European Journal of Radiology 119 (2019) 108626

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Split-bolus vs. multiphasic contrast bolus protocol in patients with pancreatic cancer or cholangiocarcinoma

Hanna Muenzfeld[a,*], Samy Mahjoub[a], Robert Roehle[b], Uwe Pelzer[d], Marcus Bahra[c], Georg Boening[a], Bernd Hamm[a], Dominik Geisel[a], Timo Alexander Auer[a,*]

[a] Department of Radiology, Charité – Universitätsmedizin Berlin, Germany
[b] Institute for Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Germany
[c] Department of Surgery, Charité – Universitätsmedizin Berlin, Germany
[d] Department of Hematology and Tumor Immunology, Charité – Universitätsmedizin Berlin, Germany

ARTICLE INFO

Keywords:
Split-bolus technique
Split-bolus CT
Pancreatic cancer
Cholangiocarcinoma
Dose reduction

ABSTRACT

Purpose: To investigate the image quality, diagnostic accuracy, and dose reduction potential of a split-bolus protocol(SBP) compared with a multiphasic protocol(MPP) in the detection of recurrent or progressive pancreatic ductal adenocarcinoma(PDAC) or cholangiocarcinoma(CC) using contrast- enhanced computed tomography(CECT).

Materials and Methods: This prospective study included 56 patients who underwent CECT, 28 with our institutional standard MPP(100 ml contrast bolus) and 28 with a novel SBP(110 ml). Radiation exposure was determined in terms of total dose- length product(DLP) and computed tomography dose index(CTDI). Image quality was measured objectively by analysis of attenuation in Hounsfield units(HU) in regions of interest(ROIs) and subjectively by two blinded readers using a Likert scale. Diagnostic accuracy and interreader variability were tested.

Results: The total DLP of the SBP group(498.1 ± 43.7 mGy*cm) was significantly lower than in the MPP group (1,092.5 ± 106.9 mGy*cm; $p < 0.001$). The SBP showed higher contrast enhancement of all critical anatomical structures including portal vein, liver, and pancreas compared with the MPP, except for the aorta(SBP: 326.9 ± 15.7 HU vs. MPP: 246.7 ± 12.2 HU; $p < 0.001$).

Subjective analysis revealed poorer image quality ratings for important landmarks with the MPP (resection surface: $p = 0.624$, portal vein: $p = 0.395$, liver $p = 0.361$). The two blinded readers correlated significantly. Sensitivity, specificity, positive and negative predictive values (PPV/NPV), and overall interreader variabilities correlated significantly. Furthermore, significantly fewer slices per exam were required for the SBP(1,823 vs. 3,235; $p < 0.001$).

Conclusion: The SBP provides the same image quality and diagnostic accuracy as an MPP while significantly lowering radiation exposure in CT follow-up of PDAC or CC.

1. Introduction

Dose reduction is an important issue in medical imaging as there is evidence that exposure to ionizing radiation correlates with cancer incidence [1,2].Computed tomography (CT) is the major contributor to ionizing radiation exposure in daily medical practice, accounting for up to 50% [3]. The ALARA principle (**As** **Low** **As** **Reasonably** **Achievable**) requires medical practitioners to constantly improve strategies and techniques to reduce patient radiation exposure. Although the lifetime risk for radiation induced malignancy is less important in oncologic patients as their life expectancy is often shortened, radiologists and clinicians should always follow the principles of ALARA [2]. Apart from technical advances, a reasonable approach to lower radiation exposure is to reduce the CT scan volume by using split-bolus protocols (SBP) instead of multi-phase protocols (MPP).

Contrast-enhanced multislice computed tomography (CE-MSCT) is essential for diagnosis, preoperative planning, and follow-up of patients with pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CC). Magnetic resonance imaging (MRI) and double- or triple-phase helical CT are the preferred imaging modalities for initial

* Corresponding authors at: Department of Radiology, Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.

