Intestinal-type gastric cancer carries a better prognosis but a higher risk of lymph node metastasis than diffuse-type: a SEER study of nearly 28,000 patients

Chanqiong Zhang
department of pathology,wenzhou people's hospital
Guangyu Chen
department of pathology,third people porvince hospital of henan
Haofeng Hong
wenzhou medical university
Jinbo Zhu
wenzhou medical univertsity
Hongyuan Zhang
Wenzhou Medical University
Chongan Huang
Wenzhou Medical University
Dan Pan
department of pathology,wenzhou people's hospital
Huajun Ye (yehuajun1911@163.com)
department of gastroenterology and hepatology, first affiliated hospital of Wenzhou Medical University
https://orcid.org/0000-0002-4793-1393

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Abstract

Background: The impact of Lauren type, namely intestinal and diffuse types, on prognosis and lymph node metastasis (LNM) for gastric cancer (GC), requires further exploration, since current samples are deficient and the results are inconsistent.We aimed to translate the widely used WHO classifications into Lauren types and analyze the impact with the largest sample size available.

Methods: Corresponding Lauren types of the WHO classification system in the Surveillance, Epidemiology, and End Results (SEER) database were included to identify all patients with histological diagnoses of intestinal-type or diffuse-type GC.

Results: 4,338 intestinal-type and 22,990 diffuse-type GC were included in our study. Compared with intestinal-type, diffuse-type had a relatively poor prognosis after adjustment for other risk factors (HR, 1.236; P<0.001). Similar to patients with all stages of GC, the prognosis of patients with early diffuse GC was also poor (HR, 1.295; P=0.001). Surgical operation and radiotherapy markedly improved the DSS for patients (P<0.05). To our surprise, the risk of intestinal LNM in all stages of GC was higher than that in the diffuse type (OR=0.891; P=0.036). Although, there was no positive correlation between LNM and Lauren's GC (OR=1.096; P=0.467) in early stage.

Conclusion: Intestinal-type GC carries a better prognosis but a higher risk of LNM than diffuse-type. Patients with intestinal-type GC are likely to gain a greater benefit from receiving surgical treatment, but it is worth noting that clinicians should pay more attention to their lymphatic metastasis.

*Contributed equally.

The first author: Chanqiong Zhang, Guangyu Chen

Introduction

Gastric cancer (GC) is regarded as one of the common malignant tumours of the digestive system. The incidence of GC is different all over the world, and this trend is particularly evident in developing countries, especially in East Asia, where GC is highly prevalent [1]. At the moment, the diagnosis of GC mainly relies on imaging and pathology. There are different standards and controversy in the clinical staging and pathological diagnosis of GC. For the pathological classification of GC, the WHO and Lauren classifications are most commonly used [2–3]. The WHO classification is more detailed and considers the degree of tumour differentiation, but it is limited by the different morphological manifestations of GC and the subjective assessments of pathologists, resulting in low reproducibility. Lauren classification is relatively simple and easy and has been favoured by researchers for many years [4–5].

Lauren classification divides the histomorphology and cell characteristics of GC into diffuse-type, intestinal-type and mixed-type. Intestinal-type GC presents a highly differentiated adenocarcinoma structure, diffuse-type GC cells have gastric mucous cell characteristics and poor differentiation and

show invasive growth and rare glandular cavity formation. The mixed type obtains the above two features, which combines multiple classifications of GC biological behaviour and provides a reference for epidemiological characteristics[6–7].

Lauren's is usually regarded as a great method of classification but there still exist different opinions. Researchers have various attitudes to the difference of prognosis between intestinal and diffuse gastric cancer[8–10]. In addition, the sample size of the largest research is only 5593. There are lots of similarities between Lauren's method and WHO, that is, most of them is correspond with each other. In order to find out the difference between them and deal with the contradiction, we attempt to combine them and then do some research. However, there is not a single conclusion due to the limited amount of cases.

The SEER database contains codes for both the Lauren and WHO classification. Therefore, we also brought corresponding intestinal and diffuse cases of the WHO classification system into the study to enlarge sample size, as to learn the clinical feature and prognosis of Lauren type GC.

Methods

We selected and analysed data from 27,328 patients with GC from the SEER database.

In both WHO and Lauren systems, the basic principle is to include GC with obvious glandular formation in the category of intestinal type. Cases in which there are isolated or small-stripe cancer cells scattered in the gastric wall during GC infiltration are categorized as diffuse. In addition to typical cases (intestinal and diffuse, ICD-O-3/WHO 2008 morphology codes 8144 and 8145, respectively), intestinal GC also includes papillary adenocarcinoma, highly differentiated tubular adenocarcinoma and medium differentiated tubular adenocarcinoma (ICD-O-3/WHO 2008 morphology codes 8260 and 8211, respectively). For the diffuse type of gastric carcinoma, signet ring cell carcinoma and poorly differentiated adenocarcinoma were also included (ICD-O-3/WHO 2008 morphology codes 8490 and 8140, respectively).

The selected primary tumour sites were classified as cardia, fundus of stomach, body of stomach, gastric antrum, pylorus, lesser curvature of stomach NOS, greater curvature of stomach NOS, overlapping lesion of stomach, stomach, or NOS (C16.0-16.9).

We selected patients with GC who met the above conditions between 2004 and 2013 from the SEER database, analysing the clinicopathological and prognostic variables.

Statistical analysis

We used the Chi-square test to compare the differences in clinicopathological characteristics between patients in two groups. Univariate and multivariate analysis of COX proportional risk regression model was carried out for both types. The survival curve was plotted by Kaplan-Meier method, and the differences among factors were calculated by Log-rank test. For the sake of adjusting potential

confounding factors, we established a multivariate logistic model for the analysis of LNM. SPSS 21.0 (IBM Corporation) was used for statistical analysis. The statistical significance was determined as $P < 0.05$.

Independent prognostic risk factors obtained by COX multivariate regression analysis were used to develop a Nomogram graph and calculate the index of concordance (C-index), which was utilized to evaluate the predictive performance. We build and verify the nomograms on statistical R software (3.3.1). $P < 0.05$ was considered statistically significant.

Results

Incidence and trends

From 2004 to 2013, the age standardized incidence rate of every 100 thousand person years showed a distinct upward trend (Fig. 1). The incidence was significantly higher in men than in women when considering total GC cases or cases of intestinal or diffuse types. The age-adjusted incidence rates of the diffuse-type declined slowly over time. The incidence of intestinal-type GC remained the same.

Demographic and clinicopathological characteristics

Table 1 provides a list of the main characteristics of the intestinal-type and diffuse-type of GCs. A total of 27,328 patients were brought into our study, including 4,338 intestinal-type and 22,990 diffuse-type. By comparing the clinicopathological features of different Lauren classification GC, it turned out that patients with intestinal-type and diffuse-type GC have significant differences in age, sex, tumour location, tumour size, lymph node metastasis, tumour stage, distant metastasis, and degree of tissue differentiation ($P < 0.001$).

Table 1
Comparison of patient baseline characteristics between intestinal and diffuse type of GC

Variables	Intestinal	Diffuse	*P* value
Sex			0.001
Male	2763(63.69%)	13762(59.86%)	
Female	1575(36.31%)	9228(40.14%)	
Age at diagnosis			0.001
65	1298(29.92%)	10921(47.50%)	
≥65	3040(70.08%)	12069(52.50%)	
Marital status			0.166
Married	2394(55.19%)	13024(56.42%)	
Unmarried	1724(39.74%)	8887(38.74%)	
Unknown	220(5.07%)	1079(4.84%)	
Race			0.001
White	2561(59.04%)	16211(70.51%)	
Black	640(14.75%)	2833(12.32%)	
Other	1111(25.61%)	3821(16.62%)	
Unknown	26(0.60%)	125(0.54%)	
Pathological Differentiation			0.001
Well differentiated	326(7.51%)	21(0.09%)	
Moderately differentiated	2030(46.80%)	201(0.87%)	
Poorly differentiated	1664 (38.36%)	20607(89.63%)	
Undifferentiated	40(0.92%)	299(1.30%)	
Unknown	278(6.41%)	1862(8.10%)	

TNM stage			0.001
I	1548(35.68%)	4378(19.04%)	
II	670 (15.44%)	2648(11.52%)	
III	524(12.08%)	2970(12.92%)	
IV	1197(27.59%)	10477(45.57%)	
Unstaged	399(9.20%)	2517(10.95%)	
Primary site			0.001
Upper stomach	943(21.74%)	7048(30.66%)	
Middle stomach	1174(27.06%)	4999(21.74%)	
Lower stomach	1511(34.83%)	5256(22.86%)	
Other/NOS	710(16.37%)	5687(24.74%)	
Tumor size			0.001
4cm	1380(31.81%)	4565(19.86%)	
4-8cm	1532(35.32%)	5776(25.12%)	
8cm	341(7.86%)	2587(11.25%)	
Unknown	1085(25.01%)	10062(43.77%)	
T status			0.001
T1	1180(27.20%)	4436(19.30%)	
T2	1611(37.14%)	6424(27.94%)	
T3	512(11.80%)	3487(15.17%)	
T4	375 (8.64%)	3341(14.53%)	
Unknown	660(15.21%)	5302 (23.06%)	
N status			0.001
N0	1945(44.84%)	8295(36.08%)	
N1	1412 (32.55%)	7586(33.00%)	

