Prescintigraphic morphine application for abdominal adenocarcinoma imaging, with technetium-99m methoxy isobutyl isonitrile

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Abstract

Imaging of tumors with cationic tracers, especially with technetium-99 methoxy isobutyl isonitrile (^{99m}Tc-MIBI), revealed high specificity for the diagnosis and follow up of various malignancies. However, these radiopharmaceuticals are of limited value for the diagnosis of malignancies of the abdominal region due to the immediate biliary secretion of the tracer and the associated high background activity. In a prospective, single-blinded protocol, patients with endoscopically diagnosed gastrointestinal malignancies were assigned to undergo ^{99m}Tc-MIBI imaging of the abdomen. To overcome biliary secretion of cationic tracer we administered 0.04mg/kg morphine hydrochloride intravenously before the administration of 600 MBq ^{99m}Tc-MIBI. Planar images were performed in the anterior and posterior views with a double-headed gamma camera and with 3min acquisition time, followed by single photon emission tomography images (3 degrees, 20 sec/frame). Results were compared to findings of endoscopy, computed tomography scan and surgery. Twenty four patients 17 male and 7 female , mean age 69 years, range 52-83, years were enrolled. All patients suffered from adenocarcinoma, (19 from colorectum, 3 from gastric, 1 from pancreatic and one patient had both gastric and colorectal adenocarcinoma, for a total of 25 tumor lesions). The primary objective-inhibition of biliary secretion- was achieved in 23 of the 24 patients. ^{99m}Tc-MIBI-imaging was accumulated intra-abdominally in 19 patients. In 2 patients the tumor was endoscopically completely removed before the scan. In these two patients ^{99m}Tc-MIBI imaging showed no intra-abdominal tracer accumulation. When compared to the endoscopic findings, ^{99m}Tc-MIBI imaging showed time positive results in 13 of the 23 remaining individual tumor lesions, false positive in 6 and false negative in 4. This study showed a sensitivity of 57% and a specificity of 20% of the above technique for the identification of intra-abnominal adenocarcinomas. Correct diagnosis did not correlate with tumor size. *In conclusion*, prescintigraphic morphine administration inhibits background activity coming from biliary secretion, and enables better intra-abdominal ^{99m}Tc-MIBI imaging but with limited sensitivity and poor specificity.

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Introduction

Gastrointestinal endoscopy is the method of choice for the diagnosis and follow-up of gastrointestinal malignancies [1]. Bowel cleaning before or pain during endoscopy, make this investigation unpleasant to patients. Several alternative methods, including virtual endoscopy with computer tomography (CT) [2, 3] or magnetic resonance imaging (MRI) [4], fluorine-18 labelled deoxyglucose (^{18}F-FDG)–positron emission tomography (PET) imaging [5] - alone or in combination with CT imaging [6], are currently under investigation.

Imaging of tumors with monocationic tracers, especially with technetium-99m methoxy isobutyl isonitrile (^{99m}Tc-MIBI), a radiopharmaceutical initially introduced as a myocardial perfusion agent [7], revealed a high specificity of more than 95% and a good sensitivity (75%) in tumor imaging. For diagnosis and surveillance of various malignancies, such as lesions of the thyroid gland, lung and breast, but also for musculoskeletal sarcomas, ^{99m}Tc-MIBI showed quite good results [8-15]. It is well known, that the cationic lipophylic tracer ^{99m}Tc-MIBI has a negligible role in subdiaphragmatic tumors detection because of its rapid passage in the intestine by immediate biliary secretion of the tracer, thus causing high background activity which makes the interpretation of images rather impossible [16]. In addition, high liver biliary tract and bladder uptake of the tracer, further complicate image analysis.

The application of morphine hydrochloride can cause biliary duct spasm and delay biliary excretion [17]. Morphine or related substances have been routinely used for the deceleration

of biliary flow in order to improve hepatobiliary scintigraphic imaging [18]. In the present study we have investigated whether biliary secretion can be delayed by a single dose of morphine hydrochloride thus enabling early gastrointestinal imaging by gaining enough time for the radiopharmaceutical to possibly image gastrointestinal malignancies.

