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Value of multi-detector computed tomography during intra-arterial infusion of contrast medium for locating insulinomas

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Abstract

Objective: This study aimed to evaluate the accuracy of multi-detector computed tomography (CT) during intra-arterial infusion of contrast medium (MDCT-IA) for locating insulinomas.

Methods: This retrospective study included patients with insulinomas who underwent surgery at the Chinese PLA General Hospital in 2013 to 2014. The patients' case notes and investigation results were reviewed. Preoperative tumor localization was carried out by MDCT-IA and non-invasive methods including MDCT, magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS). Insulinoma localization using these methods was compared with the histologically confirmed location following surgical excision.

Results: Twelve insulinomas were identified in 12 patients, all of which were treated surgically. All patients received MDCT-IA (100%), 11 patients also underwent MRI (91.7%), seven underwent CT (58.3%), and all 12 underwent CEUS (100%). Tumor localization was determined successfully in 12/12 patients by MDCT-IA (100%), in 9/11 by MRI (81.8%), 4/7 by CT (57.1%), and 7/12 by CEUS (58.3%). Overall, MDCT-IA correctly localized 100% of the lesions.

Conclusions: MDCT-IA can be used to determine the preoperative localization of insulinomas.

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Introduction

Insulinomas are rare tumors with an estimated incidence of only four per one million person-years.[1–3] However, it is the most common functioning islet cell tumor that provokes hyperinsulinemic hypoglycemia. Its classical presentation is the Whipple triad,[3,4] including symptoms of hypoglycemia, plasma glucose level <50 mg/dL, and symptom relief by glucose administration. Recurrent hypoglycemia induced by insulinoma seriously affects patient quality of life and can lead to irreversible brain damage.

Radical surgical resection is the first choice of treatment for insulinoma, and accurate preoperative localization improves the chance of cure and reduces the likelihood of complications.[2,3,5] However, preoperative localization remains a clinical challenge. We therefore conducted this study to evaluate the accuracy of multi-detector computed tomography (MDCT) during intra-arterial infusion of contrast medium (MDCT-IA) for localizing insulinomas.

Methods

This was a retrospective study including patients with insulinomas identified at a single center (Chinese PLA General Hospital) between November 2013 and October 2014. Insulinomas were confirmed by glucose tolerance test and imaging data. Clinical histories and relevant biochemical results were obtained from chart reviews. Symptomatic hypoglycemia with elevated plasma insulin and C-peptide levels were confirmed by prolonged supervised fasting and/or glucose tolerance test. Other causes of hypoglycemia were excluded. The present study was approved by the Ethics Committee of Chinese PLA General Hospital. All study participants provided written informed consent prior to therapy.

The inclusion criteria were age >18 years, insulinoma, no allergy to contrast agents, and biochemically proven endogenous hyperinsulinemic hypoglycemia. Patients were excluded if they had other severe diseases, such as kidney, heart, or liver failure, if they were allergic to contrast agents, or if they were pregnant.

In our study, CEUS were performed by doctors with >10 years' experience. MDCT imaging was performed using a 64-slice multi-detector CT scanner (GE Healthcare, Milwaukee, WI, USA). MRI was performed using a 1.5 Tesla scanner (GE Healthcare, Little Chalfont, UK). Routine MRI sequences were obtained, including axial T1- and T2-weighted images, and axial T1-weighted images with fat saturation before and after intravenous administration of gadolinium. To further demonstrate the exact location of the tumor, patients underwent MDCT-IA using an integrated digital subtraction angiography (DSA) and CT machine (Siemens Angio-CT; Siemens Healthcare, Erlangen, Germany). A 4F catheter was placed in the celiac artery (CA). After conventional celiac arteriography, sequential helical scanning of the pancreas was performed during the injection of 20 to 30 mL of contrast medium through the catheter at approximately 2 to 3 mL/second.

The MDCT scan was delayed for 3 seconds after starting the contrast medium injection. If any part of the pancreas was not enhanced in the images, MDCT-IA was repeated with the catheter placed in the superior mesenteric artery (SMA) instead of the CA.

Surgery was planned based on the information obtained from all the localization investigations. Features such as tumor size and Ki-67 score (as a surrogate for malignant potential) were evaluated by the pathologists. The anatomical and imaging localization techniques were compared with the intraoperative findings. Follow-ups were performed by reviewing hospital records and by directly contacting the patients by telephone. The last follow-up was in December 2016.

