# A multivariate analysis of clinical and pathological variables in survival after resection of gastric cancer

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*A retrospective study was performed to identify the prognostic factors of gastric carcinoma. The study consisted of 118 patients who underwent primary gastric resections. Data regarding patient's age, sex, weight loss, anemia, tumour location, type of gastric resection, extent of lymph node dissection, concomitant splenectomy, histologic type of tumour, tumour grade, tumour stage according to TNM classification, primary tumour, regional lymph node status, venous invasion, lymphatic invasion, perineural invasion, perioperative whole blood transfusion, adjuvant chemotherapy were analyzed. It was found that tumour stage, primary tumour, regional lymph node metastases, extent of lymph node dissection, tumour location, venous invasion, lymphatic invasion, and perineural invasion were associated with 3 years cumulative survival when Kaplan-Meier method was applied ( $p<0.05$, log-rank test ). By Cox's proportional hazard model, tumour stage, extent of lymph node dissection, and venous invasion were found to have significant influence on survival. [Turk J Med Res 1997; 15(1):15-20]*

**Key Words** : Gastric carcinoma, Survival, Prognosis, Multivariate analysis

Several prognostic factors for gastric carcinoma have been demonstrated, however the therapeutic value of extensive of gastric resection including regional lymphadenectomy, neighboring or multiorgan resection such as splenectomy, pancreatectomy is still controversial (1-4). The prognosis of gastric cancer remains poor in most Western countries compared with outcome from Japanese investigators. Contradictory results from Japan and Western world may be produced by the aggressive operative approach, possible different biological characteristic of the tumour, and the administration of different adjuvant therapy (1,3). Although surgical results of early gastric carcinoma are favorable, prognosis for patients with advanced gastric cancer remains unchanged in spite of radical surgery (1,5-7).

On the other hand, some studies revealed that factors other than the type or extent of surgery have been important on prognosis in patients with resectable gastric cancer. Various patient and tumour-related factors have been important for outcome of gastric cancer, however it was well established by many studies that tumour stage was the most important determinant of prognosis (8, 9).

This retrospective study was performed to evaluate our experience in patients undergoing resection for gastrie carcinoma. We therefore focused on overall survival and several clinicopathologically factors that could influence on prognosis by using univariate and multivariate analyses.

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## MATERIALS AND METHODS

### Study populations

The medical records of patients treated for gastric carcinoma from January 1990 to November 1995 at Ankara Oncology Hospital were retrospectively reviewed. Patients who had liver metastasis or locally advanced disease at presentation or laparatomy were excluded from the analysis. Seven patients who died within 30 days of curative surgery were not included in the study. Thus, the study populations consisted of 118 patients undergoing primary gastric resections whom follow-up data was available until April 1996 or death.

Data on extracted patients which included patient's age, sex, weight loss, anemia, tumour location, type of gastric resection, extent of lymph node dissection, concomitant splenectomy, histologic type of tumour, tumour grade, tumour stage according to TNM classification of American Joint Committee on Cancer (AJCC)-1992 (10), primary tumour ( depth of tumour invasion) (T), regional lymph node status (N), venous invasion, lymphatic invasion, perineural invasion, perioperative whole blood transfusion, adjuvant chemotherapy, patient's status, and follow-up time were accurately recorded and coded on a computer file. The patient characteristics were summarized in Table 1.

Table 1. Patient characteristics

| Characteristic | | |
|---|---|---|
| Available patients | 118 | |
| Mean age ( range ) | 56 + 11.3 ( 29-84)yr | |
| Sex ratio ( male/female ) | 1.4 /1 | |
| Mean follow-up time ( range ) | 26 + 16.4 ( 5-74 )months | |
| Tumour location | number of patients | % |
| upper third | 21 | 18 |
| middle third | 25 | 21 |
| lower third | 62 | 53 |
| whole stomach | 10 | 8 |
| Tumour staae | | |
| stage 1 | 11 | 9 |
| stage 2 | 19 | 16 |
| stage 3 | 65 | 55 |
| stage 4 | 23 | 20 |
| Histoloqic tvoe | | |
| adenocancer | 84 | 71 |
| mucinous cancer | 34 | 29 |

### Statistical Analysis

The length of survival was measured from the date of surgery to death of disease or April 1996. Only deaths from gastric cancer were included as events.

