

Impact of Combination Criteria of Nodal Counts and Sizes on Preoperative MDCT in Advanced Gastric Cancer

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Published online: 7 February 2015
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Abstract

Background This study was designed to establish a new diagnostic criteria of preoperative nodal status with high specificity on multidetector row computed tomography (MDCT) to extract advanced gastric cancer (GC) patients with an unfavorable prognosis.

Method From total of 480 GC patients who underwent surgical resection, 58 consecutive patients with a preoperative diagnosis of nodal metastasis on MDCT were included in this retrospective study. Nodal status on MDCT was reassessed and a prognostic analysis was performed in the present study.

Results Among several clinical nodal diagnostic criteria on MDCT, a cut-off value of the short-axis diameter measuring ≥ 15 mm showed the highest specificity (100 %). The prognostic analysis revealed that patients with nodal counts on MDCT of ≥ 3 ($p = 0.035$) as well as those with a nodal diameter ≥ 15 mm ($p < 0.001$) had a significantly poor prognosis. When patients with nodal counts ≥ 3 and at least one node that was ≥ 15 mm in diameter on MDCT were defined as having extensive lymph node metastasis (ELM) that had a significantly poor prognosis (5-year survival rates of 20 %, $p < 0.001$), and ELM was also an independent poor prognostic factor in advanced GC ($p = 0.033$, hazard ratio 4.038).

Conclusion GC patients with nodal counts ≥ 3 and at least one node that was ≥ 15 mm in diameter on MDCT have extremely worse prognose with high diagnostic specificity. This novel surrogate indicator for preoperative imaging diagnosis may help personalized therapeutic strategies for GC patients with ELM.

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide [1]. Although multimodal treatments such as surgery, chemotherapy, and radiotherapy have been used to improve survival rates, the

therapeutic outcomes of advanced GC remain unsatisfactory [2]. Recent studies clearly demonstrated that combination therapy such as surgery plus adjuvant chemotherapy improved survival rates in advanced GC, especially in East Asian countries [3, 4]; therefore, the standard treatment for advanced GC is curative gastrectomy followed by postoperative chemotherapy in East Asian countries. However, the survival rates of patients with very advanced GC [especially stage III with extensive lymph node metastasis (ELM)] have been less satisfactory. In terms of good compliance to more powerful and intensive chemotherapeutic regimens, neoadjuvant chemotherapies (NAC) have been preferably tried to improve the survival rates of very advanced GC patients in

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clinical trials [5–9]. However, the prolonged preoperative treatment occasionally causes disease progression during NAC, and therefore an indication for NAC should be crucial in order to avoid false-indication of NAC for patients with favorable prognosis treated by standard treatments, operation, and postoperative chemotherapy.

Various imaging modalities, such as multidetector row computed tomography (MDCT), endoscopic ultrasonography (EUS), and magnetic resonance imaging (MRI), have been increasingly used for accurate diagnose in clinical settings. Thin-slice MDCT may effectively and precisely diagnose nodal metastasis in GC patients [10–16]. Several reports demonstrated that preoperative nodal status diagnosed by MDCT can predict prognosis of patients with advanced GC. We previously demonstrated that patients with nodal counts on MDCT of ≥ 3 had a significantly poor prognosis [11]. On the other hand, Tokunaga et al. reported that a selection by the nodal size of the short axis ≥ 15 mm in diameter showed extremely high specificity and provided prognostic information [12]. However, the 5-year survival rate of the suspected patients with poor-prognostic groups were still around 40–50 % in these studies, which indicated about half of these patients cured by gastrectomy with D2 lymph node dissection.

This study was designed to evaluate the utility of metastatic nodal counts and sizes on MDCT as combination criteria to extract advanced GC patients with an extremely unfavorable prognosis by standard treatments. The results obtained clearly demonstrated that combination criteria of nodal counts and sizes on MDCT could be a reliable surrogate marker for an unfavorable prognosis in patients with advanced GC. Our results suggest that GC patients with nodal counts ≥ 3 and at least one node that is ≥ 15 mm in diameter on MDCT have extremely worse prognose with extremely high diagnostic specificity.

Materials and methods

Ethics statement

Written consent was obtained from all patients prior to obtaining clinicopathological data and patient anonymity has been preserved.

