Preoperative TNM Staging of Advanced Gastric Cancer with Multi-Detector Row Computed Tomography

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Abstract

Background Compared with early gastric cancer, advanced gastric cancer (AGC) has an aggressive nature and spreads easily via the lymphatic system and bloodstream. To completely remove tumours or to avoid excessive treatments, a precise assessment of their spread before surgery is important to determine the best surgical strategy. However, the accuracy of preoperative staging of TNM classification with computed tomography scans remains unsatisfactory. In this study, we evaluated the accuracy of multi-detector row computed tomography (MDCT) as a preoperative staging tool for advanced gastric cancer.

Methods Using histological staging as the gold standard, tumour node metastases (TNM) classification was preoperatively assessed with MDCT at a slice thickness of 2.5 mm and at surgery. The study included 112 consecutive patients with AGC.

Results In detecting invasion to adjacent organs (T4 category), the overall accuracy of MDCT and surgical findings including frozen section examination was 96% and 80%, respectively (no significant difference [NS]). In identifying the presence of lymph node metastasis (N1–N3), the overall accuracy of MDCT and surgery was 83% and 88% (NS), whereas it was 75% and 86%, respectively, in discriminating extended lymph node metastasis (N2–N3) from minimal (N0–N1) (NS). All six liver metastases were correctly diagnosed with MDCT, although only 6 of 15 peritoneal metastases were identified.

Conclusions These results suggest that accuracy of MDCT with 2.5-mm slice thickness for preoperative TNM classification may enable selection of more efficient and safer treatment strategies before surgery for patients with AGC.

Key words Gastric cancer, Computed tomography, Stage, Diagnosis, Sensitivity, Specificity
Introduction

Compared with early gastric cancer, advanced gastric cancer (AGC) has an aggressive nature and spreads easily via the lymphatic system and bloodstream. A cure for patients with AGC cannot be obtained without complete removal of tumour tissue throughout the body. To completely remove tumours, a precise assessment of their spread before surgery is important to determine the best surgical strategy. However, the accuracy of preoperative staging of tumour, node, and metastasis (TNM) classification with computed tomography (CT) scans remains unsatisfactory.\textsuperscript{12–17} Such inaccurate preoperative diagnoses may lead to inefficient dissections, which may increase postoperative morbidity/mortality and decrease the relapse-free survival rate.\textsuperscript{1,2} More accurate preoperative TNM staging using modern technologies is therefore desired.

Endoscopic ultrasonography (EUS) is currently considered a useful preoperative diagnostic tool.\textsuperscript{3} EUS is good at diagnosing depth of tumour infiltration, but not at evaluating invasion to adjacent organs, lymph nodes, and distant metastases. Moreover, the accuracy of EUS for tumour detection in clinical practice has been reported to be lower than was previously thought.\textsuperscript{4} Recently, positron emission tomography (PET) scans have emerged, but these scans are less accurate for diagnosing locoregional lymph nodes than ordinal CT scans because of a significant lack of sensitivity.\textsuperscript{5}

Currently, multi-detector row computed tomography (MDCT) has been introduced as a more advanced method of spiral CT.\textsuperscript{6} Improvements in both temporal and z-axis spatial resolution with multi-slice detectors permit higher-performance data acquisition and higher-speed image reconstruction. The purpose of this study was to evaluate the clinical value of MDCT with 2.5-mm slice thickness as a tool for preoperative assessment of TNM classification in AGC.

Patients and Methods

Patients

Between August 1999 and February 2002, a total of 112 consecutive patients with AGC at the Cancer Institute Hospital in Tokyo, Japan (excluding patients treated by exploratory laparotomy) were prospectively assigned to this study. All patients underwent preoperative MDCT performed within 2 weeks after endoscopy, gastrectomy plus dissection within 2 weeks after MDCT examination, and histological assessment. All patients underwent laparotomy at the time of surgery based on the recommendations of the Japanese Research Society for Gastric Cancer (JRSGC).\textsuperscript{7} All patients and their families were informed about the possible risks and benefits of the whole clinical pathway of diagnosis, including the process of MDCT, as well as treatment for the disease, and written informed consent was obtained.

