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Research Article

Long-term survival differences in gastric cancer after D_2 lymphadenectomy and an improved assessment of resectability

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Abstract

Objective. The purpose of this work is to compare the long-term survival between a control group with mostly D_1 lymphadenectomy and a study group with mostly D_2 lymphadenectomy.

Materials and Methods. We analyzed consecutive cases operated by a single surgeon performing mostly D_2 lymphadenectomy and a control group of consecutive gastric cancer patients operated by a group of surgeons, performing mostly D_1 lymphadenectomy, in a period when D_2 lymphadenectomy was not the standard and was introduced as a new technique in our center.

Results. We found 30,56% D_2 lymphadenectomy in the control groups and 85,1% in the study group. At a five years interval from surgery the control group had no survivors, while the study group had 8 (20%) survivors.

Conclusions. The spleen and pancreas preserving D_2 lymphadenectomy done by experienced surgeons, according to the current guidelines in order to select operable patients improves the overall survival of such gastric cancer patients.

Keywords: D_2 lymphadenectomy, spleen preservation, pancreas preservation

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Introduction

Gastric cancer, despite having received intense scientific attention in terms of new therapeutic approaches and despite its decrease in incidence, continues to be an important cause of cancer related deaths (1, 2). A review by He et al. analyzing 2104 articles on surgical interventions in gastric cancer finds a consensus across the literature regarding the benefits of the implementation of new techniques such as laparoscopy and robotic surgery in gastric cancer, but surprisingly does not find a consensus on the benefits of D_2 vs. D_1 lymphadenectomy (3).

Most of the major differences still come from a difference of results (4) between Eastern and Western trials comparing the benefits of an extended lymphadenectomy. The demographic differences are most probably the best explanation for these differences – Western patients are on average 10 years older and have a higher incidence of comorbidities such as obesity and cardio-vascular disease that could account for the differences found in postoperative morbidity (5). On the other hand, differences in technique could also account for the lack of homogeneity in terms of outcomes, especially when patients operated at different stages of the learning curve of the technique are included in the same study.

The aim of our study was to evaluate the differences in survival between two retrospectively selected groups of consecutive gastric cancer patients. A control group of patients operated before the D_2 lymphadenectomy technique was introduced as standard practice was compared to a study group of patients on whom the D_2 lymphadenectomy was performed by a single senior surgeon experienced in the practice of this technique.

Materials and Methods

For the means of our study we used a control group, previously used in an article describing postoperative survival in gastric cancer patients (6). This control group was composed of 143 consecutive gastric cancer patients operated in the Ist Surgical Clinic of the Sf. Spiridon University Emergency Hospital between January 1996 and December 2001 by all of the attending surgeons in the clinic, with an inhomogeneous experience in performing the D_2 lymphadenectomy and a study group composed of 56 consecutive patients treated by a single surgical team between January 1999 and September 2013, with experience in D_2 lymphadenectomy.

For both groups, the overall survival was assessed by requesting data from the Digital Data Base Population Registry concerning the status of the patient (dead vs. alive) and the date of death in case of deceased patients. The patients that could not be identified with certainty were excluded from the study. Retrospective evaluation included all relevant medical documents and we collected information regarding the sex, age, location of the tumor, type of gastrectomy, type of lymphadenectomy, oncologic quality of the resection and the pTNM staging.

The differences in overall survival between the two study groups were assessed using univariate ANOVA. For the purpose of this study we considered acceptable a statistical significance level of 5%.

Results

Based on the data obtained from the Digital Data Base Population Registry, in the control group we were able to unequivocally identify 135 patients (94,4%) while in the study group the number of patients that we were able to positively identify was 47 (83,92%).

Demographic analysis

In both groups there was a male predominance with a proportion of 66,67% men in the control group and 57,44% men in the study group. In terms of age, in both groups the majority of patients were in their 6th decade of life (Table 1).

