PROGNOSIS OF THE LONG-TERM RESULTS OF GASTRECTOMIES AT GASTRIC CANCER

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**Objectives:** to determine the prognostic factors, which affect the long-term results of surgical treatment of gastric cancer (GC) patients using methods of mathematical modeling. **Object and methods:** the prognostic factors of long-term results of gastrectomies performed in 1435 GC patients in Donetsk Regional Anticancer Center in a span of twenty years have been studied. For separation of factor signs determining long-term results and for evaluation of their influence on survival of patients, the method of construction and analysis of neural network mathematical models has been applied. Analysis has been carried out on long-term results of 1000 followed-up patients. As factor signs in the first stage of the analysis, 125 indexes have been analyzed, on which the linear neural network model has been constructed and learned. After optimization of “acceptance/rejection” threshold, sensitivity of model constructed on complete set of factor signs has constituted 69.0% (95% CI 65.0%–72.7%) on the learning set, specificity – 68.9% (95% CI 63.5% –74.2%). On the validation set, sensitivity of model was 61.2% (95% CI 49.1%–72.6%), specificity – 60.6% (95% CI 43.0% –76.9%).

**Conclusions:** It has been determined in the result of conducted analysis that long-term results of surgical treatment of GC patients are affected by the following factors: age of patient, categories T, N and postsurgical complications. With the increase of years, the risk of death statistically significantly (p<0.001) increases, HR=1.02 (95% CI 1.01-1.03) per each year. Statistically significant (p=0.028)
increase of death risk for men has also been determined, HR=1.18 (95% CI 1.02-1.37).

**Key words:** gastric cancer, gastrectomy, long-term results, prognosis.

**Relevance of the topic.** Gastric cancer (GC) remains one of the most widespread malignant neoplasms in many countries of the world. In 2012, incidence in Ukraine (raw count) has constituted 22.9 per 100,000, mortality – 18.4 per 100,000 of the population [5]. Despite the progress of modern oncology, surgery remains the only method giving hope for the radical treatment of GC patients [8]. Unfortunately, the long-term results of surgical treatment at GC remain unsatisfactory. For instance, according to the data of Nashimoto A. et al. [7], who have united the results of treatment of patients in 208 hospitals of Japan, 5-year survival rate has constituted 68.9%, most of patients had early GC at that. If tumor process is neglected, these rates constitute no more than 10-15%. Thereupon we have decided to study the prognostic factors affecting the long-term results of this category of patients.

**OBJECT AND METHODS OF STUDY**

Data of 1435 patients, who underwent gastrectomy in Donetsk Regional Anticancer Center, have been included in the study. Among patients were 954 men (66.5±1.3%) and 481 women (33.5±1.3%). Mean age has constituted 58.6±0.3. Concomitant diseases were found in 319 (22.2±1.1%) patients, the pathology of cardiovascular system has been mostly observed – 143 (10.0±0.8%). According to the data of histological studies, adenocarcinomas prevailed – 861 (60.0±1.3%). Dissemination of tumor process corresponded I stage in 56 (3.9±0.5%) patients, II-III stages – in 953 (66.4±1.3%) patients. In 426 (29.7±1.2%) observations, IV stage of disease has been marked. Two hundred twenty (15.3±1.0%) patients had different complications of tumor process before surgery.

For separation of factor signs determining long-term results of treatment and evaluation of degree of their impact on survival of patients, method of construction and analysis of neural network mathematical models has been applied [1, 4, 6]. Survival of patients after carried out treatment has been analyzed as resulting sign
(variable Y): if patient has survived 5-year period, Y=0 (positive outcome), if patient has died within 5 years, Y=1 (negative outcome).

Analysis has been carried out taking into account long-term results of treatment of 1000 patients. When constructing and analyzing mathematical models of prognosis, all patients have been randomly (using random numbers generator) divided into 3 sets: learning set (was used for construction of model and included results of treatment of 850 patients), testing set (was used for prevention of relearning of mathematical model, included 50 patients) and validation set (was used for testing of prognostic capability of mathematic model on the new data, included 100 patients) [2].

