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Assessment of Gastric Cancer Survival: Using an Artificial Hierarchical Neural Network

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Abstract: This study is designed to assess the application of neural networks in comparison to the Kaplan-Meier and Cox proportional hazards model in the survival analysis. Three hundred thirty gastric cancer patients admitted to and surgically treated were assessed and their post-surgical survival was determined. The observed baseline survival was determined with the three methods of Kaplan-Meier product limit estimator, Cox and the neural network and results were compared. Then the binary independent variables were entered into the model. Data were randomly divided into two groups of 165 each to test the models and assess the reproducibility. The Chi-square test and the multiple logistic model were used to ensure the groups were similar and the data was divided randomly. To compare subgroups, we used the log-rank test. In the next step, the probability of survival in different periods was computed based on the training group data using the Cox proportional hazards and a neural network and estimating Cox coefficient values and neural network weights (with 3 nodes in hidden layer). Results were used for predictions in the test group data and these predictions were compared using the Kaplan-Meier product limit estimator as the gold standard. Friedman and Kruskal-Wallis tests were used for comparisons as well. All statistical analyses were performed using SPSS version 11.5, Matlab version 7.2, Statistica version 6.0 and S_PLUS 2000. The significance level was considered 5% ($\alpha = 0.05$). The three methods used showed no significance difference in base survival probabilities. Overall, there was no significant difference among the survival probabilities or the trend of changes in survival probabilities calculated with the three methods, but the 4 year (48th month) and 4.5 year (54th month) survival rates were significantly different with Cox compared to standard and estimated probabilities in the neural network ($p<0.05$). Kaplan-Meier and Cox showed almost similar results for the baseline survival probabilities, but results with the neural network were different: higher probabilities up to the 4th year, then comparable with the other two methods. Estimates from Cox proportional hazards and the neural network with three nodes in hidden layer were compared with the estimate from the Kaplan-Meier estimator as the gold standard. Neither comparison showed statistically significant differences. The standard error ratio of the two estimate groups by Cox and the neural network to Kaplan-Meier were no significant differences, it indicated that the neural network was more accurate. Although we do not suggest neural network methods to estimate the baseline survival probability, it seems these models is more accurately estimated as compared with the Cox proportional hazards, especially with today's advanced computer sciences that allow complex calculations. These methods are preferable because they lack the limitations of conventional models and obviate the need for unnecessary assumptions including those related to the proportionality of hazards and linearity.

Key words: Survival, gastric cancer, survival time, Cox proportional hazards, neural networks, artificial neural network, hierarchical neural network

INTRODUCTION

Survival probability assessments date back to several decades now. One of the every day concerns in various biological and medical sciences is determining the median lifetime in different age groups of a population and associated factors so that health and survival time can be improved. Individual survival time in every population is random and therefore, it can be estimated only through statistical methods. This explains the many efforts made by biostatisticians, especially since the seventies. Survival-time and survival data exhibit characteristics, such as being censored or truncated, that make them unsuitable for analysis in traditional statistical methods

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used in other fields of statistics. One of the major activities in health research is the assessment of survival time or time to recurrence in patients receiving treatment to examine the effectiveness of treatment modalities. Such methods are frequently used in fertility studies, medical demography and social researches as well.

In recent years, survival studies have evaluated the event-free probability until time t (survival probability until time t) and of various variables influencing this event-free period (lifetime) using different methods including parametric models, life table estimations, the Kaplan-Meier estimator to estimate survival probability and models such as the Cox proportional hazards model, models based on stochastic processes and neural networks to analyze the effect of different variables on survival probability, (Klien and Moeschberger, 1997). Unlike non-parametric methods, survival analysis with parametric methods requires the probability density function to estimate survival and hazard functions. Basic methods such as lifetime tables are events occurring only within the evaluated period and therefore, survival time is not assessed in between these periods and part of the data is not used. In the Kaplan-Meier method, the simultaneity of the data does not receive enough attention and it is assumed that the occurrence of any given event is possible only during a short interval (Kaplan and Meier, 1958). The Cox proportional hazards model is recommended for the assessment of the effects of different variables on lifetime. This model makes certain assumptions such as the distribution being proportional and exponential family, while these assumptions are rarely considered in applied studies. Therefore, it seems necessary to develop models that are independent of such assumptions. In recent years, use of neural networks in medical research of diagnostic processes has been suggested, but there are limited studies done in other fields of medical research or survival.

