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Surgical outcomes of gastrectomy with D1 lymph node dissection performed for patients with unfavorable clinical conditions

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ABSTRACT

Background: Gastric cancer (GC) patients with advanced age and/or multiple morbidities have limited expected survival and may not benefit from extended lymph node resection. The aim of this study was to evaluate the surgical outcomes of these GC patients who underwent gastrectomy with D1 dissection.
Methods: We retrospectively reviewed all GC patients who underwent gastrectomy with curative intent from 2009 to 2017. The decision to perform D1 was based on preoperative multidisciplinary meeting, and/or intraoperative clinical judgment.
Results: Among 460 enrolled patients, 73 (15.9%) underwent D1 lymphadenectomy and 387 (84.1%) D2 lymphadenectomy. Male gender, older age, American Society of Anesthesiologists score (ASA) III/IV, higher neutrophil-to-lymphocyte ratio (NLR) and higher Charlson Comorbidity Index (CCI) were more common in the D1 group. Postoperative major complications were significantly higher in D1 group (24.7% vs 12.4%, $p < 0.001$) and mostly related to clinical complications. Locoregional recurrence was higher in the D1 group (53.8% vs 39.5%, $p = 0.330$) however, without statistical significance. No difference was found in disease-free survival (DFS) between D1 and D2 patients with positive lymph nodes ($p = 0.192$), whereas overall survival was longer in the D2 group ($p < 0.001$). Multivariate analysis showed a statistically significant impact on survival of age ≥70 years, CCI ≥5, total gastrectomy, D1 lymphadenectomy and advanced stages (III/IV).
Conclusions: Frail patients had high surgical mortality even when submitted to D1 dissection. DFS was comparable to D2. Extent of lymphadenectomy in high-risk patients should take in account the expectation of a decrease in surgical risk with the possibility of impairment of long-term survival.

Introduction

Gastric cancer (GC) persists as the 5th most common type of cancer worldwide and the 3rd most common cause of cancer related death [1]. As life expectancy increases, the incidence of gastric cancer in elderly frail patients with multiple age-related comorbidities also expands [2].

The basis of GC treatment is surgical resection with D2 lymphadenectomy characterized the resection of lymph nodes along the main gastric arteries [3,4]. However, this type of lymph node dissection extends surgical time and may increase surgery related morbidity and mortality when compared to a more limited dissection such as D1 lymphadenectomy [5,6]. Elder patients and those with poor clinical conditions have a shorter life expectancy and may not have the benefit from a broader lymph node dissection. Additionally, these frail patients, which are less tolerant to aggressions, would be exposed to a greater surgical risk.

Currently, we lack information concerning the results of performing D1 gastrectomy in patients with unfavorable clinical conditions. So, the aim of this study was to evaluate the short and long-term surgical results of this group of patients.

Methods

We performed a retrospective review of our institutional prospective collected database from 2009 to 2017. All patients

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submitted to gastrectomy with curative intent and D1 or D2 lymphadenectomy due to gastric adenocarcinoma were included. Patients with gastric stump neoplasia, other histological types or who underwent palliative resection were excluded.

All patients were staged with abdominal and pelvic computed tomography, upper endoscopy and laboratory tests. TNM staging was performed according to the TNM 7th edition [7].

D1 lymphadenectomy for unfavorable clinical conditions was defined as patients whose lesions would require D2 lymph node dissection for curative intent but were otherwise indicated for D1. Decision was based on preoperative multidisciplinary meeting and/or intraoperative clinical judgment of the main surgeon. Decision took in account the American Society of Anesthesiologists (ASA) classification [8], Charlson Comorbidity Index (CCI) [9], intraoperative instability, laboratory tests and nutritional status. CCI was considered without including the GC as a comorbidity [9]. From the age of 40, 1 point was added for each decade of life. CCI ≥5, ASA III/IV and age ≥70 were considered as risk factors. This cutoff age was established according to age quartile from all patients, where the last quartile was used as a cutoff point.

Surgical complications were graded according to the Clavien-Dindo's classification [10]. The length of hospital stay and the number of retrieved lymph nodes were evaluated. Major complications were considered Clavien III-V. Surgical mortality was considered when it occurred in the first 30 days after surgery or during the hospital stay after the procedure.

