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Prediction of Long-Term Gastrectomy Outcomes in Gastric Cancer

Roman V. Ishchenko[1], Igor E. Sedakov[2], Aleksandr N. Zaika[3], Rostislav V. Pavlov[4]

[1]Federal Scientific and Clinical Center of Specialized Types of Medical Care and Medical Technologies of the Federal Medical and Biological Agency of Russia, Orekhovy Boulevard, Moscow, Russia.

E-mail: ishenkorv@rambler.ru

[2]G.V. Bondar Republican Cancer Center, 2a Polotskaya, Donetsk, Donetsk People's Republic.
E-mail: Sedakov.igor.1964@mail.ru,

[3]G.V. Bondar Republican Cancer Center, 2a Polotskaya, Donetsk, Donetsk People's Republic.
E-mail: aleksandr.zaika.1973@mail.ru

[4]N.I. Pirogov Clinic of High Medical Technologies of St. Petersburg State University, Fontanka River Embankment, St Petersburg, Russia. E-mail: onko_spb@mail.ru

ABSTRACT

Aim: Assessment of prognostic factors affecting long-term outcomes among patients with gastric cancer.

Methods: Retrospective analysis included long-term outcomes of 1,000 patients – a training group (850 patients), test group (50 patients), validation group (100 patients). Cox's model was applied to study the effect of combined factors on patient survival.

Results: The risk of not surviving a 5-year period (p = 0.002) increases with patient's age, OR = 1.02 (95 % CI: 1.01–1.04) for every lived year. The risk of not surviving a 5-year period increases (p < 0.001) with a one-point change in T-category, OR = 1.6 (95 % CI: 1.3–2.0), and N-category (p < 0.001), OR = 1.5 (95 % CI: 1.3–1.7). The higher risk (p = 0.001) is also associated with postoperative complications, OR = 2.2 (95 % CI: 1.4 – 3.5). The risk of death was higher for males (p = 0.028), HR = 1.18 (95 % CI: 1.02–1.37).

Conclusions: Long-term outcomes of gastrectomy are affected by patient age, T- and N-categories, and postoperative complications. Risk of death increases with age for every lived year and is higher for males.

KEYWORDS

Gastric Cancer, Prognostic Factors, Radical Cure, Relapse, Prediction, Long-term Gastrectomy.

Background

Gastric cancer is the world's fifth most common oncological disease and ranks third as the cause of death among oncological patients. Two thirds of the patients with gastric cancer diagnosis cannot be operated upon due to advanced disease [13&]. Despite recent successes in oncology, the only treatment method providing hope for radical cure of the disease is surgery [2&]. Unfortunately, long-term outcomes of surgical treatment of gastric cancer remain unsatisfactory – despite advancements in diagnosis, surgical and combination treatment (increased volume of lymph node dissection, use of adjuvant chemotherapy), overall 5-year survival does not exceed 25-30 %, and distant metastases and local and regional recurrences develop in more than 50% of patients [16&]. Thus, according to treatment outcomes of patients from 208 Japanese clinics

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combined by Nashimoto A. et al. [3&], 5-year survival was 68.9%, with most patients being diagnosed early stages of the disease. Therefore, the authors of the present research decided to study prognostic factors affecting long-term outcomes among these patients.

Materials and Methods

The study included data on 1435 patients – 954 (66.48 ± 1.25 %) male, 481 (33.52 ± 1.25 %) female, average age 58.6 years – who underwent gastrectomy at Donetsk Regional Anticancer Center. In 319 patients, 634 (44.18 ± 1.31 %) concomitant disorders were diagnosed, most commonly pathology of the cardiovascular system (315 (49.68 ± 1.99 %)). The most common complication, ischemic heart disease, was observed in 110 (17.35 ± 1.5 %) cases. Histologically, adenocarcinoma was the most common type diagnosed in 861 (60.0 ± 1.29 %) cases. Stage I was observed in 56 (3.9 ± 0.51 %) patients, stages II-III in 953 (66.41 ± 1.25 %) patients, stage IV in 426 (29.69 ± 1.21 %) cases. Various complications related to cancer were observed in 220 (15.33 ± 0.95 %) patients.

