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Appendiceal Visualization on 2-mSv CT vs. Conventional-Dose CT in Adolescents and Young Adults with Suspected Appendicitis: An Analysis of Large Pragmatic Randomized Trial Data

Jungheum Cho[1], Youngjune Kim[2], Seungjae Lee[3], Hooney Daniel Min[1], Yousun Ko[4], Choong Guen Chee[5], Hae Young Kim[1], Ji Hoon Park[1, 3, 6], Kyoung Ho Lee[1, 3, 6, 7], for the LOCAT Group

[1]Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea; [2]Aerospace Medical Group, Air Force Education and Training Command, Jinju, Korea; [3]Department of Applied Bioengineering, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea; [4]Biomedical Research Center, Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea; [5]Department of Radiology, Asan Medical Center, Seoul, Korea; [6]Department of Radiology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea; [7]Interdisciplinary Program in Bioengineering, Seoul National University, Seoul, Korea

Objective: We compared appendiceal visualization on 2-mSv CT vs. conventional-dose CT (median 7 mSv) in adolescents and young adults and analyzed the undesirable clinical and diagnostic outcomes that followed appendiceal nonvisualization.
Materials and Methods: A total of 3074 patients aged 15–44 years (mean ± standard deviation, 28 ± 9 years; 1672 female) from 20 hospitals were randomized to the 2-mSv CT or conventional-dose CT group (1535 vs. 1539) from December 2013 through August 2016. A total of 161 radiologists from 20 institutions prospectively rated appendiceal visualization (grade 0, not identified; grade 1, unsure or partly visualized; and grade 2, clearly and entirely visualized) and the presence of appendicitis in these patients. The final diagnosis was based on CT imaging and surgical, pathologic, and clinical findings. We analyzed undesirable clinical or diagnostic outcomes, such as negative appendectomy, perforated appendicitis, more extensive than simple appendectomy, delay in patient management, or incorrect CT diagnosis, which followed appendiceal nonvisualization (defined as grade 0 or 1) and compared the outcomes between the two groups.
Results: In the 2-mSv CT and conventional-dose CT groups, appendiceal visualization was rated as grade 0 in 41 (2.7%) and 18 (1.2%) patients, respectively; grade 1 in 181 (11.8%) and 81 (5.3%) patients, respectively; and grade 2 in 1304 (85.0%) and 1421 (92.3%) patients, respectively (p < 0.001). Overall, undesirable outcomes were rare in both groups. Compared to the conventional-dose CT group, the 2-mSv CT group had slightly higher rates of perforated appendicitis (1.1% [17] vs. 0.5% [7], p = 0.06) and false-negative diagnoses (0.4% [6] vs. 0.0% [0], p = 0.01) following appendiceal nonvisualization. Otherwise, these two groups were comparable.
Conclusion: The use of 2-mSv CT instead of conventional-dose CT impairs appendiceal visualization in more patients. However, appendiceal nonvisualization on 2-mSv CT rarely leads to undesirable clinical or diagnostic outcomes.
Keywords: *Appendicitis; Tomography, X-ray computed; Abdomen; Radiation dosage*

INTRODUCTION

In many countries, CT is the mainstay of diagnostic tests in adults with suspected appendicitis. Previous meta-analyses [1-3] drew a consistent conclusion that CT outperforms ultrasonography in the diagnosis of

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Corresponding author: Kyoung Ho Lee, MD, PhD, Department of Radiology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
• E-mail: kholeemail@gmail.com

appendicitis. Due to its excellent diagnostic performance, CT is utilized 10–15 times more frequently than ultrasonography in the United States [4] and in South Korea [5]. Previous studies [6], including large randomized controlled trials [7,8], have advocated lowering of the CT radiation dose to 2 mSv for diagnosing appendicitis, since it hardly affects clinical outcomes or diagnostic performance.

Other previous studies [9-11] using conventional radiation doses have advocated the use of appendiceal nonvisualization on CT as a reliable sign to exclude appendicitis with a negative predictive value (NPV) of over 95%. However, when the radiation dose is as low as 2 mSv, radiologists may be uncertain as to whether appendiceal nonvisualization is attributable to the small size of an uninflamed appendix or to the compromised image quality hindering the detection of an enlarged appendix with inflammation. Some practitioners are concerned that appendiceal nonvisualization is more common with the use of low-dose CT instead of conventional-dose CT (CDCT), which may lead to undesirable clinical or diagnostic outcomes such as negative appendectomy, perforated appendicitis, or delay in patient management [12]. In this study, we compared appendiceal visualization on 2-mSv CT vs. CDCT in adolescents and young adults with suspected appendicitis and analyzed undesirable clinical and diagnostic outcomes that followed appendiceal nonvisualization.

MATERIALS AND METHODS

Data Source and Study Setting

Here, we report a previously unreported part of the results of a prospective pragmatic randomized controlled trial (Low-dOse CT for Appendicitis Trial, LOCAT; ClinicalTrials.gov number, NCT01925014) [8,13] that compared 2-mSv CT and CDCT in adolescents and young adults with suspected appendicitis. Additionally, we performed a *post hoc* analysis of the trial data regarding final diagnosis and patient disposition following appendiceal nonvisualization. The Institutional Review Boards of all participating sites approved the trial and the *post hoc* analysis.

The trial protocol, including CT protocols, was adopted as reported previously [14]. The trial was conducted in South Korea, and it involved 3074 patients; more than 500 care providers, including 161 radiologists; and 22 CT machines from 20 sites. All sites were teaching hospitals. At all sites, CT was the diagnostic test of choice in adults, and appendectomy was the treatment of choice for appendicitis. Except for radiation dose, which was the primary intervention of the trial, clinical management for the 2-mSv CT and CDCT groups was identical and it involved the same resources, including radiologists and CT machines.

The trial was intended to be pragmatic [14,15], and therefore, we minimized the standardization of trial procedures, except for those regarding structured history taking, structured telephone follow-up, CT radiation doses, structured CT, and pathology reports. Otherwise, the sites were allowed to maintain their usual practice pattern as much as possible for other trial procedures. We wrote this article after adhering to the reporting guidelines [16-18].

