Transabdominal ultrasonography for the preoperative diagnosis of advanced lymph node metastasis in patients with colon cancer: A retrospective cohort study

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Abstract

Purpose

Although computed tomography (CT) has been the standard modality for diagnosing lymph node metastasis (LNM), transabdominal ultrasonography (US) can be useful due to its high spatial resolution and use of Doppler signals to precisely analyze lymph nodes. This study aimed to evaluate the accuracy of US for lymph node assessment, establish US-based diagnostic criteria for LNM, and compare the capability of US with CT for the diagnosis of LNM.

Methods

This retrospective, single-institution, cohort study included patients who underwent radical surgery for clinical stage 0–III colon cancer, between March 2012 and February 2019.

Results

Overall, 34.9% (66/189) of patients had pathological LNM. The optimal US diagnostic criteria were (1) short axis ≥ 7 mm and short/long ratio ≥ 0.75 and (2) at least two of the following: the absence of hilar echoes, expansive appearance, or peripheral/mixed vascularity vascularity by the color Doppler and/or contrast-enhanced method. US showed a higher diagnostic sensitivity (54.5% vs. 43.9%; P = 0.296), higher concordance with the number of pathological LNM (correlation coefficient: US, 0.42; CT, 0.27) and pathological N diagnosis (weighted κ: US, 0.35; CT, 0.18), and higher sensitivity for advanced LNM, including multiple LNMs (47.4% vs 18.4%; P = 0.014) and N2 stage (27.8% vs 5.6%; P = 0.177), than CT.

Conclusions

US has higher sensitivity than CT for diagnosing LNM in colon cancer, along with a more accurate preoperative diagnosis of the N stage. Thus, US may be more helpful than CT for preoperatively deciding the appropriateness of neoadjuvant treatment in patients with colon cancer with advanced LNM.

Introduction

The nodal (N) status of colon cancer is an important prognostic factor [1, 2] and depends on the number of lymph node metastases (LNMs) [3]. Preoperative treatment is considered for patients anticipated to have a poor prognosis [4, 5]. The phase-III FOxTROT trial showed that preoperative chemotherapy for locally advanced colon cancer in cases with massive invasiveness or LNM might improve recurrence-free survival [6]. Thus, an accurate preoperative diagnosis of nodal involvement is essential in colon cancer management.

Computed tomography (CT) is the standard modality for diagnosing lymph node status. However, its diagnostic capability is limited, with a sensitivity of 65–88%, specificity of 65–90%, and accuracy rate of 55–95% [7]. Therefore, an alternate modality is needed to increase the diagnostic accuracy for LNM. In this regard, modalities, such as fluorodeoxyglucose–positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI), are expected to be increasingly used [8–10]. However, the optimal diagnostic modality is yet to be determined.

The potential of transabdominal ultrasonography (US) for the preoperative diagnosis of the “T” stage in colon cancer has been previously evaluated [11]. US assessment of gastrointestinal tumors has not been traditionally well received, as the wall of the colon is thin and bowel gas interferes with a detailed evaluation. However, with considerable improvements in technology, including higher image resolution and attenuation of deeper echogenicity, the use of US for detecting colorectal tumors has markedly increased.

Current US equipment has high spatial resolution, and the use of Doppler signals enables the precise analysis of lymph nodes. Moreover, contrast-enhanced ultrasound provides information on vascularity and blood flow in lymph nodes [12]. Contrast-enhanced US combined with power Doppler scanning allows for the detection of small intranodal vessels and has been used to differentiate between pancreatic cancer and chronic pancreatitis [13–16] and for small benign tumors in the pancreas [17]. However, except for hydrosonography (HS), the capability of US to diagnose LNM in colorectal cancer is still unknown [18–20]. Moreover, no US diagnostic criteria for colon cancer, including its LNM, have been established.

Thus, our primary objective was to evaluate the accuracy of US for lymph node assessment and establish US diagnostic criteria for LNM. Our secondary aim was to compare the diagnostic capability of these US criteria with that of CT criteria.

Materials And Methods

Study design and patient selection

This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board (no. 019–0182). The requirement for acquisition of informed consent from patients was waived by the ethics committee owing to the retrospective nature of this study.