All the patients underwent gastrectomy due to cancer. Reconstruction after stomach resection was performed according to Professor G.V. Bondar’s method. The following technique is used to form the esophagojejunal anastomosis – upper midline laparotomy is performed; the stomach is mobilized and resected from the duodenum; the abdominal part of the esophagus is mobilized, the jejunal loop is drawn into the wound. At the distance of 20-35 cm from the ligament of Treitz, its afferent and efferent limbs are attached to each other with seroserous suture in the shape of a racket (Fig. 1.1). Esophageal diameter is measured; depending on the diameter, 2 or 3 rubber tubes 0.5 cm in diameter are placed on the sutured jejunal loop. Around the tubes, the afferent and efferent limbs are stitched together with seroserous suture for the second time (Fig. 1.2). The widest part of the ‘loop-racket’ is used. Three tack-up sutures are applied to the esophagus and upper edge of the jejunal loop; the tubes are extracted. A specialized clamp – esophageal retractor – is passed through the opening to grab the esophagus 2-3 cm above the tumor. The stomach is resected; using the clamp, the esophagus is pulled through the opening between the intestinal loops. The upper part of the intestine is attached to the esophagus with three tack-up sutures. Using 4-5 silk sutures, the esophagus is attached to the jejunum in the round (Fig. 1.3). The efferent limb of the intestine is dissected in the transverse direction. Continuous row of sutures is applied between the esophagus and efferent limb of the intestine using catgut sutures which are easily shielded by seroserous sutures applied to the afferent and efferent limbs of the intestine (Fig. 1-4).

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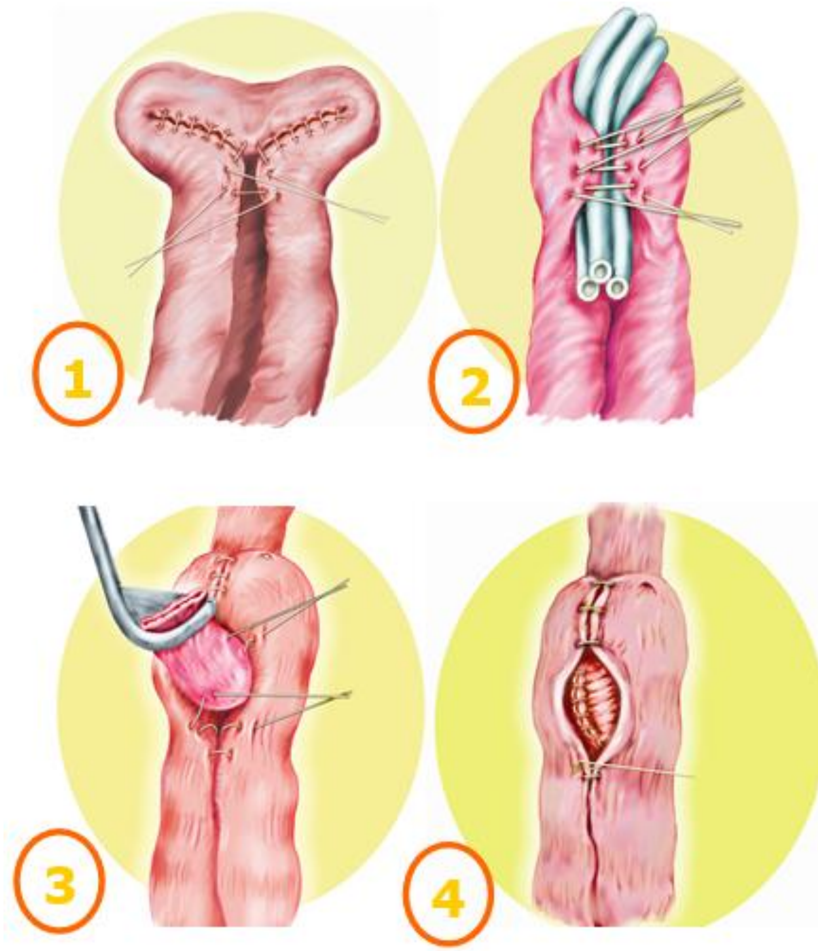

Fig. 1. Technique for forming the esophagojejunal anastomosis

1 – forming a ‘racket’ from the jejunum;
2 – forming a ‘sleeve’;
3 – passing the esophagus through the ‘sleeve’ and fixating it;
4 – applying an internal row of sutures of the anastomosis and peritonizing the inner suture row.

Intestinal anastomosis was formed in the usual way – the posterior row of seromuscular sutures was made, the walls of the afferent and efferent intestines were dissected for 4 cm in the transverse direction, a continuous suture row with absorbable suture was made and the anterior row of seromuscular sutures was applied.

