PROGNOSTICATION OF SHORT-TERM RESULTS IN GASTRECTOMY FOR GASTRIC CANCER

Bondar G.V.[1], Dumanskiy Yu.V.[1], Lyah Yu.Ye.[1], Guryanov V.G.[1],

Bondar An.V.[2], Psaras G.G.[3], Zaika A.N.[1]

[1]M. Gorky Donetsk National medical university,

[2]Donetsk regional cancer centre,

[3]Mariupol municipal (interdistrict) oncologic dispensary

Summary. The article deals with the prognostic factors of short-term results in gastrectomy, performed in 1435 gastric cancer patients, who had undergone gastrectomy in Donetsk regional cancer centre over a period of twenty years. For research results prognostication there were used mathematical model approaches. To establish the links between prognosticate indicator and input data set there were used mathematical model-building techniques such as techniques of connectionist modeling and logistic regression modeling. In model plotting, to optimize perception threshold solution, the method of operational data plotting was used. In the process of identification of the most significant indicators, there was used the method of genetic algorithm selection. It was found that intraoperative complications risk increases with the growth of the number of the removed organs and/or anatomical structures. Postoperative complications risk increases with the presence of associated diseases. Postoperative death risk in gastrectomy for gastric cancer increases with the presence of complications of neoplastic process, associated diseases, tumour location in the body of stomach, cardiac orifice or total affection.

Key words: gastric cancer, gastrectomy, short-term results, prognostic factors.

Introduction. In Ukraine over a period of 10 years (from 2002 to 2011), gastric cancer morbidity rate decreased from 29.1 to 23.0, in men from 37.9 to 29.9, and in women from 21.4 to 17.2, respectively. Mortality rate over the same period diminished from 23.5 to 18.1, in men from 31.0 до 24.2, and in women from 17.0 to 12.9, respectively [5, 6]. Until now, the surgical method has been the main method in treatment of gastric cancer patients [9, 10, 11, 12]. Gastrectomy has been the most common type of surgical intervention, used in treatment of gastric cancer patients. In spite of considerable improvement of immediate results in gastric cancer surgical treatment, performance of gastrectomy is not infrequently accompanied by the development of severe intra- and postoperative complications, and in some cases, it results in death. Therefore, prognostication of short-term results in gastrectomy for gastric cancer is a significant factor, which permits to improve the results in treatment of the given category of patients [10,12].

The purpose of research is to determine basic prognostic factors of short-term results of gastrectomy in gastric cancer patients.

Materials and methods. Information on 1435 patients, who had undergone gastrectomy in Donetsk regional cancer centre, was reviewed. There were 954 (66.48 ±1.25%) men and 481 (33.52±1.25%) women with a median age of 58.6. 319 (22.23±1.1%) patients had associated diseases, cardiovascular pathology was the most frequent one, which was observed in 143 (9.97±0.79%) cases. As for minute structure of tumour, adenocarcinoma prevailed - 861 (60.0+1.29%) cases. Lesion site corresponded to stage I in 56 (3.9±0.51%) patients, to stages II-III in 953 (66.41±1.25%) patients. In 426 (29.69+1.21%) cases there was stage IV of the disease. 220 (15.33±0.95%) patients had various preoperative complications of neoplastic process.

