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Bridging prediction and reality: AI-based external validation of predictive models for lymph node metastasis in gastric cancer

Lúcio Lara Santos [p,q,r,1], Anna Carolina Finamore [s,1], Suzanne Gisbertz [t,u], Uberto Fumagalli Romario [v], Wojciech Kielan [w], Ricccardo Rosati [x], Piotr Kołodziejczyk [y], Bas Wijnhoven [z], Ines Gockel [aa], Simone Giacopuzzi [ab], Wojciech P. Polkowski [ac], Andrew Davies [ad,ae,af], Paolo Morgagni [ag], Arnulf Hoelscher [ah], William Allum [ai], Domenico D'ugo [aj], Henk Hartgrink [ak], Maria Bencivenga [ab], Jacopo Viganò [al], Manuel Pera [am], Daniel Reim [an], Paul M. Schneider [ao], Stefan Mönig [ap], Giovanni De Manzoni [ab], Gian Luca Baiocchi [aq], Cláudia Antunes [ar,2], Paulo Matos da Costa [as,*,2], The GASTRODATA Consortium (European Chapter of International Gastric Cancer Association)

[p] *Research Center of IPO-Porto (CI-IPOP) / RISE@CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto (IPO-Porto) / Porto Comprehensive Cancer Center (P.CCC) Raquel Seruca, Porto, Portugal*
[q] *Department of Surgical Oncology, Portuguese Oncology Institute of Porto, Porto, Portugal*
[r] *School of Medicine and Biomedical Sciences, University Fernando Pessoa, FP-I3ID, Gondomar, Portugal*
[s] *Department of Marine Engineering, Escola Superior Náutica Infante D. Henrique (ENIDH) and Nova School of Business and Economics, Lisbon, Portugal*
[t] *Department of Surgery, Amsterdam UMC Location University of Amsterdam, Amsterdam, the Netherlands*
[u] *Cancer Treatment and Quality of Life, Cancer Center, Amsterdam, Amsterdam, the Netherlands*
[v] *Digestive Surgery, European Institute of Oncology, IRCCS, Milano, Italy*
[w] *University Centre of General and Oncological Surgery, Medical University Wroclaw, Poland*
[x] *Department of Gastrointestinal Surgery, San Raffaele Hospital, Milan, Italy*
[y] *Department of Surgery, Jagiellonian University Medical College Kraków, Poland*
[z] *Department of General Surgery, Erasmus Medical Center, Rotterdam, the Netherlands*
[aa] *Department of Visceral Surgery, Clarunis (University Digestive Health Care Center), University Hospital of Basel / St. Clara Hospital of Basel, Switzerland*
[ab] *Department of Surgery, General and Upper G.I. Surgery Division, University of Verona, Verona, Italy*
[ac] *Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland*
[ad] *Department of Upper Gastrointestinal and General Surgery, Guy's and St Thomas' Hospital, London, UK*
[ae] *School of Cancer and Pharmaceutical Sciences, King's College, UK*
[af] *Department of Molecular Medicine and Surgery and Upper Gastrointestinal Surgery, Karolinska Institute, Stockholm, Sweden, London, UK*
[ag] *Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì, Italy*
[ah] *Contilia Center for Esophageal Diseases, Elisabeth Hospital Essen, Germany*
[ai] *Department of Surgery, Royal Marsden NHS Foundation Trust, London, UK*
[aj] *Department of General Surgery, Fondazione Policlinico Gemelli, Rome, Italy*
[ak] *Leiden University Medical Center, the Netherlands*
[al] *Chirurgia Generale 1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[am] *Section of Gastrointestinal Surgery, Hospital del Mar, Universitat Autònoma de Barcelona, Hospital del Mar Research Institute (IMIM), Barcelona, Spain*
[an] *TUM University Hospital, Department of Surgery, Munich, Germany*
[ao] *Digestive Oncology Tumor Centre and Esophageal Cancer Centre, Hirslanden Medical Center, Zurich, Switzerland*
[ap] *Department of Surgery, University Hospital of Geneva, Geneva, Switzerland*
[aq] *Department of Clinical and Experimental Sciences, Surgical Clinic, University of Brescia, Third Division of General Surgery, Spedali Civili di Brescia, Brescia, Italy*

* Corresponding author.
E-mail addresses: llarasantos@gmail.com (L.L. Santos), annafinamore@gmail.com (A.C. Finamore), s.s.gisbertz@amsterdamumc.nl (S. Gisbertz), ubertofumagalliromario@gmail.com (U.F. Romario), wojciech-kielan@wp.pl (W. Kielan), rosati.riccardo@hsr.it (R. Rosati), p.kolo@interia.pl (P. Kołodziejczyk), b.wijnhoven@erasmusmc.nl (B. Wijnhoven), ines_gockel@hotmail.com (I. Gockel), simone.giacopuzzi@univr.it (S. Giacopuzzi), wojciech.polkowski@umlub.edu.pl (W.P. Polkowski), ardavies22@hotmail.com (A. Davies), morgagni2002@libero.it (P. Morgagni), arnulf.hoelscher@icloud.com (A. Hoelscher), wmallum@rhotmail.com (W. Allum), domenico.dugo@policlinicogemelli.it (D. D'ugo), h.h.hartgrink@lumc.nl (H. Hartgrink), maria.bencivenga@univr.it (M. Bencivenga), j.vigano@smatteo.pv.it (J. Viganò), pera@hmar.cat (M. Pera), daniel.reim@tum.de (D. Reim), paul@professor-schneider.ch (P.M. Schneider), stefan.moenig@hcuge.ch (S. Mönig), giovanni.demanzoni@univr.it (G. De Manzoni), gianluca.baiocchi@asst-cremona.it (G.L. Baiocchi), claudia.antunes@tecnico.ulisboa.pt (C. Antunes), paulomatoscosta@gmail.com (P. Matos da Costa).