In the first stage of analysis, 125 indexes have been examined as factor signs: age, sex, localization of tumor, category T, category N, category M, stage, complications of tumor process before surgery, their number and type (stenosis, perforations, abscesses, fistulas, anemia, etc.); concomitant pathology, number of concomitant diseases, their type, IHD, disorder of heart rhythm, general atherosclerosis, atherosclerotic cardiosclerosis, aortocoronary cardiosclerosis, postinfarction cardiosclerosis, stenocardia, idiopathic hypertension, other diseases of cardiovascular system, circulatory insufficiency of 0-2 stg., pancreatic diabetes, obesity, varix dilatation of lower extremities, post-thrombotic syndrome, rheumatism, pathology of liver and pancreas, chronic bronchitis, bronchial asthma, silicosis, anthracosis, focal pulmonary tuberculosis, pneumosclerosis, lung emphysema, other diseases of pulmonary system; urolithiasis, chronic pyelonephritis, prostate gland adenoma, cystitis, other diseases of urogenital system, stomach ulcer (of stomach and duodenum), chronic gastritis, nonspecific ulcerative colitis, chronic spastic colitis, polyposis of large intestine, diverticular disease of colon, dolichosigmoid, other diseases of GIT, uterine fibromyoma, ovarian cyst, other pathology of female reproductive organs; type of surgery, volume of surgery, number of resected organs and/or anatomic structures, their type (resection of seminal vesicles, resection of urinary bladder, uterine extirpation, extirpation of uterus with uterine appendages, removal of uterine
appendages, resection of small intestine, appendectomy, excision of abdominal wall, resection of corpus uteri, supravaginal uterectomy, extirpation of stump of the cervix, resection of vagina, resection of capsule of prostate gland, cholecystectomy, splenectomy, removal of fibromatous node of uterus, etc.), type of surgery, cause of palliative type of surgery; blood group, rhesus of blood, form of tumor growth, histological structure of tumor; presence of intraoperative complications, their number and type (trauma of spleen, deserosed small or large intestine, injury of veins of sacral plexus, vaginal vessels hemorrhage, lancing of abscess, lancing of lumen of large and small intestine, perforation of tumor, injury of ureter, urinary bladder, etc.); presence of postsurgical complications, their number and type (pulmonary embolism, phlegmon of retroperitoneal space, thrombosis of mesenteric vessels, DIC-syndrome, multiple organ failure, acute cystitis, adhesive intestinal obstruction, small bowel outer fistula, pulmonary edema, anemia, failure of sutures of anastomosis or stump of duodenal, abscess, peritonitis, wound abscess, anastomositis, myocardial infarction, cardio-pulmonary failure, acute cardiac failure, acute cardiovascular failure, plevritis, pneumonia, pyelonephritis, orchiepididymitis, acute orchitis, hepatic and renal failure, renal and hepatic failure, acute renal failure, acute hepatic failure, pancreatitis, intraperitoneal hemorrhage, etc.).

RESULTS AND DISCUSSION

On set of 125 factor signs, linear neural network model of prognosis of risk for the patient not survive 5-year after carried out treatment, has been constructed and learned. After optimization of “acceptance/rejection” threshold, sensitivity of model constructed on the complete set of factor signs, on learning set has constituted 69.0% (95% CI 65.0%–72.7%), specificity – 68.9% (95% CI 63.5% – 74.2%). On validation set, sensitivity of model has constituted 61.2% (95% CI 49.1%–72.6%), specificity – 60.6% (95% CI 43.0% –76.9%). Sensitivity and specificity on the learning and validation sets statistically significantly were not different (p=0.25 and p=0.44 correspondingly, at comparison by χ² criterion), that shows the adequacy of constructed model.
For detection of factors, which are to a great extent connected with risk of not surviving 5-year period, the selection of the most significant signs has been carried out using method of genetic algorithm (GA) of selection [3]. In the result, 7 factor signs have been selected: Age (X1), Category T (X4), Category N (X5), Category M (X6), Presence of complications before surgery (other) (X16), Cause of palliative type of surgery (X80), Presence of postsurgical complications (X120).

Basing on this set of factor signs, 7-factor linear neural network model has been constructed and learned. After optimization of “acceptance/rejection” threshold, sensitivity of linear model constructed on this set of factor signs, on the learning set has constituted 64.3% (95% CI 60.2%–68.2%), specificity – 62.8% (95% CI 57.3% –68.2%). On validation set, sensitivity of model has constituted 56.7% (95% CI 39.9%–68.5%), specificity – 57.6% (95% CI 39.9% –74.3%). Sensitivity and specificity on the learning and validation sets were not statistically significantly different (p=0.28 and p=0.69, correspondingly, at comparison by criterion \( \chi^2 \)), that is the evidence of adequacy of given model.

Fig. 1. Architecture of 7-factor neural network model of prognosis of risk not survive 5-year period (by triangles are designated neurons of input layer, by grey squares – neurons of hidden layer, by white square – neuron of output layer).

For registration of nonlinear connections between factor signs and resulting sign, on the same set of 7-factor signs, the nonlinear neural network model (of multilayered perceptron type) with one hidden layer (two neurons in hidden layer)
for prognosis of risk for patient not survive 5-year period after treatment has been constructed (architecture of the model is represented in Fig. 1).

After optimization of “acceptance/rejection” threshold of model, sensitivity of model has constituted 65.5% (95% CI 61.5%–69.4%), specificity – 64.2% (95% CI 58.6%–69.5%), sensitivity of model on validation set has constituted 59.7% (95% CI 47.6%–71.3%), specificity – 63.6% (95% CI 46.1%–79.5%). Sensitivity and specificity on learning set and testing set were not statistically significantly different (p=0.42 and p=0.90 correspondingly, at comparison by χ² criterion) that shows the adequacy of constructed model.