E-mail addresses: hanna.muenzfeld@charite.de (H. Muenzfeld), timo-alexander.auer@charite.de (T.A. Auer).

https://doi.org/10.1016/j.ejrad.2019.07.027
Received 14 April 2019; Received in revised form 18 July 2019; Accepted 19 July 2019

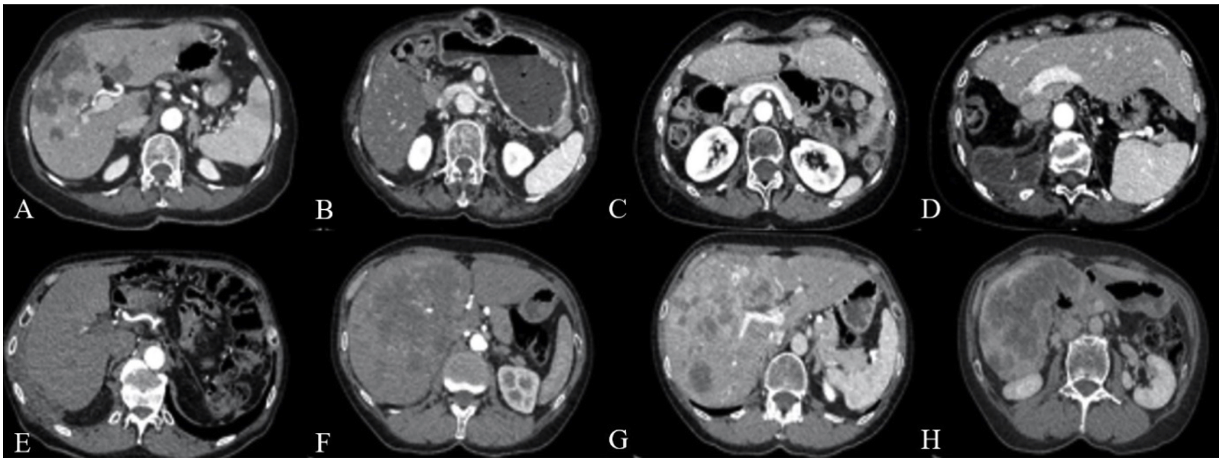

Fig. 1. Examples of images obtained with the two CT protocols investigated. **A–D SBP A:** Parenchymal contrast enhancement (CE) showing hypoattenuated liver metastases; **B:** Simultaneous CE of aorta, portal vein, superior mesenteric artery (SMA), and superior mesenteric vein; **C:** CE of aorta, vena cava, SMA, and renal veins; **D:** Simultaneous CE of aorta and portal vein; **E–H MPP E/F:** Hepatic arterial phase **G:** Portal venous phase; **H:** Delayed phase.

diagnostic assessment and follow-up of patients with PDAC or CC [4,5]. Precise radiologic characterization of malignant lesions and detailed anatomic localization usually requires three contrast phases: a hepatic arterial phase (HAP), a portal venous phase (PVP), and a delayed phase (DP) [6]. One important caveat is that repeated CECT is inherently associated with an increased radiation exposure of the patient. Following the ALARA principle SBP is a simple but effective technique incorporating the splitting of the contrast medium bolus and combining multiple contrast phases in a single scan, thus opacifying different vascular and parenchymal structures at the same time [7–11]. Previous studies have investigated this approach for different purposes (including trauma, hepatocellular carcinoma, pulmonary hemoptysis, and pulmonary embolism). While most data show that SBP are able to provide similar or even superior image quality [12–15], there is only scarce data investigating the use of a SBP in the CT assessment of patients with malignant lesions [11,16].

The challenge is to define pathologies or indications where an SBP provides equal image quality and the same diagnostic accuracy as an MPP. The purpose of this study was to investigate the imaging quality and diagnostic accuracy of an SBP and compare it with an MPP in the detection of recurrent or progressive PDAC and CC and the dose-saving potential of the SBP when used for these indications.

2. Materials and methods

2.1. Patients

Our study was approved by the institutional review board (IRB) to enrol patients prospectively and included 56 patients who underwent CE-MSCT of the chest and abdomen (internal registration number: EA2/016/14). In accordance to the clinical routine patients were dichotomized and examined either with the SBP or MPP after informed consent was obtained. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki (1975). All 56 patients had proven PDAC or CC and were sent for imaging follow up to our Department of Radiology from April to August 2018 were enrolled. Twenty-eight patients were assigned to the SBP group, and 28 patients to the MPP group.

