10-years mortality risk estimation for gastric cancer patients based on clinicopathological factors

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AIM: *In order to create a nomogram for the gastric cancer no comprehensive study has been performed in Turkey so far and in our study, we tried to forecast the 10-year survival by using risk factors in patients without distant metastasis, who have not previously been diagnosed with another cancer but who underwent curative surgery.*
MATERIAL METHOD: *The data of 411 patients who underwent gastrectomy for gastric cancer between January 2010 and January 2020 in Surgical Oncology Department were retrospectively examined.*
RESULTS: *It has been shown statistically that the high RDW value point to poor survival (p <0.001). There were 173 patients with ≤3.5g/dl and 238 patients with> 3.5g/dl. It was found out statistically significant that hypoalbuminemia indicated poor survival (p <0.001). Moreover, it was determined that high CEA and Ca19-9 with lymphovascular invasion were to be statistically significant with prognosis (p <0.001). On the based of all this data, we have created a dekstop application for the mortality estimation.*
CONCLUSION: *We think that this model will ensure individualization of the treatment for patients and will contribute to the patient's compliance with the treatment by strengthening the communication between the physician.*

KEY WORDS: Gastric cancer, Gastrectomy, Survival analysis, Prognosis

Introduction

Today there is a decline in the incidence of gastric cancer worldwide, it is the fourth most common cancer type in the world and it is the second in the deaths caused by cancer [1]. The golden standard for the treatment of non-metastatic gastric cancer is gastrectomy and appropriate lymph node dissection, in particular D2 [2]. In addition to this treatment, adjuvant therapy improves the local control and survival. While it is around 80-90% in the early-stage gastric cancers, this ratio is quite low in the advanced-stage gastric cancers [3]. While they are diagnosed in the early stages, particularly, in Korea, Japan and the United States [4], in most of the countries, including our country, they are diagnosed at an advanced stage and their prognosis is poor and 5-year survival is around 10%[5]. Since there are many factors in the development of the stomach cancer, this makes the prognosis difficult[6]. Although the treatment received by the patient is the most crucial prognostic factor, the other important parameters in the prognosis are the grade of lymph node metastasis and tissue invasion with reference to the eighth edition of the TNM classification of the American Joint Committee on Cancer (AJCC) [7]. However, the TNM classification is also sometimes inadequate in forecasting the prognosis, and since the TNM classification is based on more than 15 lymph nodes, it would not be able to accurately forecast the number of lymph nodes [8].

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In addition to these main factors; the relationship of age, gender, T stage, N stage, tumor location, tumor markers, lymphovascular invasion, hematological and biochemical parameters with prognosis has been shown [9,10].

Although molecular analysis gives us information about the prognosis, the fact that it is costly and not available anywhere leads us to other options. Since the effects of many factors on prognosis are well known, the forecasting system, which is formed by combining all these factors, can provide us a more accurate forecasting in the prognosis in the long term, and can be useful in the clinic and decision making process. Nomograms, which are generated in this way, could be efficient in forecasting the outcomes, in particular for the cancer patients [11]. Nomograms enhance the communication between the patient and the doctor since patients want simple and clear terms related to the progress of their existing disease. This ensures the patient to make his/her decision more conciously and adapt to the treatment and hence increases the individualization of the treatment. Nomograms generate the numerical probability of a clinical condition with a simple graphical representation through a simple formula using many components [12]. In the literature, there are nomograms related to prognosis forecasting of the gastric cancer and [4,13] nomograms related to other types of cancer have also been formed [14,15]. However, their homogeneity has not been verified yet. In order to create a nomogram for the gastric cancer no comprehensive study has been performed in Turkey so far and in our study, we tried to forecast the 10-year survival by using risk factors in patients without distant metastasis, who have not previously been diagnosed with another cancer but who underwent curative surgery. In this way, we would have defined the oncological prognostic factors of the patients.