Patients and methods

The present study protocol was approved by the Ethics Committee of the University of Vienna. The experiments comply with the Declaration of Helsinki including current revisions and the Good Clinical Practice guidelines [19]. Patients enrolled in this study have given their written informed consent. In a prospective, single-blinded protocol study, 24 patients with endoscopically diagnosed and histologically confirmed gastrointestinal adenocarcenomas were assigned to undergo ^{99m}Tc-MIBI imaging. Seven females and 17 males (mean age 69 years, range 52-83 years) were enrolled in this study. All patients suffered from histologically proven adenocarcinoma. In one patient both a colorectal and a gastric carcinoma was found with endoscopy and CT, adding up for a total of 25 tumor lesions for analysis (colorectum n=20, stomach n=4,

Table 1. *Comparison of endoscopic results and ^{99m}Tc-MIBI scan findings, for tumour localization*

Patients serial number	Endoscopy findings	^{99m}Tc-MIBI scan	Correlation between endoscopy ^{99m}Tc and MIBI scan 1=correct scan result 0= incorrect scan result	Tumor size confirmed by surgery/histology diameter (cm)
1	Stenosing tumor of sigmoid	Planar neg, SPET pos,correct localization	1	3.5
2	Large tumor, coecal area	Planar neg, SPET pos, incorrect localization	0	5
3	Stenosing tumor of sigmoid	Planar and SPET positive, correct localization	1	4
4	Stenosis of the pancreatic head (ERCP)	Planar and SPET negative	0	5
5	Large, stenosing sessile polyp of tumor sigmoid	Planar und SPET positive, correct localization	1	2.5
6	Polypoid tumor of rectum	Planar neg, SPET pos, correct localization	1	8.5
7	Small tumor, corpus ventriculi, mucosal resection within the same session	Planar and SPET negative (control patient)	Not applicable	Not applicable
8	a) Stenosing tumor of C. transversum/ C. descendens	Planar and SPET positive,	1	Both 5
	b) Polypoid exulcerative tumor cardia and corpus ventriculi	correct for both localizations	1	
9	Stenosing tumor C. transversum / C. descendens	Planar and SPET positive, correct localization	1	5
10	Polypoid Tumor C. of sigmoid	Planar and SPET positive, correct localization	1	2
11	Polypoid tumor, rectum	Planar neg, SPET positive, correct localization	1	6
12	Stenosing tumor C. ascendens	Planar and SPET positive, correct localization,	1	5
		additional false positive spot due to residual bile	0	
13	Tumor at gastric cardia	Planar and SPET positive, correct localization	1	3
14	Giant polypoid tumor, C. ascendens	Planar and SPET positive, incorrect localization	0	5
15	Stenosing tumor, rectum	Planar and SPET negative	0	8
16	Large tumor, C. of sigmoid	Planar and SPET positive, correct localization	1	5
17	Stenosing tumor, C. ascendens	Planar and SPET positive, incorrect localization	0	3.5
18	a) Small tumor, cardia (mucosal resection)	a) Planar and SPET negative	Not applicable	Not applicable
	b) small rectal adenoma	b) Planar and SPET positive	0	1.5 (adenoma)
19	Small tumor, rectum	Planar and SPET negative	0	1.5
20	Macroscopically invisible tumor (red irritation), C ascendens	Planar and SPET negative	0	2.7
21	Large tumor, C. transversum	Planar and SPET positive, incorrect localization	0	3.5
22	Small tumor, C. of sigmoid	Planar neg, SPET pos correct localization	1	3.5
23	Stenosing tumor, C. of sigmoid	High background, planar and SPET negative	0	3
24	Stenosing tumor, C. of sigmoid	Planar and SPET negative	0	7

C: colon, neg: negative, pos: positive

pancreas n=1). To delay biliary secretion of the cationic tracer 0.04 mg/kg of body weight morphinehydrochloride (Vendal® - morphinehydrochloride 10 mg, Lannacher Heilmittel, Lannach, Austria) was administered intravenously (iv) 20 min before the administration of 600 MBq ^{99m}Tc-MIBI (Du Pont Pharma, North Billerica, USA). Immediately after the iv application of the tracer, planar images of the abdomen were performed in the anterior and posterior views with a double-headed LVEF gamma camera, using an acquisition time of three min. After finishing planary images, SPET images of the abdomen were taken at 3 degrees for 20 sec/frame. Patients were monitored for 3 hours after the end of ^{99m}Tc-MIBI imaging. The investigator (HS) was blinded to the endoscopic results. Results were compared with endoscopy findings. Whenever performed, CT scan for staging and surgery were used to confirm the endoscopic tumor localisation within a period of two weeks before or after scintigraphy. Inhibition of biliary secretion of the tracer was defined as "successful" whenever diffuse tracer distribution in the intra-abdominal region was prevented.