For research results prognostication there were used mathematical model approaches [1, 2, 4]. To establish the links between prognosticate indicator and input data set there were used mathematical model-building techniques such as techniques of connectionist modeling and logistic regression modeling [1, 2]. In model plotting to optimize perception threshold solution, the method of operational data plotting was used [8]. In research there was set a task of identifying minimal set of input indicators, which will permit to prognosticate result. The task of assessment of each identified indicator from the point of view of the degree of its impact on result was set as well. In the process of identification of the most significant indicators, there was used the method of genetic algorithm selection (GA) of the most significant variables. It was predetermined by a great number (n>83) of input indicators in initial models under analysis [2]. GA method surpasses considerably random search method, and in terms of speed it is highly competitive with the methods of step-by-step variables omission (inclusion), outperforming them [2]. To assess model prognostication quality the standard categories were applied: sensitivity, model specificity, likelihood ratio index (+LR, –LR) [2, 3, 7]. To generalize the obtained data for their universal set, 95% confidence interval (95% CI) was rated as well [3, 7]. 'Model sensitivity' is understood as fraction of correctly prognosticated case modeling, and 'specificity' is understood as fraction of incorrectly prognosticated cases [3]. 'Likelihood ratio' is reliability ratio, which shows that the given result of the medical test will be expected in patients with pathology in comparison with probability that the same result will be expected in patients without pathology. It shows how many times the likelihood of obtaining the given test result in patients in comparison with healthy people is higher (+LR)/lower (–LR) [3]. To test model adequacy, there was applied the method of random (with the use of random number generator) partition of the analyzed data into three sets: learning set (1235 patients), control set (50 patients), and confirmatory set (150 patients) [3]. The learning set was used to develop a model, control set – to prevent model overfitting, and test (confirmatory) set – to confirm the stated model sensitivity and specificity, based on new data [2, 8]. To assess model adequacy there was also used the method of Receiver Operating Characteristic (ROC) curve analysis [2, 4], in this case area under the ROC curve (AUC) [4] and its 95% CI were rated [7]. Model is considered to be adequate in case of statistically significant difference of AUC amount from 0.5. In ROC curve analysis, the optimal value of accept threshold/threshold of failure was chosen [2]. To assess the degree and directedness of indicators in their impact on the result there was used the method of logistic regression modeling, in frames of which there was rated a risk odds ratio (OR) of negative outcome for each factor indicator and a corresponding 95% CI [1, 4, 7]. 'Odds ratio' (OR) is understood as ratio of negative assessment chance in state of patients, subjected or not subjected to factor impact [3]. In OR>1, «chance» risk increases if factor indicator amount grows, and in OR<1, «chance» risk decreases if factor indicator amount grows (if OR statistical significance does not differ from 1, it is not possible to draw a conclusion about presence of the link between factor and resulting indicators) [3, 4]. Mathematical modeling and analysis were carried out, using «Statistica Neural Networks 4.0 C» (StatSoft Inc., 1999-2009) and «MedCalc 11.6» (MedCalc Software, 1993-2011).

In the capacity of factor indicators, there were analyzed 83 markers: patient's sex, tumour localization and growth form, its histological structure, presence and character of pre-operative complications of neoplastic process, lesion site (categories T, N and M), presence of associated diseases and their character, technical features of surgery performance, extent and character of surgical intervention, number of removed organs and/or anatomical structures, presence of postoperative complications, patient's RH blood group and others.

Results and discussion. Out of 1435 patients, who had undergone gastrectomy, intraoperative complications were found in 245 (17.1±1.0%) patients. The most common intraoperative complications were physician-induced spleen injury in 220 (87.3%) patients, less noted were celioenterotomy in 7 (2.8%) patients, circulation failure of transverse colon segment and physician-induced diaphragm injury in 5 (1.9%) и 3 (1.2%) cases respectively.

There was modeled intraoperative complications risk prognostication. In analysis, as the resulting indicator Y1 there was prognosticated an intraoperative complications risk, and in case of their presence, the resulting variable had the magnitude Y1=1 (intraoperative complications were observed in 245 cases). In case of absence of intraoperative complications, the resulting variable was Y1=0. At the first stage of analysis, its conduction involved connectionist prognostication modeling, which included all 83 markers. After choosing (with application of ROC-curve analysis) the optimal accept threshold/threshold of failure model, its prognostic characteristics on the learning set were as follows: sensitivity was 83.3% (95% CI 77.9%–88.0%), specificity was 82.9% (95% CI 80.6%–85.2%). On the confirmatory set, model sensitivity was 85.2% (95% CI 68.8%–96.2%), specificity was 75.6% (95% CI 67.6%–82.8%). As a result, model learning error and generalization error do not differ in statistical significance ($p>0.05$), which demonstrates the model adequacy.

To determine a minimal set of factor indicators, linked with the risk of intraoperative complications, there was used a GA selection of factor indicators. As a result, there were selected three indicators: technical features of surgery performance (X59), extent of surgical intervention (X60), number of removed organs and/or anatomical structures (X61).