Researchers have always wondered how the human mind performs and many efforts have been made to design similar models. During the 1950s, this issue was more closely followed along with advances in computer sciences. One important step was biologic neural network simulation with computers. In 1951, McCullough and Pitts presented the first descriptions of artificial neural networks (Papik *et al*., 1998; Jerez *et al*., 2005). Later, there was more information concerning how the human neural system functions and thus, better simulations were made possible. Mathematical methods for neural network design were further developed through the works of McLelland and Rummelhart from 1982 to 1987. Patterning the neural plate is a new concept and its use has been discussed and evaluated in different fields(Jerez *et al*., 2005; Fuxe *et al*., 2007). Although traditional statistical models and neural networks are similar in some ways, their key difference lies in the fact that traditional models mainly focus on finding answers in linear environments while neural networks are nonlinear (Bakker *et al*., 2004; Park and Chung, 2006; Hirsch *et al*., 2001; Marsland *et al*., 2002).

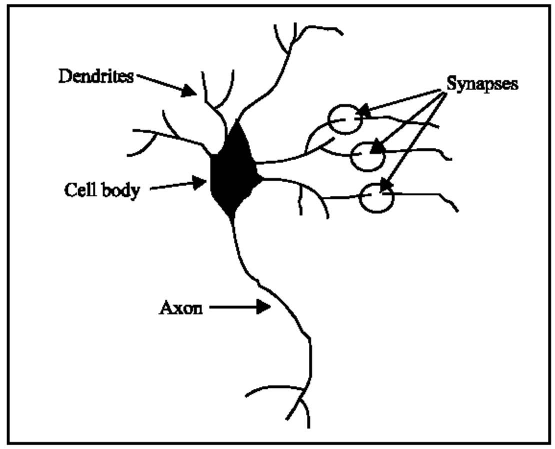

Fig. 1: Schematic view of a biologic neuron

Artificial neural networks can be considered mathematical algorithms that make essential deductions based on modest data available in primary units (Papik *et al*., 1998; Anagnostopoulos and Maglogiannis, 2006; De Laurentiis and Radvin, 1994). In biological models, the neuron is the processing element (PE) (Fig. 1). Every neural network contains a number of PEs. These PEs are interconnected through input leads. Input signals are either added to the data or transferred to the next unit through axons (Papik *et al*., 1998; Sato *et al*., 2005).

Neural networks are mathematical models emulating the properties of the human nervous system. Nerve fibers generate outputs by processing the input. A neural network receives the inputs and presents one or many outputs. The output value of every neuron is binary, but it can be modeled as a continuous variable. The input-output relation of a single neuron can be described using mathematical functions. These mathematical relationships explain the behavior of neurons. In these cases, any neuron with a constant input produces a constant and equal output. In these models, the only variable is the connect ability between neurons. Although a constant input to a function gives constant results, the connection between neurons tends to vary in time. Therefore, in a network of neurons, the functionality and connectivity is affected by the variable connection and the system is continually changing and learning. The behavior of a network and its changes in time are determined by the way the neurons in the network are connected. PEs are usually arranged in layers. There are three layers in these models: one input layer consisting of independent variables, one output layer related to the dependent variable and one or several intermediate layers known as the hidden units. All PEs in each layer are connected to all PEs in other layers.

The main issue in every neural network is finding the model coefficient(s) that transform input data to output in the layer (or middle layers) with minimum error. Usually the weight sum of the input plus a constant value (bias) in the middle layer is under the effect of a constant coefficient (e.g., logistic). Weights are determined by minimizing the sum-of-squares error function or minus the logarithm of likelihood.

In health medicine research, neural networks are mostly used for making diagnoses and there are few reports on the use of such models in medical studies. Some of these studies have assessed the results of cardiopulmonary resuscitation measures (Ebell, 1993), anti-addiction programs (Ashutosh *et al*., 1992), tumor advancement in cancer studies (Burke, 1994; Radvin *et al*., 1992) and hepatic transplant failure (Doyle *et al*., 1994). This method has been used to study the predictive value of serum enzymes for myocardial infarctions and a sensitivity of 100% and a false positive rate of 8% were determined (Baxt, 1991). Another team used EKG in addition to serum enzyme levels to increase the accuracy of their predictions (Baxt, 1992).

Use of such models has been very limited in survival studies as well. In 1992, Ravdin *et al*. (1992) first used these models in a survival study of patients with breast cancer and demonstrated that these models, compared to traditional methods, can generate relatively more accurate results. In their study, time was entered in the model as a predictive variable. For each patient, the number of intervals during which the patient was alive was considered a variable. In 1996, an article was published by Ohno-Machado (1996) in which the use of multiple neural networks in survival analyses was suggested. Data pertaining to the main event occurring at the same time were set in the same neural network and the output of each network was studied in the more general model. In this study, censored data were entered in the model as well.

