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ORIGINAL ARTICLE

Long-term results of tailored D_2 lymph node dissection after R_0 surgery for gastric cancer

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Abstract Implementation of extended lymph node dissection for gastric cancer in western non-specialized centers through tailoring its extent upon disease stage and patient comorbidities was suggested as a wise policy to reduce morbidity and mortality rates, albeit with a potential for undertreatment in elderly and/or comorbid patients. Current definition of R_0 resection for gastric cancer lacks consideration of treatment-related variables such as extended lymph node dissection. Few studies to date have tried to fill this gap in such a clinical context. A retrospective evaluation of factors influencing long-term results after R_0 surgery was done in a prospective series of a non-specialized western surgical unit during the implementation of D_2 lymphadenectomy. Univariate and multivariate analysis of 22 variables were performed on a prospective database of 233 consecutive R_0 resections performed by ten different surgeons in 10 years. Endpoint was disease-free survival calculated at 5 and at 10 years. Disease-free survival rates were independently influenced by age, American Society of Anesthesiologists (ASA) status and lymph node ratio. Subset analysis of the status at censor stratified for age and ASA status failed to identify any significant difference in disease recurrence rates. Lymph node ratio was the only treatment-related independent prognostic factor for long-term results after R_0 surgery for gastric cancer in the setting of a non-specialized western unit, where the extent of lymph node dissection needs to be tailored on the presence of comorbidities (ASA status).

Keywords Stomach neoplasms · Surgery · Prognostic factors · Lymph node ratio

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Introduction

After the discouraging results of randomized controlled trials on extended lymph node dissection in non-specialized western units at the end of last century [1–3], it appeared clear that a wise option for the implementation of extended lymph node dissection in such context was to limit splenectomy and distal pancreatectomy and to "tailor" the extent of surgery on the disease stage and especially on patient's comorbidities [4–6]. Actually, we already demonstrated that the presence of comorbidities is the main independent predictor of operative morbidity and mortality. Maintaining a standardized tailored approach coupled with adequate coaching of less-experienced surgeons led to a safe implementation of extended lymph node dissection in our unit without any influence of surgeon-related factors [7]. The main drawback of this "tailored" approach could be a potential jeopardy of oncologic radicality in elderly and/or comorbid patients. Actually, the therapeutic basis of surgery for gastric cancer are built over the opportunity to perform a curative resection, or a R_0 resection, defined as the absence of microscopic or macroscopic residual tumor by the TNM staging system [8]. This goal is reached in

50–85% of western patients, but local and/or systemic relapses are encountered in up to 50% of such cases [9, 10]. The current definition of R_0 radicality in staging systems alone is insufficient to identify patients at risk of disease recurrence, as it does not take into account the impact of treatment-related variables, such as the extent of lymph node dissection. The clinical research during the past years tried to fill this gap through the development of new prognostic scores [11–15].

The Italian Research Group for Gastric Cancer (IRGGC) developed and tested a prognostic score based on five independent variables [16]: pT status, pN status, type of lymph node dissection, age and maximum diameter of the tumor. A prognostic score allows to stratify the recurrence risk into low (IRGGC score $\leq$30), intermediate (31–60) and high (>60), with more than 80% of cases allocated into the two extreme classes.

The National Cancer Center Hospital in Tokyo developed a computer program in order to predict the percentage of lymph node metastases, based on a database of 3,843 cases treated in Japan [17]. After the input of seven variables (sex, age, macroscopic type, microscopic type, location, depth of tumor invasion, and maximum diameter) the program generates an output on the probability of metastasis in each of the 16 lymph node groups defined by the Japanese Gastric Cancer Association (JGCA) [18]. Diagnostic accuracy of this program was further tested on a German [19] and an Italian [20] population. Considering that several of the input variables are generally obtained after surgery on pathologic examination, the program was subsequently used to generate a prognostic index more than to guide the lymph node dissection in the single case: summing together the percentages of metastasis in the lymph node groups that are not removed at surgery it is possible to obtain the so-called "Maruyama index" (MI). This prognostic index has been applied to patients enrolled in the North American trial on adjuvant chemoradiation [21] and in the Dutch trial on extended lymph node dissection [22, 23], identifying a prognostic cutoff for MI = 5.

