Original Article
Pre-operative lymph node status of gastric cancer evaluated by multidetector computed tomography

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Abstract: The purpose of the present study was to perform a meta-analysis to evaluate the diagnostic value of Multidetector computed tomography (MDCT) in the pre-operative lymph node (N) staging in gastric cancer (GC) patients. The Medline, Embase and Web of Knowledge were searched for studies assessing the diagnostic value of MDCT in the pre-operative evaluation of TNM staging in GC patients. We pooled the sensitivity, specificity, positive and negative Likelihood ratio (LR+ and LR-), Diagnostic Odds Ratio (DOR) and constructed summary receiver operating characteristic curves (ROC). A total of 30 studies including 6637 GC patients were analyzed. The pooled estimates of sensitivity, specificity, LR+, LR- and DOR of MDCT in the detection of pre-operative N staging in GC patients were 0.67 (95% CI: 0.66-0.69), 0.84 (95% CI: 0.83-0.85), 3.25 (95% CI: 2.69-3.93), 0.36 (95% CI: 0.28-0.46) and 10.31 (95% CI: 7.66-13.88), respectively. The results of a summary ROC showed that the AUC and Q* were 0.8338 and 0.7661, respectively. As a control, the AUC and Q* of endoscopic ultrasonography were 0.8063 and 0.7414, respectively. Currently, it is necessary to recommend the routine clinical application of MDCT in the preoperative evaluation of lymph node status in GC patients.

Keywords: Multi-detector computed tomography, MDCT, lymph node staging, gastric cancer, meta-analysis

Introduction

Gastric cancer (GC) is one of the most common malignant tumors in the digestive system and the second most common cause of cancer-related death worldwide [1]. Although the incidence of gastric cancer has been declining in most industrial countries, it remains the most prevalent cancer in East Asian countries [2]. The proportion of early gastric cancer in Korea and Japan has increased owing to improvement in diagnostic method and population screening. However, most of patients with gastric cancer in China and other countries were advanced. The primary treatment of gastric cancer is still surgical resection [3]. However, novel therapeutic approaches have been utilized recently, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or laparoscopic treatment in patients with early GC [4, 5] and neoadjuvant chemotherapy in advanced GC [6]. Above new therapeutic approaches were based on accurate pre-surgical TNM staging, especially lymph node (N) staging.

Currently, following the improvement of imaging technique, multi-detector computed tomography (MDCT) has become one of the most common techniques for the pre-surgical TNM staging in GC patients. However, an accurate count of lymph nodes is a tremendous challenge to the radiologists. There has been no universal consensus regarding lymph nodes pathology about measuring method. Criteria for lymph node involvement have been controversial. Recently, most studies considered that the regional lymph nodes were metastases if they were larger than 8 mm in the short-axis diameter [7]. Some researches showed that the accu-
Table 1. Clinical characteristics of included studies

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<th>Mean age (Year)</th>
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P: Prospective; R: Retrospective; PSP: Post-surgery Pathology; MDCT, Multidetector Computed Tomography; NR, Not Reported; PET-CT, Positron Emission Tomography; EUS, Endoscopic ultrasonography; HGS, Hydrogastric sonography; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

Pre-operative N staging of GC by MDCT

The accuracy of MDCT concerning pre-operative staging in gastric cancer was similar with endoscopic ultrasonography (EUS). As for MDCT, the accuracy of T staging and N staging were 77.1 to 88.9% and 51 to 71%, respectively, while the accuracy of T staging and N staging concerning EUS were 65 to 92.1% and 63 to 78%, respectively [8, 9]. Obviously, the results of pre-operative N staging of MDCT have shown large variation [8-10]. It is difficult to draw a definitive conclusion about the utility of this technique. Therefore, it is urgently necessary to confirm the per-operative diagnostic value of MDCT in order to establish the therapeutic strategy of gastric cancer.

To acknowledge the diagnostic value of pre-operative N staging in gastric cancer, we performed the meta-analysis and systematic review by retrieving relevant literature. Meanwhile, the data of EUS involving in pre-surgical N staging was also analyzed for comparison.