In their article titled Neural networks as statistical methods in survival analysis, Ripley and Ripley (2001) present a comparison between classical methods and those based on neural networks in studying data from breast cancer patients. Their main purpose was to substitute a linear function with a neural network. They believe neural networks resemble powerful cars; it may be difficult and sometimes confusing to drive them well and so sometimes using a simpler would be more suitable. They used the S-Plus software in Unix and PC environments, but wrote the required codes themselves. They also believe overfitting is the major issue in implementing neural networks and considering the sensitivity and specificity of the used model, they concluded the supporting evidence was not enough to make one model preferable to the other. In another report titled Non-linear survival analysis using neural networks. Ripley and Harris (2004) published the use of neural networks in the analysis of data from 1335 patients with breast cancer. In this study, they assessed survival until the first recurrence after surgery as the independent variable and 11 personal, diagnostic and treatment variables as independent ones. Missing data was estimated through multiple linear regression and analysis was done on 680 patients with missing data. Variables were coded in a binary format and analyses were based on multi-layer perception models. These models are free of the assumptions used in conventional regression models. The report indicates the use of 7 different neural networks and their efficiency in predicting recurrence time for breast cancer has been discussed. In the first model, recurrence is divided into two periods; in the next 2 models, recurrence time is divided in 5 periods in two different ways; and in the remaining 4 models, recurrence time is considered continuous (log logistic, proportional hazard, log normal and the developed model of proportional hazard). They eventually conclude that the models were not very effective.

In terms of network architecture, the neural network known as the multilayer perception (MLP) is used most commonly. An MLP consists of an input layer of variables, an output layer and one or several hidden units. In these models, each input (x_i) has a corresponding weight (w_{ij}). A certain function (ϕ_k) affects the sum of weighted input ($\sum_{i\to j} w_{ij}x_i$) plus a constant value like α_j (usually equals 1) which is equal to the bias. In most cases a logistic function is used. Thus, for the k th output (y_k):

$$y_k = \phi_0\left(\alpha_k + \sum_{i\to k} w_{ik}\phi_h\left(\alpha_j + \sum w_{ij}x_i\right)\right)$$

In Iran, there is no reliable information on the number of cancer patients or the number of new cases per year, because the cancer registry system is inefficient and inaccurate. However, the standardized incidence in

Tehran for year 1999 was estimated 130.9 and 109.8 per 100,000 for men and women, respectively. The exact number of deaths due to cancer is not known either, but estimates indicate more than 27 thousand deaths due to cancer in the approximately 70 million population of Iran in 1999 (Mohagheghi, 2004). Several reports have stated that gastric cancer has a high prevalence in Iran (ranking second among men and fourth in the general population) and since most patients present in advanced stages, the disease has a high mortality rate (Mohagheghi *et al*., 1998, 1999; Mohagheghi, 2004).

In cancer research, it is important to determine the probability of survival. Several studies have been conducted in the regard in different countries. The 5 year survival of gastric cancer patients after surgery has been reported 29.6% in China (Ding *et al*., 2004), 4.4% in Thailand (Thong-Ngam *et al*., 2001), 37% in the United States (Schwarz and Zagala-Nevarez, 2002) and 30% in France (Triboulet *et al*., 2001). Various determinants of survival have also been studied including age, disease stage and presence of metastasis.

In Iran, the lifetime of cancer patients has been studied in different projects, including one based on the data bank of the present study with a 5 year survival of 23.6% and a median lifetime of 19.90 months. In these studies, the Cox proportional hazards model was used to show that variables of age, presence of metastases and disease stage can greatly affect the chance of survival (Zeraati *et al*., 2005).

As mentioned earlier, conventional models such as Kaplan-Meier and Cox proportional hazards model, although easily done with statistical software, require assumptions that are usually disregarded. For instance we can mention the assumptions used for simplifying models (e.g., assuming correlations and models to be linear), disregarding the effect of independent variables on each other, the doubtful assumption of the hazards being proportional, distribution uncertainty and errors related to curve fitting (Jones *et al*., 2006; Biganzoli *et al*., 2003). In the last 20 years, neural networks have been used in the subjects related to classification and failure prediction and they have found their place in classification but not prediction (Jones *et al*., 2006; Suka *et al*., 2004).

In the present study, we examine the hypothesis that use of neural networks has results similar to the Cox proportional hazards model and Kaplan-Meier.

MATERIALS AND METHODS

In this study, 330 gastric cancer patients who were admitted to and underwent surgery at Iran Cancer Institute between 1995 and 1999 were enrolled. Patients' lifetime after surgery was determined. Those who survived after the date the study ended and those who were lost to follow up from a certain date were right censored from that date. During the study period, 239 patients deceased; 13 with other causes of death who were right censored from the date of death.