Material and Method

The data of 411 patients who underwent gastrectomy for gastric cancer between January 2010 and January 2020 in Department of Surgical Oncology were retrospectively examined. All patients underwent open or laparoscopic subtotal or total gastrectomy and lymph node dissection, depending on the location of the lesion. Inclusion criteria: To be diagnosed with adenocarcinoma based on biopsy and to have undergone radical surgery. Ethics committee approval was obtained.

Patients with the following criterias were excluded from the study; who were under 18 years old, were in the stage 4, who had additional visceral organ resection, who died within 30 days after surgery, who underwent surgery due to the emergency conditions and due to another previous malignancy.

The surgery and pathology reports, preoperative hematological and biochemical parameters, tumor markers, demographic features, and overall survival of the patients were examined. The radiological examinations (chest radiography, computed tomography, ultrasonography, endoultrasonography, magnetic resonance, positron emission tomography) were examined through scanning the electronic files retrospectively. The 8th edition of the TNM classification for staging cancer of Union for International Cancer Control [16] was taken into consideration. We collected the following variables for the survival analysis: gender, age, type of surgery, T and N stage, general stage, rdw (red cell distribution with), albumin, cea (carcinoembryonic antigen), ca19-9 and lymphovascular invasion. The stage was divided into two stages, namely early and advanced. While stage 1-2 is included in the early stage; Stage 3 was included in the advanced stage. The RDW cut off value was determined with reference to the previous studies and divided into two groups as 13.4% and> 13.4% [17,17]. We analyzed the albumin value in two categories as ≤3,5g/dl and> 3,5g/dl.

Follow-up was carried out every 3 months for the first 2 years, every 6 months for the next 3 years, and every 12 months 5 years after the surgery. Follow-up examinations involve; chest x-ray, abdominal ultrasonography, thoracoabdominopelvic tomography, tumor markers, hematological and biochemical data, if required, endoscopy. The follow-up results were obtained from the polyclinic records. The follow-up interval was calculated from the date of surgery until the last follow-up date.

Statistical Analysis

In order to assess the data WEKA 3.7 and SPSS 11.5 programs were used. As the descriptive data, mean ± standard deviation and median (minimum-maximum) for quantitative variables and number of patients (percent) for qualitative variables were used.

Since the normal distribution assumptions were not realized, whether there was a statistically significant difference between the categories of the qualitative variable, which has two categories in terms of quantitative variable, was analyzed by using the Mann-Whitney U test. In order to analyze the relationship between the two qualitative variables, Chi-square and Fisher-exact tests were used. Statistical significance level was considered as 0.05. Besides, the classification methods of Naive Bayes, Logistic Regression and Random Forest were used in the WEKA program. The data set was evaluated by using the 10-fold Cross Validation test option. Accuracy, F-Measure, Matthews Correlation Coefficient (MCC), Precision-Recall Curve (PRC Area) and ROC Area were utilized as data mining performance metrics, in the WEKA program.

Results

Due to the fact that there were too many variables in the data set, the significance of the variables and the val-

