



BRIEF ARTICLE

Routine modified D2 lymphadenectomy performance in pT1-T2N0 gastric cancer

John Griniatsos, Hara Gakiopoulou, Eugenia Yiannakopoulou, Nikoletta Dimitriou, Gerasimos Douridas, Afrodite Nonni, Theodoros Liakakos, Evangelos Felekouras

John Griniatsos, Eugenia Yiannakopoulou, Nikoletta Dimitriou, Gerasimos Douridas, Evangelos Felekouras, 1st Department of Surgery, University of Athens, Medical School, LAIKO Hospital, GR 115-27, Athens, Greece

Hara Gakiopoulou, Afrodite Nonni, Department of Pathology, University of Athens, Medical School, LAIKO Hospital, GR 115-27, Athens, Greece

Theodoros Liakakos, 3rd Department of Surgery, University of Athens, Medical School, ATTIKO Hospital, GR 115-27, Athens, Greece

Author contributions: Griniatsos J and Felekouras E designed the study, performed the operations and contributed to the preparation of the manuscript; Yiannakopoulou E and Dimitriou N wrote the manuscript; Gakiopoulou H and Nonni A performed the histopathology and immunohistochemistry; Douridas G performed the operations and reviewed the literature; Liakakos T checked the final version of the manuscript and made significant comments.

Correspondence to: John Griniatsos, MD, Assistant Professor, 1st Department of Surgery, University of Athens, Medical School, LAIKO Hospital, 17 Agiou Thoma street, GR 115-27, Athens, Greece. johngriniatsos@yahoo.com

Telephone: +30-210-7456855 Fax: +30-210-7771195

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24) in the subgroup of T1-2 gastric cancer patients. All micrometastases were detected in the No. 7 lymph node station. Thus, the disease was upstaged from stage I A to I B in one patient and from stage I B to II in three patients.

CONCLUSION: In gastric cancer, true R0 resection may not be achieved without modified D2 lymphadenectomy. Until D2+/D3 lymphadenectomy becomes standard, modified D2 lymphadenectomy should be performed routinely.

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Key words: Gastric cancer; D2 gastrectomy; D2 lymphadenectomy; Micrometastases; Skip metastases; Skip micrometastases

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Abstract

AIM: To evaluate routine modified D2 lymphadenectomy in gastric cancer, based on immunohistochemically detected skip micrometastases in level II lymph nodes.

METHODS: Among 95 gastric cancer patients who were routinely submitted to curative modified D2 lymphadenectomy, from January 2004 to December 2008, 32 were classified as pN0. All level I lymph nodes of these 32 patients were submitted to immunohistochemistry for micrometastases detection. Patients in whom micrometastases were detected in the level I lymph node stations ($n = 4$) were excluded from further analysis. The level II lymph nodes of the remaining 28 patients were studied immunohistochemically for micrometastases detection and constitute the material of the present study.

RESULTS: Skip micrometastases in the level II lymph nodes were detected in 14% (4 out of 28) of the patients. The incidence was further increased to 17% (4 out of

INTRODUCTION

The lymphatic stream from a gastric tumor is wide and complicated, thus the exact pattern of lymphatic drainage remains obscure and poorly understood. However, histologically confirmed metastatic infiltration of perigastric and extragastric lymph nodes has been defined as the strongest independent dismal prognostic factor for both early^[1] and large^[2] gastric cancer patients.

Micrometastases and/or isolated tumor cells have been reported as immunohistochemically detectable in 10% of early gastric cancer patients^[3], in 52.6% of T2N0 patients^[4], and in 21%^[5] to 49%^[6] of all node-negative gastric cancer patients.

Skip metastases are defined as the detection of metastatically infiltrated extragastric lymph nodes (level II), in the absence of perigastric lymph node (level I) involve-

ment^[7]. Particularly in the subgroup of level I lymph node negative patients, the incidence of histologically detected metastases in the level II lymph nodes (skip metastases) ranges between 2.8% in cases of early^[7] and 5%^[8] to 17.4%^[9] in all other gastric cancers. Moreover, even in patients with histologically classified level I lymph node negative early gastric cancer, micrometastatically infiltrated level II lymph nodes are immunohistochemically detected in 10% of them^[10].

Most authors^[11-13] agree that, except for early gastric cancer patients^[3], patients with immunohistochemically detected micrometastases have significantly worse 5-year survival rates compared to patients with undetectable micrometastases. However, the incidence, clinical implications and clinical significance of skip micrometastases in level II extragastric lymph nodes in patients with gastric cancer have not been properly studied.

