Esophageal Varices in Cirrhotic Patients: Evaluation with Liver CT

Young Jun Kim[1,2]
Steven S. Raman[1]
Nam C. Yu[1,3]
Katherine J. To'o[1]
Rome Jutabha[4]
David S. K. Lu[1]

OBJECTIVE. The objective of this study was to evaluate the performance of routine helical liver CT in the detection and grading of esophageal varices in cirrhotic patients.

MATERIALS AND METHODS. A total of 67 consecutive cirrhotic patients who underwent both upper endoscopy and helical liver CT within a 4-week interval were evaluated. The CT protocol included unenhanced, arterial, and portal phases with a collimation of 7–7.5 mm. Two blinded abdominal imagers (6 and 7 years' experience) retrospectively interpreted all CT images to detect the presence of esophageal varices on a 5-point confidence scale and measure the largest varix identified. Receiver operating characteristic (ROC) curve analysis was performed, and the correlation between CT measurements and endoscopic grading, the reference standard, was assessed.

RESULTS. The variceal detection rates for the observers was 92% (11/12) and 92% (11/12) for large (i.e., clinically significant) varices, 53% (16/30) and 60% (18/30) for small varices, and 64% (27/42) and 69% (29/42) for all varices. The area under the ROC curve for the detection of esophageal varices of any size was 0.77 (observer 1) and 0.80 (observer 2). CT variceal grading showed a strong correlation with endoscopic grading for both observers ($p \leq 0.001$). Using a variceal diameter threshold of 3 mm on CT, sensitivity, specificity, and accuracy for distinguishing large esophageal varices from small or no varices were 92% (11/12), 84% (46/55), and 85% (57/67), respectively, for both observers.

CONCLUSION. Liver CT is useful for the detection and grading of esophageal varices. A diameter of 3 mm may be an appropriate screening threshold for large clinically significant varices.

Keywords: cirrhosis, CT, esophageal varices, esophagus, liver disease

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[1]Department of Radiological Sciences, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Los Angeles, CA 90095-1721. Address correspondence to D. S. K. Lu.

[2]Present address: Department of Radiology, Konkuk University Hospital, Gwangjin-gu, Seoul, Korea.

[3]Medical Imaging Informatics Group, UCLA Biomedical Informatics Center, Los Angeles, CA.

[4]Division of Digestive Diseases and Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.

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Most cirrhotic patients develop esophageal varices, with a lifetime incidence as high as 80–90% [1, 2]. Approximately one third of cirrhotic patients with esophageal varices develop an episode of esophageal hemorrhage, which has a high morbidity and mortality. About 20–35% of patients do not survive the first bleeding episode; those who survive will rebleed within 6 months in up to 70% of the cases, with an overall 2-year survival rate of only 30–40% after the initial episode [3, 4]. Therefore, in cirrhotic patients, detection and prevention of the first esophageal variceal hemorrhage are crucial to minimize complications.

Universal screening upper endoscopy is recommended for patients with cirrhosis to evaluate for the presence of esophageal varices [5, 6]. Patients with large esophageal varices are treated with a prophylactic nonselective β-blocker to decrease portal venous pressure and risk of hemorrhage or with preventive endoscopic ligation to eradicate the varices. Patients with no or small varices are rescreened at periodic intervals of about 2 years [5, 6]. However, upper endoscopy is invasive and expensive, which are limitations of its utility as a screening test. Thus, its role and cost-effectiveness in this setting have been debated [7–9]. As a result, many investigators have attempted to identify high-risk patients using noninvasive indexes of portal hypertension such as serum analysis, spleen size measured on sonography, or both [10–12]. The consistent utility of these models, however, could not be corroborated when applied to other independent patient series [13].

In a number of reports, the radiologic diagnosis of esophageal varices in the setting of liver cirrhosis has been described [14–18], but to our knowledge, a systematic evaluation of accuracy was performed in only two studies using sonography or MRI [19, 20]. The accuracy of multiphasic helical CT has not been studied in this setting, although CT remains a mainstay of cirrhotic liver imaging and almost always provides adequate coverage of the distal esophagus where virtually all va-

rices develop. The purpose of our study was to retrospectively evaluate the performance of routine IV contrast–enhanced CT with regard to the detection and grading of esophageal varices in patients with liver cirrhosis.