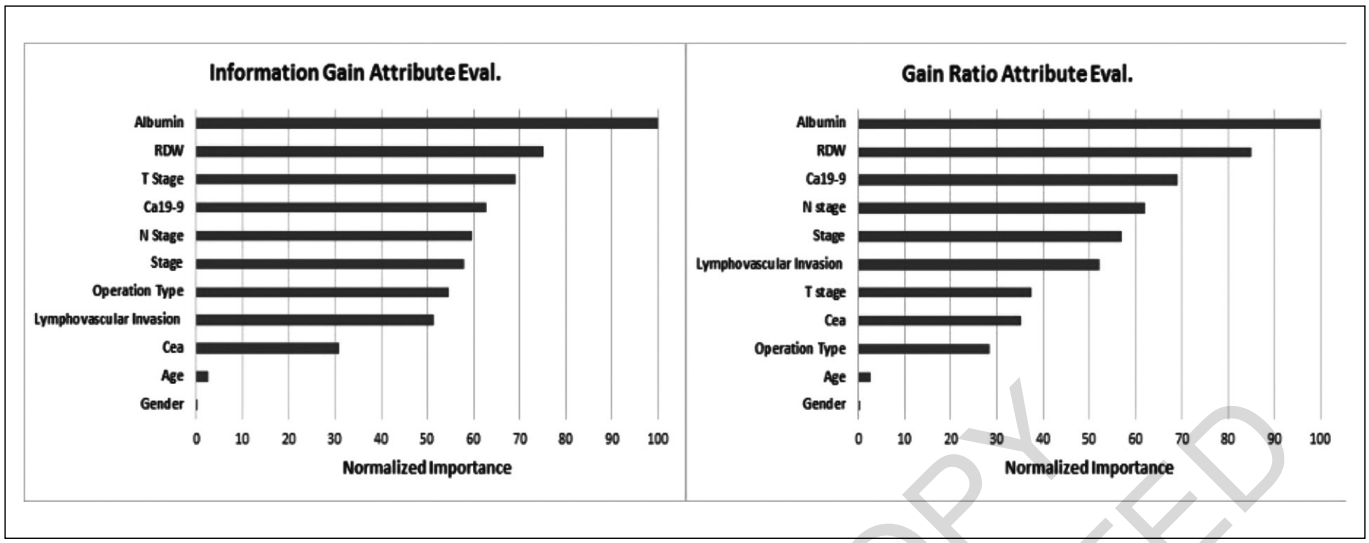

Fig. 1: Variable significance based on the mortality variable.

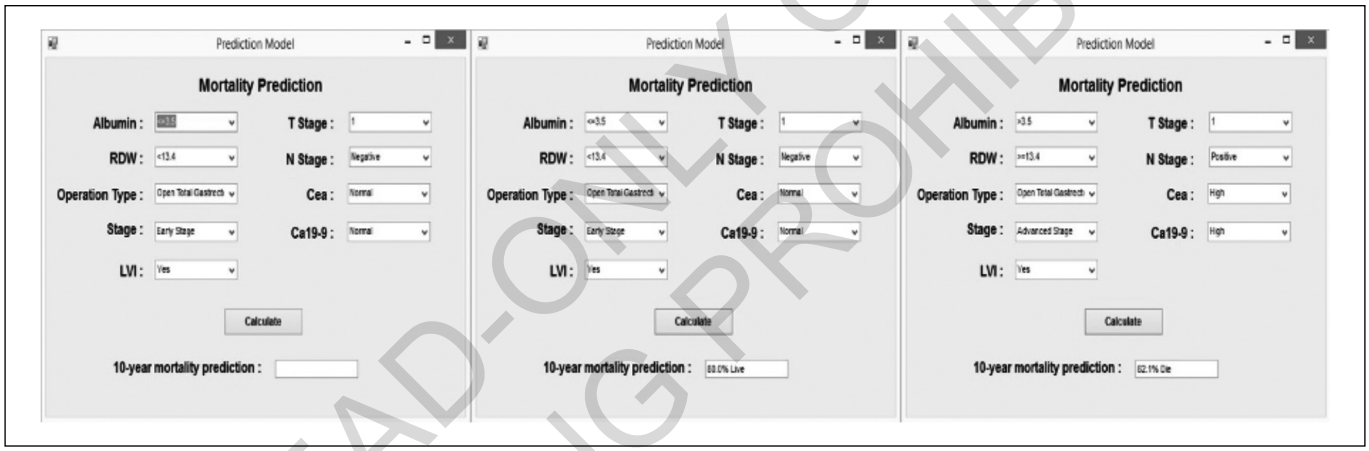

Fig. 2: Software Output.

ues they added to the data set were evaluated by using the Information Gain Attribute Eval. and Gain Ratio Attribute Eval., which are in the WEKA program, and the variables (age, gender), which were determined as insignificant by both methods and considered to be of essential importance as clinical information, were removed from the data set. Hence, a total of 10 variables (9 independent variables and 1 dependent variable) remained in the data set. These variables were Albumin, RDW, Ca 19-9, N stage, Stage, LVI, T Stage, Cea, Operation and Mortality. Based on the dependent variable mortality, percentages for the significance of variables has been presented in Fig. 1.