The postoperative follow-up was performed on a quarterly basis in the first year and every 6 months in the following years. Follow-up tests for relapse detection were performed based on the presence of symptoms. Absence in medical appointments for more than 12 months was considered as loss of follow-up.

All cases were operated by surgeons with extensive experience in the surgical treatment of GC. The surgical technique, gastric resection (subtotal vs total) and lymphadenectomy extension (D1 or D2) were performed according to the recommendations of the Japanese Gastric Cancer Association [3].

The study was approved by the hospital ethics committee (NP993/16) and registered in the "Plataforma Brasil"(CAAE: 2915516.2.0000.0065) that collects all research projects involving human beings in the country.

Statistical analysis

The Fisher's exact test or Chi-square tests were used for categorical variables and *t*-test for continuous variables. Factors associated with surgical mortality were determined by binary logistic regression analysis and Odds Ratios (OR) was obtained from model estimates. Overall survival (OS) and disease-free survival (DFS) were evaluated using the Kaplan–Meier analysis and differences in survival were examined using the Log Rank Test. To determine factors associated with DFS and OS, Hazard Ratios (HR) with 95% Confidence Intervals (CI) were calculated by univariate and multivariate Cox proportional hazard regression models. Variables that were significant on univariate analysis were included as covariates in multivariate Cox regression to determine which ones independently affected prognosis. Survival (in months) was calculated from the date of surgery until the date of recurrence or death of any cause. Patients alive were censored at the date of last follow-up. Postoperative mortality was excluded from the DFS analysis. All tests were two-sided and $p < 0.05$ was considered statistically significant. Analysis was performed using SPSS software, version 18.0 (SPSS Inc, Chicago, IL).

Results

Five hundred forty-four cases were initially evaluated. Of these, 84 did not meet the inclusion criteria. The remaining 460 patients were enrolled in the study. Of these, 73 patients (15.9%) underwent D1 lymphadenectomy and 387 (84.1%) D2. Mean age was 63 years (range 26–94), with male preponderance (60.4% vs 39.6%). Most tumors were located in the distal part of the stomach and therefore subtotal gastrectomy was the most frequent type of gastric resection (64.8%). Among the 73 patients in the D1 group, 14 patients were older than 70 years; 10 had CCI ≥5 and 10 were ASAIII/IV. Twenty-six patients had 2 of these risk variables and 13 patients had all 3 variables.

Clinical characteristics of D1 and D2 groups are summarized in Table 1. Univariate analysis revealed that male gender, older age, ASA III/IV, higher Neutrophil-to-lymphocyte ratio (NLR) and higher CCI were related to D1 group.

Subtotal gastrectomy was performed more frequently in the D1 group ($p = 0.011$). The mean number of harvested lymph node was significantly higher in the D2 group (41.3 vs 27.0, $p < 0.001$).

Well/moderately differentiated lesions ($p = 0.022$) and Lauren intestinal type tumors ($p = 0.003$) were more frequently observed in patients who received D1 lymphadenectomy.

Groups were similar concerning lymphatic ($p = 0.524$), venous ($p = 0.999$) and perineural invasion ($p = 0.073$). TNM staging was equivalent between the two groups ($p = 0.430$).

Major postoperative complications (Clavien ≥ III) were significantly higher in the D1 group (24.7% vs 12.4%, $p < 0.001$). Hospital mortality (Clavien V) occurred in 13 patients from each group, being significantly higher in the D1 group (17.8% vs 3.4%, $p < 0.001$). Nine of the 13 surgical deaths in the D1 group were due to clinical complications, with pneumonia being responsible for 4 deaths. In the D2 group 11 of the 13 surgical deaths occurred due to surgical complications and duodenal stump fistula was the most common cause, counting 4 deaths.

A binary logistic regression was performed to identify risk factors associated to surgical death (Table 2). After the multivariate analysis, age ≥70 years, ASA III/IV and D1 lymphadenectomy were independent risk factors for surgical death.