2.2. Imaging

All patients were examined in a 128- or 64-multislice CT scanner (Revolution HD and Revolution EVO, GE Healthcare, Milwaukee, WI, USA). First, a posterior-anterior scout was acquired for phase planning. All patients received a nonionic contrast agent (either Ultravist 370, Bayer Schering, Berlin, Germany, Xenetix 350, Guerbet, Villepinte, France or Imeron 400, Bracco, Milan, Italy). In the SBP group Ultravist 370 was administered in 46% and Xenetix 350 in 54% of the study collective. In the MPP group Ultravist 350 was administered in 50%, Xenetix 350 in 46% and Imeron 400 in 4% of all patients. For administration a mechanical injection system was used (Medtron CT2, MEDTRON AG, Saarbrücken, Germany). The MPP included HAP, PVP and DP scans following administration of a single contrast agent bolus of 100 mL injected at a rate of 4.0 ml/s followed by a 20 mL saline flush. In patients with an abnormally body constitution (severe obesity or cachexia) the amount of contrast media was individually adjusted. In the SPB group the amount In the SPB group the amount differed in five patients from the standardized amount of 110 mL (1 x 70 ml, 1 x 80 ml, 2 x 100 mL and 1 x 120 ml). In the MPP group the amount differed in 18 patients from the standardized 100 mL (9 x 80 ml, 2 x 90 ml, 5 x 120 ml, 1 x 150 mL and 1 x 170 ml). Automated bolus tracking software (SmartPrep, GE Healthcare, Milwaukee, WI, USA) with placement of a region of interest (ROI) in the abdominal descending aorta was used to identify the optimal time point for starting the HAP (cutoff > 100 HU, approximately 20 s delay). PVP and DP scan started with a fixed delay of 40 and 80 s after the threshold was reached with bolus tracking.

In the SBP group, patients were administered a first contrast agent bolus of 80 ml at 2.5 ml/s followed by 20 ml saline at 2.5 ml/s. After a delay of 10 s, a second bolus of 30 ml was administered at 3.5 ml/s *(*Fig. 1*)*. The scan started 75 s after injection of the first bolus. For both imaging sections tube voltage was 120 keV. In patients with an abnormal body constitution keV levels were adjusted individually to maintain image quality. In all patients an iterative reconstruction algorithm (ASIR) was used at a percentual level between 30–50.

The CT examination consisted of seven series: the scout, axial planes (slice thickness of 5 mm, 2.5 mm and 0.625 mm), the maximal intensity projection, and multiplanar reformations in sagittal and coronal planes. All axial and MPR were acquired for every contrast bolus phase and were sent to the PACS (Picture Archiving and Communication System, GE Healthcare, Milwaukee). Radiation exposure was measured by determining the total dose-length product (DLP) and the computed tomography dose index (CTDI). The total number of slices per scan was noted.

2.3. Image analysis

All diagnoses were confirmed by a board-certified radiologist. Objective attenuation in HU was determined by calculating mean values for standardized regions of interest (ROIs) placed in the aorta, the portal vein, the inferior vena cava as well as in organ parenchyma (liver

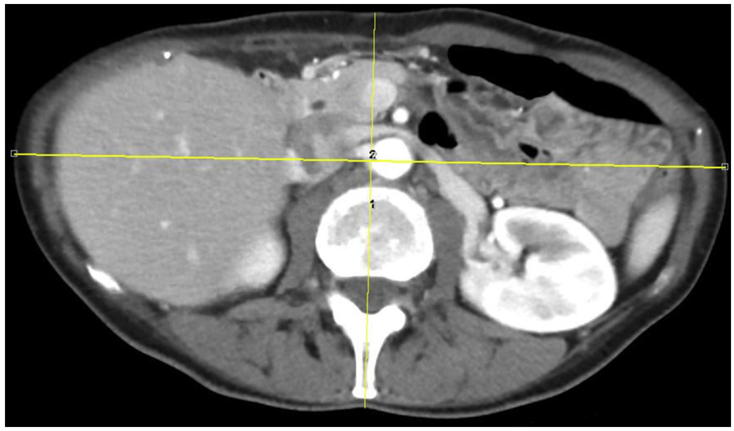

Fig. 2. Measurement of the abdominal anterior-posterior (AP)- and transversal diameter to compare patients body constitutions.