Kaplan-Meier method was used to examine the effects of individual variables on cumulative 3-year survival. Significance of the observed difference between groups was calculated by the log-rank test.

The combined and independent effects of the variables on survival were evaluated using Cox proportional hazards regression model for censored survival data (11). All the variables were thereby selected in steps until no further useful effect upon prognosis could be demonstrated. The effect of variables on death rates rather than times to death is modelled. If A.(t) is the hazard rate, then the proportional hazards model is given by MO ᵐ MO ᵉ ˣ P ⁺ £>2'2 ⁺ ^3ˣ3 ᵉ¹ᶜ-) where $b_2$...) are the regression coeffiecients, ($x_1$, $x_2$...) are the observed values of the variables and $X_0(t)$ is the baseline hazard rate. Integer scores were reallotted to each variable on the basis of the regression coefficients ($b_1$( $b_2$ ...) in the best fitting model.

Computer software included SPSS for univariate analysis and COXSURV (12) for the Cox model. For all test, a p value less than 0.05 was accepted as significant.

## RESULTS

The mean age of studied patients was 56±11.3 years (range : 29-84). There were 69 male and 49 female patients. The follow-up period varied from 5 to 74 months (mean : 26±16.4).

Seventy-two patients underwent total gastrectomy, while subtotal gastrectomy was performed in 46 patients. Splenectomy was added in 48 patients. Radical lymph node dissection ($D_{2-3}$) was performed in 56 patients. When patients who underwent $D_{2-3}$ dissections and who did not were compared on the basis of actual time in the operating room under anesthesia, postoperative hospital stay, complication, and intraoperative blood transfusion requirement, no significant differences were found between the two groups ( data not shown ).

All the patients were categorized into stage by TNM classification of AJCC-1992. There were only 4 patients in Stage IA, 7 patients in Stage IB, 19 patients in Stage II, 26 patients in Stage IIIA, 39 patients in Stage 1MB and 23 patients in Stage IV. The majority were Stage III disease (55.1% of all patients).

The outcomes of survival analysis by univariate method are shown in Table 2. Survival was strongly related to tumour location (p=0.0198), extent of lymphadenectomy (p=0.0004), primary tumour (p=0.0278), regional lymph node status (p=0.0002), tumour stage (p=0.0002), venous invasion (p<0.0001), lymphatic invasion (p=0.0019), and perineural invasion (p=0.0274). No significant statistical differences were found in the remaining ten variables.

### Multivariate Analysis

The data were further analyzed using the Cox's proportional hazard model to evaluate significant relationship between clinicopathologic features and patient survival and to examine the effects of more than one factor on prognosis. The independent variables entered into the analysis is outlined in the "Method" section.

Table 3 summarizes the results of first step of the analysis for those variables obtained to have statistically significant coefficients in the multivariate method. At the final step, following three factors could not be removed from the model : tumour stage, extent of lymph node dissection, and venous invasion. Advanced stage was seen to be the most important prognostic factor. Other factors which had negative influence on survival were as follows: stage III disease, conventional lymphadenectomy (so-called D1 dissection), and tumour with venous invasion (Table 4).

## DISCUSSION

Various surgical and histopathological variables have been evaluated for prognostic factors in patients with gastric carcinoma (13-18). In this retrospective study, we examined a cohort of patients with gastric cancer operated on for cure. Among eighteen variables analyzed by univariate method, whole stomach location of tumour, limited lymphadenectomy, deeper infiltration of the gastric wall, metastatic lymph nodes, tumour stage, vascular neoplastic invasion, perineural invasion, and lymphatic-vessel invasion were significantly correlated with lower 3-year survival rate. Subsequently, multivariate analysis using Cox model indicated that only three variables were the most important prognostic factors : extent of lymphadenectomy, tumour stage, and vascular invasion.