261 (63.5%) of the patients were male and 150 (36.5%) were female. The mean ± standard deviation and median (minimum-maximum) values of the patients' age were found to be 61.50 ± 12.98 and 62.00 (22.00-93.00), respectively. We divided the patients into two groups as age groups ≤60 and> 60. ≤60 age group was 185 (45.1%) and> 60 age group was 226 (54.9%) patients, and there was no statistically significant relationship between the two age groups in terms of survival (p = 0.137).

For the RDW cut off value, it was considered as 13.4% based on the previous studies, and it was divided into two groups as <13.4% and ≥13.4%. While it was <13.4% in 119 patients; it was ≥13.4% in 292 patients. It has been shown statistically that the high RDW value point to poor survival (p <0.001). We also examined the albumin value in two categories. There were 173 patients with ≤3.5g / dl and 238 patients with> 3.5g / dl. It was found out statistically significant that hypoalbuminemia indicated poor survival (p <0.001).

Moreover, it was determined that high CEA and Ca19-9 with lymphovascular invasion were to be statistically significant with prognosis (p <0.001). All descriptive variables are presented in Table I.

When the data mining methods in Table II was considered based on the performance criteria, it wasdeter-

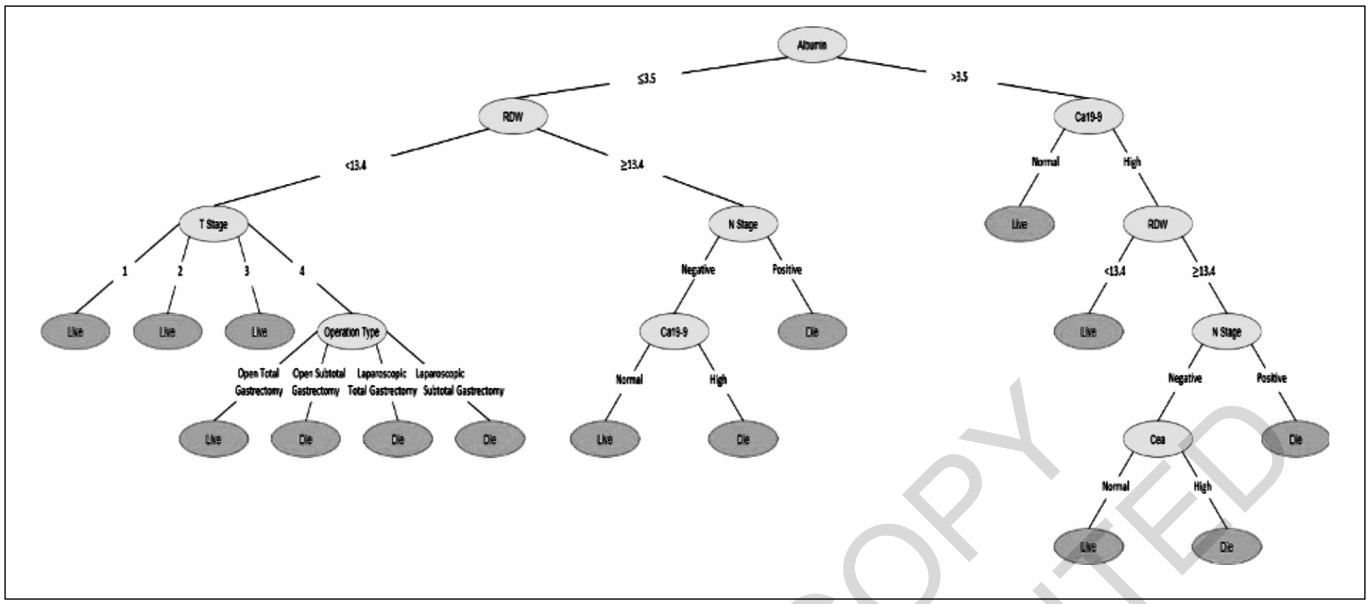

Fig. 3: Random Forest Tree Example

TABLE I - *Descriptives based on mortality*

Variables		Mortality				
		Ex		Live		
		N	%	N	%	P value
Gender	Male	131	63.1	131	63.9	0.867
	Female	76	36.9	74	36.1	
Age	≤ 60	85	41.5	100	48.8	0.137
	> 60	121	58.5	105	51.2	
Operation Type	Open total gastrectomy	86	42.0	45	22.0	<0.001
	Open subtotal gastrectomy	79	38.5	54	16.3	
	Laparoscopic total gastrectomy	11	5.4	32	15.6	
	Laparoscopic subtotal gastrectomy	29	14.1	74	36.1	
T stage	1	16	7.8	48	23.5	<0.001