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[ar] Instituto Superior Técnico, Universidade de Lisboa, INESC INOV Lab, Lisboa, Lisboa, Portugal
[as] Faculdade de Medicina, Universidade de Lisboa (Hospitais de Santa Maria and Garcia de Orta), Lisboa, Portugal

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ABSTRACT

Introduction: The optimal extent of lymphadenectomy in gastric cancer surgery remains a subject of ongoing debate. Our previous modelling work indicated that identifying at least 26 lymph nodes may reveal occult nodal metastases in patients undergoing more limited dissections, thereby reducing the risk of under-staging. However, those analyses were population-based and lacked individual-level validation of clinical outcomes, including disease-free and overall survival. This study sought to externally validate, using artificial intelligence (AI)–driven modelling, the predicted risk of *pN* upstaging associated with simulated increases in retrieved lymph node counts.

Materials and methods: The PT cohort comprised 209 patients with gastric adenocarcinoma who underwent curative-intent gastrectomy between 2004 and 2022, all with fewer than 26 examined lymph nodes, *pN* + status, and M0 disease. External validation was conducted using the European GASTRODATA (GD) cohort, which included 392 patients from a multinational registry (2019–2022). Patients in both cohorts met identical eligibility criteria. Cohort comparability was assessed using a combination of AI-trained regression models, Random Forest algorithms with cross-validation, and multidimensional projection analysis, ensuring robust evaluation of dataset equivalence. Proportional and exponential simulation models were subsequently applied to the combined dataset ($n = 601$) to explore different assumptions regarding nodal yield scaling.

Results: The two cohorts were statistically comparable across key clinicopathological variables, supporting their suitability for external validation. Simulations predicted increases of 21% (proportional model) and 16% (exponential model) in the number of metastatic lymph nodes, indicating a clinically meaningful risk of under-staging when lymphadenectomy yield falls below recommended thresholds.

Conclusion: These findings externally validate, in a larger multicentre cohort, the previously developed simulation models and reinforce the recommendation that harvesting at least 26 lymph nodes during gastrectomy is essential to optimise staging accuracy and prognostic assessment in gastric cancer, regardless of institutional setting.

1. Introduction

The optimal extent of lymphadenectomy in gastric cancer (GC) treatment remains an ongoing subject of controversy and debate. Recent expert consensus from East Asian and Western countries [1] established D2 or D1+ lymphadenectomy with retrieval of at least 16 lymph nodes as the standard. However, failure to adhere to standardised procedures results in significant variability in the number of nodes retrieved across different studies ([2], [3], [4], [5], [6], [7], [8]).

The current literature indicates that the ideal upper limit for lymph node harvesting is 24-30 nodes ([2], [3], [4], [5], [9], [10], [11], [12], [13]) to ensure complete oncologic resection (R0) and improve survival outcomes, while reducing the risk of recurrence.

The effectiveness of extended lymphadenectomy as a standard procedure for all patients, regardless of tumour stage, histologic type, anatomic location, and adjuvant therapies, has been questioned ([3], [14]).

In a previous study by Costa et al. [15], simulations were conducted to estimate the potential increase in positive lymph nodes (metLn) if a 26-node lymphadenectomy (tLn = 26) was performed on patients originally with 1-25 dissected nodes. Two scenarios were tested to evaluate Stage Migration (*SM*), which identified between 7 and 28% of SM cases. The Will Rogers phenomenon was rejected by the simulation of the Overall Survival (*OS*) comparisons. But this calculation addresses group survival, not individual survival, nor the disease-free survival of patients at risk of incomplete *metLn* harvesting.

The role of negative lymph nodes (*negLn*) as an independent prognostic factor was well demonstrated.

In this disruptive context, the robustness of our models to predict SM should be demonstrated. An AI-based external validation of our methods was performed on the GASTRODATA dataset [16], a wide multinational registry in European countries.

The results of merging the two datasets are expected to shed light on setting the lymphadenectomy threshold, based on the estimated number of expected *metLn*.

2. Objective

The objective of this study was to externally validate probability prediction models designed to estimate the increased detection of metastatic lymph nodes had patients received a 26-node lymphadenectomy, using simulated redistribution.

3. Materials and Methods

To reach this goal, the same methods were applied to two cohorts of comparable patients.

3.1. Data sources

This study analyses two cohorts described in Table 1.

The Portuguese clinical cohort previously reported by Costa et al. [15] includes retrospectively analysed, prospectively collected cases of gastric cancer (GC), 209 (of 830) patients who underwent potentially curative gastrectomy (2004 to 2022) and had pathology-confirmed gastric adenocarcinoma. The inclusion criteria were patients with fewer than 26 *dissected lymph nodes* (*tLn<26*) and a positive metastatic node count (*metLn>0*). M1 patients were excluded.

The validation cohort (GD) was extracted from the prospectively maintained, multinational GASTRODATA registry spanning 11 European countries (from 2019 to 2022), as detailed by Baiocchi [16]. Of 3060 registry patients, 392 met the same eligibility criteria as the PT cohort and were included as the GD cohort.

For locally advanced tumours (≥T2) in patients biologically suitable for surgery, a D1+/D2 dissection was intended in all cases. It should be noted that only *pN* + patients were enrolled in the study cohorts, which inherently reflects a selection of cases with established nodal disease, further reinforcing the oncological rationale for extended dissection.

[1] Authors 1 and 2 share the first authorship criteria.
[2] Authors 26 and 27 meet the last authorship criteria.

Table 1
Demographic, pathologic, and surgical data for each dataset.