Median hospital stay was 9 days for both groups (D1: range 4–73 days, mean of 14.2 days; D2: range 4–59 days, mean of 11.5 days).

Survival analysis

The median follow-up was 24.4 months (mean of 28.9 months, SD ± 21.8) for surviving patients. At the time of this review, 121 patients died and 94 had disease recurrence. A total of 9.3% patients were lost during follow-up. OS and DFS rates were 73.7% and 78.3%, respectively. Adjuvant therapy was administered in 31.5% and 56.3% patients in the D1 and D2 groups, respectively ($p < 0.001$).

After excluding the postoperative deaths, recurrence in the remaining 434 patients was 21.7% (13/60 cases) for D1 and 21.7% (81/374 cases) for D2. DFS was equivalent for D1 and D2 groups ($p = 0.652$). Locoregional recurrence was higher in the D1 group, but this was not statistically significant (53.8% vs. 39.5%, $p = 0.330$). When adjusted for the presence of lymph node metastasis, there was also no significant difference in DFS between D1 pN+ and D2 pN + cases (62.1% vs 66.5%, respectively, $p = 0.192$; Fig. 1).

As observed in Fig. 1, the D2 group had longer OS rates (76% vs 61.6%, $p < 0.001$). The mean OS for D2 patients were 64.7 months (SD ± 2.18, median time not reached) and 38.5 months (SD ± 4.50, median of 38.5 months) for D1 patients. During follow-up, after excluding the postoperative mortality, death with recurrence occurred in 13.3% (8/60 cases) of D1 group and in 15% (56/374

Table 1
Clinicopathological variables and surgical results for D1 and D2 groups.

Variables	Lymphadenectomy Group		
	D1 n = 73 (%)	D2 n = 387 (%)	*p-value*
Age (years)			**< 0.001**
Mean (range)	72.4 (41–94)	61.2 (26–86)	
Gender			**0.023**
Male	53 (72.6)	226 (58.4)	
Female	20 (27.4)	161 (41.6)	
BMI (Kg/cm^2)			0.105
Mean (range)	23.7 (44)	24.7 (5.0)	
Hemoglobin (g/dL)			0.650
Mean (SD)	13.2 (14.7)	12.4 (2.2)	
Albumin (mg/dL)			0.113
Mean (SD)	3.8 (0.7)	4.1 (1.7)	
Neutrophil lymphocyte ratio (NLR)			
Mean (SD)	3.14 (2.4)	2.61 (2.5)	**0.026**
<3	47 (64.4)	297 (75.7)	
>3	26 (35.6)	90 (23.3)	
Charlson Comorbidity Index (CCI)[a]			**< 0.001**
<5	44 (60.3)	362 (93.5)	
>5	29 (39.7)	25 (6.5)	
ASA (American Society of Anesthesiologists)			**< 0.001**
I/II	32 (43.8)	331 (85.5)	
III/IV	41 (56.2)	56 (14.5)	
Tumor site			0.155
Upper	4 (5.5)	42 (10.9)	
Middle	13 (17.8)	84 (21.7)	
Lower	56 (76.7)	250 (64.6)	
Entire	0 (0)	11 (2.8)	
Type of resection			**0.009**
Subtotal	57 (78.1)	241 (62.3)	
Total	16 (21.9)	146 (37.7)	
Tumor size (cm)			0.273
Mean (SD)	4.4 (2.7)	4.9 (3.4)	
Grade histological type			**0.022**
Well/moderately differentiated	45 (61.6)	181 (46.8)	
Poorly differentiated	28 (38.4)	206 (53.2)	
Lauren type			**0.003**
Intestinal	50 (69.4)	189 (48.8)	
Diffuse/mixed	22 (30.6)	183 (47.3)	
Undetermined	0 (0)	15 (3.9)	
pT status			0.957
pT1	23 (31.5)	110 (28.4)	
pT2	8 (11.0)	47 (12.1)	
pT3	23 (31.5)	125 (32.3)	
pT4	19 (26.0)	105 (27.1)	
Harvested lymph nodes			**< 0.001**
Mean (SD)	27 (12.7)	41.3 (17.4)	
pN status			0.500
pN negative	35 (47.9)	169 (43.7)	
pN positive	38 (52.1)	218 (56.3)	
Stage			0.817
I/II	42 (57.5)	217 (56.1)	
III/IV	31 (42.5)	170 (43.9)	
Postoperative complication (Clavien-Dindo Classification)			**< 0.001**
No complication	41 (56.2)	264 (68.2)	
Grade I-II	14 (19.2)	75 (19.4)	
Grade III-IV	5 (6.8)	35 (9.0)	
Grade V	13 (17.8)	13 (3.4)	