Materials and methods

Literature search

A comprehensive computerized systematic literature search was carried out to retrieve abstracts of publications from studies which assessed MDCT as a diagnostic tool for initial staging before surgery or any treatment in patients with gastric cancer. We retrieved relevant articles with PubMed/Medline, ISI Web of Knowledge and Embase databases (Last updated on 23 Aug 2014). We utilized a search algorithm that was based on a combination of the following text words: (a) Multidetector Computed Tomography or MDCT, (b) gastric cancer or gastric carcinoma or gastric neo-

Pre-operative N staging of GC by MDCT

plasm or stomach cancer or stomach carcinoma or stomach neoplasm, (c) staging. The searches were restricted to studies done in humans. Two investigators, who were blinded to the author, journal, date of publication and institution, independently retrieved all the articles. Potentially related documents were assessed by reviewing their titles and abstracts and all the studies meeting the eligible criteria were retrieved. For studies utilizing the same samples in different articles, only the most complete information was selected. Information of patients was collected to obtain clinical data with approval of our hospital’s ethics committee (Table 1).

Study included criteria

Articles were selected if they fulfilled all of the following inclusion criteria: (a) MDCT was used to evaluate gastric cancer patients without surgery or any other treatment; (b) pre-operative lymph node staging of gastric cancer was investigated in the articles and the regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter; (c) sufficient data were obtained to calculate the true-positive (TP), false-positive (FP), true negative (TN) and false-negative (FN) values; (d) post-operation histopathological evaluation was served as a reference standard; (e) articles were published in English and Chinese; (f) 20 or more patients were included; (g) About the quality of the study design, only the study in which the number of the answer “yes” for the 14 items in the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [11] was more than nine was selected; (h) when data were published in more than one article, the publications with the most details was included. Review articles, letters, case reports, conference records, comments as well as publications that did not provide raw data, were excluded.

Data extraction

The methodological quality of the included studies was evaluated by two investigators independently. The QUADAS checklists were applied to assess the methodological quality of the selected articles. To perform accuracy analysis, we extracted data about the characteristics of patients and studies, including first author, year of publication, sample size, characteristics of study population (gender and age), study design, gold standard, the diagnostic equipment as well as whether the results of MDCT were blinded to the pathological diagnosis.

For each study, we obtained the number of TP, FP, TN and FN cases for MDCT in diagnosing the staging of primary gastric cancer. The data was also recorded for EUS, which was utilized for comparison with MDCT in the eligible articles.

Statistical analysis

Data about the diagnostic performance of MDCT were pooled quantitatively across eligible articles. Data were used to construct 2x2 contingency tables to calculate sensitivity, specificity and diagnostic odds ratio estimators with confidence intervals (CIs), which were plotted graphically in forest plots. A value of 0.5 was added to all cells of studies which con-
### Table 2.Diagnostic value of MDCT in detection of involved lymph node in preoperative GC patients

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GC, Gastric Cancer; MDCT, Multidetector Computed Tomography; V, Value; CI, Confidence interval; LR, Likelihood ratio; TP, True positive; FP, False positive; TN, True Negative; FN, False negative. *There are 451 lymph node in total in 278 gastric cancer patients. **There are 3 cases in 66 gastric cancer patients have complete data of lymph node involvement.
Pre-operative N staging of GC by MDCT

A

B

C

D

Sensitivity (95% CI)

Specificity (95% CI)

Diagnostic OR (95% CI)

Sensitivity

Spec-1-

Pooled Sensitivity = 0.67 (0.66 to 0.69)
Chi-square = 456.63; df = 29 (p = 0.0000)
Inconsistency (I²) = 94.1%

Pooled Specificity = 0.84 (0.83 to 0.85)
Chi-square = 462.23; df = 29 (p = 0.0000)
Inconsistency (I²) = 93.7%

Symmetric SROC

SE(AUC) = 0.0156
SE(G) = 0.0152

Fujikawa H
0.04 (0.01 - 0.15)

