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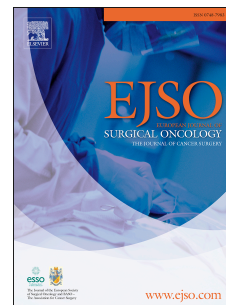
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# Accepted Manuscript

Extended lymphadenectomy in elderly and/or highly co-morbid gastric cancer patients: a retrospective multicenter study

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**Extended lymphadenectomy in elderly and/or highly co-morbid gastric cancer patients: a retrospective multicenter study**

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**Original article**

## ABSTRACT

### BACKGROUND

Gastrectomy with extended lymphadenectomy is considered the gold standard treatment for advanced gastric cancer, with no age- or comorbidity-related limitations. We evaluated the safety and efficacy of curative gastrectomy with extended nodal dissection, verifying survival in elderly and highly co-morbid patients.

### METHODS

In a retrospective multicenter study, we examined 1 322 non-metastatic gastric-cancer patients that underwent curative gastrectomy with D2 versus D1 lymphadenectomy from January 2000 to December 2009. Postoperative complications, overall survival (OS), and disease-specific survival (DSS) according to age and the Charlson Comorbidity Score were analyzed in relation to the extent of lymphadenectomy.

### RESULTS

Postoperative morbidity was 30.4%. Complications were more frequent in highly co-morbid elderly patients, and, although general morbidity rates after D2 and D1 lymphadenectomy were similar (29.9% and 33.2%, respectively), they increased following D2 in highly co-morbid elderly patients (39.6%). D2-lymphadenectomy significantly improved 5-year OS and DSS (48.0% vs. 37.6% in D1,  $p<0.001$  and 72.6% vs. 58.1% in D1,  $p<0.001$ , respectively) in all patients. In elderly patients, this benefit was present only in 5-year DSS. D2 nodal dissection induced better 5-year OS and DSS rates in elderly patients with positive nodes (29.7% vs. 21.2% in D1,  $p=0.008$  and 47.5% vs. 30.6% in D1,  $p=0.001$ , respectively), although it was present only in DSS when highly co-morbid elderly patients were considered.

**CONCLUSION**

Extended lymphadenectomy confirmed better survival rates in gastric cancer patients. Due to high postoperative complication rate and no significant improvement of the OS, D1 lymphadenectomy should be considered in elderly and/or highly co-morbid gastric cancer patients.

Key words:

Lymphadenectomy, gastric cancer, elderly, high morbidity, tailored treatment.



## INTRODUCTION

Although worldwide incidence of gastric cancer has decreased [1], it still remains the fourth most common type of cancer and the second leading cause of cancer-related death, with a growing prevalence in the elderly owing to increased life expectancy [2,3]. The literature often shows limited and discordant data regarding the prognostic value of age in gastric-cancer patients [4,5]. Generally, disease-specific survival does not seem to be worse in the elderly when compared with younger patients [6,7]. This evidence leads to the standardization of surgery in gastric cancer patients, whatever the age (and comorbidity) [8,9]. Gastrectomy with extended lymphadenectomy for advanced tumors is considered “standard” surgical therapy for operable patients, with no age- or comorbidity-related limitations. Following the initial doubts concerning its safety in the first randomized controlled studies [10,11], extended lymphadenectomy in gastric-cancer surgery now shows good results. Recent trials, minimizing the impact of nodal dissection on early postoperative outcome, show a survival benefit for extended nodal dissection compared with the more limited method, particularly in advanced stages [12,13]. Some of these studies show age (and comorbidities) to be a relevant predictor of postoperative complications, conditioning the safety of the surgical procedure itself [14-16].

The aim of this multicenter study was to evaluate the safety of curative gastrectomy with extended lymphadenectomy, and to verify its results in terms of overall and disease-specific survival in elderly and high-risk (due to comorbidities) patients.

## METHODS

We followed 1 322 patients who underwent curative surgery for non-metastatic gastric cancer from January 2000 to December 2009 at 13 high-volume centers belonging to the Italian Research Group for Gastric Cancer (IRGGC). Patients with microscopic or macroscopic residual disease, fewer than 16 retrieved nodes, and without follow-up data were excluded. All surgery was carried out by gastric cancer experts, who selected the extent of resection and nodal dissection according to international guidelines [8,9].