The aim of the present study was to evaluate retrospectively the necessity for routine modified D2 lymphadenectomy in all gastric cancer patients, (as a prerequisite for R0 resection for locoregional control of the disease), based on the immunohistochemical detection of micrometastases in level II lymph node stations in patients who had been classified histologically and immunohistochemically as level I lymph node negative and histologically as level II lymph node negative.

MATERIALS AND METHODS

Between January 2004 and December 2008, 207 patients with a preoperative diagnosis of gastric adenocarcinoma were subjected to surgery with curative intent, in our department. None of them had undergone preoperative chemotherapy or radiotherapy. In 95 patients, a modified D2 lymphadenectomy was offered as the standard surgical procedure. Postoperatively, the standard histological examination by hematoxylin and eosin (HE) staining disclosed metastatic infiltration of at least one lymph node in the level I or II lymph node stations in 63 of these patients. Thirty-two patients were classified as pN0, since standard histology did not disclose any evidence of metastatic infiltration of level I and level II peri- and extragastric lymph node stations. All level I lymph nodes of these 32 patients were submitted to immunohistochemistry for micrometastases detection. Patients in whom micrometastases were detected in the level I lymph node stations ($n = 4$) were excluded from further analysis.

The level II lymph nodes of the remaining 28 patients were studied immunohistochemically for micrometastases detection and constituted the material of the present study.

Surgical technique

The proximal resection margin of the stomach was calculated according to the location of the primary tumor. At least a 6-cm tumor-free (based on the frozen section result) proximal resection margin from the most proximal macroscopic border^[14] was achieved in all cases. The dissection of the regional lymph nodes was based on the

Japanese Classification of Gastric Carcinoma^[15]. Thus, for D1 lymphadenectomy, the appropriate (depending on the location of the primary tumor) nos. 1-6 lymph node stations were included in the gastrectomy specimen, whereas in the modified D2 lymphadenectomy, the nos. 7, 8a, 9, 11p, 11d and 12a lymph node stations, were routinely dissected. The level II lymph node stations were recognizable as they had been sent separately to the Pathology Department with special indices demonstrating their exact location. Dissection of the No. 10 lymph node station, splenectomy or distal pancreatectomy was not performed in any of the patients. For staging of the tumors, the TNM classification system according to the AJCC Staging Manual, 6th edition, was used^[16].

Histopathology and immunohistochemistry

Primary tumors and lymph nodes were fixed in formalin and embedded in paraffin. The presence or absence of lymph node metastasis was examined routinely by HE staining by using a representative cut section through the largest diameter of the lymph nodes.

One additional section of 4- μ m thickness from each node was prepared for immunohistochemical staining with a monoclonal anti-cytokeratin (CK) antibody cocktail (AE1/AE3; Dako, Glostrup, Denmark) that reacts with a broad spectrum of human CKs, to detect micrometastases and/or clusters of isolated tumor cells. Briefly, for AE1/AE3 immunostaining, paraffin-embedded sections were deparaffinized in xylene and rehydrated through graduated ethanol to water. Endogenous peroxidase activity was blocked by incubation for 30 min with a solution of 1% hydrogen peroxide, and antigen retrieval was performed by autoclaving sections in 0.01 mol/L citrate buffer, pH 6.0 for 20 min at 800 W. A monoclonal mouse anti-human CK antibody (clone AE1/AE3) was applied at a dilution of 1:50. The Dako Real Envision kit was then used. Diaminobenzidine was used as a chromogen. Lymphoid tissue was used as an internal negative control, while additional sections from the primary tumors were used as positive controls.

Based on the 6th TNM classification^[16], micrometastasis (N1mi) was defined as metastatic focus > 0.2 mm but ≤ 2 mm, and cluster of tumor cells [N0 (+)] was defined as cluster < 0.2 mm according to previously accepted conventions.

RESULTS

Pathologic review did not detect patients with previously missed evidence of lymph node metastasis on conventional HE staining.

In four patients, micrometastases were detected in the level I lymph node stations. These patients were excluded from further analysis.

The remaining 28 patients were 16 men with a median age of 72.5 years (IR 69-75) and 12 women with a median age of 66.5 years (IR 58-69.5) (Table 1). Skip micrometastases in the level II lymph node stations were immunohistochemically detected in four patients ($n = 4$). All micrometastases were detected in the No. 7 lymph node station.