Results

This study enrolled 12 patients with insulinomas who met the inclusion criteria. The preoperative localization methods included CEUS in 12 patients, MDCT in seven patients, MRI in 11 patients, and MDCT-IA in 12 patients. All 12 insulinomas were successfully treated by complete surgical resection. The patient, tumor, and surgical details are given in Table 1. Immunohistochemistry revealed that all cases were positive or weakly positive for insulin.

MDCT scans correctly localized the lesion in four of the seven cases examined (57.1%) and failed to localize the lesion in the remaining three, CEUS correctly localized the lesion in seven of 12 cases (58.3%), and MRI localized the lesion in nine of 11 cases (81.8%). The use of these combined noninvasive approaches ensured that 10 of the 12 lesions were localized correctly prior to surgery (83.3%).

All 12 patients underwent additional MDCT-IA because of the surgeon's preference for additional anatomical information. All 12 lesions were correctly localized by this method, including tumors <1 cm and those incorrectly localized by all the aforementioned methods (Figure 1). Four patients received MDCT-IA twice because different parts of their pancreases were supplied separately by the CA and SMA (Figure 2).

All patients were cured after surgery without recurrence or secondary diabetes after a median follow-up period of 30 months, and no adjuvant therapy was performed in this patient cohort.

Discussion

This study examined the outcomes of 12 patients with insulinomas treated by surgery. MDCT-IA correctly localized the tumor in all patients (100%), compared with 81.8% of patients examined by MRI, 57.1% by CT, and 58.3% by CEUS.

Radical surgical resection is the first choice of treatment for insulinoma, and its accurate preoperative localization increases the success rate and decreases the risk of complications.[2,3,5] Recent advances in imaging technology, including MDCT, MRI, CEUS, endoscopic ultrasonography (EUS), and DSA, have considerably improved in the quality and sensitivity of the detection of insulinomas. However, approximately 80% of these tumors are <2 cm in diameter, and their preoperative localization thus remains a clinical challenge.[2,6] However, some reports suggested that MDCT-IA could effectively detect insulinomas, which generally occur as small nodules with a hypervascular nature.[7–10]

Ultrasonography, CT, and MRI are the most widely used noninvasive diagnostic methods. The sensitivity of ultrasonography is affected by various factors, such as the physician's expertise, patient's body weight, tumor size, and tumor location, leading to reported sensitivities of 0% to 86.5%. However, An et al.[2,5,11] reported

Table 1. Patient characteristics.

			Lesion features					Localization investigations			
Patient no.	Sex/age	BMI	Tumor localization	Max. diameter (cm)	Pathologic classification	Ki-67 score	Operation style	CT	MRI	CEUS	MDCT-IA
1	F/60	33.3	Head	2	G1	2%	Enucleation	Correct	Correct	Fail	Correct
2	F/59	24.2	Junction of body/tail	1.5	G2	3%	Distal pancreatectomy	–	Correct	Correct	Correct
3	F/42	27	Head	3.5	G1	2%	Enucleation	Fail	Correct	Correct	Correct
4	F/43	24.5	Head	1.7	G2	3%–5%	Pancreatico-duodenectomy	–	Fail	Correct	Correct
5	F/46	30.3	Tail	1.6	G1	<2%	Enucleation	–	Correct	Correct	Correct
6	F/52	28.3	Tail	1.7	G1	2%	Distal pancreatectomy	–	Correct	Fail	Correct
7	F/45	30.2	Body	1.5	G2	3%–5%	Enucleation	Correct	Correct	Correct	Correct
8	M/35	29.6	Head	1.5	G1	1%	Enucleation	Correct	Correct	Correct	Correct
9	M/58	24.7	Body	2	G1	<2%	Distal pancreatectomy	Correct	Correct	Fail	Correct
10	F/48	21.3	Body	0.7	G1	<2%	Enucleation	Fail	Fail	Fail	Correct
11	F/64	31.6	Body	0.6	G2	3%–5%	Enucleation	Fail	–	Fail	Correct
12	F/49	29.4	Tail	1.3	G1	<2%	Enucleation	–	Correct	Correct	Correct

BMI, body mass index (weight (kg)/height $(m)^2$); F, female; M, male; CT, computed tomography; MRI, magnetic resonance imaging; CEUS, contrast-enhanced ultrasound; MDCT-IA, multi-detector CT during intra-arterial infusion of contrast medium.

