

Are the type of gastrectomy and the presence of complications prognostic factors in patients with gastric cancer without lymph node involvement?

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Received: 2020-05-23

Accepted: 2020-05-30

UDC: 618.1

J Clin Med Kaz 2020; 4(58):23-27

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Abstract

Objective: Lymph node involvement is one of the leading prognostic factors in patients with gastric cancer without distant metastasis, although disease-related death also occurs in patients without lymph node involvement. The present study investigates whether gastrectomy type and complication presence is a prognostic factor in gastric cancer patients without lymph node involvement.

Material and methods: The data of 262 patients who underwent curative gastrectomy at our clinic between November 2006 and December 2018 was reviewed retrospectively.

Results: No lymph node involvement was identified in 33.2% of the patients who underwent curative gastrectomy, and survival in this group was better than in the patient group with lymph node involvement (75.9% vs. 32.6%). A comparison of the two groups revealed significant differences in terms of Borrmann's classification, Lauren classification, T stage, vascular invasion, perineural invasion, tumor diameter and total number of lymph nodes. Disease-related death occurs also in patients without lymph node involvement, with tumor diameter, T stage, gastrectomy type and the presence of complications all found to be factors affecting the risk of death.

Conclusion: Patients without lymph node involvement have a better prognosis, and aside from tumor diameter and T stage, the present study found gastrectomy type and the presence of complications to be prognostic risk factors.

Key words: negative lymph nodes, prognostic factors, gastric cancer, overall survival

ГАСТРЭКТОМИЯНЫҢ ТҮРІ ЖӘНЕ АСҚЫНУЛАРДЫҢ БОЛУЫ ЛИМФА ТҮЙІНІНІҢ ҚАТЫСУЫНСЫЗ АСҚАЗАН ҚАТЕРЛІ ІСІГІ БАР НАУҚАСТАРДА БОЛЖАМДЫ ФАКТОРЛАР БОЛЫП ТАБЫЛАДЫ МА?

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ТҰЖЫРЫМДАМА

Мақсаты: Лимфа түйіндерінің зақымдалуы метастаздарсыз асқазан қатерлі ісігі бар пациенттердің жетекші болжамды факторларының бірі болып табылады, дегенмен ауруға байланысты өлім лимфа түйінінің қатысуы жоқ пациенттерде де кездеседі. Осы зерттеу лимфа түйінінің қатысуынсыз асқазан қатерлі ісігі бар пациенттерде гастрэктомия түрі мен асқынулардың болжамды факторлары болып табылатындығын зерттейді.

Материалдар мен әдістер: 2006 жылдың қарашасы мен 2018 жылдың желтоқсан айы аралығында біздің клиникада емдік гастрэктомия жасаған 262 пациент туралы мәліметтер ретроспективті түрде қарастырылды.

Нәтижелері: Емдік гастрэктомиядан өткен науқастардың 33,2%-ында лимфа түйіндерінің таралуы анықталмады, және бұл топтағы өмір сүру деңгейі лимфа түйіндерінің қатысуымен ауыратындар тобына қарағанда жақсы (32,6%-ға қарсы 75,9%). Екі топты салыстыру кезінде Борманның жіктелуі, Лорен жіктелуі, Т сатысы, тамырлы инвазия, перинуральды инвазия, ісік диаметрі және лимфа түйіндерінің жалпы саны тұрғысынан айтарлықтай айырмашылықтар анықталды.

Ауруға байланысты өлім лимфа түйінінің қатысуымен, ісік диаметрімен, Т-сатысымен, гастрэктомия түрімен және өлім қаупіне әсер ететін факторлар ретінде көрсетілген асқынулармен ауыратын науқастарда да кездеседі.

Қорытынды: лимфа түйінінің қатысуы жоқ пациенттердің болжамдары жақсырақ, және ісік диаметрі мен Т сатысынан басқа, бұл зерттеу гастрэктомия түрі мен асқынулардың болуы қауіпті факторлар болып табылатындығын көрсетті.

Негізгі сөздер: лимфа түйінінің зақымдалуының болмауы, болжамды факторлар, асқазан қатерлі ісігі, жалпы өмір сүру

ЯВЛЯЮТСЯ ЛИ ТИП ГАСТРЭКТОМИИ И НАЛИЧИЕ ОСЛОЖНЕНИЙ ПРОГНОСТИЧЕСКИМИ ФАКТОРАМИ У ПАЦИЕНТОВ С РАКОМ ЖЕЛУДКА БЕЗ ПОРАЖЕНИЯ ЛИМФОУЗЛОВ?