Prior to surgery, 273 (19.02 ± 1.04 %) complications of the tumor process were diagnosed in 220 patients. The most common complication was pyloric stenosis caused by the tumor (41.4 ± 2.9 %), the second most common was anemia of varying severity (30.8 ± 2.8 %), and the third most common was tumor hemorrhage (17.2 ± 2.3 %). Table 1 presents data on preoperative complications.

Table 1. Preoperative complications

Preoperative complication	**Number of cases (abs.)**	**Percentage of cases, %**
Partial bowel obstruction	4	1.5 ± 0.7
Anemia	84	30.8 ± 2.8

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Stenosis	113	41.4 ± 2.9
Hemorrhage	47	17.2 ± 2.3
Ascites	1	0.4 ± 0.4
Cachexia	1	0.4 ± 0.4
Tumor perforation	1	0.4 ± 0.4
Peritonitis	1	0.4 ± 0.4
Dysphagia	21	7.7 ± 1.6
Total	273	100.0

D2 lymph node dissection was performed only in 88 (6.1 ± 0,6%) patients, due to the fact that patient data included cases since 1986. In recent years, D2 lymph node dissection is performed in all patients through both open and laparoscopic access. Table 2 presents data on the extent of lymph node dissection.

Table 2. Extent of performed lymph node dissections after gastrectomy

Extent of lymph node dissection	Number of cases (abs.)	Percentage of cases, %
D2 lymph node dissection	88	6.1 ± 0.6
D1 lymph node dissection	1347	93.9 ± 0.6
Total	1435	100.0

In the postoperative period, 65 (4.53 ± 0.55 %) patients died due to postoperative complications. The most common cause of death was pulmonary embolism in 24 (36.9 ± 5.9 %) patients; the second most common was postoperative pancreatitis in 10 (15.4 ± 4.5 %) patients. All causes of death are listed in Table 3.

Table 3. Causes of death

Cause of death	Number of cases (abs.)	Percentage of cases, %
Dehiscence	8	12.3 ± 4.1%
Abdominal abscess	3	4.6 ± 2.6%
Peritonitis	2	3.1 ± 2.1%
Cardiopulmonary failure	6	9.2 ± 3.6%
Pneumonia	1	1.5 ± 1.5%
Acute renal failure	1	1.5 ± 1.5%
Hepatorenal failure	2	3.1 ± 2.1%
Postoperative pancreatitis	10	15.4 ± 4.5%
Intraabdominal bleeding	1	1.5 ± 1.5%
Pulmonary embolism	24	36.9 ± 5.9%
Adhesive intestinal obstruction	5	7.7 ± 3.3%
Mesenteric vessel thrombosis	1	1.5 ± 1.5%
Cerebral edema	1	1.5 ± 1.5%
Total deaths	65	100.0

To identify factors affecting long-term outcomes and to evaluate their influence on patient survival, neural network mathematical models were developed [8&], [6&], [9&], [10&], [11&], [14&].

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For the endpoint (Y variable), patient survival after treatment was chosen: in case of patient survival after 5 years, Y = 0 (positive outcome); in case of patient death in 5 years, Y = 1 (negative outcome).

The analysis included long-term outcomes of 1,000 followed-up patients. In the development and analysis of the neural network, patients were randomly (using a random number generator) assigned to one of three groups: a training group (850 patients, used for model development), test group (50 patients, used to prevent overtraining of the model) and validation group (100 patients, used to evaluate prognostic capabilities of the model on new data) [5&], [15&].