Yoshikawa T
0.85 (0.72 - 0.93)

Hasagawa S
0.47 (0.37 - 0.57)

Kim SH
0.90 (0.82 - 0.97)

Feng XY
0.85 (0.81 - 0.88)

Zhai P
0.91 (0.82 - 0.97)

Zhong BY
0.80 (0.68 - 0.89)

Manzelli D
0.95 (0.88 - 0.99)

Ha TK
0.70 (0.51 - 0.84)

Kim EY
0.75 (0.62 - 0.87)

Yan C
0.77 (0.59 - 0.90)

Yan C
0.99 (0.90 - 1.00)

Lee JH
0.27 (0.12 - 0.46)

Venkataraman
0.63 (0.45 - 0.77)

Park SR
0.57 (0.54 - 0.61)

Heieng SW
0.46 (0.34 - 0.56)

Atts HS
0.17 (0.08 - 0.31)

Yan C
0.73 (0.50 - 0.90)

Yang QM
0.60 (0.44 - 0.80)

Park SR
0.77 (0.59 - 0.95)

Yang DM
0.84 (0.60 - 0.97)

Chen CY
0.92 (0.78 - 0.98)

Ren G
0.31 (0.19 - 0.50)

Shinohara T
0.68 (0.60 - 0.75)

Kim HY
0.79 (0.64 - 0.89)

Yun M
0.91 (0.79 - 0.97)

Bhandari S
0.80 (0.66 - 0.94)

Lee DH
0.62 (0.52 - 0.72)

O’Ella F
0.97 (0.90 - 1.00)

Hundt W
0.95 (0.82 - 0.99)

Pooled Sensitivity = 0.67 (0.66 to 0.69)
Chi-square = 456.63; df = 29 (p = 0.0000)
Inconsistency (I²) = 94.1%

Fujikawa H
0.99 (0.97 - 1.00)

Yoshikawa T
0.36 (0.17 - 0.59)

Hasagawa S
0.99 (0.97 - 1.00)

Kim SH
0.90 (0.82 - 0.97)

Feng XY
0.61 (0.54 - 0.68)

Zhai P
0.61 (0.41 - 0.78)

Zhong BY
0.82 (0.68 - 0.92)

Manzelli D
0.56 (0.48 - 0.64)

Ha TK
0.69 (0.53 - 0.82)

Kim EY
0.92 (0.82 - 1.00)

Yan C
0.73 (0.54 - 0.88)

Yan C
0.59 (0.30 - 1.00)

Lee JH
0.98 (0.94 - 1.00)

Venkataraman
0.67 (0.59 - 0.79)

Park SR
0.57 (0.54 - 0.61)

Heieng SW
0.46 (0.34 - 0.56)

Atts HS
0.17 (0.08 - 0.31)

Yan C
0.73 (0.50 - 0.90)

Yang QM
0.60 (0.44 - 0.80)

Park SR
0.77 (0.59 - 0.95)

Yang DM
0.84 (0.60 - 0.97)

Chen CY
0.92 (0.78 - 0.98)

Ren G
0.31 (0.19 - 0.50)

Shinohara T
0.68 (0.60 - 0.75)

Kim HY
0.79 (0.64 - 0.89)

Yun M
0.91 (0.79 - 0.97)

Bhandari S
0.80 (0.66 - 0.94)

Lee DH
0.62 (0.52 - 0.72)

O’Ella F
0.97 (0.90 - 1.00)

Hundt W
0.95 (0.82 - 0.99)

Random Effects Model
Pooled Diagnostic OR = 10.21 (7.66 to 13.88)
Cochran-O = 91.56, df = 29 (p = 0.0000)
Inconsistency (I²) = 63.3%
Tau-squared = 0.3513
Pre-operative N staging of GC by MDCT

Figure 2. The forest plot and summary ROC curve of MDCT in evaluating pre-operative lymph node staging in gastric cancer patients are illustrated. (A-C) Showed the forest plot of pooled sensitivity (A), specificity (B) and Diagnostic Odds Ratio (C), respectively. (D) Revealed the summary ROC curve of MDCT. MDCT, Multidetector Computed Tomography; ROC, receiver operating characteristic.