Table 1 Characteristics of the study population

Parameter	n
Sex	16
Males	12
Females	0
Age (yr) (median + IR)	70.5 (63.5–74)
Tumor location	
Upper third	0
Middle third	6
Lower third	22
Histological type (WHO classification)	
Enteric type	19
Diffuse type	5
Mixed type	4
Differentiation	
High	4
Moderate	19
Low	5
T	
T1	4
T2	20
T3	4

The profiles of these patients are presented in Table 2. There were three female and one male patients, with T1 ($n = 1$), T2a ($n = 2$) and T2b ($n = 1$) tumors, located in the lower third ($n = 2$) or middle third ($n = 2$) of the stomach. Thus, following micrometastases detection, the disease was upstaged from stage I A to I B in one patient and from stage I B to II in three patients.

Based on the above, the overall incidence of micrometastases detection was 25% (8 out of 32 patients), while skip micrometastases in the level II lymph nodes were detected in 14% (4 out of 28) of gastric cancer patients, who had been classified histologically and immunohistochemically as level I lymph node negative. Furthermore, the incidence of skip micrometastases was increased to 17% (4 out of 24) in the subgroup of T1-2 gastric cancer patients.

DISCUSSION

The present study disclosed that skip micrometastases in the level II lymph node stations were detected in 14% (4 out of 28) of the patients, who had been classified histologically and immunohistochemically as level I negative. This incidence was further increased to 17% (4 out of 24 patients) in the subgroup of T1-2 gastric cancer tumors.

Despite AJCC/UICC guidelines, which require the pathological examination of at least 15 lymph nodes for accurate gastric cancer staging^[16], only 29% of gastric cancer patients had more than 15 lymph nodes retrieved^[17]. However, D2 lymphadenectomy clearly offers the mean number of the required lymph nodes for pathological examination, independently to the pathologist^[18].

Although D2 lymphadenectomy is recommended by the Japanese Surgical Society as the surgical option for gastric cancer treatment^[19], its performance has not gained popularity worldwide, since prospective randomized studies^[20-24] and meta-analysis^[25] have revealed significantly higher postoperative morbidity and mortality

rates and no 5- and 11-year survival benefit compared to D1 lymphadenectomy.

D2 lymphadenectomy increases the long-term survival of gastric cancer patients with lymph node metastases, however, it has been proposed as unnecessary for patients without lymph node metastases^[9]. On the other hand, D2 lymphadenectomy improves survival even in node-negative early gastric cancer patients, probably due to the resection of the coexisting micrometastases^[26].

Thus, the favorable overall survival rates which were published following the Japanese-type, compared to the Western-type gastric cancer surgery, indicate that, with more extended lymph node dissections, more R0 resections are achieved^[27]. This probably leads to locoregional control of the disease, better outcome and increased survival^[28].

Three methods have been used for the identification of micrometastasis, serial sectioning, immunohistochemical staining, and reverse-transcriptase polymerase chain reaction (RT-PCR). Serial sectioning constitutes a histological method, which can detect lymph node metastasis previously missed by the conventional technique, but it may still fail to identify isolated tumor deposits^[13]. RT-PCR has been reported as highly sensitive^[29], but it is compromised by false-positive results caused by biological contamination^[30]. Positive RT-PCR results indicate the presence of tumor DNA, however, they may not indicate the presence of viable tumor cells^[31]. Thus, immunohistochemistry with human anti-CK antibodies represents the most accurate method for micrometastasis detection^[32] and the most frequently applied technique in research^[3]. One limitation of the method is CK expression by some dendritic cells in the lymph nodes^[33].

Based on the results of studies in colorectal^[34] and non-small cell lung cancer^[35], it has been proposed that N1(-)/N2(+) patients represent a subgroup of pN2 disease with more favorable prognosis^[35]. However, the clinical significance of skip metastases in gastric cancer patients remains controversial. The controversies are related mainly to the small number of patients enrolled in skip metastasis studies^[26], the probably different prognosis of patients with histologically *vs* micrometastatically detected skip metastases^[32], and the concern that patients with histologically detected skip metastases may represent cases of overlooked histological metastasis or micrometastasis in level I lymph nodes, thus being misclassified as patients with skip metastasis^[36].