Patients

The eligibility criteria for the trial were patients aged 15–44 years who were referred from the emergency departments for CT examination under the suspicion of appendicitis [14]. From December 2013 through August 2016, 3074 patients (mean age ± standard deviation, 28 ± 9 years) were randomized into either the 2-mSv CT (n = 1535) or CDCT group (n = 1539) (Table 1, Fig. 1). There were 1672 female and 1374 male enrolled in the study. We did not collect data from a small number of patients who withdrew from the trial or from those who were inappropriately enrolled in the study.

Diagnostic Intervention

The patients underwent either 2-mSv CT (n = 1468) or CDCT (n = 1478) as randomized, which was the diagnostic intervention in the trial and the index test of this study. CT techniques have been detailed elsewhere [8]. We used CT machines with 16–640 channels from different manufacturers. The section thickness had to be 5 mm or thinner, with an overlap of 20% or greater. We did not mandate the use of iterative reconstruction; however, we recommended it for 2-mSv CT. All patients received intravenous contrast agents. None of the patients received an oral contrast agent.

A total of 161 site radiologists read the CT images as a daily practice. The radiologists were able to access medical records and confer with the referring physicians. According to the trial protocol [14], predefined diagnostic criteria and a standardized CT report form [19] (Supplementary Table 1) were used to rate appendiceal visualization using a 3-point Likert scale: grade 0, not identified; grade 1, unclearly or partially visualized; and grade 2, clearly and

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Table 1. Baseline Patient Characteristics

Characteristic	All Randomized Patients¶		Patients with Appendiceal Visualization Grade 0 or 1	
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	2-mSv CT Group (n = 222)	CDCT Group (n = 99)
Age, years	28 (21 to 35)	28 (21 to 35)	24 (19 to 31)	23 (18 to 33)
Sex, %				
Female	838 (54.6)	834 (54.2)	146 (65.8)	69 (70)
Male	688 (44.8)	686 (44.6)	76 (34.2)	30 (30)
Ethnic origin, %				
Korean	1520 (99.0)	1504 (97.7)	219 (98.6)	99 (100)
Non-Korean	6 (0.4)	16 (1.0)	3 (1.4)	0 (0)
Body size, %				
Body mass index, kg/m^2	21.9 (19.8 to 24.5)	22.1 (19.9 to 24.7)	20.4 (18.8 to 22.6)	20.3 (18.5 to 22.2)
< 18.5 (underweight)	151 (9.8)	147 (9.6)	40 (18.0)	23 (23)
18.5–24.9 (normal)	1044 (68.0)	1005 (65.3)	155 (69.8)	65 (66)
25.0–29.9 (overweight)	268 (17.5)	292 (19.0)	23 (10.4)	9 (9)
≥ 30.0 (obese)	50 (3.3)	61 (4.0)	3 (1.4)	0 (0)
Effective diameter, cm*	22.8 (20.7 to 25.2)	22.8 (20.8 to 25.4)	21.4 (20.0 to 23.3)	21.1 (19.6 to 23.1)
< 20.0	227 (14.8)	242 (15.7)	55 (24.8)	34 (34)
20.0–24.9	891 (58.0)	847 (55.0)	130 (58.6)	52 (53)
25.0–29.9	362 (23.6)	386 (25.1)	33 (14.9)	13 (13)
≥ 30.0	46 (3.0)	45 (2.9)	4 (1.8)	0 (0)
Chief complaint, %				
Abdominal pain	1439 (93.7)	1439 (93.5)	203 (91.4)	93 (94)
Nausea and vomiting	37 (2.4)	35 (2.3)	9 (4.1)	4 (4)
Fever	28 (1.8)	24 (1.6)	3 (1.4)	1 (1)
Other	22 (1.4)	22 (1.4)	7 (3.2)	1 (1)
Duration of symptoms, %				
≤ 12 hours	606 (39.5)	621 (40.4)	89 (40.1)	35 (35)
13–24 hours	402 (26.2)	430 (27.9)	52 (23.4)	22 (22)
2–3 days	381 (24.8)	354 (23.0)	59 (26.6)	26 (26)
≥ 4 days	137 (8.9)	115 (7.5)	22 (9.9)	16 (16)
Location of abdominal pain, %†				
Right lower quadrant	1344 (87.6)	1340 (87.1)	193 (86.9)	88 (89)
Suprapubic	228 (14.9)	204 (13.3)	36 (16.2)	16 (16)
Right flank	209 (13.6)	190 (12.3)	34 (15.3)	16 (16)
Periumbilical	172 (11.2)	173 (11.2)	27 (12.2)	15 (15)
Epigastric	156 (10.2)	118 (7.7)	27 (12.2)	10 (10)
Other areas	177 (11.5)	136 (8.8)	32 (14.4)	9 (9)
No pain	22 (1.4)	32 (2.1)	4 (1.8)	1 (1)
Migration of pain, %‡				
Yes	466 (30.4)	452 (29.4)	55 (24.8)	32 (32)
No	1060 (69.1)	1068 (69.4)	167 (75.2)	67 (68)
Abdominal tenderness, %†				
Right lower quadrant	1305 (85.0)	1303 (84.7)	191 (86.0)	88 (89)
Epigastric	147 (9.6)	151 (9.8)	28 (12.6)	8 (8)
Left lower quadrant	124 (8.1)	97 (6.3)	21 (9.5)	10 (10)
Suprapubic	112 (7.3)	115 (7.5)	20 (9.0)	15 (15)
Periumbilical	104 (6.8)	129 (8.4)	16 (7.2)	8 (8)
Other areas	106 (6.9)	89 (5.8)	15 (6.8)	6 (6)
No tenderness	142 (9.3)	139 (9.0)	20 (9.0)	6 (6)

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Table 1. Baseline Patient Characteristics (Continued)