Materials and Methods

This study was approved by our institutional review board; informed consent was not required for review of the medical records because a waiver was granted.

Patients

By query of our institutional database, two authors retrospectively identified 79 consecutive patients with liver cirrhosis who underwent contrast-enhanced helical liver CT within 4 weeks of upper gastrointestinal endoscopy from January 2000 to March 2004. Of those patients, six were excluded because they had undergone endoscopic band ligation of esophageal varices before CT. Five patients who had nasogastric tubes, which interfere with evaluation of the esophagus, were excluded. One patient with hiatal hernia was also excluded because the distal esophagus was displaced upward by the herniated stomach and was not in the field of view. The remaining 67 patients (39 men and 28 women; age range, 33–77 years; mean age, 56.2 years) were included in the study. The causes of liver cirrhosis were hepatitis B (n = 15), hepatitis C (n = 24), combined hepatitis B and C (n = 6), alcoholic hepatitis (n = 15), primary biliary cirrhosis (n = 5), and cryptogenic (n = 2). In the evaluation of liver function using the Child-Pugh classification, 16 patients were in class A, 25 were in class B, and 26 were in class C.

On endoscopy, esophageal varices were graded as none, small, or large. Small varices were defined as those that flatten with insufflation or protrude minimally into the esophageal lumen, whereas large varices were defined as those that protrude into the esophageal lumen and touch each other (i.e., presence of confluence) [21]. In each case, the endoscopic diagnosis was determined from a review of the endoscopist's procedure report.

CT

CT was performed either on a single-detector helical CT scanner (HighSpeed CT/i, GE Healthcare) in 46 patients or on a 4-MDCT scanner (LightSpeed QX/i, GE Healthcare) in 21 patients. After unenhanced scanning, helical CT images were obtained during the hepatic arterial dominant phase using a 30-second delay and the portal venous dominant phase using a 65-second delay after the initiation of IV injection of 120 mL of nonionic contrast material (iohexol [Omnipaque 350, Nycomed]) at a rate of 3 mL/s using a power injector. During all phases, single-detector CT images were obtained with a 7-mm collimation, pitch of 1.5, and 7-mm reconstruction intervals, whereas MDCT images were obtained with a 7.5-mm section thickness, pitch of 1.3:1, and 7.5-mm reconstruction intervals. Images were obtained from the dome of the diaphragm to the lower pole of the right kidney during a single breath-hold. All patients received oral contrast material (800–1,000 mL of diluted diatrizoate meglumine and diatrizoate sodium [Gastroview, Bristol-Myers Squibb] or 2.1% weight/volume barium [Readi-Cat, E-Z-EM]) over 45–60 minutes before examination. All CT images were acquired at end inspiration.

Image Analysis

Two gastrointestinal radiologists who had been interpreting abdominal CT images for 6 and 7 years, respectively, at the time of the study were asked to independently evaluate the CT images. They were informed that all patients had liver cirrhosis, but they were blinded to any other information including endoscopic findings. Interpretation of the CT images was performed on a workstation (Precision workstation, Dell) equipped with specialized software (Vitrea [version 2], Vital Images).

The CT images were reviewed for the presence and size of esophageal varices. Combined interpretation of unenhanced, hepatic arterial dominant phase, and portal dominant phase images was performed. Each observer recorded a confidence level for the presence of esophageal varices using a 5-point scale (1 = definitely absent, 2 = probably absent, 3 = possibly present, 4 = probably present, 5 = definitely present). A score of 5 was assigned for discrete enhancing nodular lesions abutting the luminal surface of the esophageal wall or protruding into luminal space; a score of 3 was given if ill-defined nodular enhancing lesions appeared to be contacting or protruding into the lumen; and a score of 1 was given if no enhancing lesions were seen in the esophageal wall. Scores of 2 and 4 were assigned if CT findings were between 1 and 2, and 3 and 5, respectively, therefore being somewhat dependent on subjective decision of each observer.

