

**ORIGINAL  
ARTICLE**

**Necdet Fatih Yasar<sup>1</sup>**  
**Bartu Badak<sup>1</sup>**  
**Setenay Oner<sup>2</sup>**  
**Ersin Ates<sup>1</sup>**  
**Adnan Sahin<sup>1</sup>**  
**Uğur Bilge<sup>3</sup>**  
**Tarik Caga<sup>1</sup>**

<sup>1</sup>Department of General Surgery,  
Eskisehir Osmangazi University,  
Medical School, Eskisehir, Turkey

<sup>2</sup>Department of Biostatistics, Eskisehir  
Osmangazi University, Medical  
School, Eskisehir, Turkey

<sup>3</sup>Department of Family Medicine,  
Eskisehir Osmangazi University,  
Medical School, Eskisehir, Turkey

**Corresponding Author:**

Ugur Bilge

Department of Family Medicine, Eskisehir  
Osmangazi University, Medical School,  
Eskisehir 26480, Turkey

Phone: +90 222 239 29 79

Email: dr\_ubilge@windowslive.com

Received: 09.04.2017

Acceptance: 19.06.2017

DOI: 10.18521/kt.d.305030

**Konuralp Medical Journal**

e-ISSN1309-3878

konuralptipdergi@duzce.edu.tr

konuralptipdergisi@gmail.com

www.konuralptipdergi.duzce.edu.tr

## Is There A Relation Between the Changes in Tumor Marker Levels and The Extent of Lymph Node Dissection in Gastric Cancer?

### ABSTRACT

**Objective:** We aimed to investigate the effects of the levels of lymph node dissection on the changes in the tumor markers including CEA and CA19-9, retrospectively.

**Methods:** We divided 52 patients who underwent radical gastrectomy between January 2014 and December 2016 into 3 groups according to the levels of lymph node dissections (D1, n=18; D1+, n=10; and D2, n=24). The number of the metastatic lymph nodes, the tumor stages, preoperative CEA, CA19-9 levels and postoperative CEA, CA19-9 levels were recorded. The ratio of preoperative tumor marker levels to postoperative levels were compared between the groups.

**Results:** There was no difference at the number of the metastatic lymph nodes, the tumor stages nor in the preoperative and postoperative tumor marker levels between groups. The changes in CEA levels were similar in all groups at all stages. However, the reduction rates in CA19-9 levels in group D1 were less than in group D1+ and D2 whereas there was no difference between groups D1+ and D2. Further analysis showed that the reduction rates in CA19-9 levels was greater in group D2 compared to group D1 only in stage III.

**Conclusion:** The tumor markers may be affected by the extent of the lymph node dissection. The greater level of dissection, the greater reduction in CA19-9 levels was observed in the present study.

**Keywords:** Gastric Cancer; Tumor Marker; Lymph Node Dissection

## Mide Kanserlerinde Lenf Nodu Diseksiyonunun Genişliği İle Tümör Belirteçlerinin Düzeylerindeki Değişikliklerle İlişkisi Var Mıdır?

### ÖZET

**Amaç:** Retrospektif olarak lenf nodu diseksiyon düzeylerinin CEA ve CA19-9 tümör belirteçleri üzerindeki etkilerini araştırmayı amaçladık.

**Yöntem:** Ocak 2014 ile Aralık 2016 tarihleri arasında radikal gastrektomi ameliyatı yapılan 52 hastayı lenf nodu diseksiyon düzeylerine göre 3 gruba ayırdık (D1, n=18; D1+, n=10; ve D2, n=24). Metastatik lenf nodu sayısı, hastalığın evresi ile preoperatif ve postoperatif CEA ve CA 19-9 düzeyleri kaydedildi. Preoperatif tümör belirteçlerinin düzeyleri postoperatif düzeylerine olan oranları gruplar arasında karşılaştırıldı.

**Bulgular:** Metastatik lenf nodu sayıları, tümör evreleri ve preoperatif ve postoperatif tümör belirteçleri açısından gruplar arasında fark yoktu. Tüm gruplarda CEA düzeylerindeki değişiklikler evrelerin hepsinde benzerdi. Öte yandan, CA 19-9 düzeylerinde D1 grubunda D1+ ve D2 grubuna kıyasla azalma oranları daha azdı. Buna karşılık D1+ ile D2 grupları arasında bir fark yoktu. Daha detaylı değerlendirildiğinde, CA 19-9 düzeylerindeki azalma oranları sadece evre III'te D2 grubunda D1 grubuna kıyasla daha yüksekti.

**Sonuç:** Tümör belirteçleri lenf nodu diseksiyonunun genişliğinden etkilenebilmektedir. Bu araştırmada, lenf nodu diseksiyon düzeyi arttıkça, CA19-9 düzeylerindeki azalmanın daha fazla olduğu gözlemlendi.

