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Computer-Guided Surgery for Gastric Carcinoma

Jernej Mekicar and Mirko Omejc

Department of Abdominal Surgery, University Medical Centre, Ljubljana, Slovenia

ABSTRACT

Lymphadenectomy offers the only hope for cure when lymph nodes are involved. In gastric cancer, three approaches have been pursued to preoperatively predict node status in individual patients, modern radiological imaging techniques, sentinel node and technique that uses a computerized database of information to convert a large amount of information and experience to a treatment decision for an individual patient. The aim of this study was to evaluate accuracy in preoperative prediction of lymph node status in selected patients with the help of computer analysis for stage-appropriate surgery. With the help of computer programs Win Estimate and Microsoft Access, we constructed an artificial neural network that calculated a statistical prediction of nodal status in an observed patient with preoperatively gathered data. In 110 patients who have undergone R0 resection with D2 lymphadenectomy, the differences between the individual results generated by artificial neural network calculation and the actual data were compared. The accuracy of computerized predictions of N0 stage for study group is 91%, sensitivity 94% and specificity 87%. The results of accuracy of computerized preoperative prediction of N2 stage are 88%, with sensitivity 94% and specificity 88%. Preoperative analyses of patient data and tumour characteristics offers a rational approach to individualizing tumour therapy where the extent of lymph node dissection is tailored to the type, site, and stage of the tumour, thereby minimizing the disadvantages associated with the extensive operative procedure.

Key words: *gastric cancer, lymph node metastases, artificial neural network, stage appropriate surgery*

Introduction

Despite a decrease in incidence, particularly in the United States and Western Europe, since the early decades of previous century, adenocarcinoma of the stomach remains a significant health problem throughout the world[1]. Interestingly, this decrease has not been the result of any planned world health promotion program or major change in treatment intervention.

Gastric cancer usually arises as a localized tumour. Abundant lymphatic channels are present within the submucosal and subserosal layers of the gastric wall. Microscopic or subclinical spread well beyond the visible gross lesion (intramural spread) occurs via these lymphatic channels. The lymph node metastatic pattern varies with different locations of the primary tumour within the stomach[2,3]. Radical resection of gastric cancer requires a complete removal of the primary tumour, combined with a sufficiently wide dissection of lymph nodes. For such suitably wide dissection of lymph nodes, an understanding of lymphatic spread as it relates to location of the primary tumour is of practical importance, considering the status of the lymphatics can be determined with confidence only after the resection has been completed. The optimal extent of lymph node dissection for gastric cancer has not yet been established. The issue of performing extensive lymph node dissection when performing a gastrectomy for stomach cancer has been the subject of large and endless debates over the last 30 years[2–4]. It was first addressed by Japanese surgeons in the late 1960s and 1970s, and extended lymph node dissections were strongly believed to have contributed to the radical improvement of the prognosis of gastric cancer patients observed in Japan. Whether extended node dissection over limited dissection improves survival or is simply of predictive value only, continues to be controversial[5–13]. The ideal lymphadenectomy for gastric cancer should reduce postoperative complications and improve prognosis by avoiding removal of uninvolved lymph nodes and selectively and completely removing all metastatic lymph nodes. Because gastric lymphatic drainage follows different routes according to the location of the primary tumour and, if blocked by tumour deposits, may become unpredictable in individual patients, some

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intraoperative guidance on how to accomplish optimal lymphadenectomy would be welcome.

To remove all of the involved lymph nodes and to avoid unnecessary removal of lymph nodes that are not at risk of tumour, a new approach has been developed. In contrast to other types of tumours, the preoperative staging of gastric carcinoma can be performed with the help of a validated and well-established computer program to convert a large amount of information and experience into a treatment decision for an individual patient[9]. Maruyama and his co-workers developed a computer program Win Estimate[9,10] to calculate the probability of nodal spread to each individual lymph-node station using histopathological features of the primary tumour. Depths of infiltration, tumour size, tumour location, grading, typing, and macroscopic appearance are all factors used to predict the probability of nodal metastases. Application of this program resulted in a diagnostic accuracy between 74% and 94%, respectively[10–12]. However, the point at which lymph-node dissection should be done is not clear. Maruyama and colleagues initially recommended a cutpoint of 18%. If this recommendation was used, however, up to a fifth of patients would have incomplete operations.