Performance of MDCT

The CT images were obtained using a four channel MDCT scanner (Light Speed QX/i, GE Yokokawa Medical, Tokyo, Japan). Scanning was done in a standard abdominal examination. Scopolamine butylbromide was administered alone just before scanning. Neither water nor non-ionic contrast medium was administered perorally. In all cases, MDCT scanning was performed in the supine position at 120 kV and 200 mA with a standard algorithm and a 512 × 512 matrix size. A total of 100 ml of non-ionic contrast medium (Iopamiron 300; iopamidol 300 mg/dl, Nion Schering, Tokyo, Japan) was administered intravenously by power injector using a biphasic technique, with 100 ml rapid bolus at a flow rate of 3 ml/s through an 18-F plastic catheter placed in the antecubital vein. MDCT scanning for acquisition of the first sequence during the arterial phase was started 30 s after initiating intravenous injection of the contrast medium, with the second sequence started 60 s later during the maxi-
mal portal phase. Each acquisition was performed during 20–30s of a single breath-hold. The scanning range was planned starting from the level of the dome of the diaphragm to include the entire liver to the inferior pole of the kidneys, and in some cases, to the pelvic floor. Technical parameters for the MDCT examinations were as follows: beam collimation 4×2.5 mm at a pitch of 0.75 and gantry rotation time 0.8 s. Image reconstruction was performed with a 2.5-mm slice thickness and interval.

**MDCT assessment**

The CT images, both hardcopy axial images and Cine-mode display with CT equipment, were analyzed independently by two readers (T.S and O.S) preoperatively, without information on endoscopic or X-ray examination findings. When there was a difference of opinion between observers, final classification was reached by consensus. MDCT images were prospectively analysed for detectability of the TNM classification proposed by the JRSGC. For tumour invasion, MDCT images were used to detect only direct invasion to adjacent organs, with T1–T3 category determined using a combination of EUS and X-ray examinations. Adjacent organs included the pancreas, liver, spleen, and transverse colon. These were considered to be involved when MDCT images indicated obliteration of the fat layer between the gastric tumour and the adjacent organs. MDCT also played a role in identifying lymph node metastases and distant metastases. Regional lymph nodes were considered to display metastatic involvement if they displayed either a diameter larger than 8 mm and a round configuration or high-contrast medium enhancement (>100 HU). Regional lymph nodes of the stomach were categorized according to 16 different anatomic sites and classified into three N category compartments in accordance to the guidelines of the JRSGC. Grades in the N1, N2, and N3 categories comprised perigastric lymph nodes, lymph nodes along the left gastric artery, along the common hepatic artery, around the celiac axis and along the splenic artery, and lymph nodes in the hepatoduodenal ligament at the posterior aspect of the head of the pancreas and para-aorta. For distant metastases, any hepatic lesion other than a cyst was regarded as potentially malignant and nodular thickening of the peritoneum or ascites was assumed to indicate peritoneal dissemination.

**Statistical analysis**

Preoperative staging with MDCT and surgical staging were compared with histological staging. Accuracy was first calculated as correctly predicted stages for histological TNM classification divided by the number of patients. Accuracy was further expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Differences in sensitivity were tested using the exact McNemar test and values of \( P < 0.05 \) were considered significant. All statistical evaluations were performed using STATA 8.0 software (STATA Corporation, College Station, Texas, USA).

