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Original article

D2-Lymphadenectomy in gastric cancer: Analysis of risk factors for morbility and mortality in a single institution experience and short literature review

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SUMMARY

AIM: Lymph node metastasis is the most important prognostic factor in gastric cancer and for this reason gastrectomy with lymphoadenectomy is the only curative treatment option for this disease. The influence of D2-lymphadenectomy on morbidity, mortality and long-term survival is still controversial: the data of Western institutions generally reported a significant increase in postoperative complications after D2 resection compared to Japanese institutions. The aim of this study was to analyze the risk factors for complications after D2 dissection in a single-institution experience. METHODS: For the present retrospective study we only considered 93 patients (53 male and 40 female) that were undergoing surgical resection and D2 dissection for gastric adenocarcinoma from January 2003 to February 2009. Thirty-two total gastrectomies were performed; distal pancreatectomy was only performed in the cases of direct invasion of pancreatic tail (4 cases) and lymphadenectomy of splenic hilum (7 cases) which was always achieved by pancreas preserving splenectomy. The mean number of removed lymph nodes was 34±10 (Range 65-14) and in 64 pN+ patients we found a mean of 15±10 positive lymph nodes. The potential risk factors for morbidity and mortality were analyzed by univariate and multivariate analysis. RESULTS: Postoperative morbidity and mortality rates were 33% (31patients) and 2% (1 patient) respectively. Pancreatic fistula, abdominal abscess and pneumonia were the three most important observed complications. A univariate analysis shows that patients who underwent a splenectomy or a splenopancreasectomy, submitted to non-curative surgery, and that received perioperative blood transfusion showed a significant association with the incidence of postoperative complications. Low preoperative level of haemoglobin and high creatinine level and ASA score are also directly related to postoperative complications. Mortality rate was associated with advanced age, presence of cardiopulmonary disease, surgical radicality and, finally, with creatinine level (18%). In a multivariate analysis splenopancreasectomy, high creatinine level and ASA class II/III were independent factors related to postoperative complications. CONCLUSION: In our experience the D2 standard lymphoadenectomy, according to the results of Japanese institutions, seems to be the most attractive procedure in the surgical management of gastric cancer. In specialized centers this approach may be performed with an acceptable risk of postoperative complications and deaths: in our experience the incidence of postoperative complications do not differ from those reported in different Japanese and some European studies. Moreover the majority of the reported complications in our casuistry could be resolved favorably with a specific medical approach. The correct patient selection and the evaluation of the potential risk factors in addition to adequate surgical approach and postoperative management and care can considerably reduce the incidence of postoperative problems and deaths.

Key Words: D2, Lymphadenectomy, Gastric cancer, Gastric tumour, Gastric adenocarcinoma

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INTRODUCTION

Gastric cancer remains an important cause of cancerous deaths in the world even if its incidence rate is de-

creasing. Surgery remains the only potential treatment for curable gastric cancer: chemotherapy shows a limited impact and only helps to prolong survival in advanced cases. Based on tumour location the extent of resection is widely defined by the general attempt to obtain a curative surgery (R0 resection); on the contrary the extent of lymphadenectomy is controversial and there is no worldwide consensus.[1, 2]

Lymph node metastases occur during the early stage of the disease and lymphadenectomy is considered to be a crucial aspect of gastric cancer surgery. In relation to this evidence Japanese surgeons introduced in the 1960s the extended lymphadenectomy (D2) that consists of the systematic removal of the first (perigastric) and second (celiac artery and its branches) level lymph nodes.[3]

D2 lymphadenectomy is associated with excellent results: many early studies reported that approximately 40% of patients with positive lymph nodes of the second tier survived longer than 5 years after this procedure.[4] The Japanese nationwide registry shows an operative mortality of less than 2% for D2 gastrectomy.[5,6] but on the contrary two European randomized controlled trials compared D1 to D2 gastrectomy and demonstrated high morbidity and a high operative mortality, exceeding 10%, of this procedure compared to D1 dissection and failed to show a survival benefit.[7-9] It is for this reason that in Western countries limited lymphadenectomy (D1) is generally the standard treatment for gastric cancer patients: the Dutch trial which confirmed a survival benefit of D2 dissection in the N2 positive patients but recommended the removal of the second level lymph nodes only in specialized centers.