and pancreas), bone, air, muscle, and fat. This was done by two radiologists in consensus. They were blinded to patient data and had similar levels of experience in abdominal radiology (three years). In the MPP group, contrast attenuation of liver and pancreas was assessed in the contrast phase that showed the highest contrast attenuation for the respective structure of interest (e.g., the HAP for the aorta or the PVP for the portal vein). Additionally, blinded subjective image analysis was performed using a five-point Likert scale (ranging from 0 = not acceptable to 5 = excellent). Special attention was paid to the visibility of the anastomosis (for example, biliodigestive anastomosis or pancreaticogastrostomy, if present) as well as contrast attenuation and visibility of local tumor, nodal involvement, and distant metastases. Tumor recurrence and progression were documented. The standard of reference was a histopathological report, if available. Otherwise CT and / or MRI follow up examinations in combination with clinical and paraclinical surveillance parameters (laboratorial tests, tumor markers, ECOG performance test etc.) served as a reference standard. To compare patients body constitutions the anterior–posterior (AP) and the transverse diameters were measured as done previously (Fig. 2) [17].

2.4. Statistics

Statistical analysis was performed using SPSS software (IBM; New York, USA) and Graph Pad PRISM (Graph Pad Software, Inc.). Sample size was calculated with a two-group *t*-test of equivalence in means using nQuery Advisor V. 7.0 at a significance level of $\alpha = 0.05$ and a desired power of 0.8. All values, unless otherwise indicated, were provided as mean ± standard deviation (SD). Histograms and plots indicated that normal distributions should not be assumed for metric parameters. An unpaired *t*-test was performed for comparison of mean values between the two groups. For distributions of the AP-diameter between the two groups the Kolmogorov-Smirnov test was chosen. The chi-square test was used for comparison of the incidence of tumor recurrence or progression. $\alpha < = 0.05$ was considered statistically significant. Correlation of the subjective Likert scores was determined by a pairwise two-sided Spearman rank correlation test. Cohen's k was determined for interreader variability.

3. Results

3.1. Patients

The 56 patients included had a mean age of 65.8 ± 10.1 years. There were 30 men and 26 women. In the SBP group, mean age was 65.8 ± 1.8 years and 12 patients were male and 16 female. In the MPP group, mean age was 65.2 ± 2.2 years and 18 patients were male and 10 female ($\boldsymbol{p} > \boldsymbol{0.05}$ for all distributions). Overall there had been 30 patients suffering from PDAC and 15 from CC. One patient had a combined PDAC/CC situation. Subdivided there have been 17 patients with PDAC, ten with CC and one with combined PDAC/CC in the SBP group. In the MPP group 13 patients suffered from PDAC and 15 from CC. Mean AP-diameter in the SBP group was 23.3 cm ± 4.1 (range: 15.7–33.2 cm) vs. 24.4 cm ± 4.1 (range: 17–32.8 cm). Kolmogorov-Smirnov test showed no significant difference for the two groups with $p = 0.203$. (Table 1).

3.2. Radiation dose

The total DLP in the SBP group was 498.1 ± 43.7 mGy*cm and significantly lower than in the MPP group (1092.5 ± 106.9 mGy*cm; $\boldsymbol{p} < \boldsymbol{0.001}$). The CTDI did not differed significantly between the two groups (SBP: 7.1 ± 0.5 mGy vs. MPP: 7.5.0 ± 0.9 mGy, $p = 0.648$). The total number of slices acquired was significantly lower in the SBP group than in the MPP groups (average of 1828 vs. 3235 slices; $\boldsymbol{p} < \boldsymbol{0.001}$; Table 1).