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РЕЗЮМЕ

Цель: Поражение лимфоузлов является одним из ведущих прогностических факторов у пациентов с раком желудка без отдаленных метастазов, хотя смерть, связанная с заболеванием, также происходит у пациентов без поражения лимфатических узлов. Настоящее исследование рассматривает, является ли тип гастрэктомии и наличие осложнений прогностическим фактором у пациентов с раком желудка без поражения лимфоузлов.

Материалы и методы: Данные о 262 пациентах, которым была проведена лечебная гастрэктомия в нашей клинике в период с ноября 2006 года по декабрь 2018 года, были рассмотрены ретроспективно.

Результаты: Поражение лимфоузлов не выявлено у 33,2% пациентов, перенесших лечебную гастрэктомию, и выживаемость в этой группе была лучше, чем в группе пациентов с поражением лимфоузлов (75.9% vs. 32.6%). Сравнение двух групп выявило значительные различия с точки зрения классификации Бормана, классификации по Лорен, Т-стадии, сосудистой инвазии, перинеуральной инвазии, диаметра опухоли и общего количества лимфатических узлов. Связанная с болезнью смерть возникает также у пациентов без поражения лимфатических узлов с диаметром опухоли, Т-стадии, типом гастрэктомии и наличием осложнений, которые, как было установлено, являются факторами, влияющими на риск смерти.

Заключение: Пациенты без поражения лимфоузлов имеют лучший прогноз, и кроме диаметра опухоли и Т-стадии, настоящее исследование показало, что тип гастрэктомии и наличие осложнений являются прогностическими факторами риска.

Ключевые слова: отсутствие поражения лимфатических узлов, прогностические факторы, рак желудка, общая выживаемость

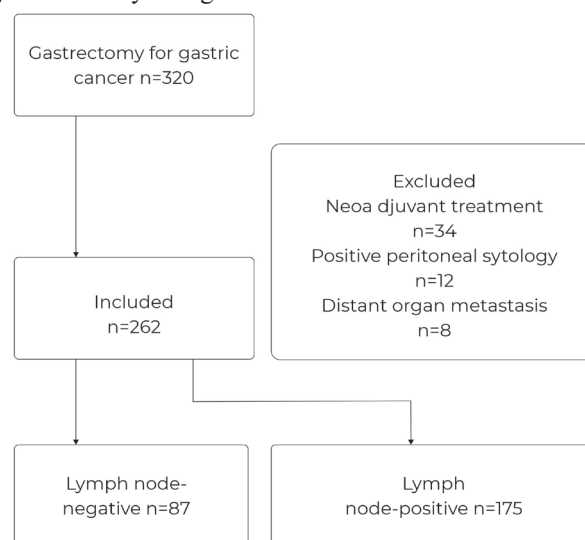
Introduction

Gastric cancer is one of the most common forms of cancer worldwide, ranking close to the top among cancer-related deaths. The optimum approach to treatment in locally-advanced gastric cancer involves multimodal management, including surgery, chemotherapy and chemoradiotherapy [1]. Gastrectomy and D2 lymphadenectomy are widely recognized as the standard surgical treatment for accurate staging and local disease control in locally-advanced gastric cancer [1,2]. The presence of lymph node metastasis is the leading prognostic factor in gastric cancer, with the absence of lymph node involvement being associated with improved overall survival. That said, recurrences or distant metastases occur in a significant proportion of these patients following curative surgery [3,4]. Although previous studies have indicated that the depth of tumor invasion is an important independent prognostic factor in gastric cancers without lymph node involvement, the other risk factors are still being debated [4,5]. The present study will evaluate age, gender, Borrmann's type, gastrectomy type, tumor localization, tumor diameter, tumor grade, T stage, total number of lymph nodes, stage, vascular invasion, perineural invasion and the presence of complications that may affect survival in lymph node-negative gastric cancer. In addition, the type of gastrectomy and the presence of complications will be investigated whether it is a prognostic factor.