		PT	GD	p-value	PT + GD
Nr patients					
	Total	209	392		602
	N in [1−15]	60 (29%)	101 (26%)		161 (27%)
	N in [16 - 25]	149 (71%)	291 (74%)		441 (73%)
Age	(median)	72	71	0.845	71
	[Q1 - Q3]	[62 - 79]	[63 - 78]		[63 - 79]
tLn		19	19	0.418	19
		[15 - 22]	[15 - 23]		[15 - 22]
metLn		5	4	0.04	4
		[2 - 9]	[2 - 7]		[2 - 8]
node ratio		0.29	0.22	0.022	0.23
		[0.11 - 0.54]	[0.10 - 0.40]		[0.10 - 0.45]
negLn		12	14	0.022	13
		[7−16]	[9−18]		[8−17]
Sex				0.409	
	Female	82 (39%)	139 (35%)		222 (37%)
	Male	127 (61%)	253 (65%)		380 (63%)
pN				0.148	
	N1	66 (32%)	139 (35%)		206 (34%)
	N2	65 (31%)	137 (35%)		203 (34%)
	N3a	62 (30%)	100 (26%)		161 (27%)
	N3b	16 (8%)	16 (4%)		32 (5%)
pT				0.031	
	T1a	7 (3%)	3 (1%)		10 (2%)
	T1b	8 (4%)	31 (8%)		39 (6%)
	T2	33 (16%)	47 (12%)		80 (13%)
	T3	84 (40%)	179 (46%)		263 (44%)
	T4a	65 (31%)	116 (30%)		182 (30%)
	T4b	12 (6%)	16 (4%)		26 (5%)
Site					
	Upper	38 (18%)	95 (24%)	0.011	133 (22%)
	Middle	80 (38%)	122 (31%)	0.093	202 (34%)
	Lower	114 (55%)	184 (47%)	0.091	299 (50%)
NAT				0	
	No	196 (94%)	232 (59%)		429 (71%)
	Yes	13 (6%)	159 (41%)		172 (29%)
TNM stage				0.296	
	IA	0 (0%)	0 (0%)		0 (0%)
	IB	9 (4%)	23 (6%)		32 (5%)
	IIA	23 (11%)	36 (9%)		59 (10%)
	IIB	37 (18%)	78 (20%)		115 (19%)
	IIIA	63 (30%)	136 (35%)		201 (33%)
	IIIB	57 (27%)	98 (25%)		154 (26%)
	IIIC	20 (10%)	21 (5%)		41 (7%)
Gastrectomy					
	Proximal	0 (0%)	14 (4%)		13 (2%)
	Subtotal	88 (42%)	194 (49%)		280 (47%)
	Total	118 (56%)	158 (40%)		275 (46%)
	Extended	0 (0%)	30 (8%)		30 (5%)
Histology_Lauren					
	Intestinal	101 (48%)	85 (22%)		186 (31%)
	Diffuse	67 (32%)	62 (16%)		129 (21%)
	Mixed	39 (19%)	14 (4%)		53 (9%)
	Indeterminate	1 (0%)	85 (22%)		83 (14%)

The extent of lymph node dissection (*tLn*) is reported in Table 1: the median number of retrieved lymph nodes was 19 [IQR 15–22] in the PT cohort, 19 [IQR 15–23] in the GD cohort, and 19 [IQR 15–22] in the merged PT + GD cohort.

A total of 601 patients were involved.

3.2. Study design

The study comprises two steps: first, examining and comparing the statistical distributions of both cohorts to assess their similarity, and second, validating previous PT cohort findings by reproducing the earlier simulations using the combined dataset.

3.2.1. Study of the statistical distributions in the two cohorts

To ensure reproducibility and generalisability of previous findings, cohorts must have sufficiently similar core characteristics. This was systematically assessed by examining their statistical distributions, which provided a basis for evaluating cohort similarity and confirming the validity of cross-cohort comparisons.

Initially, similarity was evaluated using a univariate approach. For numerical variables, the Mann-Whitney *U* test [17] was used to compare medians, with p-values indicating the statistical significance of the differences. The non-parametric test, the Wilcoxon rank-sum test, is resilient to outliers and does not assume a Gaussian distribution. For categorical variables, the chi-square test was used to assess distributional consistency. In both cases, the null hypothesis stated no difference between cohort distributions; p-value$\geq$0.05 indicates data consistent with no difference.

However, univariate analysis provides only isolated pairwise checks, failing to capture covariance structures or confounding factors. Apparent alignment on individual variables may conceal meaningful multivariable imbalances relevant to surgical oncology outcomes.

To address this limitation, a multivariate analysis employed three approaches.

3.2.1.1. Classification test. This method determines whether samples can be reliably distinguished based on their variables. A binary variable indicating cohort membership (PT or GD) was created, and a random forest model [18] was trained on the merged dataset. If the model cannot effectively distinguish between cohorts (accuracy $\approx$ 50%), datasets are highly similar and likely originate from the same population.

3.2.1.2. Projection-based comparison. Dimensionality reduction methods represent high-dimensional datasets in a lower-dimensional space while retaining data structure. This concentrates information along orthogonal axes, capturing most variation. Similarity is assessed visually and quantitatively by examining record overlap and centroid positions.

Principal Component Analysis (PCA) [19] and Multiple Correspondence Analysis (MCA) [20] were employed for these visualisations. To statistically validate these observations, a permutation test was applied to assess the significance of cohort separations. By computing a p-value, we determined the evidence required to reject the null hypothesis – the cohorts are identical in several aspects, including mean, variance, and shape. A p-value>0.05 indicates no significant difference between the cohorts.