A finding of circumferential esophageal wall thickening alone without any nodular enhancing lesion was not considered to indicate the presence of esophageal varices. A luminal protruding lesion without enhancement was also not deemed an esophageal varix. A temporal enhancement pattern reflecting that of the portal vein—for example, progressive opacification spanning the arterial and portal phases or enhancement in the portal phase alone—was considered to reflect esophageal varices that constitute portal venous collaterals via the left gastric vein. Thus, early enhancement in the arterial dominant phase with washout in the portal phase pattern was not considered to indicate varices. Because positive oral contrast medium could potentially interfere with the identification of esophageal varices, observers were asked to carefully compare the enhanced images with the unenhanced images to distinguish residual oral contrast agent from a real enhancing lesion on the luminal surface of the esophagus.

Observers were informed that a score of 3 or more would be considered to be a positive decision about the presence of varices in later statistical analysis. For each case with a score of 3, 4, or 5, observers were asked to measure the short-axis diameter of the largest visible esophageal varix with electronic calipers.

Statistical Analysis

A receiver operating characteristic (ROC) curve was fitted to each observer's confidence rating data by means of a maximum-likelihood estimation determined using statistics software (LABMRMC 1.0B, Metz CE, University of Chicago). Observer performance was estimated by calculating the area under the ROC curve (A_z). When a patient was assigned a score of 3, 4, or 5 (possibly present, probably present, or definitely present, respectively), the patient was regarded as having positive findings for the presence of esophageal varices.

The sensitivity, specificity, and accuracy in the CT diagnosis of esophageal varices were calculated. The positive predictive value and negative predictive value were also determined. Kappa statistics were used to evaluate interobserver agreement with regard to the presence of esophageal varices. A kappa value of up to 0.20 was considered to indicate a slight agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect [22]. For all positive CT cases, correlations between the size measurements of the esophageal varices on CT and the endoscopic grading were performed using Spearman's rank correlation test. Also for these cases, the difference between the CT measurement for true small and true large varices was tested using the Mann-Whitney U test. A p value of less than 0.05 was considered to indicate a statistically significant difference.

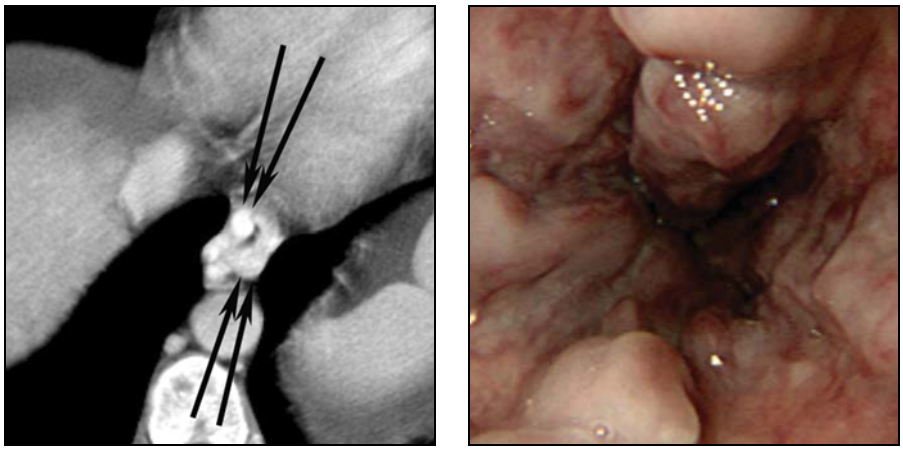
Results

Of the total of 67 patients, 25 (37%) patients had no varices, 30 (45%) had small varices, and 12 (18%) had large varices according to the endoscopic findings. The 12 patients with large varices were evenly distributed among Child-Pugh classes A, B, and C, with four patients in each group. No patients had a significant endoscopic abnormality other than esophageal varices, such as esophageal mass, ulcer, or inflammation.