Patients

Of a total of 480 GC patients treated at our institution between 2005 and 2009, 58 patients diagnosed with nodal metastasis on preoperative MDCT were included in the present study. The diagnostic accuracy, equivalent to that of other studies, of nodal metastasis was demonstrated previously [10, 11]. All 58 patients underwent curative

gastrectomy with Japanese style D2 lymphadenectomy including the perigastric lymph nodes (LN) along the left gastric, common hepatic, and splenic arteries. All patients attended a postoperative follow-up or received additional treatments including those for tumor recurrence at our institution or affiliated hospitals. The median follow-up periods were 34.4 months. Total of 14 patients developed recurrence, of which 3 was peritoneal recurrence, 4 LN recurrence, 5 distant site recurrence, and 3 unknown recurrent site. The number of the recurrent site category described above was overlapped. As for the postoperative adjuvant treatment, the patients with pStage II–III GC after 2008 were essentially received postoperative adjuvant chemotherapy including S-1 chemotherapy as the result of ACTS-GC trial [3]. Of the 58 patients, 19 patients have received adjuvant chemotherapy. As for intraoperative cytology, 43 of the 58 patients were examined by intraoperative cytology, and only 1 patient showed positive status. The other clinicopathological features of our patients were shown in Table 1.

MDCT protocol

Preoperative or pretreatment MDCT was performed on patients who had fasted for more than 8 h using a 64-detector row computed tomography (CT) scanner (Philips Healthcare, Japan). Neither water nor non-ionic contrast medium was administered orally. In all cases, MDCT scanning was performed with patients in the supine position at 120 kV and 300 mA with a standard algorithm and 512×512 matrix size. A total of 2.0 ml/kg of non-ionic contrast medium was administered intravenously by an automatic injector at a flow rate of 4.0 ml per second through a 20-gage needle placed in the antecubital vein. CT scanning was performed in the late arterial phase [start delay, 6 s after the CT number at the bifurcation of the celiac artery marked by a range of interest (ROI) reached 200 Hounsfield unit (HU)], portal venous phase (30 s), and delayed phase (60 s). The scanning range included the whole abdomen and pelvis, from the level of the diaphragmic domes to the anal verge. We reconstructed raw data at 1.0 mm thicknesses for transverse CT images. In the present study, the portal venous phase was used to evaluate nodal metastasis and the arterial phase was used to identify the anatomical localization of arteries such as the left and right gastric arteries. All of the MDCT protocols were according to those used in regular routine work at our institution [10, 11].

Clinical and pathological diagnosis of lymph node metastasis

As demonstrated in our previous studies [10, 11], we mainly used a cine-mode display of CT images and

Table 1 Clinicopathological characteristics of gastric cancer patients with clinical diagnosis of nodal metastasis on preoperative MDCT

Variables	<i>n</i> = 58
Gender	
Male	40
Female	18
Age	
<64	18
>65	40
Gross type	
Localized	28
Diffuse	30
Histology	
Differentiated	31
Undifferentiated	27
Location	
U	16
M	22
L	20
Tumoe depth ^a	
pT1	13
pT2	7
pT3	21
pT4	17
Pathological nodal metastasis ^a	
pN0	17
pN1	11
pN2	11
pN3	19
Lymphatic invasion	
Negative	18
Positive	40
Vessel invasion	
Negative	28
Positive	30
Tumor size (mm)	
Mean (range)	55.4 (5–160)
pStage ^a	
I	15
II	13
III	30
Surgical procedure	
Total gastrectomy	27
Distal gastrectomy	28
Proximal gastrectomy	3

^a The 7th TNM classification

precisely counted all regional LN considered to show metastatic involvement if they had a diameter larger than 8 mm, high contrast medium enhancement that was defined as attenuation greater than 100 HU in the postcontrast

portal venous phase, and a round shape [13, 15, 17]. The average CT value of the nodal section was measured for each lymph node. Independent radiologists at our institution had previously confirmed all metastatic regions. Regional LN were counted and categorized according to 16 different anatomic sites based on the Japanese gastric cancer classification (JCGC) [18]. Both the shortest and longest diameters of all metastatic LN were subsequently measured and reassessed at each regional site by the reconstructed data of pretreatment MDCT.

After surgery, all dissected LN were subjected to a pathological examination, fixed in buffered formalin, and embedded in paraffin. Pathologists in our institution examined embedded LN by sectioning slices in the plane of the largest node dimension to confirm the presence of metastasis.

Statistical analysis

Univariate analysis of the relationship between clinicopathological features and the two groups of combination criteria of ELM on MDCT was performed using the χ^2 test and Fisher's exact probability test. To assess survival, Kaplan–Meier survival curves were constructed for groups based on univariate predictors and differences between the groups were tested with the log-rank test. The Cox proportional hazards model was used for further evaluations of multivariate survival analysis. *p* value <0.05 was considered significant. Statistical analyses were conducted using JMP 10 (SAS Institute Inc., Cary, NC).