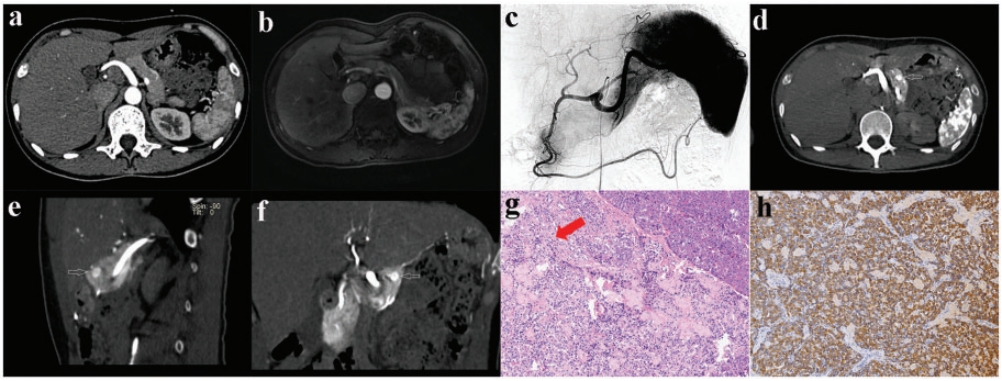

Figure 1. Findings in a 48-year-old woman. Dynamic helical CT (a) and MRI (b) failed to show the insulinoma in the pancreas. Following a conventional celiac arteriogram (c), MDCT-IA was performed and showed a small well-enhanced, round lesion in the pancreatic body (d–f, arrow). The insulinoma and surrounding normal pancreas tissues were shown by hematoxylin and eosin staining (red arrow) (g), and strong immunoreactivity for insulin was detected (brown staining) (h). Magnification ×100 (g and h).

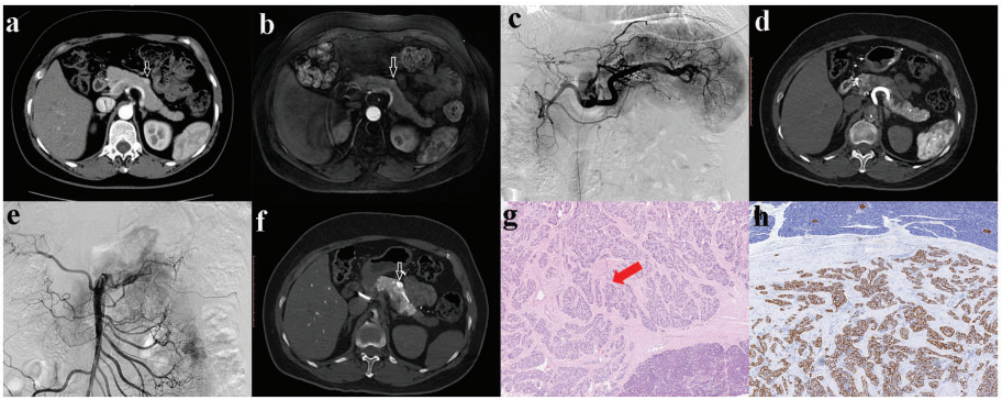

Figure 2. Findings in a 45-year-old woman. Dynamic helical CT (a) and MRI (b) correctly localized the insulinoma in the pancreas body. After celiac arteriography (c), MDCT-IA was performed but the pancreatic body was not enhanced (d). Second celiac arteriogram after placement of the catheter in the SMA (e); the insulinoma was clearly demonstrated after repeat MDCT-IA with the catheter placed in the SMA (f, arrow). The insulinoma and surrounding normal pancreas tissues were shown by hematoxylin and eosin staining (red arrow) (g), and strong immunoreactivity for insulin was detected (brown staining) (h). Magnification ×100 (g and h).

