Limited detection of small (≤ 10 mm) colorectal liver metastasis at preoperative CT in patients undergoing liver resection

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Abstract

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Protocol

Step 1.

Study overview

The institutional review board of Seoul National University Bundang Hospital approved this retrospective study and waived the requirement for informed consent. All data were fully anonymized and aggregated prior to analysis. We retrospectively included 211 patients who underwent 229 liver resections for CRLM following preoperative CT. We analyzed the size distribution of the CRLM nodules identified in pathological examination, and calculated the per-nodule sensitivity of CT for each nodule-size category.

Study sample

From the surgical database of Seoul National University Bundang Hospital, a teaching hospital in Korea, we identified 284 patients who had pathologically confirmed colorectal cancer and underwent 311 liver resections from 2003 through 2014. We excluded 55 liver resections without preoperative contrast-enhanced CT within 30 days before liver resection, and eight liver resections from which no solid nodule was identified on pathology examination. In the remaining 248 liver resections performed in 230 patients, the pathological examination revealed 485 solid hepatic nodules. We additionally excluded 24 pathologically confirmed non-CRLM nodules in 22 patients, including hepatocellular carcinoma (n = 9), cholangiocarcinoma (n = 6), non-neoplastic lesions (n = 5), hemangioma (n = 3), and metastasis from gallbladder cancer (n = 1). The study finally included 461 pathologically confirmed CRLM nodules in 211 patients who underwent 229 liver resections. The 211 patients (mean

age ± standard deviation, 66.4 ± 10.9 years) comprised 140 men (67.5 ± 10.7 years) and 71 women (64.2 ± 11.2 years). Among these patients, 16 patients underwent liver resection twice and a single patient underwent liver resection three times.

CT imaging and reporting

Intravenous contrast-enhanced CT images were obtained during the portal venous phase using 16- or higher detector-row machines. From each helical scan, transverse images were reconstructed with a thickness of 4 or 5 mm and an increment of 3 or 4 mm using a standard filtered back projection. Coronal images were reformatted with the same thickness and increment.

Five abdominal radiologists with 3–13 years of experience made the CT reports prospectively as part of their daily practice. Narrow window settings (typically with the window width and level of 200 and 100 Hounsfield units, respectively) were used to evaluate the liver. The radiologists recorded the location (Couinaud segment) and size (maximum transverse diameter in millimeters) of each suspected CRLM nodule in the CT reports according to a standardized structured report form. Throughout the study period, we adhered to the strict policy of using the structured report form for preoperative CT in patients with colorectal cancer to standardize the communication among radiologists, surgeons, and pathologists.

MR imaging

For 204 liver resections in 186 of the 211 patients, preoperative liver MR imaging was performed following CT. While no clear guidelines were available regarding the use of liver MR imaging in patients with colorectal cancer during the study period, our surgeons and physicians generally added MR imaging if CT showed potentially resectable CRLM or indeterminate focal hepatic lesions that could not be characterized with CT.

Due to the installation of new MR equipment and the introduction of new contrast agents, our MR techniques changed during the study period. We used 1.5-T magnets during the initial part of the study, and 3-T magnets during the later part of the study (Philips Healthcare, The Netherlands). The contrast agent used changed from gadodiamide (Omniscan; GE Healthcare, Princeton, NJ) (n = 2) to ferucarbotran (Resovist; Schering, Berlin, Germany) (n = 39), and eventually to gadoxetic acid disodium (n = 163). Imaging generally consisted of dual-echo in- and opposed-phase spoiled gradient-echo T1-weighted, fat-suppressed fast spin-echo T2-weighted, diffusion-weighted, and dynamic fat-suppressed spoiled gradient-echo T1-weighted imaging. The abdominal radiologists interpreted the images.