Characteristic	All Randomized Patients[¶]		Patients with Appendiceal Visualization Grade 0 or 1	
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	2-mSv CT Group (n = 222)	CDCT Group (n = 99)
Rebound tenderness, %				
Yes	634 (41.3)	570 (37.0)	90 (40.5)	29 (29)
No	892 (58.1)	950 (61.7)	132 (59.5)	70 (71)
Body temperature, °C	36.8 (36.5 to 37.2)	36.8 (36.5 to 37.2)	36.8 (36.5 to 37.3)	36.9 (36.5 to 37.3)
Blood-test results				
White blood cell, $10^3/mm^3$	10.6 (7.8 to 13.6)	10.6 (8.0 to 13.9)	9.9 (7.4 to 12.6)	9.3 (7.6 to 11.6)
Segmented neutrophil, %	75.0 (64.0 to 82.0)	75.0 (64.0 to 82.0)	73.0 (61.0 to 82.0)	74.0 (61.5 to 80.0)
C-reactive protein, mg/dL	0.8 (0.2 to 3.5)	0.7 (0.1 to 3.5)	0.6 (0.1 to 4.7)	0.6 (0.1 to 4.7)
Clinical risk scores for appendicitis, %				
Alvarado score				
Low risk (0–4)	564 (36.7)	588 (38.2)	87 (39.2)	41 (41)
Indeterminate risk (5–6)	483 (31.5)	467 (30.3)	68 (30.6)	37 (37)
High risk (7–10)	472 (30.7)	457 (29.7)	66 (29.7)	21 (21)
Appendicitis inflammatory response score				
Low risk (0–4)	841 (54.8)	846 (55.0)	133 (59.9)	61 (62)
Indeterminate risk (5–8)	643 (41.9)	624 (40.5)	85 (38.3)	38 (38)
High risk (9–12)	20 (1.3)	33 (2.1)	2 (0.9)	0 (0)
Time of CT examination, %				
Working hours[§]	655 (42.7)	651 (42.3)	88 (39.6)	36 (36)
After hours	871 (56.7)	869 (56.5)	134 (60.4)	63 (64)
CT machine, %				
16-channel	301 (19.6)	300 (19.5)	43 (19.4)	11 (11)
64-channel	385 (25.1)	384 (25.0)	74 (33.3)	35 (35)
128-channel	568 (37.0)	564 (36.6)	71 (32.0)	33 (33)
256- or 640-channel	272 (17.7)	272 (17.7)	34 (15.3)	20 (20)
Target effective dose, % (2-mSv CT vs. CDCT)[‖]				
2 mSv vs. 3 mSv	25 (1.6)	23 (1.5)	2 (0.9)	2 (2)
2 mSv vs. 5 mSv	34 (2.2)	34 (2.2)	4 (1.8)	0 (0)
2 mSv vs. 6 mSv	398 (25.9)	396 (25.7)	39 (17.6)	17 (17)
2 mSv vs. 7 mSv	527 (34.3)	523 (34.0)	89 (40.1)	49 (49)
2 mSv vs. 8 mSv	542 (35.3)	544 (35.3)	88 (39.6)	31 (31)
Individual radiation dose				
Dose-length product, mGy·cm	132 (119 to 151)	486 (390 to 561)	125 (112 to 135)	417 (356 to 508)
Volume CT dose index, mGy	2.6 (2.2 to 2.7)	9.3 (7.6 to 10.4)	2.5 (2.2 to 2.6)	8.0 (6.9 to 9.8)
Size-specific dose estimate, mGy	4.1 (3.7 to 4.5)	14.4 (12.9 to 16.2)	4.1 (3.6 to 4.5)	14.0 (12.8 to 15.3)
Iterative reconstruction, %				
Used	593 (38.6)	158 (10.3)	87 (39.2)	8 (8)
Not used	933 (60.8)	1362 (88.5)	135 (60.8)	91 (92)
Radiologist who made initial CT report, %				
Attending radiologist	886 (57.7)	863 (56.1)	99 (44.6)	44 (44)
On-call radiologist or trainee	640 (41.7)	657 (42.7)	123 (55.4)	55 (56)
Site				
2-mSv CT experience in the previous single-center trial				
Yes	159 (10.4)	159 (10.3)	26 (11.7)	14 (14)
No	1367 (89.1)	1361 (88.4)	196 (88.3)	85 (86)

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Table 1. Baseline Patient Characteristics (Continued)

Characteristic	All Randomized Patients[¶]		Patients with Appendiceal Visualization Grade 0 or 1	
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	2-mSv CT Group (n = 222)	CDCT Group (n = 99)
Number of beds				
< 650	363 (23.6)	360 (23.4)	51 (23.0)	12 (12)
650–949	541 (35.2)	535 (34.8)	74 (33.3)	28 (28)
≥ 950	622 (40.5)	625 (40.6)	97 (43.7)	59 (60)
Annual number of appendectomies				
< 150	59 (3.8)	58 (3.8)	9 (4.1)	6 (6)
150–299	329 (21.4)	323 (21.0)	55 (24.8)	15 (15)
300–449	518 (33.7)	516 (33.5)	60 (27.0)	34 (34)
≥ 450	620 (40.4)	623 (40.5)	98 (44.1)	44 (44)

Data are presented as n (%) or median (interquartile range). For each characteristic, data were missing in less than 2.5% of all randomized patients. *The square root of the product of the anteroposterior diameter and lateral diameter of the abdomen, as measured on the transverse CT image at the umbilicus level, [†]Patients could fit into more than one category, [‡]Defined as pain starting in the epigastrium or periumbilical area and migrating to the right lower quadrant within a few hours, [§]0800–1700 hours, working days, [‖]The target effective dose for CDCT was individualized for each CT machine following the institutional normal dose, [¶]Previously reported [8]. CDCT = conventional-dose CT

entirely visualized. If a patient had phlegmon or abscess, grade 2 was assigned if there was clear continuity between the lesion and the remaining appendiceal base, indicating that the lesion had originated from the appendix.
The radiologists' likelihood score for appendicitis was rated on a 5-point Likert scale. The predefined primary diagnostic criterion of appendicitis on CT was an enlarged appendix (> 6 mm in diameter) with mural thickening and periappendiceal fat stranding. Secondary diagnostic criteria included abnormal mural enhancement, appendicolith, phlegmon, and abscess [20,21]. Prior to opening the trial at each site, we asked all potentially involved radiologists to complete an online training course [22] on interpreting 2-mSv CT. Nearly all the on-call radiologists were residents at the site hospitals.

Co-Intervention and Follow-Up

Site emergency physicians performed the initial clinical assessment, determined the necessity and timing of diagnostic tests, including imaging studies, and decided when to discharge the patient from the emergency department. For patients whose clinical diagnosis of appendicitis remained equivocal after initial CT, additional abdominal ultrasonography or CDCT was performed if needed. The site surgeons determined the surgical plan for each patient. Hereinafter, we use the term appendectomy to refer to simple appendectomy or more extensive surgery (e.g., ileocecectomy) performed for the treatment of presumed appendicitis.