Table 1. Main characteristics of the groups included in our study

Analyzed variable		Control group	Study group
Sex	Male	90 (66,67%)	27 (57,44%)
	Female	45 (33,33%)	20 (42,55%)
Age	>30	4 (2,96%)	1 (2,12%)
	>40	16 (11,85%)	2 (4,25%)
	>50	19 (14,07%)	9 (19,14%)
	>60	56 (41,48%)	18 (38,29%)
	>70	37 (27,4%)	16 (34,04%)
	>80	3 (2,22%)	1 (2,12%)
Tumour stage	I	1 (0,74%)	8 (17,02%)
	II	16 (11,85%)	22 (46,80%)
	III	43 (31,85%)	17 (36,17%)
	IV	75 (55,55%)	0 (0%)
Lymph node dissection	D1	50 (69,44%)	7 (14,9%)
	D2	22 (30,56%)	40 (85,1%)

Tumour characteristics and survival

As can be seen in Table 1, from a point of view of the stage of the tumor at presentation we found that in the control group most of the patients presented with later stages of the disease (31,85 % with stage III and 55,55% with stage IV) while in the study group most of the patients presented in earlier stages of the disease (46,8% presented with stage II).

The patients in the control group presenting with stage IV gastric cancer allowed us to compare the survival differences between the subgroup of patients that underwent a simple exploratory laparotomy versus those that underwent a palliative resection. The results of this comparison can be seen plotted in Figure 1. We also did not find a statistically significant difference in survival between the locally advanced stage IV and the metastatic stage IV patients in the control group. In the study group, an adequate preoperative staging protocol was introduced and we also faced a change in the strategy of treatment concerning stage IV gastric cancer, according to international protocols. As such, there was no patient with stage IV disease undergoing a surgical resection in the study group.

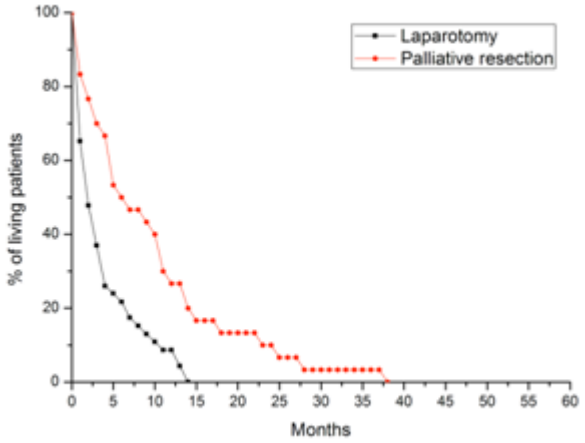

Fig. 1. Survival curves for stage IV patients with laparotomy and palliative procedures.

In the control group we had no surviving patients five years after the surgical procedure, but in the study group 8 (20%) patients were alive after 60 months of follow-up. Within this subgroup of surviving patients there was 1 (12,5%) patient staged pN_2 and 1 (12,5%) patient staged pN_3, while the rest of 6 patients were equally distributed between the pN_0 and pN_1 stages. Also, within this subgroup of survivors we found 5 (62,5%) patients with distally located tumors, 3 (37,5%) patients with tumors located within the middle third of the stomach and no patients with proximal tumors.

Oncologic quality of the gastric resection and the type of lymphadenectomy

The oncologic quality of the gastric resection was classified as R_0 – no microscopic remnant neoplastic tissue or R_1 – remnant cancer tissue, including both microscopic and macroscopic positive resection margins. In the control group we were able to compare the outcomes in terms of survival between R_0 procedures, R_1 procedures and simple laparotomies and found a statistically significant ($p<0,05$) difference in survival between these groups of patients, favoring radical procedures as can be seen from the survival

curves in Figure 2. Such a comparison was not possible in the current study group due to the small number of patients that had an R_1 resection (4 patients).

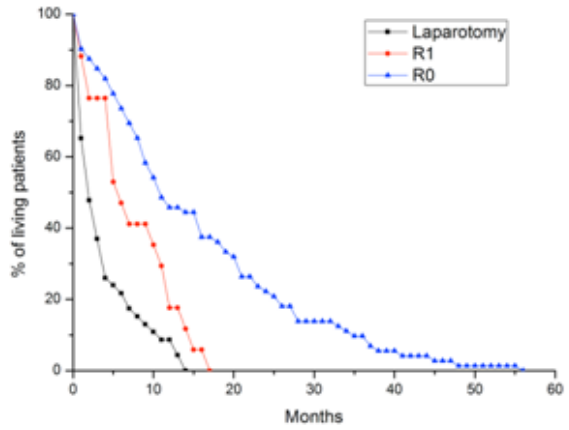

Figure 2. Survival curves for different types of procedures within the control group.

We then proceeded to compare the survival of the patients with an R_0 resection in the control group and that of the patients with an R_0 resection in the study group and found significantly better survival intervals in the study group ($p<0,001$). The survival curves are plotted in Figure 3 and the difference in survival is clearly noticeable.