N2	401(9.24%)	2292(9.97%)	
N3	125(2.88%)	985(4.28%)	
Unknown	455(10.49%)	3832(16.67%)	
M status			0.001
M0	3111(71.72%)	12421(54.03%)	
M1	988(22.78%)	9039(39.32%)	
Unknown	239(5.51%)	1530(6.66%)	
Summary Stage			0.001
Localized	1384(31.90%)	3907(16.99%)	
Regional	1638(37.76%)	7863(34.20%)	
Distant	1025(23.63%)	9459(41.14%)	
Unknown	291(6.71%)	1761(7.66%)	
Surgery			0.001
Yes	2953(68.07%)	10315(44.87%)	
No	1345(31.01%)	12371(53.81%)	
Unknown	40(0.92%)	304(1.32%)	
Surgery type			0.001
Total/near total	587(13.53%)	2678(11.65%)	
Partial*/subtotal	2205(50.83%)	6770(29.45%)	
Local tumor destruction	67(1.54%)	222(0.97%)	
surgery NOS	94(2.17%)	645(2.81%)	
Unknown	20(0.46%)	125 (0.54%)	
No surgery	1365(31.47%)	12550(54.59%)	
Radiation			0.001

Yes	960(22.13%)	5999(25.70%)
No	3306(76.21%)	16711(72.69%)
Unknown	72(1.66%)	370(1.61%)

Univariate and Multivariable Survival Analysis

To identify prognostic factors in the intestinal type of GC, we conducted univariate and multivariate Cox regression analysis. By univariate analysis, the intestinal-type showed that the factors in Table 2 were significantly different, except for sex and age, and the P values of the remaining factors were < 0.001. Multivariate analysis showed that age > 65, poorly differentiated, more advanced TNM stage, upper stomach tumour site, larger tumour size, T3, N3, no surgery, and no radiation were significantly associated with poorer DSS. But results revealed that M status (P = 0.761) and surgery type (P = 0.286) were not associated with DSS.

Table 2
Univariate and multivariate analyses for DSS for intestinal type patients identified in the SEER Program database from 2004 to 2013.

Category	Univariate		P-value	Multivariable		P-value
	HR	(95% CI)		HR	95% CI	
Age						
65	Ref			Ref		
≥65	1.099	0.999-1.210	0.054	1.490	1.348-1.648	0.001
Sex						
Male	Ref			Ref		
Female	0.956	0.872-1.047	0.332	1.023	0.931-1.124	0.637
Race						
White	Ref		0.001	Ref		0.001
Black	1.064	0.939-1.206	0.329	1.089	0.958-1.238	0.193
Other	0.781	0.701-0.869	0.001	0.832	0.744-0.931	0.001
Unknown	0.580	0.260-1.293	0.183	0.407	0.181-0.916	0.030
Pathological Differentiation						
Well differentiated	Ref		0.001	Ref		0.001
Moderately differentiated	1.768	1.415-2.210	0.001	1.188	0.947-1.491	0.136
Poorly differentiated	2.344	1.876-2.929	0.001	1.426	1.135-1.793	0.002
Undifferentiated	2.939	1.868-4.623	0.001	1.470	0.927-2.329	0.101
Unknown	3.907	3.011-5.071	0.001	1.453	1.112-1.899	0.006
TNM stage						
I	Ref			Ref		

			0.001			0.001
II	1.834	1.553-2.166	0.001	1.253	0.956-1.644	0.103
III	3.264	2.785-3.826	0.001	1.643	1.232-2.191	0.001
IV	7.921	6.961-9.012	0.001	1.845	1.314-2.592	0.001
Unstaged	5.600	4.737-6.619	0.001	2.504	1.779-3.524	0.001
Primary site						
Upper stomach	Ref		0.001	Ref		0.002
Middle stomach	0.646	0.571-0.731	0.001	0.831	0.730-0.946	0.005
Lower stomach	0.625	0.556-0.702	0.001	0.902	0.793-1.025	0.114
Other/NOS	1.054	0.924-1.202	0.436	1.062	0.927-1.216	0.388
Tumour size						
4cm	Ref		0.001	Ref		0.001
4-8cm	2.019	1.782-2.287	0.001	1.284	1.124-1.466	0.001
8cm	2.960	2.491-3.518	0.001	1.458	1.211-1.756	0.001
Unknown	4.346	3.831-4.929	0.001	1.237	1.062-1.441	0.006
T status						
T1	Ref		0.001	Ref		0.013
T2	1.336	1.170-1.525	0.001	1.131	0.960-1.333	0.141
T3	2.586	2.215-3.019	0.001	1.418	1.157-1.738	0.001
T4	3.912	3.324-4.603	0.001	1.209	0.989-1.478	0.063
Unknown	5.459	4.736-6.293	0.001	1.176	0.974-1.420	0.092

N status						
N0	Ref		0.001	Ref		0.001
N1	1.703	1.529-1.896	0.001	1.044	0.906-1.203	0.553
N2	2.225	1.917-2.581	0.001	1.467	1.193-1.803	0.001
N3	3.232	2.587-4.039	0.001	1.705	1.258-2.311	0.001
Unknown	4.496	3.925-5.151	0.001	1.076	0.911-1.271	0.390
M status						
M0	Ref		0.001	Ref		0.811
M1	4.927	4.473-5.427	0.001	0.929	0.580-1.489	0.761
Unknown	2.990	2.514-3.557	0.001	0.925	0.710-1.206	0.565
Summary Stage						
Localized	Ref		0.001	Ref		0.001
Regional	2.513	2.195-2.877	0.001	1.510	1.164-1.958	0.002
Distant	8.944	7.793-10.265	0.001	2.435	1.456-4.071	0.001
Unknown	5.863	4.844-7.097	0.001	0.859	0.608-1.213	0.388
Surgery						
Yes	Ref		0.001	Ref		0.001
NO	4.693	4.277-5.150	0.001	3.059	2.542-3.682	0.001
Unknown	3.635	2.461-5.368	0.001	3.304	1.939-5.629	0.001
Surgery type						
Total/near total	Ref		0.001	Ref		0.789
Partial*/subtotal	0.724	0.626-		0.989	0.849-	0.889

		0.836	0.001		1.153	
Local tumor destruction	0.613	0.370-1.017	0.058	1.327	0.789-2.235	0.286
surgery NOS	0.878	0.622-1.241	0.462	0.929	0.655-1.318	0.681
Unknown	2.760	1.546-4.928	0.001			
No surgery	3.644	3.161-4.201	0.001	0.829	0.378-1.821	0.641
Radiation						
Yes	Ref		0.001	Ref		0.001
No	1.361	1.221-1.518	0.001	1.380	1.228-1.552	0.001
Unknown	1.323	0.918-1.907	0.133	1.362	0.913-2.032	0.130

The results of the multivariate analysis of diffuse-type GC are shown in Table 3. The variables included in the univariate analysis were age, race, pathological differentiation, TNM stage, tumour location, tumour size, regional node positivity, LN metastases, distant metastases, summary stage, history of surgery, surgery type and history of radiation. By multivariate analysis, significantly poorer survival were seen in age ≥ 65, African American, more advanced TNM stage, larger tumour size, N3, distant metastasis, were found to increase the risk of death for patients with diffuse-type GC. Furthermore, history of surgery was markedly bound up with a decreased hazard of DSS, and partial /subtotal surgery type and history of radiation. Interestingly, we found that T status was not significantly related to DSS.

Table 3
Univariate and multivariate analyses for DSS for diffuse type patients identified in the SEER Program database from 2004 to 2013.

Catagory	Univariate		P-value	Multivariable		P-value
	HR	(95% CI)		HR	95% CI	
Age						
65	Ref			Ref		
≥65	1.227	1.189-1.267	0.001	1.416	1.370-1.463	0.001
Sex						
Male	Ref			Ref		
Female	0.989	0.958-1.022	0.521	0.978	0.946-1.011	0.188
Race						
White	Ref		0.001	Ref		0.001
Black	0.980	0.934-1.029	0.415	1.059	1.008-1.112	0.023
Other	0.723	0.691-0.757	0.001	0.823	0.786-0.863	0.001
Unknown	0.614	0.461-0.818	0.001	0.547	0.410-0.729	0.001
Pathological Differentiation						
Well differentiated	Ref		0.001	Ref		0.402
Moderately differentiated	1.082	0.597-1.960	0.795	1.192	0.658-2.161	0.562
Poorly differentiated	1.517	0.861-2.672	0.149	1.280	0.727-2.256	0.393
Undifferentiated	1.333	0.744-2.388	0.334	1.336	0.745-2.396	0.330
Unknown	2.090	1.184-3.689	0.011	1.224	0.693-2.162	0.486
TNM stage						
I	Ref			Ref		