In order to overcome the problem of stage migration induced by extended lymph node dissection [24, 25], during the past years a new independent prognostic factor was largely investigated and validated: the lymph node ratio (LNR), defined as the absolute ratio between metastatic and examined lymph nodes, appeared to be a strong independent indicator of prognosis [26–29], even in case of inadequate nodal staging (<15 examined lymph nodes) [30]. The IRGGC defined four prognostic intervals for LNR [21]: 0, 0.01–0.09, 0.10–0.25, >0.25. These intervals corresponded to a definite different prognosis even within the same pN status, independently from the extent of nodal dissection.

Currently, little or nothing has been published concerning these prognostic factors outside eastern or specialized centers. The purpose of this study was therefore a retrospective evaluation of factors influencing long-term results in a prospective database of R_0 resections built during the implementation of extended lymph node dissection in our surgical unit.

Materials and methods

From 1998 to 2007, surgery for gastric adenocarcinoma was performed on 387 consecutive patients in our unit. Of these, 63 patients (16.3%) were not resected. The remaining 324 cases (83.7%) were submitted to resection of the tumor. Ninety-one cases were excluded from this study: 22 gastric stump neoplasms; 9 Siewert type II cardia neoplasms; 6 palliative resections with D_0 lymph node dissection due to poor general conditions and emergency (bleeding) or a synchronous malignant neoplasm in other organs; 6 resections of a recurrent tumor; 2 resections after neo-adjuvant chemotherapy and 46 R_{1-2} resections. The remaining 233 cases constitute the population of this study. All perioperative data of these patients were prospectively recorded into a database and outpatient follow-up scheduled every 6 months during the first 3 years and yearly thereafter, up to the study censor scheduled at 31 December 2009.

Setting

All the operations were performed according to a standardized protocol of pre-, intra- and post-operative care in a tertiary care, 700-bed hospital of the Italian National Health System. In 1998, extended lymph node dissection (D_2) according to the JGCA [18] was introduced into the clinical practice of the unit. Two surgeons (M.C., G.B.G.) with previous specific training in extended lymph node dissection obtained through stages in Japanese surgical centers, personally monitored its implementation and diffusion, coaching the other eight surgeons participating in the study.

Patient-related variables

There were 127 males and 106 females, mean $\pm$ SD age was 66.9 $\pm$ 11.5 years (median 68, range 36–95) and it was categorized according to its median value in univariate analysis or calculated as a continuous variable in multivariate analysis. Concerning the presence of comorbidities, patients were classified utilizing the American Society of Anesthesiologists (ASA) system: 147 were ASA class I–II and 86 ASA class III–IV. Body mass index (BMI, expressed as kg/m^2) mean $\pm$ SD was 25.4 $\pm$ 3.7 (median 25.4, range 15.2–37.9) and it was categorized according to its median value in univariate analysis or calculated as a continuous variable in multivariate analysis.

Neoplasm-related variables

Location of the tumor was classified according to JGCA [18] into lower third, middle third and upper third. The mean ± SD maximum diameter of the tumor was 43.3 ± 25.0 mm (median 40, range 5–130), and it was categorized according to its median value in univariate analysis or calculated as a continuous variable in multivariate analysis. The sixth edition UICC-TNM staging system [8] was used to define depth of invasion (pT), nodal status (pN), stage grouping and grading. Microscopic type was defined as "intestinal" or as "non intestinal" (diffuse or mixed) according to Lauren [31].

Treatment-related variables

All operations were carried out in an elective setting under a strict perioperative care protocol including antibiotic and antithromboembolic prophylaxis. Details about the extent of organ resection and lymph node dissection according to patient- and neoplasm-related variables have been previously published [7, 32].

Overall mean ± SD number of examined lymph nodes per patient was 28.9 ± 14.4 (median 27, range 2–78). It was 17.8 ± 9.4 (median 15, range 2–52) after $D_{1\alpha\text{-}\beta}$ lymph node dissection and 34.0 ± 13.9 (median 32, range 9–78) after D_2 lymph node dissection, according to JGCA [18]. Overall number of cases with inadequate nodal staging (<15 examined lymph nodes) was 34 (14.6%), 29 (37.2%) after $D_{1\alpha\text{-}\beta}$ lymph node dissection and 5 (3.2%) after D_2 lymph node dissection.