On the base of the determined set of three indicators, there was built a linear prognostication model. On the learning set, model sensitivity was 85.6% (95% CI 80.6%–90.1%), specificity was 75.4% (95% CI 72.8%–78.0%). On the confirmatory set, model sensitivity was 85.2% (95% CI 68.8%–96.2%), specificity was 56.1% (95% CI 47.2%–64.8%).

To assess the adequacy of three-factor model, there was applied a method of operational data curve plotting and analysis (ROC-curve model is shown on Fig. 1).

Area under the ROC curve of three-factor model AUC=0.78±0.01, statistical significance ($p<0.001$) differs from 0.5, therefore the model is adequate. The optimal accept threshold/threshold of failure for the model was determined with the help of Yoden index (**J**) optimization**:**

J = max {sensitivity + specificity - 1}   (1).

In optimal threshold selection, the sensitivity of three-factor model of intraoperative complications risk prognostication (for all 1435 cases) turned out to be equal to 84.9% (95% CI 79.8% – 89.1%), specificity was 73.5% (95% CI 70.9% – 76.0%). The likelihood ratio for the prognostication model: +LR=3.2 (95% CI 2.9–3.6); –LR=0.21 (95% CI 0.20–0.30).

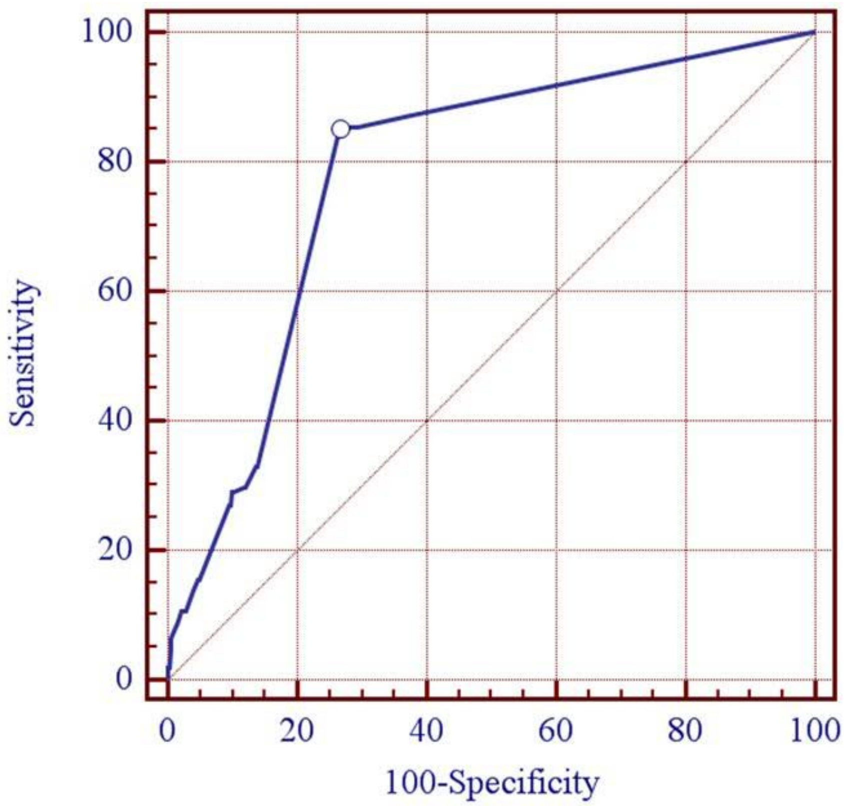

Fig. 1. ROC-curve of three-factor linear connectionist model of intraoperative complications risk prognostication (modeled from the results of prognostication of all 1435 cases), o – symbol for optimal value of model sensitivity and specificity.

To assess impact degree of the determined three-factor indicators on intraoperative complications risk, there was built a regression logistic model. The analysis, carried out within the frames of the given logistic model, shows that intraoperative complications risk rate increases ($p<0.001$) with the growth of the number of removed organs and/or anatomical structures, OR=3.2 (95% CI 2.7 – 3.9). It is explained by the fact that the number of removed organs and/or anatomical structures grows in patients with widespread neoplastic process while performing the surgery with significant adhesive process. Additional neighboring organs mobilization in widespread neoplastic process increases the intraoperative complications risk, for example, circulation failure of transverse colon segment. Significant adhesive process in the left flank increases considerably the risk of physician-induced spleen injury, especially in patients with short gastrolienal ligament.