[a] Value without neoplasia and with age.

cases) of D2 group.

Univariate and multivariate analysis were performed to evaluate the prognostic factors affecting OS (Table 3) and DFS (Table 4). Univariate analysis identified 7 variables that influenced the OS. After multivariate analysis, older age (≥70 years), CCI ≥ 5, total gastrectomy, D1 lymphadenectomy and more advanced stages (III/IV) were independent factors associated with significantly lower OS. Regarding DFS, total gastrectomy and stage III/IV were factors associated with worse DFS after multivariate analysis.

Discussion

Gastrectomy with D2 lymphadenectomy is the standard operation for patients with advanced GC. When compared to D1, it increases OS at the expense of an increased risk of early complications [5,6]. While this should be taken into account for all patients, it is particularly important to weight this decision in elderly and/or frail patients, since they have a shorter life expectancy [2,11]. This topic is subject of intense debate [12,13]. Patients who underwent D2 dissection showed an improvement in the OS and cancer-specific survival (CSS). However, age may not be so important to CSS. Some reports even show less recurrence in the elderly patients [14,15]. This may be partially explained by the higher frequency of Lauren's intestinal type tumors (consequence of the long term chronic inflammation of the gastric mucosa) which is associated with better prognosis (compared to diffuse type) [16,17]. Indeed, in our analysis the D1 group had more cases of intestinal type tumor. Furthermore, the frequency of GC with microsatellite instability, which correlates with less advanced stages and better survival outcomes, is also higher in older patients [18,19]. On the other hand, elderly patients are less prone to tolerate adjuvant therapy, which may worsen the survival of those with more advanced stages [20–22]. In our study, only 31.5% of the D1 patients received adjuvant therapy.

The present study was developed to further address this complex matter. Even though a D1 lymphadenectomy was performed in the group with clinical unfavorable medical conditions, in an attempt to reduce surgical morbidity and mortality, it remained notably high. As expected, when patients in the D1 group had major surgical complications, they died in a higher proportion than in the D2 group. This confirms their lower capacity to endure complications [23]. Interestingly, the risk factors for surgical death after multivariate analysis were age ≥70, ASA III/IV and D1 dissection. However, it does not mean that D1 dissection is more aggressive and prone to surgical mortality than D2. As previously described, the decision to perform D1 was based on the clinical judgment of the surgeon or at preoperative multidisciplinary meeting. So, this clinical evaluation effectively identified this high-risk group (composed of elderly and highly comorbid patients) and selected them to a less extended D1 dissection. This result highlights the importance of meticulous preoperative evaluation and the value of the surgeon's clinical perception in categorizing these high-risk patients.

Compared to the D2 group, the D1 had a male preponderance, more subtotal resections, and, as expected, patients were older and with more comorbidities. Possible explanations for having more subtotal resections are the previous discussed higher number of intestinal type lesions, were margins can be more easily obtained; and the different disease pathogenesis in the elder, with more distal lesions related to chronic gastritis [14,15,18].

NLR was also higher in the D1 group. NLR reflects inflammatory status and an elevated NLR has being associated with increased postoperative infectious complications and worse OS in GC patients [24,25]. In the D1 group, 69% of the deaths were due to pneumonia, while the majority of deaths in the D2 group were associated with surgical complications. This was expected, since less aggressive surgery was performed for the frail patients and their complications were mainly related with their clinical status. Instead, D2 patients mostly died from surgical complications with feature for duodenal stump fistula, which has been reported as the most lethal complication following D2 gastrectomy [26].