### *Statistical analysis*

All variables are presented with mean  $\pm$  standard deviation or median and range as appropriate. We analyzed: age, gender, type of gastrectomy (total vs. subtotal), extent of lymphadenectomy (D1 vs. D2) according to the latest Japanese Guidelines [8], pT (T1, T2, T3, T4a and T4b), and pN (N0, N1, N2, N3a and N3b) according to 7th TNM edition [17], grading, histotype (intestinal, diffuse, mixed type, other) according to the Lauren classification [18]; comorbidities at time of surgery classified according to the Charlson Comorbidity Score (Table 1) [19]; postoperative complication grade (0, I-II, IIIa-IIIb, IV and V) according to the Clavien-Dindo Classification [20]. We used 5 as cut-off of the Charlson Comorbidity Score (CCS) so as not to consider *high-risk* patients  $\geq 70$  years old with a single comorbidity, or patients between 80 and 90 years old without comorbidities. We defined patients with a CCS  $< 5$  as low-morbidity and patients with a CCS  $\geq 5$  as high-morbidity.

We used non-parametric tests (Chi-square and Mann-Whitney) to assess the statistical significance of the differences resulting from each comparison. Five-year observation following surgery was completed for each patient analyzed; patients lost during follow up

were censored at the moment of last contact. End points were death in overall survival (OS), and cancer-induced death in disease-specific survival (DSS). Survival rates were calculated using the Kaplan-Meier method, and survival differences were assessed using the log-rank test. Values of  $p < 0.05$  were considered statistically significant. Statistical analysis was carried out using SPSS software, version 20.0 (SPSS™ Inc., Chicago, IL, USA).

## RESULTS

Mean age was 67.0 years ( $\pm$  12.0; median: 70 years, range 26-91); patients were categorized in two groups according to median age: <70 years (686, 51.9%) and  $\geq$ 70 (636, 48.1%). A total of 998 patients (75.6%) presented CCS <5, and 324 patients (24.4%) presented CCS  $\geq$ 5. Two hundred-fifty patients (18.9%) underwent D1 lymphadenectomy, while 1072 patients (81.1%) underwent D2 lymphadenectomy.

### *Bivariate analysis*

Table 2 shows the clinicopathological features of age-classified patients. The mean number of harvested nodes in the entire sample was 34.5 ( $\pm$  16.8); 36.4 ( $\pm$ 18.1) in the younger-age group and 32.4 ( $\pm$ 15.2) in the elderly group ( $p$ <0.001).

The postoperative morbidity rate was 30.4% (402/1 322): 42 cases with grade V (3.2%), 7 with grade IV, 106 with grade IIIa-IIIb, 247 with grade I-II. Complications occurred in 189 patients (27.5%) in the younger group (<70 years) and in 213 patients (33.5%) in the elderly group ( $\geq$ 70 years) ( $p$ <0.001), and in 286 patients (28.6%) with CCS <5 and 116 patients (35.8%) with CCS  $\geq$ 5 ( $p$ <0.001). Among the elderly, 30.5% of patients (113/370) with CCS <5 and 37.6% of patients (100/266) with CCS  $\geq$ 5 presented complications ( $p$ =0.007). Table 3 shows complication rates according to age and CCS. The differing complication rates following extended lymphadenectomy and D1 were not considered to be statistically significant (29.9% vs. 33.2%). This was also the case when complication rates were analyzed in the elderly population. However, postoperative morbidity rates after extended lymphadenectomy (compared with D1) increased in elderly patients with CCS  $\geq$ 5, although no statistically significant differences were noted (39.6% vs. 35.2%, respectively, vs. 31.6% and 32.1% in the elderly with CCS <5).

### *Survival*

During follow-up, 124 patients (9.4%) resulted as lost before 5 years: median follow-up was 45 months (range 1-184). Five-year OS and DSS rates for the entire sample were 45.3% and 69.9%, respectively: elderly patients showed a 5-year OS of 37.6% (vs. 52.1% in the younger group,  $p<0.001$ ), and DSS was 64.3% (vs. 74.2% in the younger group,  $p=0.001$ ). The Charlson Comorbidity Score does not stratify survival in the entire elderly group, neither OS nor in DSS.

Complications negatively affected 5-year OS (42.8% vs. 48.4% in non-complicated patients,  $p=0.004$ ), but not DSS (69.5% vs. 73.0% in non-complicated patients,  $p= n.s.$ ); complicated patients  $\geq 70$  years showed worse 5-year OS (36.2% vs. 44.4% in non-complicated patients  $\geq 70$ ,  $p=0.037$ ) (Figure 1a). This rate further decreased in elderly patients with CCS  $\geq 5$  with postoperative complications (34.0% vs. 51.2% in non-complicated elderly patients with CCS  $\geq 5$ ,  $p<0.001$ ) (Figure 1b).