Patients and Methods

Artificial neural networks are relatively crude electronic models based on the neural structure of the brain. The brain essentially learns from experience. The basic concept used by Win Estimate computer program presumes that the spread of lymph node metastases in comparable cases is statistically equal or at least approximately equal. For an analysis to be performed, a database of patients with prospectively gathered data is needed. After considering different variables, a selection of those most statistically important for prediction of lymph node metastasis is possible. Statistical analysis then enables calculation of the rate of nodal involvement in observed patients on the basis of a group of patients from its database with same preoperative variables. The results presented from computer program Win Estimate are the proportions of positive nodes in lymph node location, according to the numbering system of Japanese Research Society for Gastric Cancer JRSGC[9]. As shown by the former studies[10–12], this information is not applicable straight forward to surgical planning. To make this prediction more accurate and useful, we used a method of artificial neural networks in their second stage of calculation. Individual information of lymph node groups' involvement where modified to TNM staging system. In the second stage of calculation, all preoperative variables were categorized and evaluated. From their assigned mathematical values, a second calculation was performed. This calculated number can then raise or lower the first calculated N- stage of the observed patient from the first stage. The receiver operating characteristic curve was used to discover the best cutoff value for the second stage calculation of nodal status prediction. The final result of the program is the predictable nodal status of observed patient as described in TNM staging system of the International Union Against Cancer[9].

In our study, we used database from the computer program Win Estimate, developed by K. Maruyama. The program uses data from 4302 primary gastric cancer patients treated at the National Cancer Center Hospital in Tokyo between 1968 and 1989. All patients underwent D2 lymphadenectomy, extending the dissection in some patients to N3 or even N4 lymph nodes if necessary. All lymph nodes were examined from the specimen and labelled according to the numbering system of the JRSGC. Patients with multiple or extensive metastases underwent palliative surgery and were excluded from the database. From this Japanese database we used seven preoperative variables that are considered to be important prognostic factors, namely gender, age, tumour type, depth of invasion, location, diameter of the primary tumour and histological type. All seven preoperative variables plus survival time and lymph node metastases for 4302 treated patients are stored in an ASCII file database. The computer program with appropriate statistical calculation then recalls and analyzes all cases that are similar to the patient in question (Figure 1). Further analysis and calculation were performed with help of Microsoft Access program.

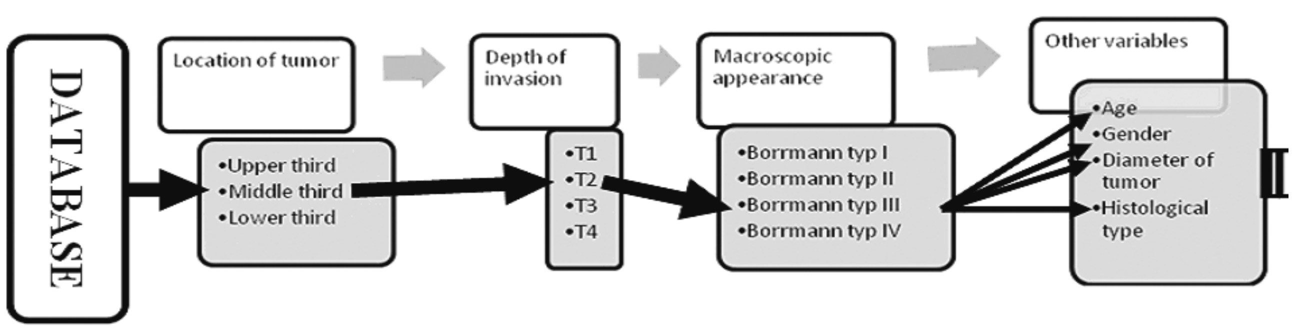

Fig. 1. Flow chart of matching the patients from database with the observed patient with help of artificial neural network for calculation of lymph node involvement.

The goal of this study was to compare the prediction for lymph node metastases made by artificial neural networks with real data from a group of patients treated in the same manner.