OS was significantly worse in the D1 group. While this result might be greatly influenced by the occurrence of non-cancer related deaths, it is noticeable that D1 lymphadenectomy was an independent risk factor for reduced survival after multivariate

Table 2
Univariate and multivariate analysis for the risk of surgical death (Clavien V).

Variables[a]	Univariate		*p*	Multivariate		*p*
	Odds Ratio	95% CI		Odds Ratio	95% CI	
Age 0–69 vs. ≥70 years	4.24	1.84–9.76	**0.001**	2.92	1.21–7.04	**0.017**
Female vs. Male	2.24	0.88–5.70	0.089	–	–	–
ASA I/II vs ASA III/IV	4.95	2.21–11.09	**<0.001**	2.93	1.20–7.17	**0.018**
NLR <3 vs >3	1.93	0.85–4.39	0.115	–	–	–
Charlson <5 vs. Charlson >5	2.42	0.93–6.32	0.071	–	–	–
Subtotal vs. Total gastrectomy	1.16	0.52–2.63	0.715	–	–	–
D2 vs. D1 gastrectomy	6.25	2.76–14.13	**<0.001**	2.96	1.18–7.43	**0.021**
Intestinal vs. Diffuse type	0.44	0.18–1.01	0.069	–	–	–
Stage I/II vs. stage III/IV	0.95	0.42–2.11	0.891	–	–	–

[a] Reference category listed first.