In the first step, three methods of Kaplan-Meier, Cox proportional hazards model and the neural network were used to compute the observed baseline survival time, regardless of the independent variables and then the results were compared with the 95% confidence limits of the Kaplan-Meier limit estimates using the Borgan-Listol method. In the next step, independent variables were coded in a binary form: age (<70 years = 0, ≥ 70 years = 1), gender (female = 0, male = 1), site (cardia = 1, other = 0), pathology (adenocarcima = 1, other = 0), presence of metastasis (no = 0, yes = 1), T-stage (1 and 2 = 0, 3 and 4 = 1), N-stage (0 = 0, 1-3 = 1) and M-stage (0, 1). Then probabilities of survival in time were calculated by entering these variables into the model. For testing the models and assessment of reproducibility, data were randomly divided into two groups of 165 cases each. We used multiple logistic regression and Chi-square tests to ensure group similarity and random division of the data and log-rank test to compare subgroups. Then probabilities of survival were computed for 6, 12, 18, 24, 36, 48 and 60 months of time through the Cox proportional hazards model and the neural network. For this purpose, Cox coefficients and estimates and neural network weights (with 3 hidden layers) were calculated based on data from the reference group and used for predictions in the study group. Predictions made with these two methods were compared with the Kaplan-Meier limit estimates as the gold standard. Friedman and Kruskal-Wallis tests were used to make these comparisons. Staging was done according to the 6th edition of the TNM system. Analyses were done using SPSS version 11.5, Matlab version 7.2, Statistica version 6.0 and S_PLUS 2000 and the level of significance was considered 0.05.

RESULTS

Based on the report by Zeraati *et al*. (2005), 69.1% of the patients were male and their median age was 68 years (range, 32 to 96). The pathology was adenocarcinoma in 85.2% of patients and in the remaining patients it was other pathologies (squamous cell carcinoma, small cell carcinoma, carcinoid tumor, sarcoma, stromal tumor, malignant lymphoma, or spindle cell tumor). One hundred and 92 patients (58.2%) had metastasis and the type of surgery was total gastrectomy (TG) in 55.7%, subtotal gastrectomy (SG) in 27.2%, partial gastrectomy (PG) in 8.8%, proximal gastrectomy (PXG) in 8.5% and distal gastrectomy (DG) in 3.1%. Esophagojejunostomy was performed in 50.9%, gastrojejunostomy in 27.6%, esophagogastrostomy in 13.6%, colon bypass in 3.3%, Billroth II in 3.1% and colostomy in 1.5%. Studying the stage of the disease showed that 3% were in stage IA, 3.6% in IB, 18.2% in II, 13% in stage IIIA, 3.3% in IIIB and 58.8% in IV. All cases of stage IV disease had N3 or T4, or had T3 and M1. While 20.3% of patients had never received any secondary treatment, 26.1% of them had alternate treatments 3 times. The 5 year survival probability for the studied patients was 23.6%, the survival probability in the first year was 66.7% and the median lifetime in the study was 19.90 months (Zeraati *et al*., 2005).

In the first step, all data were used to compute the observed baseline survival in time and using the three methods of Kaplan-Meier limit estimator, Cox proportional hazards model and neural network the overall survival probabilities were determined regardless of the independent variables. By calculating the 95% confidence limits for Kaplani-Meier limit estimates using the Borgan-Listol method, it was observed that these intervals did not include estimates by the other two methods and there were no significant differences between estimates generated by these three methods (Fig. 2).

In the second step, data were randomly divided into two groups (reference and study) of 165 cases each. To ensure there was no significant difference between the distributions of independent variables in these two groups, we used chi-square tests (Table 1) and multiple logistic regression models (Wald's statistics = 0.10 to 2.46), the log-rank test was used to ensure patients' lifetime in the two groups were similar ($p = 0.58$) and it was determined that there were no significant differences between the two groups.

The log-rank test was used in each group (reference and study) to assess the effect of binary independent variables on patients' lifetime and results indicated that gender, pathology type, presence of metastasis, T-stage, N-stage, or M-stage had no significant effect on people's lifetime, while in both groups, age and history of receiving supplementary treatment significantly affected lifetime ($p<0.0001$). Additionally, we used the Cox proportional hazards model to assess the interactions between these variables on lifetime in each group. Results indicated significant correlations with age, presence of metastasis, history of receiving supplementary treatment and N-stage ($p<0.05$).