TABLE 1: Sensitivity, Specificity, Accuracy, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for Detection of Esophageal Varices of Any Size

Performance Measure	Observer 1		Observer 2	
	Values	95% CIs	Values	95% CIs
Sensitivity (%)				
All esophageal varices	69 (29/42)	54–81	64 (27/42)	49–77
Large esophageal varices	92 (11/12)	63–100	92 (11/12)	63–100
Small esophageal varices	60 (18/30)	42–75	53 (16/30)	36–70
Specificity (%)	76 (19/25)	56–89	88 (22/25)	69–97
Accuracy (%)	72 (48/67)	60–81	73 (49/67)	61–82
PPV (%)	83 (29/35)	67–92	90 (27/30)	74–97
NPV (%)	59 (19/32)	42–75	60 (22/37)	44–74

Note—Data in parentheses are number of patients who were used to calculate performance measures.



A **B**

Fig. 1—69-year-old woman with liver cirrhosis and large esophageal varices.
A, Portal phase dominant axial MDCT image of lower esophagus shows multiple nodular, enhancing, intraluminally protruding lesions (*arrows*) within esophagus wall. In this patient, largest varix was measured as 8.2 and 9.1 mm in short diameter, respectively, by two observers.
B, Endoscopic image shows multiple large varices.

Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for the CT detection of any size esophageal varices are shown in Table 1. Of the 12 patients with large esophageal varices, 11 (92%) were detected by both observers (Figs. 1 and 2), whereas 16 (53%) and 18 (60%) of the 30 patients with small varices were detected by each observer (Fig. 3). Both observers detected the same 11 cases of large varices, whereas 14 cases of the 30 cases of small varices were detected by both of the observers.

The A_z values calculated from ROC analysis were 0.770 (95% CI, 0.657–0.884) for observer 1 and 0.802 (95% CI, 0.690–0.914) for observer 2. The kappa value for interobserver agreement of variceal detection was 0.614, indicating substantial agreement obtained between the two radiologists.

For all positively interpreted CT cases, the CT measurements of variceal size stratified into three groups (none, small, or large esophageal varices, based on endoscopy) are depicted for each observer in Figure 4. Correlations between CT measurements of varix size and endoscopic grading were significant in both observers with a correlation coefficient r of 0.58 for observer 1 ($p < 0.001$) and 0.56 for observer 2 ($p = 0.001$). For observer 1, the CT measurement for true-positive large esophageal varices ranged from 3.5 to 8.2 mm (mean ± SD, 5.1 ± 1.2 mm) and the measurement for true-positive small varices ranged from 1.7 to 7.3 mm (3.2 ± 1.7 mm) ($p < 0.001$). For observer 2, true-positive large and small varices measured 4–9.1 mm (5.7 ± 1.4 mm) and 1.5–6.8 mm (3.4 ± 1.5), respectively ($p < 0.0017$).

Retrospective application of a 3-mm-diameter criterion on CT yielded sensitivity, specificity, and accuracy of 92%, 84%, and 85%, respectively, for distinguishing large varices from small varices or no varices for both observers (Table 2). Using a 4-mm criterion, sensitivity, specificity, and accuracy were 83–92%, 91–91%, and 90–91%, respectively, for the two observers.

Discussion

Because many patients with cirrhosis undergo CT examinations for the evaluation of other complications of cirrhosis, CT could provide an opportunity to evaluate esophageal varices without any added cost, inconvenience, or risk. For example, biannual CT has been advocated for hepatocellular carcinoma screening in patients awaiting liver transplantation [23, 24], a group for whom variceal screening is especially crucial. Such a dual-screening strategy, in fact, would further improve the cost-effectiveness of CT in this setting. In addition, evaluation of esophageal varices on CT does not require much additional effort or time for radiologists. These factors constitute a major theoretic advantage of CT over endoscopy, which imposes additional burden on patients and on limited health care resources.