In 2006 a randomized controlled trial performed by Wu et al demonstrated a significant result in the overall survival for extend lymphadenectomy compared to D1 dissection with no increase in operative mortality.[10]

Extended dissection (D3), that consists of the removal of the Para-aortic station (PAND), is also often performed in Japanese centers for advanced gastric cancer forms and two studies demonstrate that this approach may be performed without increasing the risk of postoperative complications and deaths except for selected groups of patients.[11,12]

Moreover, recently Sasako et al demonstrated that D2 lymphadenectomy alone versus D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer.[13]

The American intergroup study showed that chemoradiotherapy after D1 dissection reduced the local recurrence rate and increased long-term survival (MAGIC trial). Finally the data reported by Rukos et al. shows that the combination of D1 plus chemoradiotherapy gives a survival benefit in some patients groups.[14,15]

Currently the standard treatment for resectable gastric cancer could be gastrectomy with D2 dissection or gastrectomy with D1 dissection plus postoperative chemoradiation.

In this study we have only analyzed the result of D2 lymphadenectomy for gastric cancer with special reference to postoperative complications, morbidity and risk factor analysis in a single institution experience.

PATIENTS AND METHODS

From January 2003 to February 2009 a total of ninety-three patients (53 male and 40 female) were considered for the present study: all those patients who were undergoing a gastric resection and D2 standard dissection by the same surgical team. Due to the small number of D1 dissection (13) performed in our institution, we have not considered them for this study.

Preoperative staging, which included an upper digestive endoscopy with a biopsy, a chest X-ray, a liver ultrasound and an abdominopelvic CT-scan, was performed in all patients. For tumours located in the middle and lower third of the peritoneal cavity we performed a sub-total gastrectomy with free resection margin from the tumor not inferior to 5 cm: in doubtful cases we performed an intraoperative frozen section of the surgical resection margin. Stage T2 was subdived into stage T2a and T2b as specified by the UICC (Union International Contra le Cancer) TNM classification.

D2 standard lymphadenectomy was performed in all cases as described in the 12th edition of JRSGC. D2 "extended" lymphadenectomy, as described in the 13th edition of the Japanese classification, as the tumor located in the lower third of the stomach was frequently performed in the specialized center: in our experience the removal of hepatoduodenal ligament lymph nodes (stations number 12a and 12p) retropancreatic (station number 13) and nodes along the superior mesenteric vein (station number 14v) was performed in 45%, 27% and 26% of cases respectively.

At the end of the operation the surgeon examined each lymph node station individually in the resected specimen to isolate the lymph node and then submitted it to histopathological examination.

Total gastrectomy was performed in 32 cases (34%); distal pancreatectomy was performed only in the cases of direct invasion of pancreatic tail (4 cases) and lymphadenectomy of splenic hilum (7 cases) was always achieved by pancreas preserving splenectomy. Complete bursectomy was performed in all patients.

The method of reconstruction of gastrointestinal tract was Billroth II technique and Roux-en-Y for subtotal gastrectomy and total gastrectomy respectively. Patients resumed oral intake three days after the operation in cases of subtotal gastrectomy and on postoperative day seven, after radiological contrastrografic exam, in case of total gastrectomy. All normal surgical prophylaxes were performed. Surgical radicality was classified according to the UICC.

EVALUATION OF OPERATIVE MORBIDITY AND MORTALITY

Hospital death was defined as death which occurred during the period of hospitalization for the operation or death within 30 days after a surgical procedure. All surgical or medical complications that occurred in the same period were recorded for morbidity classification.

Anastomotik leak was diagnosed radiologically either on postoperative contrast or after clinical suspicion. Pancreatic fisula was diagnosed when fluid with a high amylase concentration was drained from the pancreatic area for more than 7 days.

The risk factors analysis for morbidity and mortality was considered for all patients. We have divided all potential risk factors in various categories related to patients and tumour characteristics (Table. 1) and surgical procedures (Table. 2). Cardiac diseases were considered based on demonstrated electrocardiographic or echocardiographic alterations; pleuropulmonary disease was recorded only in the cases of alterated spirometry or in the presence of specific alterations that required continuous medical treatment.

STATISTICAL ANALYSIS

Factors related to postoperative morbidity and mortality were analyzed by means of a logistic regression model: the significant variables were included in the model with a default level of $P<0.5$. Numerical variables were compared to the analysis of variance (ANOVA) test. Statistical analysis was done using the Statistical Package for the social Science software (version 11.0) (SPSS, Chicago, Illinois)