This retrospective, single-institution cohort study included patients who underwent tumor resection for colorectal tumors in our department between January 2011 and July 2019. During this period, both CT and US were basically performed for preoperative diagnosis in all patients. Among 707 patients, we excluded those with stage IV tumors (n = 122), neoadjuvant therapies (n = 29), tumors that were not carcinoma or had rare histopathology (n = 27), and tumors located in the middle or lower rectum (because visualization of the primary tumor using the transabdominal method is poor in these areas) or the appendix (n = 122). We also excluded 172 patients who had not undergone US or whose US was

performed at more than 30 days before surgery. Furthermore, 46 patients whose CT was performed at more than 30 days before surgery or was not compliant with the CT protocol (e.g., the slice thickness was not 5 mm or no enhancement) were excluded. Finally, 189 patients were included in this study (Fig. 1).

With respect to tumor location, the right colon was defined as the area from the cecum to the transverse colon, and the left colon was defined as the area from the descending colon to the rectosigmoid colon. The staging was according to the 8th American Joint Committee on Cancer TNM edition [21]. Histological grades were classified as low (well or moderately differentiated and papillary adenocarcinoma) or high (poorly differentiated or mucinous adenocarcinoma, signet-ring cell carcinoma, and neuroendocrine carcinoma).

CT protocol and evaluation

All patients underwent thoracic, abdominal, and pelvic contrast-enhanced CT scans to evaluate nodal and distant metastases before the surgical treatment. All CT scans were obtained with six multidetector row CT scanners: Aquilion 64, Aquilion PRIME, and Aquilion ONE ViSION (Canon Medical Systems, Otawara, Japan), LightSpeed VCT (GE Healthcare, Milwaukee, WI, USA), SOMATOM Sensation64 (Siemens AG Medical Solutions, Erlangen, Germany), and Brilliance iCT Elite (Philips Medical Systems, Eindhoven, Netherlands). The contrast-enhanced CT protocol used a single-phase scan performed 70–80 s after the injection of contrast material (450–480 mgI/kg) with a slice thickness of 5 mm. The lymph nodes were screened on axial images. The CT images were interpreted by certified diagnostic radiologists. Based on previously reported CT diagnostic criteria [7, 22–27], we developed our own criteria as follows: criterion 1: long axis ≥ 7 mm and short/long (S/L) ratio ≥ 0.8; criterion 2: long axis ≥ 7 mm and S/L ratio < 0.8 or long axis ≥ 5 to < 7 mm and S/L ratio ≥ 0.8; and criterion 3: one or more of the following characteristics: heterogeneous texture, irregular border, and ≥ 100 Hounsfield units (region of interest ≥ 5 mm^2).

A lymph node that matched with CT criterion 1 or with both CT criteria 2 and 3 was diagnosed as LNM.

US protocol and evaluation

Aplio XG (SSA-770A/790A) 500 and i800 ultrasound units (Canon Medical Systems) with a 3.75/6.0-MHz center frequency convex transducer or a 7.5-MHz center frequency linear transducer and LOGIQ E9 (GE Healthcare) with a 4.0-MHz center frequency convex transducer or a 9.0-MHz center frequency linear transducer were used for each examination. Patients underwent an 8-hour fasting protocol, which prohibited intake of water or added preparations, prior to the procedure. Patients generally remained in the supine position during the examination or the left or right decubitus position, as needed. The colon of each patient was sequentially assessed from the cecum to the rectosigmoid colon to identify the tumor as a hypoechoic mass, as previously described [11]. Lymph nodes around the tumor were evaluated following primary tumor evaluation. The evaluation area of lymph nodes was defined as the region adjacent to the tumor (5 cm on the oral and anal sides) and proximally along the vessels to the branch artery.

Lymph node characteristics, such as the long and short axes, S/L ratio, echo level, echo texture, hilum of the lymph node, expansive appearance, and vascular pattern were determined using US. Color Doppler and/or contrast-enhanced US were used to determine the vascular pattern of the lymph nodes. The contrast-enhanced pattern was evaluated in the vascular phase and by an accumulation imaging study. A low mechanical index (0.16–0.22) was implemented for 45 s after the infusion of Sonazoid® (GE Healthcare; 0.0075–0.01 mL/kg). The vascular phase was acquired from 10 s to 45 s after the infusion. After capturing the phase, Sonazoid® was disrupted by high acoustic pressure, followed by the replenishment of microbubbles, maintenance of the maximum brightness of each harmonic signal, and construction of a map of the vascular pattern, thereby obtaining accumulation images. Representative images are shown in Fig. 2. All US examinations were performed by one of the eight sonographers, all of whom are registered in the Japan Society of Ultrasonics in Medicine. All still images and movie clips were analyzed and interpreted by two registered medical sonographers. All US images were interpreted through consensus, with blinding of patient information and pathological diagnosis. US findings, such as isoechoic/hypoechoic levels, homogeneous texture, absence of hilar echoes, expansion appearance, and peripheral/mixed vascularity, were selected as characteristics of suspected malignancy, as per earlier reports [13, 15, 28–33].