Site investigators identified serious adverse events during follow-up and determined the attributes [23] of these adverse events [14]. The follow-up included a 3-month telephone interview, in which the patients were asked a question regarding additional hospitalization due to recurrence or exacerbation of abdominal symptoms. We collected only reportable adverse events which were potentially associated with an incorrect diagnosis of appendicitis or other clinically important diseases.

Reference Standard

Independent outcome assessors (two emergency department physicians and five radiologists with 2–3 years of clinical experience) adjudicated the final diagnosis of appendicitis based on the trial data, including surgical findings, pathologic findings, and follow-up results [14]. The assessors were blinded to the CT findings. Site pathologists examined appendectomy specimens, and they were asked to adhere to the definition of acute appendicitis as mural neutrophil infiltration or mucosal neutrophils with ulcerations [14,24]. The absence of appendicitis was confirmed based on the negative histopathologic findings from the appendectomy specimen (i.e., negative appendectomy), gross surgical findings, or clinical follow-up, including the telephone interview. The presence of appendiceal perforation was based on the spillage of the appendiceal contents, peritonitis, or abscess observed

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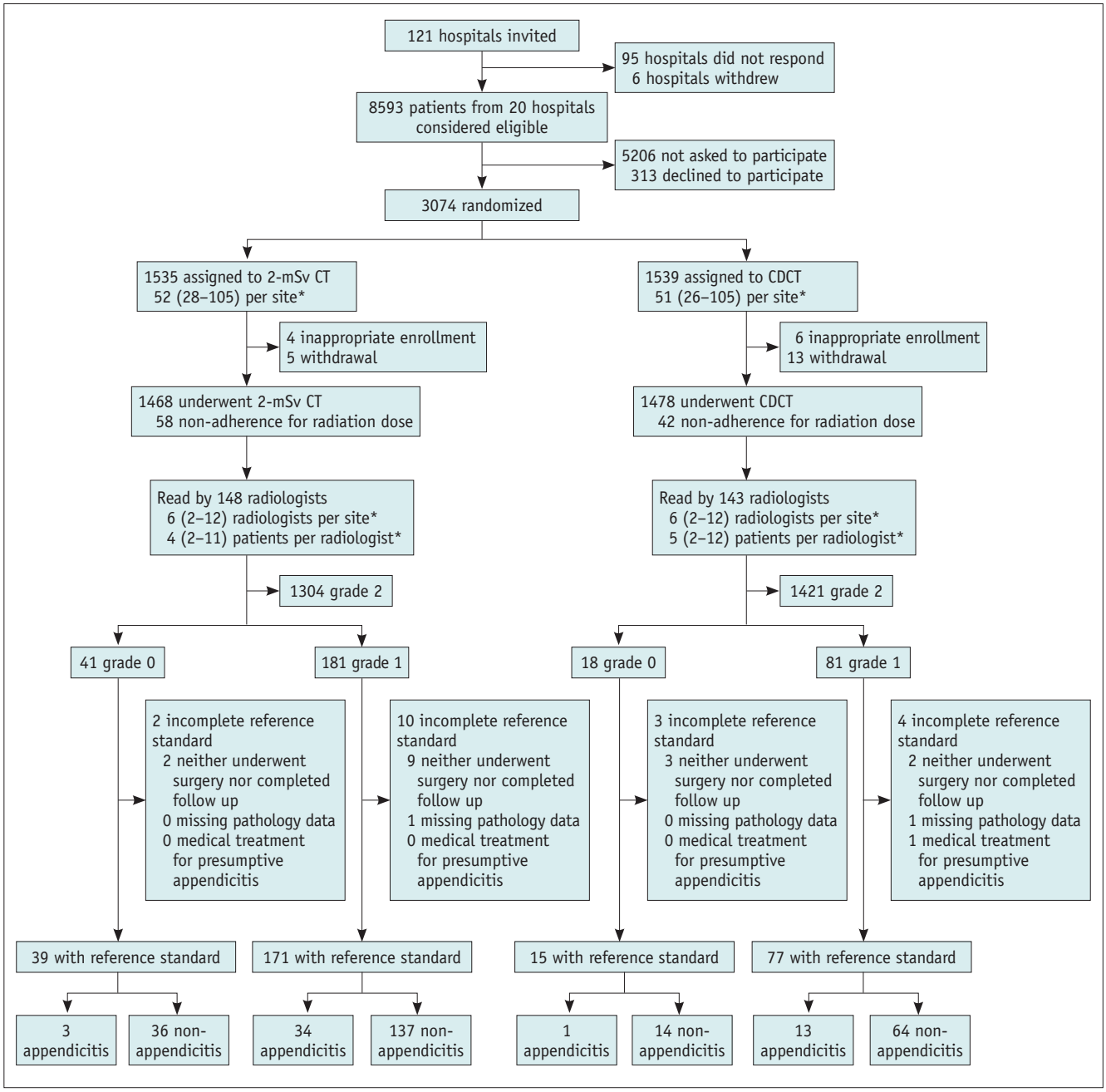

Fig. 1. Patient flow diagram. Grades are for appendiceal visualization. Unless otherwise indicated, data are numbers of patients. *Data are median (interquartile range). CDCT = conventional-dose CT

during surgery or pathologically confirmed appendiceal wall defect due to transmural necrosis [14,25].

Endpoints

Appendiceal nonvisualization was defined as appendiceal visualization grade 0 or 1 in the primary analysis. We compared the 2-mSv CT and CDCT groups for appendiceal visualization, which was a predefined endpoint of the trial [14]. As in previous studies [9-11] that have suggested appendiceal nonvisualization as a helpful sign for exclusion of appendicitis, we calculated the NPV of appendiceal nonvisualization to rule out appendicitis in each group.