Table 1. Patients and Tumour Characteristics

Patients Variables	**No. of Cases**
Male-female ratio	50/43 = 1.32
Age, Years (median 69; range 32-88)	
≤ 62	23
63-71	47
≥ 72	23
Pleuropulmonary and/or Cardiac Disease	
Absent	69
Present	24
Hemoglobin Preoperative Level	
≥ 10.5 gr/dL	81
≤ 10.5 gr/dl	12
American Society of Anesthesiologists' (ASA) class	
ASA I	24
ASA II	44
ASA III	25
Creatinine levels	
≥ 1.30 mg/dL	13
≤ 1.30 mg/dL	80
Tumour Variables	
Tumour diameter, cm	
Median	5.57
Range	1.7-14.7
T-stage	
T2-SS	35
T3	53
T4	5
Tumour location	
Upper 1/3	24
Middle 1/3	30
Lower 1/3	39
Number of removed lymph nodes	
≤ 14	15
15-30	48
≥ 30	30

RESULTS

Distal pancreatectomy was performed only in the cases of direct invasion of pancreatic tail accounting for 12% of all total gastrectomy. The median operation time was 226 minutes and 380ml was the median

Table 2. Operative Details

Gastrectomy	
Total	32
Distal subtotal	61
Splenectomy	25
Distal Pancreatectomy	4
Operation Time, Minutes	Median 226; Range125-618
Blood Transfusion	
No. Of cases	18
%	16.7
Blood Loss, mL	Median 380; Range 28-1.599
No of removed nodes	Median 34±10 ; Range 65-14
≤ 14	15
15-30	48
≥ 30	30

blood loss. Blood transfusion was required approximately twice as often.

During the surgical procedures and after lymph nodes stations examination in the resected specimen a mean number of 34±10 (range: 65-14) lymph nodes were removed. We found a mean of 15±10 (range: 26-2) positive lymph nodes in 45 pN+ patients. The overall morbidity rate (multiple complication included) was 33%; reoperation was needed in 3 patients (2.8%). Pancreatic fistula, abdominal abscess and pneumonia were the three most important observed complications. Median hospital stay after surgery was 13 days. There were three hospital deaths (2.8%).

Postoperative complications are shown in Table 3: pancreatic fistula, abdominal abscess and pneumonia were the three most important observed complications. The two cases of anastomotic leak that had demanded a reoperation died successively of multiple organ failure. The other death was related to an acute myocardial infarction.

Table 3. Operative morbidity and mortality (multiple complications are included)

	No of patients	**%**
Pancreatitis	4	3.7
Pancreatic fistola	5	4.6
Abdominal abscess	5	4.6
Obstruction /ileus	2	1.9
Lymphorrhea	1	0.9
Wound infection	2	1.9
Pneumonia	6	5.7
Anastomotik leak	2	1.9
Cardiac	1	0.9
Reoperation	3	2.8
Mortality	4	4
Morbidity	31	33

In our casuistry a detailed analysis of potential risk factors for postoperative complications and mortality was performed. The results of univariate analysis of morbidity and mortality related to the different variables are shown in Table 4.

Patients who underwent a splenectomy or a splenopancreasectomy, submitted to a non-curative surgery, were older than 72 years old and who received perioperative blood transfusions showed a significant association with the incidence of postoperative complications for that it concerns the operative variables. Low preoperative level of haemoglobin and high creatinine level and ASA score are also directly related to postoperative complications.

In particular the highest percentages of postoperative complications were observed in those patients who were undergoing a more aggressive surgery with splenopancreasectomy (58%) and who presented alterations in haemoglobin (58%) or creatinine levels (55%). On the contrary patients with ASA class I, aged 60 years old or over that did not received blood transfusion showed in general a very low incidence of morbidity. Mortality rates were associated with advanced age, presence of cardiopulmonary disease, surgical radicality and, finally, with creatinine level (18%).

In a multivariate analysis performed by logistic regression model splenopancreasectomy (performed vs. not performed), high creatinine level and ASA class (II/III vs. I) were independent factors related to postoperative complications. Altered creatinine level was also evidenced in our experience as an independent factor strictly related to postoperative death as are surgical radicality (R1/R2 vs. R0) and the presence of cardiopulmonary disease. No statistically significant difference was found in the other variables (Table 5).

DISCUSSION

The D2 gastrectomy procedure is known as “extended lymphadenectomy” in Western countries. Instead Japanese surgeons use D2 as a “standard” procedure in the treatment of gastric cancer: the term “extended” in this second case is reserved only for para-aortic node dissection (PAND).