**Results**

**Findings at surgery**

The 112 patients studied included 74 men and 38 women; mean age was 62 years (range 33–86 years). The tumours were located in the proximal \((n = 22)\), corpus \((n = 46)\), and antrum \((n = 44)\). According to Lauren’s histological classification, intestinal and diffuse types were seen in 33 and 79 cases, respectively. Total gastrectomy \((n = 47)\), partial gastrectomy \((n = 58)\), Appleby surgery \((n = 1)\), pancreatico-duodenectomy \((n = 2)\), and left upper abdominal evisceration \((n = 4)\) were performed. In 83 of 112 cases \((74\%)\), curative resection was performed by removal of the primary gastric tumour with or without invaded organs and regional lymph nodes. Splenectomy \((n = 40)\), distal pancreatectomy \((n = 15)\), partial hepatectomy \((n = 1)\), and transverse colectomy \((n = 2)\) were performed in some cases. For the remaining 29
patients (26%), palliative resection was performed due to the presence of bulky lymph node metastases, liver metastases, and/or peritoneal dissemination. In patients treated with palliative surgery, regional lymph nodes were not always resected and histologically analysed. These patients were therefore not included in evaluation for N category. Suspected metastatic lymph nodes (mean, 3.3 ± 2.2 SD) were submitted for frozen-section examination using hematoxylin-eosin staining during surgery. In the 83 patients who underwent curative resection, standard D2 dissection included complete dissection of N1 and N2 category nodes (n = 39), and more radical D3 dissection included complete dissection of N1, N2, and N3 category nodes (n = 44).

**Accuracy of MDCT in discriminating invasion to adjacent organs**

Using histological staging as the gold standard, depth of tumour invasion (T) was assessed with MDCT or surgery (Fig. 1). Although only 6 of 112 patients displayed histological evidence of invasion into adjacent organs (T4), the accuracy of assessing the tumour invasion into adjacent organs with MDCT and surgical findings was 96% (95% CI: 90% to 99%) and 80% (95% CI: 88% to 95%), respectively (Table 1). The sensitivity to detect tumour invasion into adjacent organs was not significantly different with the McNemar test between MDCT and surgical assessment. Specificity was also equivalent between MDCT and surgical findings.

**Accuracy of MDCT in lymph node metastasis**

Staging of lymph node metastases with
MDCT and surgical findings was compared with histological staging only for patients treated using curative surgery (Table 2). Lymph node metastasis was found in 86 patients (77%). The frequencies of nodal category were as follows: 26 patients (23%) with N0 category, 30 patients (27%) with N1 category, 28 patients (25%) with N2 category, and 28 patients (25%) with N3 category as a final histological study. Overall accuracy of N0 to N3 categories was 59% (95% CI: 49% to 68%) for MDCT and 74% (95% CI: 65% to 82%) for surgical findings.

MDCT could discriminate the presence of lymph node metastases (N1 to N3) from the absence of lymph node metastasis (N0) with diagnostic accuracy as follows: overall 83% (95% CI: 75% to 89%); sensitivity 87% (95% CI: 78% to 93%); specificity 69% (95% CI: 48% to 86%); PPV 90% (95% CI: 82% to 96%); NPV 62% (95% CI: 42% to 79%). On the other hand, findings during surgery, including frozen section examination, could discriminate the presence of lymph node metastases with diagnostic accuracy as follows: overall 88% (95% CI: 80 to 93%); sensitivity 93% (95% CI: 85% to 97%); specificity 69% (95% CI: 48% to 86%); PPV 91% (95% CI: 83 to 96%); NPV 75% (95% CI: 53% to 90%). The sensitivity to discriminate the presence of lymph node metastases (N1 to N3) from the absence of lymph node metastasis (N0) was not significantly different with the McNemar test between MDCT and surgical assessment. Specificity was also equivalent between MDCT and surgical findings.

Next, the ability of MDCT to discriminate peritumoural lymph nodes (N0–N1 category) from locoregional lymph nodes (N2–N3 category) was evaluated with the following findings: overall 75% (95% CI: 66% to 83%); sensitivity 73% (95% CI: 60% to 84%); specificity 77% (95% CI: 64% to 87%); PPV 76% (95% CI: 62% to 87%); NPV 74% (95% CI: 61% to 85%). Similarly, the ability of surgical findings, including frozen section examination, to discriminate peritumoural lymph nodes from locoregional lymph nodes was evalu-
ated with the following findings: overall 86% (95% CI: 80% to 93%); sensitivity 86% (95% CI: 74% to 94%); specificity 89% (95% CI: 78% to 96%); PPV 86% (95% CI: 74% to 94%); NPV 86% (95% CI: 75% to 94%). The sensitivity to discriminate peritumoural lymph nodes (N0–N1 category) from locoregional lymph nodes (N2–N3 category) was not significantly different with the McNemar test between MDCT and surgical assessment. Specificity was also equivalent between MDCT and surgical findings.