			0.001			0.001
II	1.301	1.211-1.398	0.001	1.281	1.147-1.430	0.001
III	1.935	1.812-2.066	0.001	1.604	1.434-1.795	0.001
IV	4.574	4.338-4.824	0.001	1.769	1.558-2.008	0.001
Unstaged	3.874	3.624-4.141	0.001	1.636	1.448-1.848	0.001
Primary site						
Upper stomach	Ref		0.001	Ref		0.001
Middle stomach	0.809	0.774-0.847	0.001	0.946	0.902-0.992	0.023
Lower stomach	0.817	0.782-0.854	0.001	1.020	0.972-1.071	0.421
Other/NOS	1.327	1.273-1.383	0.001	1.098	1.050-1.148	0.001
Tumour size						
4cm	Ref		0.001	Ref		0.001
4-8cm	1.639	1.553-1.730	0.001	1.243	1.176-1.314	0.001
8cm	2.390	2.246-2.543	0.001	1.448	1.355-1.547	0.001
Unknown	3.228	3.074-3.390	0.001	1.368	1.295-1.445	0.001
T status						
T1	Ref		0.001	Ref		0.001
T2	0.870	0.826-0.916	0.001	0.946	0.891-1.003	0.065
T3	1.184	1.119-1.253	0.001	1.071	0.998-1.150	0.058
T4	2.147	2.032-2.268	0.001	1.082	1.014-1.155	0.018
Unknown	2.638	2.508-2.775	0.001	0.995	0.935-1.059	0.879

N status						
N0	Ref		0.001	Ref		0.001
N1	1.136	1.092-1.182	0.001	0.969	0.925-1.015	0.187
N2	1.057	0.998-1.119	0.058	1.198	1.115-1.288	0.001
N3	1.326	1.227-1.434	0.001	1.333	1.202-1.478	0.001
Unknown	2.476	2.366-2.591	0.001	1.130	1.072-1.192	0.001
M status						
M0	Ref		0.001	Ref		0.001
M1	3.273	3.163-3.388	0.001	1.315	1.145-1.510	0.001
Unknown	2.617	2.456-2.789	0.001	1.066	0.974-1.167	0.167
Summary Stage						
Localized	Ref		0.001	Ref		0.001
Regional	1.659	1.566-1.757	0.001	1.337	1.207-1.482	0.001
Distant	4.731	4.475-5.003	0.001	1.280	1.092-1.500	0.002
Unknown	3.891	3.609-4.194	0.001	1.109	0.977-1.257	0.109
Surgery						
Yes	Ref		0.001	Ref		0.001
NO	3.709	3.581-3.842	0.001	2.378	2.220-2.547	0.001
Unknown	2.238	1.941-2.582	0.001	1.538	1.282-1.845	0.001
Surgery type						
Total/near total	Ref		0.001	Ref		0.001
Partial*/subtotal	0.743	0.699-		0.883	0.829-	

		0.789	0.001		0.941	0.001
Local tumor destruction	1.369	1.149-1.631	0.001	1.498	1.252-1.792	0.001
surgery NOS	1.038	0.927-1.162	0.522	1.123	1.001-1.260	0.048
Unknown	2.597	2.113-3.192	0.001			
No surgery	3.058	2.896-3.228	0.001	1.547	1.202-1.992	0.001
Radiation						
Yes	Ref		0.001	Ref		0.001
No	1.710	1.647-1.776	0.001	1.352	1.297-1.409	0.001
Unknown	1.393	1.222-1.589	0.001	1.234	1.073-1.420	0.003

Survival analysis

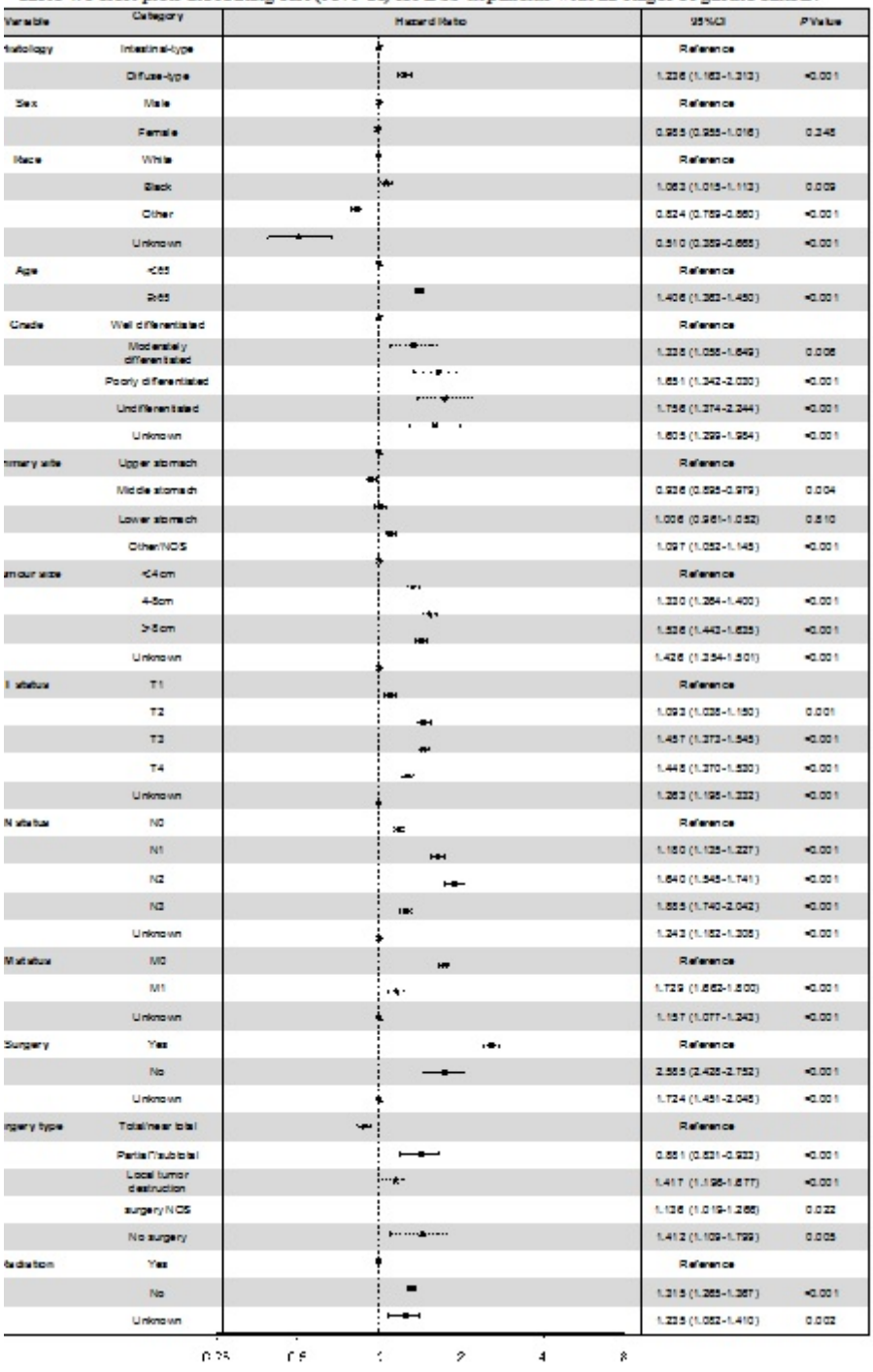
According to our research, 1,996 intestinal-type patients and 15,404 diffuse-type patients died due to GC. The median cause-specific survival time of intestinal-type GC was 29.79 months. The 1-, 3-, and 5-year DSS rates of intestinal-type group were 70.6%, 47.6%, and 42.8%, respectively. For GC patients with the diffuse type of disease, the median cause-specific survival time was 10.41 months, and the 1-, 3-, and 5-year DSS rates for the diffuse type were 49.0%, 26.4% and 21.4%, respectively.

As shown in Fig. 2, the results showed that the survival rate of GC patients with intestinal-type disease was markedly higher than that of patients with diffuse-type($P < 0.001$). Furthermore, the Kaplan-Meier analysis, as shown in Fig. 3, illustrated that patients with advanced-stage disease had significantly less survival time than that of patients with other diseases ($P < 0.001$). As the size of the tumour increased, the survival time of the patients similarly decreased. However, we also found that survival was worse for patients with T4, N3, and M1 disease than for patients with other stages of disease ($P < 0.001$) (Fig. 3, 4). Additionally, Fig. 5 displays the Kaplan-Meier analysis of DSS, which indicated that the survival outcome was improved by receiving radiation and undergoing surgery.