Two European randomized trials, Dutch and British, comparing D1 with D2 gastrectomy reported mortali-

ty rates of 10% and 13% respectively. The most important criticism of this randomized trial was undoubtedly the lack of experience of many surgeons participating in these trials: surgical experience, specific anatomic knowledge and postoperative management and care are crucial factors for this type of surgery. Conversely two Western studies, performed in specialized centers by sufficiently expert surgeons reported an acceptable operative mortality rate: a randomized trial conducted by Degiuli et al,[16] comparing D1 vs D2 gastrectomy and the study conducted by Marrelli et al.[11] comparing D2 vs D3 lymphadenectomy with gastrectomy. Finally in a Taiwanese single-institution trial comparing D1 vs D2 gastrectomy, where all the surgeons had performed at least 80 D2 procedures before participating in the study, there were no deaths in either group.[17]

In the British and Dutch trials splenectomy with or without pancreatectomy was underlined as a major risk factor for postoperative complications and deaths: effectively the risk of complications can be reduced to saving pancreatic tail and spleen resection such as that reported by Kodera et al[18] and de Manzoni et al.[2] The risk of complications can be reduced by avoiding this resection: in fact this factor influencing morbidity and mortality of the two European randomized trials without improvement in long-term survival. Total gastrectomy is generally associated with a higher morbidity compared to distal gastrectomy: the incidence of proximal tumours rapidly increases in Western countries compared to Japan and this evidence partly explains the different mortality rates in the two systems.[19-21] However in the trial conducted by the Japan Clinical Oncology Group (JCOG) the low report-

Table 4. Univarite analysis of 93 patients, only the significatives variables are repoted.

Varaible	No. of Cases	%	Morbid ity	%	P value	Mortality	%	P value
Age, Years								
≤ 62	23	25	6	26	0.077	0	0	0.187
63-71	47	50	16	34		1	2	
≥ 72	23	25	9	39		3	13	
Pleuropulmonary and/or Cardiac Disease								
Absent	69	74	21	30	0.069	0	0	0.001
Present	24	26	10	41		4	17	
Hemoglobin Preoperative Level								
≥ 10.5 gr/dL	81	87	24	30	0.002	3	4	0.64
≤ 10.5 gr/dl	12	13	7	58		1	8	
Creatinine level								
≥ 1.3	18	19	10	55	0.004	3	17	0.006
< 1.3	75	81	21	28		1	1	
American Society of Anesthesiologists' (ASA) class								
ASA I	24	26	4	16	0.001	0	0	0.026
ASA II	44	47	17	39		2	5	
ASA III	25	27	10	40		2	8	
Splenectomy and Pancreatectomy								
Not Performed	60	64	10	16	0.28	1	2	0.173
Performed	33	36	21	58		3	9	
Surgical Radicality (UICC)								
R0	77	83	23	30	0.003	1	1.2	0.008
R1-R2	16	17	8	50		3	18	
Perioperative blood trasfusion								
Not performed	54	58	13	24	< 0.001	2	4	0.976
Performed	39	42	18	46		2	5	

Table 5. Multivariate analysis of risk factors from morbidity and mortality in all the patients included in this study.

Variable	Coefficient	SE of coefficient	P value	Relative risk (95% CI)
Morbidity				
Splenopancreasectomy (performed vs. not performed)	0.21	0.07	0.005	0.61 (0.37-0.99)
ASA class (II/III vs. I)	0.31	0.09	0.002	0.83 (0.43-1.58)
Creatinine level (<1.3 vs. ≥1.3 gr/dL)	0.23	0.11	0.010	0.65 (0.29-1.41)
Mortality				
Creatinine level (<1.3 vs. ≥1.3 gr/dL)	0.39	0.18	0.086	1.13 (0.32-3.97)
Surgical radicality (R1/R2 vs. R0)	0.43	0.17	0.033	1.31 (0.39-4.36)
Cardioplumonary disease (present vs. not present)	0.31	0.11	0.008	0.31 (0.29-0.33)

ed mortality rate was not justifiable based on the number of different surgical procedures: no differences were observed in the distribution of the primary tumour location regarding Dutch trial cohort and the proportion of total to distal gastrectomy was also very similar.[22]

Moreover there is a tightened relation between the number of cases treated in specialized center and outcomes in the surgical treatment of gastric cancer: in the two European trials comparing D1 to D2 gastrectomy the excessive number of early deaths could have darkened the difference in OS between the two groups of patients.

However in Western countries the limited (D1) lymphadenectomy remains the standard treatment: the removal of perigastric and regional lymph nodes to reach the surgical radicality intent or to obtain correct staging is on the contrary strictly recommended by the Japanese authors.[23] De Manzoni et al[24] affirmed that the D2 dissection guarantees the removal of at least 15 lymph nodes with a optimal oncological radicality and correct disease staging: in this case it is necessary to emphasize that the incidence of metastases in the second tier nodes is present in over 25% of all cases.[25]

Due to lymphatic stomach drainage the involvement of para-oartic nodes may be regarded as the final diffusion stage of metastasis originating from the lymphatic system: from here they catch up with the systemic circulation through the thoracic duct.