One hundred and twenty-five (125) characteristics were assessed as factors at the first stage of analysis: age, gender, tumor localization, T-category, N-category, M-category, stage, tumor complications prior to surgery, their number and type (stenoses, perforations, abscesses, fistulas, anemia, other), number of concomitant disorders, their type (coronary heart disease (CAD), cardiac rhythm disorders, general atherosclerosis, atherosclerotic cardiosclerosis, aortic coronary cardiosclerosis, postinfarction cardiosclerosis, stenocardia, high blood pressure, other cardiovascular disorders), circulatory failure stages 0-2A, diabetes mellitus, obesity, varicose veins in the lower extremities, post-thrombotic syndrome, rheumatism, liver and pancreatic pathology, chronic bronchitis, bronchial asthma, silicosis, anthracosis, pulmonary tuberculosis, pneumosclerosis, pulmonary emphysema, other pulmonary disorders, kidney stone disease, chronic pyelonephritis, prostate adenoma, cystitis, other urogenital disorders, ulcers (of the stomach and the duodenum), chronic gastritis, nonspecific ulcerative colitis, chronic spastic colitis, colonic polyposis, ileal diverticulosis, dolichocolon, other GIT disorders, uterine fibroids, ovarian cyst, other female genital disorders, surgery type, surgery scale, number of resected organs and/or anatomical structures, their type (resection of the seminal vesicles, bladder resection, hysterectomy, radical hysterectomy, resection of the uterine adnexa, small bowel resection, appendectomy, abdominal wall resection, resection of the uterine body, supracervical uterus amputation, cervical stump extirpation, vaginal excision, prostate resection, cholecystectomy, splenectomy, uterine fibroid resection, other), surgery features, reason for palliative character of the surgery, blood type, rhesus factor, shape of tumor growth, tumor histological structure, presence of intraoperative complications, their number and type (spleen injury, deserozation of the small or large intestine, injury of the sacral plexus veins, vaginal bleeding, abscess incision, incision of the lumen of the large or small intestine, tumor perforation, injury of the ureter, bladder, other), postoperative complications, their number and type (pulmonary embolism, retroperitoneal phlegmon, mesenteric venous thrombosis, disseminated intravascular coagulation, multiple organ dysfunction, acute cystitis, adhesive intestinal obstruction, external small bowel fistula, pulmonary edema, anemia, anastomotic failure or duodenal stump leakage, abscess, peritonitis, wound abscess, anastamositis, myocardial infarction, pulmonary heart disease, cardiopulmonary failure, acute heart failure, acute cardiovascular failure, pleuritis, pneumonia, pyelonephritis, epididymo-orchitis, acute orchitis, hepatorenal insufficiency, hepatorenal syndrome, acute renal failure, acute liver failure, pancreatitis, intraabdominal bleeding, and others).

Results and Discussion

A linear neural network was developed and trained based on the 125 factors. After optimization of the acceptance/rejection threshold, sensitivity of the developed model with the full set of

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factors for the training group was 69.0 % (95% CI: 65.0 %-72.7 %), specificity was 68.9 % (95 % CI: 63.5 %-74.2 %). For the confirmation group, sensitivity was 61.2 % (95 % CI: 49.1 %-72.6 %), specificity was 60.6 % (95 % CI: 43.0 %-76.9 %).

Sensitivity and specificity for the training and confirmation groups were not significantly different ($p = 0.25$ and $p = 0.44$, respectively, per the χ^2-test) confirming validity of the constructed model.

To identify the most important factors strongly associated with the risk of not surviving a 5-year period, genetic algorithm method was used. Consequently, 7 factors were selected: age (X1), T-category (X4), N-category (X5), M-category (X6), preoperative complications (other) (X16), reason for palliative character of the surgery (X80), postoperative complications (Y3).

A 7-factor linear neural network was developed and trained using these factors. After optimization of the acceptance/rejection threshold, sensitivity of the model for the training group was 64.3 % (95 % CI: 60.2 %-68.2 %), specificity was 62.8 % (95 % CI: 57.3 %-68.2 %). For the confirmation group, sensitivity was 56.7 % (95 % CI: 39.9 %-68.5 %), specificity was 57.6 % (95 % CI: 39.9 %-74.3 %).
Sensitivity and specificity for the training and confirmation groups were not significantly different ($p = 0.28$ and $p = 0.69$, respectively, per the χ^2-test) confirming validity of the model.
To account for possible nonlinear connections between the factors and the endpoint, a nonlinear neural network (multilayer perceptron) with one hidden layer (two neurons in the hidden layer) was developed based on the same 7 factors. The network predicted a patient's risk of not surviving a 5-year period after treatment (model architecture is presented in Figure 2).

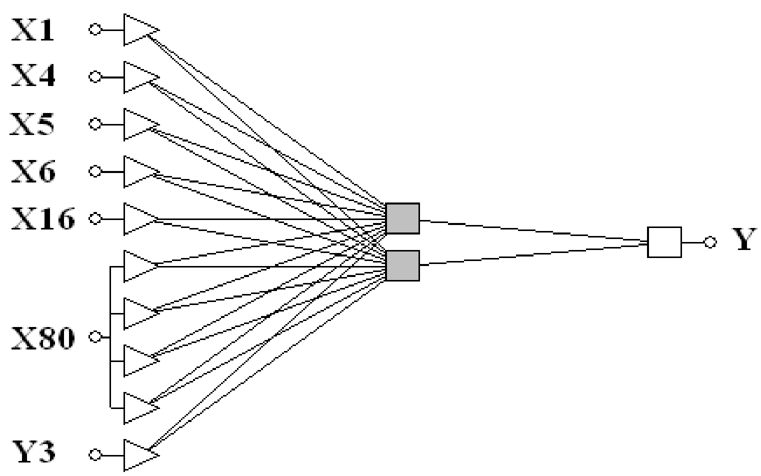

Fig. 2. Architecture of the neural network for predicting the risk of not surviving a 5-year period (triangles correspond to neurons of the input layer, gray squares – to neurons of the hidden layer, white square – to the neuron of the output layer).