CT findings of esophageal wall thickening, intraluminal protrusions or irregularities, and nodular enhancement within the wall suggest the presence of esophageal varices [14, 17, 18]. However, wall thickening and intraluminal protrusions are not specific for esophageal varices because the normal esophagus could show such findings owing to peristalsis or redundant mucosal folds [14]. Also, such findings may be present in other esophageal diseases, including esophageal carcinoma or esophagitis [19]. Paraesophageal varices may be seen as dilated veins closely juxtaposed to the outer wall of the esophagus. It is not always easy to distinguish paraesophageal varices from esophageal varices, especially if the esophageal wall is collapsed, given their intimate anatomic relationship [20]. Therefore, in this study, we defined CT criteria of esophageal varices more specifically as nodular or tubular enhancing lesions within the esophageal wall that are contacting the intraluminal surface, thus minimizing inclusion of paraesophageal varices.

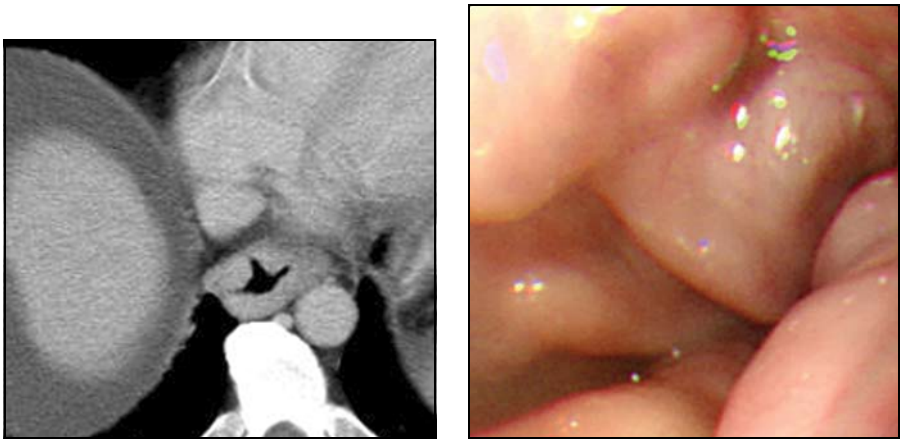


Fig. 2—68-year-old man with liver cirrhosis and large esophageal varices.
A, Portal phase dominant axial single-detector CT image of lower esophagus shows nodular thickening of esophageal wall, but without any discrete enhancing lesions. Thus, this patient was considered to have no varix by both observers.
B, Endoscopic image shows, however, multiple large variceal columns.

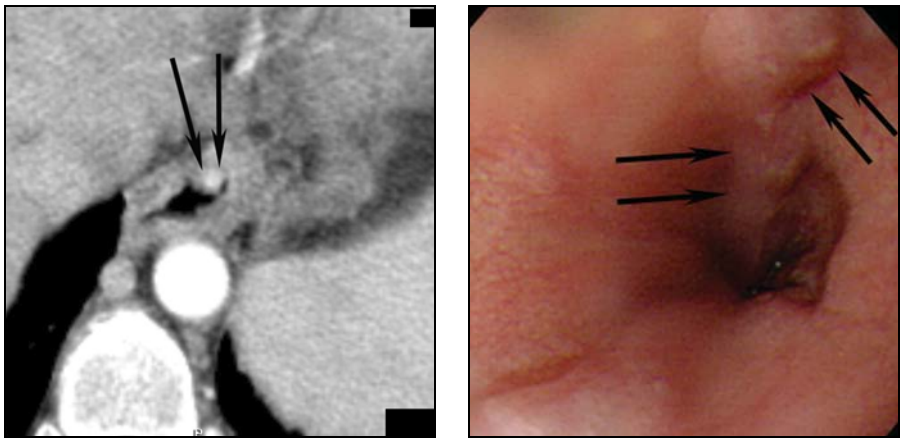


Fig. 3—54-year-old woman with liver cirrhosis and small esophageal varices.
A, Portal phase dominant axial MDCT image of lower esophagus shows enhancing lesion (*arrows*) protruding into luminal space; lesion was measured as 3.6 and 3.8 mm in short diameter, respectively, by two observers.
B, Endoscopic image shows small esophageal varix (*arrows*).