Postoperative complications were present in 159 (11.1±0.8%) cases. The most common were pulmonary artery thromboembolia (24 (9.6%) patients), abscesses (25 (10.0%) patients), and peritonitis (22 (8.8%) observations). Mathematical model approach was applied to analyze postoperative complications risk. In analysis, as a resulting indicator Y3 there was prognosticated postoperative complications risk, and in case of postoperative complications presence the resulting variable is Y3=1 (postoperative complications were observed in 159 cases). In case of postoperative complications absence, the resulting variable is Y3=0. In the capacity of factor indicators, there were analyzed 83 markers.

At the first stage of analysis there was built a connectionist prognostication model, which included all 83 markers. To determine a minimal set of factor indicators, connected with postoperative complications risk, there was used GA factor indicators selection. As a result of the selection there were determined six indicators: sex (X2), tumour location (X3), preoperative complications of neoplastic process (X8), presence of associated diseases (X17), coronary heart disease (X19), general atherosclerosis, atherosclerotic cardiosclerosis, aortocoronary cardiosclerosis, postinfarction cardiosclerosis (X21).

On the selected set of six indicators, there was built a non-linear connectionist prognostication model. Figure 2 depicts the obtained connectionist model architecture.

On the learning set, model sensitivity was 60.1% (95% CI 51.8%–68.2%), specificity was 64.4% (95% CI 61.6%–67.3%). On the confirmatory set, model sensitivity was 61.5% (95% CI 31.9%–87.1%), specificity was 59.9% (95% CI 51.5%–68.0%).