The effect of extended or radical lymphadenectomy (so-called $D_{2-3}$ dissection) on prognosis in gastric cancer

Table 2. Univariate survival analysis

| Variable | Uncensored | Censored | % surviving 3 yr | Median survival time ( month ) | P value" |
|---|---|---|---|---|---|
| Age | | | | | |
| <40yr ( n=11 )* | 7 | 4 | 0 | 11 | |
| >40 yr(n=107) | 45 | 62 | 44 | 29 | 0.0522 |
| Sex | | | | | |
| Male (n=69)* | 33 | 36 | 36 | 24 | |
| Female (n=49) | 19 | 30 | 50 | 37 | 0.2837 |
| Weight loss | | | | | |
| No (n=90 )* | 38 | 52 | 46 | 29 | |
| Yes (n= 28 ) | 14 | 14 | 30 | 24 | 0.6007 |
| Anemia | | | | | |
| No (n= 31 )* | 10 | 21 | 56 | 34 | |
| Yes (ri= 87 ) | 42 | 45 | 34 | 24 | 0.0887 |
| Tumour location | | | | | |
| Upper third (n= 21 )* | 7 | 14 | 43 | 36 | |
| Mid third (n=25 ) | 15 | 10 | 34 | 18 | |
| Lower third (n=62 ) | 22 | 40 | 51 | 40 | 0.0198 |
| Whole stomach (n=10 ) | 8 | 2 | 15 | 12 | |
| Type of gastric resection | | | | | |
| Subtotal gastrectomy (n=46)* | 20 | 26 | 33 | 25 | |
| Total gastrectomy (n= 72 ) | 32 | 40 | 43 | 29 | 0.9315 |
| Lymph node dissection ( D ) | | | | | |
| Do-1 ( n=62 )* | 38 | 24 | 32 | 19 | |
| D2-3 ( n= 56 ) | 14 | 42 | 64 | 39 | 0.0004 |
| Splenectomy | | | | | |
| No ( n= 70 )* | 27 | 43 | 50 | 37 | |
| Yes ( n= 48 ) | 25 | 23 | 37 | 24 | 0.1306 |
| Primary tumour (T) | | | | | |
| T1 (n= 5 )* | 0 | 5 | 100 | *** | |
| T2 (n= 12 ) | 2 | 10 | 80 | 44 | |
| T3 (n=57 ) | 28 | 29 | 36 | 23 | 0.0278 |
| T4 (n= 44 ) | 22 | 22 | 38 | 24 | |
| Regional lymph node (N) | | | | | |
| No (n=30)* | 7 | 23 | 75 | 42 | |
| N1 (n= 40) | 18 | 22 | 38 | 26 | |
| N2 (n= 48 ) | 27 | 21 | 9 | 18 | 0.0002 |
| Tumour stage | | | | | |
| Stage 1 (n= 11 )* | 0 | 11 | 100 | *** | |
| Stage 2 (n= 19 ) | 4 | 15 | 77 | 41 | |
| Stage 3 (n= 65 ) | 36 | 29 | 23 | 20 | 0.0002 |
| Stage 4 (n= 23 ) | 12 | 11 | 15 | 17 | |
| Tumour grade (G) | | | | | |
| G1 (n= 34 )* | 10 | 24 | 64 | 42 | |
| G2 (n= 18 ) | 7 | 11 | 47 | 29 | 0.0861 |
| G3 (n= 66 ) | 35 | 31 | 30 | 24 | |
| Histologic type | | | | | |
| Adenocancer (n=84 )* | 33 | 51 | 53 | 37 | |
| Musinous cancer (n=34) | 19 | 15 | 17 | 20 | 0.0990 |
| Venous invasion | | | | | |
| Absent (n= 87 )* | 28 | 59 | 58 | 44 | |
| Present (n=31 ) | 24 | 7 | • 7 | 14 | 0.0000 |
| Lymphatic invasion | | | | | |
| Absent (n= 84 )* | 29 | 55 | 58 | 39 | |
| Present (n= 34 ) | 23 | 11 | 15 | 17 | 0.0019 |
| Perineural invasion | | | | | |
| Absent (ri- 102)* | 42 | 60 | 48 | 30 | |
| Present (n=16 ) | 10 | 6 | 0 | 14 | 0.0274 |
| Chemotherapy | | | | | |
| No (n= 34 )* | 20 | 14 | 31 | 20 | |
| Yes (n= 84 ) | 32 | 52 | 48 | 36 | 0.1061 |
| Blood transfusion | | | | | |
| < 2 units (n= 22 )* | 7 | 15 | 60 | 38 | |
| > 2 units (n= 96 ) | 45 | 51 | 40 | 26 | 0.2435 |

* : reference category ** : p values given refer to log-rank test.
***: survival time estimates can not be computed since all observations are censored.