At the study censor, the chief surgeon (G.B.G., surgeon #1) performed more than 50% of the operations and six out of ten participating surgeons performed at least ten cases each.

The MI [21–23] (mean 17.2 ± 29.3, median 6, range 0–200) was categorized as < or ≥5 in univariate analysis or calculated as a continuous variable in multivariate analysis. The IRGGC score [16] (mean 46.9 ± 35.0, median 35.1, range 1.59–99.9) was categorized as ≤30, 31–60 and >60 in univariate analysis or calculated as a continuous variable in multivariate analysis. The LNR (mean 0.16 ± 0.24, median 0.03, range 0.0–0.94) was categorized as 0, 0.01–0.09, 0.10–0.25 and >0.25 in univariate analysis or calculated as a continuous variable in multivariate analysis. The eventual association of an adjuvant treatment (chemotherapy or chemo-radiation therapy) as well as the accrual year was also recorded and evaluated.

Endpoints and statistical analysis

All data were analyzed with StatsDirect© statistical software, version 2.7.7 (StatsDirect Ltd., Altrinchan, UK).

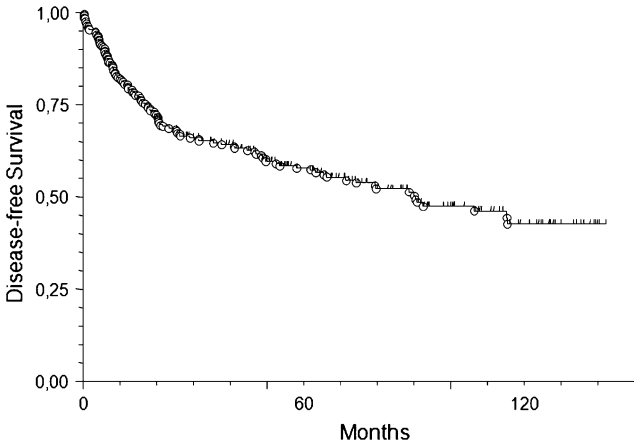

Fig. 1 Disease-free survival curve

Disease-free survival was calculated at 5 and at 10 years from the operation by the Kaplan–Meier method [33]. Univariate analysis was performed applying the log-rank test [34]. All the resulting significant variables were considered into a multivariate analysis applying Cox's proportional hazards model [35], generating "dummy" variable indicators for non-dichotomic variables and avoiding automated model building in order to eliminate any potential bias induced by the stepwise procedure [36]. Independent patient-related variables identified at multivariate analysis were further cross-matched with the status at censor (alive without disease, death due to operative mortality, alive with or death due to recurrent disease, death due to other causes or lost to follow-up) and the different subsets analyzed with the generalized Cochran–Mantel–Haenszel tests [37]. Statistical significance was assumed for p values <0.05.

Results

After a mean ± SD follow-up of 57.2 ± 39.2 months (median 52, range 0.1–142.2), 132 patients (56.6%) were alive at the study censor and 122 (52.4%) were without any evidence of recurrent disease. Causes of death of the remaining 101 patients were 10 cases (4.3%) of operative mortality (calculated as any death occurring within 60 days from the operation), other causes in 29 patients (12.4%), disease recurrence in 60 patients (25.7%) and two patients (0.9%) lost to follow-up.

Disease-free survival (mean ± SE) was 57.1 ± 3.1% at 5 years and 42.9 ± 4.2% at 10 years (Fig. 1). After univariate analysis (Table 1), gender, age, ASA status, stage, extent of lymph node dissection, MI, IRGGC score and LNR were considered into a multivariate analysis (Table 2). Disease-free survival was independently influenced by growing age (hazard ratio 1.03, 95% CI 1.01–1.05), ASA