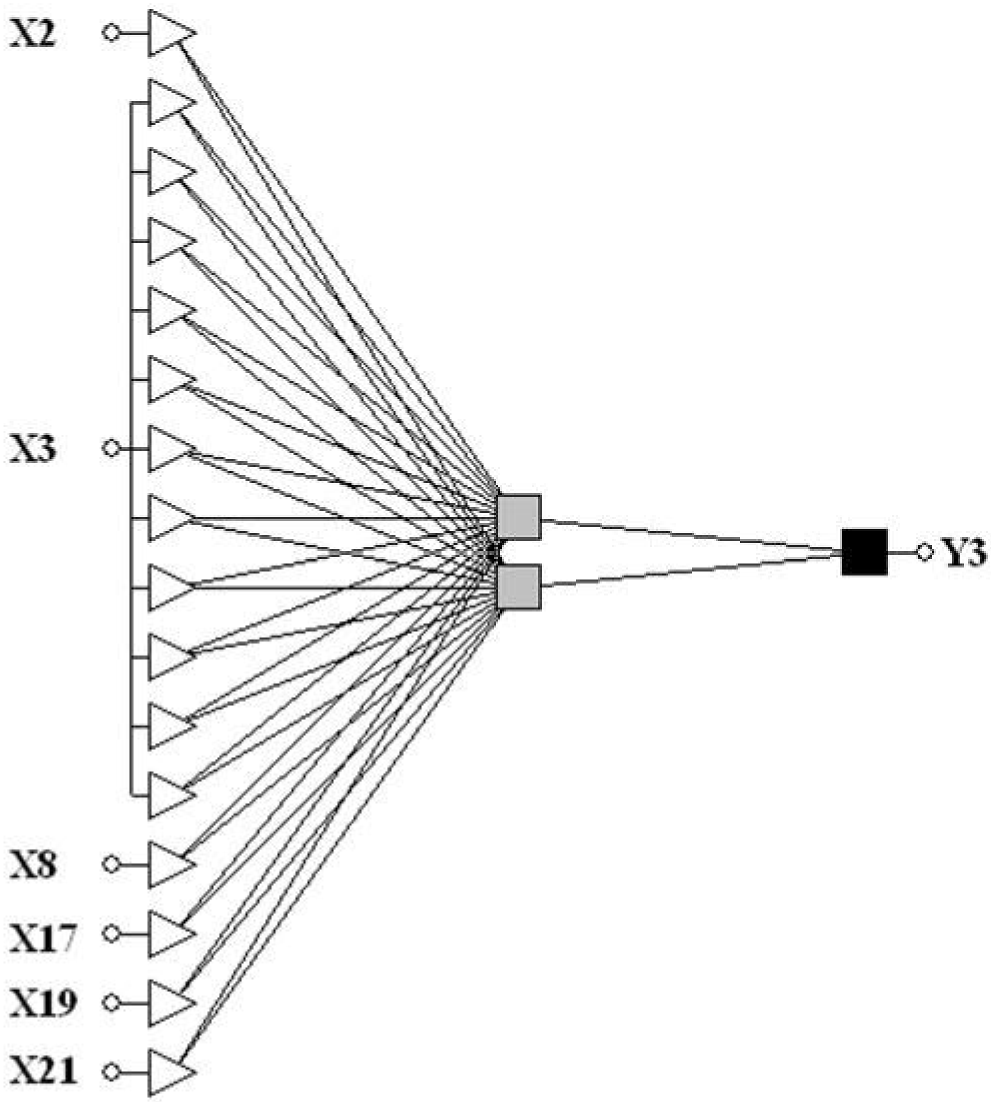

Figure 2. Architecture of connectionist prognostication model (type multi-layer perceptron) of postoperative complications risk (the neurons of input layer

are depicted as triangles, the neurons of hidden layer are depicted as grey boxes, the neuron of output layer is depicted as a black box).

By comparison of prognostication characteristics of the model, obtained on the learning and confirmatory sets, there was not found out a statistically significant difference in sensitivity markers (p=0.84) and specificity markers (p=0.34), which testifies the absence of coefficient fitting and possibility of using the model on the base of new data. It should be emphasized that the reduction of input indicators did not change statistical significance of sensitivity and specificity of six-factor connectionist model (MLP) in comparison with the model, built on all 83 factor indicators (p>0,05), which confirms high value of the selected markers.

To assess adequacy of the obtained six-factor model, there was applied the method of operational data curve plotting and analysis (ROC-curve model is shown on Fig. 3).

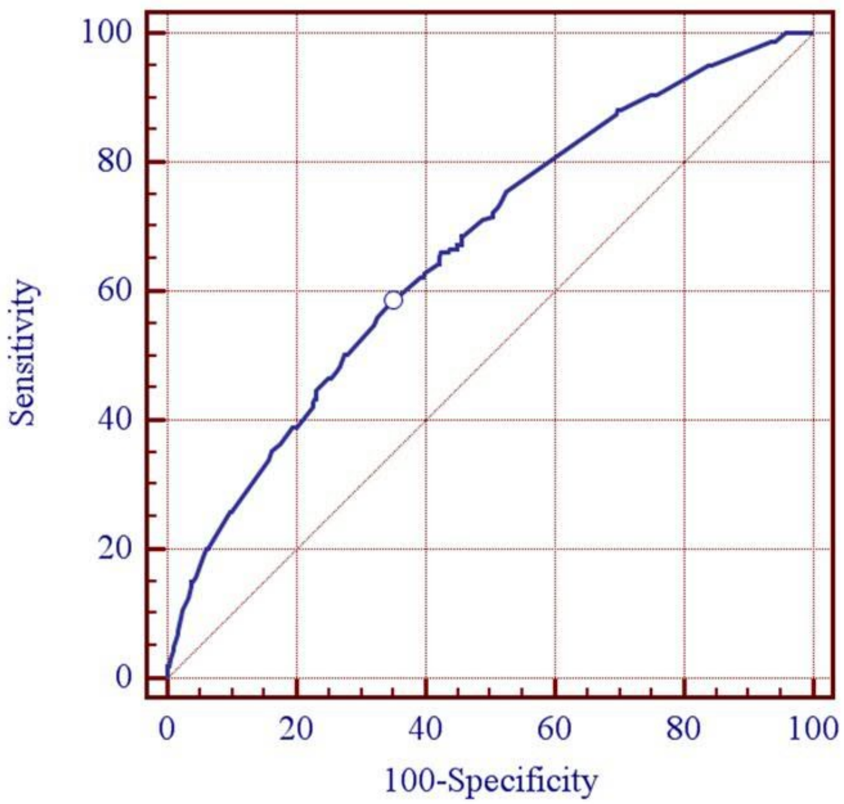

Fig. 3. ROC-curve of six-factor non-linear connectionist model of postoperative complications risk prognostication (modeled from the results of prognostication of all 1435 cases), o – symbol for optimal value of model sensitivity and specificity

