Lymphoscintigraphy in detection of the regional lymph node involvement in gastric cancer

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ABSTRACT

INTRODUCTION Involvement of regional lymph node is a critical sign in prognosis of gastric cancer. Radiological techniques are commonly used to evaluate the extension of gastric cancer. But their sensitivity and specificity are low especially in the early stage. Our aim was to assess the value of gastric lymphoscintigraphy in identifying regional lymph node involvement in patients with gastric cancer, as compared to the abdominal ultrasonography, computed tomography and postoperative histopathological evaluation.

PATIENTS AND METHODS: 50 patients (12 females) with a median age of 61 years (range, 35–73 years) were included in the study. Pre-operative staging in all cases included upper gastrointestinal endoscopy and biopsy, followed by ultrasound, computed tomography and lymphoscintigraphy. 148 MBq Technetium-99m lymphoscint was injected around the tumour during endoscopy and immediately after injection, anterior, lateral and posterior images were taken in 5-min intervals using a gamma camera. Findings were compared to the findings of other tests. The sensitivity, specificity, positive predictive value, and negative predictive value of each test were calculated and compared.

RESULTS: Histologically, 68% of cases (34/50) had metastasis in regional lymph nodes and all cases were accurately diagnosed by lymphoscintigraphy. Lymphoscintigraphy was significantly more sensitive for detecting lymph node involvement ($P < 0.01$). Both abdominal ultrasonography and CT had very low sensitivity in identifying lymph nodes.

CONCLUSIONS: Lymphoscintigraphy is a promising test in the identification of regional lymph nodes pre-operatively in patients with gastric cancer. It might help the surgeon to plan the extent of dissection before surgery which may decrease postoperative complications related to unnecessary extensive lymph node dissection.

KEYWORDS

Lymphoscintigraphy – Gastric cancer – Lymph node involvement – Pre-operative staging

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Gastric cancer continues to be a significant health problem world-wide. Surgical resection with a lymph node dissection remains the only potentially curative treatment with gastric cancer.¹ The overall prognosis for patients with gastric cancer remains poor, with 5-year survivals ranging from 5% to 15%.^{2,5}

The status of lymph node metastasis and the depth of invasion are the two most important factors affecting prognosis in patients with gastric cancer without distant metastasis.^{4,6} Dissection of lymph nodes is another important factor.⁷ Extended lymph node dissection has, therefore, been recommended on the basis of studies of lymphatic flow and nodal spread of cancer cells.^{8,9} However, it is not clear whether such extended resections should be done in gastric cancer patients.

Some authors have reported that extensive lymph node dissection does not improve the prognosis of node-negative patients. Extensive lymphadenectomy is also fiercely debated because it is associated with a higher morbidity, larger blood transfusion requirement, and a longer hospital stay.^{6,10–12} Determination of the extent of lymph node dissection required in patients with gastric cancer on the basis of actual node involvement is important as less extensive dissection may reduce postoperative morbidity and mortality rates.¹³

Therefore, accurate diagnosis of lymph node metastasis is essential in selecting patients for whom an extensive lymph node dissection will be an appropriate choice.

Figure 1 Lymphoscintigram of patient with T2 tumour and lymph node involvement. Abdominal lymph nodes in midline and periportal area.

Radiological techniques are commonly used to evaluate the extension of gastric cancer. Although, it is extremely useful to know the involvement of lymph nodes before surgery, there is no simple and accurate test to evaluate lymph node status pre-operatively. Diagnostic imaging techniques including computed tomography (CT) and ultrasonography (US) are still unsatisfactory and do not provide enough evidence for an accurate prediction of metastasis in the regional lymph nodes draining gastric cancer.¹⁴

Pre-operative lymphatic mapping by lymphoscintigraphy is being used successfully to avoid the unnecessary resection and morbidity of operation in melanoma and breast cancer.¹⁵⁻¹⁷ Lymphoscintigraphy may be used to avoid unnecessary operation and to determine the clinical stage in gastric cancer.

In this study, our aim was to assess the value of gastric lymphoscintigraphy in identifying regional lymph node involvement in patients with gastric cancer, as compared to abdominal ultrasonography, CT and postoperative histopathological evaluation.

Patients and Methods

The study population consisted of 50 (12 female) patients with gastric cancer who had undergone gastrectomy with extensive lymphadenectomy, including the sampling of para-aortic lymph nodes (D2- α) at the Department of Surgery, Ankara Numune Teaching and Research Hospital, Turkey.