Table 1 Univariate analysis

Variable	Pattern	No.	%	Disease-free survival				
				% 5 years	% 10 years	HR	95% CI	p^a
Gender	Females	106	45.5	65.8	47.7	1.00		0.02
	Males	127	54.5	49.9	37.8	1.57	1.08–2.27	
Age	≤68 years	118	50.6	67.7	52.9	1.00		<0.001
	>68 years	115	49.4	45.6	30.8	1.95	1.34–2.84	
ASA status	I–II	147	63.1	68.9	51.3	1.00		<0.001
	III–IV	86	36.9	36.8	27.4	2.41	1.60–3.64	
BMI (kg/m^2)	≤25.4	118	50.6	57.1	45.6	1.00		0.738
	>25.4	115	49.4	57.4	39.1	1.01	0.73–1.55	
Location	Lower third	127	54.5	54.6	39.8	1.00		0.748
	Middle third	65	27.9	60.4	45.2	0.99	0.67–1.43	
	Upper third	41	17.6	60.1	46.9	0.87	0.53–1.37	
Diameter	≤40 mm	129	55.4	63.5	50.8	1.00		0.119
	>40 mm	104	44.6	49.3	33.9	1.34	0.92–1.95	
pT	pT_1	52	22.3	69.9	61.6	1.00		<0.001
	pT_2	113	48.5	60.1	46.9	1.31	0.83–2.09	
	pT_3	64	27.5	40.7	20.7	2.43	1.39–4.22	
	pT_4	4	1.7	25.0	0.0	3.76	0.76–18.4	
pN	pN_0	111	47.6	77.6	66.4	1.00		<0.001
	pN_1	55	23.6	53.3	24.8	2.37	1.51–3.74	
	pN_2	41	17.6	26.1	17.4	4.13	2.34–7.29	
	pN_3	26	11.2	26.4	13.2	4.93	2.38–10.2	
Stage	Ia	46	19.7	72.3	63.1	1.00		<0.001
	Ib	60	25.7	78.0	67.1	0.76	0.45–1.29	
	II	44	18.9	61.8	30.5	1.54	0.87–2.75	
	IIIa	30	12.9	38.1	32.6	2.56	1.29–5.10	
	IIIb	26	11.2	25.2	0.0	3.67	1.71–7.88	
	IV	27	11.6	25.4	12.7	4.13	1.88–9.09	
Grading	G1	16	6.9	60.2	60.2	1.00		0.525
	G2	78	33.5	59.26	43.4	1.39	0.63–3.05	
	G3	139	59.6	54.5	41.2	1.59	0.74–3.40	
Microscopic type	Intestinal	140	60.1	55.1	43.0	1.00		0.708
	Non-intestinal	93	39.9	60.4	42.2	0.93	0.64–1.36	
Gastric resection	Subtotal	170	73.0	56.6	43.5	1.00		0.996
	Total	63	27.0	59.0	41.4	0.99	0.66–1.51	
Lymph node dissection	$D_{1\alpha\text{-}\beta}$	78	33.5	43.3	23.2	1.00		<0.001
	D_2	155	66.5	64.1	52.0	0.49	0.33–0.75	
Adjacent organs resection	No	205	88.0	58.3	42.5	1.00		0.834
	Yes	28	12.0	51.5	41.9	1.06	0.69–1.85	
Surgeon	#1	127	54.5	60.5	49.3	1.00		0.16
	All others	106	45.5	53.0	27.9	1.30	0.89–1.89	
Single surgeon	#1	127	54.5	60.5	49.3	1.00		0.535
	#2	28	12.0	43.5	25.2	1.59	0.87–2.92	
	#3	22	9.4	61.4	0.0	0.92	0.49–1.75	
	#4	13	5.6	69.2	23.1	1.29	0.53–3.13	
	#5	11	4.7	54.5	54.5	1.26	0.48–3.29	
	#6	11	4.7	60.0	60.0	0.94	0.37–2.37	
	Others (<10 cases each)	36	17.1	39.5	19.7	1.55	0.78–3.08	