3.2.1.3. Propensity score analysis. Propensity score analysis [21] provides a rigorous framework for mitigating selection bias and confounding in observational studies. In this context, the score represents the conditional probability of cohort membership given observed baseline characteristics, estimated using logistic regression. By condensing the multivariate distribution into a single balancing scalar, the propensity score ensures that patients with similar scores share a comparable covariate profile. Crucially, this analysis involves verifying the overlap coefficient to assess the common support between cohorts; values above 0.75 indicate high distributional similarity.

3.2.2. Stage migration simulation and pN-progression

The *stage migration* (SM) study replicates the approach outlined by Costa et al. [15]. As before, two scenarios were developed assuming different probability distributions for the number of metastatic lymph nodes (*metLn*). In both cases, these distributions were used to estimate the *metLn* (*metLn*') if a 26-node dissection were offered to patients who did not undergo such a procedure.

The first scenario, called *proportional-based simulation*, estimates *metLn*' using the *node ratio* (*metLn/tLn*), calculated separately for each

patient, which determines the percentage of pathologically harvested nodes.

The second scenario, known as *exponential-based simulation*, estimates *metLn*' through the statistical distribution of *metLn* determined within the group of patients in the cohort who underwent a mid-range dissection ($16 \leq tLn < 26$). This represents the conditional probability of finding metastatic nodes given a mid-range dissection count. Based on this distribution, the number of patients who would have shown a higher number of pathologic nodes (*metLn*'>*metLn*) with a more extensive dissection ($tLn = 26$) is identified. The selection of patients for migration was based on their node ratios and *pT* values, which were identified as important factors for SM by Random Forest models trained on the PT cohort, as described in Ref. [15].

All analyses were performed in Python using Pandas for data manipulation, SciPy, StatsModels, and Prince for statistical tests, scikit-learn for AI modelling, and Matplotlib and Seaborn for visualisation.

4. Results

Demographic, pathological, and surgical data for both cohorts are summarised in Table 1. PT (n = 209), GD (n = 392) and PT + GD (n = 601).

4.1. Study of the statistical distributions in the two cohorts

From univariate analysis, there is no evidence of significant differences across several variables in both cohorts, specifically age, sex, *tLn*, TNM stage, *and Site* (*p*-values>0.05). However, the PT cohort has significantly higher median values for *metLn* and *node ratio* (*p-value*<0.05). There is also evidence that the variables *pT, negLn, siteUpper,* and *NAT* follow different distributions across the cohorts.

However, when both NAT and non-NAT sub-cohorts of the merged one were compared in terms of the total number of lymph nodes harvested ($tLn_{NAT} = tLn_{nonNAT} = 19$), the number of pathologically positive nodes ($metLn_{NAT} = metLn_{nonNAT} = 4$) and the ratio node ($ratio_{NAT} = 0.22$, $ratio_{nonNAT} = 0.24$), no statistically significant differences were observed ($p > 0.05$), supporting the applicability of the proposed threshold across both subgroups.

The multivariate analysis using a classification test (Random Forests with cross-validation) achieved an accuracy of 0.542 (standard deviation = 0.065). This shows that the model cannot distinguish between the two cohorts, supporting the hypothesis that the observations (patients) from the two sources are very similar in their overall multivariate characteristics.

A similar result was observed with the projection-based comparison.

The PCA plot (Fig. 1 – left) shows that patients from PT (red) and GD (blue) are heavily mixed and overlap in the space defined by principal components 1 and 2. There is no clear separation, indicating that, based on the underlying variables, the patients do not form distinct clusters by cohort, which was supported by a p-value of 0.054. Additionally, the mean centroids for PT and GD in the PCA plot are very close to each other (an Euclidean distance of 0.194 in the normalised space). The overlap in patients and the proximity of the mean scores support the conclusion that there is no evidence of differences between the distributions of both cohorts.

With MCA, a more robust method for handling non-numeric variables, the evidence of similarity between the distributions is stronger, with a p-value of 0.090. As before, the visualisation after the MCA transformation shows that patients from PT and GD are highly intermixed and occupy the same regions of the dimensional space (Fig. 1 – right). The mean points for PT and GD are even closer to each other in this new normalised space (Fig. 1– right), with an Euclidean distance of 0.067. The overlap between patients and the proximity of the centroids in the MCA support the conclusion that the distributions of the two cohorts are similar.

When the multivariate analysis was restricted to variables identified as influential in the simulation studies (*nLn*, *metLn*, *nR*, *pT*, *pTNM*, *pN*), the similarity between cohorts became even more pronounced, with the permutation tests yielding p-values of 0.74 and 0.21 for the PCA and MCA projections, respectively.

Finally, the results of the Propensity Score across both cohorts (considering all variables) show that the percentage of PT patients in the safety range (0.1 to 0.9) is very high (97.1%), which strongly supports the conclusions from previous analyses – PT and GD patients are highly comparable based on their multivariate profiles. However, there are some differences: the PT cohort distribution is broad, centred around 0.5, with values ranging from approximately 0.3 to over 0.9; the GD cohort distribution is bimodal, exhibiting two distinct peaks and generally trending towards higher scores. It features a large, dense cluster of observations near 0.9 to 1 and another notable density in the mid-range around 0.5 to 0.6.

