

Prognostic Significance of Extracapsular Invasion in Gastric Cancer

Mide Kanserlerinde Ekstrakapsüler Invazyonun Prognostik Önemi

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Öz

Amaç: Bu çalışmanın amacı, mide kanserinde ekstrakapsüler invazyonun prognostik önemi ve klinikopatolojik verilerle ilişkisini araştırmaktır.

Hastalar ve Yöntem: 2013-2020 yılları arasında total ve subtotal gastrektomi yapılan toplam 190 primer mide kanseri hastası çalışmaya dahil edildi. Hastaların 133'ü (%70)'ü erkek, 57'si (%30) kadındı. Metastatik lenf nodu kapsülünün dışına tümör hücrelerinin invazyonunun saptanması ekstrakapsüler invazyon olarak tanımlandı ve bunun yanısıra histolojik tip, lenf nodu pozitifliği, lenfovasküler ve perinöral invazyon, invazyon derinliği ve metastatik lenf nodu sayıları değerlendirildi.

Bulgular: 136 (%71.4) hastada lenf nodu metastazı saptandı. Bunların 87'sinde (%64) ekstrakapsüler invazyon izlendi. Ekstrakapsüler invazyonlu olguların 36'sı (%65,5) diferansiye, 51'i (%63) andiferansiye idi ve sırasıyla 68 (%68) ve 80 (%68,4) olguda perinöral - lenfovasküler invazyon görüldü. Perinöral invazyon (p=0.01), lenfovasküler invazyon (p=0.008), invazyon derinliği (p=0.001) ve metastatik lenf nodu sayısı (p=0.001) ile ekstrakapsüler invazyon arasında istatistiksel olarak anlamlı bir ilişki gözlemlendi. Ekstrakapsüler invazyon cinsiyet, histolojik tip ve rezeksiyon tipi ile ilişkili değildi. Çok değişkenli analizde mide kardias yerleşimli tümörlerde ekstrakapsüler invazyon olma riski 5,501 kat, perinöral invazyon olanlarda ise ekstrakapsüler invazyon olma riski 11,44 kat daha fazla olduğu gözlemlenmiştir.

Sonuç: Ekstrakapsüler invazyon görülen vakalar kötü prognostik parametrelerle ilişkilidir. Mide kanserlerinin gelecekteki evreleme sistemine ekstrakapsüler invazyon durumu dahil edilmeli ve patoloji raporları ekstrakapsüler invazyon durumu hakkında bilgi içermelidir.

Anahtar Kelimeler: Ekstrakapsüler invazyon, lenf nodu metastazı, mide kanseri

Abstract

Aim: The aim of this study was to investigate the prognostic significance of extracapsular invasion and its relationship with clinicopathological data in gastric cancer.

Patients and Methods: A total of 190 patients with primary gastric carcinoma underwent total and subtotal gastrectomy between 2013 and 2020 were included in the study. 133 (70%) were men, and 57 (30%) were women. Tumour invasion beyond the lymph node capsule was diagnosed as extracapsular involvement. and evaluated in addition to histological type, lymph node positivity, lymphovascular and perineural invasion, depth of invasion, and numbers of lymph node metastasis.

Results: 136 patients (71.4%) had lymph node metastasis. Of these, 87 patients (64%) had extracapsular invasion. Of the cases with extracapsular invasion, 36 (65.5%) were differentiated and 51 (63%) were undifferentiated and perineural - lymphovascular invasion was seen in 68 (68%) and 80 (68.4%) cases, respectively. A statistically significant association was observed with extracapsular invasion in terms of perineural invasion (p=0.01), lymphovascular invasion (p=0.008) and depth of invasion (p=0.001) and number of metastatic node (p=0.001). Extracapsular invasion was not associated with sex, histological type, and resection type. In the multivariate analyse, the risk of extracapsular invasion is 5,501 higher in those with cardia localization. Those with perineural invasion have an 11,44 higher risk of having extracapsular invasion.

Conclusion: Cases with extracapsular invasion are associated with poor prognostic parameters. It should be included in the future staging system of gastric cancers and pathology reports should include information about extracapsular invasion.