Table 3. Comparison of the accuracy of pre-operative N staging in gastric cancer using MDCT and EUS

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Number of study</th>
<th>Diagnostic Threshold</th>
<th>Pooled Sensitivity</th>
<th>Pooled Specificity</th>
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<th>Negative LR</th>
<th>Pooled DOR</th>
<th>AUC</th>
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<td>0.84 (0.83-0.85)</td>
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<td>EUS</td>
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<td>0.53 (0.30-0.94)</td>
<td>8.08 (5.68-11.50)</td>
<td>0.8063</td>
<td>0.7414</td>
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</table>

MDCT, Multidetector Computed Tomography; EUS, Endoscopic ultrasonography; LR, Likelihood Ratio; DOR, Diagnostic Odds Ratio; AUC, area under the curve.

Table 3. Comparison of the accuracy of pre-operative N staging in gastric cancer using MDCT and EUS

In Table 1, we indicated a count of zero to avoid subsequent problems in odds calculations for articles with sensitivity or specificity of 100%. Likelihood ratios (LR) are also metrics that pool sensitivity and specificity in the calculations. In previous papers, a test was considered clinically useful when positive LR was greater than 5.0 and negative LR was less than 0.2 [12]. Heterogeneity was evaluated by $X^2$-test and $P < 0.05$ was considered as existing obvious heterogeneity. If heterogeneity existed, a random-effect model was utilized for the primary meta-analysis to obtain a summary estimate for sensitivity with 95% CI.

Testing of the diagnostic threshold was performed by Spearman's correlation test. Then we used the derived estimates of sensitivity, specificity and respective variances to construct summary receiver operating characteristic (ROC) curves. The area under the summary ROC curves was used as an alternative general measure of test performance [13, 14]. The SROC curve shows the trade-off between sensitivity and specificity across the selected articles [15]. A summary ROC curve located near the upper left corner indicates the better diagnostic modality. All the statistical computations were carried out using Meta-disc (version 1.4, http://www.hrc.es/investigacion/metadisc_en.htm) [16]. Meta-disc is an free software to perform a meta-analysis of researches of assessment of diagnostic tests and screening. $P < 0.05$ was thought to be statistically significant.

Results

Literature retrieval and inclusion of articles

After the computerized search was performed and reference lists were comprehensively cross-checked, 272 literatures were yielded, of which 223 were excluded according to their titles and abstracts. 49 potentially appropriated articles were included for further retrieval through screening the full text. Among them, 20 articles were excluded because of following reasons: case only reports (n=3), reviews (n=3), only T staging (n=5), essential data missing to construction 2×2 contingency tables (n=7) and overlapping study (n=2). Therefore, 29 eligible articles, meeting all of the inclusion criteria, were included for the analysis [7, 17-44]. Yan C et al. reported two independent studies (305 cases prospectively and 61 cases retrospectively) about N staging of gastric cancer patients in an articles [26]. Therefore, 30 studies involved in N staging of gastric cancer patients utilizing MDCT were included for following analysis. The detailed procedure of study inclusion in the meta-analysis was revealed in Figure 1.

Study characteristics and study quality assessment

The characteristics of the included studies are presented in Table 1. There are a total of 6637 gastric cancer patients in the 30 included studies. Among them, one study reported that 278 GC patients performed MDCT examination and 451 regional lymph nodes detected for evaluating pre-operative N staging [38]. 14 studies enrolled patients prospectively while the other 16 studies were retrospective or not reported. The ratio of male and mean age of every study was revealed in Table 1. In all the 30 studies, post-surgery pathology was served as the gold standard and MDCT was utilized as a diagnostic instrument for pre-operative N staging in gastric cancer patients. Among the 30 included studies, EUS was used in five studies for pre-operative N staging including 1014 gastric cancer patients. There were 20 studies in which the MDCT reviewers were blinded to patients'
Figure 3. The forest plot and summary ROC curve of EUS in evaluating pre-operative lymph node staging in gastric cancer patients are presented. (A-C) illustrated the forest plot of pooled sensitivity (A), specificity (B) and Diagnostic Odds Ratio (C), respectively. (D) Showed the summary ROC curve of EUS. ROC, receiver operating characteristic; EUS, endoscopic ultrasonography.
Pre-operative N staging of GC by MDCT

clinical data and other test results while the other 10 studies did not report whether they adopted the blinding.