Forest plot

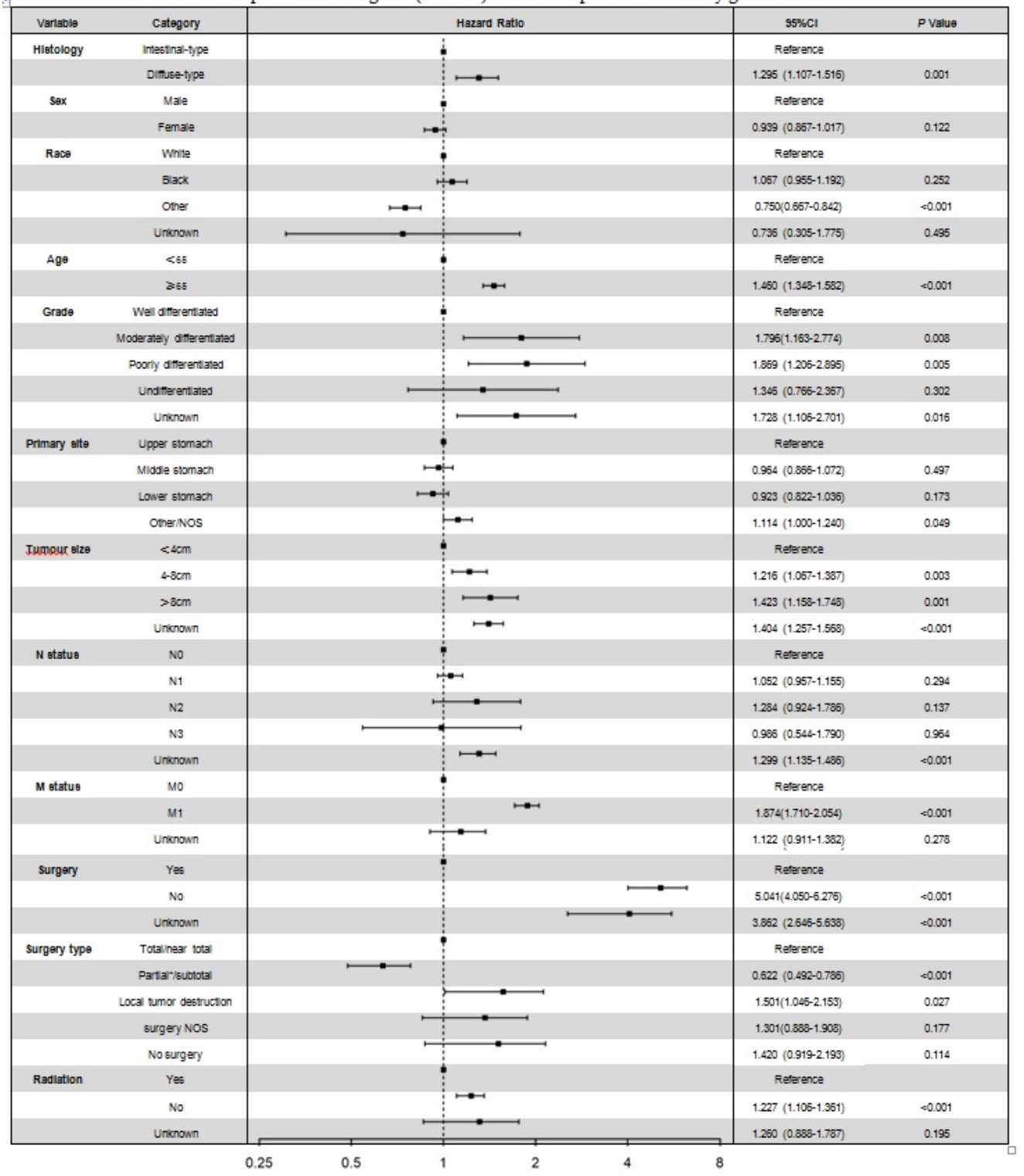
We performed forest plot to show the results of the multivariate Cox regression model (Table 4), Lauren classification, race, age, tumour grade, tumour size, invasion depth, regional lymph node depth, distant metastasis, surgery, radiation, primary tumour site, and local tumour destruction were all independent predictors in all stages of GC.

Table 4. Forest plots illustrating HR (95% CI) for DSS in patients with all stages of gastric cancer.



Furthermore, Table 5 showed that diffuse type, age ≥ 65, poorly differentiated, large tumour size, no history of surgery, and no history of radiation, were significantly related with less DSS benefits in the early GC.

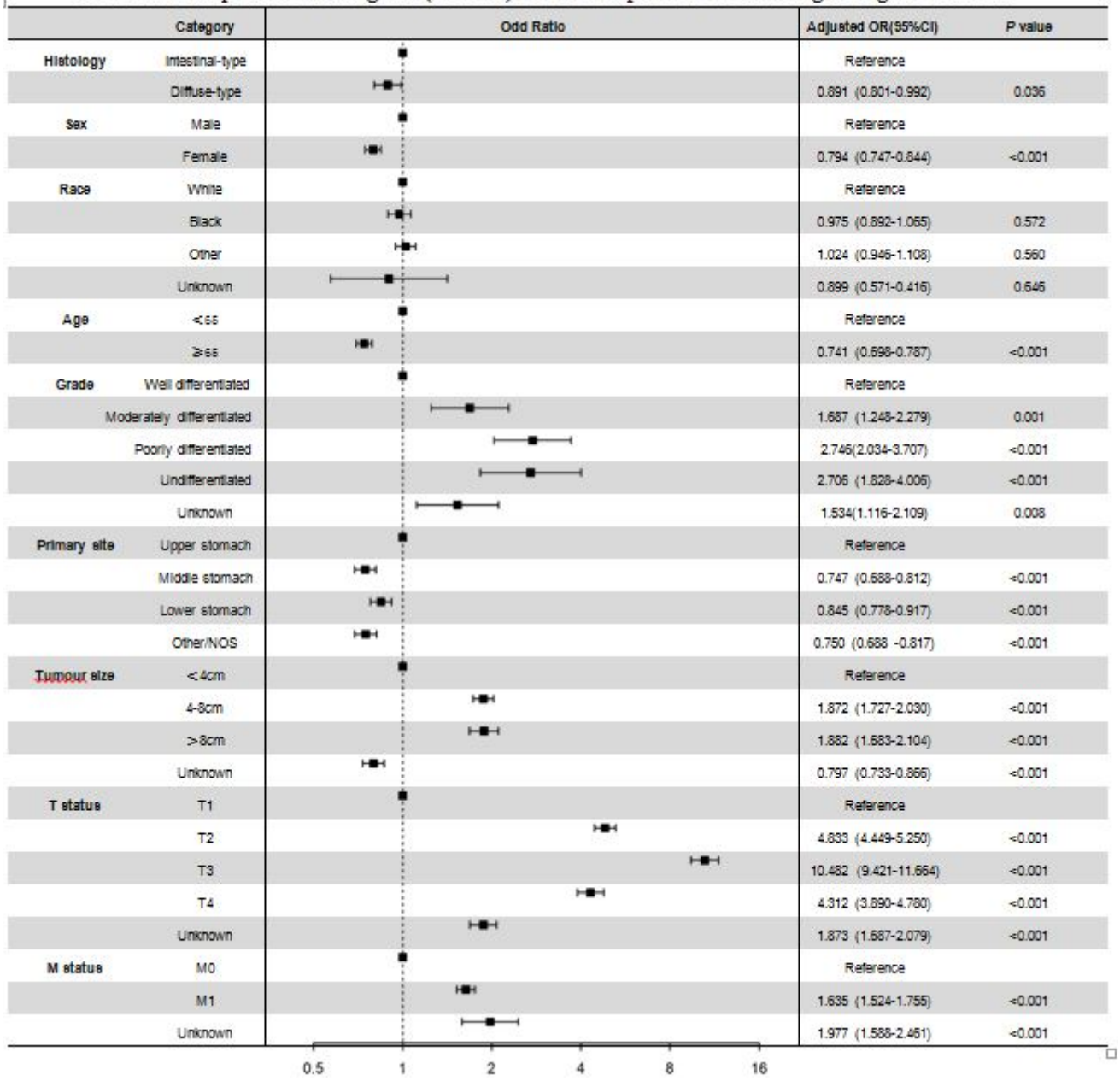
Table 5. Forest plots illustrating HR (95% CI) for DSS in patients with early gastric cancer.



LNM and histology

A multivariate logistic model for the analysis of LNM was established for the sake of adjusting potential confounding factors. The findings (Table 6) indicated that intestinal type, male sex, large tumour size, undifferentiated state, young age, upper stomach tumour site, deep invasion depth, and distant metastasis were obviously related toa higher hazard of LNM in GC.

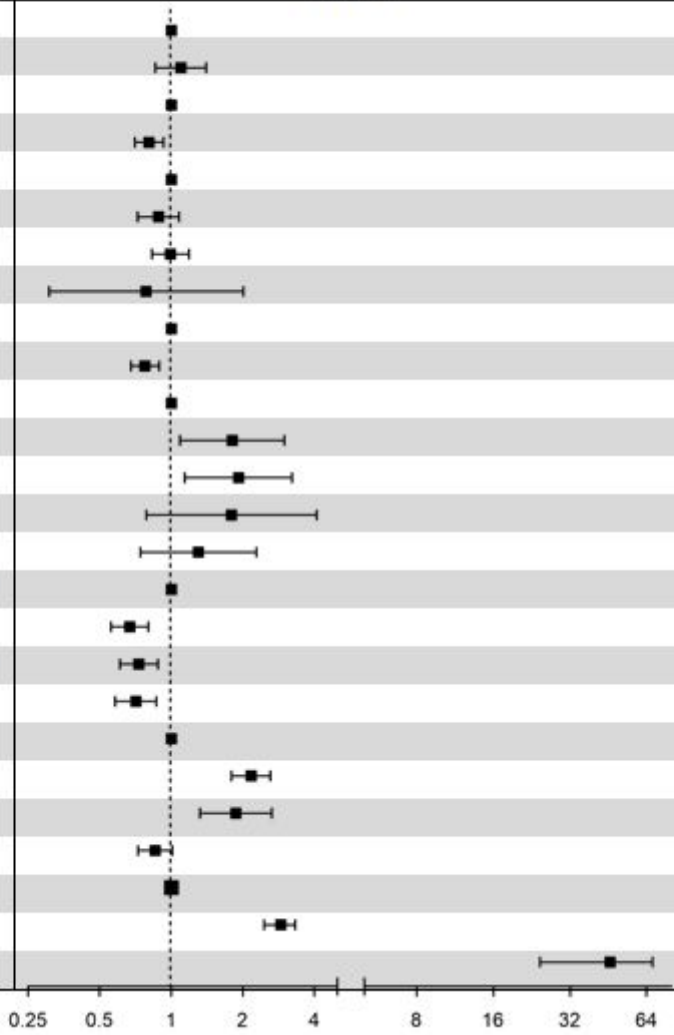
Table 6. Forest plots illustrating OR (95% CI) for DSS in patients with all stages of gastric cancer.