When the analysis was restricted to the variables of interest for the SM study, the propensity score results show an overlap coefficient of 0.848, confirming strong similarity between the groups. Furthermore,

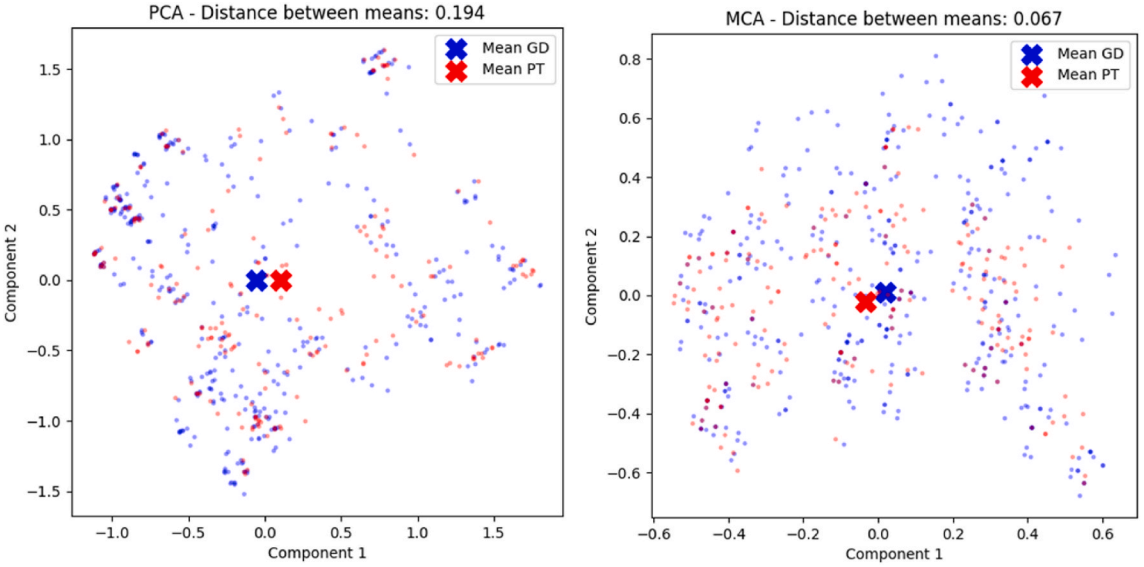

Fig. 1. Overlapping of populations PT and GD and corresponding centroids with PCA (left) and MCA (right).

100% of PT patients fall within the safe range (0.1 to 0.9). These results are presented in Fig. 2, which shows that both cohorts exhibit a high degree of distributional alignment, with the PT cohort (red) and the GD cohort (blue) showing concentrated densities in the mid-to-high range, specifically between 0.6 and 0.8. The PT distribution is slightly broader, indicating a more diverse clinical profile, while the GD cohort shows a more pronounced peak around 0.7.

4.2. Stage migration

Since there is no evidence of significant differences between the two cohorts, as shown above, we combined all the records from both groups to create a new dataset (PT + GD). The description of this new dataset is provided in Table 1 (column on the right).

As in the previous study [15], when using the proportional-based simulation, the number of patients who would have a worse staging is significant, reaching 126 patients (21% of the PT + GD population, compared to 28% in the PT cohort). Most of the SM (98%) occur between stages IIIA, IIIB, and IIIC, with only 4 patients migrating from stage IB to IIA, 1 from stage IB to IIB, and 9 from stage IIA to IIB.

Fig. 3 offers a different perspective on this phenomenon. It shows *metLn* versus *metLn'*, grouped by *pN*, since their difference could imply a *pN*-progression. Please note that the simulations do not affect the *pT* value, and only M0 patients were considered.

From it, the *ratio* is one of the determining factors for SM, with patients with larger ratios migrating to higher *pN* levels. Note that more than half of patients (316) experience an increase in the number of metastatic nodes, but only a fraction (126) reaches the threshold for progression to the next stage.

The first step of the *exponential-based simulation* revealed that the PT + GD dataset aligns with the previously observed properties of PT [15], exhibiting a negative exponential distribution (Fig. 4).

However, it is noticeable that the parameters of the distributions differ slightly, with the PT number of patients decreasing at a slower rate than PT + GD ones (exponential distributions with $\lambda_{PT} = 1/6.06 = 0.17$ and $\lambda_{PT\ +\ GD} = 1/5.08 = 0.20$). In practical terms, this shows a higher percentage of PT + GD patients with a few metastatic nodes ($metLn < 7$) and a higher percentage of PT patients with more positive nodes ($metLn \geq 7$).

As expected, the number of patients experiencing SM is smaller than what was previously identified for the PT cohort. In this case, only 17 patients (3%) will have their diagnosis worsen by at most one degree in the TNM classification. As before, the patients selected to undergo SM were those with the worst stage within their *pTNM* (higher *pT* and higher *node ratio*), which increases the likelihood of SM at higher stages.

Despite this, the estimated number of *pN* is now limited by the observed exponential distribution (Fig. 4), which reduces the number of patients with a high number of metastatic nodes ($metLn \geq 7$). Under these constraints, we estimate that 96 patients (16%) would experience an increase in metastatic nodes, but only 17 patients (3%) would have a *pN*-progression. In fact, most patients (69%) would have only 1 additional metastatic node than observed in the smaller dissection ($tLn < 26$). Fifteen patients would have 2 additional metastatic nodes, 5 would have 3 or 4 more, and 2 would have 5, 6, or 7 more. No patient would show an increase of more than 7 metastatic nodes (Fig. 5).

5. Discussion

This study investigated the external validation of previously developed prediction algorithms as an important step toward assessing their reproducibility and generalisability. The lack of external validation may reduce the clinical applicability and impact of the models ([22], [23]).

The first step in the process was to assess the similarity between the two cohorts and the overlap in their propensity scores. Given the wide patient provenance, a robust statistical analysis was planned and conducted, supported by univariate and multivariate tests, conventional and AI-trained (regression analysis, Random Forests with cross-validation, projection-based comparison).

Although univariate analysis revealed minor discrepancies in individual pathological variables, the multivariate results consistently demonstrate high distributional homogeneity across the cohorts. The inability of the Random Forest model to distinguish between the groups, together with extensive spatial overlap in PCA and MCA projections, confirms that the PT and GD populations are highly comparable. Crucially, when the analysis was restricted to the specific variables of interest for the SM study, the statistical alignment became even more pronounced, as evidenced by higher p-values in the permutation tests and a high propensity score overlap coefficient. These findings confirm the similarity between the two datasets and support the broad applicability of the study's findings across both cohorts.