As a *post hoc* analysis, we additionally analyzed undesirable clinical and diagnostic outcomes following appendiceal nonvisualization. First, in terms of final diagnosis, we included patients with perforated appendicitis and negative appendectomy. Negative appendectomy and perforated appendicitis are reciprocal—arguably

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established measures of quality of care [26]—representing the consequences of false-positive and false-negative (i.e., delayed) diagnoses [27], respectively. Second, in terms of patient disposition following appendiceal nonvisualization, we considered the extensive surgeries to treat appendicitis (more extensive than simple appendectomy), surgeries other than appendectomy, and additional imaging tests, and we measured the interval between CT and appendectomy, length of hospital stay associated with appendectomy, and interval between CT and hospital discharge without surgery. Third, in terms of diagnostic outcomes, we counted false-negative and false-positive diagnoses on the CT reports, and calculated the sensitivity and specificity following appendiceal nonvisualization. For these analyses, the five-point scale for the likelihood of appendicitis was collapsed to a binary variable for grades 3–5 as a positive diagnosis. Finally, we counted the adverse events that were collected during the trial, following appendiceal nonvisualization. Of these endpoints, we were particularly interested in negative appendectomy and perforated appendicitis, as well as in false-positive and false-negative diagnoses.

Statistical Analysis

A radiologist and a statistician planned and performed all analyses after the trial data collection. We primarily performed intention-to-treat analyses. We added per-protocol analyses by excluding patients with protocol non-adherence with regard to their eligibility or radiation dose [14]. We predefined the size of our study sample for the primary purpose of the trial, which proved the non-inferiority of 2-mSv CT to CDCT with regard to the negative appendectomy rate [14].

Importantly, we set the denominator for all compared event rates as the number of all randomized patients

Table 2. Appendiceal Visualization and Likelihood of Appendicitis in the CT Reports

	Intention-to-Treat Analysis		Per-Protocol Analysis	
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	2-mSv CT Group (n = 1459)	CDCT Group (n = 1479)
Appendiceal visualization grade 0	41 (3)	18 (1)	38 (3)	18 (1)
Likelihood of appendicitis grade 1	14 (0)	8 (0)	12 (0)	8 (0)
Likelihood of appendicitis grade 2	20 (0)	9 (0)	19 (0)	9 (0)
Likelihood of appendicitis grade 3	2 (0)	1 (1)	2 (0)	1 (1)
Likelihood of appendicitis grade 4	4 (2)	0 (0)	4 (2)	0 (0)
Likelihood of appendicitis grade 5	1 (1)	0 (0)	1 (1)	0 (0)
Appendiceal visualization grade 1	181 (34)	81 (13)	176 (34)	80 (13)
Likelihood of appendicitis grade 1	61 (2)	29 (0)	61 (2)	29 (0)
Likelihood of appendicitis grade 2	85 (4)	29 (0)	80 (4)	28 (0)
Likelihood of appendicitis grade 3	9 (5)	7 (1)	9 (5)	7 (1)
Likelihood of appendicitis grade 4	14 (12)	7 (4)	14 (12)	7 (4)
Likelihood of appendicitis grade 5	12 (11)	9 (8)	12 (11)	9 (8)
Appendiceal visualization grade 2	1304 (487)	1421 (550)	1240 (456)	1368 (526)
Likelihood of appendicitis grade 1	709 (4)	737 (6)	682 (4)	711 (6)
Likelihood of appendicitis grade 2	67 (5)	74 (5)	62 (4)	74 (5)
Likelihood of appendicitis grade 3	26 (13)	45 (17)	25 (13)	42 (16)
Likelihood of appendicitis grade 4	94 (77)	77 (64)	92 (76)	76 (63)
Likelihood of appendicitis grade 5	408 (388)	488 (458)	379 (359)	465 (436)
NPV of appendiceal nonvisualization for ruling out appendicitis, %*†				
Appendiceal nonvisualization defined as visualization grade 0 or 1‡	77.9 [173/222] (71.8 to 83.1)	79 [78/99] (69 to 86)	77.6 [166/214] (71.3 to 82.9)	79 [77/98] (69 to 86)
Appendiceal nonvisualization defined as visualization grade 0§	88 [36/41] (73 to 95)	78 [14/18] (52 to 93)	87 [33/38] (71 to 95)	78 [14/18] (52 to 93)

Unless otherwise specified, data are number of patients, and data in parentheses are number of patients confirmed to have appendicitis. The data do not add up to the number of all randomized patients, because we did not collect the data of a small number of patients who withdrew from the trial or were inappropriately enrolled in the trial. *Numerators are numbers of patients confirmed as not having appendicitis, and denominators are numbers of patients with appendiceal nonvisualization, †Data in parentheses are 95% confidence intervals, ‡Primary analysis, §Sensitivity analysis. CDCT = conventional-dose CT, NPV = negative predictive value

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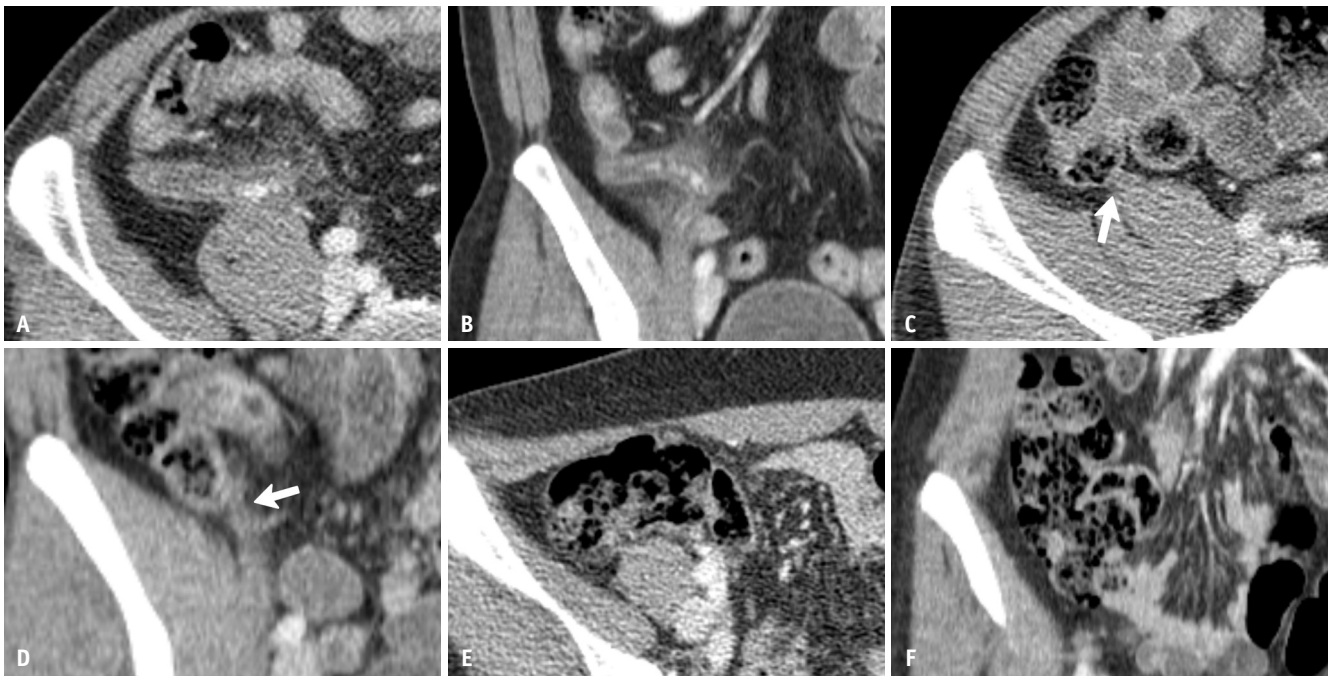