To make further discussion about whether intestinal-type EGC revealed as high of a risk as diffuse-type EGC, we adjusted the potential confounding factors with multivariate logistic model to analyse the correlation between the histological type of EGC and the hazard of LNM. No positive association was found (P = 0.467) between Lauren type and LNM (Table 7). We also carried out a subgroup analysis, which demonstrated tumour size and depth of invasion were also considered as independent risk factors of LNM in early-stage GC.

Table 7. Forest plots illustrating OR (95% CI) for DSS in patients with early gastric cancer.

Variable	Category	Odd Ratio	Adjusted OR(95%CI)	P value
Histology	Intestinal-type		Reference	
	Diffuse-type		1.096 (0.856-1.403)	0.467
Sex	Male		Reference	
	Female		0.807 (0.702-0.928)	0.003
Race	White		Reference	
	Black		0.883 (0.722-1.080)	0.226
	Other		0.992 (0.829-1.186)	0.927
	Unknown		0.784 (0.306-2.012)	0.614
Age	<65		Reference	
	≥65		0.775 (0.677-0.888)	<0.001
Grade	Well differentiated		Reference	
	Moderately differentiated		1.806 (1.089-2.993)	0.022
	Poorly differentiated		1.917 (1.139-3.224)	0.014
	Undifferentiated		1.793 (0.786-4.093)	0.165
	Unknown		1.301 (0.742-2.282)	0.359
Primary site	Upper stomach		Reference	
	Middle stomach		0.668 (0.557-0.801)	<0.001
	Lower stomach		0.732 (0.608-0.880)	0.001
	Other/NOS		0.710 (0.581-0.866)	0.001
Tumour size	<4cm		Reference	
	4-8cm		2.163 (1.793-2.610)	<0.001
	>8cm		1.871 (1.321-2.648)	<0.001
	Unknown		0.856 (0.725-1.010)	0.065
M status	M0		Reference	
	M1		2.865 (2.467-3.328)	<0.001
	Unknown		42.596 (26.297-69.002)	<0.001



Moreover, to make a prediction of the DSS of patients, the significant variables obtained from multivariate Cox regression model were used to generate nomogram (Figs. 6, 7). The C-index of the intestinal type was estimated to be 0.784, 95% CI = 0.774–0.794, while the C-index of the diffuse type was estimated to be 0.739, 95% CI = 0.735–0.743.

Discussion

Lauren classification is widely used in scientific research, but there are still different opinions on this method. One reason is that the sample size is too small, with most of the cases included in the study range from several hundred to thousand, Therefore, there is no substantial progress owing to the less representativeness of these research results. Although Li et al. recently reported a study of Lauren classification in early GC based on the SEER database [11], they included 5593 cases and only focused on early GC. In our study, we have a lot of data available with 28000 patients, so we can get the desired and more reliable results theoretically.

Analysis of the clinicopathological features showed that the age of onset of intestinal-type GC was older (≥ 65) ($P < 0.001$) than that of diffuse-type GC; additionally, when comparing intestinal-type GC with

diffuse-type GC, there were more males affected than females (P < 0.001), there was a higher degree of pathological differentiation (P < 0.001), disease occurred at an earlier stage (P < 0.001), disease was more likely to be distributed in the lower stomach (P < 0.001), tumour size was more likely to be 4–8 cm (P < 0.001), there was more invasion into the muscularis propria (P < 0.001), there was less lymph node metastasis (P < 0.001), and there was less distant metastasis (P < 0.001). Compared with diffuse-type, the prognosis of intestinal-type was significantly better. Different from intestinal-type group, patients in diffuse-type group have relatively poor pathological differentiation (P < 0.001), and diffuse cases were often at an advanced stage when they were diagnosed, to be located in the upper stomach, and to have distant metastasis (P < 0.001) compared with intestinal cases.

LNM is often considered an important determinant of outcomes and treatment strategy choices in EGC [12–13]. While many studies have reported a high rate of diffuse lymph node metastasis, our study concluded that two groups didn't significantly differed in lymph node metastasis; Thus, the LNM risk of intestinal and diffuse GC is considered similar. Our findings indicated that there was no positive correlation between LNM and Lauren type (OR = 1.096; 95% CI: 0.856–1.403; P = 0.467), but we demonstrated that the hazard of intestinal lymph node metastasis in all stages of GC was higher than that in the diffuse type (OR = 0.891; 95% CI, 0.801–0.992; P = 0.036).

The cause of these contradictory results may be the fact that the patients who basically register the information in the SEER database are mainly postoperative pathology. Moreover, the general surgery patients were mainly without metastasis and peripheral lymph node metastasis, while the proportion of distant metastasis in the surgical enrollment group was relatively small. In this study, the proportion of patients with intestinal type GC undergoing surgery was 68.07%, and the proportion of patients with diffuse GC undergoing surgery was 44.87%. As a result, we obtained this result when we estimated the risk of lymph node metastasis. However, theconclusion of this large sample of studies also remind us that we should pay more attention to lymphatic metastasis of intestinal type GC than before.

Another reason may be that our definitions of intestinal and diffuse types differ from those of other studies. In addition to Lauren classification, we also used WHO classification. Intestinal GC also includes papillary adenocarcinoma, highly differentiated/moderately differentiated tubular adenocarcinoma, diffuse GC including signet-ring cell carcinoma, and low-differentiated adenocarcinoma. Different inclusion criteria may have resulted in inconsistent analysis results. Based on the conclusion that the hazard of lymph node metastasis in intestinal-type GC is high, clinicians must be cautious when choosing surgical treatment for intestinal-type GC.

The most obvious finding to emerge from the analysis is that the prognosis of diffuse-type GC was worse than that of intestinal-type GC. The median DSS time of intestinal-type patients was 29.79 months, compared with 10.41 months in diffuse-type patients, and the 5-year survival DSS rate was 42.8% and 21.4%, respectively. These findings are consistent with previous reports [14] and may be partially explained by the tendency of the diffuse-type to present at more advanced T and N stages.

Previous research findings related to GC are inconsistent and contradictory with our results, and the studies have showed that the prognosis of intestinal-type GC is worse than that of diffuse-type GC. In particular, studies by Li et.al [11], which are based on the SEER database, analysed only early GC patients. The results showed that patients of different GC subtypes had similar prognoses, or even that the prognosis of intestinal-type GC was worse than that of diffuse-type GC. Therefore, we further analysed the differences in prognosis between patients with early-stage GC and diffuse-type GC. it was concluded that the prognosis of diffuse-type GC was worse than that of intestinal-type GC in both early stage and all-stage GC populations.

Most studies have concluded that intestinal-type GC is common in older men, has a low degree of invasion, has a high level of lymph node metastases, and has vascular invasion [15]. Diffuse GC is common in young and female patients and has serous invasion; additionally, lymph node metastasis occurs very early [16–19].

In intestinal-type GC, the median DSS time decreased according to tumour infiltration depth (T1, T2, T3, and T4), indicating that an increase in tumour infiltration depth was negatively correlated with the prognosis of patients. Analysis of lymph node metastasis revealed that patient survival time decreased with the increase of the number of lymph node metastasis. The survival time of patients with distant metastases was evidently shorter than that of patients without distant metastases. The relationship between tumour invasion depth, lymph node metastasis, distant metastasis and prognosis in diffuse GC also showed the same trends. Studies have shown that lymph node metastasis is an independent factor in the prognosis of patients [20–21]. Patients with node-negative disease have a higher 5-year survival rate than that of patients with lymph node metastasis, and the survival time of patients with lymph node metastasis decreases with an increase in the number of metastatic lymph nodes. The larger extent of metastasis from lymph nodes in diffuse GC than intestinal GC suggests that the prognosis of diffuse GC is worse than that of intestinal-type GC. Invasive depth of diffuse patients

The proportion of GC patients with T3 and T4 disease in diffuse-type is higher than that in intestinal-type. Previous researches have shown that the depth of invasion is an independent factor in the prognosis of GC [22–24]. According to our study, the prognosis of diffuse GC is worse than that of intestinal-type GC. In patients with diffuse TNM, the proportion of patients with stage I and II disease was lower than that of patients with intestinal-type disease ($P = 0.004$), while the percentage of patients with stage IV was significantly higher than that of patients with intestinal-type disease ($P = 0.008$). Previous studies have shown that patients with stage III and IV GC have poor prognosis, and the 5-year survival rate is significantly lower in these patients than in patients with stage I and II disease [25–26]. The prognosis of diffuse GC is worse than that of intestinal-type GC.