	2	14	6.8	29	14.1	
	3	51	24.9	79	38.5	
	4	124	60.5	49	23.9	
N stage	Negative	39	19.0	109	53.2	<0.001
	Positive	166	81.0	96	46.8	
RDW	<13.4	23	11.2	96	46.8	<0.001
	≥13.4	183	88.8	109	53.2	
Albumin	≤ 3.5	133	64.6	40	19.5	<0.001
	<3.5	73	35.4	165	80.5	
Stage	Early Stage	61	29.6	132	64.7	<0.001
	Advanced Stage	145	70.4	72	35.3	
Cea	Normal	123	59.7	170	82.9	<0.001
	High	83	40.3	35	17.1	
Ca19-9	Normal	108	52.4	176	85.9	<0.001
	High	98	47.6	29	14.1	
Lymphovascular Invasion	Yes	158	76.7	91	44.4	<0.001
	No	48	23.3	114	55.6	

mined that the best method was Logistic Regressionthe. Because of this, the 10-year survival software designed for the study was made according to the findings of the Logistic Regression data mining method and has been presented in the Fig. 2. Furthermore, the results of the Logistic Regression have been indicated in Table III. The structure of a sample tree of 100 trees used by the Random Forest method is presented in Fig. 3.

In order to simplify all its complexity, we have created a dekstop application. Fig. 2 indicates the outputs of the software, which has been developed for the 10-year survival prognosis. Fig. 2 shows the first overview of the

TABLE II - *Performance comparison of data mining methods.*

Methods		Accuracy	F-Measure	MCC	PRC Area	ROC Area
Naive Bayes	Ex	0.791	0.793	0.586	0.855	0.860
	Live	0.795	0.793	0.586	0.862	0.860
	General	0.793	0.793	0.586	0.859	0.860
Logistic Regression	Ex	0.806	0.808	0.616	0.858	0.864
	Live	0.810	0.808	0.616	0.861	0.864
	General	0.808	0.808	0.616	0.860	0.864
Random Forest	Ex	0.757	0.757	0.513	0.842	0.837
	Live	0.756	0.756	0.513	0.818	0.837
	General	0.757	0.757	0.513	0.830	0.837

Legend: RDW: Red Distribution With; CEA: Carcinoembryonic antigen; MCC: Matthews Correlation Coefficient; PRC: Precision-Recall Curve; LVI: Lymphovascular invasion