**Accuracy of MDCT in discriminating presence of distant metastasis**

Distant metastases were macroscopically found in 21 patients, including 6 patients with liver metastasis (Fig. 3A) and 15 patients with peritoneal space metastasis (Fig. 3B). In addition, histologic findings showed cancer cells in samples from the peritoneal space in 9 patients. MDCT detected 6 of 6 liver metastases and 6 of 15 peritoneal metastases.

**Discussion**

The study confirmed sufficient diagnostic value of MDCT as a preoperative diagnostic tool, since its accuracy was equivalent to assessment during surgery. Particularly, MDCT was effective in detecting invasion to adjacent organs, presence of lymph node metastasis and liver metastasis. Moreover, peritumoural lymph nodes (N0–N1 category) could be distinguished from locoregional lymph nodes (N2–N3 category). On the other hand, MDCT had limitations in detecting...
peritoneal metastasis. The overall accuracy was considered as excellent compared with previous literature.\textsuperscript{3,4,12–17}

Previous studies have reported that the sensitivity for a diagnosis of invasion to adjacent organs varied, ranging from 0\% to 69\%\textsuperscript{14–17} Some authors suggested that laparotomy has been considered the gold standard in staging T4 category. However, surgical assessment for T4 category is not 100\% accurate in others’ studies, as well as ours.\textsuperscript{14,18} There is a high incidence of false-positive findings due to the difficulties in distinguishing between inflammatory adhesions, edema, and true tumour invasion, even during surgery. In our study, overall accuracy of detecting invasion to adjacent organs with MDCT and with surgical findings, including frozen section examination, displayed good scores: 96\% and 80\%, respectively. The faster acquisition time and smaller scan collimation of MDCT, which allows less respiratory miss-registration and decreased partial volume effects, may have contributed to the accuracy of the results.

Detection of involved lymph nodes represents one of the most powerful predictors of survival following curative resection for AGC.\textsuperscript{19–21} Overall accuracy to discriminate the presence of lymph node metastases was 83\% for MDCT and 88\% for surgical findings using frozen section examination. Moreover, the accuracy to discriminate loco-regional lymph nodes metastases from peritumoural lymph nodes was 75\% for MDCT and 86\% for surgical findings. MDCT is thus clinically worth performing for preoperative N category, given the importance of selecting an appropriate surgical strategy. According to the Japanese gastric cancer treatment guidelines,\textsuperscript{22} D2 dissection and sometimes more radical D3 dissection are the preferred options for AGC. Extensive lymphadenectomy is expected to improve survival time in patients with resectable AGC.\textsuperscript{20} Conversely, even with radical lymphadenectomy, some of patients with locally advanced disease (ie, N2 and N3 category) cannot achieve total resection of tumours.\textsuperscript{21} Recently, preoperative neoadjuvant chemotherapy in such cases has received increasing attention.\textsuperscript{23,24} The preoperative demonstration of loco-regional lymph nodes with MDCT may help clinicians decide on the need for preoperative neoadjuvant chemotherapy in patients with locally advanced disease.

For radical resection, the most important information required is whether distant metastases are present, as these imply that potentially curative resection is not feasible, or that patients should be treated with preoperative chemotherapy to reduce tumour size and clear distant metastasis. Resection should be particularly avoided for patients with two or more metastatic sites, as no significant survival advantage is conferred.\textsuperscript{25} MDCT could predict the presence or absence of liver metastases with high sensitivity and specificity. On the other hand, nine patients were diagnosed with malignant ascites without peritoneal metastases, which was hard to assess using MDCT. Even with thinner-sliced MDCT, it was difficult to accurately detect peritoneal metastases before surgery.

In conclusion, MDCT with 2.5-mm slice thickness may raise the accuracy of preoperative TNM classification, enabling selection of more efficient and safer treatment strategies for patients with AGC before surgery.

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References