Material and methods

A total of 320 patients who underwent a total or subtotal gastrectomy and D2 lymph node dissection in the Gastroenterological Surgery clinic at Kartal Koşuyolu High Specialty Training and Research Hospital between November 2006 and October 2018 due to a gastric adenocarcinoma were analyzed retrospectively (Figure 1). The cut-off date for the survival analysis was December 31, 2018. The D2 dissection was performed in accordance with the principles of the Japanese Research Society for the Study of Gastric Cancer (JRSSG) [6]. The Tumor, Node, Metastasis (TNM) classification system proposed by the American Joint Committee on Cancer (AJCC) (7th ed, 2010) was used in the present study. The data was obtained using the follow-up forms uploaded into the database of our clinic, and pathology results were recorded. Patients diagnosed with distant organ metastasis at the time of surgery (8 patients had liver metastasis), patients with a positive peritoneal cytology (12 patients), patients receiving neoadjuvant chemoradiotherapy (34 patients) and those who had positive

Figure 1 - Study Design



surgical margins (4 patients) were excluded from the study, even if they had undergone a gastric resection. A total of 262 patients were included in the final analysis. Complications occurring within 30 days of surgery were recorded as being surgery-related.

Statistical analysis

A Chi-square test, Fisher's exact test, and Mann-Whitney U test were used to analyze the differences in the study variables from the comparison of patients with and without lymph node involvement. A Kaplan-Meier analysis was used to identify any difference between lymph node-positive and lymph node-negative patients in terms of survival, and the risk factors affecting survival in lymph node-negative patients were investigated using a Cox regression analysis. SPSS 22 software was used for the statistical analysis, and the level of statistical significance was set at an alpha of 0.05.

Results

In this retrospective study, 262 patients underwent gastrectomy and D2 lymphadenectomy due to gastric cancer, of which 87 (33.2%) were lymph node negative and 175 (66.8%) were lymph node-positive. A comparison of the lymph node-negative and lymph node-positive groups revealed no significant difference in terms of gender, type of surgery, tumor localization, age and length of hospital stay. There were significant differences in terms of Borrmann's classification, Lauren histology, T stage,

vascular invasion, perineural invasion, tumor diameter and total number of lymph nodes. Of the patients without lymph node involvement, based on Borrmann's classification, 49.4% had ulceroinfiltrative lesions, compared to 67.7% in patients with positive lymph node involvement ($p<0.05$). Of patients without lymph node involvement based on the Lauren classification, 23.4% had a diffuse type, compared to 76.6% in patients with positive lymph nodes ($p<0.01$). Of the patients without lymph node involvement based on T stage, 14.9% had mucosal and 10.3% had submucosal lesions, and this rate was 0% in lymph node-positive patients. In patients with negative lymph nodes, 10.3% had serosal involvement, compared to 50.3% in lymph node-positive patients ($p<0.01$). Lymph node involvement was

negative in 81.4% of patients without vascular invasion, and positive in 84% of patients with vascular invasion ($p<0.01$). Lymph node involvement was negative in 60% of patients without perineural invasion, and positive in 80.6% of patients with perineural invasion ($p<0.01$). No complications were recorded in 86.2% of patients without lymph node involvement, and this rate was 68.6% in the lymph node-positive patients ($p<0.05$). The mean tumor diameter was 4.22 ± 2.90 cm in lymph node-negative patients and 5.86 ± 2.50 cm in lymph node-positive patients ($p<0.01$). The mean total number of removed lymph nodes was 23.99 ± 12.04 in lymph node-negative patients, which was lower than in the lymph node-positive patients (26.58 ± 11.84) ($p<0.05$) (Table 1).

Table 1 Comparison of clinicopathological characteristics between lymph node-positive and lymph node negative patients

| | Lymph Node Negative n(%) | Lymph Node Positive n(%) | |
|-------------------------------|-----------------------------|-----------------------------|---------|
| | | | .398b |
| Gender | | | |
| Male | 56 (64.4%) | 123 (70.3%) | |
| Female | 31 (35.6%) | 52 (29.7%) | |
| | | | .013c* |
| Borrmann's classification | | | |
| Polypoid | 12 (15.2%) | 19 (11.4%) | |
| Ulcerovegetative | 26 (32.9%) | 35 (21.0%) | |
| Ulceroinfiltrative | 39 (49.4%) | 113 (67.7%) | |
| Diffuse | 2 (2.5%) | 0 (0.0%) | |
| | | | .362b |
| Gastrectomy | | | |
| Subtotal | 48 (55.2%) | 86 (49.1%) | |
| Total | 39 (44.8%) | 89 (50.9%) | |
| | | | .000c** |
| Depth of invasion | | | |
| T1a | 16 (18.4%) | 0 (0.0%) | |
| T1b | 9 (10.3%) | 0 (0.0%) | |
| T2 | 17 (19.5%) | 10 (5.7%) | |
| T3 | 36 (41.4%) | 77 (44.0%) | |
| T4 | 9 (10.3%) | 88 (50.3%) | |
| | | | .000b** |
| Vascular invasion | | | |
| Negative | 70 (81.4%) | 28 (16.0%) | |
| Positive | 16 (18.6%) | 147 (84.0%) | |
| | | | .000b** |
| Perineural invasion | | | |
| Negative | 51 (60.0%) | 34 (19.4%) | |
| Positive | 34 (40.0%) | 141 (80.6%) | |
| | | | .002b** |
| Complications | | | |
| No | 75 (86.2%) | 120 (68.6%) | |
| Yes | 12 (13.8%) | 55 (31.4%) | |
| | Mean±SD | Mean±SD | |
| Age | 59.75±13.01 | 61.20±11.11 | .373a |
| Tumor diameter | 4.22±2.90 | 5.86±2.50 | .000b** |
| Number of removed lymph nodes | 23.99±12.04 | 26.58±11.84 | .033a* |
| Length of hospital stay | 11.08±6.09 | 14.10±14.06 | .092a |