In 2 patients endoscopic resection of the tumor was performed due to the small size and resectability during the same endoscopic procedure before ^{99m}Tc-MIBI-imaging. The diameter of the 23 not endoscopically removed tumors had a median of 4 cm (mean 4.2 cm) (range 1.5 to 8.5 cm). For every patient, results of endoscopy and ^{99m}Tc-MIBI-imaging are described in Table 1.

All statistical analyses were performed using Statistica for Windows, Version 6.0 (Tulsa, OK, USA). Differences between groups were assessed by the Mann-Whitney U Test. A P-value less than 0.05 was set to define significance.

Results

Biliary secretion was inhibited successfully in 23 out of the 24 patients. Except for one patient who felt nausea after morphine administration, no side effects were noted during the observation period.

^{99m}Tc-MIBI SPET imaging, showed positive accumulation after morphine application in 19/24 patients. In 14 patients planar images were also positive.

Sensitivity

After endoscopic removal of the tumor in two patients and due to separate calculation of the two tumor entities in one patient, 23 individual tumor lesions were identified for further analysis. When these findings were compared with findings of endoscopy, CT and surgery, correct positive results were shown for 13/23 tumor lesions (Table 2), corresponding to a sensitivity of 57%, and a positive predictive value of 62% (Fig. 1).

For 10 tumor lesions the ^{99m}Tc-MIBI results were incorrect and therefore false negative when calculating sensitivity: In four patients ^{99m}Tc-MIBI imaging showed no intrabdominal tracer accumulation, in six patients the location of the malignancy did not correlate with the site of the tracer accumulation (Fig. 2).

Table 2. *2-by-2 contingency table*

2-by-2 contingency table	Tumor in situ	No Tumor in situ	Total
Positive ^{99m}Tc-MIBI scan	13/23 (correct pos.)	8/10 (false pos.)	21 (total pos.) PPV: 62%
Negative ^{99m}Tc-MIBI scan	10/23 (false neg.)	2/10 (correct neg.)	12 (total neg.) NPV: 17%
	23 (total tumor)	10 (total no tumor)	33 (total)
	Sensitivity: 57%	Specificity: 20%	

pos.: positive, neg.: negative

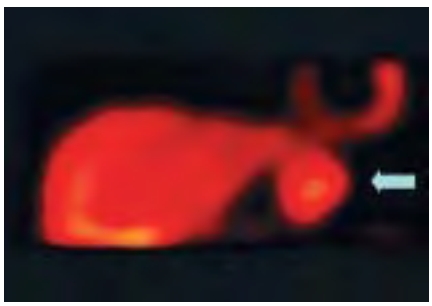

Figure 1. Patient MF (number 13), male, 54 years old: After morphine application ^{99m}Tc-MIBI SPET reveals a tumor at the gastric cardia

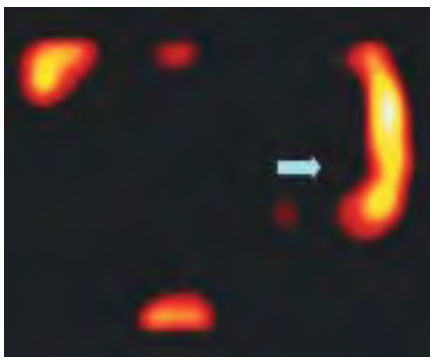

Figure 2. Patient WA (number 14), male, 83 years old. After morphine application the tracer accumulates left in the intestine, corresponding to residual bile. The tumor was endoscopically and surgically identified in the ascending colon

Specificity

Incorrect localization of the tracer accumulation in the imaging for the above mentioned six lesions had to be added as false positive results. Additionally, one of the patients with no residual tumor had a positive tracer accumulation, found at a different site, likely corresponding to a tiny rectal adenoma of 15 mm. In another patient besides a correctly identified tumor, a second hot spot was found reflecting tracer excreted via the bile in the small intestine. These two patients therefore had false positive tracer accumulation. In two patients a correct negative imaging result was obtained, corresponding to the endoscopically completely removed lesions. Consequently, we achieved a poor specificity of only 20% (2 of 10) and a negative predictive value of 17% for this investigation (Table 2).