Area under the ROC curve of the obtained model AUC=0.67±0.02, statistical significance (p<0.001) differs from 0.5, therefore the model is adequate.

In optimal threshold selection, the sensitivity of six-factor model of postoperative complications risk prognostication (for all 1435 cases) turned out to be equal to 58.5% (95% CI 50.4% – 66.2%), specificity was 65.3% (95% CI 62.6% – 67.9%). The likelihood ratio for the prognostication model: +LR=1.7 (95% CI 1.4–2.0); –LR=0.6 (95% CI 0.5–0.8).

To assess impact degree of the determined six-factor indicators on postoperative complications risk, there was built a regression logistic model. The analysis, carried out within the frames of the given logistic model, shows that postoperative complications risk rate increases (p<0.001) with the presence of associated diseases, OR=1.8 (95% CI 1.3 – 2.6).

It is explained by the fact that in 52.4% of cases, the patients were over 60, with significant associated pathology, predominantly of the cardiovascular system.

Postoperative mortality rate was 4.5±0.6% (65 patients). Mathematical model approach was applied to analyze death risk. In analysis, as a resulting indicator Y2 there was prognosticated a postoperative death risk, and in case of death the resulting variable is Y2=1 (deaths were observed in 65cases). In case of absence of postoperative death, the resulting variable is Y2=0. In the capacity of factor indicators, there were analyzed 84 markers.

At the first stage of analysis, there was built a connectionist prognostication model, which included all 84 markers. To determine a minimal set of factor indicators, connected with death risk, there was used GA factor indicators selection. As a result of the selection, there was determined one indicator: presence of postoperative complications. Therefore, to analyze death risk there was built a logistic regression model based on the same six factor indicators, as in case with the model of postoperative complications risk prognostication.

The analysis, carried out in the frames of the obtained logistic model, shows that postoperative death risk increases ($p=0.029$) with the presence of preoperative complications of neoplastic process, OR=2.2 (95% CI 1.1 – 3.6). Postoperative death risk also increases ($p=0.003$) with the presence of associated diseases, OR=2.2 (95% CI 1.3 – 3.7). It was also determined that postoperative death risk is higher ($p=0.019$), if tumour is located in the body of stomach and cardiac orifice, and in case of overall affection as well, OR=2.2 (95% CI 1.1 – 4.1) in relation to tumour location in antrum and subtotal affection. Death risk increase due to the presence of preoperative complications of neoplastic process is explained by the severity of the latter ones. In our study, in 3.28 ± 0.47 % of patients there developed preoperative hemorrhage, that worsened patients' state considerably, and consequently, affected surgery result. Moreover, in 9.27+0.77% of patients there was stenosis of varying severity, which leads to development of severe electrolyte imbalance, and consequently to the dysfunction of the whole range of organs and systems, which also increases death risk. Presence of grave somatic diseases also increases death risk considerably. Many postoperative complications resulted from decompensation of grave preoperative associated diseases, mainly cardiovascular ones. Tumour location in the body of stomach and cardiac orifice, and its overall affection as well, increase surgical injury rate, and consequently, death risk. Surgery in case of lower-located stomach tumours (excluding tumours, which spread to duodenum) is less traumatic and complex from the technical point of view than the surgery in patients with proximally-located tumours or with total affection of stomach.

Conclusion.

1. There were separated three factor indicators, which in the main determine intraoperative complications risk: technical features of surgery performance, extent of surgical intervention, number of removed organs and/or anatomical structures, – model sensitivity was 84.9% (95% CI 79.8% – 89.1%), specificity was 73.5% (95% CI 70.9% – 76.0%). The likelihood ratio for the model: +LR=3.2 (95% CI 2.9–3.6), –LR=0.21 (95% CI 0.20–0.30).