** $p<0.01$ * $p<0.05$ a: Mann-Whitney U test p value b:Fisher's Exact test p value c:Chi Square test p value

Of the 87 patients (75.9%) without lymph node involvement, 66 survived, whereas 54 out of the 174 patients (32.6%) with lymph node involvement survived. There was a significant difference in survival between the study groups, as shown in Table 2 ($p<0.01$).

| Table 2 Evaluation of survival according to lymph node status using Kaplan-Meier analysis | | | |
|--|-----------------------------|-------------------|--------|
| Lymph node status | Mean | | |
| | Estimate (.median) \pm SE | 95% CI | p |
| Node Negative | 27.645 (15) \pm 2.530 | (22.685 - 32.604) | 0.002* |
| Node Positive | 19.865 (13) \pm 2.749 | (14.477 - 25.253) | |
| Overall | 24.185(14) \pm 4.054 | (16.240 - 32.131) | |

** $p<0.01$ CI: Confidence Interval

The mean survival of patients with negative lymph nodes was higher than that of patients with positive lymph nodes (27.645 (15) \pm 2.530 months vs.19.865 (13) \pm 2.749 months). Patient survival according to the lymph node status is presented in Figure 2.

Figure 2 - Comparison of survival according to the lymph node status

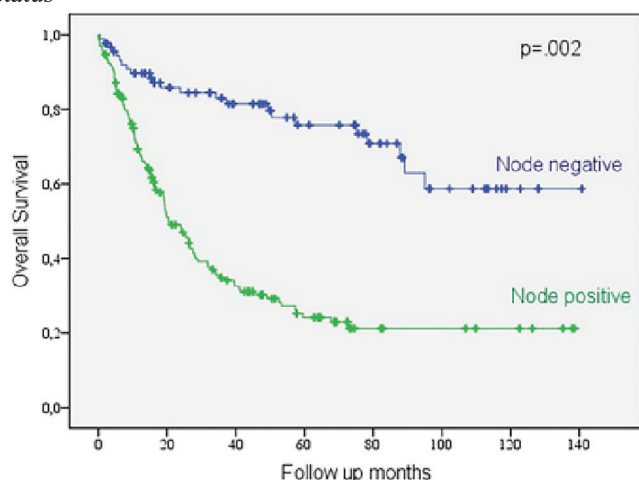


Table 3 Cox regression analysis of the effect of negative lymph node status on survival

| Variables | B \pm SE | OR (95% CI) | p |
|-------------------------------|--------------------|---------------------|---------|
| Gender | 1.343 \pm 1.040 | 3.832 (499-29.416) | 0.196 |
| Age | -0.055 \pm 0.035 | 0.946(0.884-1.013) | 0.113 |
| Borrmann's classification | 0.742 \pm 0.622 | 2.101-7.105) | 0.232 |
| Gastrectomy | -3.632 \pm 1.441 | 0.026(0.002-0.446) | 0.012* |
| Location | -0.869 \pm .884 | 0.419(0.074-2.371) | 0.325 |
| Tumor diameter | 0.338 \pm 0.119 | 1.402(1.110-1.771) | 0.005** |
| Lauren histology | -0.474 \pm .296 | 0.622(0.348-1.112) | 0.109 |
| Depth of invasion | 4.20 \pm 1.403 | 66.9(4.28-1046.91) | 0.003** |
| Number of removed lymph nodes | -0.085 \pm 0.039 | 0.919(0.850-0.992) | 0.031* |
| Vascular invasion | -0.754 \pm 1.118 | 0.471(0.053-4.210) | 0.500 |
| Perineural invasion | -1.620 \pm 0.935 | 0.198(0.032-1.237) | 0.083 |
| Complications | -4.165 \pm 1.849 | 0.0168(0.000-0.582) | 0.024* |