For the evaluation of accuracy of prediction, we used a group of 110 patients treated in Clinical Department for Abdominal Surgery, University Medical Centre in Ljubljana between 2004 and 2005 under same criteria. Only patients with gastric cancer who underwent R0 resection with D2 lymphadenectomy without any pre- or postoperative adjuvant treatment, for whom the pathologist examined at least 15 lymph nodes in the resected specimen, were included in the study. Patients with gastric stump or cardia cancer as well as patients who died postoperatively were also excluded from the study. The lymph node involvement was classified by the TNM-UICC system as N0, N1, N2, and N3. We assume that lymphatic spread is the same in the two groups of patients.

We also performed statistical analysis with SPSS software (version 15.0, SPSS Inc, Chicago, IL) in order to predict factors of lymph node metastases. First bivariate comparisons of those patients with or without metastases were unpaired, and all tests computed with Pearson's correlation coefficient, Spearman's rho, and Kendall's tau-b with their significance levels. Comparative analysis of categorical variables was performed using an X^2 testing with Yates's continuity correction. Continuous variables were analyzed using Student's t tests for normally distributed variables; otherwise, the Mann-Whitney U test was employed. Independent variables with a P value ? 0.2 for an association with development of metastases by bivariate statistics were included in the multivariate analysis as was determined prior to the analysis. Then a multivariate analysis, in which development of metastases was the dependent outcome variable, was performed by logistic regression employing backward stepwise elimination selection. Statistical significance was defined as $p<0.05$. The prediction of lymph node metastases was analyzed using Bayes theorem.

Results

4302 Japanese patients that suit the selected criteria were included in the study for the core of database (1746 (40.6%) exhibited early gastric cancer; 2556 (59.4%) exhibited advanced gastric cancer). The mean number of nodes examined by the pathologist was 28. 110 Slovenian patients that suited the selected criteria were included in the control group with uniform clinical-pathological protocol (27 (24.5%) with early and 83 (75.5%) with advanced gastric cancer). The mean age of patients was 68.8 ± 9.8 years; the male to female ratio was 1.05:1. The mean number of nodes examined by the pathologist was 24. Database and study group of patients are compared (Table 1). Results show that both groups are statistically different ($p<0.005$) between themselves regarding depth of tumour invasion and type of gastrectomy performed, but similar in location of tumour and lymph node involvement. Because of the selection from the database and with help of artificial neural network to match the patients from database with the control group for lymph node involvement calculation, this difference is not so

TABLE 1
COMPARISON OF STUDY GROUP AND DATABASE GROUP REGARDING NUMBER OF PATIENTS, LOCATION OF THE TUMOR, T AND N STAGE, AND TYPE OF GASTRECTOMY PERFORMED

Parameter	Database group of patients	Study group of patients	
Number of patients	4302	110	
Location of primary tumour			p>0.005
Upper third	830 (19.3%)	27 (24.5%)	
Middle third	1845 (42.9%)	28 (25.5%)	
Lower third	1627 (37.8%)	55 (50.0%)	
Depth of tumour invasion (pT)			p<0.005
pT1	1746 (40.6%)	27 (24.5%)	
pT2	729 (16.9%)	44 (40.0%)	
pT3	1231 (28.6%)	37 (33.6%)	
pT4	596 (12.9%)	2 (1.9%)	
Nodal status (pN)			p<0.005
pN0	2250 (52.3%)	47 (42.7%)	
pN1	698 (16.1%)	30 (27.3%)	
pN2	944 (21.9%)	21 (19.1%)	
pN3	410 (9.5%)	12 (10.9%)	
Type of gastrectomy			p>0.005
Proximal subtotal	258 (6%)	0	
Distal subtotal	2968 (69%)	58 (52.7%)	
Total	1076 (25%)	52 (47.3%)	

TABLE 2
RESULTS OF STATISTICAL ANALYSIS WITH BIVARIATE COMPARISONS OF THOSE PATIENTS WITH OR WITHOUT METASTASES COMPUTED WITH PEARSON'S CORRELATION COEFFICIENT, SPEARMAN'S RHO, AND KENDALL'S TAU-B WITH THEIR SIGNIFICANCE LEVELS

Parameter	Significance levels
Gender	$p<0.2$
Age	$p<0.2$
Blood group	$p>0.005$
Histological type of tumour	$0.05<p<0.2$
Histological grade of tumour	$p>0.05$
Location of tumour	$0.05<p<0.2$
Infiltration of tumour	$p>0.05$
Borrmann classification	$p>0.05$
Diameter of tumour	$p>0.05$

important (Figure 1). With the use of bivariate and multivariate analyses, we determined the predictor variables for lymph node metastasis. Due to their statistical significance, the following variables were important: depth of tumour invasion, maximal diameter, Borrmann classification and histology. The results are presented in Table 2 and 3. The validity of computerized prediction of lymph node status is presented in Table 4.