Fig. 2. Representative cases of appendiceal visualization on 2-mSv CT.
A, B. Grade 2 (i.e., clearly and entirely visualized). Contrast-enhanced 2-mSv axial and coronal CT images of a 41-year-old male with confirmed appendicitis. **C, D.** Grade 1 (i.e., unsure or partly visualized). Axial and coronal CT images of a 38-year-old male who was confirmed not to have appendicitis through follow-up (arrows). **E, F.** Grade 0 (i.e., not identified). Axial and coronal CT images of a 16-year-old male who was confirmed not to have appendicitis through follow-up.

to ensure between-group comparability. Had we set the denominator as any patient subset (e.g., appendiceal nonvisualization) rather than all randomized patients, the comparability would have been jeopardized [8,28,29]. Accordingly, we did not perform statistical comparisons for the NPV of appendiceal nonvisualization, diagnostic sensitivity, or specificity. Since the two randomized groups were well balanced for baseline patient characteristics [8], we used univariable tests instead of multivariable tests for between-group comparisons. We used the chi-square test and Mann-Whitney U test to compare the 2-mSv CT and CDCT groups. For very small event rates, we used Z-pooled unconditional exact tests instead of chi-square tests [30].

Appendiceal visualization (or nonvisualization) is intrinsically a matter of subjective decision by the involved radiologists. Therefore, we performed sensitivity analysis by defining appendiceal nonvisualization as only visualization grade 0 instead of grade 0 or 1. Statistical significance was defined as a two-sided *p* value less than 0.05. As missing data were rare, we did not include them in the analysis. All analyses were performed using R software version 3.6.3 (www.R-project.org, The R Project for Statistical Computing).

RESULTS

Since the results of intention-to-treat analysis and per-protocol analysis were very similar, we present the former primarily. In the 2-mSv CT and CDCT groups, appendiceal visualization was rated as grade 0 in 41 (2.7%) and 18 (1.2%) patients, grade 1 in 181 (11.8%) and 81 (5.3%) patients, and grade 2 in 1304 (85.0%) and 1421 (92.3%) patients, respectively ($p < 0.001$) (Table 2, Fig. 2). Of the 222 (14.5%) patients with appendiceal nonvisualization (defined as visualization grade 0 or 1 in the primary analysis) in the 2-mSv group, 37 were confirmed to have appendicitis, while 173 were confirmed not to have appendicitis. Of the 99 (6.4%) patients with appendiceal nonvisualization in the CDCT group, 14 were confirmed to have appendicitis, while 78 were confirmed not to have appendicitis. We were unable to determine the final diagnosis of appendicitis in 12 and 7 patients in the two groups, respectively, due to incomplete reference standards. Therefore, the NPVs of appendiceal nonvisualization for ruling out appendicitis were 77.9% (173/222; 95% confidence interval [CI], 71.8%–83.1%) and 79% (78/99; 95% CI, 69%–86%) in the two groups, respectively.

The clinical and diagnostic outcomes following

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Table 3. Clinical Outcomes Following Appendiceal Visualization Grade 0 or 1

	Intention-to-Treat Analysis				Per-Protocol Analysis			
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	Difference (95% CI)	*P*	2-mSv CT Group (n = 1459)	CDCT Group (n = 1479)	Difference (95% CI)	*P*
Final diagnosis, %								
Appendicitis	37 (2.4)	14 (0.9)			37 (2.5)	14 (0.9)		
Perforated appendicitis	17 (1.1)	7 (0.5)	0.7 (-0.0 to 1.3)	0.06	17 (1.2)	7 (0.5)	0.7 (-0.0 to 1.4)	0.06
Unperforated appendicitis	20 (1.3)	7 (0.5)			20 (1.4)	7 (0.5)		
No appendicitis	173 (11.3)	78 (5.1)			166 (11.4)	77 (5.2)		
Negative appendectomy	3 (0.2)	1 (0.1)	0.1 (-0.2 to 0.5)	0.33	3 (0.2)	1 (0.1)	0.1 (-0.2 to 0.6)	0.33
Based on surgical findings	9 (0.6)	3 (0.2)			8 (0.5)	3 (0.2)		
Based on clinical follow-up including telephone interview	161 (10.5)	74 (4.8)			155 (10.6)	73 (4.9)		
Incomplete reference standard	12 (0.8)	7 (0.5)			11 (0.8)	7 (0.5)		
Neither underwent surgery nor completed follow up	11 (0.7)	5 (0.3)			10 (0.7)	5 (0.3)		
Missing pathology report	1 (0.1)	1 (0.1)			1 (0.1)	1 (0.1)		
Underwent medical treatment for presumptive appendicitis	0 (0.0)	1 (0.1)			0 (0.0)	1 (0.1)		
Patient disposition, %								
Surgery	49 (3.2)	18 (1.2)			48 (3.3)	18 (1.2)		
Appendectomy	40 (2.6)	15 (1.0)			40 (2.7)	15 (1.0)		
Simple appendectomy	38 (2.5)	12 (0.8)			38 (2.6)	12 (0.8)		
More extensive	2 (0.1)	3 (0.2)	-0.1 (-0.5 to 0.3)	0.75	2 (0.1)	3 (0.2)	-0.1 (-0.5 to 0.3)	0.75
Other surgery	9 (0.6)	3 (0.2)	0.4 (-0.1 to 0.9)	0.15	8 (0.5)	3 (0.2)	0.3 (-0.2 to 0.9)	0.22
Gastrointenstinal	4 (0.3)	2 (0.1)			4 (0.3)	2 (0.1)		
Hepatobiliary	2 (0.1)	0 (0.0)			1 (0.1)	0 (0.0)		
Gynecologic	3 (0.2)	1 (0.1)			3 (0.2)	1 (0.1)		
Delay in patient disposition								
Need for additional imaging test	9 (0.6)	3 (0.2)	0.4 (-0.1 to 0.9)	0.15	9 (0.6)	3 (0.2)	0.4 (-0.1 to 0.9)	0.14
Ultrasonography	8 (0.5)	3 (0.2)			8 (0.5)	3 (0.2)		
CT	1 (0.1)	0 (0.0)			1 (0.1)	0 (0.0)		
Interval between CT and appendectomy (hours)	8.7 (4.8 to 17.1)	5.9 (4.2 to 13.9)	2.8 (-2.0 to 5.7)	0.51	8.7 (4.8 to 17.1)	5.9 (4.2 to 13.9)	2.8 (-2.0 to 5.7)	0.51
Length of hospital stay associated with appendectomy (days)	3.4 (2.2 to 5.6)	3.7 (3.0 to 7.1)	-0.3 (-2.0 to 1.0)	0.58	3.4 (2.2 to 5.6)	3.7 (3.0 to 7.1)	-0.3 (-2.0 to 1.0)	0.58
Interval between CT and discharge without surgery (hours)	1.8 (1.1 to 4.2)	1.8 (1.0 to 5.4)	0.1 (-0.4 to 0.4)	0.91	1.8 (1.1 to 4.3)	1.8 (1.1 to 5.5)	0.0 (-0.4 to 0.4)	0.95