** $p<0.01$ * $p<0.05$ B: regression coefficient, SE: Standard error OR: odds ratio CI: confidence interval

The factors affecting survival in lymph node-negative patients were analyzed with a Cox regression analysis (Table 3). The type of surgery, tumor diameter, T stage and presence of complications were identified as risk factors affecting mortality ($p<0.05$). The risk of mortality was 0.26 times lower in patients undergoing a subtotal gastrectomy than in patients undergoing a total gastrectomy, and 0.16 times lower in patients with complications than in those without complications. The risk of mortality increased with increasing tumor diameter (1.40 fold), and the risk of mortality decreased with the increasing number of removed lymph nodes (0.919 fold).

Discussion

Advanced-stage gastric cancer is a systemic rather than local disease with a poor prognosis [7]. R0 resection and lymph node involvement are the strongest prognostic factors affecting survival [8,9]. Accordingly, D2 lymph node dissection and the removal of at least 15 lymph nodes have become the widely accepted approach, worldwide [10]. Previous studies have identified advanced age, tumor localization, Lauren subtype, T invasion, stage, resection margin, tumor diameter, and the presence of lymphovascular and perineural invasion to be other prognostic factors in gastric cancer [11-14]. The present study found significant differences between the two groups in terms of Borrmann's tumor type III, Lauren diffuse histology, T3-T4 stage, presence of vascular invasion, presence of perineural invasion, large tumor diameter and the total number of removed lymph nodes.

Lymph node involvement is one of the leading prognostic factors in gastric cancer, and so survival is greater among patients without lymph node involvement than in patients with lymph node involvement. Studies have reported a 5-year survival rate of 72–92% in patients without lymph node involvement [15,16], although some patients with gastric cancer without lymph node involvement still die from the disease [17], which raises the question of what are the effects of other prognostic factors in this disease [17]. In the present study, 75.9% of patients without lymph node involvement survived and 24.1% died.

A wide range of clinicopathological factors affecting survival in patients with gastric cancer without lymph node involvement have been presented [17]. These include tumor size, serosal invasion, lymphovascular invasion, tumor localization, age, gender, perineural invasion and total number of removed lymph nodes [18-22]. The present study identified surgery type, tumor diameter, T stage and presence of complications as the factors affecting mortality risk. Tumor diameter was found to be more influential than other risk factors, and different from other studies, the gastrectomy type and the presence of postoperative complications were identified as important factors affecting the risk of mortality. In addition, perineural invasion approached statistical significance ($p=0.08$).

The limitations of the present study include its retrospective, single-center study design, the small number of patients, the absence of patients without lymph node involvement but who developed a recurrent disease, and the lack of an analysis of the factors affecting the development of recurrent disease.

In conclusion, overall survival was better in patients with gastric cancer without lymph node involvement than in patients with lymph node involvement. Consistent with literature, tumor diameter and T stage were identified as the factors affecting survival, while in contrast to previous studies, gastrectomy type and a presence of complications were identified as other risk factors affecting overall survival.

Statement of ethics

The study protocol was approved by the Kartal Koşuyolu High Specialty Training and Research Hospital Ethics Committee with number 2019.8/01-243. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Disclosures: We report no proprietary or commercial interests in any of the products mentioned or concepts discussed in this article. We claim that none of the material in the article has been published or is under consideration for publication elsewhere. We state that no conflicts of interest or funding

sources exist in the preparation and submission of this article.

Funding sources: We state that no funding sources exist in the preparation and submission of this article.

Acknowledgment

Authors' contributions: Uzun O., Senger A.S., and Gülmez S., Ofluoglu CB., Olmez T. performed most of the study; Uzun O., Gülmez S. designed the study and analyzed the data; Uzun O., Senger A.S., Gülmez S., Bozkurt H. wrote the manuscript; and Polat E. and Duman M. revised the manuscript. Uzun O. and Duman M. approved the final version of the manuscript.

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How to cite this article: Orhan Uzun, Selçuk Gülmez, Aziz Serkan Senger, Cem Batuhan Ofluoglu, Tolga Ölmez, Hilmi Bozkurt, Erdal Polat, Mustafa Duman. H Are the type of gastrectomy and the presence of complications prognostic factors in patients with gastric cancer without lymph node involvement? *J Clin Med Kaz*. 2020; 4(58):23-27