Statistical analysis

The receiver operating characteristics (ROC) curves of continuous data were drawn using a univariable logistic model and compared by bootstrapping the original dataset. The cutoff values for predicting pathological LNM were determined from the ROC curves. Diagnostic capabilities were evaluated with respect to sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and diagnostic odds ratio (DOR). The diagnostic capability of CT was compared with that of US using Fisher's exact test. Concordance between CT and US diagnoses was assessed using κ statistics. The correlation between the number of metastatic lymph nodes by CT or US and the number of pathological metastatic lymph nodes was calculated using Spearman's rank correlation coefficient. Concordance between the N stage diagnosis by CT or US and the pathological N stage was assessed using the weighted κ index. The κ values were interpreted as proposed by Landis and Koch [34]. All statistical analyses were performed using EZR version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander version 2.6-0, which is designed to add statistical functions and is frequently used in biostatistics [35]. All P-values < 0.05 were considered statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Overall, 66 (34.9%) patients had pathological LNM. The number of pathological LNM ranged from 0 to 15. Pathological N stages were N1a, N1b, N2a, and N2b in

28 (14.8%), 20 (10.6%), 10 (5.3%), and 8 (4.2%) patients, respectively.

US diagnostic criteria

Lymph nodes could be identified in 105 patients. Among those in whom multiple lymph nodes could be identified, the lymph node with the largest short axis was regarded as the representative lymph node. In 105 representative lymph nodes, the median long axis was 9.0 mm (3.5–25.0), median short axis was 6.1 mm (2.9–21.8), and median S/L ratio was 0.74 (0.22–0.99). The echo levels of the representative lymph nodes were hyperechoic, isoechoic, and hypoechoic in 14 (13.3%), 86 (81.9%), and 5 (4.8%) cases, respectively. The echo textures of the representative lymph nodes were heterogeneous and homogeneous in 45 (42.9%) and 60 (57.1%) cases, respectively. No hilar echoes were observed in 81 (77.1%) patients. Expansive appearance was observed in 37 (35.2%) patients. Peripheral or mixed vascularity was seen in 45 (42.9%) patients.

ROC curves determined the optimum cutoff value as 9 mm for the long axis, 7 mm for the short axis, and 0.75 for the S/L ratio because they were closest to the top-left corner in the ROC plot. The diagnostic capability of these cutoff values and lymph node characteristics are shown in Online Resource 1. The US diagnostic criteria were determined using the bootstrapping method, which included these parameters. Considering expert consensus and Akaike's information criteria for the bootstrapping process, the optimal US diagnostic criteria were as follows: criterion 1: short axis ≥ 7 mm and S/L ratio ≥ 0.75 and criterion 2: two or more of the following characteristics: the absence of hilar echoes, expansive appearance, and peripheral or mixed vascularity.

A lymph node that met one of these two criteria was diagnosed as LNM.

Diagnostic capability of the US criteria

Comparisons of diagnostic capabilities between CT and US, according to our US criteria, are shown in Table 2. Overall, 61 (32.3%) and 75 (39.7%) patients with preoperative LNM were diagnosed using CT and US, respectively. US was not significant for the preoperative diagnosis of LNM, but it had higher diagnostic capability than CT. Further, the DOR of US was higher than that of CT. The κ-coefficient value between CT and US was 0.52.

Sensitivity and specificity related to clinicopathological features by CT and US

Results of the analysis on the relationship between clinicopathological factors and sensitivity or specificity of CT and US are shown in Online Resource 2. CT had lower sensitivity for the preoperative diagnosis of LNM in tumors < 50 mm and ≤ T2. In contrast, the diagnostic capability of US did not vary according to tumor size or type. US could detect LNM in cases with a high histological grade and showed higher sensitivity than CT. However, the difference was not significant because of the low number of cases. There were differences in sensitivity and specificity between CT and US according to the short-axis

lymph node size, with US tending to have higher sensitivity than CT in patients with lymph nodes measuring < 5 mm.