Discussion

In order to allow each individual case stage-appropriate surgery to be performed at the level of which lymph node clearance is dictated by the extent of the disease, a method for reliably distinguishing potentially a curable disease from an incurable disease is required. Stage-appropriate surgery aims to remove the group of lymph nodes that are involved with the tumour. To perform such a lymphadenectomy, the surgeon must preoperatively know the nodal status of the patient. Radiological imaging techniques with transabdominal ultrasonography (US), endoscopic ultrasonography (EUS), computerized tomography (CT) and magnetic resonance imaging (MRI) have the accuracy of lymph node detection from 40% to 90%[13–19]. CT accuracy in staging tumours is modest: only 70% for advanced lesions and 44% for early lesions[16–18]. CT assesses lymph node involvement primarily on the basis of node size. Thus, its sensitivity for N1 and N2 disease is low, ranging from 24% to 43%; however, its specificity is high, approaching 100%. Technical advances, such as spiral (helical) CT with intravenous contrast, plus appropriate gastric distension with 600 to 800 ml of water have allowed for modest improvements in the overall staging with CT. Given the limitations of CT, staging with endoscopic ultrasonography is vital for accurately assessing whether regional nodes (N stage) or even mediastinal or para-aortic lymph nodes may be involved. In studies comparing preoperative findings from EUS with pathologic findings at operation, EUS was 60–100% sensitive for N0 disease and 40–66.7% sensitive for N1 disease[14,15]. The diagnostic accuracy of N staging of EUS is 60–70% overall. Staging accuracy of MRI is 50–60% for N stage and 75–90% for M stage[19–22]. With the use of ferumoxtran-10-enhanced MRI in one study, the accuracy rate of MRI for N stage was 94%[23].

Another method for preoperative assessment of nodal status of the patient uses relevant preoperative variables and statistical analysis in conjunction with artificial neu-

TABLE 3
RESULTS OF STATISTICAL ANALYSIS OF MULTIVARIATE ANALYSIS BY LOGISTIC REGRESSION EMPLOYING BACKWARD STEPWISE ELIMINATION SELECTION, IN WHICH DEVELOPMENT OF METASTASES WAS THE DEPENDENT OUTCOME VARIABLE

ANOVA[g]

Model 1	Sum of squares	df	Mean square
Regression	4711,430	11	428,312
Residual	9449,070	230	41,083
Total	14160,500	241	

a Predictors: infiltration of tumour, Borrmann classification, histological grade of tumour, location of tumour, blood group, diameter of tumour *
[g] Dependent variable: lymph node metastasis

Coefficients[a]

Parameter	Significance levels
Histological grade of tumour	$p>0.05$
Infiltration of tumour	$p>0.05$
Borrmann classification	$p>0.05$
Diameter of tumour	$p>0.05$

[a] Dependent Variable: lymph node metastasis
* The significance levels of predictor variables location of tumour and blood group were not significant

TABLE 4
VALIDITY OF COMPUTERIZED PREDICTION OF LYMPH NODE STATUS

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
N0 prediction	0.94	0.87	0.91	0.91	0.91
N2 prediction	0.94	0.88	0.77	0.97	0.88