Results

Diagnostic accuracy of nodal metastasis based on the reassessment of preoperative MDCT for gastric cancer patients

A diagnostic reassessment was performed based on each cut-off value of the lymph node size on MDCT in this GC cohort. The results obtained demonstrated that the cut-off value of the short axis ≥ 15 mm in diameter showed the highest specificity (100 %) for the diagnosis of lymph node metastasis (Table 2). The results of accuracy including other cut-off values were compatible with previous findings [12, 15, 16].

Survival analyses of each group divided according to the nodal counts and/or sizes

We previously demonstrated that metastatic nodal counts on MDCT correlated with the pathological diagnosis using Spearman's correlation test, and a function was derived

Table 2 Diagnostic accuracy of nodal metastasis based on a reassessment of preoperative MDCT for gastric cancer patients

	Cut-off value of the short axis ≥ 10 mm in diameter		Cut-off value of the short axis ≥ 15 mm in diameter		Cut-off value of the long axis ≥ 10 mm in diameter	
	Negative	Positive	Negative	Positive	Negative	Positive
MDCT diagnosis						
Negative	10	14	17	29	3	2
Positive	7	27	0	12	14	39
Sensitivity (%)	65.8		29.2		95.1	
Specificity (%)	58.8		100		17.6	

from the analysis, $y = 1.63x + 2.50$, between nodal counts on MDCT and the pathological diagnosis (y , pathologic nodal counts; x , nodal counts on MDCT) [11]. Nodal counts on MDCT of ≥ 3 corresponded to pathogenic N3 based on the forecast function of the Spearman's correlation test. According to the prognostic analysis, patients with nodal counts on MDCT of ≥ 3 ($p = 0.035$; Fig. 1a) as well as those with a nodal diameter ≥ 15 mm ($p < 0.001$; Fig. 1b) had a significantly poor prognosis. Since the patients with nodal counts ≥ 3 and at least one node that was ≥ 15 mm in diameter on MDCT were defined as having

ELM, they had a significantly poor prognosis ($p < 0.001$) (Fig. 1c).

Multivariable survival analysis by the Cox proportional hazards model

No correlation was observed between the clinicopathological factors and the status of the combination criteria of ELM on MDCT, except for pathological nodal status (Table 3). Multivariable survival analysis using Cox proportional hazards model demonstrated that the combination

