







# RADICAL SURGERY IN EARLY STAGE GASTRIC CANCER: SINGLE CENTER EXPERIENCE

## ERKEN EVRE MİDE KANSERİNDE RADİKAL CERRAHİ: İSTANBUL ÜNİVERSİTESİ TIP FAKÜLTESİ HASTANESİ DENEYİMİ

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### ABSTRACT

**Objective:** This study was performed to determine the overall early stage gastric cancer (ESGC) prevalence and to evaluate the short and long-term postoperative outcomes of patients with ESGC who underwent radical surgery.

**Method:** All 391 gastric cancer patients who underwent radical surgery between 2006 and 2013 were included in the study. Thirty nine patients who were diagnosed with ESGC were evaluated retrospectively in terms of demographics, pathological findings and clinical outcomes.

**Results:** Thirteen (33%) patients had morbidity and mortality rates of zero. The depth of tumor invasion was submucosal in 26 (67%) patients, intramucosal in 13 (33%). Eleven (28%) patients had lymph node involvement. While lymph node involvement rate in intramucosal tumors was 14%, the rate rose up to 34.6% in submucosal tumors. The average follow-up period was 73.6 months. The long term outcomes in 4 (10%) patients had a recurrence and 3 (7.5%) patients died. Thirty-five (%89.7) patients are being monitored tumor-free at the time of publication.

**Conclusion:** When compared to Asian countries, the prevalence of ESGC was lower in our study. However, lymph node involvement in ESGC was higher. Only 1.8% of patients were found appropriate for endoscopic resection according to the Japanese Endoscopic Treatment Guidelines. In line with these data, we find that radical surgery is an appropriate treatment choice for ESGC in our country.

**Keywords:** Early stage of gastric cancer, metastatic lymph nodes, radical surgery

### ÖZET

**Amaç:** Mide kanseri nedeniyle radikal cerrahi uygulanan olgular arasında erken evre mide kanseri sıklığı ve bu olgularda postoperatif erken ve geç dönem sonuçlarının değerlendirilmesi amaçlanmıştır.

**Yöntem:** Bu çalışmada 2006–2013 yılları arasında mide kanseri nedeniyle radikal cerrahi uygulanan 391 olgudan, histopatolojik değerlendirme sonucunda erken evre mide kanseri saptanan 39 olgunun demografik verileri, patolojik bulguları ve klinik sonuçları retrospektif olarak incelenmiştir.

**Bulgular:** Morbidite 13 (%33) hastada izlenirken, mortalite görülmedi. İnvazyon derinliği olguların 26'sında (%67) submukozal, 13'ünde (%33) intramukozal idi. Hastaların 11'inde (%28) lenf nodu metastazı saptanmıştır. İnteramukozal yerleşimli tümörlerde lenf nodu metastazı oranı %14'iken submukozal tümörlerde bu oran %34,6'ya çıkmaktaydı. Ortalama takip süreleri 73,6 ay (48-111 ay) idi. Uzun dönem takiplerinde 4 olguda (%10) hastalık nüksü saptanırken 3 olgu (%7,5) eks olmuştur. Olguların 35'i (%89,7) hastaliksız olarak takip edilmektedir.

**Sonuç:** Uzak Doğu Ülkelerine kıyasla, çalışmamızda erken evre mide kanseri prevalansı daha düşük olarak bulunmuştur. Bununla birlikte, erken evre mide kanserinde lenf nodu tutulumunun daha yüksek olduğu saptanmıştır. Japon Endoskopik Tedavi Kılavuzuna göre hastaların sadece %1,8'i endoskopik rezeksiyona uygun bulunmuştur. Bu veriler doğrultusunda, ülkemizde radikal cerrahinin erken evre mide kanseri için en uygun tedavi seçeneği olduğunu düşünüyoruz.