Table 1 continued

Variable	Pattern	No.	%	Disease-free survival				
				% 5 years	% 10 years	HR	95% CI	p^a
Examined lymph nodes	<15	34	14.6	57.6	36.9	1.00		0.492
	≥15	199	85.4	57.1	43.8	0.83	0.49–1.43	
Maruyama index	<5	105	45.1	70.4	60.2	1.00		<0.001
	≥5	128	54.9	45.9	27.2	2.12	1.46–3.08	
IRGGC score	≤30	100	42.9	77.2	68.2	1.00		<0.001
	31–60	37	15.9	65.8	48.9	1.38	0.84–2.28	
	>60	96	41.2	31.0	13.6	3.76	2.49–5.68	
Lymph node ratio	0	111	47.6	77.6	66.4	1.00		<0.001
	0.01–0.09	26	11.2	67.6	54.1	1.71	0.96–3.04	
	0.10–0.25	39	16.7	45.3	36.1	2.44	1.45–4.11	
	≥0.26	57	24.5	18.1	9.0	5.62	3.29–9.61	
Adjuvant treatments	No	158	67.8	56.2	47.5	1.00		0.838
	Yes	75	32.2	59.4	28.4	1.04	0.70–1.55	
Accrual year	1	24	10.3	50.0	37.5	1.00		0.604
	2	20	8.6	55.0	55.0	0.68	0.31–1.48	
	3	21	9.0	57.1	34.3	0.97	0.45–2.10	
	4	22	9.4	66.7	61.9	0.54	0.26–1.16	
	5	24	10.3	58.3	45.4	0.91	0.42–1.98	
	6	23	9.9	43.5	43.5	1.36	0.58–3.18	
	7	26	11.2	57.7	28.8	0.97	0.44–2.15	
	8	27	11.5	64.8	Na	0.70	0.32–1.54	
	9	20	8.6	63.0	Na	0.88	0.36–2.17	
	10	26	11.2	53.0	Na	1.25	0.53–2.93	

HR Hazard ratio, *CI* confidence interval, *Na* non available

[a] Log-rank test

Table 2 Multiple variable analysis

Variable	Pattern	Coefficient	Coefficient SE	HR	95% CI	*p*
Gender	Females versus males	−0.35	0.21	0.70	0.47–1.05	0.089
Age	Continuous	0.03	0.01	1.03	1.01–1.05	0.005
ASA status	III–IV versus I–II	0.85	0.22	2.35	1.53–3.61	<0.001
Stage	Ib versus Ia	−0.29	0.42	0.74	0.32–1.70	0.481
	II versus Ib	0.20	0.58	1.22	0.39–3.86	0.731
	IIIa versus II	0.01	0.84	1.01	0.19–5.23	0.996
	IIIb versus IIIa	0.21	0.97	1.24	0.18–8.28	0.825
	IV versus IIIb	−0.49	1.11	0.61	0.07–5.32	0.654
Lymph node dissection	D_2 versus $D_{1\alpha\text{-}\beta}$	−0.38	0.28	0.68	0.39–1.18	0.173
Maruyama Index	Continuous	−0.01	0.01	0.99	0.98–1.01	0.161
IRGGC score	Continuous	0.01	0.01	1.01	0.99–1.03	0.489
Lymph node ratio	Continuous	2.93	0.72	18.7	4.58–76.8	<0.001

SE Standard error, *HR* hazard ratio, *CI* confidence interval

Deviance (likelihood ratio) $\chi^2 = 101.41$, $df = 12$, $p < 0.001$

Table 3 Status at censor stratified by age group and ASA status

Patterns	Status at censor no. (%)				Total
	Alive without disease	Operative mortality	Alive with or dead due to recurrent disease	Dead due to other causes[a]	
Age ≤ 68 ASA I–II	63 (67.0)	–	23 (24.5)	8 (8.5)	94 (40.3)
Age ≤ 68 ASA III–IV	10 (41.6)	1 (4.2)	9 (37.5)	4 (16.7)	24 (10.3)
Age > 68 ASA I–II	28 (52.8)	1 (1.9)	19 (35.9)	5 (9.4)	53 (22.8)
Age > 68 ASA III–IV	21 (33.9)	8 (12.9)	19 (30.6)	14 (22.6)	62 (26.6)
Total	122 (52.4)	10 (4.3)	70 (30.0)	31 (13.3)	233