**Fig. 2.** ROC-curves of models of prognosis of risk not survive 5-year period, 1 – linear neural network model constructed on 125 factor signs; 2 – linear neural network model constructed on 7 selected factor signs, 3 – nonlinear neural network model constructed on 7 selected factor signs.
For evaluation of significance of selected factor signs and comparison of prognostic features of three models, method of construction of ROC-curves – receiver operating characteristic curves has been used (Fig. 2).

When comparing ROC-curves, insignificant, but statistically significant decrease of area under curve has been determined for linear neural network model constructed on 7 selected factor signs (AUC2=0.69±0.02) compared with linear neural network model constructed on the 125 factor signs (AUC1=0.73±0.02), p=0.007. Also area under curve for nonlinear neural network model constructed on 7 selected factor signs (AUC3=0.72±0.01) decreases insignificantly compared with linear neural network model constructed on the 125 factor signs, p=0.004. Thus, at decrease of number of factor signs from 125 to 7, prognostic qualities of model have not almost changed that indicates the high significance of selected factor signs: (Age (X1), Category T (X4), Category N (X5), Category M (X6), Presence of complications before surgery (other) (X16), Cause of palliative type of surgery (X80), Presence of postsurgical complications (X120)) for prognosis of risk not survive 5-year period.

For detection of strength and direction of influence of 7 selected factor signs, logistic model of regression of prognosis of risk not survive 5-year period has been constructed. Model is adequate ($\chi^2=110.7$ at 9 ranges of discretion, p<0.001); results of analysis of coefficients of the model are represented in Table 1.

<table>
<thead>
<tr>
<th>Factor sign</th>
<th>Value of coefficients of prognostic model, $b\pm m$</th>
<th>Level of significance of difference from regression coefficient 0</th>
<th>Odds ratio, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>0.022±0.007</td>
<td>0.002*</td>
<td>1.02 (1.01 – 1.04)</td>
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<tr>
<td>X4</td>
<td>0.47±0.12</td>
<td>&lt;0.001*</td>
<td>1.6 (1.3 – 2.0)</td>
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<tr>
<td>X5</td>
<td>0.38±0.07</td>
<td>&lt;0.001*</td>
<td>1.5 (1.3 – 1.7)</td>
</tr>
<tr>
<td>X6</td>
<td>-4.9±100</td>
<td>&gt;0.999</td>
<td>-</td>
</tr>
<tr>
<td>X16</td>
<td>-0.014±0.203</td>
<td>0.941</td>
<td>-</td>
</tr>
<tr>
<td>X80</td>
<td>0.47±0.45</td>
<td>0.299</td>
<td>-</td>
</tr>
<tr>
<td>X120</td>
<td>0.79±0.24</td>
<td>0.001*</td>
<td>2.2 (1.4 – 3.5)</td>
</tr>
</tbody>
</table>

Analysis of coefficients of logistic model has showed that risk of not survive 5-year period statistically significantly (p=0.002) increases with age of patients, OR=1.02 (95% CI 1.01 – 1.04) per each year. Also increase (p<0.001) of risk not survive 5-year period at increase of category T per each unit, OR=1.6 (95% CI 1.3 – 2.0) and category N (p<0.001), OR=1.5 (95% CI 1.3 – 1.7) per each unit has been determined. The increase (p=0.001) of risk of not survive 5-year period at presence of postsurgical complications has been determined, OR=2.2 (95% CI 1.4 – 3.5).

Thus, the long-term results of gastrectomies are influenced by 4 groups of factors. First one is connected with dissemination of tumor process (category T, N) – the more is dissemination of tumor process, the higher is probability of its progression in the form of local relapse or development of remote metastases.

Second group is represented by factors describing physiological state of patient, to be exact, his age and connected with it degree of ageing of his organism. It should be mentioned that short-term presurgical preparation in series of cases makes impossible to evaluate fairly the whole spectrum of concomitant diseases, which can be present in aged and old patients. In this situation, age of patient acts as independent prognostic factor, but it is understood as age and connected with it hardly evaluated degree of organism ageing.

Third group of factors is connected with postsurgical complications, which occurrence can cause, on the one hand, lethal outcome in postsurgical period, and, on the other hand, cause such changes in homeostasis, which in the future can, in turn, cause the development of other diseases finally causing lethal outcome. For
instance, development of severe pancreatitis can provoke further development of pancreatic diabetes.

CONCLUSIONS

1. The following factors influence the long-term results of surgical treatment of GC patients: age of patients, categories T, N and presence of postsurgical complications.

2. Risk of not survive 5-year period statistically significantly (p=0.002) increases with ages, OR=1.02 (95% CI 1.01 – 1.04) per each year.

3. The increase of risk of not survive 5-year period at increase of category T has been determined, OR=1.6 (95% CI 1.3 – 2.0) per each unit, and category N (p<0.001), OR=1.5 (95% CI 1.3 – 1.7) per each unit.

4. The increase (p=0.001) of risk of not survive 5-year period at presence of postsurgical complications has been determined, OR=2.2 (95% CI 1.4 – 3.5).

REFERENCES