Between-group comparisons were made for the *post hoc* endpoints. Data are presented as n (%) or median (interquartile range). CDCT = conventional-dose CT, CI = confidence interval

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appendiceal nonvisualization were as follows. In terms of final diagnosis following appendiceal nonvisualization (Table 3), perforated appendicitis was rare in both groups; however, it tended to be more frequent in the 2-mSv CT group than in the CDCT group, showing minute differences (1.1% [17/1535] vs. 0.5% [7/1539]; difference, 0.7 percentage points [-0.0 to 1.3]; $p = 0.06$). Negative appendectomy following appendiceal nonvisualization was also rare and comparable between the two groups (0.2% [3/1535] vs. 0.1% [1/1539]; difference, 0.1 percentage points [95% CI, -0.2 to 0.5]; $p = 0.33$).

In terms of patient disposition following appendiceal nonvisualization, undesirable outcomes were rare in both groups. The 2-mSv CT and CDCT groups did not differ significantly in the need for extensive surgery to treat appendicitis (0.1% [2/1535] vs. 0.2% [3/1539], $p = 0.75$), surgeries other than appendectomy (0.6% [9/1535] vs. 0.2% [3/1539], $p = 0.15$), and additional imaging tests (0.6% [9/1535] vs. 0.2% [3/1539], $p = 0.15$), which mostly comprised of ultrasonography (0.5% [8/1535] vs. 0.2% [3/1539]). The two groups did not significantly differ in the interval between CT and appendectomy (median, 8.7 vs. 5.9 hours in 40 and 15 patients, respectively, $p = 0.51$), length of hospital stay with appendectomy (3.4 vs. 3.7 days in 40 and 15 patients, respectively, $p = 0.58$), or interval between CT and discharge without surgery (1.8 vs. 1.8 hours in 161 and 74 patients, respectively, $p = 0.91$), following appendiceal nonvisualization.

In terms of diagnostic outcomes, the majority of patients with appendiceal nonvisualization on CT still had true-positive or true-negative results for the presence of appendicitis. Therefore, false-negative and false-positive diagnoses were rare in both groups (Tables 2, 4). False-negative diagnoses (Supplementary Table 2) following appendiceal nonvisualization were noted only in the 2-mSv CT group (0.4% [6/1535] vs. 0.0% [0/1539], difference, 0.4 percentage points [0.1–0.9], $p = 0.01$). False-positive diagnoses following appendiceal nonvisualization were comparable between the two groups (0.7% [10/1535] vs. 0.5% [8/1539]; difference, 0.1 percentage points [-0.5–0.7]; $p = 0.81$). There were six and five adverse events following appendiceal nonvisualization in the two groups, respectively (Supplementary Table 3). All events were resolved without sequelae.

In the sensitivity analysis by defining appendiceal nonvisualization as only visualization grade 0 (Supplementary Table 4), the results were largely consistent with those of

Table 4. Diagnostic Outcomes Following Appendiceal Visualization Grade 0 or 1

	Intention-to-Treat Analysis				Per-Protocol Analysis			
	2-mSv CT Group (n = 1535)	CDCT Group (n = 1539)	Difference (95% CI)	*P*	2-mSv CT Group (n = 1459)	CDCT Group (n = 1479)	Difference (95% CI)	*P*
False negative, %*	6 (0.4)	0 (0.0)	0.4 (0.1 to 0.9)	0.01	6 (0.4)	0 (0.0)	0.4 (0.1 to 0.9)	0.01
False positive, %*	10 (0.7)	8 (0.5)	0.1 (-0.5 to 0.7)	0.81	10 (0.7)	8 (0.5)	0.1 (-0.5 to 0.8)	0.79
True positive, %*	31 (2.0)	14 (0.9)			31 (2.1)	14 (0.9)		
True negative, %*	163 (10.6)	70 (4.5)			156 (10.7)	69 (4.7)		
Sensitivity, %†	84 [31/37] (67 to 93)	100 [14/14] (73 to 100)	NC	NC	84 [31/37] (67 to 93)	100 [14/14] (73 to 100)	NC	NC
Specificity, %†	94 [163/173] (89 to 97)	90 [70/78] (80 to 95)	NC	NC	94 [156/166] (89 to 97)	90 [69/77] (80 to 95)	NC	NC

Between-group comparisons were made for the *post hoc* endpoints. *Data are n (% of the total number of randomized patients), †Data in brackets are n/N, and data in parentheses are 95% CIs. CDCT = conventional-dose CT, CI = confidence interval, NC = not calculated because of limited comparability

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the primary analysis (Supplementary Tables 5, 6). Undesirable outcomes following appendiceal nonvisualization were very rare, showing minute between-group differences with narrow 95% CIs. The majority of the diagnostic results of the CT reports were true positives or true negatives.