Patient selection and evaluation

All patients had histologically confirmed primary adenocarcinoma of the stomach. Excluded were patients with tumours invading the adjacent organs, those with liver metastasis, and those with peritoneal dissemination.

Figure 2 Para-oesophageal, perigastric and omental lymph nodes in the mid-abdomen.

All patients enrolled into this study gave written informed consent.

Pre-operative staging in all cases included upper gastrointestinal endoscopy and biopsy, followed by ultrasound, computed tomography and lymphoscintigraphy. Neither of the examiners aware of the other test results.

Ultrasound and computed tomography

Ultrasonography was always performed after an overnight fast and prior to CT. The ultrasound examinations were carried out using a Hitachi EUB 2000 unit (EUB 2000, Hitachi, Japan), and CT was performed using a Radix Turbo CT scanner (Hitachi, Japan). Scanning was done in a standard abdominal examination form after an overnight fast. Intravenous and oral contrast agents were used, and the sequences of 10-mm sections were read by the consultant radiologist. Reading of the ultrasonography and CT data was performed independently.

Lymphoscintigraphy

All patients with histologically proven primary adenocarcinoma of the stomach, underwent endoscopic examination and a total volume of 148 MBq (2 ml) Technetium-99m-radiolabelled filtered sulphur colloid solution (Lymphoscint, Amersham, UK) was injected in four quadrants around the tumour, into the submucosal layer using endoscopic puncture needle 2-3 days before the surgery. Anterior, posterior, lateral images were taken in 5-min intervals using a gamma camera after the injection. The lymphatic drainage was evaluated qualitatively (Fig. 1).

Surgical procedure

Following the diagnostic procedures, all patients underwent total gastrectomy with extensive lymphadenectomy, including the dissection of second tiers (D2) and sampling of para-aortic

Figure 3. Lymph nodes in para-oesophageal and periportal area.

Figure 4 Lymph nodes around antral area.

lymph nodes (α). However, the extent of para-aortic lymph node dissection was not specified (*i.e.* dissection of selected nodes or systematic dissection). Lymph node dissections were classified according to Volpe *et al.*¹⁸ Roux-en-y oesophagojejunostomy using stapler was the procedure of choice for reconstruction in all patients.

After operations, the status of lymph node metastasis was classified according to the anatomical distribution of positive lymph nodes outlined by the Japanese Gastric Cancer Association.¹⁹ According to the guidelines of the Japanese Gastric Cancer Association, lymph nodes in groups 1, 2 and 3 are referred to as n1, n2 and n3, respectively, based on the degree of lymph node metastasis.¹⁹

Histological evaluation

All removed specimens were fixed in 10% formalin and embedded in paraffin. Sections (5 mm) were taken, stained with haematoxylin-eosin (H-E) and evaluated under light microscopy by the same histopathology groups. Lymph nodes were classified according to JRS GC.

Analyses and comparison of test results

Findings of each test for lymph node metastasis were compared to histological findings using the following definitions: sensitivity, (true positive)/(true positive + false negative); specificity, (true negative)/(true negative + false positive); positive predictive value, (PPV) (true positive)/(true positive + false positive); and negative predictive value (NPV), (true negative)/(true negative + false negative).

The sensitivity, specificity, positive predictive value, and negative predictive value of the techniques were compared using the Chi-square test for dependent samples. *P*-values < 0.05 were considered significant.

Results

In total, 50 gastric cancer patients with a median age of 61 years (range, 35–73 years) were included. The clinicopathological characteristics of patients enrolled in the study are summarised in Table 1. There were no unexpected toxicities or complications related to administration of radioactive tracer.

Surgery was uneventful in all patients. There was no in-operative or in-hospital death. Eleven patients had some minor complications including prolonged abdominal drainage, delayed gastric emptying, respiratory complications and wound infections.