**Anahtar Kelimeler:** Mide Kanseri; Tümör Belirteci; Lenf Nodu Diseksiyonu

## INTRODUCTION

Gastric cancer remains the second leading cause of cancer deaths and the most important prognostic factor of gastric cancer is probably lymph node metastasis (1). Serum tumor markers are associated with less favorable outcome and suggested as indicators for recurrence after radical gastrectomy (1-4). The most commonly used markers for gastric cancer are carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. Clinically, the prevalence of high level of tumor markers among resectable gastric cancer patients is rather low and has been considered to provide little in predicting the prognosis (1,3,5). However, early CEA or CA19-9 normalization after radical gastrectomy has been shown to be a strong prognostic factor for gastric cancer (5).

D2 lymphadenectomy has been shown to be associated with lower locoregional recurrence and gastric-cancer-related death rates than D1 surgery and has become the optimal type of surgery in patients with resectable cancer (6). However morbidity affects from probably the most important handicap of D2 resection and may be a problem in patients with higher risk factors.

In this retrospective study, we aimed to evaluate any possible relations between the levels of lymphadenectomy (D1, D1+, D2) and changes in the tumor marker levels since both are associated with prognosis of gastric cancer.

## MATERIAL AND METHODS

Between January 2014 and December 2016, we enrolled 52 patients who underwent radical gastrectomy as an initial treatment due to resectable gastric cancer and divided into 3 groups according to the levels of lymph node dissections (D1, n=18; D1+, n=10; and D2, n=24). D1 dissection included only perigastric node stations, D1+ dissection included D1 plus resection of the lymph nodes along the left gastric and common hepatic whereas D2 dissection was described as extended lymphadenectomy including removal of the lymph

nodes along the celiac and splenic arteries and the hepatoduodenal ligament additional to D1+. Even if there was not a uniform criteria for patient selection for the specific type of surgery, the surgeons in our clinic had the tendency of performing D1 and D1+ dissection in older patients with relatively worse for health status, in whom the extent of the dissection would affect morbidity and mortality.

Basic patient demographics such as age and gender, total number of the harvested lymph nodes and metastatic lymph nodes, stages of the disease as well as preoperative and postoperative CEA and CA19-9 levels were recorded. The patient demographics were compared using chi square test. The ratio of preoperative tumor marker levels to postoperative levels in groups, without regarding the stages of the disease and also according to the stages, were compared using Kruskal Wallis test since the measurement variable did not have normal distribution.

## RESULTS

The patient age was greater in D1 group than in D2 group ( $p<0.05$ ) while the gender distribution in the groups similarly. There were no differences in the number of the metastatic lymph nodes, the tumor stages between the groups nor in the preoperative and postoperative tumor marker levels ( $p>0.05$ ). The changes in CEA levels were similar in all groups in all stages, either. On the other hand, the reduction rates in CA19-9 levels in group D1 were less compared to group D1+ and D2 (median values of ratios of preoperative levels to postoperative levels respectively; 1.09; 0.67; 0.51;  $p=0.040$  for D1 vs D1+;  $p<0.001$  for D1 vs D2) whereas there were no difference between groups D1+ and D2 ( $p>0.05$ ). When further analyzed according to the tumor stages, the reduction rates in CA19-9 levels were significantly greater in group D2 compared to group D1 only in stage III ( $p<0.001$ ) and no other difference was observed between the groups in other stages ( $p>0.05$ ).

**Table 1.** Patient demographic and preoperative / postoperative tumor marker levels according to dissection groups

Groups	Age ( $\pm$ SD)	Gender (no of males)	Preoperative CEA levels (25%-75%)	Postoperative CEA levels (25%-75%)	Preoperative CA19-9 levels (25%-75%)	Postoperative CA19-9 levels (25%-75%)
D1 (n=18)	<b>76.3*</b> ( $\pm$ 1.51)	13	3,03 (2,16-4,60)	2,04 (1,50-3,79)	7,01 (2,64-16,82)	9,06 (3,62-34,62)
D1+ (n=10)	70.8 ( $\pm$ 1.02)	7	2,65 (1,53-6,36)	2,58 (1,70-3,67)	17,10 (13,64-22,63)	12,06 (5,64-26,54)
D2 (n=24)	<b>66.1</b> ( $\pm$ 1.13)	18	2,82 (1,75-4,16)	2,47 (1,41-3,57)	12,20 (4,60-24,07)	6,62 (1,89-10,47)

\* $P<0,05$  versus group D2

**Table 2.** Ratios of preoperative tumor marker levels to postoperative levels

Groups	CEA ratios (25%-75%)	Stage specific CEA ratios		CA19-9 ratios (25%-75%)	Stage specific CA19-9 ratios	
D1 (n=18)	0,89 (0.52-1.15)	I	1,12	<b>1,09<sup>*,**</sup></b> <b>(0.99-1.34)</b>	I	1,09
		II	0,35		II	1,09
		III	0,96		III	<b>1,20</b>
D1+ (n=10)	0,75 (0.57-1.37)	I	0,57	<b>0,67</b> <b>(0.49-1.03)</b>	I	0,50
		II	1,09		II	0,81
		III	0,83		III	0,66
D2 (n=24)	0,91 (0.74-1.18)	I	0,90	<b>0,51</b> <b>(0.35-0.72)</b>	I	0,63
		II	0,88		II	0,38
		III	0,93		III	<b>0,51<sup>**</sup></b>

\*P<0,05 versus group D1+; \*\*P<0,001 versus group D2

## DISCUSSION

The main finding of our study was that the reduction rates in preoperative CA 19-9 levels with respect to postoperative levels were significantly greater in locally advanced gastric cancer patients who underwent radical surgery with D2 lymphadenectomy.

