

Significance of super-extended (D3) lymphadenectomy in gastric cancer surgery



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BACKGROUND: *The extension of lymphadenectomy is a matter of debate in gastric cancer surgery. The purpose of the present study was to analyse our experience on D3 lymphadenectomy in the treatment of gastric cancer with special reference to post-operative morbidity and mortality, incidence of para-aortic nodal metastases and long-term prognosis.*

METHODS: *The results of 201 patients who underwent potentially curative gastrectomy with D3 lymphadenectomy for non-metastatic gastric adenocarcinoma at the First Department of General Surgery, University of Verona, from January 1988 to December 2004, were analysed statistically. The analysis did not include gastric stump and linitis plastica type tumors.*

RESULTS: *Twenty-six out of the 201 patients (12.9%) showed para-aortic nodal metastases. Para-aortic node involvement was significantly higher in upper third tumors (29.1%) with respect to middle (6.1%) and lower third (7.5%) ($P < 0.001$). Sixty-two patients (30.8%) developed post-operative complications with pulmonary affections (7%), pancreatic fistulas (4.5%) and abdominal abscesses (4.5%) as the most frequently observed complaints. In-hospital mortality was 1.5%. Overall 5-year survival rate for R0-patients was 53.6%. Considering survival in relation to nodal involvement, interestingly, patients with non-regional lymph node metastases (M1a) showed a slightly better prognosis with respect to pN3 patients (3-year survival: 13.9% and 19.4% for pN3 and M1a classes, respectively).*

CONCLUSIONS: *D3 lymphadenectomy should be considered in curative surgery for advanced gastric cancer, especially for upper third tumors, with an acceptable morbidity and no increase in mortality. Further studies with a larger number of patients are required to confirm its prognostic value.*

KEY WORDS: D3 lymphadenectomy, Gastric cancer, Prognosis, Surgery.

Introduction

The reduction in mortality from stomach cancer reported by Japanese authors during recent years has been attributed to the increased detection of early gastric cancers and to the spreading of extended lymphadenectomy¹. There is no evidence from randomised controlled trials published to date that extended lymph node dissection (D2 lymphadenectomy) provides better prognosis than limited procedures (D1 lymphadenectomy)^{2,3}. However, Japanese literature reports encouraging long-

term results after extended and super-extended lymphadenectomy and, also some western countries' institutions described survival benefit from extension of nodal dissection⁴⁻⁶. In a previous paper we identified lymphadenectomy, together with depth of tumour invasion and nodal involvement, as independent prognostic factors for survival, showing a more favourable prognosis with the enlargement of nodal dissection. Patients who underwent super-extended (D3) dissection showed a lower risk of cancer related death if compared to patients who underwent D1 ($P = 0.001$) and even D2 dissection ($P = 0.053$), although the difference between extended (D2) and super-extended lymphadenectomy (D3) requires further confirmation⁷.

The purpose of the present study was to analyse our experience on super-extended lymphadenectomy in the treatment of gastric cancer with special reference to post-operative morbidity and mortality, incidence of para-aortic nodal metastases and long-term prognosis.

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Patients and methods

The study includes 201 patients observed at the First Department of General Surgery, University of Verona, Italy, between January 1988 and December 2004 who underwent a macroscopic potentially curative gastrectomy with super-extended (D3) lymph node dissection for non-metastatic gastric adenocarcinoma. The analysis did not include gastric stump and linitis plastica type tumors. Main demographic and clinical characteristics of the cohort in relation to tumor location are reported in Table I.

Lymph node dissection was standardized according to the Japanese rules for gastric cancer surgery (Japanese Gastric Cancer Association, JGCA): D1 lymphadenectomy (resection of perigastric nodes in position 1-6), D2 lymphadenectomy (resection of nodes in position 1-11) and D3 lymphadenectomy (resection extended to nodes in position 12-16) ⁸.

Perigastric nodes were dissected from the excised specimen by the surgeons immediately after resection, assigned to the appropriate station according to the JGCA classification, and sent for histological examination. To avoid errors caused by difficulties in assigning the lymph nodes to the correct station after en bloc resection, the second and third tier nodes were subdivided by the surgeon himself during lym-

phadenectomy as previously described in detail ⁹.

Tumors were staged according to the 1997 pathologic classification (pTNM) of the International Union Against Cancer ¹⁰. The histological classification followed the criteria of Lauren.