According to follow-up statistics, the difference in survival rate 5 years after surgery for intestinal GC and diffuse GC was statistically significant ($P < 0.05$), and the survival rate of diffuse GC was lower than that of intestinal GC after 5 years (see Fig. 2). The 5-year survival rate of patients receiving surgery was significantly higher than that of patients without surgery $P < 0.05$) (see Fig. 5A). In patients with diffuse

GC, there was a statistically significant difference between the 5-year survival rate of those receiving radiotherapy and the 5-year survival rate of patients who did not receive radiotherapy ($P > 0.05$), and the 5-year survival rate of patients receiving radiotherapy was higher than that of patients who did not receive radiotherapy (see Fig. 5B).

We found that there was a recent article that was also based on the SEER database and Lauren classification of GC, but its conclusions were very inconsistent [11]. This article suggests that diffuse-type has a better prognosis than intestinal-type GC. The results also showed that diffuse types occur in younger female patients and tend to occur in upper gastric areas, with smaller sizes and more lymph nodes involved than those in intestinal types. Table 1 detailed the clinical characteristics of both types, however, the differences between them may be due to several reasons. Firstly, early GC was included in this study, it meant all stages of GC were contained. Secondly, in addition to the intestinal and diffuse coding, the coding of the WHO classification was also included in this research.

At the same time, we should admit that the study has some shortcomings. First, some important clinical information is missing from the SEER database, such as chemotherapy used, omics data for bioinformatics analysis, and the data of modern prognostic factors such HER-2 status were not complete in SEER. Hence, a few potential prognostic factors cannot be applied into our study. In addition, a majority of cases were not updated to the newest AJCC staging system in the database. Our results suggested that diffuse-type carried a worse prognosis but a lower risk of LNM than intestinal-type. It is remarkable that clinicians should take their lymphatic metastasis seriously.

Declarations

Authors' contribution:

Chanqiong Zhang and Guangyu Chen: data collection, writing–original draft; Haofeng Hong and Jinbo Zhu: analyzing data; Hongyuan Zhang, Chongan Huang,and Dan Pan: statistical analysis and making figures; Huajun Ye: study design, writing–review and editing. All authors read and approved the final manuscript.

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Figures

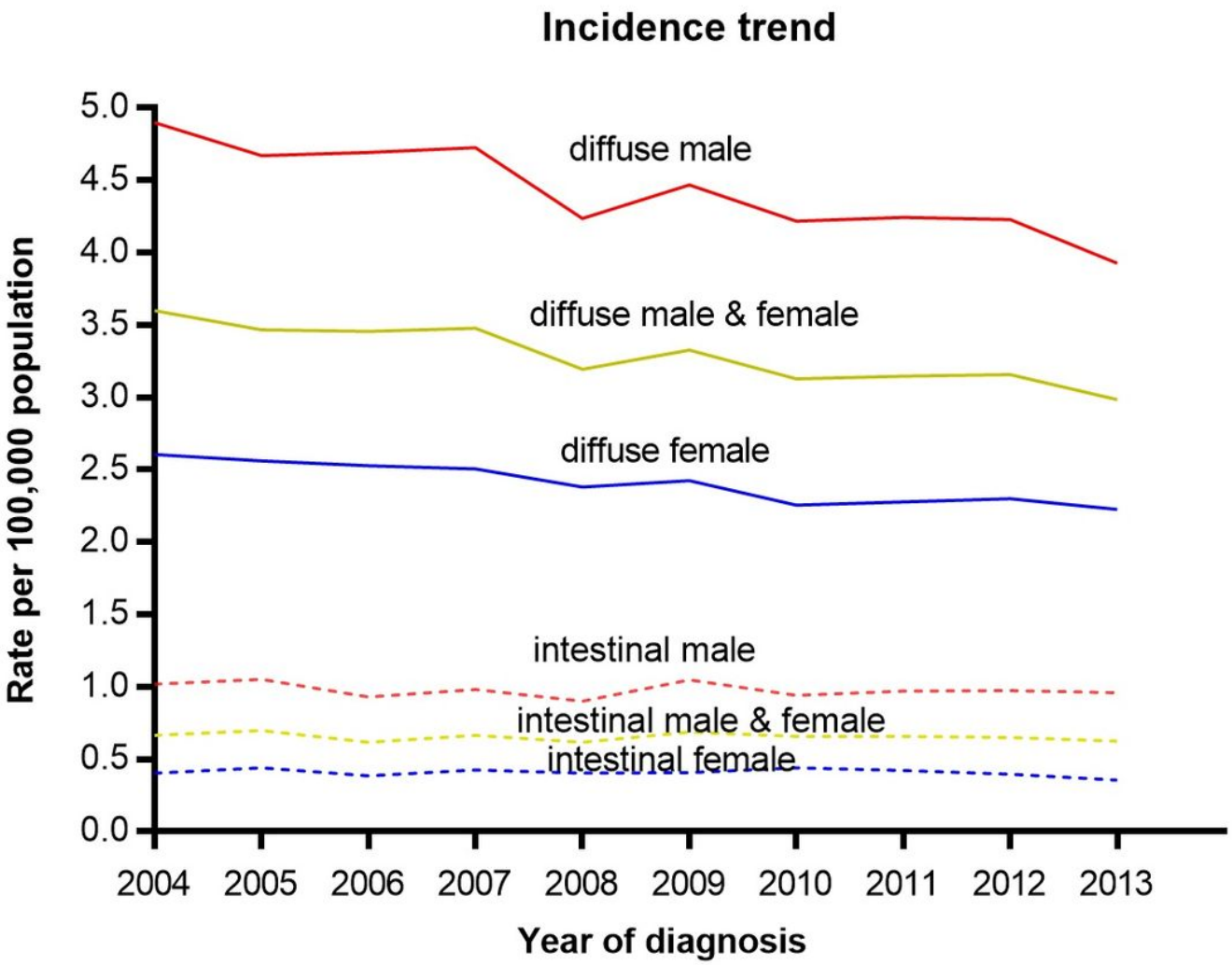

Figure 1

Analysis of incidence trend of intestinal and diffuse type of GC. (incidence per 100,000) from 2004 to 2013.

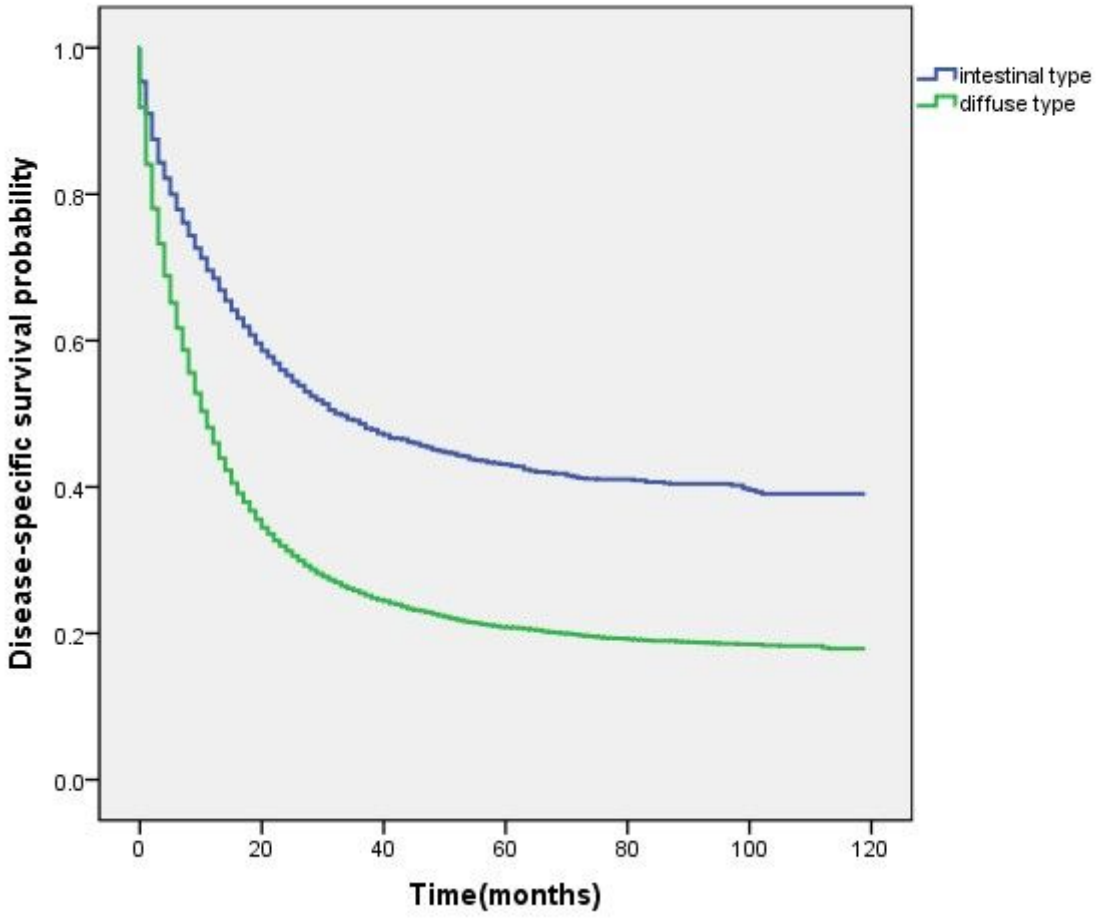

Figure 2

Kaplan-Meier estimated DSS in patients with intestinal and diffuse type DSS: Disease-specific survival