3.3. Image quality

Two readers assessed image quality subjectively on a five-point Likert scale. The Spearman rank correlation coefficient showed significant correlation between the two protocols for the aorta ($\boldsymbol{p} = \boldsymbol{0.007}$), the inferior vena cava ($\boldsymbol{p} = \boldsymbol{0.077}$), and for the pancreas ($\boldsymbol{p} = \boldsymbol{0.021}$). For the anastomosis and/or resection surface ($\boldsymbol{p} = \boldsymbol{0.624}$), the portal vein ($\boldsymbol{p} = \boldsymbol{0.395}$), and for the liver ($\boldsymbol{p} = \boldsymbol{0.361}$) ranks did not correlate significantly, showing higher mean average values for the SBP for the above-mentioned anatomical structures that were tested. Correspondingly, a negative correlation coefficients for the MPP

Table 1
Descriptive statistics and radiation doses, including cancer origin and AP-diameter to assume body constitutions. The radiation dose is significantly lower for the SBP compared to the MPP. No. = number, DLP = dose-length product, CDTI = computed tomography dose index.

	Split-bolus protocol	Multiphasic protocol	p-value*
No. of patients	28	28	
Mean age (years)	65.8 ± 1.8	65.2 ± 2.2	*> 0.05*
PDAC	17	13	
CC	10	15	
PDAC/CC	1	0	
Total DLP (mGy * cm)	498.1 ± 43.7	1092.5 ± 106.9	**< 0.0001**
CDTI (mGy)	7.1 ± 0.5	7.5 ± 0.9	*p = 0.648*
AP-diameter *(transverse diameter)*	23.3 cm ± 4.1	23.4 cm ± 3.9	*p = 0.203*
Mean No. of slices	1823	3235	**< 0.0001)**

* Significant p-values highlighted in bold fonds.

Table 2
Subjective Likert scores of crucial anatomical regions and inter-reader correlation. IVC = inferior vena cava.

Likert score (1-5)	Split-bolus protocol**	Multiphasic protocol**	p-value*	Interreader* correlation
Anastomosis / tumour	**4.0**	3.4(-)	**0.624**	< ***0.001***
Aorta	**4.2**	4.1	**0.007**	***0.004***
Portal vein	**3.6**	3.3(-)	0.395	< ***0.001***
IVC	2.4	**2.5**	**0.077**	< ***0.001***
Liver	**3.6**	3.0(-)	0.361	< ***0.001***
Pancreas (if present)	**3.2**	**3.2**	**0.021**	***0.035***

* Significant p-values highlighted in bold fonds.
** Higher subjective values between both groups also highlighted in bold fonds.

(marked with a minus sign in Table 2). Interreader variability was tested by Cohen's *kappa* and proved a significant correlation between both readers (***p*** < ***0.001-0.035***).

Furthermore, objective analysis by means of ROI-based HU attenuation analysis of pivotal anatomical structures revealed no significant differences between the two groups for the inferior vena cava, and for organ parenchyma (liver and pancreas), bone, air, muscle, and fat (p > 0.05). The results are compiled in Table 4. Only the aorta and the portal vein showed significantly higher HU values in the MPP group with 326.9 ± 15.7HU vs. 247.7 ± 12.2 - (***p*** < ***0.001***) and 202.1 ± 10.8HU vs. 172.7 ± 5.8HU (***p*** = ***0.037***) (Table 3 and Fig. 3).

3.4. Diagnostic accuracy

Cancer recurrence and/or progression was detected in 42 of the 56 patients. In the SBP group, sensitivity was 90% vs. 95% (SBP vs. MPP). Sensitivity was 50% (MPP: 66%), PPV was 81% (MPP: 91%), and NPV was 66% (MPP: 80%). Inter-reader variability correlated significantly for sensitivity, specificity, PPV and NPV (***p*** < ***0.001***) (Table 4).