Extended lymphadenectomy (D2) significantly improved 5-year OS (48.0% vs. 37.6%,  $p<0.001$ ) and DSS (72.6% vs. 58.1%,  $p<0.001$ ) compared with D1. In elderly patients ( $\geq 70$  years), the survival benefit of D2 was not present in 5-year OS (38.4% in D2 group vs. 35.1% in D1 group,  $p= n.s.$ ), while its statistical significance was still evident in patients  $<70$  years (53.8% for D2 lymphadenectomy vs. 41.5% for D1,  $p=0.013$ ) (Figure 2 a-b). In both age groups, the extent of lymphadenectomy was statistically significant when considering DSS (66.6% for D2 vs. 57.7% for D1 in the elderly group,  $p=0.009$ ; 76.6% for D2 vs. 59.0% for D1 in younger patients,  $p=0.003$ ).

Extended lymphadenectomy was associated with better OS and DSS independently on the CCS, although its prognostic impact in patients with CCS  $\geq 5$  was less evident (OS in

CCS <5, D2 vs. D1: 47.5% vs. 36.7%,  $p=0.002$  and DSS in CCS <5, D2 vs. D1: 74.2% vs. 57.3%,  $p<0.001$ , respectively and OS in patients with CCS  $\geq 5$ , D2 vs. D1: 46.3% vs. 39.3%,  $p=0.023$  and DSS in CCS  $\geq 5$ , D2 vs. D1: 67.0%, vs. 59.5%,  $p=0.032$ , respectively). In highly co-morbid elderly patients, OS was not influenced by the extent of lymphadenectomy (5-year OS in patients  $\geq 70$  years with CCS  $\geq 5$ , D2 vs. D1: 43.1% vs. 39.6%,  $p= n.s.$ ), while DSS rates showed a trend towards statistical significance (5-year DSS in patients  $\geq 70$  years with CCS  $\geq 5$ , D2 vs. D1: 66.1% vs. 59.6%,  $p= 0.070$ ) (Figure 3 a-b).

Finally, considering elderly-patient survival analysis according to tumor stage, the extent of lymphadenectomy for different pT groups and for pN0 patients did not show any statistically significant differences in 5-year OS and DSS. Conversely, D2 nodal dissection in patients  $\geq 70$  induced better 5-year OS rates in patients with positive nodes (D2 vs. D1: 29.7% vs. 21.2%,  $p=0.008$ ), which were confirmed in DSS (D2 vs. D1: 47.5% vs. 30.6%,  $p=0.001$ ). While this significant difference was confirmed for DSS despite CCS, in 5-year OS this result was maintained only in elderly CCS <5 patients (D2 vs. D1: 30.2% vs. 19.0%,  $p=0.019$ ; in CCS  $\geq 5$  D2 vs. D1, 29.0% vs. 23.3%,  $p= n.s.$ ).

## DISCUSSION

In developed countries, mean life expectancy has increased in recent decades [21], with a proportionally higher risk of neoplastic disease with age [22]. Aging is associated with the onset of several, at times severe, comorbidities. In everyday clinical practice highly co-morbid geriatric patients, who are potentially eligible for gastrectomy, represent a relevant population in oncologic surgical procedures. Gastric cancer in the elderly seems to be less aggressive than in younger patients [6,14,23], with a prevalence of well-differentiated distal tumors. This less aggressive pattern might induce surgeons to use a less aggressive approach in elderly patients, as suggested in the literature, with particular regard to the extent of lymphadenectomy [23].

The aim of our study was to validate the safety and efficacy of standard gastric-cancer curative surgery in an unselected geriatric population.

Our data confirm the less aggressive pattern of gastric adenocarcinoma in the elderly: a higher rate of intestinal tumors according to the Lauren classification (66.5% vs. 48.1% in patients <70 years,  $p < 0.001$ ) requiring distal resection (60.4% vs. 53.1% in patients <70 years,  $p = 0.004$ ) has been observed in patients  $\geq 70$  years (Table 2). These favorable prognostic factors, along with advanced age and comorbidities, might explain the higher rate of limited lymphadenectomy in this group (D1 23.7% vs. 14.4% in patients <70 years,  $p < 0.001$ ), with a significantly lower number of harvested nodes in our series.