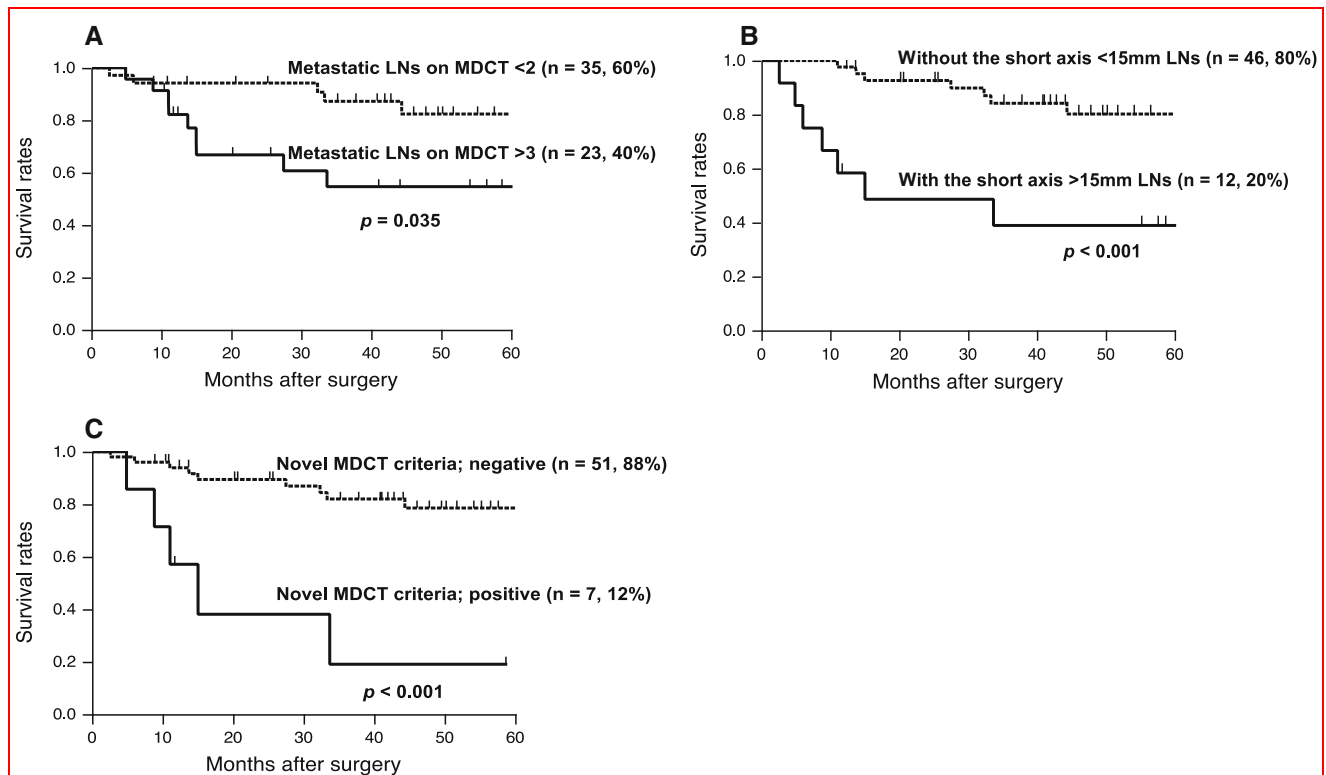


Fig. 1 Survival analysis of each group according to nodal counts and sizes on MDCT (Kaplan–Meier survival curve and log-rank test). Patients with nodal counts on MDCT of ≥ 3 ($p = 0.035$, **a**) as well as those with a nodal diameter ≥ 15 mm ($p < 0.001$, **b**) had a

significantly poor prognosis. When patients with nodal counts ≥ 3 and at least one node that was ≥ 15 mm in diameter on MDCT were defined as having extensive lymph node metastasis (ELM), they had a significantly poor prognosis ($p < 0.001$) (**c**)

Table 3 Relationship between clinicopathological factors and combination criteria of ELM^a on MDCT

<i>n</i> = 58	Combination criteria of ELM ^a on MDCT		
	Negative (<i>n</i> = 51)	Positive (<i>n</i> = 7)	<i>p</i> value
Gender			
Male	35	5	1.000
Female	16	2	
Age			
<64	15	3	0.665
>65	36	4	
Gross type			
Localized	26	2	0.425
Diffuse	25	5	
Histology			
Differentiated	28	3	0.694
Undifferentiated	23	4	
Location			
U	14	2	1.000
ML	37	5	
Clinical tumor depth ^b			
cT1–2	16	1	0.661
cT3–4	35	6	
Pathological nodal metastasis			
Negative	17	0	0.093
Positive	34	7	

ELM extensive lymph node metastasis

^a Patients with >3 swelling LNs and >15-mm short axis diameter on MDCT were diagnosed as positive

^b The 7th TNM classification

criteria of ELM on MDCT was an independent poor prognostic factor in patients with advanced GC ($p = 0.033$, hazard ratio 4.038) as well as the tumor gross type and tumor location (Table 4).

Discussion

The emergence of high-performance modalities such as MDCT has recently allowed for the precise perioperative diagnosis of GC staging [10–13, 16, 17]. Pathological number of metastatic LN was previously defined as one of the most important prognostic factors in GC patients [19–23]. Therefore, a preoperative or pretreatment diagnosis of metastatic nodes is essential for establishing appropriate therapeutic strategies. We previously demonstrated that metastatic nodal counts (especially four LN or more) on preoperative MDCT were associated with the surgical curability of GC. Regarding surgical curability, diagnostic laparoscopy has recently been performed on patients suspected of having locally advanced and/or distant metastases

in order to evaluate the extent of the cancer. Laparoscopy prior to surgical resection provides useful information regarding resectability in these patients. On the other hand, Tokunaga et al. also demonstrated that preoperative nodal sizes on MDCT could affect the long-term prognosis of GC patients [12]. These findings suggested that the preoperative nodal status on MDCT is extremely important for assessing the malignant status and therapeutic strategies in each case of GC.