Lymph node metastasis and depth of tumor invasion are the most important prognostic factors according to the AJCC TNM classification (1). It has been reported that high preoperative CEA and CA 19-9 levels are prognostic for patients who underwent radical gastrectomy while CEA is associated with clinical stage and CA 19-9 is rather correlated with lymph node metastasis (2,7-9). Yet, tumor markers have been considered to provide little prognostic information for gastric cancer. However, it has been demonstrated that increasing tumor markers is associated with recurrence (3,10). On the other hand, Nam et al provided a different point of view and showed that early CEA and CA 19-9 normalization after radical gastrectomy was significantly associated with disease-free survival and overall survival (5).

Long term follow-up results of the Dutch D1D2 trial D2 lymphadenectomy has shown that D2 surgery was associated with lower locoregional recurrence and gastric-cancer-related death rates than D1 surgery. However, it was also associated with higher mortality and morbidity rates (6). Currently, D2 lymphadenectomy is the type of surgery recommended for curable gastric cancer.

In the present study, we investigated any possible relation between the changes in tumor marker levels and lymph node dissection levels in gastric cancer since both of these parameters may be prognostic for the gastric cancer.

In the present study, there were not any difference in the number of the metastatic lymph nodes and in the tumor stages between the groups. We did not observe any difference in the preoperative and postoperative tumor marker levels

as well. We believe that this was probably caused by the ununiform distribution of the tumor marker levels which were in a wide range. The preoperative positivity rates of CEA and CA 19-9 were 21.8% and 33.6% in consistency with previous studies in which the rates were between 20.2-25% and 25-52%, respectively (5). Based of all these researches, we investigated all changes in tumor marker levels without ignoring the normal preoperative values instead of using only the response in increased tumor marker levels.

Nom et al have suggested that since CEA and CA19-9 act as intercellular adhesion molecules and cells expressing these glycoproteins may have greater invasive potential, the early normalization of tumor markers might be correlated with successful radical operation (5). This suggestion seems to be consistent with our study in which the reduction rates in CA19-9 levels were significantly greater in group D2 compared to group D1. Further investigation also showed that the difference was actually significant only in stage III locally advanced gastric cancer in which more metastatic lymph nodes were expected to exist.

The major limitation of our study was the setting. The optimal staging of gastric cancer can be done with D2 dissection, therefore the staging in D1 and D1+ groups may be defective. Additionally, the groups were not similar and the surgeons in our clinic have the tendency of performing D1 dissection in older patients with relatively worse health status. Besides, small sample size was another limitation.

As a result, it has been observed that differences in perioperative tumor marker changes between the dissection groups in gastric cancer patients. D2 lymphadenectomy was associated greater reduction rate in CA 19-9 levels. Further studies may provide a better understanding of the relations between the tumor markers and the dissection levels.

## REFERENCES

- 1- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17(6):1471-4.

- 2- Reiter W, Stieber P, Reuter C, et al. Prognostic value of preoperative serum levels of CEA, CA 19-9 and CA 72-4 in gastric carcinoma. *Anticancer Res* 1997;17(4B):2903–6.
- 3- Takahashi Y, Takeuchi T, Sakamoto J, et al. The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study. *Gastric Cancer* 2003;6(3):142–5.
- 4- Marrelli D, Roviello F, De Stefano A, et al. Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. *Oncology* 1999;57(1):55–62.
- 5- Nam DH, Lee YK, Park JC, et al. Prognostic value of early postoperative tumor marker response in gastric cancer. *Ann Surg Oncol* 2013;20(12):3905–11.
- 6- Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11(5):439-49.
- 7- Fan B, Xiong B. Investigation of serum tumor markers in the diagnosis of gastric cancer. *Hepatogastroenterology* 2011;58(105): 239–45.
- 8- Dilege E, Mihmanli M, Demir U, et al. Prognostic value of preoperative CEA and CA 19-9 levels in resectable gastric cancer. *Hepatogastroenterology* 2010;57(99-100):674–7.
- 9- Song YX, Huang XZ, Gao P, et al. Clinicopathologic and prognostic value of serum carbohydrate antigen 19-9 in gastric cancer: A Meta-Analysis. *Dis Markers* 2015;2015:549843.
- 10- Kim DH, Oh SJ, Oh CA, et al. The relationships between perioperative CEA, CA 19-9, and CA 72-4 and recurrence in gastric cancer patients after curative radical gastrectomy. *J Surg Oncol* 2011;104(6):585–91.