Saito *et al*^[36] have reported 5-year survival rates of 70.2%, 62.0% and 31.2% in patients with skip metastases, metastases in level I lymph nodes and metastases in level II lymph nodes, respectively. The prognosis of patients with metastases in the level II lymph nodes was significantly worse than that of the patients with either skip metastases or metastases in the level I lymph nodes. The authors have indicated that the clinicopathological characteristics and the prognosis of patients with skip metastases were similar to patients with level I lymph node metastases, but not to the patients with level II lymph node metastases. On the other hand, Li *et al*^[9] have concluded that the cumulative survival rate is not statistically different between gastric cancer patients with solitary skip lymph node metastases, compared to

Table 2 Profiles of the patients with skip micrometastases

Pt	Sex	Age (yr)	No. of LN retrieved	(+) LN station	Location of the tumor	T size (mm)	T stage	Histological type	Lymphatic invasion	Vessel invasion
1	F	62	51	7	L, post	4	T2b	Mixed	+	-
2	F	56	16	7	M, less	30	T1	Diffuse	-	-
3	M	54	38	7	M, less	17	T2a	Enteric	-	-
4	F	71	29	7	L, post	26	T2a	Diffuse	-	-

Pt: Patient; LN: Lymph node; T: Tumor; L: Lower third; M: Middle third.

patients with solitary level I lymph node metastases. Moreover, Park *et al*^[26] have reported that, in patients with positive nodes extending into the level II lymph nodes, the survival curves did not show significant differences between skip(+) and skip(-) groups of patients, which further supports the theory that the number but not the level of lymph node metastases has prognostic significance.

The result of the present study, that all skip micrometastases were detected in the left gastric artery lymph node station, probably indicates that the clinical application of the sentinel node biopsy technique in selected cases might be useful, and lead to selective lymphadenectomy. Although the method has been reported as highly accurate (< 10% false-negative results) in breast cancer surgery^[37], similar findings have not been confirmed in gastric cancer surgery, since 20%-36% of positive lymph nodes were located outside of the sentinel lymph node basin^[38]. Thus, the method is recommended currently to be used in conjunction with D2 lymphadenectomy^[39].

It has been suggested that the most likely route for para-aortic lymph node metastases is from the left gastric artery nodes, passing by the celiac artery^[40]. Other common sites of skip metastasis are the 8a and 9 lymph nodes (around the celiac artery). Thus, these lymph nodes should always be evaluated, regardless of the mode of operation, even in the case of minimally invasive surgery. Moreover, Yanagita *et al*^[41] have investigated the clinical significance of morphological distribution of metastatic foci (metastasis, micrometastasis or isolated tumor cells) in sentinel lymph nodes with gastric cancer, and have concluded that, in patients with non-marginal sinus type sentinel node metastasis, attention should be paid to the possibility of non-sentinel node or even pN2 metastases. Thus, if the sentinel node cannot be identified in the perigastric lymph nodes, those around the celiac artery lymph nodes should be explored to reduce the likelihood of false-negative results in sentinel node mapping^[7].

In conclusion, the present study addressed the fact that, in up to 17% of T1-2 gastric cancer patients, true R0 resection may not be achieved without modified D2 lymphadenectomy. Thus, until D2+ or even D3 lymphadenectomy becomes the standard surgical option, modified D2 lymphadenectomy should be considered as the surgical option of choice in gastric cancer patients.

COMMENTS

Background

R0 resection constitutes the prerequisite for the locoregional control of gastric

cancer. However, the extent of the oncologically required lymphadenectomy (D1 or D2) remains a matter of debate and contradictory results have been published.

Research frontiers

True R0 resection is characterized by complete resection of all viable tumor cells. As histology detects metastases > 2 mm, immunohistochemistry can detect micrometastases between 0.2 and 2 mm or even isolated tumor cells.

Innovations and breakthroughs

Immunohistochemistry with human anti-cytokeratin antibodies showed clearly that, in level II extragastric lymph nodes, viable tumor deposits (skip micrometastases) were present in 17% of the gastric cancer patients who had been classified previously as node-negative by conventional histology.

Applications

By understanding that, without modified D2 lymphadenectomy, true R0 resection may not be achieved, the present study indicates the usefulness of routine modified D2 lymphadenectomy in all gastric cancer patients.

Terminology

Modified D2 lymphadenectomy offering the mean number of the required lymph nodes for pathological examination, contributes to accurate staging of the disease, probably defying the subgroups of patients who may benefit from adjuvant therapy.

Peer review

The authors suggest that D2 lymphadenectomy might be necessary for complete resection of T1-2 N0 gastric cancer, which highlights clearly that skip metastases may be an overlooked problem with standard resection performed routinely in many countries.

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