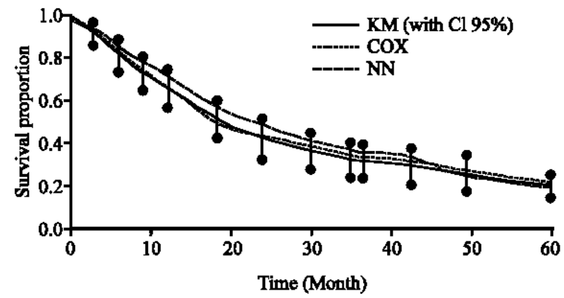

Fig. 2: Baseline survival probabilities with all three methods and the 95% confidence intervals

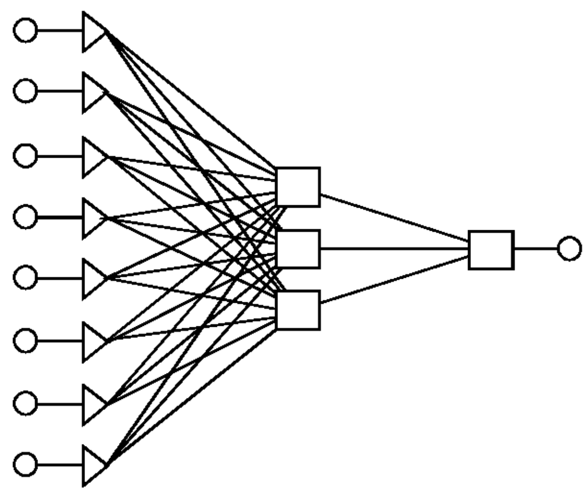

Fig. 3: The neural network with three nodes in hidden layer used in this study

In the third step, probabilities of survival were computed for 6, 12, 18, 24, 36, 48 and 60 months of time through the Cox proportional hazards model and the neural network with 3 hidden layers (Fig. 3). For this purpose, Cox coefficients and estimates and neural network weights were used for predictions in the study group and predictions made with these two methods were compared with the Kaplan-Meier limit estimates as the gold standard (Fig. 4). We found no significant difference between predictions made with these two methods and results obtained from the Kaplan-Meier method, except for Cox predictions for 48 and 54 months; the predicted five year survival probability in this method was not significantly different from standard probabilities in the Kaplan-Meier method though. To use the neural network, we first estimated model weights based on data from the reference group and these weights were used to predict the lifetime of patients in the study group. This prediction was then used in the Kaplan-Meier method and the probabilities of survival were estimated in the study

Table 1: Distribution of independent variables in the reference and prediction groups and results of their comparison

Variable		Reference group (n = 165)	Prediction group (n = 165)	Total (n = 330)	Results
Gender	Female	49 (29.7%)	53 (32.1%)	102 (30.9%)	$\chi^2 = 0.23$
	Male	116 (70.3%)	112 (67.9%)	228 (69.1%)	p = 0.63
Age (years)	<70	93 (56.4%)	96 (58.2%)	189 (57.3%)	$\chi^2 = 0.11$
	≥70	72 (43.6%)	69 (41.8%)	141 (42.7%)	p = 0.74
Pathology	Adenocarcinoma	137 (83.0%)	144 (87.3%)	281 (85.2%)	$\chi^2 = 1.17$
	Other	28 (17.0%)	21 (12.7%)	49 (14.8%)	p = 0.28
Metastasis	Yes	99 (60.0%)	93 (56.4%)	192 (58.2%)	$\chi^2 = 0.45$
	No	66 (40.0%)	72 (43.6%)	138 (41.8%)	p = 0.50
T-stage	1-2	24 (14.5%)	15 (9.1%)	39 (11.8%)	$\chi^2 = 2.36$
	3-4	141 (85.5%)	150 (90.9%)	291 (88.2%)	p = 0.13
N-stage	0	100 (60.6%)	101 (61.2%)	201 (60.9%)	$\chi^2 = 0.01$
	1-3	65 (39.4%)	64 (38.8%)	129 (39.1%)	p = 0.91
M-stage	0	150 (90.9%)	152 (92.1%)	302 (91.5%)	$\chi^2 = 0.16$
	1	15 (9.1%)	13 (7.9%)	28 (8.5%)	p = 0.69
Supplementary treatment	Yes	39 (23.6%)	28 (17.0%)	67 (20.3%)	$\chi^2 = 2.27$
	No	126 (76.4%)	137 (83.0%)	263 (79.7%)	p = 0.13
Final status	Alive	45 (27.3%)	46 (27.9%)	91 (27.6%)	$\chi^2 = 0.02$
	Deceased	120 (72.7%)	119 (72.1%)	239 (72.4%)	p = 0.90