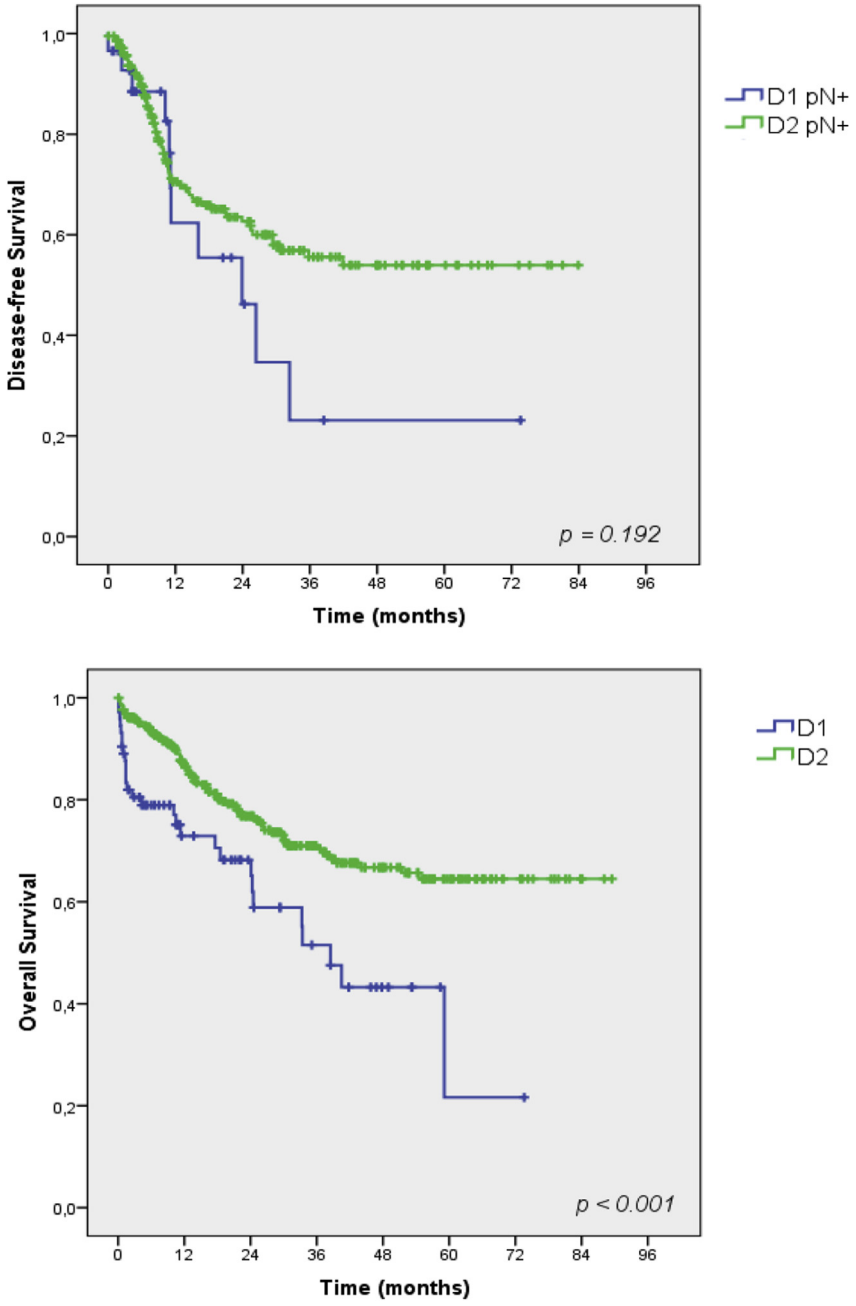

Fig. 1. Kaplan-Meier survival analysis. DFS for D1 and D2 groups with positive lymph node (pN+) and OS for all patients.

Table 3
Univariate and multivariate analysis for the risk of death (OS).

Variables[a]	Univariate		p	Multivariate		p
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Age 0–69 vs. ≥70 years	1.61	1.12–2.31	**0.010**	1.61	1.09–2.37	**0.017**
Female vs. Male	1.22	0.85–1.77	0.284	–	–	–
NLR <3 vs >3	1.21	0.81–1.82	0.357	–	–	–
Charlson <5 vs. Charlson >5	1.91	1.15–3.15	**0.012**	1.92	1.70–3.44	**0.029**
Subtotal vs. Total gastrectomy	1.81	1.27–2.59	**0.001**	1.93	1.34–2.77	**< 0.001**
D2 vs. D1 gastrectomy	2.17	1.42–3.32	**< 0.001**	2.24	1.38–3.61	**0.001**
Intestinal vs. Diffuse type	1.48	1.03–2.11	**0.033**	1.44	0.99–2.10	0.059
Stage I/II vs. stage III/IV	3.26	2.22–4.78	**< 0.001**	3.20	2.14–4.78	**< 0.001**
Clavien-Dindo 0-II vs. > III	3.93	2.65–5.83	**< 0.001**	4.14	2.76–6.22	**< 0.001**

[a] Reference category listed first.

Table 4
Univariate and multivariate analysis for the risk of recurrence (DFS).

Variables[a]	Univariate		p	Multivariate		p
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Age 0–69 vs. ≥70 years	0.79	0.50–1.24	0.304	–	–	–
Female vs. Male	1.22	0.80–1.85	0.368	–	–	–
NLR <3 vs >3	0.97	0.60–1.58	0.904	–	–	–
Charlson <5 vs. Charlson >5	0.96	0.47–1.98	0.914	–	–	–
Subtotal vs. Total gastrectomy	2.37	1.58–3.57	**< 0.001**	3.13	1.42–3.20	**< 0.001**
D2 vs. D1 gastrectomy	1.14	0.64–2.06	0.652	–	–	–
Intestinal vs. Diffuse type	1.75	1.16–2.63	0.008	1.19	0.79–1.81	0.406
Stage I/II vs. stage III/IV	7.58	4.48–12.83	**< 0.001**	7.04	4.13–12.02	**< 0.001**
Clavien-Dindo 0-II vs. III-IV	0.92	0.44–1.89	0.812	–	–	–

[a] Reference category listed first.

analysis with other covariates such as age, CCI and clinical stage.

DFS was similar between groups. Afterwards, we verify DFS specifically in patients with positive lymph nodes in the surgical specimen. In theory, patients with positive lymph nodes corresponded to the group that would most benefit from a more extensive lymphadenectomy, since it already had the demonstration of lymph node dissemination [27]. However, no significant differences were found in recurrence rates regardless of the extent of lymphadenectomy. Nevertheless, there was a tendency for a better result in the D2 group. Also, D1 patients are expected to have more regional recurrences, compared to peritoneal/hematogenic, than those of D2 group. Again, data suggest that a tendency occurred, however, without reaching statistical significance. The inclusion of more cases and a longer period of follow-up may turn this tendency to a significant result.