Disease-specific or disease-free survival after curative gastrectomy can be compared in elderly and younger patients [6,7,23]. Gastrectomy with D2 lymphadenectomy is nowadays considered the gold standard in the treatment of advanced resectable disease, without any exception regarding age or comorbidities [8,9]. To verify the real

survival benefit of surgical treatment in an elderly population, we need to show an improvement in the overall survival curve, as this reflects the real survival of patients. While OS in younger patients often corresponds to disease-specific survival, the potential influence of age and comorbidities on short-term and long-term surgical outcome should have a negative effect on OS. We retrospectively analyzed the impact of curative gastrectomy with extended, rather than limited, lymphadenectomy on the survival of elderly vs. younger patients. Well known controversial initial results about lymphadenectomy [10-13,24] led to resistance against extended lymphadenectomy in the Western world. Particularly, when the causes of the high postoperative morbidity with worsening OS observed after this surgical treatment were investigated, age was consistently associated with negative short-term outcome [10]. The link between age and postoperative morbidity following gastric cancer surgery has recently been confirmed [14-16,25-27].

As already described in the literature [28], our survival analysis showed the benefits of extended lymphadenectomy (D2) compared with limited nodal dissection (D1, involving at least 16 removed nodes according to TNM guidelines [17]), both in OS and DSS. However, when lymphadenectomy was considered in different age groups, OS (not DSS) benefits lost their significance in patients aged  $\geq 70$  years (Figure 2 a-b).

Although 70 is a widely used cut-off in age-based analysis, continuous quality-of-life improvements in the geriatric population has led to the introduction of other objective criteria to discriminate risk classes among the elderly. The Charlson scoring system, proposed in 1987 [19], thus acquired relevance in surgical studies. We analyzed the impact of surgery in patients  $\geq 70$  years on the basis of different CCS values ( $< 5$  for low-morbidity versus  $\geq 5$  for high-morbidity).



To justify the discrepancy between OS and DSS owing to the extent of lymphadenectomy in the elderly, in agreement with the above-mentioned literature, we considered the negative effect of complications. As already reported [10,11,15, 29], we also saw how complications negatively influence OS but not DSS (Figure 1a): this was more significant in the OS of highly co-morbid elderly patients (Figure 1b).

Overall, our data demonstrated a higher complication rate in elderly patients with CCS  $\geq 5$  after gastrectomy, and, although there were no significant differences between morbidity after D2 lymphadenectomy (29.8%) or D1 (33.2%), the complication rate following D2 in highly co-morbid patients  $\geq 70$  years increased exponentially (39.6%). These data show that extended lymphadenectomy does not improve OS in all patients, and the non-negligible possibility of complications following D2 in highly co-morbid elderly patients might be the cause.

The literature argues that extended node dissection positively influences the survival of patients with locally advanced disease [13,24,28]. To avoid the risk of surgical under-treatment in patients who might benefit from a more aggressive approach, we tested our suppositions in elderly patients with locally advanced tumors. The elderly patients in our series who underwent D2 dissection showed positive results in advanced stages, specifically in N+ tumors. In these patients, extended lymphadenectomy resulted in better DSS (47.5% vs. 30.6% in D1 group), which was also confirmed in OS (29.7% vs. 21.2% in D1 group). Once again, in highly co-morbid elderly patients this significant difference persisted in DSS but disappeared in OS. In selected geriatric patients limited lymphadenectomy (with the removal of more than 15 nodes) still represents an option not to be refused a priori.

Evident methodological limitations limit the relevance of our conclusions. Firstly, the

retrospective design of our study implies non-homogeneous groups, unavoidably influenced by the surgeons' choice with particular regard to lymphadenectomy.

Secondly, the Charlson Comorbidity Score (giving one additional point for each decade after 40 years) represents a valuable solution for patient stratification, but in a specifically age-addressed analysis it leads us to evaluate this parameter twice. Finally, we did not consider any adjuvant therapy: although analysis would have been influenced by the administration of different regimens with different schedules, survival might have been modified, thus conditioning the interpretation of results. With this regard, an analysis specifically addressed to the efficacy of surgery after neoadjuvant treatment in elderly patients could become interesting in the near future.

In conclusion, extended lymphadenectomy confirmed its efficacy in determining better survival rates in gastric cancer patients. However, after extended nodal dissection OS in highly co-morbid elderly patients, even with nodal involvement, does not show clear benefits owing to the high risk of perioperative complications.