After discharge from the hospital all patients were personally followed-up at 4 months and subsequently at 6-month intervals. Median follow-up period for surviving patients was 57.2 months (range, 3 to 200 months), and no patient was lost to follow-up procedure.

In 185 cases there was pathological confirmation that a potentially curative resection (classified as R0) was achieved. On the contrary, microscopic residual tumour (R1) or positive peritoneal cytology were diagnosed in 16 cases that were excluded from survival analysis.

Post-operative deaths were computed while deaths from causes other than tumor recurrence were considered censored observations at the time of decease. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Chi-square test was used for categorical data and ANOVA test for continuous variables.

Analyses were performed using the Statistical Product and Service Solutions, SPSS 10.0 for Windows, 2000, SPSS Inc., Chicago IL.

TABLE I - Main demographic and clinical characteristics of the cohort according to the tumor location*.

	Upper third (n=55)	Middle third (n=66)	Lower third (n=80)	Total (n=201)
<i>Age (years)</i>				<i>P= 0,04</i>
Mean (range)	64,1 (41-82)	61,7 (32-84)	59,1 (23-78)	61,3 (23-84)
<i>Gender</i>				<i>P= 0,284</i>
Male	39 (70,9)	45 (68,2)	47 (58,8)	131 (65,2)
Female	16 (29,1)	21 (31,8)	33 (41,3)	70 (34,8)
<i>Lauren classification</i>				<i>P= 0,074</i>
Intestinal	36 (65,5)	40 (60,6)	34 (42,5)	110 (54,7)
Diffuse	14 (25,5)	20 (30,3)	33 (41,3)	67 (33,3)
Mixed	5 (9,1)	6 (9,1)	13 (16,3)	24 (11,9)
<i>Depth of invasion (pT)</i>				<i>P= 0,001</i>
pT1	1 (1,8)	6 (9,1)	15 (18,8)	22 (10,9)
pT2	22 (40)	26 (39,4)	27 (33,8)	75 (37,3)
pT3	24 (43,6)	22 (33,3)	37 (46,3)	83 (41,3)
pT4	8 (14,5)	12 (18,2)	1 (1,3)	21 (10,4)
<i>Nodal involvement (pN)</i>				<i>P= 0,011</i>
pN0	9 (16,4)	19 (28,8)	28 (35)	56 (27,9)
pN1	14 (25,5)	27 (40,9)	23 (28,8)	64 (31,8)
pN2	11 (20)	11 (16,7)	14 (17,5)	36 (17,9)
pN3	4 (7,3)	5 (7,6)	5 (6,3)	14 (7)
M1a	17 (30,9)	4 (6,1)	10 (12,5)	31 (15,4)

* Number represented in parenthesis are percentages.

Results

In the series of 201 patients, the total number of dissected lymph nodes was 9557, with a mean (\pm SD) of 45.1 (\pm 14.7) dissected nodes per case (median 42, range 15-108). The mean (\pm SD) number of metastatic nodes was 7.5 (\pm 9.8) (median 4, range 0-50) in the overall series and 10.4 (\pm 10.1) (median 7, range 1-50) in pN+ patients.

No differences in the average number of dissected nodes were observed in relation to the depth of tumor invasion (pT) ($P=0.302$). On the other hand, the mean (\pm SD) number of metastatic nodes increased progressively from pT1 to pT4 tumors (0.7 (\pm 2.0) for pT1, 4.9 (\pm 6.9) for pT2, 10.9 (\pm 11.3) for pT3 and 10.2 (\pm 11.1) for pT4; $P<0.001$).

The total number of retrieved nodes from the para-aortic stations was 1101, with a mean (\pm SD) of 5.5 (\pm 3.6) per case (median 5, range 0-20). Twenty-six patients (12.9%) showed para-aortic nodes involvement for a total number of 79 nodes. Hence, the mean (\pm SD) number of metastatic nodes was 3.0 (\pm 3.0) (median 2.5, range 1-15).

Considering only para-aortic stations, no increase in the average number of dissected ($P=0.833$) as well as positive nodes (0.0 for pT1, 0.4 (\pm 1.9) for pT2, 0.5 (\pm 1.4) for pT3 and 0.4 (\pm 0.9) for pT4; $P=0.626$) were observed in relation to the depth of tumor invasion (pT). Furthermore, the increase in the frequency of involvement of para-aortic stations according to pT classes was not statistically significant (0% for pT1, 12.0% for pT2, 15.7% for pT3 and 19.0% for pT4; $P=0.206$).