a high sensitivity of 86.5% for CEUS in patients with insulinomas. According to Chinese standards, four patients (33.3%) in the present study were overweight (body mass index (BMI) $\geq$24.0 and $<$28.0 kg/m^2) and seven patients (58.3%) were obese (BMI $\geq$28.0 kg/m^2). Although CEUS was performed by physicians with more than 10 years' experience, the tumor was only localized correctly in seven patients (58.3%) using this technique. CT and MRI scans with contrast enhancement were performed routinely to detect tumors and rule out liver metastases. As reported

previously, the sensitivity of CT ranged from 2% to 95.3%, with approximately 90% of studies showing an average sensitivity of <70%.[2] Compared with other noninvasive imaging techniques, MRI has shown the highest sensitivity, but the mean sensitivity was still only approximately 45%.[2,12,13] In the present study, CT and MRI correctly localized 57.1% and 81.8% of the lesions, respectively, and the combined use of the three noninvasive methods correctly localized 10 lesions (83.3%) prior to surgery.

If noninvasive studies fail to localize the tumors, invasive methods may be required. Invasive methods may also be performed to confirm the localization of the tumor due to the surgeon's preference for more accurate anatomical information. The most common invasive methods include arteriography, somatostatin receptor scintigraphy, EUS, transhepatic portal venous sampling, and selective arterial calcium stimulation testing. The rich blood supply of the insulinoma means that arteriography can depict the lesion as hypervascular or nodular-staining. However, false-positive results are relatively common because the accessory spleen, lymph nodes, or opaque intestinal loops are easily mistaken for insulinoma.[3,7,14] The reported sensitivity rates of arteriography range from 29% to nearly 90%.[14,15] Arteriography is currently usually performed as a supplement to other methods. The sensitivity of somatostatin receptor scintigraphy is significantly affected by the tumor size and the density of somatostatin receptors, and we have relatively limited experience with this technique. EUS is highly operator-dependent, with a low visualization rate in the pancreatic tail.[16–18] Furthermore, despite high reported accuracy rates, we have generally not adopted transhepatic portal venous sampling and selective arterial calcium stimulation because these are used more for regionalization than for true localization.

MDCT-IA is a new, invasive, and technically demanding method for insulinoma localization. It involves a combination of MDCT and catheter angiography, and can provide data with both sufficient arterial enhancement during the optimal temporal window and high spatial resolution for thin collimation derived from MDCT.[7–9] A catheter is initially placed in the CA, as the main artery feeding the pancreas. Sequential helical scanning of the pancreas is then carried out during injection of the contrast medium through the catheter. MDCT-IA can be repeated if necessary, with the catheter placed in the SMA as another possible feeding artery of the pancreas. In the present study, four patients received MDCT-IA twice because different parts of their pancreases were supplied separately by the CA and SMA.

The main advantage of MDCT-IA is in improving the concentration of the contrast medium in the local blood flow.[7–9] Owing to their abundant blood supply, insulinomas are significantly enhanced, in sharp contrast to the normal pancreatic tissue. Meanwhile, the axial display and reconstructions of coronal and sagittal sections can avoid interference from the surrounding tissue. MDCT-IA and common angiography can be used to supplement each other to further improve the localization accuracy of insulinomas. Given that 5% to 10% of insulinomas may be multiple and associated with hereditary multiple endocrine neoplasia type-1 syndrome,[2,19] arteries filled with the contrast medium should be identified carefully to avoid missing small tumors. In the present study, MDCT-IA accurately localized all the insulinomas, including tumors <1 cm, and the significantly enhanced tumors were carefully discriminated from the vessels and normal tissues by thin-slice scanning and reconstructions of the coronal and sagittal sections.

Accurate preoperative localization of the tumors meant that all patients who received pancreas-preserving surgery were cured, without recurrence or secondary diabetes.

The main disadvantage of MDCT-IA is its invasive and complicated nature. However, the use of a Siemens Angio-CT, which integrates the functions of DSA and MDCT, makes the procedure easier, and the patient does not need to be moved from the catheterization laboratory to the CT room after placement of the catheter.

This study had some limitations. First, it was a retrospective study, rather than a randomized controlled trial. Second, the sample size was small. Further, large, multicenter clinical trials are therefore needed to confirm the present results. Third, the follow-up period was relatively short, and longer clinical follow-up is needed in future studies.

In conclusion, MDCT-IA is a useful method for the preoperative localization of insulinomas, especially in the case of tumors <1 cm in diameter.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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