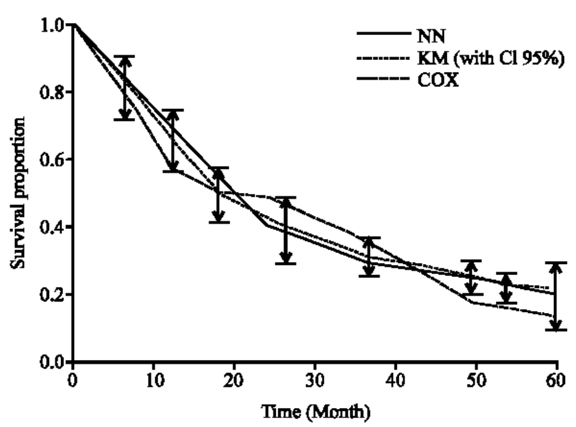

Fig. 4: Predicted probabilities of survival in the study group with Cox proportional hazards model and the neural network in comparison with Kaplan-Meier (95% confidence intervals)

group. With the neural network, the probabilities of survival were insignificantly higher than with the standard method up to around the 22nd month, generally lower than standard values afterwards and then very close to standard during the final months of the study (around the 42nd month). Findings were compared using the log-rank test and there were no significant differences among the probabilities of survival by the three methods. Although the Friedman test showed no significant difference in the trend of changes in survival probabilities generated from these three methods, the Kruskal-Wallis test demonstrated that the 4 year (month 48) and 4.5 year (month 54) survival probabilities with Cox were significantly different from that with the standard method and the predicted probabilities with the neural network ($p<0.05$). In the study group, the mean standard errors of the survival probabilities with the three methods of Kaplan-Meier, Cox estimates and the neural network were 0.03366, 0.03607 and 0.03386, respectively. The standard error ratio of Cox estimates and the neural network to the Kaplan-Meier method were 1.0717 and 1.0062, respectively, which although not significantly different from each other or from the standard (Kaplan-Meier), indicated better accuracy for the neural network.

DISCUSSION

The 5 year survival probability for the patients in this study was 23.6% with Kaplan-Meier and 22.3% with the neural network, which are similar values and are both lower than that in other countries such as the United States (Schwarz and Zagala-Nevarez, 2002), France (Triboulet *et al*., 2001) and China (Ding *et al*., 2004).

As expected, the observed baseline survival in time with Kaplan-Meier limit estimator and Cox proportional hazards model gave similar results, but was slightly different with the neural network, showing a higher survival up to the fourth year and then close to the other two methods; differences that were not statistically significant. In the study by Jones *et al*. (2006), the neural network showed higher probabilities of survival throughout the study with less difference after the third year. In fact we do not expect neural network-based models to generate appropriate estimates regardless of the training constraints. Apart from classification and discrimination which are important features of neural networks, in studies like the present one, prediction is an essential issue. In a neural network model, the objective is to design a suitable network (a nonlinear model and estimating the weights of the model) that is capable of making predictions for new entries and correcting the model at every stage with the new information so that it would generate more accurate predictions. The baseline survival computed with the neural network may not be very reliable, because it is greatly affected by the sample number and more importantly, the function is in the middle layer (logistic). The starting point in a neural network model is the input layer (i.e., where independent variables are introduced) and when their effect is ignored, there is no appropriate standard to correct the coefficients in the model except data on independent variables in the reference group (affected by the sample size) and the function used in the middle layer. This is confirmed by other studies as well (Ravdin and Clark, 1992; Ripley and Ripley, 2001; Jones *et al*., 2006). Therefore, when computing the baseline survival from a databank, we recommend with the Kaplan-Meier product limit estimator which can easily be done by statistical software such as SPSS and STATA and suggest arcsinus or Borgan-Liestol methods to determine the confidence intervals.

In the main analysis, when we used Cox proportional hazards and a neural network with three nodes in hidden layer (Fig. 3) to calculate Cox estimates and coefficients and neural network weights based on data from the reference group, used the results to predict survival probabilities at 6, 12, 18, 24, 36, 48 and 60 months and compared the predictions with estimates from Kaplan-Meier as the gold standard (Fig. 4), we found that neither prediction had significant differences with that by Kaplan-Meier, except for Cox predictions at 48 and 54 months; although the predicted five year survival probability in this method was not significantly different from standard probabilities in the Kaplan-Meier method. With the neural network, the probabilities of survival were insignificantly higher than with the standard method up to around the 22nd month, generally lower than standard values afterwards and then very close to standard during the final months of the study (around the 42nd month). In the study group, the mean standard errors of the survival probabilities were 0.03366, 0.03607 and 0.03386 with the three methods of Kaplan-Meier, Cox estimates and the neural network, respectively. The standard error ratio of Cox estimates and the neural network to the Kaplan-Meier method were 1.0717 and 1.0062, respectively, which although not significantly different from each other or from the standard (Kaplan-Meier), indicated better accuracy for the neural network. Use of such models has been very limited in survival studies as well. Ravdin *et al*. (1992), who have used neural networks in a survival study of patients with breast cancer, also report that these models can generate relatively more accurate results compared to traditional methods. In their study, missing data were not considered and time was entered in the model as a predictive variable. For every patient, the number of time intervals the patient survived was considered an independent variable and other independent variables were not considered very much. Therefore, our findings are more valid. In our study, an overestimation of survival probabilities is seen compared to the standard method. A similar observation was made by Ripley and Ripley (2001), but they claimed there was not enough evidence to make one method superior to others. In a study by Ripley and Harris (2004), in which they assessed survival until the first recurrence after surgery as the independent variable and 11 personal, diagnostic and treatment variables as independent ones and variables were coded in a binary fashion and analyses were done based on a multilayer perception, it was concluded that use of neural network models may not be very beneficial. Jones *et al*. (2006) observed results similar to ours and concluded neural networks were more accurate than Cox models in making predictions. Similarly, independent variables were grouped in a binary method in their study and three nodes in hidden layer were used.