Evaluation of LNM and N stage by CT and US

US diagnosis showed a stronger correlation with the pathological diagnosis than CT diagnosis (Fig. 3). The correlation coefficient between the number of LNM in imaging diagnosis by CT, and pathological diagnosis was 0.27 ($P < 0.001$). Meanwhile, the correlation coefficient between the number of LNM in US imaging and pathological diagnosis was 0.42 ($P < 0.001$). Further, US staging achieved higher concordance with the pathological N stage than did CT staging (Table 3). The concordance between the pathological N stage and CT staging showed slight agreement (weighted $\kappa = 0.18$, $P = 0.007$). Meanwhile, the concordance between the pathological N stage and US staging was in fair agreement (weighted $\kappa = 0.35$, $P < 0.001$).

Diagnostic capability for advanced LNM (multiple LNMs and N2 stage)

In the preoperative diagnosis of multiple LNMs (≥ 2), US showed a significantly higher sensitivity than CT but had the same specificity. The DOR of US was higher than that of CT. As for N2 staging (LNM ≥ 4), US did not show significantly improved sensitivity; however, it was still higher than that of CT. The DOR of US was higher than that of CT (Table 4).

Discussion

The study showed that US had a higher sensitivity than CT for diagnosing LNM. US could detect LNM, especially in small lymph nodes, small tumors, and tumors with shallow invasion. Moreover, the N stage, as predicted by US, was highly concordant with the pathological N stage. Thus, patients with advanced LNM, such as those with multiple LNMs or N2 stage, could be diagnosed preoperatively using US. This study is the first to investigate the usefulness of US for the preoperative diagnosis of LNM in colon cancer.

Preoperative diagnosis of LNM in colon cancer is important, as LNM is a stronger prognostic factor than the depth of invasion, and advanced LNM worsens prognosis [1–3]. Recently, neoadjuvant chemotherapy has been proven to be beneficial for patients with colon cancer with a poor prognosis. A retrospective study showed that neoadjuvant chemotherapy could improve survival in patients with clinical T4b colon cancer [36]. The FOxTROT trial found evidence of histological regression in 59% of cases [6]. Therefore, preoperative treatment should be recommended for patients with a poor prognosis. However, for this, preoperative diagnosis needs to be more accurate.

A recent study on multidetector row CT (MDCT) found accuracy rates of 64–77% for the N stage in colorectal cancer [37]. FDG-PET has been shown to have accuracy rates of 63–69% for assessing lymph node involvement in the colorectum [8, 9]. Regarding MRI assessment, Nerad et al. reported that the sensitivity and specificity for detecting nodal involvement were 47–68% and 64–86%, respectively [10].

Our findings show that the capability of US to accurately diagnose LNM in colon cancer is comparable to that of other modalities.

Furthermore, US is less invasive compared to other modalities. Most previous reports have used endoscopic ultrasound (EUS), which can accurately evaluate the primary tumor and lymph node status close to the primary tumor [28, 31, 33]. However, EUS has limitations and involves a complex technique for assessing tumors in the right side of the colon. Furthermore, EUS may be difficult to perform in cases where lymph nodes are far from the primary tumor and in cases with multiple LNMs. For such cases, the transabdominal approach could be useful. The effectiveness of the transabdominal method for determining the depth of invasion in colon cancer has been previously defined [11]. Further, there have been reports on the usefulness and accuracy of HS for the transabdominal assessment of LNM in colorectal cancer [18–20, 38, 39]. However, while HS is highly sensitive in detecting primary tumors, it has low sensitivity in assessing the N stage [38, 39] and LNM, ranging widely from 25–82% [18–20].

In this study, we developed US diagnostic criteria for LNM in colon cancer. The criteria consisted of short axis ≥ 7 mm, S/L ratio ≥ 0.75, absence of hilar echoes, expansion appearance, and peripheral or mixed vascularity. Earlier reports have shown that these characteristics indicate lymph node malignancy [12, 30, 32]. Lymph node vascularity on EUS was also reported to be indicative of malignancy [12]. In our US criteria, vascularity had the highest accuracy, consistent with a previous report [12]. Furthermore, these criteria showed a higher agreement than CT. Collectively, these findings support that US can identify a patient with advanced LNM who should undergo preoperative treatment, with higher sensitivity than CT.