We used the QUADAS tool to assess each selected study. All included studies in the meta-analysis fulfilled nine or more of the fourteen criteria in the QUADAS tool for study quality, which could be found in Table 1. There were no uninterpretable and/or intermediate test results reported (100% for “No” response to question 13). Furthermore, 10 studies were not blinded in the results of the index test results (33.3% for “No” response to questions 10 and 11).

Diagnostic accuracy of pre-surgical N staging using MDCT

All the 30 studies, including 6637 GC patients, involved in pre-operative N staging using MDCT. The data of each study and the results of the statistical pooling are shown in Table 2. The pooled estimates of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR) of MDCT in the detection of pre-operative lymph node staging in GC patients were 0.67 (95% CI: 0.66-0.69), 0.84 (95% CI: 0.83-0.85), 3.25 (95% CI: 2.69-3.93), 0.36 (95% CI: 0.28-0.46) and 10.31 (95% CI: 7.66-13.88), respectively.

Heterogeneity were found in sensitivity, specificity, LR+, LR- and DOR between 30 included studies after assessment by plotting the above parameters from each study on a forest plot and calculating the heterogeneity $x^2$, which could be seen in Figure 2A-C. The threshold effect was one important extra source of variation in the meta-analysis. To judge whether the threshold effect existed, the spearman correlation test was utilized to verify it. The spearman correlation coefficient was 0.630 and $P$ value was 0.000, which suggested that the threshold effect existed in this meta-analysis. Then we fitted a summary ROC to assess the diagnostic accuracy of MDCT, which could be seen in Figure 2D. The Q* index was calculated as a globe measure of diagnostic accuracy. The AUC and Q* were 0.8063 and 0.7414, respectively (Table 3 and Figure 3D).

Discussion

Gastric cancer is often diagnosed at an advanced stage in most countries including China. Though the primary management of GC is surgical resection, the treatment principle of GC currently was comprehensive therapy including surgery, chemotherapy, radiotherapy, molecular targeted therapy and other treatment. Accurate preoperative clinical staging, especially N staging, is essential to select proper individualized therapeutic strategy. EUS and MDCT are the most common techniques for the preoperative staging of GC patients. However, the results of pre-operative N staging of MDCT in GC patients were differently reported. To the best of our knowledge, this is the first meta-analysis to evaluate the value of MDCT concerning the pre-operative N staging in gastric cancer patients.

The diagnostic performance of the 30 studies discussed in the systematic review was patient-based. The pooled sensitivity, specificity, positive LR, negative LR and DOR of MDCT in the diagnosis of preoperative lymph node metastasis in GC patients were 0.67, 0.84, 3.25, 0.36 and 10.31, respectively. The global diagnostic accuracy was 0.7661. Though the sensitivity was not satisfactory, the results (a high specificity) suggested that MDCT was a specific diagnostic tool for the evaluation of lymph node metastasis. When compared with EUS, another preoperative diagnostic tool, the global diagnostic accuracy of MDCT was higher when assessing preoperative N staging in GC patients because the Q* of EUS and MDCT was 0.7661 and 0.7414, respectively. Moreover, MDCT was a non-invasive examination and universal in clinical application. Therefore, there is enough evidence to support the routine use of MDCT to
evaluate possible lymph node metastasis in GC patients.