**Table** 3. Results of 18 variables entered into Cox proportional hazard model

| Variable | 0 | S.E | | P value |
|---|---|---|---|---|
| Age | | | | |
| (<40 vs > 40 yr) | -0.76 | 0.41 | 0.47 | 0.0617 |
| Sex | | | | |
| ( Male vs female) | -0.30 | 0.29 | 0.74 | 0.2924 |
| Weight loss | | | | |
| ( no vs yes ) | 0.16 | 0.31 | 1.17 | 0.6062 |
| Anemia | | | | |
| ( no vs yes ) | 0.59 | 0.35 | 1.79 | 0.0979 |
| Type of gastric resection | | | | |
| ( Total vs subtotal) | -0.02 | 0.29 | 0.98 | 0.9325 |
| Lymph node dissection | | | | |
| ( Di vs $D_{2}$-$_{3}$) | -1.04 | 0.31 | 0.35 | 0.0009 |
| Splenectomy | | | | |
| ( no vs yes ) | 0.41 | 0.28 | 1.51 | 0.1389 |
| Tumour location | | | | |
| ( upper vs middle ) | 0.69 | 0.45 | 2.0 | 0.1302 |
| ( upper vs lower) | 0.19 | 0.43 | 1.22 | 0.6470 |
| ( upper vs whole stomach) | 1.27 | 0.52 | 3.56 | 0.0149 |
| Primary tumour (T) | | | | |
| ( Ti and $T_2$ vs $T_3$) | 1.62 | 0.73 | 5.05 | 0.0270 |
| ($T_1$ and $T_2$ vs $T_4$ ) | 1.93 | 0.74 | 6.89 | 0.0093 |
| Regional lymph node(N) | | | | |
| ( No vs Ni ) | 1.16 | 0.45 | 3.18 | 0.0105 |
| ( No vs $N_2$ ) | 1.52 | 0.44 | 4.57 | 0.0005 |
| Tumour Stage ( S ) | | | | |
| (Si and $S_2$vs $S_3$ ) | 1.95 | 1.53 | 7.05 | 0.0003 |
| ( Si and $S_2$ vs $S_4$ ) | 2.15 | 0.59 | 8.62 | 0.0003 |
| Tumour histology | | | | |
| (adenocancer vs mucinous) | 0.46 | 0.29 | 1.59 | 0.1071 |
| Tumour Grade ( G) | | | | |
| ( $G_1$ vs $G_2$) | 0.26 | 0.49 | 1.29 | 0.6030 |
| ( $G_1$ vs $G_3$ ) | 0.72 | 0.36 | 2.06 | 0.0446 |
| Venous invasion | | | | |
| ( absent vs present) | 1.25 | 0.28 | 3.49 | 0.0000 . |
| Lymphatic invasion | | | | |
| ( absent vs present) | 0.84 | 0.28 | 2.32 | 0.0030 |
| Perineural invasion | | | | |
| ( absent vs present) | 0.75 | 0.35 | 2.12 | 0.0336 |
| Blood transfusion | | | | |
| (<2 vs >2 units ) | 0.46 | 0.41 | 1.59 | 0.2545 |
| Chemotherapy | | | | |
| ( no vs yes ) | -0.45 | 0.29 | 0.64 | 0.1142 |

(3: estimated coefficient $e^{\beta}$ : hazard ratio

**Table** 4. Results of final step of Cox proportional hazards model

| Variable | 3 | P value | eP | 95% CI |
|---|---|---|---|---|
| Stage 3 tumour | 1.62 | 0.0028 | 5.05 | 1.75-14.59 |
| Stage 4 tumour | 1.91 | 0.0017 | 6.72 | 2.04-22.14 |
| Lymph node dissection | -0.89 | 0.0055 | 0.41 | 0.22-0.76 |
| Venous invasion | 0.74 | 0.0109 | 2.10 | 1.19-3.72 |

P : estimated coefficient $e^{\beta}$: hazard ratio

is still a matter of discussion. Rationale for gastrectomy with radical lymphadenectomy is the premise that better locoregional tumour control improves patient survival. Although in Japan, excellent results associated with $D_{2-3}$ resection have been reported, gastrectomy with conventional or limited lymphadenectomy (so-called DQ^ dissection) remains standard treatment in most Western countries (2,3,19-21).