In a previous MR study with regard to the detection of esophageal varices in patients with chronic liver disease, the A_z was 0.64, with a sensitivity of 81% and specificity of 45% [20]. A trend toward improved performance in our study (A_z for observers 1 and 2: 0.77, 0.80) may be attributed to higher resolution and thinner slice thickness used in our CT study (512 × 512 matrix, 7- to 7.5-mm slice thickness) than in the previous MR study (512 × 224 matrix, 8- to 10-mm slice thickness). The authors of the MR study defined esophageal varices as dilated vessels in or adjacent to the wall of the esophagus, thus likely resulting in nonspecific inclusion of some paraesophageal varices, whereas we defined esophageal varices as only enhancing nodular or tubular lesions in the esophageal wall that were in contact with the luminal surface. Our lower sensitivity and higher specificity compared with those reported in the MR study likely stem predominantly from this difference in the definition of esophageal varices.

The overall sensitivities for detecting esophageal varices of any size were less than 70% due to unsatisfactory detection of small varices. Poor sensitivity for low-grade disease can be attributed to several factors. First, small esophageal varices are presumably more susceptible to hemodynamic and respiratory factors, so they may at times be collapsed and not visible on CT; for example, some small varices are detectable only during the Valsalva maneuver [4]. Second, it is sometimes difficult to visualize small enhancing varices almost embedded in the wall of esophagus [18] because the wall itself enhances to variable degrees. Finally and the foremost factor, in this retrospective study, a conventional liver CT protocol was used rather than a dedicated protocol optimized for the evaluation of esophageal varices. All studies included positive oral contrast agent, so residual contrast material coating the luminal surface may have interfered with the detection of some small varices, despite our attempt to minimize this phenomenon by carefully comparing unenhanced and enhanced images. In addition, the slice thickness, 7–7.5 mm, was not optimal for the detection of lesions smaller than 5 mm. Finally, variceal enhancement may have been suboptimal because we used a fixed time delay rather than a bolus-tracking technique, which would allow more accurate timing of arterial and portal venous phases [25].

Despite its low performance for small varices, CT depicted advanced-grade disease with high sensitivity (11/12, 92%) for both observers. Furthermore, a significant positive correlation was observed between CT and endoscopic grading: The varices that were detected could be distinguished by size. This correlation is significant because identification of high-risk patients, for which prophylactic therapy is indicated, is the main purpose of variceal screening. The current guidelines, advocating screening endoscopy followed by medical prophylaxis for large varices in cirrhotic patients [5, 6], are based on the propensity of large varices to bleed at a rate of 20–30% per year, whereas small ones rupture at a rate of 6% per year [26–28]. Our results suggest 3 mm is a useful CT threshold size for defining large esophageal varices. Although a 4-mm cutoff would likely yield improved specificity and positive predictive value, the more conservative criterion of 3 mm may be prudent for screening applications in which sensitivity and negative predictive value should receive priority (92% and 98%, respectively, in our series). Likewise, a recent preliminary report (Chiorean M et al., presented at the 2004 annual meeting of the

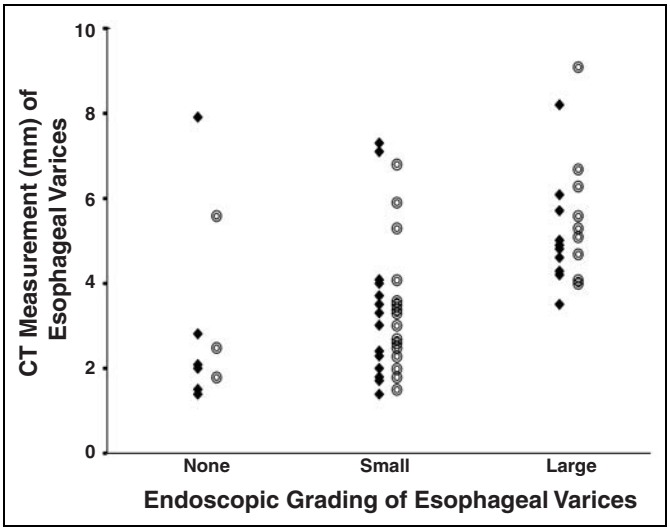


Fig. 4—Scattergram shows correlation between short-diameter measurements of perceived esophageal varices in positive CT cases and actual grade on endoscopy (none, small, and large varices) for each observer. Note that data points in small and large esophageal varices groups represent true-positive fraction, whereas those in none group correspond to false-positive fraction.