Currently, two major classifications are used concerning gastric cancer. The Japanese classification is more elaborate and is based on anatomic involvement, especially the lymph node stations [45]. The other staging system developed by the AJCC and UICC, which was based on the number of involved lymph node and a minimum of 15 examined lymph nodes was recommended for adequate staging [46]. All of the selected studies in this meta-analysis adopted the AJCC/UICC staging system. It is difficult to distinguish the accurate number of involved lymph node when evaluating the pre-operative N staging using MDCT. Therefore, we divided N staging into two groups (N0 and N+ group) to perform the following analysis. As for the assessment standard of metastatic lymph node when using MDCT before operation, there were several different criterias. Most literatures showed that the regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter [7, 17, 18, 47]. Some researches thought that lymph nodes were considered positive for metastasis when the short-axis diameter was larger than 6 mm for perigastric lymph nodes and larger than 8 mm for the extraperigastric lymph nodes, especially rounded nodes with enhancement on contrast-enhanced CT that were sometimes necrotic [20, 21]. Kim SH et al. reported that LN metastasis was considered present if the short-axis diameter of any LNs was larger than 8 mm, if there was a cluster of three or more perilesional nodes regardless of size, if the LNs showed strong enhancement (> 100 HU), or if LNs with central necrosis and perinodal infiltration [7].

Lymph node metastasis is the most important prognostic factor of GC and the therapeutic strategy is established based on precise staging. Comprehensive therapy for nodal positive or locally advanced disease was considered to improve survival and reduce the risk of local recurrence, especially in gastric cancer. This meta-analysis showed that the pooled sensitivity was 67%. It is not a satisfactory result due to its inability to detect microscopic nodal invasion, which is common in gastric cancer [48]. However, the pooled sensitivity of MDCT was superior to that of EUS in this study, maybe because EUS was limited by the detection distance. Our meta-analysis results revealed that MDCT, along with EUS, was a specific diagnostic tool for the evaluation of lymph node involvement. Because of existing of the threshold effect, we fit a summary ROC to evaluate the diagnostic accuracy of MDCT. The AUC and Q* were 0.8338 and 0.7661, respectively, suggesting that MDCT was a good diagnostic tool concerning pre-operative N staging in GC patients. As a control, The AUC and Q* of EUS were 0.8063 and 0.7414, respectively, implying that the diagnostic value of MDCT involving in pre-operative N staging in GC patients was superior to that of EUS. Furthermore, some studies reported that MRI, PET-CT and other imaging equipment was also used to evaluate the diagnostic value of pre-operative N staging in GC patients. However, the number of literatures as well as the sample size was so few that there were no reliable results to analyze the diagnostic value.

We should acknowledge some potential limitations in this meta-analysis. Firstly, the presence of clinical heterogeneity in the study design, patient population and quality in these included studies influences the generalization of the results. Secondly, one third studies did not report whether they adopted the blinding. The interpretation of MDCT scans was performed qualitatively in the majority of studies. So there is a risk of subjective interpretation. Thirdly, 14 studies enrolled patients prospectively while the other 16 studies were retrospective. And only 5 studies included conventional imaging (EUS) as a control. Above factors impaired the performance and application of MDCT. To minimize bias in the selection of studies and data extraction, reviewers who blinded to the journal, authors and institution independently retrieved articles according to the inclusion criteria. Moreover, we used the QUADAS tool to guarantee that all the included articles were high quality articles. Finally, the current analysis did not allow region-by-region or node-by-node comparison, which might provide other crucial information.

In conclusion, the present analysis revealed that the diagnostic accuracy of MDCT concerning pre-operative N staging in gastric cancer patients was superior to that of EUS. So currently there is enough evidence to support the
Pre-operative N staging of GC by MDCT

routine clinical application of MDCT in the pre-operative evaluation of lymph node status in GC patients.

Acknowledgements

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Disclosure of conflict of interest

None.

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References

Pre-operative N staging of GC by MDCT


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GC, Gastric Cancer; EUS, Endoscopic ultrasonography; V, Value; CI, Confidence interval; LR, Likelihood ratio; TP, True positive; FP, False Positive; TN, True Negative; FN, False Negative.