The current study has some limitations. First, this was a retrospective study conducted in a single center. Second, the LNM detected by either US or CT was not always concordant with pathological LNM. However, we analyzed concordance in the number of LNM between US or CT and pathological assessment, thus minimizing the effect of this limitation. Third, US assessment of LNM is not recognized as a standard examination of gastrointestinal tumors because US practitioners believe that it requires advanced technical skills. Systematic educational programs may be needed to increase the number of experienced technicians. Fourth, the interval between US and surgery was shorter than that between CT and surgery. Thus, US could evaluate lymph node status closer to the operation, as compared with CT.

However, our findings provide evidence that US may be useful for the diagnosis of colon cancer. A new vascular evaluation method, superb microvascular imaging, may be further useful for diagnosing malignant lymph nodes by US, as it yields more information about nodal vessels than power Doppler ultrasound [40]. This technique could further enhance the diagnosis of LNM by US. Furthermore, we believe that evaluations using a contrast-enhanced mode with a higher frame rate than the current study or further utilizing the properties of Sonazoid® introduced into reticuloendothelial cells will contribute to an even more accurate assessment of lymph nodes. Further prospective studies, with a larger number of patients, should be performed to validate the role of US in the management of colon cancer.

In conclusion, US has higher sensitivity for diagnosing LNM in colon cancer than CT and may yield a more accurate preoperative diagnosis of the N stage. Thus, US may be more helpful than CT for

preoperative decision-making regarding the appropriateness of neoadjuvant treatment in patients with colon cancer with advanced LNM.

Declarations

Author contributions: KI, SH, MN, TS, RS, YK, SO, HM, YM, NI, TY, NT, and AT contributed to the study concept and design. KI, SH, and MN wrote the manuscript. MN, YK, and SO interpreted the ultrasonography images. TS and RS interpreted the computed tomography images. IY and RT performed the statistical analyses. KI, SH, HM, YM, NI, TY, and NT performed the operations and collected clinicopathological data. AT supervised the study. KI, SH, and MN participated in the interpretation of the results and writing of the report. All authors have read and approved the final manuscript.

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Code availability: Not applicable.

Ethics approval: This study was approved by the institutional review board.

Consent to participate: The requirement for acquisition of informed consent from patients was waived by the ethics committee owing to the retrospective nature of this study.

Consent for publication: Not applicable.

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Tables

Due to technical limitations, table 1, 2, 3, 4 is only available as a download in the Supplemental Files section.