Cochran–Mantel–Haenszel test coefficient 2.22, $p = 0.136$

[a] Includes two patients lost to follow-up

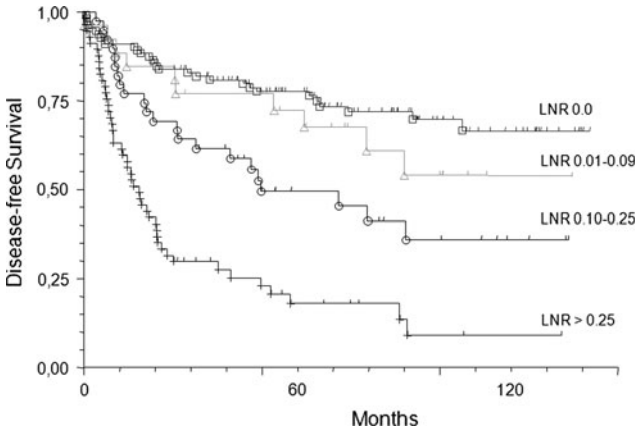

Fig. 2 Disease-free survival curves according to the lymph node ratio (*LNR*) categories

status III–IV (hazard ratio 2.35, 95% CI 1.53–3.61) and by growing LNR (hazard ratio 18.7, 95% CI 4.58–76.8).

Subset analysis of the patterns of age and ASA status cross-matched with the status at censor is represented in Table 3. No significant trends were identified (coefficient = 2.22, $p = 0.136$).

Discussion

A 5-year disease-free survival rate above 50% (Fig. 1) with an overall 30% rate of disease recurrence (Table 3) in this selected population of R_0 resections is within the range of results previously reported in specialized western centers [28, 38] and well beyond those reported by western population-based studies [39]. However, the fact that long-term disease-free survival was independently affected by growing age and by the presence of comorbidities in this study can be interpreted as a lack of radicality in elderly and comorbid patients. Actually, subset analysis for the causes of death (Table 3) showed that recurrence rates are not significantly different among subgroups and that worst survival of elderly and comorbid patients is mainly due to operative mortality and death due to other causes. Particularly, the 4.3% operative mortality rate recorded in this study is higher than 1.7% reported in a series from a non-specialized western center adopting the same "tailored" policy [6]; nonetheless, 80% of these deaths were recorded in the group of elderly and comorbid patients (Table 3).

Concerning the other patient-related variable analyzed, BMI did not influence survival in our study, as it did not considering early results and lymph node retrieval [7, 32], while in eastern centers the presence of overweight (BMI > 25 in about 15% of cases) adversely affects both early and late results [40]. It should not be surprising while considering that overweight and obesity are a definite characteristic of 50–60% of western patients, western surgeons being probably more used than their eastern colleagues to deal with it [41]. Another possible issue of jeopardy of oncologic radicality may be represented by inadequate lymph node retrieval (<15 examined lymph nodes), already identified as having an independent negative impact on long-term results [42]. Notwithstanding a significantly higher incidence of inadequate lymph node retrieval in $D_{1\alpha\text{-}\beta}$ versus D_2 lymph node dissection [32, 43], it simply had no effect on long-term disease-free survival in this study. A possible explanation of this phenomenon may rely on one of the independent determinants of inadequate lymph node retrieval in our series, the single pathologist performing lymph node retrieval on formalin-fixed en-bloc specimens [32], meaning that inadequate nodal examination by the pathologist does not automatically translate into inadequate nodal clearance by the surgeon. The absence of any effect of the single surgeon or of the chief surgeon versus the others, as well as the absence of any time-trend depending on the accrual year can lead to the inference that the process of standardization and coaching during the implementation of extended lymph node dissection in our unit was effective and stable from the beginning of the experience.

Concerning the prognostic factors after R_0 surgery, LNR was the only independent predictor of long-term disease-free survival, with four well-defined subgroups of patients according to the intervals determined by the IRGGC [28] (Fig. 2). This study suggests that LNR should therefore be used to evaluate the long-term prognosis after R_0 surgery for gastric cancer also in a non-specialized western center.

It was already demonstrated that LNR is not significantly influenced by the number of examined lymph nodes [28, 32, 44], therefore limiting the stage-migration phenomenon induced by extended lymph node dissection and a tumor-ratio-metastasis (TRM) instead of a tumor-node-metastasis (TNM) staging system already suggested [45]. In the recent new seventh edition of the TNM staging system [46], the UICC elected to retain the pN classification based on the number of metastatic nodes, modifying pN grouping with a new pN_1 group with 1 or 2 metastatic lymph nodes and to introduce a different stage grouping. It seems that this new pN stage-grouping is more accurate as a prognostic predictor than its precursor [47]. It will be interesting, in a near future, to investigate the prognostic yield of this new TNM stage-grouping faced to LNR.

Conflict of interest The authors declare that they have no conflict of interest.

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