Liver resection

The need for liver resection for each patient was determined at a weekly multidisciplinary conference involving surgeons, oncologists, radiologists, and pathologists. During surgery, the surgeons with 3–17 years of experience mobilized and evaluated the liver by inspection and/or palpation. In

addition, the surgeons or radiologists who had full knowledge of the preoperative imaging findings performed intraoperative liver ultrasonography (SSD-3500, Aloka, Japan; MyLab 25 Gold, Esaote Biomedica, Italy; or iU22, Philips Medical Systems, The Netherlands).

Pathological examination

Pathological examinations were performed by one of two pathologists with 3–12 years of experience. In cutting liver specimens for gross examination, it was our internal guideline to keep the tissue slice as 5 mm or thinner, although a tissue thickness up to 10 mm is generally accepted. For each slice, a gross photograph was obtained. The pathologists identified solid nodules by careful macroscopic inspection of the liver slices. All suspected nodules were sampled, embedded in paraffin blocks, and stained with hematoxylin-eosin for microscopic examination. For each nodule, the pathologist recorded the location in terms of the Couinaud segment and the nodule size in millimeters in the pathology reports. This information served as the reference standard for the subsequent analyses. Hereafter, the size of a given nodule refers to the size recorded in the pathology report.

Nodule-matching algorithm

For a pathologically identified nodule to be regarded as a true positive, the same nodule had to be documented in the prospective CT report. Any pathologically confirmed CRLM nodule that was not documented in the CT reports was categorized as a false negative. False-positive nodules were not counted because our retrospectively collected study sample included only pathologically confirmed CRLM nodules.

Two study coordinators (radiologists with clinical experience of 13 and 4 years), who did not participate in making CT or MR reports, conducted the matching of nodules between the pathology reports and the CT reports following a predefined algorithm. First, the study coordinators together reviewed the CT reports and pathology reports to select true-positive nodules by using the following predefined criteria. For a pathologically identified nodule to be regarded as a true positive, the pathological report and CT report had to be concordant for both the segmental location and the size of the nodule. For nodule size, an acceptable margin of error was empirically set as 3 mm for small (≤ 10 mm) nodules and 5 mm for larger (≥ 10 mm) nodules. If two or more nodules were found in the same liver segment, the larger nodule(s) was matched preferentially based on the assumption that larger nodules were more detectable at both CT and pathological examination than smaller nodules. Second, for nodules that were pathologically identified but left uncategorized as true positive or false negative in the first step of the nodule matching, the study coordinators in consensus adjudicated the nodule matching. For the adjudication to link the pathological reports with the CT reports, the study coordinators reviewed all available CT and MR images, specimen photographs, and surgical records.

Statistical analysis

Two radiologists and a statistician planned all analyses before the data collection. A histogram of the nodule-size distribution was created by categorizing nodule size by 5-mm increments. The per-nodule

CT sensitivity was calculated for each size category. The population-averaged sensitivity estimates and their 95% confidence intervals (CIs) were adjusted for correlations within a liver resection case by using the generalized estimating equations approach across size-categorized subgroups. We used an intercept-only model and assumed an exchangeable working correlation structure. Logistic regression with a logit link was used for the binary outcome (i.e., sensitivity). A Chi-square test was performed to identify the difference in 1-year recurrence rate of CRLM nodules between the liver resections with known false negatives and the resections where the preoperative CT successfully detected all CRLM nodules found on pathological examination. Statistical analyses were performed using Stata version 14.0 software package (StataCorp, College Station, TX).

Additionally, the same analyses were performed separately for the liver resections following preoperative gadoxetic acid-enhanced MR imaging and for the resections without preoperative gadoxetic acid-enhanced MR imaging. We did not formally compare these two subgroups because such a comparison would be confounded by many factors including the indications for MR imaging, MR equipment, and institutional experience, all of which were affected by the study period. We did not compare the sensitivity between CT and MR imaging, since CT preceded MR imaging in each patient and the two studies were not read independently. The diagnostic yield (in terms of the number of CRLM nodules) of additional gadoxetic acid-enhanced MR imaging in our center has been previously reported.