The second step of the process involved merging data from the Portuguese cohort (PT) and the eligible European patients (GD) into a

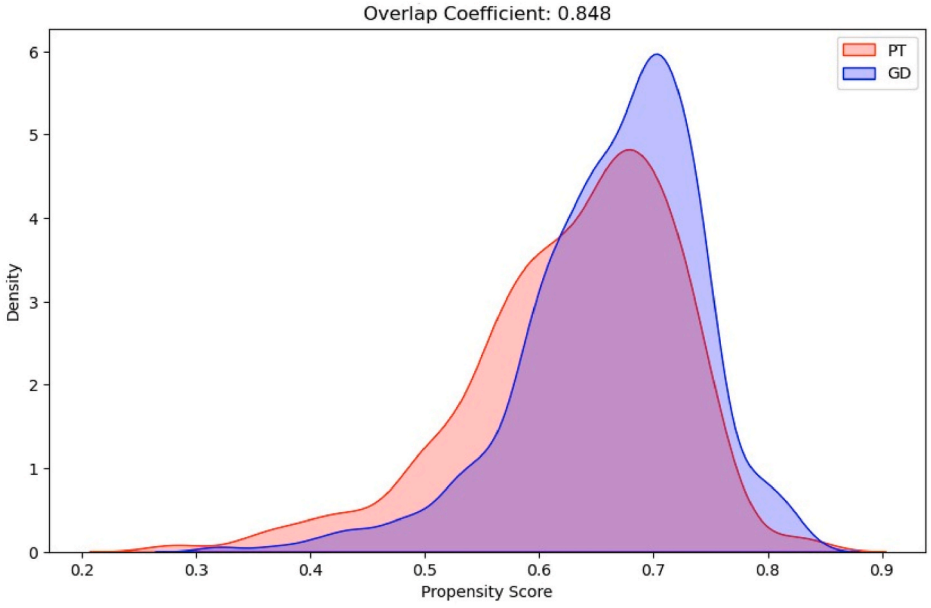

Fig. 2. Propensity score overlap between populations PT and GD.

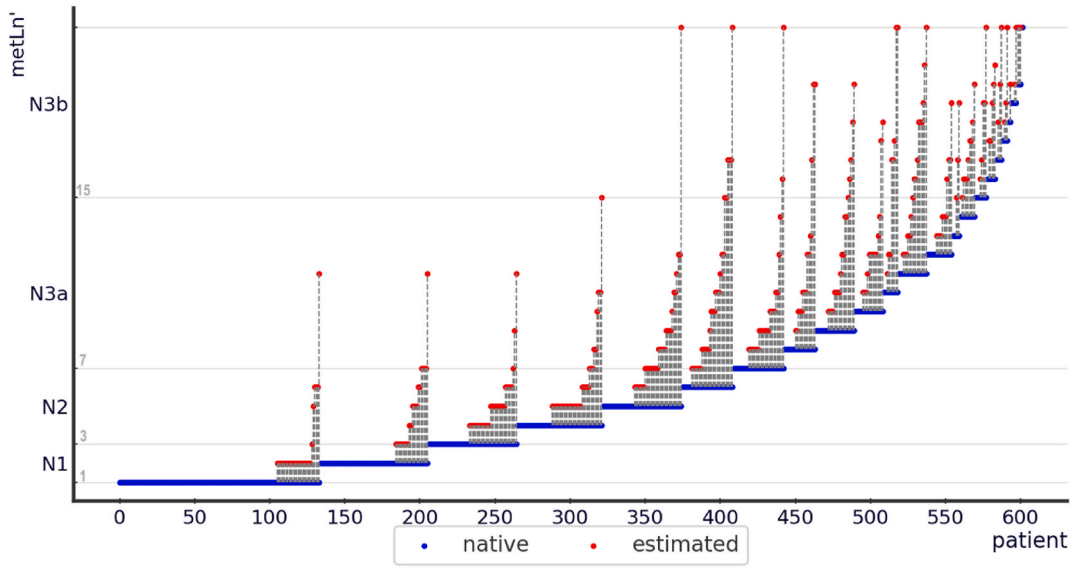

Fig. 3. Estimated metastatic nodes to harvest (*metLn'*) based on proportional scenario, with patients sorted by *metLn*, *ratio* and *pT* in ascending order per N level [15]. Each blue dot represents a patient; the increase in *metLn* is represented by the grey dotted lines, achieving the *metLn'* represented as red dots. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

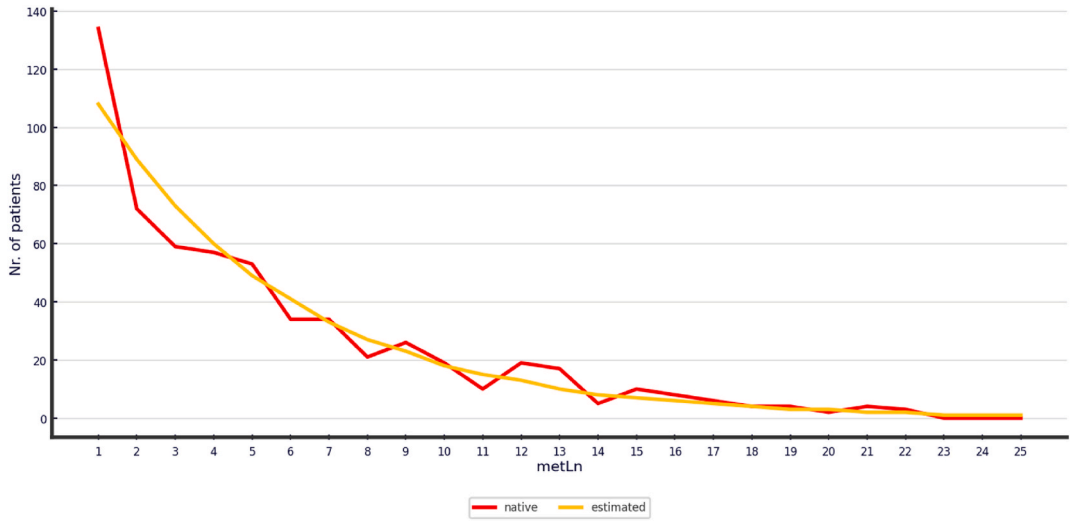

Fig. 4. Number of patients showing each number of metastatic nodes (PT + GD).

single combined cohort (PT + GD).