**Anahtar Kelimeler:** Erken evre mide tümörü, metastatik lenf nodu, radikal cerrahi

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## INTRODUCTION

Early gastric cancer (adenocarcinoma) is defined as invasive gastric cancer that invades no more deeply than the submucosal layer, irrespective of lymph node metastasis (T1, any N) (1-3). Thanks to screening programs conducted due to commonly seen tumors in Far East countries such as Japan, Korea and China, the incidence of gastric cancer that is detected in early stages has increased and early stage gastric cancer is detected in 50% of the resections that are made because of a stomach tumor (3-6). The incidence of early gastric cancer in western countries without screening programs are lower and about 15-21% (3,7,9). Depending on the experience and clinical approach between centers, there is a wide range of treatment modalities such as endoscopic resections (endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD)) and radical surgery (radical gastrectomy), which are applied for the treatment of early gastric cancer (10,11). In our study, we aimed to assess the frequency of early stage gastric cancer in patients who had radical resection because of gastric cancer, their early postoperative follow-up results and long-term results.

## MATERIALS AND METHODS

All patients who underwent radical resection because of gastric cancer between 2006–2013 were included in the study. All patients' information was acquired from the clinical database. Thirty-nine patients were detected as early stage gastric cancer through histopathological evaluation from the 391 cases that underwent radical surgery. All patients' demographics, tumor localization site, surgical procedures, morbidity, mortality, pathological data and survival analysis were retrospectively evaluated.

## RESULTS

In our clinic, 516 patients were treated with a diagnosis of gastric cancer and radical surgery was performed on 391 of these patients who were diagnosed with adenocarcinoma through histopathology results. In the 391 patients who were hospitalized due to gastric cancer, the female/male ratio was 1:1.48 and tumors were located in the antrum in 140 cases (35.8%), in the corpus in 187 cases (47.8%), and in the cardia region in 58 cases (14.8%). Linitis plastica was detected in six patients (1.6%). In the pathological examinations of the 391 patients, 39 patients (10%) were detected as having early stage gastric cancer. Twenty-five of these patients were men (64%) and 14 were female (36%). The average age was 59 years (31-89 years). Tumor locations were in the antrum in 21 of the patients (54%), in the corpus in 14 of the patients (36%), and in the cardia region in four of the patients (10%). Twenty of the patients (51%) had distal radical gastrectomy, and 19 of the patients (49%) underwent total radical gastrectomy surgery. During surgery, seven (18%) of the patients

were had additional procedures performed. Two patients underwent splenectomy, one patient had a liver biopsy, one patient had a cholecystectomy, one patient underwent splenectomy and cholecystectomy, one patient had partial small bowel resection and one patient had partial nephrectomy performed due to a renal tumor. Postoperatively, 13 (33%) patients were observed with morbidity, but with no mortality. The causes of morbidity are shown in Table 1. In three (7.5%) of the patients with morbidity, relaparotomy was performed and in two (5%) of the patients, percutaneous drainage was performed by interventional radiology because of intra-abdominal fluid collection. Other cases were followed with conservative methods such as the use of antibiotic therapy, restriction of oral intake and nasogastric decompression.

The average duration of hospital stay was nine (5-24) days. Tumor types were identified histopathological examinations to be adenocarcinoma in 22 cases (56%), mucinous adenocarcinoma in 15 patients (38%), signet ring cell carcinoma in one patient (3%), and one patient (3%) was identified as having medullary carcinoma. The depth of invasion was submucosal in 26 (67%) cases and intramucosal in 13 (33%) cases. The average tumor size was 3.34 cm (0.4 to 8 cm). The average number of dissected lymph nodes was 32 (13-77). Lymph node metastasis was not detected in 28 (72%) of the patients, and lymph node metastasis was detected in 11 (28%) of the patients. The average number of metastatic lymph nodes was 4.6 (1-20). The lymph node metastasis detection rate in intramucosal localized tumors was 15% (2/13), while the detection rate in submucosal tumors increased to 35% (9/26). The mean follow-up period was 77 months (range 48-111 months) in our study. During long-term follow-up, disease recurrence was detected in four patients (10%), and three patients (7.5%) died due to several reasons. Two of the patients who died were lost due to systemic diseases and the other one was lost because of a stroke. Another patient who had systemic diseases continues treatment with chemotherapy and is still alive. 90% of pa-