CONCLUSION

In light of advancements in computer sciences, neural networks are expected to improve in terms of practicality and effectiveness and although we do not recommend them for estimating baseline survival, they do seem to predict survival probabilities more accurately than the Cox proportional hazards model, especially now that limitations regarding sophisticated computations have been removed. These methods are preferred because they lack the limitations of conventional models and obviate the need to accept unnecessary assumptions such as those related to proportionality of hazards and linearity. Taking independent variables as continuous variables dependent on time is another issue under investigation and publication by the authors of the present report.

REFERENCES

Anagnostopoulos, I. and I. Maglogiannis, 2006. Neural network-based diagnostic and prognostic estimations in breast cancer microscopic instances. Med. Biol. Eng. Comput., 44 (9): 773-784.

Ashutosh, K., H. Lee, C.K. Mohan, S. Ranka, K. Mehrotra and C. Alexander, 1992. Prediction criteria for successful weaning from respiratory support: Statistical and connectionist analyses. Crit. Care Med., 20 (9): 1295-301.

Bakker, B., T. Heskes, J. Neijt and B. Kappen, 2004. Improving cox survival analysis with a neural-bayesian approach. Stat. Med., 23 (19): 2989-3012.

Baxt, W.G., 1991. Use of an artificial neural network for the diagnosis of myocardial infarction. Ann. Int. Med., 115 (11): 843-848.

Baxt, W.G., 1992. Analysis of the clinical variables driving decision in artificial neural network trained to identify the presence of myocardial infarction. Ann. Emerg. Med., 21 (12): 1439-1444.

Biganzoli, E., P. Boracch, D. Coradini, M. Grazia Daidone and E. Marubini, 2003. Prognosis in node-negative primary breast cancer: A neural network analysis of risk profiles using routinely assessed factors. Ann. Oncol., 14 (10): 1484-1493.

Burke, H.B., 1994. Artificial neural networks for cancer research: Outcome prediction. Seminars in Surgical Oncol., 10 (1): 73-79.

De Laurentiis, M. and P.M. Radvin, 1994. A technique for using neural network analysis to perform survival analysis of censored data. Cancer Lett., 77 (2-3): 127-138.

Ding, Y.B., G.Y. Chen, J.G. Xia, H.Y. Yang, L. Yang and Y.X. Liu, 2004. Correlation of tumor-positive ratio and number of perigastric lymph nodes with prognosis of patients with surgically-removed gastric carcinoma. World J. Gastroenterol., 10 (2): 182-185.

Doyle, H.R., I. Dvorchik, S. Mitchell, I.R. Marino, F.H. Ebert, J. McMichael and J.J. Fung, 1994. Predicting outcomes after liver transplantation. Ann. Surg., 219 (4): 408-415.

Ebell, M.H., 1993. Artificial neural networks for predicting failure to survive following in-hospital cardiopulmonary resuscitation. J. Fam. Practice, 36 (3): 297-303.

Fuxe, K., A. Dahlstrom, M. Hoistad, D. Marcellino, A. Jansson, A. Rivera, Z. Diaz-Cabiale, K. Jacobsen, B. Tinner-Staines, B. Hagman, G. Leo, W. Staines, D. Guidolin, J. Kehr, S. Genedani, N. Bellurado and L.F. Agnati, 2007. From the golgi-cajal mapping to the transmitter-based characterization of the neural networks leading to two modes of brain communication: Wiring and volume transmission. Brain Res. Rev., 55 (1): 17-54.

Hirsch, S., J. Shapiro, M. Turega, T.L. Frank, R. Niven and P.I. Frank, 2001. Using a neural network to screen a population for asthema. Ann. Epidemiol., 11 (6): 369-376.