The third step involved validating the previously described algorithms by running them on data from the PT + GD cohort.

In the proportional-based simulation, projections of the increment of *pN* + nodes were taken on the stability of the individual node ratio. This assumption was virtually improbable, but for the sake of testing the Will Rogers phenomenon, it was considered a doom scenario to "challenge the dogma" [15]. In the PT + GD cohort, 126 patients (21%) reached an SM, compared with 28% in the PT cohort. These percentages were very similar, as was the pattern of change (which mainly occurred within *pTNM* stage III).

The present study is not focused on *pTNM* SM, mainly because the follow-up in the GD cohort was not assessed. A more detailed analysis of this simulation was centred on the escalation through the *pN* stages (*pN*-progression), returned by the algorithm. More than half of the patients (316) experienced an increase in the number of metastatic nodes, as represented in Fig. 3, but only 126 would progress to an upper pN stage.

In the other scenario, an *exponential-based simulation,* was estimated based on the statistical distribution determined in the group of patients who underwent a resection of 16 to 25 nodes. This distribution represents the conditional probability of finding metastatic nodes given a mid-range dissection count (≥16).

The PT + GD dataset aligns with the previously observed PT properties [15]. The *metLn* influences the negative exponential distribution (Fig. 4). This fact translates into a reduction to <25% of the probability of patients achieving *metLn*≥*7*. Under these constraints, 96 patients (16%) would experience an increase in metastatic nodes (1-7), but only 17 patients would have a *pN*-progression (Fig. 5).

The turning point for *pN* stage 3a is 7 nodes. Regardless of the extent of lymphadenectomy, the percentage of patients staged as pN3a and pN3b is generally very low for $pT < 4$, and the rate of pathological nodes and pN + patients is modest ([13], [15], [24], [25], [26], [27], [28]), as in our series.

But the risk of pN-progression for each patient was not yet assessed, and as we have demonstrated, should not be neglected. The number of patients who would transition from a stage not meeting criteria for

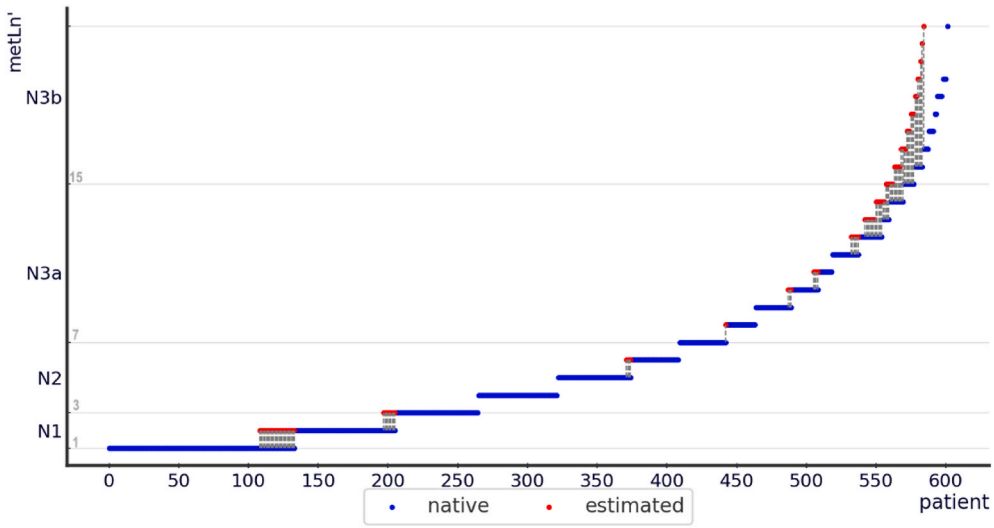

Fig. 5. Estimated metastatic nodes to harvest (*metLn'*) based on exponential scenario, with patients sorted by *metLn*, *ratio* and *pT* in ascending order [15]. Each blue dot represents a patient; the increase in *metLn* is represented by the grey dotted lines, achieving the *metLn*' represented as red dots. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

adjuvant chemotherapy to one where chemotherapy is indicated (e.g., stage IB → stage II), or who would be eligible for escalation from single-agent to combination regimens, has been estimated based on current guideline-recommended treatment algorithms. This analysis substantially enhances the real-world clinical relevance of the simulation findings and has been incorporated jointly with the discussion of NAT effects given their shared relevance to treatment decision-making.

The controversy on the extent of lymphadenectomy and the associated upper limit of nodes to be harvested remains ongoing ([13], [29], [30]). We have selected the threshold (26) between the most proposed limits and at a range exhibiting a negative exponential distribution (Fig. 4) with very low probability of *pN* stage progression.

Recently, two European reports failed to demonstrate an overall advantage of enlarged resection (>16 nodes) ([3], [14]). The apparent tension between numerical adequacy and anatomical completeness reflects the multifactorial nature of prognostication in gastric cancer. Numerical thresholds should not override surgical judgment regarding completeness and station-based dissection.