4. Discussion

CT scans acquired with the split-bolus protocol are comparable to the multiphasic protocol in terms of image quality and diagnostic accuracy while significantly lowering radiation exposure (up to 55%) in the follow-up of PDAC or CC.

CT dose reduction without a loss of image quality and diagnostic accuracy is a key concern for every radiologist in daily clinical routine. Current scientific efforts aim at lowering radiation exposure by using lead shields, tube current and tube voltage modulation and iterative reconstruction algorithms [18–22]. Other very simple and effective techniques to reduce radiation doses include scan protocol modification and scan volume optimization approaches. In our prospective study, patients with PDAC or CC were examined with either an SBP or an MPP.

Table 3
Contrast attenuation analysis for crucial anatomical regions showing comparable HU values for the tested structures / organs except for the aorta.

ROI-based HU analysis	Split-bolus protocol**	Multiphasic protocol**	p-value*
Aorta	247.7 ± 12.2	**326.9 ± 15.7**	**< 0.001**
Portal vein	172.7 ± 5.8	**202.1 ± 10.8**	**0.037**
IVC	117.7 ± 5.1	**121.3 ± 6.6**	0.806
Liver	**103.7 ± 4.5**	102.0 ± 4.7	0.471
Pancreas (if present)	**109.6 ± 3.8**	100.5 ± 6.8	0.119

* Significant p-values highlighted in bold fonds.
** Higher objective attenuation values between both groups also highlighted in bold fonds.

Table 4
Analysis of inter-reader variability. There is strong correlation for sensitivity, Specificity, PPV (positive predictive value), and NPV (negative predictive value).

Diagnostic accuracy: **	Split-bolus protocol	Multiphasic protocol	Interreader Correlation*
Reader 1:			**< 0.001**
Sensitivity	90%	95%	
Specificity	50%	66%	
PPV	81%	91%	
NPV	66%	80%	
Reader 1:			**< 0.001**
Sensitivity	90%	86%	
Specificity	50%	50%	
PPV	100%	100%	
NPV	75%	66%	

* Significant p-values highlighted in bold fonds.
** The standard of reference was a histopathological report if available. Otherwise like for the majority of patients CT and / or MRI follow-up examinations in combination with clinical surveillance served as reference standard including paraclinical parameters (laboratorial tests, tumor-markers, ECOG etc.).

The objective analyses of dose reduction resulted in a significantly lower DLP in the SBP group as compared to the MPP group (***p*** < ***0.001***). For subjective analysis, all CT datasets were assessed by two blinded readers rating critical anatomical structures on a five-point Likert scale. Again, our results clearly show the same image quality for the SBP, which was not assigned lower scores than the MPP for any of the categories tested. On the contrary, scores for the SBP group were even better for visibility of the anastomosis and/or resection surface, the portal vein, and the liver.

In the objective ROI-based analysis of the same anatomical regions that were rated subjectively, the aorta showed significantly higher contrast attenuation in the MPP group than in the SBP group with (***p*** < ***0.001***) as well as the portal vein (***p*** = ***0.037***). However, this did not seem to have an effect on the subjective impression as both readers (***p*** < ***0.001***) assigned similar scores to the aorta for both CT protocols (SBP: 4.2 vs. MPP: 4.1), and ranks correlated positively (***p*** = ***0.007***) as well as for the portal vein (SBP: 3.6 vs. MPP: 3.3; ***p*** < ***0.001***). Overall, our results suggest that the two protocols yield comparable image quality. Even if a remote amount of contrast was varying between 100 (MPP) and 110 ml (SBP), we do not see evidence that this might have affected the image quality significantly.

Similarity of the two protocols is further corroborated by our results for diagnostic accuracy. There was significant correlation between the SBP and MPP for sensitivity, specificity, PPV, and NPV. Interreader variability also correlated significantly between both blinded readers.

We believe that, in addition to providing similar image quality at a considerably lower radiation dose, the SBP has further crucial advantages: the SBP minimizes the number of slices acquired per scan, resulting in more efficient diagnostic assessment as it reduces CT reading time for the radiologist. Additionally, all critical structures are opacified in one single phase as in three different phases, also reducing the reading time and less prone to diagnostics mistakes. This, in turn, can contribute to an improved cost efficiency for the facility.