Figures

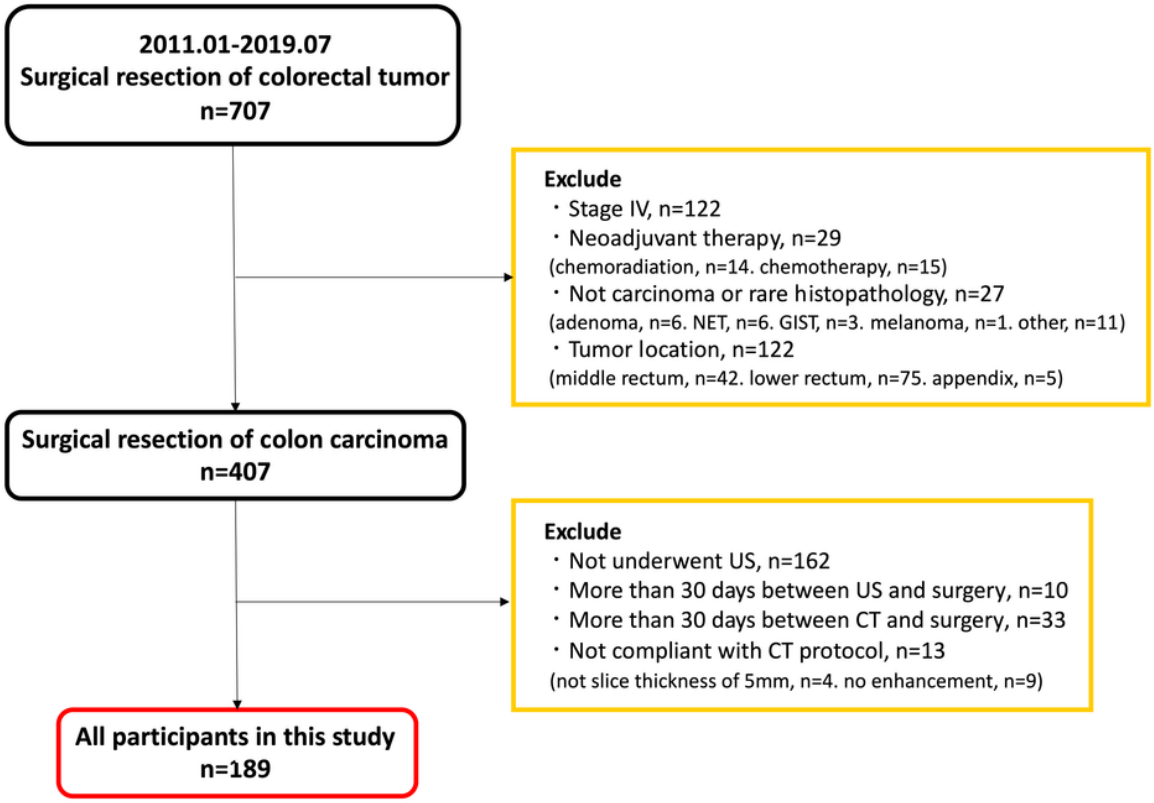

Figure 1

Patient enrollment flowchart NET: neuroendocrine tumor; GIST: gastrointestinal tumor; US: transabdominal ultrasonography; CT: computed tomography

Figure 2

Representative images of lymph node metastasis by transabdominal ultrasonography. (a) Normal image. (b) Contrast-enhanced (Sonazoid) image. White arrows indicate the lymph node LN: lymph node.

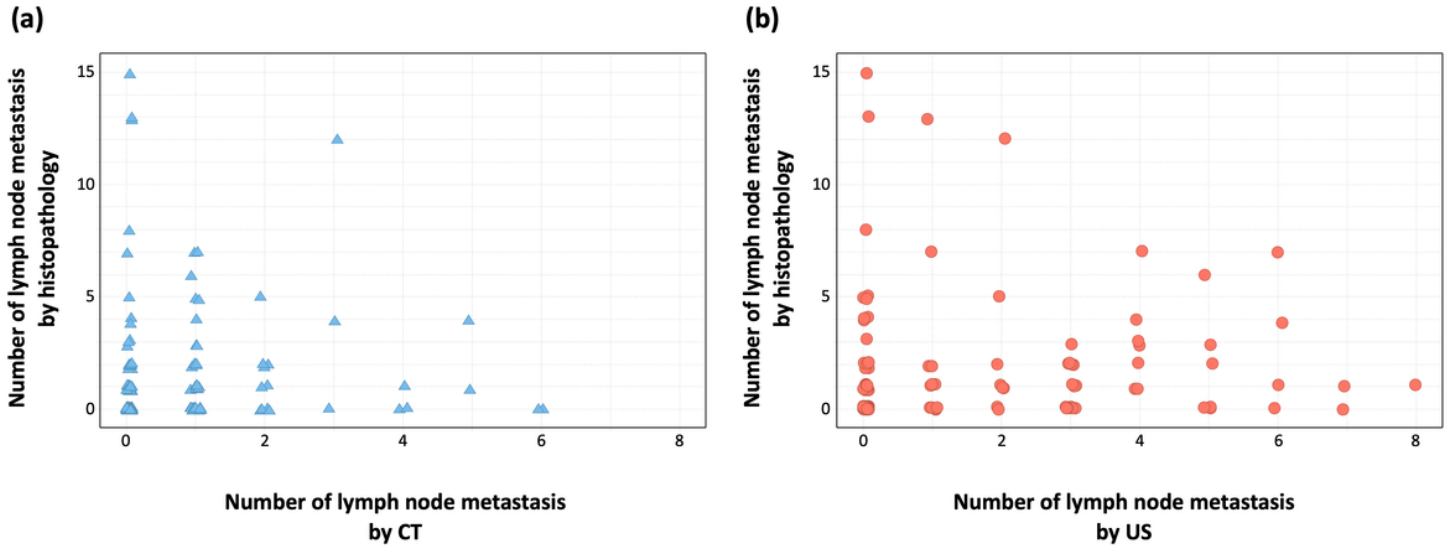

Figure 3

Scatterplot of the distribution of lymph node metastasis. Comparison in the number of lymph node metastasis between histopathology and (a) computed tomography (blue triangle) and (b) transabdominal ultrasonography (red circle) CT: computed tomography; US: transabdominal ultrasonography

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- OnlineResource1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx
- OnlineResource2.xlsx
- OnlineResourcessubmit.docx