Histologically, 68% (34/50) of cases had metastasis in regional lymph nodes. The mean number of excised lymph nodes per patient was 36.8 and the number of metastatic lymph nodes was 10.2 per patient, which corresponded to

Table 1 Patient characteristics

Age (years)	61 (range, 35–73)
Sex ratio (M:F)	38:12
Histological type	
Well differentiated	11 (22%)
Moderately differentiated	25 (50%)
Poorly differentiated	9 (18%)
Signet ring cell	5 (10%)
Anatomical subsite	
Upper third	14 (28%)
Middle third	25 (50%)
Lower third	11 (22%)
Depth of invasion	
T1	10 (20%)
T2	33 (66%)
T3	7 (14%)

Table 2 Diagnostic accuracy of all tests

Sensitivity	Specificity	PPV	NPV	
Ultrasonography	0.21	0.56	0.5	0.25
Computed tomography	0.32	0.63	0.65	0.29
Lymphoscintigraphy	1*	1*	1*	1*

PPV, positive predictive value; NPV, negative predictive value.
* $P < 0.05$.

the positive nodes/total nodes ratio of 0.16. Metastasis were located in first tier (n1) in 22 (65%) patients and second tier (n2) were also involved in other 12 (35%) patients.

When the histology results are taken as final diagnosis, the sensitivity, specificity, positive predictive value, and negative predictive values of ultrasonography, CT and lymphoscintigraphy are listed in Table 2. Lymphoscintigraphy was significantly more sensitive for detecting lymph node metastasis than other tests ($P < 0.01$). All cases were accurately diagnosed by lymphoscintigraphy (Table 3). Involved node tier was also accurately estimated by lymphoscintigraphy. Both abdominal ultrasonography and CT had very low sensitivity in identifying involved lymph nodes.

Discussion

Gastric cancer is one of the leading causes of cancer death and most common malignancy among men and the second most common among women world-wide.²⁰ In countries besides Japan, the presentation of gastric cancer is usually late and the overall prognosis of the disease is poor.²⁰

Surgery is the only curative therapy for gastric cancer and controversy still exists on the extent of surgery. As the stage of disease has a definitive influence on survival, early diagnosis is very important. Depth of invasion, lymph node metastases, presence of distant metastases are all found to be essential prognostic factors.^{4-6,21} If the primary lesion is removed *en bloc* with the regional lymph nodes without leaving any residual tumour, patients might be cured.^{19,22} Therefore, as cancer staging is of paramount importance in planning the treatment approach, we focused on pre-operative detection of lymph node metastasis and accurate staging.

The rationale for extensive lymph node dissection is that of it may achieve an R0 resection due to clearance of the metastatic lymph nodes and better locoregional tumour control which improves patient survival.²⁵⁻²⁷ Several Japanese studies reported that favourable results were obtained with extensive lymphadenectomy with a positive nodes/total nodes ratio of less than 0.2 (0.16 in the present study) and they suggested that curative gastric resection

should be performed with extensive lymphadenectomy up to the second lymph node group (D2) as a standard procedure.^{7,23-27} However, some authors in Western countries have suggested that extensive lymph node dissection did not augment survival⁶ and have shown a significant increase in postoperative morbidity and mortality rates in extensive lymph node dissection.^{5,28,29}

However, for patients with gastric cancer, surgical resection with lymph node dissection seems the only potentially curative treatment; however, it is important to avoid excessive lymphadenectomy when considering postoperative quality of life of patients especially in an early stages.

Diagnostic imaging techniques including computed tomography and ultrasonography are commonly used to evaluate the extension of lymph node involvement,^{30,31} although the overall diagnostic sensitivity and specificity is still unsatisfactory and do not give an accurate prediction of metastasis in the regional lymph nodes draining a gastric cancer site.^{14,32,33}

The overall accuracy of CT for identifying lymph node involvement has been evaluated in a number of studies, yielding results ranging from 50% to 60%³⁵ which was 65% in the present study. Abdominal ultrasonography is usually not indicated for the study of the gastrointestinal tract because artefacts from endoluminal gas prevent an accurate analysis of the presence and extent of a neoplastic disease.³² In the present study, ultrasonography was the worst diagnostic test. As a result, ultrasonography is almost always combined with other tests.

Neither conventional ultrasonography nor CT scanning are adequate for predicting lymph node involvement and an important diagnostic gap exists in evaluation of lymph node dissection required in patients with gastric cancer.