In contrast to the Japanese results, some Western studies demonstrated that there was no survival difference between DQ^ and $D_2$.3 resections (2,3,20-22). Moreover, radical lymphadenectomy in their series car-

ried increased mortality and morbidity rates. Our retrospective results were not confirmed by these reports. In our series, multivariate analysis using Cox proportional hazards model revealed that the extent of lymphadenectomy ($p<0.05$, eP = 0.41) was an independent prognostic factor statistically for survival and that the limited lymphadenectomy was significantly associated with lower survival rate as well as high tumour stage and venous carcinomatous invasion. In our experience it is clearly shown that D2-3 resection as a safe an appropriate choice of the surgical treatment with a low morbidity rate for gastric cancer should be performed in order to obtain the best prognosis.

In addition to the extent of lymphadenectomy, the role of extended gastrectomy including removal of the neighboring organ, especially splenectomy, remains controversial. Some surgeons from Japan suggested that splenectomy should be performed for advanced stage tumour (23). In contrast to this, Kockerling et al. demonstrated that 5-year survival rates following extended radical resections of gastric carcinoma were lower than those seen after nonextended radical resections (16 % vs. 36 %) (24). However some authors reported that according to univariate method, survival time of patients with splenectomy was significantly less than those for whom splenectomy was not done. Furthermore, in multivariate analysis there was no correlation whatever with splenectomy (25,26). Although our follow-up time was not long enough, our results also indicated that splenectomy did not correlate with prognosis in patients undergoing curative gastrectomy for gastric cancer.

According to Shui et al. series, total gastrectomy was superior to subtotal gastrectomy (17) but, others revealed that type of operation (total gastrectomy or subtotal gastrectomy) did not affect the prognosis (6,27). Interestingly, Jatzko et al. reported that patients who underwent total gastrectomy had poor prognosis by univariate and multivariate analyses (26). Considering our finding, it also has agreed that total gastrectomy should be performed in order to obtain tumour-free margins for large tumours.

•As demonstrated in many studies, pathological tumour stage in our study was found to be a prognostic factor independent of other covariates. It should be emphasized that patients with advanced tumour stage were carefully evaluated and followed.

The influence of vessel neoplastic invasion on prognosis in patients with gastric cancer was evaluated in a few studies. The authors reported that venous neoplastic invasion was the more important factor for predicting prognosis in accordance with Cox regression model (15,28).

Since our findings also confirmed them, it was agreed that a careful search for venous invasion in gastric cancer may provide additional useful information for identifying patients who may be candidates for adjuvant therapy in future clinical trials as well as patients with advanced tumour stage.

In conclusion, our retrospective study based on Cox proportional hazard model revealed that high tumour stage, the extent of lymphadenectomy, and venous neoplastic invasion were all of independent prognostic factors. It became clear from our results that gastrectomy with radical lymph node dissection may be the operation of choice as far as curability is concerned.

**Mide kanseri rezeksiyonu sonrası sağkalımda klinik ve patolojik değişkenlerin multivaryan analizi**

*Mide kanserinde prognostik faktörleri belirlemek için yapılan bu retrospektif çalışma, primer olarak mide rezeksiyonu uygulanan 118 olgudan oluştu. Hastanın yaşı, cinsiyeti, kilo kaybı, tanı sırasında anemi, tümörün midedeki lokalizasyonu, mide rezeksiyonunun tipi, lenf nodu diseksiyonunun genişliği, splenektominin eklenmesi, tümörün histolojik tipi, tümörün grade'i, TNM sınıflandırmasına göre hastalığın evresi, tümörün mide duvarındaki invazyon derinliği, bölgesel lenf nodlarının durumu, tümörün venöz, lenfatik veya perinöral invazyon yapması, perioperatif tam kan transfüzyonu, adjuvant kemoterapi hakkındaki bilgiler istatistiksel olarak değerlendirildi. Kaplan-Meier metoduna göre tümörün evresi, invazyon derinliği, lenf nodlarının durumu, lenfadenektominin genişliği, venöz, lenfatik ve perinöral invazyon 3 yıllık sağkalım ile ilişkili faktörler olarak bulundu ( $p<0.05$). Cox orantısal hasar modeli uygulandığında ise sadece tümörün evresi, lenfadenektominin genişliği ve venöz invazyonun sağkalıma etkili faktörler olduğu saptandı.*
*[T Klin Araştırma 1997; 15(1):15-20]*

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