DISCUSSION

Appendiceal nonvisualization occurred in 222 (14.5%) and 99 (6.4%) patients in the 2-mSv CT and CDCT groups, respectively. In both groups, the majority of patients with appendiceal nonvisualization on CT still had true-positive or true-negative results for the presence of appendicitis, and undesirable events were rare. Perforated appendicitis and false-negative diagnosis following appendiceal nonvisualization were slightly more frequent in the 2-mSv CT group than in the CDCT group; however, the differences were minute. The two groups were comparable for negative appendectomy and false-positive diagnosis, as well as for other undesirable outcomes following appendiceal nonvisualization.

Our results have important implications for managing patients with appendiceal nonvisualization, which is a challenging situation in practice. First, although the appendix is well visualized in more than 85% of patients even on 2-mSv CT, as shown in previous studies [31,32], appendiceal visualization is slightly hampered by the use of 2-mSv CT instead of CDCT. This is in line with practitioners' concerns regarding the use of 2-mSv CT [12]. Second, appendiceal nonvisualization rarely leads to undesirable outcomes, even with the use of 2-mSv CT instead of CDCT. The between-group differences for most endpoints were minute with narrow 95% CIs, implying that the two groups were comparable. Overall, our results provide further evidence justifying the use of 2-mSv CT instead of CDCT. It is particularly interesting that the radiologists could still correctly diagnose or rule out appendicitis in most cases with appendiceal nonvisualization. We do not have a clear explanation for this finding. We assumed that radiologists could rely on secondary findings, such as fat infiltration or fluid collection in the right lower quadrant of the abdomen. Third, more caution should be exercised in clinical decision-making following appendiceal nonvisualization on 2-mSv CT instead of CDCT, particularly to avoid the risk of false-negative diagnosis and subsequent appendiceal perforation. As seen in our patients with false-negative diagnosis (Supplementary Table 2), some cases with initial negative CT results (i.e., lower likelihood of appendicitis) and appendiceal nonvisualization may benefit from a second reading by more experienced radiologists or from additional imaging tests (i.e., ultrasonography or CDCT) [33], for a more accurate diagnosis and appropriate patient disposition. Fourth, from our results showing NPVs below 80% in both groups, we conclude that appendiceal nonvisualization cannot serve solely as a sign for ruling out appendicitis, not only on 2-mSv CT but also on CDCT. The disparity from previous retrospective studies [9-11] that reported NPVs over 95% may be partly attributable to the inconsistent definition of appendiceal nonvisualization, which is intrinsically a matter of radiologists' subjective decisions. In cases of true-positive diagnosis following appendiceal nonvisualization, the diagnosis of acute appendicitis may have been drawn based on other findings such as fluid collection, abscess, or peritoneal infiltration in the right lower quadrant of the abdomen.

Our study had the merit of using data from a large pragmatic randomized controlled trial. First, our data involved 3074 patients and more than 500 care providers from 20 hospitals. This large data size allowed us to investigate an infrequent however clinically relevant situation of appendiceal nonvisualization on CT. Second, our data showed enhanced between-group comparability owing to randomization. It should be noted again that we set the denominator of most endpoints as the number of all randomized patients to ensure comparability. Third, our data has enhanced generalizability owing to the multicenter pragmatic trial design. This is an important merit because appendicitis is a common disease. The participating sites followed their usual practices, including co-interventions. They had little prior experience with low-dose CT. Many of the initial CT reports were made by radiology residents, which reflected the common practice pattern in the study region.

Our study has some limitations. First, the diagnostic performance of CT could have been overestimated in both groups, since only the patients with positive CT results (i.e., higher likelihood of appendicitis) underwent pathological verification of appendicitis. Second, despite the large scale and pragmatic nature of the trial [8], the generalizability of our study results could have been compromised for the following reasons. All participating sites were teaching hospitals, likely to have better access to resources or higher enthusiasm for 2-mSv CT than non-participating hospitals. Only a third of the eligible patients were enrolled in the

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trial due to logistical reasons. The trial was conducted in South Korea, where appendiceal CT is prevalently used, appendectomy is the standard choice of treatment for appendicitis, and patients with extremely large body habitus are rare.

In conclusion, the use of 2-mSv CT instead of CDCT impairs appendiceal visualization in more patients. However, appendiceal nonvisualization on 2-mSv CT rarely leads to undesirable clinical or diagnostic outcomes. Nevertheless, we encourage a second reading by more experienced radiologists or additional imaging tests when the appendix is not visualized on 2-mSv CT to prevent an increase in potential false-negative diagnosis or appendiceal perforation.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0504.

Availability of Data and Material

The datasets generated or analyzed during the current study are available on reasonable request. Please refer to the website; www.locat.org/data_sharing.

Conflicts of Interest

Kyoung Ho Lee received a research grant from the National Research Foundation of Korea and Seungjae Lee received salary support from the research grant. Jungheum Cho received a research grant from the Seoul National University Bundang Hospital. Other authors declare there is no conflict of interest.

Author Contributions

Conceptualization: Kyoung Ho Lee, Jungheum Cho. Data curation: all authors. Formal analysis: Seungjae Lee. Funding acquisition: Kyoung Ho Lee, Jungheum Cho. Investigation: all authors. Methodology: Kyoung Ho Lee, Jungheum Cho. Project administration: Kyoung Ho Lee, Jungheum Cho. Resources: all authors. Supervision: Kyoung Ho Lee, Jungheum Cho. Writing—original draft: Kyoung Ho Lee, Jungheum Cho. Writing—review & editing: all authors.

ORCID iDs

Jungheum Cho
https://orcid.org/0000-0003-3412-0863
Youngjune Kim
https://orcid.org/0000-0002-3698-6807
Seungjae Lee
https://orcid.org/0000-0001-5508-8634
Hooney Daniel Min
https://orcid.org/0000-0001-8665-9997
Yousun Ko
https://orcid.org/0000-0002-2181-9555
Choong Guen Chee
https://orcid.org/0000-0003-4589-0724
Hae Young Kim
https://orcid.org/0000-0002-9508-4280
Ji Hoon Park
https://orcid.org/0000-0002-6794-4909
Kyoung Ho Lee
https://orcid.org/0000-0001-6045-765X

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