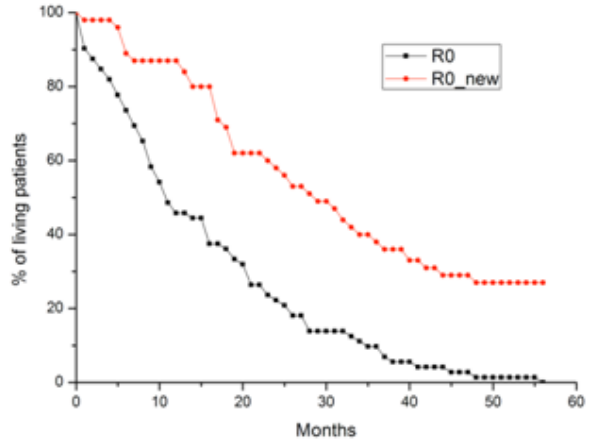

Figure 3. Survival curves for R0 resections in the two study groups

A further step in our analysis was to compare the outcome following D_2 lymphadenectomy in the control group versus the study group. In the study group a spleen preserving D2 lymphadenectomy was performed whenever possible and pancreatic preservation was the rule, except for cases where a pancreatic resection was required to achieve an R_0 resection. An increase in the percentage of the D_2 lymphadenectomy in the study group (85,1%, 40 patients) versus the control group (30,56%, 22 patients) was clearly visible. The survival curves of the patients that underwent D_2 lymphadenectomy in the control and the study group are plotted in Figure 4 with a clearly visible improvement in survival in the study group. An ANOVA analysis also revealed a statistically significant ($p<0,001$) increase in the survival of patients with D_2 lymphadenectomy in the study group compared to the control group.

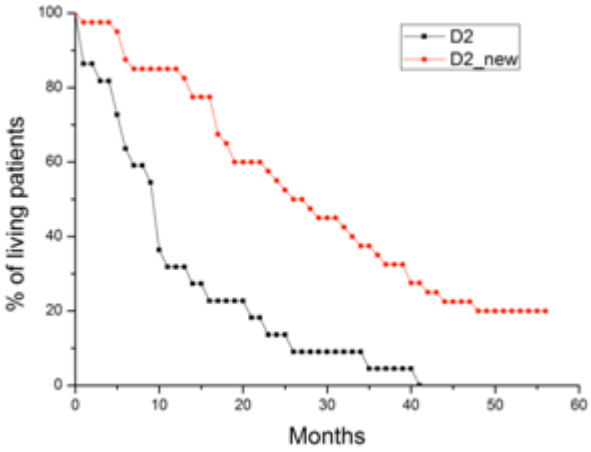

Figure 4. Survival curves for D_2 lymphadenectomy in the two groups.

Discussions

Our study has shown an improvement in survival in the study group compared to the control group. Such a difference could be explained by the fact that patients in the study group presented in earlier stages of the disease, the indications for surgery were strictly respected in accordance with current international guidelines and the D_2 lymphadenectomy in the study group has been performed by a single surgeon whose experience is located on the plateau of the learning curve, ensuring homogeneity from the point of view of the surgical technique.

As expected, we found that the highest incidence in both groups was during the 6th decade of life, while

the sex distribution revealed a higher incidence in male patients, with higher male to female ratio in the control group of patients compared to the study group (Table 1). A noteworthy difference between the two groups was the fact that in the control group we found a high incidence of patients presenting and being operated in the presence of a stage IV disease while in the study group there were no stage IV patients undergoing surgical procedures.

A possible explanation for this fact is the improvement in the preoperative staging of the tumor and a shift from surgical to less invasive procedures in the palliative management of the stage IV patients. In the control group, where we found a large number of late stage patients, some of them undergoing exploratory laparotomy and some undergoing palliative resections which were acceptable in the time interval when the patients in the control group were operated, we were able to compare the survival benefits between a simple surgical exploration of the abdomen and a palliative resection and found a statistically significant difference in survival in favor of the patients that had more than an exploratory laparotomy done.

Such a difference in survival could potentially be explained by the fact that the patients with an exploratory laparotomy were improperly staged preoperatively and the exploratory laparotomy may have revealed later stages of the disease than expected which did not warrant a palliative resection.