Recently a randomized trial compared D2 lymphadenectomy plus PAND gastrectomy to D2 lymphadenectomy alone and showed no improvement in overall or recurrence free survival: the improvement of overall incidence of postoperative complications was 28.1% vs 20.9% respectively (p=0.07) but above all the frequency of minor complications was significantly higher in the first group (20.0% vs 9.1%, p<0.001).[13] For these reasons extended D2 lymphadenectomy plus PAND should not be used to treat curable stage gastric cancer: probably this technique would confer a survival advantage compared to D2 dissection only in a sub-group of patients with a tumour diameter measuring 50-100 mm and pN2 disease.[26] In the report of Sasako et al. the incidence of para-aortic nodes was lower than expected (8,5%) and D2 lymphadenectomy plus PAND in node positive patients results in worse survival rates: probably D2 dissection plus PAND should have resulted in better survival rates if the number of patients with para-oartic node metastases had been higher.[13]

The most important factors influencing postoperative morbility and mortality, in our limited casuistry, were also normally present in major world reports: our result, in fact, according to the world literature, underlined the importance of surgical variables able to influence postoperative outcomes and at the same time the central role of general patient condition. Obviously the older patients should have an elevated probability to have postoperative complications also because often they present a high ASA score due to contemporary presence of cardiac or pulmonary disease. Moreover cardiac or pleuropulmonary disease are able to influence the postoperative course also in patients younger than 72 years old that received perioperative blood transfusion or have elevated serum creatinine level. The influence of perioperative blood transfusion on postoperative morbidity was reported: this procedure seems to be strictly related to septic complications and for this reason the management of the blood during surgery should

be limited only if strictly necessary. Marrelli et al did not recommend extended lymphadenectomy in patients aged over 75 years old in which R0 resection cannot be performed because these cases showed a high postoperative morbidity and mortality.[11] On the contrary some authors emphasize a potential benefit of extended limphadenectomy also in non-curative cases.[27] Based on our limited casuistry we agree to assert the importance of R0 resection and to limit the lymphadenectomy extent in the non curative gastrectomy above all in the patients that presented multiple risk factors.

Finally several papers have reported a correlation between morbidity and albumin serum levels.[28-30] The albumin serum level reflects the proteins synthesis ability of the patient and seems to be that low albumin levels are strongly related to an insufficient plastic power: in the world literature in fact those patients present a high incidence of postoperative complications, above all anastomotic leakage. In our experience we did not find this correlation, probably due to the small number of cases. On the contrary the importance of serum level creatinine, as found in our experience, in influencing postoperative morbidity and mortality could probably be related with subclinical chronic renal failure that would get worse after surgical procedure: the next end point could be to investigate the postoperative variation of serum level creatinine in those patients in association with continuous monitoring of tubular necrosis enzymes such as NAG and AAP.

In conclusion there is a wide variation in operative morbility and mortality following gastric cancer surgery among countries and institutions. The type of gastrectomy and the extent of lymphadenectomy must be planned for each patient with gastric cancer: the Japanese guidelines define D2 gastrectomy as a standard procedure with excellent results while the British cancer guidance discourage this procedure.[31,32] Based on our experience we believe that it could favorable to perform D2 lumphoadenectomy by expert surgeons who have achieved an acceptable mastery of this tecnique. The role of postoperative course is also a very important determining factor of the postoperative outcomes: the availability of an expert medical team with sufficient experience within this field is most important in the management of the patients. Based on our experience we believe that only specialized surgeons could perform D2 lymphadenectomy and only in specialized centers: the postoperative care is also a very important factor determining the postoperative outcomes. Our limited experience confirmed that D2 lymphadenectomy represents a feasible procedure with acceptable morbidity and mortality rates: in fact the morbility rate was not negligible but the majority of complications were favourably resolved with appropriate clinical care. In our analysis the identification of subgroup of patients with high risk postoperative complications, according to the world literature, suggests that the correct patient selection and particular postoperative care in this case will probably contribute to a reduction in postoperative complication rates.

CONCLUSION

In our experience the D2 standard lymphoadenectomy, according to the Japanese institutions results, seems to be the most attractive procedure in the surgical management of gastric cancer. In specialized centers this approach may be performed with an acceptable risk of postoperative complications and deaths: in our experience the incidence of postoperative complication did not differ from those reported by different Japanese and some European studies. Moreover the majority of reported complications in our casuistry could be resolved favourably with a specific medical approach.

The correct patient selection and the evaluation of the potential risk factors in addition to adequate surgical approach and postoperative management and care can considerably reduce the incidence of postoperative problems and death.

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