Considering para-aortic nodal metastases according to the tumor location, the frequency was significantly higher in upper third tumors (29.1%) with respect to middle

(6.1%) and lower third (7.5%) cases ($P<0.001$). Similarly, it was for the mean (\pm SD) number (0.9 (\pm 2.4) for upper third, 0.1 (\pm 0.5) for middle third, 0.3 (\pm 1.0) for lower third; $P=0.008$).

POST-OPERATIVE MORBID-MORTALITY

Sixty-two out of the 201 patients developed post-operative general and surgical complications (in-hospital morbidity: 30.8%). In 3 cases the complication was cause of death of the patient (in-hospital mortality: 1.5%). Table II lists the type of complications and their frequency. As shown pulmonary affections (7%), pancreatic fistulas (4.5%) and abdominal abscesses (4.5%) were the most frequently observed complaints.

SURVIVAL ANALYSIS

The 5-year survival rate for the 185 patients who underwent R0-resection was 53.6% with a median survival time beyond the observation period (Fig. 1). Figure 2 shows Kaplan-Meier estimates according to the depth of tumor invasion (pT). Survival curves in relation to the level of lymph nodal involvement (pN) are illustrated in Fig. 3. It is interesting to note that patients with non-regional lymph node metastases showed a slightly better prognosis with respect to pN3 patients (pN3 class, 3-year survival: 13.9%, median: 14.9 months; M1a class, 3-year survival: 19.4%, median: 19.3 months).

TABLE II - Major post-operative complications observed in the cohort*.

Type of complication	No. of cases (on 201 patients)
Pulmonary	14 (7)
Pancreatic fistula	9 (4,5)
Abdominal abscess	9 (4,5)
Gastric stump paresis	6 (3)
Anastomotic leak	3 (1,5)
Paralytic ileus	3 (1,5)
Lymphorrea	3 (1,5)
Duodenal stump leak	2 (1)
Anastomotic hemorrhage	2 (1)
Abdominal hemorrhage	2 (1)
Severe pancreatitis	1 (0,5)
Biliary fistula	1 (0,5)
Cardiovascular	3 (1,5)
Others	4 (2)
Total	62 (30.8)

*Number represented in parenthesis are percentages.

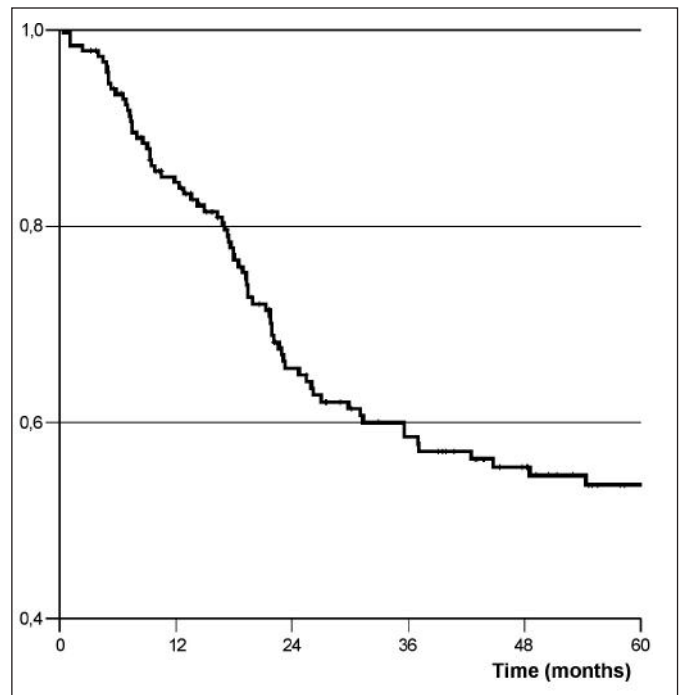


Fig. 1: Kaplan-Meier estimates of survival probability in the 185 patients who underwent potentially curative gastrectomy with super-extended (D3) lymphadenectomy.