TABLE III - *The Results of Logistic Regression Based on Mortality.*

Variables(References)		β	S.E.	p value	OR	95% C.I. for O.R. Lower	Upper
Operation Type (Laparoscopic total gastrectomy)	Open total gastrectomy	1.716	0.395	<0.001	5.560	2.564	12.057
	Open subtotal gastrectomy	1.448	0.392	<0.001	4.256	1.975	9.169
	Laparoscopic subtotal gastrectomy	0.131	0.412	0.751	1.140	0.508	2.559
T Stage (1)	2	0.370	0.435	0.395	1.448	0.617	3.397
	3	0.661	0.340	0.052	1.937	0.995	3.771
	4	2.027	0.334	<0.001	7.592	3.942	14.621
N Stage (Negative)	Positive	1.575	0.226	<0.001	4.833	3.101	7.532
RDW (<13.4)	≥ 13.4	1.947	0.262	<0.001	7.008	4.195	11.706
Albumin (>3.5)	≤ 3.5	2.017	0.229	<0.001	7.515	4.801	11.765
Stage (Early)	Advanced	1.472	0.212	<0.001	4.358	2.879	6.597
Cea (Normal)	High	1.187	0.234	<0.001	3.278	2.073	5.182
Ca19-9 (Normal)	High	1.706	0.244	<0.001	5.507	3.412	8.887
Lymphovascular Invasion (No)	Yes	1.417	0.217	<0.001	4.124	2.697	6.305

β: Beta coefficient; S.E.: Standard error; OR: Odds Ratio; C.I.: Confidence Interval

program and sample outputs produced according to the parameters for "Live" and "Die" states. In this software, there are more than 50 scenarios depending on the parameter selections and only 2 example of these scenarios are shown in Fig. 2.

Discussion

Surgery is still the most curative treatment option for stomach cancer. Many factors are effective in postoperative prognosis. Determination of the prognosis accurately is very valuable in individualizing the disease and revealing the special treatment options. Scientists state that thanks to the genetic researches the prognostic factors will increase in the near future [19,20] however, its disadvantages are; test time, cost and limited number of cases. What we need is that it is accessible, applicable and easy to interpret.

It was found out that the factors, which affect prognosis in our study, were the type of operation, TN stage, general stage, rdw, albumin, cea, ca19-9 and lymphovascular invasion (p <0.001). A model consisting of these variables was developed. The rdw and albumin have been added to the model since they are significantly associated with the overall survival and also easily accessible. The relation of the rdw and the albumin with the survival has been revealed in the literature [17,21].

Nowadays, prognosis forecasting is mostly performed based on the staging system of the AJCC (American Joint Committee on Cancer) and the clinicopathological and demographic data are not included. From our point of view, incorporating this data in a model will enable us to make more accurate prognostic interpretations. Thus, it will help us in approaching the patients on an individual basis. In this study, we created and evaluated a model, which is based on a large Turkish cohort, for forecasting the 10-year mortality after gastrectomy and lymph node dissection due to gastric cancer. Previously it did not have such a wide range of modeling in Turkey and the high number of patients increases the precision of the results.

There are such previous studies in the literature [13,22]. However, there are some differences between the literature and our work. In our study, the gender was removed from our model, since it was considered insignificant in terms of the value it would add to the data set. However, contrary to our study Han et al., Kattan et al., Hirabayashi et al. have revealed that the female gender has a better prognosis and they have added it to their models. Yet, in our study there was no statistically significant difference between the two groups (p = 0.867). We think that this can be explained by the geographical and living conditions differences. However, age was also removed from our model.

In the literature, it has been stated that the prognosis is more inaccurate particularly at young ages [23]. We think that the age is not a negative prognostic factor in our model, due to the fact that now we can diagnose young patients earlier.

With reference to the TNM classification, one of the most important factors in the prognosis is stated as lymph node metastasis, but they can not forecast the patients with less than 15 lymph node dissections. In our model, we evaluated the lymph node metastasis based on its existence and thus, we tried to forecast the prognosis in patients who had undergone surgery. The lymph node metastasis was found to be significantly associated with the prognosis and was added to our model (p <0.001). We consider that thanks to this finding we can have an idea about the prognosis in patients who are with inadequate lymph nodes. At the same time, since D2 dissection was performed in almost all of the gastric cancers in our clinic, it indicates us that taking the lymph node dissection in a positive or negative manner without specifying the regions of the lymph nodes is adequately addressed. In the literature, the lymph node metastasis and its rates have been examined and it has been shown to be an crucial component for the prognostic forecasting [24,25]. The tumor stage indicates heterogeneity in the studies and it is noteworthy that particularly in some American-based studies, the majority is advanced stage. In our study, due to the fact that the R0 resected patients were included in the study, the results may be different. However, the adjuvant therapy, which is given based on the stage, is controversial. Adjuvant treatment regimens are being tried in almost all stages, more in the advanced stages. This modeling will enable us to predict who might actually be more beneficial for. The lymphovascular invasion also has been added to our model and it has been shown to be significantly associated with the prognosis. (p<0.001). Also in the literature [26] LVI has been shown to provide poor survival. We added the LVI to our model since it was stated in the pathology reports, it was easily accessible and had a remarkable impact on the prognosis.