Another aspect to consider is that the SBP involves a relatively long time of approximately 75 s between the first bolus and the start of the scan. In contrast, the triple phase protocol has a delay of only approximately 30 s until the HAP starts. This time span can be used for a careful observation of the contrast injection process and early assessment for possible injection-related complications such as extravasation, a malfunctioning injection system, or allergic reactions.

In summary, the multi-phase CECT continues to have an important role in clinical routine, especially for the assessment of inconclusive lesions or for preoperative planning. In the follow-up setting of patients

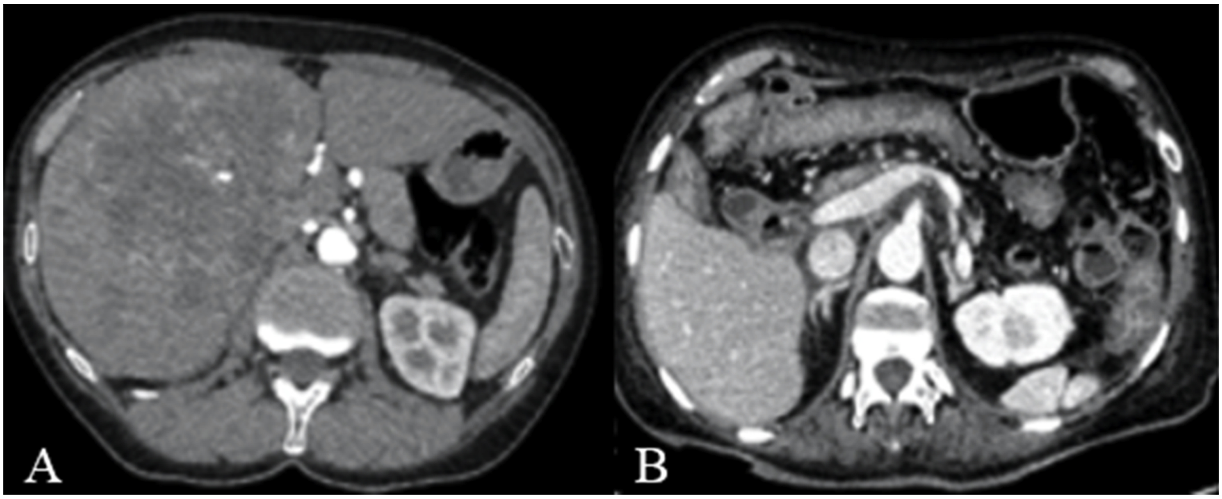

Fig. 3. Comparison of arterial contrast enhancement (measured in the aorta) with the two protocols investigated. **A: MPP**: 339 HU **B/C: SBP**: 223 and 276 HU, respectively.

with PDAC or CC, however, the split-bolus protocol presented here provides similar and entirely satisfactory image quality at about half the radiation exposure of the standard protocol. Our promising results should encourage further studies investigating this potential of SBP CT imaging in other clinical contexts.

4.1. Limitations of the study

Our patient sample size is relatively small. The different amounts and concentrations of contrast agent used in the split-bolus and standard protocol groups could be another confounder. Furthermore, all participants were aware of the study design, which may have introduced a detection bias.

4.2. Conclusion

The SBP is equal to the MPP regarding imaging quality and diagnostic accuracy while significantly lowering radiation exposure in the follow-up setting of PDAC and CC. Moreover, the smaller scan volume can improve diagnostic efficiency in terms of reading time and thus contribute to cost reduction. Our prospective study contributes further evidence that split bolus MDCT is easy and safe to perform. The future task will be to define clear indications where SBP CT can be used to minimize radiation exposure by avoiding unnecessary multiphasic scans.

Declaration of Competing Interest

None.