After optimization of the acceptance/rejection threshold for the network, for the training group, sensitivity was 65.5 % (95 % CI 61.5 %-69.4 %), specificity was 64.2 % (95 % CI: 58.6 %-69.5 %); for the confirmation group, sensitivity was 59.7 % (95 % CI: 47.6 %-71.3 %), specificity was 63.6 % (95 % CI: 46.1 %-79.5 %). Sensitivity and specificity were not significantly different for the training and confirmation groups ($p = 0.42$ and $p = 0.90$, respectively, per the χ^2-test), which

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confirms validity of the developed model.

Receiver operating characteristic curves (ROC curves) were used to evaluate the significance of the identified factors (Figure 3).

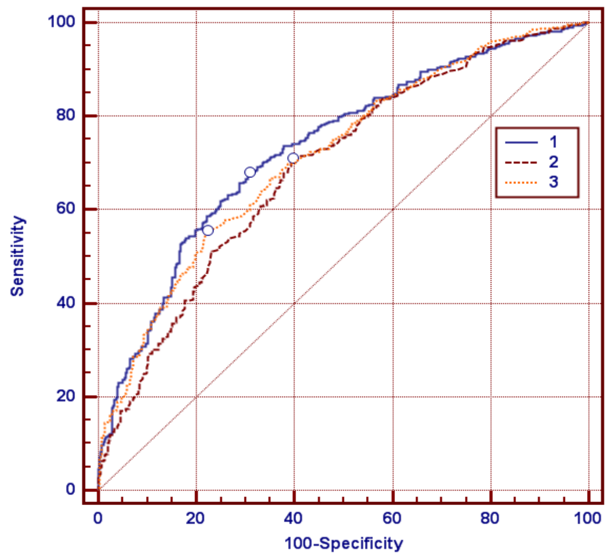

Fig. 3. ROC curves of the neural network predicting the risk of not surviving a 5-year period, 1 – linear neural network based on the 125 factors; 2 – linear neural network based on the 7 selected factors, 3 – nonlinear neural network based on the 7 selected factors

A small but statistically significant (p = 0.007) decrease of the area under curve for the linear neural network based on the 7 selected factors (AUC2 = 0.69 ± 0.02) compared to the linear neural network based on all 125 factors (AUC1 = 0.73 ± 0.02) was identified through comparison of the ROC curves. Furthermore, the area under curve for the 7-factor nonlinear neural network (AUC3 = 0.72 ± 0.02) was also smaller than the area under curve for the 125-factor model, p = 0.004. Therefore, decreasing the number of factors from 125 to 7 does not affect the prognostic capabilities of the model indicating high significance of the selected factors (age (X1), T-category (X4), N-category (X5), M-category (X6), preoperative complications (other) (X16), reason for palliative character of the surgery (X80), postoperative complications (Y3)) for predicting the risk of not surviving a 5-year period.

A logistic regression model was developed to estimate the strength and direction of the 7 selected factors; the model is satisfactory (χ^2 = 110.7 for 9 degrees of freedom, p < 0.001). Table 4 presents the results of coefficient analysis.

Table 4. Coefficients of the 7-factor model predicting the risk of not surviving a 5-year period (logistic regression model)

Factor	**Coefficients of the prognostic model, b ± m**	**Significance level of difference compared to regression coefficient 0**	**Odds ratio, OR (95 % CI)**
X1	0.022 ± 0.007	0.002*	1.02 (1.01–1.04)

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X4	0.47 ± 0.12	< 0.001*	1.6 (1.3–2.0)
X5	0.38 ± 0.07	< 0.001*	1.5 (1.3–1.7)
X6	–4.9 ± 100	> 0.999	-
X16	–0.014 ± 0.203	0.941	-
X80	0.47 ± 0.45	0.299	-
Y3	0.79 ± 0.24	0.001*	2.2 (1.4–3.5)

Analysis of the logistic regression model coefficients demonstrates that the risk of not surviving a 5-year period significantly (p = 0.002) increases with patient's age, OR = 1.02 (95 % CI: 1.01-1.04) for every lived year. Furthermore, the risk of not surviving a 5-year period increases (p < 0.001) with a one-point change in T-category, OR = 1.6 (95 % CI: 1.3-2.0), and N-category (p < 0.001), OR = 1.5 (95 % CI: 1.3-1.7). The higher risk of not surviving a 5-year period (p = 0.001) is also associated with the presence of postoperative complications, OR = 2.2 (95 % CI: 1.4-3.5).

