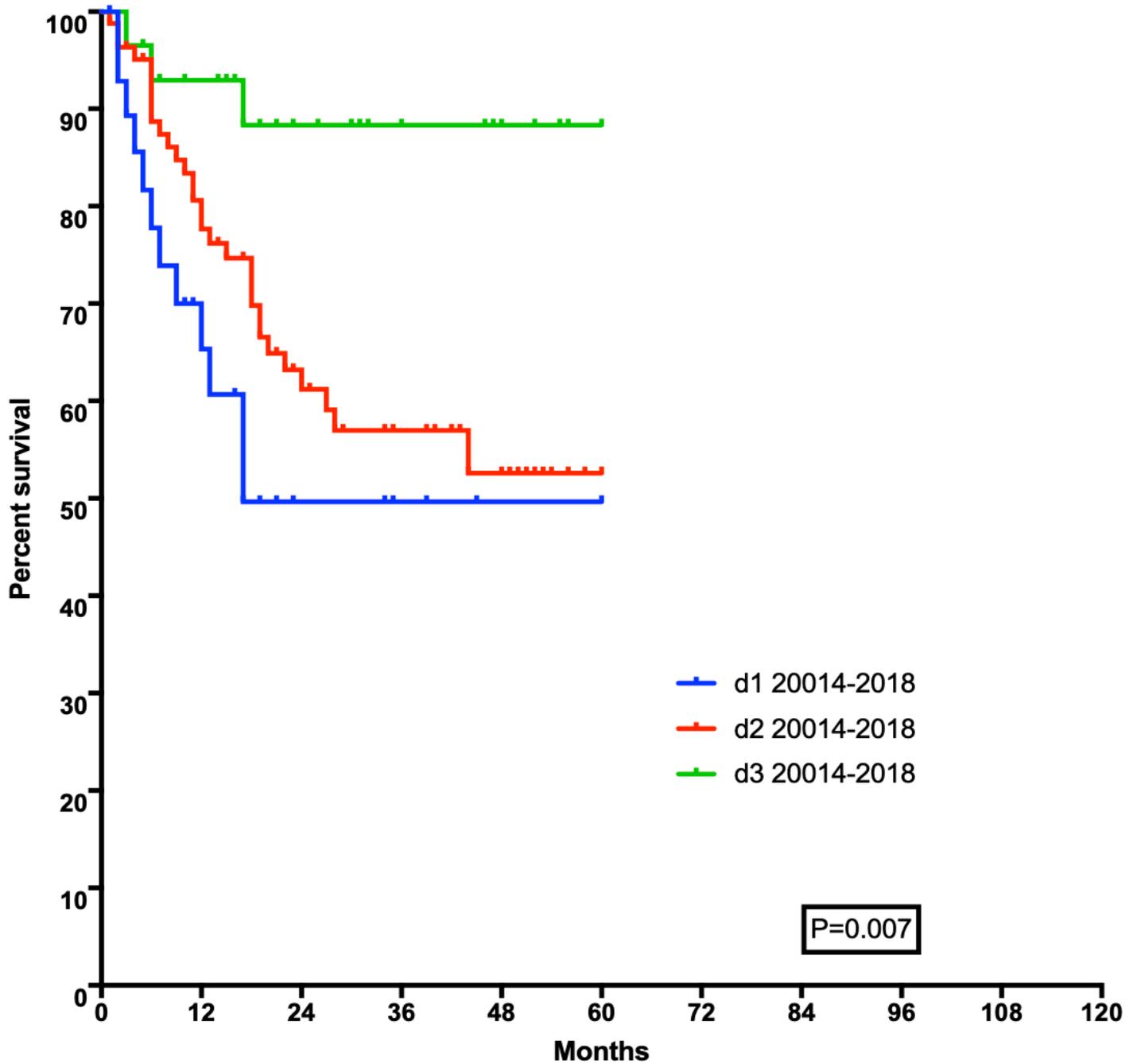


Figure 5

Overall survival according to lymphadenectomy approach between 2014 and 2018.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigures.pdf](#)