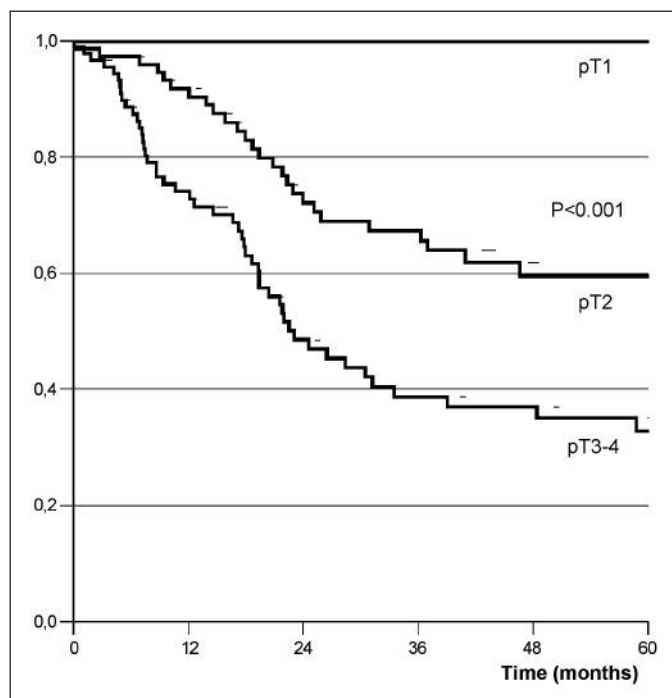


Fig. 2: Kaplan-Meier estimates of survival probability in the 185 patients who underwent potentially curative gastrectomy with super-extended (D3) lymphadenectomy according to the depth of tumor invasion (pT).

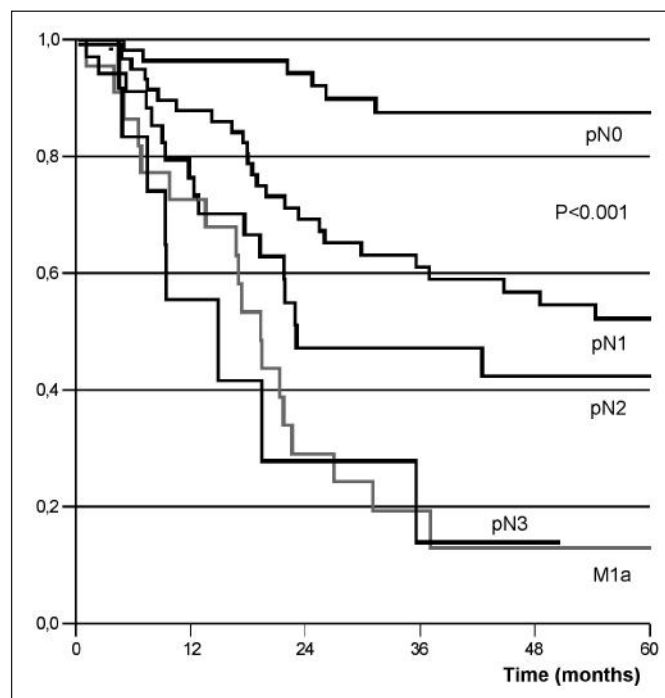


Fig. 3: Kaplan-Meier estimates of survival probability in the 185 patients who underwent potentially curative gastrectomy with super-extended (D3) lymphadenectomy according to nodal involvement (pN).

Discussion

The extension of lymphadenectomy is a matter of debate in gastric cancer surgery. The well-known randomized Dutch² and British³ trials that compared limited (D1) versus extended (D2) lymphadenectomy showed no significant differences in 5-year survival rates between the two groups. Recently this topic was addressed also by a Cochrane Review¹¹. The Authors concluded that “randomised studies show no evidence of overall survival benefit (after D2 dissection), but possible benefit in T3+ tumours. These results may be confounded by surgical learning curves and poor surgeon compliance. Non-randomised comparisons suggest a possible survival benefit for D2 in intermediate UICC stages”.

Nevertheless, lymph nodal metastases are an early event in gastric cancer and one of the most important prognostic factors. Extended (D2) and super-extended (D3) lymph node dissection has been demonstrated to lead to a better staging and better long-term results in several prospective non-randomized trials^{7,12-14}. In particular, in a previous experience we proved as D2 and D3 lymphadenectomy enables to remove positive nodes, which would have not been excised with limited lymphadenectomy (D1) in 39%¹³. Similar findings were reported by a Dutch study, where 32% of the patients had positive nodes removed in the second and third tiers¹². In our study, the percentage of patients requiring extended or super-extended lymphadenectomy to remove positive nodes in the second and third levels was 9% in pT1 tumors,

42% in pT2, 56% in pT3 and 67% in pT4¹³. Furthermore, it has also been demonstrated that excision of lymph nodes, although negative at microscopic examination, can improve survival¹⁵ and lymphadenectomy seems beneficial only when it encompasses the disease widely¹⁶, probably because cancer cells are present in the regional nodes even in cases classified as pN0¹⁷. Para-aortic nodal involvement is regarded as distant metastasis in the TNM classification, but the results recently reported by Japanese surgeons after super-extended lymphadenectomy (i.e. with complete dissection of the para-aortic stations) have cast doubts on this statement. These studies revealed that the incidence of para-aortic nodes involvement is higher than expected, ranging from 8 to 20% in patients with advanced gastric cancer and that the 5-year survival rate for this subgroup of patients after super-extended lymph node dissection is 13 to 20%^{18,19,20,21}.