#### **CONFLICT OF INTEREST STATEMENT**

The Authors have no conflict of interest to declare.

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**Figure legends**

**Figure 1 (a-b):** **a)** Overall survival of elderly patients ( $\geq 70$  years) according to postoperative complications ( $p=0,037$ ); **b)** Overall survival of highly co-morbid ( $CCS \geq 5$ ) elderly patients ( $\geq 70$  years) according to postoperative complications ( $p<0,001$ ).

**Figure 2 (a-b):** **a)** Overall survival of elderly patients ( $\geq 70$  years) according to the extent of lymphadenectomy ( $p= n.s.$ ); **b)** Overall survival of younger patients ( $<70$  years) according to the extent of lymphadenectomy ( $p=0,013$ ).

**Figure 3 (a-b):** **a)** Overall survival of highly co-morbid ( $CCS \geq 5$ ) elderly patients ( $\geq 70$  years) according to the extent of lymphadenectomy ( $p= n.s.$ ); **b)** Disease-specific survival of highly co-morbid ( $CCS \geq 5$ ) elderly patients ( $\geq 70$  years) according to the extent of lymphadenectomy ( $p= 0.070$ ).

**Table 1.** Charlson Comorbidity Score.

Score	Condition	Age
1	Myocardial infarction (history, not ECG changes only)	 40 yy +1 50 yy +2 60 yy +3 70 yy +4 80 yy +5 90 yy +6 100 yy
	Congestive heart failure	
	Peripheral vascular disease (includes aortic aneurysm $\geq$ 6 cm)	
	Cerebrovascular disease: accident with mild or no residua or TIA	
	Dementia	
	Chronic pulmonary disease	
	Connective tissue disease	
	Peptic ulcer disease	
	Mild liver disease (without portal hypertension, includes chronic hepatitis)	
Diabetes without end-organ damage (excludes diet-controlled alone)		
2	Hemiplegia	
	Moderate or severe renal disease	
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)	
	Tumor without metastases (exclude if > 5 year from diagnosis) *	
	Leukemia (acute or chronic)	
3	Lymphoma	
	Moderate or severe liver disease	
6	Metastatic solid tumor	
	AIDS (not just HIV positive)	

\* The score has been calculated for each patient without inclusion of gastric cancer.



**Table 2.** Clinico-pathological features of patients classified according to age.

	Age <70 years (# 686)		Age ≥70 years (# 636)		<i>p</i>
	#	%	#	%	
<b>Gender</b>					
M	416	60,6	372	58,5	n.s.
F	270	39,4	264	41,5	
<b>Charlson Comorbidity Score</b>					
<5	628	91,5	370	58,2	<0,001
≥5	58	8,5	266	41,8	
<b>Type of gastrectomy</b>					
Subtotal	364	53,1	384	60,4	0,004
Total	322	46,9	252	39,6	
<b>Extent of lymphadenectomy</b>					
D1	99	14,4	151	23,8	<0,001
D2	587	85,6	485	76,2	
<b>Histotype *</b>					
Intestinal	275	48,1	373	66,5	<0,001
Diffuse	210	36,7	123	21,9	
Mixed	44	7,7	38	6,8	
Other	43	7,5	27	4,8	
<b>Grading *</b>					
1	49	11,1	40	9,2	n.s.
2	132	29,8	140	32,3	
3	256	57,8	248	57,1	
4	6	1,3	6	1,4	
<b>pT</b>					
1	201	29,3	152	23,9	n.s.
2	138	20,1	125	19,7	
3	206	30,0	211	33,2	
4a-b	141	20,6	148	23,2	
<b>pN</b>					
0	284	41,4	284	44,6	n.s.
1	99	14,4	107	16,8	
2	106	15,5	111	17,5	
3a-3b	197	28,7	134	21,1	

\* Some data are missing.

**Table 3.** Details of postoperative complications according to age and Charlson Comorbidity Score (CCS).

		Clavien-Dindo classification			
		I-II	IIIa-IIIb	IV	V
		%	%	%	%
<b>CCS &lt;5</b>	<b>Age &lt;70 years</b>	44,5	50,9	28,6	16,6
	<b>Age ≥70 years</b>	27,1	31,2	28,6	26,2
<b>CCS ≥5</b>	<b>Age &lt;70 years</b>	4,5	2,8	0	4,8
	<b>Age ≥70 years</b>	23,9	15,1	42,8	52,4