Key words: Extracapsular invasion, lymph node metastasis, gastric cancer

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INTRODUCTION

Gastric cancer is common as it is the second most causing mortality following lung cancer. (1-3). Survival rates are poor due to its biological aggressiveness when the diagnosis is missed especially in countries without specific screening programs. Defining the prognostic factors, characteristics of patients and the recurrence risks are very important in the treatment process which involvement of lymph node with metastasis and extensive dissection of it is has a direct effect on survival (4, 5). The TNM is widely accepted classification system of gastric cancer for determining treatment strategy and options as well as prognosis (6). TNM staging is done according to metastatic lymph node number (pN stage) (7), however prognosis may differ in the same stage which some patients are cured by surgery, some have recurrence even after adjuvant therapy. Staging system including prognostic factor that can identify patients for a higher risk of recurrence may provide a steady classification to adequately depict cancer prognosis (6). Extracapsular invasion (ECI) of lymph node metastases is a very important prognostic factor in

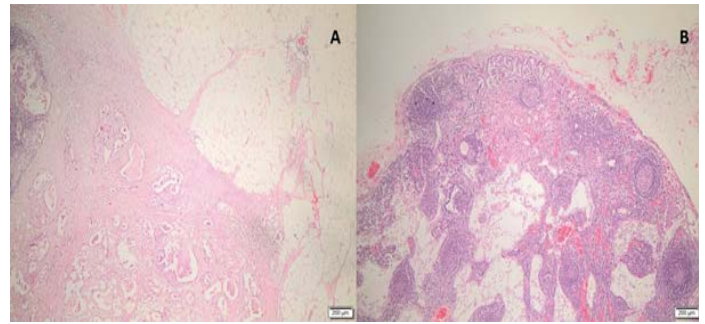


Figure 1. A. Tumor cells infiltration of extranodal adipose tissue beyond the capsule of the lymph node (ECI-positive) (HEx40). B. A metastatic lymph node without extracapsular invasion (ECI-negative) (HEx40).

cancer progression, however any other classification systems did not evaluate the histological features of lymph node metastases (8-15). Prognostic value of ECI in gastric cancer have only been reported in few studies (2, 4, 6, 16-18). Therefore, the aim of this

Table 1. Patient demographics and Histopathological Characteristics

	Lymph node metastases		Negative	Positive	p value
Gender					
	Male	n (%)	36 (27,1%)	97 (72,9%)	0,528
	Female	n (%)	18 (31,6%)	39 (68,4%)	
Lauren Classification					0,26
	Diffuse	n (%)	8 (21,1%)	30 (78,9%)	
	Intestinal	n (%)	46 (30,3%)	106 (69,7%)	
Histological type					0,002**
	Differentiated	n (%)	35 (38,9%)	55 (61,1%)	
	Undifferentiated	n (%)	19 (19,0%)	81 (81,0%)	
Localization					0,971
	Lower	n (%)	17 (27,4%)	45 (72,6%)	
	Middle	n (%)	30 (28,8%)	74 (71,2%)	
	Upper	n (%)	7 (29,2%)	17 (70,8%)	
Perinoral invasion					0,001**
	No	n (%)	37 (50,7%)	36 (49,3%)	
	Yes	n (%)	17 (14,5%)	100 (85,5%)	
Lymphovascular invasion					0,001**
	No	n (%)	30 (61,2%)	19 (38,8%)	
	Yes	n (%)	24 (17,0%)	117 (83,0%)	
Resection type					0,069
	Subtotal	n (%)	22 (37,3%)	37 (62,7%)	
	Total	n (%)	32 (24,4%)	99 (75,6%)	
pT (Depth of invasion)					0,001**
	pT1	n (%)	18 (72,0%)	7 (28,0%)	
	pT2	n (%)	14 (50,0%)	14 (50,0%)	
	pT3	n (%)	12 (24,5%)	37 (75,5%)	
	pT4	n (%)	10 (11,4%)	78 (88,6%)	
Metastasis					0,993
	No (-)	n (%)	52 (28,4%)	131 (71,6%)	
	Yes (+)	n (%)	2 (28,6%)	5 (71,4%)	
Extracapsular invasion					
	No (-)	n (%)	0 (0,0%)	49 (100%)	
	Yes (+)	n (%)	0 (0,0%)	87 (100,0%)	

**p<0,01

present study was to investigate correlations between extracapsular invasion (ECI) of nodal metastases with clinicopathological parameters and to determine whether ECI can be used as a prognostic factor in gastric cancer.