**Table 1:** Complications

	n	%
Intra abdominal abscess	5	13
Pneumonia	2	5
Subileus	1	2.5
Enterocutaneous fistula	1	2.5
Cystic stump leak	1	2.5
Thrombocytopenia	1	2.5
Urinary tract infection	1	2.5
Wound site infection	1	2.5

tients (n=35) are being monitored as free of disease at the time of publication.

## DISCUSSION

Radical gastrectomy is the only method that has been proven for its efficacy in the treatment of early stage gastric cancer, but there are also centers world-wide that practice minimally invasive procedures such as EMR and ESD, for early stage gastric cancer. Gastric cancer patients are detected at an earlier stage through national screening programs being carried out in countries such as Japan, where high incidence and high prevalence of gastric cancers occurs. In cases of early gastric cancer, which are appropriate in tumor size, histology and

have a low ratio of metastatic lymph node, application of minimally invasive treatment methods is reasonable. The application criteria for the endoscopic treatment options are set out in the National Endoscopic Treatment Guide of Japan (Table 2) (10). In a study at the National Center Cancer Hospital and Cancer Institute in Japan, 5265 patients who had gastrectomy and lymph node dissection because of early stage gastric cancer were examined retrospectively (12,13). The aim of this study was to determine the nine clinicopathological factors such as the depth of invasion, histological type, tumor size and the presence of ulcers, that would be useful for predicting lymph node metastasis existence before the procedure. Metastatic lymph node involvement was not detected

**Table 2:** Endoscopic treatment criteria (Guidelines of Japanese Gastric Cancer Treatment) (10)

Absolute criteria (all criteria must be met)	Extended criteria
Adenocarcinoma (well-differentiated histologic type)	pT1a one of the following criteria:
The lack of ulcer presence	Differentiated, non-ulcerated, ≤2cm in diameter adenocarcinoma
Clinically T1a (tumor limited to the mucosa)	Differentiated, with ulcers, ≤3cm in diameter adenocarcinoma
Tumor ≤2 cm in diameter	Undifferentiated, non-ulcerated, ≤2cm in diameter adenocarcinoma

Note: Expanded Criteria is for ESD indication.

**Table 3:** Clinicopathological parameters associated with metastatic lymph nodes (14)

	Total	LN (+)	LN (-)	%	P-value
<b>Gender</b>					
Male	2057	254	1803	12,3	NS
Female	1786	250	1536	14,0	NS
<b>Tumor localization</b>					
Superior 1/3	345	49	296	14,2	
Mid 1/3	2586	310	2276	12,0	
Inferior 1/3	912	145	767	15,9	0,009
<b>Tumor depth</b>					
Mucosa	2163	105	2058	4,9	
Submucosa	1680	399	1281	23,8	<0,0001
<b>Tumor size</b>					
≤20 mm	1107	77	1030	7,0	
≥21 mm	2736	427	2309	15,6	<0,0001
<b>Presence of ulcers</b>					
Non-present	1319	167	1152	12,7	
Present	2524	337	2187	13,4	NS
<b>Lymphovascular involvement</b>					
Non-present	3266	249	3017	7,6	
Present	577	255	322	44,2	<0,0001

in tumors that were smaller than 3 cm in diameter, well differentiated, independent of the presence of an ulcer (n=1230), in non-ulcerated tumors (n=929) or in tumors that were well differentiated, smaller than 3 cm in size, and where lymphovascular invasion was undetected and confined to the submucosa (n=145).