Jerez, J.M., L. Franco, E. Alba, A. Llombart-Cussac, A. Lluch, N. Ribelles, B. Munarriz and M. Martin, 2005. Improvement of breast cancer relapse prediction in high risk intervals using artificial neural networks. Breast Cancer Res. Treatment, 94 (3): 265-272.

Jones, A.S., A.G. Taktak, T.R. Helliwell, J.E. Fenton, M.A. Birchall, D.J. Husband and A.C. Fisher, 2006. An artificial neural network improves prediction of observed survival in patients with laryngeal squamous carcinoma. Eur. Arch. Otorhinolaryngol., 263 (6): 541-547.

Kaplan, E.L. and P. Meier, 1958. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc., 53 (282): 457-481.

Klien, J.P. and M.L. Moeschberger, 1997. Survival Analysis Techniques for Censored and Truncated Data. Springer-Verlag: New York.

Marsland, S., J. Shapiro and U. Nehmzow, 2002. A self-organising network that grows when required. Neural Networks, 15 (8-9): 1041-1058.

Mohagheghi, M.A., A. Musavi Jarahi, S. Shariat Torbaghan and H. Zeraati, 1998. Annual Report of the Emam Khomeini Medical Center Hospital Based Cancer Registry 1995. The Cancer Institute Publication, Tehran, Iran.

Mohagheghi, M.A., A. Musavi Jarahi, S. Shariat Torbaghan and H. Zeraati, 1999. Annual Report of Tehran University of Medical Sciences District Cancer Registry 1997. The Cancer Institute Publication, Tehran, Iran.

Mohagheghi, M.A., 2004. Annual Report of Tehran Cancer Registry 1999. The Cancer Institute Publication, Tehran, Iran.

Ohno-Machado, L., 1996. Sequential use of neural networks for survival prediction in aids. J. Am. Med. Inform., 3 (2): 170-174.

Papik, K., B. Molnar, R. Schaefer, Z. Dombovari, Z. Tulassay and J. Feher, 1998. Application of neural networks in medicine a review. Med. Sci. Monit., 4 (3): 538-546.

Park, Y.S. and Y.J. Chung, 2006. Hazard rating of pine trees from a forest insect pest using artificial neural networks. For. Ecol. Manage., 222 (1): 222-233.

Ravdin, P.M., G.M. Clark, S.G. Hilsenbeck, M.A. Owens, P. Vendely, M.R. Pandian and W.L. McGuire, 1992. A demonstration that breast cancer recurrence can be predicted by neural network analysis. Breast Cancer Res. Treatment, 21 (1): 47-53.

Ravdin, P.M. and G.M. Clark, 1992.A practical application of neural network analysis for predicting outcome of individual breast cancer patients. Breast Cancer Res. Treatment, 22 (3): 285-293.

Ripley, B.D. and R.M. Ripley, 2001. Neural Networks as Statistical Methods in Survival Analysis. Cambridge University Press: Cambridge.

Ripley, R.M. and A.L. Harris, 2004. Tarassenko L. Non-linear survival analysis using neural networks. Statist. Med., 23 (5): 825-842.

Sato, F., Y. Shimada, F.M. Selaru, D. Shibata, M. Maeda, G. Watanabe, Y. Mori, S.A. Stass, M. Imamura and S.J. Meltzer, 2005. Prediction of survival in patients with esophageal carcinoma using artificial neural networks. Cancer, 103 (8): 1596-1605.

Schwarz, R.E. and K. Zagala-Nevarez, 2002. Recurrence patterns after radical gastrectomy for gastric cancer: Prognostic factors and implications for postoperative adjuant therapy. Ann. Surg. Oncol., 9 (4): 394-400.

Suka, M., S. Oeda, T. Ichimura, K. Yoshida and J. Takezawa, 2004. Comparison of proportional hazard model and neural network models in a real data set of intensive care unit patients. Medinfo, 11 (Pt 1): 741-745.

Thong-Ngam, D., P. Tangkijvanich, V. Mahachai and P. Kullavanijaya, 2001. Current status of gastric cancer in thai patients. J. Med. Assoc. Thai., 84 (4): 475-482.

Triboulet, J.P., S. Fabre, B. Castel and H. Toursel, 2001. Adenocarcinomas of the distal esophagus and cardia: Surgical management. Cancer Radither, 5 (Suppl 1): 90-97 (In French).

Zeraati, H., M. Mahmoudi, A. Kazemnejad and K. Mohammad, 2005. Postoperative life expectancy in gastric cancer patients and its associated factors. Saudi Med. J., 26 (8): 1203-1207.