Also in the present investigation para-aortic nodal deposits were found in 13% of the cases with a long-term outcome consistent with literature results (Figure 3). As already reported⁹, metastatic spread to para-aortic nodes was significantly more frequent in upper third tumors (29%) with respect to middle (6%) and lower third (7.5%) ($P < 0.001$).

Extended and super-extended lymphadenectomy are charged to be associated with a large increase in post-operative morbidity and mortality. This is true for some trials, especially from UK (22) and The Netherlands², where the volume of interventions per centre (and sur-

geon) was very low. On the contrary, no association between post-operative mortality and extension of lymphadenectomy was observed in other European high volume centres^{4,7,23,24}. In Japan, mortality after D2 dissection is less than 2% in the nationwide registry and less than 1% in specialized institutions^{25,26}. In a recent Chinese randomized controlled trial, super-extended (D3) lymphadenectomy showed to be associated with a significantly higher morbidity with respect to limited (D1) procedures (17% versus 7%) but without an increase in post-operative mortality²⁷. In the present experience, about 30% of the patients developed a post-operative general or surgical complication with pulmonary affections (7%), pancreatic fistulas (4.5%) and abdominal abscesses (4.5%) as the most frequently observed complaints. Consistently with best data reported in literature the in-hospital mortality rate was 1.5%. In conclusion, our data suggest that super-extended lymphadenectomy should be considered in curative surgery for advanced gastric cancer, especially for upper third tumors, with an acceptable morbidity and no increase in mortality, even though further studies with a larger number of patients are required to confirm its prognostic value.

Riassunto

BACKGROUND: L'estensione della linfadenectomia è argomento di discussione nella chirurgia del cancro gastrico. Il significato del presente studio è di analizzare la nostra esperienza sulla linfadenectomia D3 nel trattamento del cancro gastrico con particolare riferimento alla morbilità e mortalità post-operatoria, all'incidenza di metastasi ai linfonodi para-aortici ed alla prognosi a distanza.

METODI: Sono stati analizzati statisticamente i risultati relativi a 201 pazienti sottoposti a gastrectomia potenzialmente curativa con linfadenectomia D3 per adenocarcinoma gastrico non metastatico presso il Primo Dipartimento di Chirurgia Generale, Università di Verona, da Gennaio 1988 a Dicembre 2004. Dall'analisi sono stati esclusi i casi di cancro su moncone gastrico e di linite plastica.

RISULTATI: Ventisei su 201 pazienti (12.9%) hanno evidenziato metastasi ai linfonodi para-aortici. Il coinvolgimento dei linfonodi para-aortici è stato significativamente più elevato nei tumori del terzo superiore (29.1%) in confronto al terzo medio (6.1%) ed inferiore (7.5%) (<0.001). Sessantadue pazienti (30.8%) hanno sviluppato complicanze post-operatorie di cui le più frequentemente rilevate sono state affezioni polmonari (7%), fistole pancreatiche (4.5%) e ascessi intra-addominali (4.5%). La mortalità intraospedaliera è stata dell'1.5%. Il tasso di sopravvivenza globale a 5 anni per i pazienti R0 è risultato del 53.6%. Valutando la sopravvivenza in relazione al coinvolgimento linfonodale, è interessante notare come i pazienti con metastasi ai linfo-

nodi non-locoregionali (M1a) abbiano mostrato una prognosi leggermente migliore rispetto ai pazienti pN3 (sopravvivenza a 3 anni: 13.9% e 19.4% per le classi pN3 e M1a, rispettivamente).

CONCLUSIONI: La linfadenectomia D3 dovrebbe essere presa in considerazione nella chirurgia curativa per i casi di cancro gastrico avanzato, soprattutto per le lesioni del terzo superiore, con una morbilità accettabile e senza incremento di mortalità. Ulteriori studi con un numero maggiore di pazienti sono necessari per confermarne il significato prognostico.

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