By the results of the aforementioned study, it is shown that lymphovascular spread is associated with lymph node metastasis in intramucosal tumors with a tumor size greater than 3 cm and in all submucosal tumors independent of the tumor size (14). In another study at the same institution, 13.1% of 3843 patients who underwent gastrectomy and lymph node dissection due to the early stages of undifferentiated tumor were detected with lymph node metastasis, and the lymph node metastasis was shown to be associated with tumor depth and size of the tumor (Table 3). Lymph node metastasis was observed in 4.9% of undifferentiated tumors that were limited to the mucosa, while lymph node metastasis was seen in 23.8% of tumors with a submucosal site. In this study, lymph node metastasis was not detected in the undifferentiated early stage gastric tumors that were located intramucosally, smaller than 2 cm in size, non-ulcerated, and free of lymphovascular invasion.

Based on these two studies Japan's National Endoscopic Treatment Guidelines was developed (10). In our study, a lymph node metastasis rate in 39 patients who were diagnosed with early stage gastric cancer and had total gastrectomy performed was determined to be 28%. This ratio rose to 35% for tumors with submucosal invasion. These results are higher than metastatic lymph node rates identified by Gotoda and Hirasawa (13,14). However, compared with publications from Japan that contain higher numbers of patients, the rate of early stage gastric cancer cases in our study is low and this leads to bias. These results support the view suggesting that there may be differences in gastric cancer tumor biology and environmental factors between Far East countries and Western countries.

In Paris, in 2002, at the consensus conference for the feasibility of Japanese Endoscopic Classification and the endoscopic superficial cancer classification (early stage gastric tumors that are invading submucosa) were classified as sm1 and sm2. The cut-off value that is used to

determine the depth of invasion between sm1 and sm2 is defined as 500 $\mu$ , and when the cases with invasion less than 500 $\mu$  are compared to the cases exceeding this limit, it is observed that there are fewer lymph node metastases (5.66% vs. 20.70%). The rate of metastatic lymph nodes is also associated with the tumor diameter size other than the submucosal cut-off value. It was noted that an increase in tumor diameter size also significantly increases the rate of lymph node metastasis (15). Also, one of the limitations of our study is that the submucosal depth was undefined and that is why not mentioned. For this reason, an assessment could not be made in terms of grading the depth of invasion in submucosal tumors in our study.

The most comprehensive publication comparing EMR (n=172) and radical gastrectomy (n=379) where both were performed because of an early stage gastric cancer, is a retrospective study involving 551 cases. In this study, where the follow-up period was above 80 months, recurrence was observed in only two patients who were applied EMR (1.2%) and in four patients who underwent total radical gastrectomy (1.1%) (p=0.85). As a result of this study, it has been shown that there is no significant difference in survival rates between patients treated with EMR and patients who underwent gastrectomy (Table 4) (16).

In our study, from 39 patients, one patient died in the first year, and one patient died due to systemic disease in the second year (5%). Even though we perform radical surgical procedures because of early stage gastric cancer, our recurrence rate was 10% (n= 4) which is much higher than the loco-regional recurrence rate that Choi detected after endoscopic treatment, which was 1.2%. This result also suggests that there are other factors affecting the tumor spread.

Another result of Choi's research is that even though the incidence rates of complications is similar in the groups who underwent EMR and surgery, metachronous gastric cancer is more common in patients who are treated with EMR (5.8% vs. 1.1%; p=0.002) (16). In previously conducted studies, the risk of metachronous cancer development after endoscopic resection because of a gastric cancer was shown to be 2.5 – 14% in the first 10 years after the procedure (17). Many factors such as microsatellite insta-

**Table 4:** Long-term outcomes of EMR and gastrectomy (16)

	Matched cohort (n=551)			
	EMR (n=172)	Surgery (n=379)	Risk rates (%95)	P-value
Number of deaths	31 (%18)	56 (%14,8)	1,39 (0,87-2,23)	0,17
Recurrence	2 (%1,2)	4 (%1,1)	1,18 (0,22-6,35)	0,85
Metachronous gastric cancer	10 (%5,8)	4 (%1,1)	6,72 (2,0-22,6)	0,002

bility, intestinal claudine positive cancers, *Helicobacter pylori*, and high pepsinogen II values in blood have been tested to see if they can be predictive in metachronous cancer development. But research is dominated by the idea that the most important reason is the synchronous early stage gastric cancer that is not detected during the first resection due to its histopathological and morphological features. Because of this reason, metachronous gastric cancer does not occur in the follow-ups that are more than 10 years.