Also the ratio of positive lymph nodes harvested from stations 10 and 12 increase according to *pT* stages are relatively low, *pT2* (18/810 = 2%), *pT3* (32/551 = 6/%), *pT4* (268/3056 = 8%) [31], as is the case in *pT1b* for stations 11p (36/1042 = 3.5%) and 12a (36 = 2.3%) [32], [33].

Even though it has been reported that skip node metastasis may be around 2.7% after standard lymphadenectomies [28]. These findings, together with our results, namely the greater probability of individual pN-progression in patients with stage III support the adherence to well-conducted D1+/D2 dissection.

Do preoperative radiomics help selectively identify these nodal stations in each case? What is the impact of image-guided surgery (e.g., IGC) in this context? Altogether, these issues underscore the role of chemotherapy and target therapies in the treatment of gastric cancer, as a meaningful complement to surgery.

A substantial body of published works from Western and Eastern series confirms the node ratio ([15], [24], [31], [34], [35], [36], [37]) and the number of negative nodes as independent prognostic factors, consistent with the results we have reported ([6], [15], [24], [38], [39], [40]). The lower the node ratio, the higher the overall survival. For each patient, this fact highlights the individual importance of the number of negative nodes resected ([6], [41], [42], [43], [44], [45]).

In our series of 830 patients [15], the Kaplan-Meier curves for groups of patients with negative nodes <16 (n = 233), between 16 and 25 (n = 258), and ≥26 (n = 339) were significantly different ($p < 0.001$) and independent of *pN* and *pT*. The negative nodes play an overwhelming role in OS.

From a clinical standpoint, current internationally accepted guidelines for gastric cancer increasingly recommend neoadjuvant treatment for locally advanced disease, and the proportion of *NAT*-treated patients is expected to grow. Importantly, as discussed in our preceding work [15], patients who received adjuvant or neoadjuvant chemotherapy were included in prior analyses, given the reported significant correlations between negative lymph node count (*negLn*), node ratio (*nR*), and overall survival (OS). Furthermore, tumour regression in lymph node metastases has been documented [15], raising the conceptually relevant question of whether regressed nodes should be counted as metastatic nodes. If so, adhering to defined anatomic nodal stations during dissection — rather than relying solely on numerical thresholds — may carry prognostic significance even in the NAT setting.

It is possible to perform an adequate oncologic lymphadenectomy even when fewer than 26 lymph nodes are retrieved/analysed. Anatomic variations, tumour biology, surgical technique, and pathological processing are possible reasons for fewer nodes harvested. A recent proposal, "PhotoNodes Protocol," as a potential framework for objectively classifying the extent of lymphadenectomy (D1, D1+, or D2) based on documented removal of specific nodal stations [46]. This proposal aligns well with our institutional experience and the broader concern of moving beyond purely numerical metrics.

6. Conclusions

The primary objective of this study was to externally validate algorithms for predicting an increase in the number of lymph nodes when 26-node harvesting is offered to patients undergoing fewer dissections. The present data are consistent with validation. The merger of the two cohorts, PT and GD, shed more light on the relevance of the extent of lymphadenectomy.

To ensure the removal of pathological lymph nodes while maintaining safety standards, lymphadenectomy should aim to harvest at least 26 nodes. This also allows patients to benefit from harvesting negative lymph nodes and to reduce their individual risk of *pN*-progression. These data should be considered in further recommendations.

Ethical statement

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964. The study was approved by the Ethical Committees of the Lisbon Academic Medical Center (Refa N∘353/17, 12/12/2017), Hospital Garcia de Orta (Affiliated Hospital to this Academic Center (HGO/CE – 25/03/21) and Instituto Português de Oncologia, Porto (CES145A/020).

The scientific committee of the European GASTRODATA group approved sharing the dataset for this external validation, with it receiving approval from the Registry Senior Advisors Board. Approvals were granted by the ethics committees at the participating institutions.

Data availability statement

Data were anonymised and deposited on a dedicated server at Instituto Superior Técnico - Universidade de Lisboa. Access to the anonymisation keys is restricted to the main authors. The data of this study are restricted by ethic committees to protect patient privacy. Data are available from the corresponding author to researchers who meet the criteria for access to confidential data. The data are authentic and reliable, without plagiarism.

Credit authorship contribution statement

Lúcio Lara Santos: Conceptualisation, Study design, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Writing – review & editing, Manuscript review, Project administration, Validation, **Anna Carolina Finamore**: Conceptualisation, Study design, Quality control of data and algorithms, Formal analysis, and interpretation, Formal analysis, Manuscript preparation, Writing – review & editing, Project administration, Validation, **Suzanne Gisbertz**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing, **Uberto Fumagalli Romario**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Wojciech Kielan**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Ricccardo Rosati**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Piotr Kołodziejczyk:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Bas Wijnhoven**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review **Ines Gockel:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing, **Simone Giacopuzzi**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review. **Wojciech P. Polkowski**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Andrew Davies**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Paolo Morgagni**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Arnulf Hoelscher**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **William Allum**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Domenico D'ugo**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Henk Hartgrink**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Maria Bencivenga:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing, **Jacopo Viganò**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Manuel Pera**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Daniel Reim:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing, **Paul Schneider**: Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing, **Stefan Mönig:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Giovanni De Manzoni:** Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review, **Gian Luca Baiocchi**: Conceptualisation, Data curation, Formal analysis, Project administration, Resources, Validation, manuscript review and writing. **Cláudia Antunes**: Conceptualisation, Study design, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Writing – review & editing, Project administration, Validation, **P. Matos da Costa**: Conceptualisation, Study design, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Writing – review & editing, Manuscript review, Project administration, Validation.

Declaration of competing interest

The authors have no conflicts of interest, financial or otherwise, regarding the present study.

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