ral networks. All the preoperative variables needed are collected with standard preoperative diagnostic work up. In the study, we determined the accuracy of predictions of N0 stage to be 91%. Rates of sensitivity (94%) and specificity (87%) are also very high and can be compared with the best results of sentinel node concept[24–27] for the prediction of metastatic lymph nodes and is better than radiological imaging techniques. In addition, it is also non-invasive, repeatable, less time consuming and all the preoperative variables needed to make analysis are collected with standard diagnostic work up, which can be regarded as an advantage in preoperative decision making. When we compare the result of our study with the result of similar studies[10–12,28,] the results in accuracy are comparable. But we believe that our results presented as TNM stage are more useful for preoperative surgical planning. As shown by the statistical analysis, the location of tumour is not an independent predicting factor for N stage. It is plausible, as infiltration of tumour to lymph vessels is the same in upper or lower third of the stomach which is dependent only of tumour size, stage and histological type. The location of the tumour is important for the surgeon to plan proper gastrectomy and lymphadenectomy, but not for the N stage. Results primarily taken from the computer program Win Estimate for individual lymph node group are not usable because the accuracy for individual lymph node group is too low. Also, piecemeal surgery is impractical for daily use and is time consuming, which can explain the failure of the Win Estimate's implementation in daily use. Furthermore, when we look closely at the artificial network in study by Bollshweiler et al. for analysis[28], we see that they used information of metastasis in lymph node group 3 as an additional parameter. This method now more clearly resembles the sentinel node concept and not only statistical analysis. If they removed this additional parameter, the accuracy of prediction was only 79%. But this difference demonstrates important information regarding the significance of properly constructing artificial networks and of including more parameters better accuracy in analyses. The results in favour of using artificial neural networks for preoperative prediction of N stage are even more promising if we compare the accuracy of predictions of N2 stage for our study model 88%, with sensitivity 94% and specificity 88%.

We see the applicability of the computer method in a subgroup of gastric cancer patients. Many studies have proven that the performance of D2 lymphadenectomy in all gastric cancer patients is an overtreatment, as only patients with N+ nodal status actually benefit from D2 lymphadenectomy[5–8,29]. Some preoperative selection is needed to guide the surgeon. Because modern radiological imaging techniques and sentinel node methods have low accuracy for preoperative nodal status, a new approach is needed. As shown in our study, the use of a method of statistical analysis with artificial neural networks reliably determines the N stage and allows stage-appropriate surgery to be performed in each individual case. In early gastric cancer, the selection of N0 nodal status patients suitable for endoscopic mucosal resection or laparoscopic resection is possible. In advanced gastric cancer, the selection of N2 or N3 nodal status patients suitable for neoadjuvant oncologic therapy is possible. Also in older patients with co-morbidities, a preoperative selection of those that can benefit from D2 lymphadenectomy can be done. For such analysis, only minimal preoperative examinations are needed and result represented as N stage is sufficient for operative planning, because en-bloc resection of the stomach with extended D2 lymphadenectomy or more is performed according to guidelines of the JRSGC[9] which are dictated by human anatomy and piecemeal surgery is avoided.

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M. Omejc

University Medical Centre, Department of Abdominal Surgery, Zaloška 7, 1525 Ljubljana, Slovenia
e-mail: mirko.omejc@mf.uni-lj.si

KOMPJUTERSKI VOĐENA OPERACIJA ŽELUČANOG KARCINOMA

S A Ž E T A K

Limfadenektomija je jedini način izlječenja kad su u pitanju tumori limfnih čvorova. Kod raka želuca, individualno su primijenjena tri pristupa predoperativne procjene statusa limfnih čvorova kod pojedinih pacijenata: moderne radiološke tehnike snimanja, tehnika odstranjenja »sentinel node« te tehnika kompjuterizirane datoteke koja konvertira velike količine podataka i prethodnih iskustava u svrhu individualnog odabira terapije. Cilj ovog istraživanja bio je procijeniti preciznost predoperativne procijene statusa limfnih čvorova kod odabranih pacijenata uz pomoć kompjuterske analize za procjenu prikladne operacije s obzirom na stadij tumora. Uz pomoć kompjuterskih programa Win Estimate i Microsoft Access, konstruirali smo umjetnu neuralnu mrežu za statistički izračun procjene statusa limfnih čvorova kod istraživanih pacijenata s predoperativno prikupljenim podacima. Kod 110 pacijenata koji su prošli R0 resekciju s D2 limfadenektomijom, uspoređene su razlike između individualnih rezultata dobivenih izračunom umjetne neuralne mreže i stvarnih podataka. Točnost kompjuteriziranih predoperativnih procjena za istraživane grupe stadija N0 bila je 91%, uz osjetljivost 94% i specifičnost 87%. Točnost za stadij N2 bila je 88%, sa osjetljivošću 94% i specifičnošću 88%. Predoperativne analize podataka o pacijentu i osobinama tumora pružaju racionalni pristup individualiziranju tumorske terapije, gdje je opseg izrezivanja limfnog čvora prilagođen tipu, mjestu i stadiju tumora, čime se minimaliziraju nuspojave povezane s ekstenzivnim operativnim zahvatom.