There are several other methods to detect lymph nodes including dyes for visual detection, radio-opaque contrast agents for demonstration, and radioactive materials for detection by gamma-camera imaging or with hand-held detection probes. Lymphography might be either direct (when the agent injected directly into the lymphatic vessel) or indirect (when a tracer is injected into the interstitium of the tissue where the

Table 3 Comparison of the tests in detecting lymph node involvement

	<i>n</i> (50)	Histologically +ve (<i>n</i> = 34)	Histologically -ve (<i>n</i> = 16)	Sn	Sp	PPV	NPV
Ultrasonography				0.21	0.56	0.5	0.25
Positive	15	7 (TP)	7 (FP)				
Negative	35	27 (FN)	9 (TN)				
Computed tomography				0.32	0.63	0.65	0.29
Positive	18	11 (TP)	6 (FP)				
Negative	32	23 (FN)	10 (TN)				
Lymphoscintigraphy				1*	1*	1*	1*
Positive	34	34 (TP)	0 (FP)				
Negative	16	0 (FN)	16 (TN)				

TP, true positive; FN, false negative; FP, false positive; TN, true negative; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.
**P* < 0.05.

lymphatic vessels take up the material from the injection site and carry it through the flow route).³⁴ We also used the indirect method as the tracer injected around the tumour.

The lymphography technique using radio-opaque agents was developed by Kinmonth.³⁵ He first injected patent blue violet into the interstitium in order to make lymphatic vessels visible and then vessels were cannulated and radio-opaque dye (namely thorium dioxide) was carefully injected. This technique provided detailed radiograms of the lymphatic system.

Lymphoscintigraphy is the injection of radioactive particles that are then imaged as they pass through lymphatic vessels to their respective lymph nodal drainage basins. Lymphoscintigraphy is receiving increasing interest as a means to stage regional lymph nodes in early stage malignancy. The lymph-node scintigram was first described in 1958 by Sage and Gozun.³⁶ Colloidal Au-198 was initially used and then replaced by technetium-99m (Tc-99m) because of a better safety profile. Tc-99m has a short half-life, no significant β -emission and a low dose is required for the good detection energy. It was bound to different pharmaceuticals including human serum albumin, antimony trisulphide, sulphur colloid and tin colloid that determine its uptake pattern.^{37,38} Its first successful modern application has been in the localisation of the true nodal drainage basins of melanomas situated in regions of highly variable drainage, in particular the trunk and head and neck.^{39,40}

Lymphoscintigraphy may be performed for any patient to evaluate lymph nodes, whereas sentinel node navigation

has several indications including tumour size, location, previous treatments. In common practice, as the purpose of sentinel node navigation is to detect micrometastasis in cases with relatively low incidence of lymph node involvement, cases with the tumour invasion limited to muscularis propria or submucosal layer are most suitable candidates for this procedure. Advanced cases with large tumours and massive lymph node involvement must be excluded in order to avoid poor results due to obstruction or alteration of the lymphatic drainage route.

The feasibility of lymphoscintigraphy in gastric cancer and its diagnostic reliability remains unclear because the lymphatic network may be more complex than that in breast cancer or melanoma.

Although there are limited number of studies on the evaluation of sentinel nodes in gastric cancer,^{41–45} we believe the present work is one of the first detailed studies on the value of gastric lymphoscintigraphy in identifying regional lymph node involvement in patients with gastric cancer, as compared to abdominal ultrasound, computed tomography and postoperative histological evaluation. Despite the increasing interest in the sentinel node concept in gastric cancer patients, it seems more important to know the involvement of lymph nodes before surgery as standard D2 lymph node dissection was performed in all previous sentinel node studies without taking into consideration of involved nodes.^{41–46} Because of the high incidence of lymph node involvement even in T1–T2 tumours in those studies, which was around 4–57% in sentinel nodes and 1–7.1% in

non-sentinel nodes, it seems logical to perform D2 dissection to stage the patients accurately. We found histologically confirmed lymph node metastases in 34 patients most of which (65%; 22 patients) were located in the first tier. The higher incidence of involvement in the second tier (35%; 12 patients) in our study may partly be due to patients with T3 tumours. With this higher incidence of involvement, it does not seem logical to apply the sentinel node concept in gastric cancer patients.

Conclusions

The diagnostic performance of lymphoscintigraphy was found to be encouraging in detecting lymph node involvement in gastric cancer and is definitely superior to conventional imaging techniques. Therefore, we conclude that lymphoscintigraphy is a promising test in the identification of regional lymph nodes pre-operatively in gastric cancer patients. It helps the surgeon to plan the extent of dissection before surgery which may decrease postoperative complications related to unnecessary extensive lymph node dissection.

Acknowledgement

This paper was presented, in part, at the 10th Congress of the Euro Surgery in Istanbul, 2000.

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