PATIENTS AND METHODS

We designed a retrospective study in a cohort of patients who had undergone gastric resection and regional lymphatic node dissection for primary gastric carcinoma at our institution between 2013 and 2020. Resected specimens including lymph nodes and its surrounding adipose tissue were evaluated and these formalin fixed parafin embedded and hemotoxylin-eosin stained tissues were all grouped. Gastric stump localized carcinoma, patients having another malignancy besides gastric carcinoma and/or chemotherapy treatment history were excluded from the study. Location of tumour was grouped as upper, middle and lower third of stomach. Primary tumour and regional lymph nodes slides were reviewed by pathologists and histologically; well-moderately differentiated tubular and papillary adenocarcinoma were grouped as differentiated; poorly differentiated

tubular, signet cell, and mucinous adenocarcinoma, and other types were grouped as undifferentiated tumours. Eight edition of the American Joint Committee on Cancer staging system (AJCC) were used to define the tumour invasion depth and lymph node metastasis (7, 19). In addition, International Union Against Cancer staging system (UICC) were used to determine the nodal status. Hematoxylin eosin stained lymph node sections were re-analyzed to define the existence of ECI. ECI was defined as cancer cells infiltration and extension beyond the lymph node capsule (Fig. 1A, 1B). An imaginary line symbolizing the original lymph node capsule was drawn in circumstances that the pre-existing lymph node capsule was difficult to identify. Tumour emboli in lymphatic channels (afferent or efferent) outside the lymph node capsule were not considered as ECI or direct invasion of tumour into a lymph node. Lymphovascular invasion (LVi) was present when tumour cells were identified in a tubular space lined by endothelial cells or inside a vascular wall structure. Perineural invasion was diagnosed when malignant cells were present in the perineural space. When extracapsular invasion was detected in one or more of the metastatic lymph nodes, it was

Table 2. Clinicopathological characteristics of patients with lymph node involvement with and without ECI

			Extracapsular invasion		p value
			Negative	Positive	
Gender	Male	n (%)	3 (34,0%)	64(66,0%)	0,442
	Female	n (%)	16(41,0%)	23(59,0%)	
Lauren Classification	Diffüz	n (%)	9(30,0%)	21(70,0%)	0,436
	Intestinal	n (%)	40(37,7%)	66(62,3%)	
Histological type	Differentiate	n (%)	19(34,5%)	36(65,5%)	0,766
	Undifferentiate	n (%)	30(37,0%)	51(63,0%)	
Localization	Lower	n (%)	19(42,2%)	26(57,8%)	0,421
	Middle	n (%)	23(31,1%)	51(68,9%)	
	Upper	n (%)	7(41,2%)	10(58,8%)	
Perineural invasion	No	n (%)	17(47,2%)	19(52,8%)	0,01**
	Yes	n (%)	32(32,0%)	68(68,0%)	
Lymphovascular invasion	No	n (%)	12(63,2%)	7(36,8%)	0,008**
	Yes	n (%)	37(31,6%)	80(68,4%)	
Resection type	Subtotal	n (%)	16(43,2%)	21(56,8%)	0,284
	Total	n (%)	33(33,3%)	66(66,7%)	
pT (Depth of invasion)	pT1	n (%)	6(85,7%)	1(14,3%)	0,001**
	pT2	n (%)	9(64,3%)	5(35,7%)	
	pT3	n (%)	17(45,9%)	20(54,1%)	
	pT4	n (%)	17(21,8%)	61(78,2%)	
Metastasis	No (-)	n (%)	49(37,4%)	82(62,6%)	0,049*
	Yes (+)	n (%)	0(0,0%)	5(100,0%)	

**p < 0.05

Table 3. pN stage in patients with extracapsular invasion

		n (%)	pN stage			p value
			1	2	3	
Extracapsular invasion	No (-)	n (%)	23 (46,9%)	14 (28,6%)	12 (24,5%)	0,001**
	Yes (+)	n (%)	5 (5,7%)	16 (18,4%)	66 (75,9%)	

**p < 0.01

considered as ECI-positive. Ethical approval for this study was obtained from the Clinical Research Ethics Committee. (Decision number 05.10.2020, 97/02)

Statistical analysis

SPSS version 25.0 was used to analyze the data. Shapiro-Wilk test was used to determine whether continuous variables were normally distributed and the Levene test to evaluate the homogeneity of variances. The data are shown as the mean±standard deviation. In order to model the probability of ECI detection, Binary logistic regression was used. Categorical data were analyzed with Chi-Square and Fisher's Exact test. When the expected frequencies are less than 20%, "Monte Carlo Simulation method" included these frequencies in the analysis to evaluate. p<0.05 and p<0.01 was considered to be statistically significant.