Also an interesting difference that can be explained by a better use of the diagnostic tools available and by the increasing accessibility of screening programs to patients is the fact that in the study group the majority of patients presented in stage II of the disease as opposed to the control group where the patients presented in the IIIrd and IVth stages of the disease.

A surprising result derived from our study is the lack of a survival difference between the Ist, IInd and IIIrd stage of the disease in the control group. Other authors have described a difference in the survival stage III gastric cancer patients depending on the total number of harvested lymph nodes (7).

Such a difference could be explained on one hand by the fact that statistically speaking the analysis of more lymph nodes increases the chances of discovering positive lymph nodes and on the other hand by the extent of the lymphadenectomy required to retrieve more lymph nodes which improves survival.

Also, lymph node micro metastases that go undiagnosed using conventional histological examination could imply understaging that leads to a bias in the assessment of survival (8). Similarly, incorrect N staging either due to an insufficient number of harvested lymph nodes or to undetected micro metastases could account for the similar survival we found across stages.

In the study group a subgroup of patients surviving at five years after D_2 lymphadenectomy deserves special consideration. They represent 20% of the patients, a percentage comparable to the literature. Out of these patients only a small percentage presented with pN2 and pN3 stages which could lead us to believe that lymph node tumor burden is a more important predictor of survival than the accuracy of the surgical technique. Also, none of the patients within this subgroup of survivors presented with a proximal cancer but they had either a distal or mid-gastric tumor.

Concerning the outcomes of D_1 vs. D_2 lymphadenectomy in gastric cancer in terms of postoperative morbidity and survival recent reviews of the literature show controversial results and the lack of consensus between Eastern and Western authors (3, 5). Two major European prospective randomized trials – the Medical Research Council Gastric Cancer Surgical Trial (MRC ST01) and the Dutch trial reported a statistically significant increase in postoperative morbidity after D_2 lymphadenectomy and no overall survival benefit (9-11). One of the possible explanations offered for the differences between the results of Asian and European authors was the difference in the experience of performing the D_2 lymphadenectomy (11-13). More in depth demographic studies of gastric cancer patients also point out to another reason why postoperative morbidity is significantly higher in Western studies – Asian patients tend to be younger and present fewer cardiovascular comorbidities and obesity which are in themselves predisposing factors for postoperative complications (5, 14). Finally one other explanation is that the comorbidity in case of D_2 lymphadenectomy is mostly due to the spleno-pancreatectomy associated to the procedure (15). This is the reason why spleen and pancreas preserving strategies have been proposed and tested in prospective randomized control trials and have now been proven to yield similar survival benefits in terms of disease-specific survival but with a lower postoperative morbidity (16).

Our study does not aim to compare the D_1 and D_2 lymphadenectomy procedures but only to compare the survival differences between a group of patients with D_2 lymphadenectomy operated by several surgeons in our center whose level of experience was located at different points on the learning curve and a second group of patients operated by a single senior surgeon whose experience in performing D_2 lymphadenectomy is placed on the plateau of the learning curve. Collaterally we were also able to draw some conclusions regarding the differences in the survival of the patients based on parameters such as stage of the tumor, extent of the surgical procedure and the curative vs. palliative character of the procedure.

The comparison of the survival differences based on the type of resection (R_0 vs R_1) and the type of lymphadenectomy (D_1 vs. D_2) reveals significant differences. A significant increase in survival is clearly shown in Figure 3 between patients that had a curative resection in the control study group and those that had the same type of resection in the study group. A similar difference is also noticeable in Figure 4 between patients with D_2 lymphadenectomy in the control study group and those with a D_2 lymphadenectomy in the study group. The explanation could be that patients in the control group were operated by an inhomogeneous group of surgeons relative to their experience, most of them still in the process of learning the D2 lymphadenectomy procedure, while the study group is operated by a surgeon who has an experience level located on the plateau of the learning curve. A possible explanation could also be that the spleen preservation was achievable in most of the patients of the study group - 38 (80,85%) patients, and pancreas preservation was possible in all patients. A comparison of survival between patients with and without splenectomy in the study group revealed no statistically significant differences in survival.

The quality of life of patients was not assessed and the cause of death was not specified in the Digital Data Base Population Registry which is why we based our study on the overall survival of the patients in both groups.

Conclusions

A significant improvement in survival can be seen in patients undergoing D2 lymphadenectomy and R0 resections in the current study group compared to the control study group, due to the experience accumulated in performing the technique, correct preoperative staging and spleen and pancreas preservation strategies.

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