As a benchmark for our study, it is worthy to mention Rausei et al. [12] who analyzed elderly Italian patients and found no increase in OS for patients over 70 years with comorbidities submitted to D2 lymphadenectomy compared to D1. OS was improved only in those without comorbidities. Regarding CSS in patients submitted to D2 in the whole population, there was a tendency for better survival even though without a statistical significance. At the same time, the analysis including only patients with positive lymph nodes demonstrated a better CSS for the D2 group.

Some limitations in the present study should be considered. This was a single-center study and some patients have a relatively short follow-up. Also, differences in adjuvant chemotherapy regimens exist among groups. A major limitation of our study is the difficulty to define “unfavorable clinical condition”. Although this decision employs laboratory parameters and validated risk scores, it remains subjective and, therefore, exposed to great variation among surgeons. Recent improvements in quality of life and health promotion measures make inappropriate using only “age” as a measure. The application of the CCI assists in this categorization, since it creates a score based on the number of relevant clinical comorbidities. However, CCI does not discriminate the severity of each disease. On the other hand, ASA classification is based on the patient physical status, and reflects the grade of severity of the comorbidity. Accordingly, defining an effective and practical daily risk score is still required [2,28].

A point worth mentioning is the high number of lymph nodes present in the D1 lymphadenectomy group. While this may be influenced by the use of Carnoy's solution as tissue fixative [29,30], we believe that a certain degree of "contamination", which means resection of lymph nodes outside the territory of D1 lymphadenectomy, may have occurred. Possibly, this fact may have added morbidity to the D1 group and impaired the comparison of survival between groups [27].

Among the strengths of the study, it was conducted in a high-volume center and patients and procedures were performed by specialized surgeons. Additionally, they were all previously discussed in meetings, so most were judged as unfavorable in the preoperative by a multidisciplinary team. Also, to avoid bias, only D1 and D2 gastrectomy with potentially curative intent was considered.

Currently, with the diffusion of employment of D2 lymphadenectomy worldwide, there are few opportunities to compare oncological surgical results between the two types of lymphadenectomy [5,6,31–33]. Although there was no statistical difference, the curve in the survival chart shows a tendency for better survival for D2 group. Probably, with a large sample of patients and a longer follow-up time this may reach statistical significance.

Progressively, it has been observed an increasing number of patients presenting multiple comorbidities that are candidates for surgical procedure [34]. Despite the proven superior oncologic outcome of patients submitted to D2 lymphadenectomy, patients with a bad performance status may not tolerate the more extensive lymphadenectomy. It may be associated with increased surgical morbidity and mortality, and therefore may render the former benefit irrelevant [35]. Patients with low expected survival due to

the presence of severe comorbidities may not have time to benefit from this improvement in survival attributed to D2 dissection. Judgment and careful preoperative evaluation should be performed in these cases. It must be remembered that the Dutch D1D2 trial took 15 years of follow-up to identify a lower locoregional and gastric-cancer-related death rate of the D2 arm [36].

Conclusion

Frail patients with unfavorable clinical conditions have high surgical morbidity and mortality even when a more limited D1 lymphadenectomy is performed. There was no difference in DFS between D1 and D2 groups. Extent of lymphadenectomy in high-risk patients should take in account the expectation of a decrease in surgical risk with the possibility of impairment of long-term survival.