In our study, the highest accuracy classification rate (accuracy) of 10 years was found as 0.808 (80.8%) by using the logistic regression method. This high value is very important for a 10-year survival forecasting. The value, which was found out in our study, was higher than the some studies in the literature, and it enables us to make high accuracy predictions [13,27]. It was also close to the model made by an Italian group [28]. The accuracy of the model is not only about predicting the mortality, but it should also enable us to make a patient-based estimate in the consideration of the risk factors. The fact that the number of patients in the study was adequate and that we did not include missing data and added complete and precise data in the study led to high forecasting. The clinical usage of the model will be more important for adjuvant therapies, particularly in the advanced stage patients. Since the data included in our model can be obtained easily in every clinic, it is highly applicable in daily life. The study has some limitations as we did not include adjuvant treatments in the model. Since our model has postoperative pathology data, its preoperative effect on neoadjuvant therapy is limited. Moreover, disease-free survival was not evaluated in our model because the most valuable of cancer patients is that we think of it as overall survival. Our forecast gives information only about the Turkish population, and it is needed to verify the suitability for other countries with data from these. So this will show the accuracy of our model. Furthermore, the model can be adjusted in the future by adding the results of the adjuvant therapies and the ongoing genetic studies. Our model can help with the individual treatment plans and postoperative counseling, thanks to its good prognostic ability. Hence, we could ensure the closer follow-up of poor prognostic patients.

As a result, we have established a clinically simple model for forecasting the 10-year overall survival for the patients who underwent gastrectomy and lymph node dissection due to the gastric cancer. We think that this model will ensure individualization of the treatment for patients and will contribute to the patient's compliance with the treatment by strengthening the communication between the physician. In order to compute the accurate risk forecasting with an algorithm, meta-analyzes, which includes large groups of patients from different races and geographies, are needed.

Riassunto

Finora non è stato condotto nessuno studio completo in Turchia al fine di creare un nomogramma per il cancro gastrico, e nel nostro studio abbiamo cercato di prevedere la sopravvivenza a 10 anni utilizzando fattori di rischio in pazienti senza metastasi a distanza, che non sono stati precedentemente diagnosticati con un altro cancro ma che hanno subito un intervento chirurgico curativo.

Per questo sono stati esaminati retrospettivamente i dati di 411 pazienti sottoposti a gastrectomia per cancro gastrico tra gennaio 2010 e gennaio 2020 presso il Dipartimento di Chirurgia Oncologica

Risultati: è stato dimostrato statisticamente che l'alto valore di RDW indica una scarsa sopravvivenza (p <0,001). C'erano 173 pazienti con ≤3,5 g / dl e 238 pazienti con> 3,5 g / dl. È stato riscontrato statisticamente significativo che l'ipoalbuminemia indicava una scarsa sopravvivenza (p <0,001). Inoltre, è stato determinato che un CEA e un Ca19-9 elevati con invasione linfovascolare dovevano essere statisticamente significativi con la prognosi (p <0,001). Sulla base di tutti questi dati, abbiamo creato un'applicazione dekstop per la stima della mortalità. Conclusione: riteniamo che questo modello garantirà l'individualizzazione del trattamento per i pazienti e contribuirà alla compliance del paziente al trattamento rafforzando la comunicazione con il medico.

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