In addition, some of the patients who underwent endoscopic resection required radical surgery in the early post-operative period for different reasons. In Korea University Hospital, 2006-2010, Lee et al. had to perform radical gastrectomy for several reasons (such as incomplete resection, bleeding, metachronous cancer, recurrence and perforation) in 29 (6%) of 481 cases who underwent EMR and/or ESD due to early stage gastric cancer. Lymph node metastasis was detected in 23% of 13 patients (n=3) who had radical surgery because of an incomplete resection (18).

There is still no consensus about the use of standardized criteria (Table 2) of endoscopic treatment methods i.e. EMR and ESD for early stage gastric cancer in compatible patients between Far East countries and Western countries. It is known that gastric cancer incidence, prognosis and survival rates may be related to racial factors (19). The prognosis of patients who have had treatment because of the same stage gastric cancer in Germany and Japan have been found to be different regarding overall survival or disease-free survival rates. The 2-year and 5-year survival results of patients from two different countries were shown to be significantly in favor of Japanese patients (88% vs. 58% and 77% vs. 44%) (19). One of the most important prognostic factors to affect the results was ascertained to be the center itself where the operations took place. Furthermore, there is significant difference observed in terms of clinical data, such as lymph node metastasis and local recurrence rate after endoscopic resection among the patients with Far East origins who immigrated to the US and were born and raised there, and the compatriots of them who are living in the Far East countries (3). These results suggest that environmental factors such as eating habits, air pollution, stress and regional factors contribute to the prognosis of gastric cancer. Another problem appearing with the endoscopic treatment options (EMR/ESD) is that these approaches require expert experience. This could be due to the lower incidence of gastric cancer, the lack of a national screening program and fewer encounters with the early stage gastric cancer in Western countries. Another concern is that in our country and in Western countries, follow-ups (i.e. a national endoscopic follow-up program) are inadequate for patients who undergo endoscopic therapy with the presence of a possible meta-

chronous cancer, incomplete resection or unknown lymph node metastasis.

In another study, clinical-pathological parameters that determined lymph node metastasis of 126 patients who were diagnosed with early stage gastric cancer, were analyzed (20). At the end of the study, the only significant parameter predicting the presence of lymph node metastasis in early stage gastric tumors was found to be tumor budding. Detection of tumor budding in a patient with an early stage gastric cancer who has undergone an endoscopic process, can be a parameter for predicting lymph node metastasis.

In addition, when 39 patients in our series who underwent total gastrectomy because of early stage gastric cancer were evaluated retrospectively, only 7 (17.5%) patients were found to be actually eligible for endoscopic therapy according to the criteria specified in Japan's National Endoscopic Treatment Guidelines. Considering the entire study, this rate was reduced to 1.8% (7/391). Regarding the higher lymph node metastasis rates in early stage gastric tumors in our country's conditions, we believe that radical gastrectomy is the appropriate treatment option.

## CONCLUSION

Detection of early stage gastric cancer and endoscopic treatment appliance rates are high in Far East countries, where screening programs are carried out intensively because of the high incidence rate of gastric cancer. In our study, lymph node metastasis rates were found to be greater than the specified number obtained from the Far East countries. In this single-centered study, the proportion of patients that could have been treated by endoscopic surgery in accordance with the criteria of Japan's National Endoscopic Treatment Guideline is below 2%. Regarding the given data, we believe that the treatment for early stage gastric tumors is still radical surgery, currently in our country.

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