Conflict of interest statement

It was not funded and the authors declare that there is no conflict of interest.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Canc 2015;136:E359–86.
[2] Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. J Geriatr Oncol 2016;7:249–57.
[3] Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1–19.
[4] Ajani JA, In H, Sano T, et al. American joint committee on cancer (AJCC). In: Cancer staging manual. eighth ed., vol 17. Stomach: Springer; 2017. p. 203–20.
[5] Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908–14.
[6] Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Canc 1999;79:1522–30.
[7] Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077–9.
[8] Doyle DJ, Garmon EH. American society of Anesthesiologists classification (ASA Class). StatPearls. Treasure. Island FL: StatPearls Publishing LLC.; 2017.
[9] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.
[10] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[11] Hsu JT, Liu MS, Wang F, et al. Standard radical gastrectomy in octogenarians and nonagenarians with gastric cancer: are short-term surgical results and long-term survival substantial? J Gastrointest Surg 2012;16:728–37.
[12] Rausei S, Ruspi L, Rosa F, et al. Extended lymphadenectomy in elderly and/or highly co-morbid gastric cancer patients: a retrospective multicenter study. Eur J Surg Oncol 2016;42:1881–9.
[13] Ruspi L, Galli F, Pappalardo V, et al. Lymphadenectomy in elderly/high risk patients: should it be different? Transl Gastroenterol Hepatol 2017;2.
[14] Takeshita H, Ichikawa D, Komatsu S, et al. Surgical outcomes of gastrectomy for elderly patients with gastric cancer. World J Surg 2013;37:2891–8.
[15] Takeuchi D, Koide N, Suzuki A, et al. Postoperative complications in elderly patients with gastric cancer. J Surg Res 2015;198:317–26.
[16] Nagini S. Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol 2012;4:156–69.
[17] Bosman TF, Carneiro F, Hruban RH, et al. WHO classification of tumours of the digestive system. In: International agency for research on cancer (IARC). fourth ed. Lyon: IARC Press; 2010.
[18] Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513:202–9.
[19] Pereira MA, Ramos M, Faraj SF, et al. Clinicopathological and prognostic features of Epstein-Barr virus infection, microsatellite instability, and PD-L1 expression in gastric cancer. J Surg Oncol 2018:829–39. https://doi.org/10.1002/jso.25022.
[20] Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315–21.
[21] Serra-Rexach JA, Jimenez AB, García-Alhambra MA, et al. Differences in the therapeutic approach to colorectal cancer in young and elderly patients. Oncol 2012;17:1277–85.
[22] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
[23] Barchi LC, Charruf AZ, de Oliveira RJ, et al. Management of postoperative complications of lymphadenectomy. Transl Gastroenterol Hepatol 2016;1.
[24] Szor DJ, Roncon Dias A, Pereira MA, et al. Neutrophil-lymphocyte ratio is associated with prognosis in patients who underwent potentially curative resection for gastric cancer. J Surg Oncol 2018.
[25] Mohri Y, Tanaka K, Toiyama Y, et al. Impact of preoperative neutrophil to lymphocyte ratio and postoperative infectious complications on survival after curative gastrectomy for gastric cancer: a single institutional cohort study. Medicine (Baltim) 2016;95:e3125.
[26] Ramos MFKP, Pereira MA, Barchi LC, et al. Duodenal fistula: the most lethal surgical complication in a case series of radical gastrectomy. Int J Surg 2018;53:366–70.
[27] Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg 2014;101:23–31.
[28] Takama T, Okano K, Kondo A, et al. Predictors of postoperative complications in elderly and oldest old patients with gastric cancer. Gastric Cancer 2015;18:653–61.
[29] Dias AR, Pereira MA, Mello ES, et al. Carnoy's solution increases the number of examined lymph nodes following gastrectomy for adenocarcinoma: a randomized trial. Gastric Cancer 2016;19:136–42.
[30] Pereira MA, Dias AR, Faraj SF, et al. Carnoy's solution is an adequate tissue fixative for routine surgical pathology, preserving cell morphology and molecular integrity. Histopathology 2015;66:388–97.
[31] Degiuli M, De Manzoni G, Di Leo A, et al. Gastric cancer: current status of lymph node dissection. World J Gastroenterol 2016;22:2875–93.
[32] El-Sedfy A, Dixon M, Seevaratnam R, et al. Personalized surgery for gastric adenocarcinoma: a meta-analysis of D1 versus D2 lymphadenectomy. Ann Surg Oncol 2015;22:1820–7.
[33] Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006;7:309–15.
[34] Jorgensen TL, Hallas J, Friis S, et al. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Canc 2012;106:1353–60.
[35] Jiang L, Yang KH, Chen Y, et al. Systematic review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. Br J Surg 2014;101:595–604.
[36] Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439–49.