References

[1] D.A. Pierce, D.L. Preston, Radiation-related cancer risks at low doses among atomic bomb survivors, Radiat. Res. 154 (2) (2000) 178–186.
[2] Task Group on Control of Radiation Dose in Computed, T, Managing patient dose in computed tomography. A report of the International Commission on Radiological Protection, Ann. ICRP 30 (4) (2000) 7–45.
[3] N.E. Bolus, NCRP report 160 and what it means for medical imaging and nuclear medicine, J. Nucl. Med. Technol. 41 (4) (2013) 255–260.
[4] M. Fusari, et al., Comparison between multislice CT and MR imaging in the diagnostic evaluation of patients with pancreatic masses, Radiol. Med. 115 (3) (2010) 453–466.
[5] M.R. Engelbrecht, et al., Imaging of perihilar cholangiocarcinoma, AJR Am. J. Roentgenol. 204 (4) (2015) 782–791.
[6] F.E. Boas, et al., Classification of hypervascular liver lesions based on hepatic artery and portal vein blood supply coefficients calculated from triphasic CT scans, J. Digit. Imaging 28 (2) (2015) 213–223.
[7] M. Scialpi, et al., Split-bolus multidetector-row computed tomography technique for characterization of focal liver lesions in oncologic patients, Iran. J. Radiol. 13 (2) (2016) e20143.
[8] M. Scialpi, et al., Split-bolus versus triphasic multidetector-row computed tomography technique in the diagnosis of hepatic focal nodular hyperplasia: a case report, J. Med. Case Rep. 8 (2014) 425.
[9] M. Scialpi, et al., Detection and characterization of focal liver lesions by split-bolus multidetector-row CT: diagnostic accuracy and radiation dose in oncologic patients, Anticancer Res. 34 (8) (2014) 4335–4344.
[10] M. Kekelidze, et al., Kidney and urinary tract imaging: triple-bolus multidetector CT urography as a one-stop shop–protocol design, opacification, and image quality analysis, Radiology 255 (2) (2010) 508–516.
[11] O.R. Brook, et al., Split-bolus spectral multidetector CT of the pancreas: assessment of radiation dose and tumor conspicuity, Radiology 269 (1) (2013) 139–148.
[12] J. Jiang, et al., Preoperative assessment of hepatocellular carcinoma with split-bolus combined phase contrast-enhanced computed tomography, Med. Sci. Monit. 23 (2017) 1834–1841.
[13] C. Jeavons, et al., A review of split-bolus single-pass CT in the assessment of trauma patients, Emerg. Radiol. 25 (4) (2018) 367–374.
[14] J.C. Godt, et al., Triple-split-bolus versus single-bolus CT in abdominal trauma patients: a comparative study, Acta Radiol. 59 (9) (2018) 1038–1044.
[15] P. Meena, et al., Single-phase split-bolus dual energy computed tomography angiography for evaluation of hemoptysis: a novel application, J. Thorac. Imaging (2018).
[16] A. Camacho, et al., Split-bolus pancreas CTA protocol for local staging of pancreatic cancer and detection and characterization of liver lesions, Abdom. Radiol. (NY) 43 (2) (2018) 340–350.
[17] F. Zarb, L. Rainford, M.F. McEntee, AP diameter shows the strongest correlation with CTDI and DLP in abdominal and chest CT, Radiat. Prot. Dosimetry 140 (3) (2010) 266–273.
[18] A. Winklehner, et al., Automated attenuation-based tube potential selection for thoracoabdominal computed tomography angiography: improved dose effectiveness, Invest. Radiol. 46 (12) (2011) 767–773.
[19] M.K. Kalra, et al., Techniques and applications of automatic tube current modulation for CT, Radiology 233 (3) (2004) 649–657.
[20] H. Greess, et al., Dose reduction in CT examination of children by an attenuation-based on-line modulation of tube current (CARE Dose), Eur. Radiol. 12 (6) (2002) 1571–1576.
[21] S.L. Brady, et al., Pediatric CT: implementation of ASIR for substantial radiation dose reduction while maintaining pre-ASIR image noise, Radiology 270 (1) (2014) 223–231.
[22] M.K. Kalra, et al., Strategies for CT radiation dose optimization, Radiology 230 (3) (2004) 619–628.