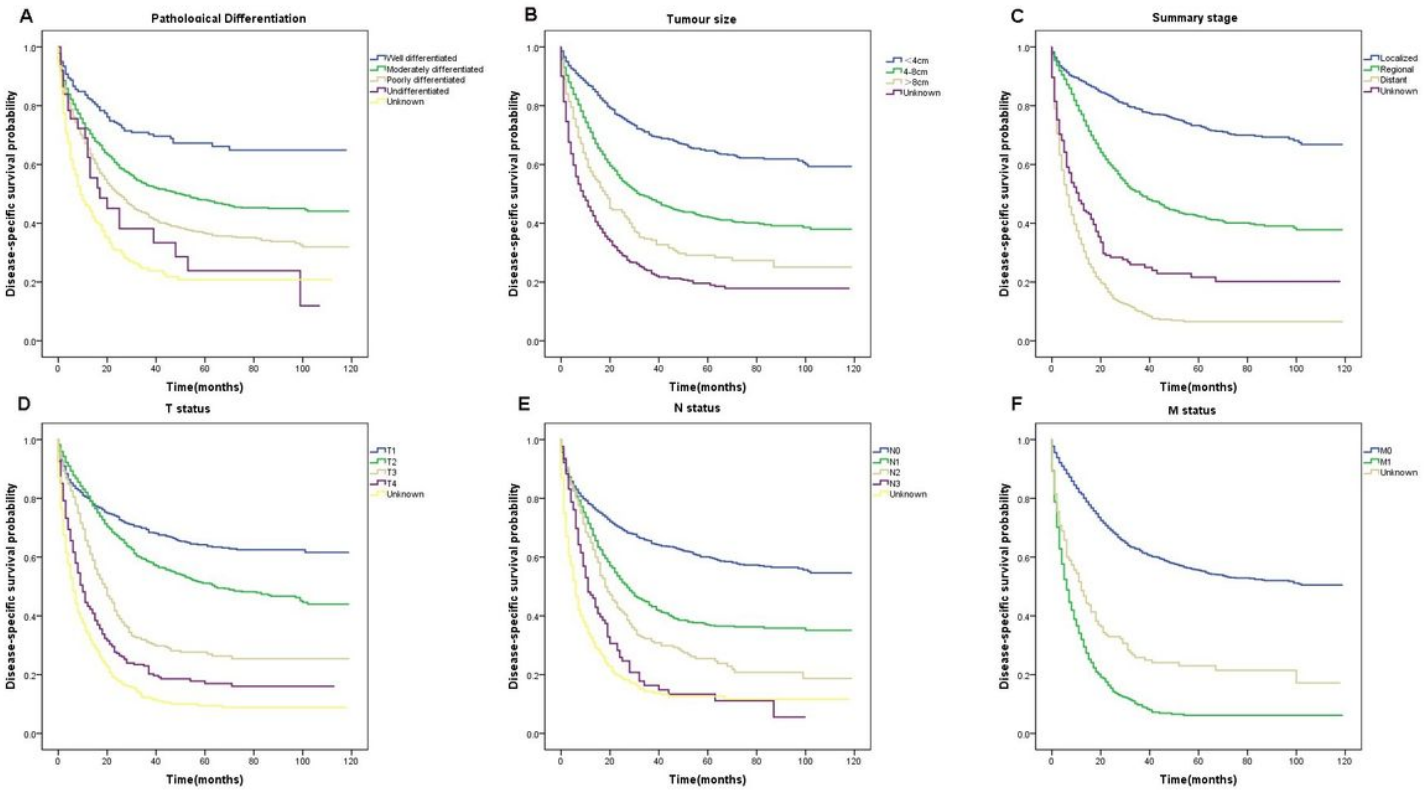

Figure 3

Kaplan-Meier estimated DSS in patients with intestinal type GC stratified by pathological differentiation (A), tumour size (B), summary stage(C), T status(D), N status(E), M status(F). DSS: Disease-specific survival

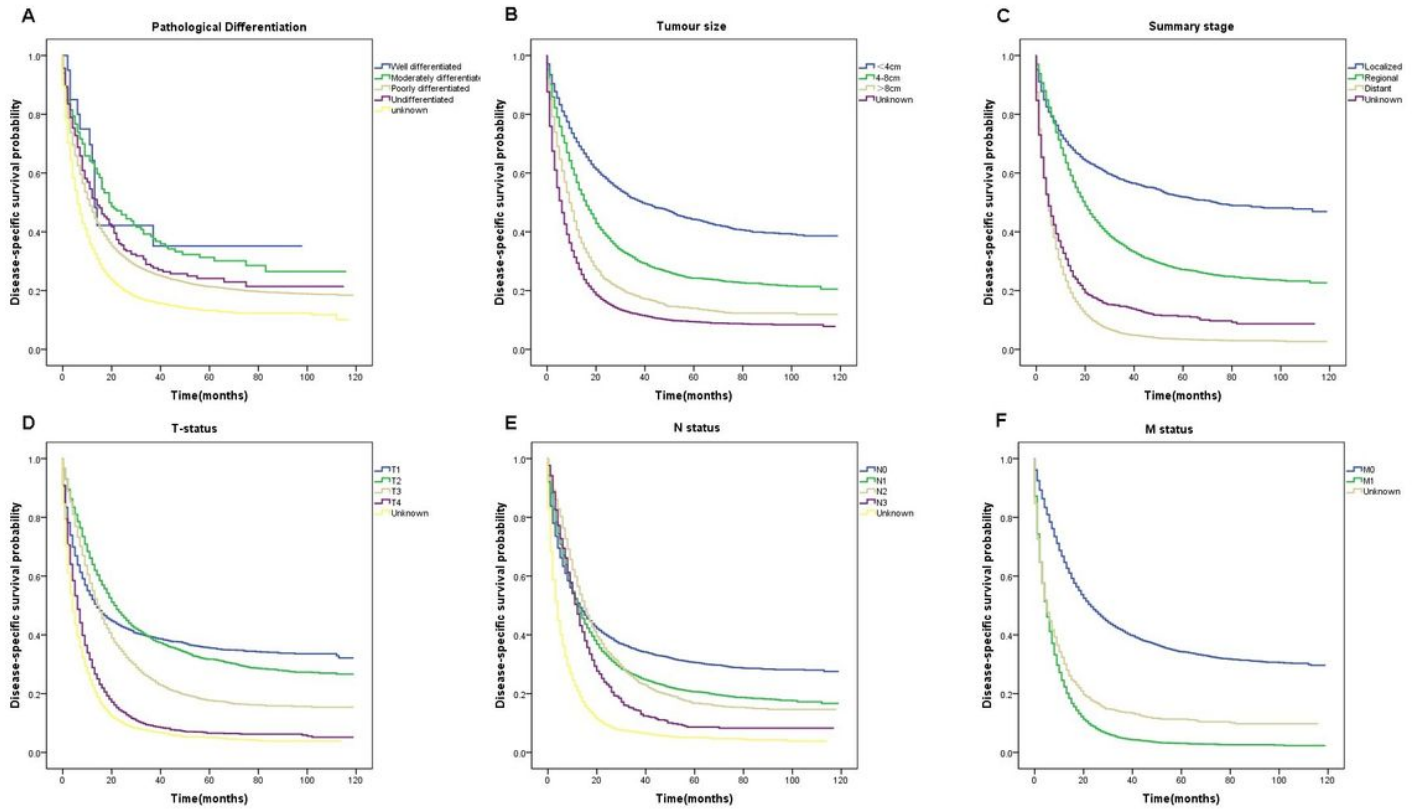

Figure 4

Kaplan-Meier estimated DSS in patients with diffuse type GC stratified by pathological differentiation (A), tumour size (B), summary stage(C), T status(D), N status(E), M status(F). DSS: Disease-specific survival