Cox's proportional hazards model was applied to study the effect of combined factors on patient survival and to analyze the strength and direction of this effect [12&].

For the Cox's model, 24 variables were selected. To identify significant factors, a method of backward variable selection [12&] was applied (selection threshold p > 0.3). The analysis returned 13 factors: X1, X2, X3, X4, X8, X59, X80, X81, X83, X84, Y1, Y3, Y4. Based on these factors, a Cox's proportional hazards model for predicting patient survival was developed. The model was satisfactory (χ^2 = 229.3 for 28 degrees of freedom, p < 0.001). Table 5 lists the model coefficients and evaluation of their effect on survival.

The analysis demonstrated that the risk of death significantly (p < 0.001) increases with every lived year, hazard ratio (HR) = 1.02 (95 % CI: 1.01-1.03). The risk of death was also significantly higher for males (p = 0.028), HR = 1.18 (95 % CI: 1.02-1.37).

Table 5. Coefficients of the 13-factor Cox's model for predicting survival

Factor	Coefficients of the prognostic model, b ± m	Significance level of difference compared to regression coefficient 0	Hazard ratio, HR (95 % CI)
X1	0.019 ± 0.004	< 0.001*	1.02 (1.01–
X2="m"	0.17 ± 0.07	0.028*	1.18 (1.02–1.37)
X3="v2"	2.0 ± 0.7	0.006*	7.31 (1.81–29.5)
X3="v7"	–0.49 ± 0.40	0.225	–
X4	0.23 ± 0.06	< 0.001*	1.26 (1.11–1.42)
X8	0.36 ± 0.26	0.162	–
X59="v2"	0.27 ± 0.11	0.017*	1.32 (1.05–1.65)
X59="v3"	0.54 ± 0.18	0.003*	1.71 (1.2–2.4)

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X80="v1"	0.43 ± 0.13	0.002*	1.53 (1.18–1.99)
X80="v2"	0.46 ± 0.20	0.022*	1.58 (1.07–2.34)
X80="v3"	1.3 ± 0.4	0.004*	3.61 (1.53–8.5)
X81="v3"	0.16 ± 0.09	0.070	–
X83="v2"	–0.13 ± 0.11	0.230	–
X83="v3"	–0.20 ± 0.08	0.014*	0.82 (0.69–0.96)
X84="v11"	2.1 ± 1.0	0.045*	7.84 (1.06–58.2)
X84="v12"	0.40 ± 0.17	0.016*	1.49 (1.08–2.06)
X84="v2"	0.27 ± 0.18	0.143	–
X84="v25"	0.71 ± 0.15	< 0.001*	2.04 (1.5–2.75)
X84="v27"	1.00 ± 0.51	0.049*	2.72 (1.01–7.3)
X84="v5"	1.9 ± 0.7	0.009*	6.74 (1.64–27.7)
X84="v6"	0.32 ± 0.09	< 0.001	1.38 (1.16–1.64)
Y1	0.23 ± 0.09	0.015*	1.26 (1.05–1.52)
Y3	0.33 ± 0.21	0.112	–
Y4	0.29 ± 0.11	0.010*	1.33 (1.07–1.66)

Conclusions

1. Long-term outcomes of surgical treatment of patients with gastric cancer are affected by the following factors: patient age, T- and N-categories, postoperative complications.
2. Risk of death significantly increases with age ($p < 0.001$), HR = 1.02 (95 % CI: 1.01-1.03) per every lived year. Furthermore, the risk of death is significantly higher ($p = 0.028$) for males, HR = 1.18 (95 % CI: 1.02-1.37).

Brief Annotation

In assessment of long-term outcomes the risk of not surviving a 5-year period increases with patient's age and one-point change in T-category, N-category, presence of postoperative complications and male gender.

Header for Footer

Prediction of long-term gastrectomy outcomes.

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