2. It was found that intraoperative complications risk increases ($p<0.001$) with the growth of the number of removed organs and/or anatomical structures, OR=3.2 (95% CI 2.7 – 3.9).

3. There were separated six factor indicators, which in the main determine postoperative complications risk: sex, tumour location, presence of preoperative complications, presence of associated diseases, character of associated diseases (coronary heart disease, general atherosclerosis, atherosclerotic cardiosclerosis, aortocoronary cardiosclerosis, postinfarction cardiosclerosis) – model sensitivity was 58.5% (95% CI 50.4% – 66.2%), specificity was 65.3% (95% CI 62.6% – 67.9%). The likelihood ratio for the prognostication model: +LR=1.7 (95% CI 1.4–2.0), –LR=0,6 (95% CI 0.5–0.8).

4. It was found that postoperative complications risk increases ($p<0.001$) with the presence of associated diseases, OR=1.8 (95% CI 1.3 – 2.6).

5. It was found that postoperative death risk increases ($p=0.029$) with the presence of preoperative complications of neoplastic process, OR=2.2 (95% CI 1.1 – 3.6). Postoperative death risk also increases ($p=0.003$) with the presence of associated diseases, OR=2.2 (95% CI 1.3 – 3.7). It was also determined that postoperative death risk is higher ($p=0,019$), if tumour is

located in the body of stomach and cardiac orifice, and in case of overall affection as well, OR=2.2 (95% CI 1.1 – 4.1) in relation to tumour location in antrum and subtotal affection.

REFERENCES

1. Гланц С. (1999) Медико-биологическая статистика. Практика, Москва, 459 с.

2. Казаков В.Н., Лях Ю.Е., Кутько И.И. (2001) Теоретические и практические аспекты автоматизированной информационной системы «Депрессии». Серия «Очерки биологической и медицинской информатики». Из-во ДонГМУ, Донецк, 160 с.

3. Лях Ю.Е., Гурьянов В.Г., Хоменко В.Н., Панченко О.А. (2006) Основы компьютерной биостатистики. Анализ информации в биологии, медицине и фармации статистическим пакетом MedStat. Донецк: Папакица Е.К., 214 с.

4. Петри А. К., Сэбин К. (2003) Наглядная статистика в медицине (Пер. с англ.). ГЭОТАР-МЕД, Москва, 144 с.

5. Рак в Україні в 2002-2003 р. (захворюваність, смертність, показники діяльності онкологічної служби) (2012) Бюлетень національного канцер-реєстру України, Київ, 5: 105 с.

6. Рак в Україні в 2010-2011 р. (захворюваність, смертність, показники діяльності онкологічної служби) (2012) Бюлетень національного канцер-реєстру України, Київ, 13: 111 с.

7. Altman D.G., Machin D., Bryant T.N. (2003) Statistics with confidence. Confidence intervals and statistical guidelines. BMJ Books, Bristol, 240 p.

8. Metz C.E., Kronman H.B. (1980) Statistical significance tests for binormal ROC curves. J. Math. Psychol., 22: 218 – 243.

9. Pisanu A. Montisci A., Piu S., Uccheddu A. (2007) Curative surgery for gastric cancer in the elderly: treatment decisions, surgical morbidity, mortality, prognosis and quality of life. Tumori., 93(5): 478-484.

10. Schauer M., Peiper M., Theisen J., Knoefel W. (2011) Prognostic factors in patients with diffuse type gastric cancer (linitis plastica) after operative treatment. Eur. J. Med. Res., 16(1): 29-33.

11. Tokunaga M., Tanizawa Y., Bando E., Kawamura T., Terashima M. (2013) Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann. Surg. Oncol., 20(5): 1575-1583.

12. Qiu M.Z., Wang Z.Q., Luo H.Y., Zhang D.S., Zhou Z.W., Li Y.H., Jiang W.Q., Xu R.H. (2011) Prognostic analysis in node-negative gastric cancer patients in China. Tumour Biol., 32(3): 489-492.