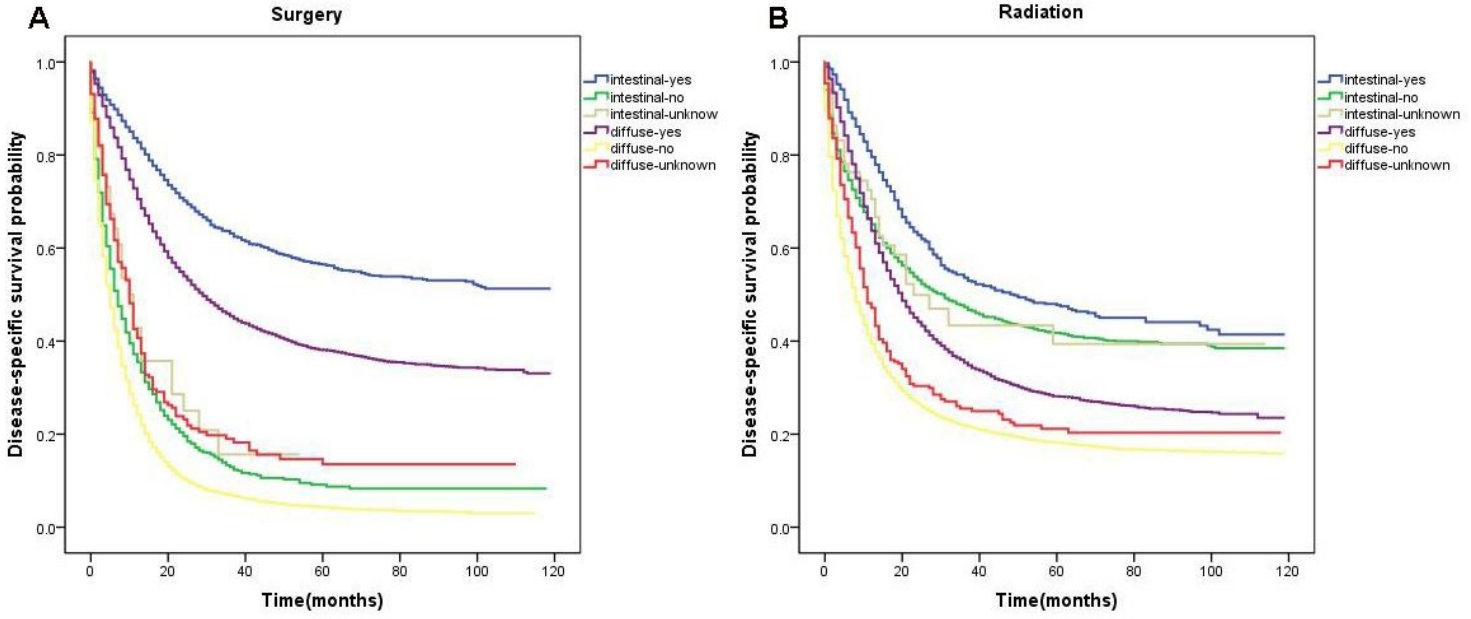

Figure 5

Kaplan-Meier estimated DSS in patients with intestinal and diffuse type GC stratified by surgery (A), radiation (B). DSS: Disease-specific survival

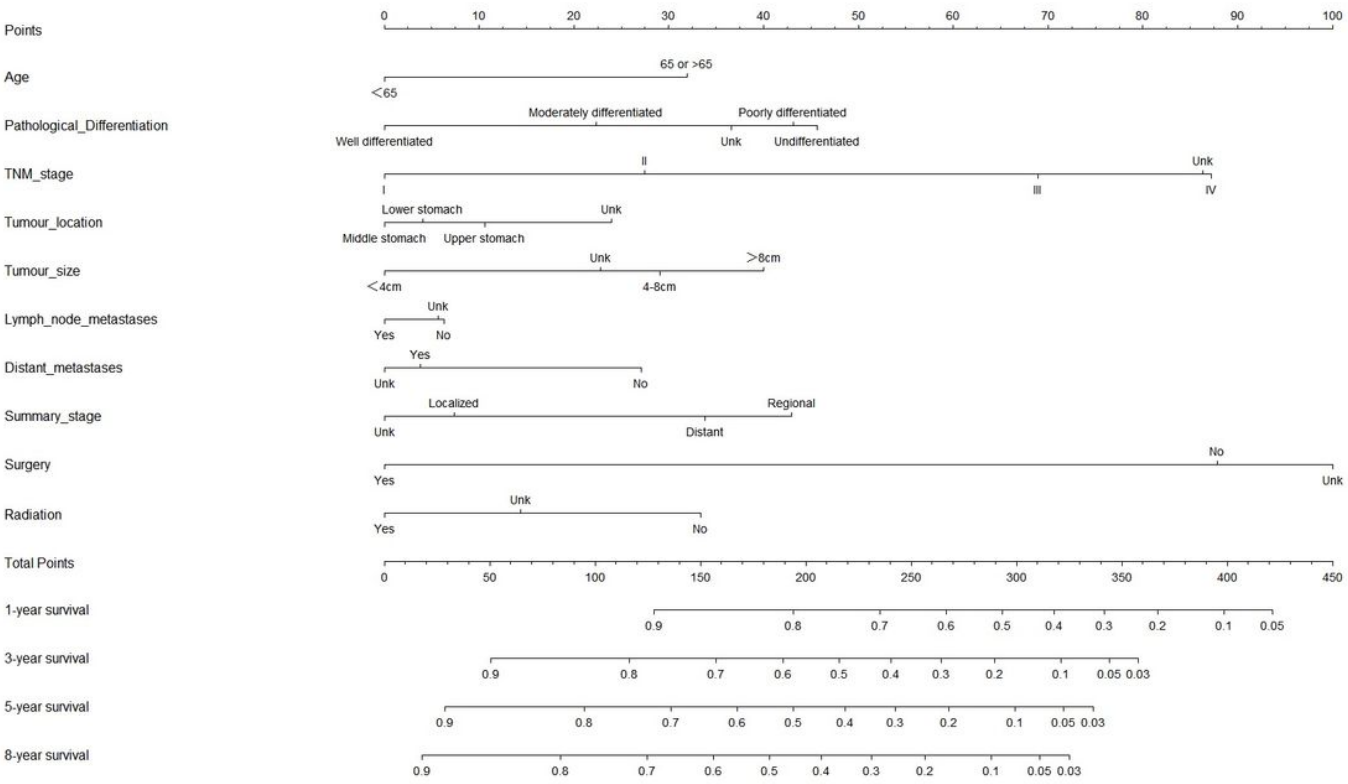

Figure 6

Nomograms predicting 1-, 3- , 5-, and 8-year DSS of patients with intestinal type GC.

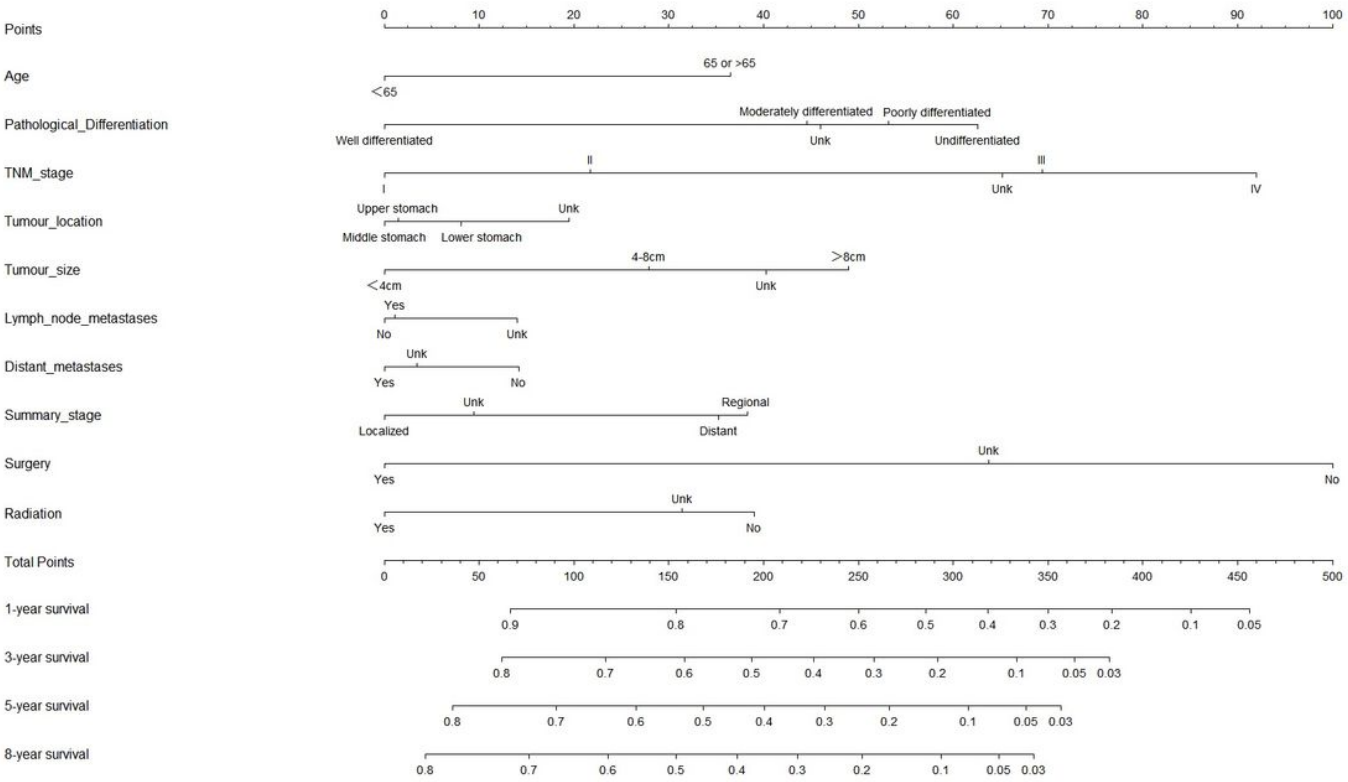

Figure 7

Nomograms predicting 1-, 3- , 5-, and 8-year DSS of patients with diffuse type GC.