TABLE 2: Sensitivity, Specificity, Accuracy, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for Identification of Large Esophageal Varices from Small or No Varices Using 3-mm Diameter as a CT Criterion

Performance Measure	Observer 1		Observer 2	
	Values	95% CIs	Values	95% CIs
Sensitivity (%)	92 (11/12)	63–100	92 (11/12)	63–100
Specificity (%)	84 (46/55)	72–91	84 (46/55)	72–91
Accuracy (%)	85 (57/67)	75–92	85 (57/67)	75–92
PPV (%)	55 (11/20)	34–74	55 (11/20)	34–74
NPV (%)	98 (46/47)	88–100	98 (46/47)	88–100

Note—Data in parentheses are number of patients who were used to calculate performance measures.

ARRS), of a study in which 41 patients were included, also suggested a 3-mm criterion for CT differentiation of large esophageal varices from small varices.

Because this conservative cutoff will inevitably capture a proportion of low-risk patients without large varices (specificity of 84% and positive predictive value of 55%, in our series), endoscopy may be used for definitive diagnosis in the identified group before initiation of prophylactic therapy. In this way, CT, rather than obviating endoscopy, may play an adjunctive role by allowing a more targeted, cost-effective application of diagnostic and therapeutic endoscopy. Alternatively, it may be reasonable to medically treat such an inclusive group without endoscopic confirmation. Some authors, in fact, have even suggested that universal β-blocker therapy may be appropriate for cirrhotic patients given the significant cost associated with endoscopy [7–9]. However, the side-effect profile for β-blockers is often underestimated and can be significant, especially in cirrhotic patients who are often debilitated and hypotensive at baseline; in one study, the side effects from propranolol resulted in 30% of patients withdrawing from primary prophylactic treatment [29]. This concern is particularly germane because medical prophylaxis needs to be lifelong for many patients. Using CT, most low-risk patients may be spared low-yield endoscopy and unnecessary pharmacotherapy.

There are some limitations in this study. First, our CT protocol was not ideal for the evaluation of esophageal varices, as mentioned earlier. We believe that optimization of the CT protocol including the use of a thinner slice thickness, a negative oral contrast agent, a bolus-tracking technique, and multiplanar reformation could improve the efficacy of CT diagnosis in esophageal varices. In one study, with a thinner slice thickness of 2.5–3 mm, sensitivity, especially for the detection of small varices, was higher (Chiorean M, et al., 2004 ARRS meeting). However, additional studies are needed to validate this hypothesis. Second, the time interval between endoscopy and CT was up to 4 weeks; therefore, some true interval progression or regression of disease cannot be ruled out, although it is unlikely given the known rate of natural progression of esophageal varices (from none to small varices, 5% at 1 year; from small to large varices, 12% at 1 year) [30]. It should be noted, however, that variceal size and shape may be subject to esophageal distention and peristalsis [31] and to hemodynamic changes, such as body fluid status, that may vary with time. Third, this study evaluated CT correlation only to endoscopy, which suffers as a reference standard given the subjective nature of endoscopic grading systems in which a considerable degree of inter- and intraobserver disagreement is known to occur [32]. Although correlation with clinical outcomes (e.g., prediction of hemorrhage) based on CT variceal grading would have been useful, this was not possible because patients were appropriately treated based on concurrent endoscopic findings. Last, given the retrospective nature of the study, the patient population did not represent a consecutive group in a screening setting. However, the proportions of small and large varices in our study were similar to rates typically reported in prospective series, and the predictive value of CT should therefore not be significantly affected.

In conclusion, our results suggest a potential role for CT in the evaluation of esophageal varices. The use of an optimized CT protocol may yield increased CT accuracy and allow CT to function as an important alternative or adjunct to endoscopic screening and surveillance. A criterion of a 3-mm-or-larger diameter on CT for large varices could be useful in identifying high-risk patients who would benefit most from selective endoscopy, prophylactic therapy, or both in a cost-efficient manner.

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