RESULTS

A total of patients who had undergone total-subtotal gastrectomy for primary gastric carcinoma were included in the study. Ages ranged between 27 and 90 years with an average of 64.8 years. 133 (70%) were men, and 57 were women (30%). In 54 (28.6%) patients, metastasis of lymph node was not detected,

136 (71.4%) patients had lymph node metastasis. Significant difference was found to be between the histological type (p=0.02), lymphovascular invasion (LVi) (p=0.001), perineural invasion (PNI) (p=0.001), and depth of invasion (pT) (p=0.001) between the group with and without lymph node involvement. (Table 1). Among the patients with lymph node involvement, 87 (64%) patients had ECI, however in 49 (36%) patients ECI was not detected. Of the cases with ECI, 36 (65.5%) were differentiated and 51 (63%) were undifferentiated. Cases with ECI, PNI was not seen in 19 (52.8%) patients and PNI was seen in 68 (68%). While LVi was present in 117 cases, ECI was detected in 80 cases (68.4%) of LVi, however 7 (36.8%) cases had ECI without LVi. In cases with lymph node involvement, a statistically significant association was observed with extracapsular invasion in terms of PNI (p=0.01), LVi (p=0.008) and pT (p=0.001) (Table 2). According to the AJCC staging system, the numbers of lymph node metastasis in 1, 2, and 3 were 5 (5.7%), 16 (18.4%), 66 (75.9%), respectively in patients with extranodal extension. There is statistically significant difference between ECI and pN stage (p=0.001) (Table 3). The risk of Extracapsular Invasion is 5,501 higher in those with upper localization. Those with

Table 4. Multivariate Analysis

		p	Odds Ratio	95% C.I. for Odds Ratio	
				Lower	Upper
Sex		0,258	0,476	0,131	1,723
Lauren		0,813	1,211	0,248	5,907
Histological Type		0,287	4,731	0,27	82,924
Localization	Lower	0,08			
	Middle	0,487	2,034	0,275	15,066
	Upper	0,043*	5,501	0,981	30,842
Perineural invasion (PNI)		0,009**	11,444	1,846	70,956
Lenfovascular invasion (LVi)		0,168	0,322	0,064	1,612
pN stage	1	0			
	2	0	0,008	0,001	0,059
	3	0,008**	0,138	0,032	0,602
pT1		0,019			
pT2		0,565	2,289	0,136	38,496
pT3		0,892	1,216	0,072	20,395
pT4		0,104	11,909	0,6	236,221

perineural invasion (PNI) have an 11.44 higher risk of having Extracapsular Invasion (Table 4).

DISCUSSION

Extracapsular invasion describes the neoplastic cell extension beyond the lymph node capsule that extra-capsular growth in metastatic lymph nodes may be a factor for poor prognosis in many malignancies, such as gastric carcinoma. In the present study a relationship was seen between the presence of ECI and LVi, PNI, pT, and pN stage in patients with lymph node involvement significantly. ECI was found more frequently along with vascular invasion, perineural invasion, and pT-pN stages. It may be suggested that aggressive behavior is closely associated with the presence of ECI. Therefore metastatic lymph node specimens should be examined so carefully that ECI presence should be reported clearly in cases of gastric carcinoma with lymph node metastasis. The presence of ECI as a prognostic factor in patients with gastric carcinoma has been evaluated in only a few studies. Lee et al. was one of these authors reporting ECI as an independent risk factor in early and advanced gastric carcinoma for poor prognosis in association with perineural and lymphovascular invasion and increased lymph node metastasis (6). Tanaka et al. suggested that this extracapsular involvement may have a role in the development of peritoneal metastasis in gastric cancer patients (20). Okamoto et al. reported that ECI was an independent prognostic factor for survival in patients with gastric cancer and ECI was suggestive of tumor cell aggressiveness (18). In the study of Nakamura et al. and Di Giorgio et al. ECI was significantly related to N-stage, T-stage, increased number of resected lymph nodes and serosal invasion of the tumor (21, 22). The results are consistent with our findings. The presence of ECI could indicate that the tumor manifests a highly aggressive behaviour.

Extra-capsular growth may be a prognostic value in early and advanced gastric cancer and accurate macroscopic examination and sampling is a very important first step in examining the tissue. While performing gross sampling, in order not to miss an extranodal invasion, it is necessary to pay attention to sample the lymph node with its surrounding adipose tissue. A strict protocol have to be followed during gross sampling which may affect the histological results. It is important and advisable to sample and examine the each lymph node with its perinodal adipose tissue and not to sample only a portion of the

enlarged node. However, the size of the metastatic lymph node and its association with the presence of ECI are the facts which need to be investigated.

ECI reflects the sign of tumor dissemination through lymphatic spread with increased invasiveness and aggressive behaviour (23) and ECI may be recognized as a strong prognostic factor, such as T and N factors.

So that, the identification of ECI should be included in TNM classification, in addition to the presence of positive lymph nodes. According to our study and the previously performed studies, it can be concluded that the presence of ECI is an important factor that affects prognosis and must be included in the future revised staging systems.

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