The standard treatment for advanced GC in East Asian countries is currently curative gastrectomy followed by postoperative chemotherapy [3, 4]. More potent postoperative chemotherapy and preoperative chemotherapy have been attempted in order to further improve the prognosis of patients with very advanced GC [5–7, 24, 25]. Several clinical trials have been conducted to evaluate the efficacy of neoadjuvant chemotherapy in GC patients, many of which were intended for GC patients with type 4 or ELM [6, 8, 9]. Recently, results of two clinical trial on neoadjuvant chemotherapy were reported, one for GC patients with clinically resectable type 4 and large type 3 and the other for GC patients with bulky lymph node metastasis along the coeliac artery and its branches and/or para-aortic lymph node metastasis [9, 26]. Both trials suggested that neoadjuvant chemotherapy was safe and effective for some of the study patients with extremely poor prognosis; however, neoadjuvant chemotherapy followed surgery achieved a better prognosis in GC patients with ELM compared to those with type 4 or large type 3. These finding may suggest that the treatment strategy, surgery after neoadjuvant chemotherapy, is appropriate for GC patients with ELM [6, 9]. Patients with pathologically confirmed ELM have an extremely poor prognosis; however, an accurate preoperative evaluation of lymph node metastasis is generally considered too difficult. The eligibility criteria of several clinical trials for ELM on MDCT have been broadly defined in many ways.

We initially provided forecast nodal counts on MDCT of ≥ 3 , corresponding to pathological N3, using the correlation function described in our previous study [11]. According to the survival analysis, patients with nodal counts on MDCT of ≥ 3 ($p = 0.035$; Fig. 1a) had a significantly poor prognosis. However, the 5-year survival rate of patients with nodal counts on MDCT of ≥ 3 was still more than 50 %, which indicated that the criteria included patients with relatively a good prognosis. Some patients with nodal counts on MDCT of ≥ 3 were found to be negative for lymph node metastasis. On the other hand, a selection by the nodal size of the short axis ≥ 15 mm in diameter, as previously reported by Tokunaga et al. showed extremely high specificity (100 %) and also provided prognostic information. However, patients with the nodal size of the short axis ≥ 15 mm in diameter still had a 5-year survival

Table 4 Multivariate prognostic analysis for clinical factors by Cox proportional hazards model

Variables	Multivariate prognostic analysis				
	HR	95 % CI		<i>p</i> value	
Gender					
Female vs. male	1.835	0.503	–	6.552	0.346
Age					
>65 vs. <64	1.562	0.513	–	5.378	0.439
Gross type					
Diffuse vs. localized	7.204	1.415	–	63.273	0.015
Histology					
Undifferentiated vs. differentiated	2.678	0.711	–	12.280	0.148
Location					
U vs. ML	5.478	1.337	–	25.724	0.019
Clinical tumor depth ^a					
cT1–2 vs. cT3–4	1.367	0.176	–	6.999	0.734
MDCT criteria of ELM ^b					
Positive vs. negative	4.038	1.129	–	13.745	0.033

Bold values are statistically significant

HR hazard ratio, CI confidential interval, ELM extensive lymph node metastasis

^a The 7th TNM classification

^b Patients with >3 swelling LNs and >15-mm short axis diameter on MDCT were diagnosed as positive

of approximated 40 %. This finding indicated that some of these patients only had lymph node metastasis in one node and were cured by gastrectomy with D2 lymph node dissection. Therefore, we hypothesized that the combination criteria of nodal counts and sizes on MDCT may enable us to provide a surrogate indicator for ELM with high specificity, and also to extract advanced GC patients with an unfavorable prognosis. The results of the present study clearly demonstrated that our combination criteria of ELM on MDCT (nodal counts of ≥ 3 and at least one node that is ≥ 15 mm in diameter) could extract patients with an extremely poor prognosis whose 5-year rate survival was less than 20 %, and was also an independent poor prognostic factor in patients with advanced GC with clinically positive nodes. The counterpart group of our combination criteria still had a relatively good 5-year survival rate of more than 75 %, although all patients were suspected of having clinically lymph node metastasis on MDCT. These results indicate that our combination criteria accurately extracted patients with an extremely poor prognosis only, and most counterparts were cured by standard treatments consisting of gastrectomy with D2 lymph node dissection and post-operative chemotherapy.

One of the limitations on imaging diagnosis is inter-observer difference. Inter-observer differences are a crucial problem in prospective multicenter studies using imaging modalities. However, our criteria were simply defined by nodal counts and the sizes of LN; therefore, we considered

our combination criteria to be highly reproducible and also relevant to clinical practice. Therefore, further studies with a large cohort are needed to confirm these results.

In conclusion, GC patients with nodal counts of ≥ 3 and at least one node that is ≥ 15 mm in diameter on MDCT have an extremely poor prognosis with high diagnostic specificity. These patients may be suitable as candidates in future clinical trials to investigate the efficacy of NAC.

Conflict of interest None.

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