The correct diagnosis did not correlate with tumor size (P=0.88), or the positive results TNM-stage (P=0.74) or histological grading (P=0.55) (Fig. 3). In two patients who showed time positive results chemotherapy was initiated 7 and 12 days before the ^{99m}Tc- MIBI imaging.

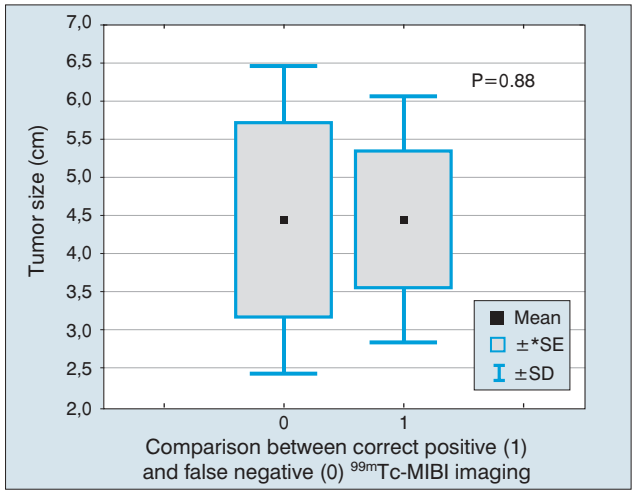

Figure 3. No statistically significant difference was seen when comparing the tumor size of correct positive and false negative ^{99m}Tc-MIBI scans

Discussion

^{99m}Tc-MIBI-imaging has up to now showed promising results for the detection, of some tumors as compared to ^{18}F-FDG-PET [20]. Since the advantages of ^{99m}Tc-MIBI imaging are better availability and power cost, we have tried to improve imaging technique to better visualize intra-abnominal adenocarcinoma with the above radiopharmaceutical.

The low specificity in our findings would have been considerably higher if a higher number of tumor free patients have been studied. Only two of our patients happened to be tumor free. Ethical precautions do not support studies with tumor free patients.

By pre-scintigraphic morphine administration effective biliary blockage was achieved. In only one patient with a 3 cm rectal tumor, and no focal tracer accumulation of the radiopharmaceutical there was elevated background activitiy. However, several limitations should be stated: Normal accumulation of the tracer in the bile duct and in the liver makes imaging of tumors located adjacent to this area like pancreatic tumors or colon cancer, almost impossible. Also the accumulation of the tracer in the urinary bladder, despite pre-investigational voiding, is a limitation for the diagnosis of rectosigmoidal tumors. In two of our patients, one with a 5 cm carcinoma of the pancreatic head and one with a 7 cm carcinoma of the sigmoid colon, no tracer accumulation was noted, due to increased accumulation of the tracer in the overlapping liver and urine bladder, respectively.

The tumor size had no impact on the sensitivity and specificity of ^{99m}Tc-MIBI imaging, however, it has been reported that tumors size smaller than 1.5 cm are not likely to be diagnosed by abdominal ^{99m}Tc-MIBI imaging [21, 22].

The striking drawback of this method is the high number of "false positive" scans. The reason for that might be decreased intestinal motility causing delayed transport of the tracer due to morphine administration and also focal accumulation of the tracer in certain areas of the small intestine. Another pitfall could be due to the tracer kinetics, as the concentration of the ^{99m}Tc-MIBI is not steady during the image acquisition time of 20 min.

In the study of Maurea et al (1998), ^{99m}Tc-MIBI SPET was used for the diagnosis of lymphomas [9]. The authors stressed that, besides tumor size, a major limitation was the high intestinal background activity. In a study of Krolicki et al (2002) planar ^{99m}Tc-MIBI imaging was used to detect gynaecological tumors and results were compared to the conventional abdominal ultrasound technique [16]. For this group of patients, ^{99m}Tc-MIBI scintigraphy showed moderate sensitivity and specificity for the identification of the pelvic tumor lesions, but better results for the abdominal metastases. Probably pre-scintigraphic morphine administration could be useful to enhance the imaging sensitivity and specificity of the above tumors. Several studies have reported that abdominal uptake of ^{99m}Tc-MIBI may interfere with the visualization of myocardial defects when used for myocardial perfusion imaging. Also various substances as metoclopramide have been investigated but failed to reduce abdominal background activity due to ^{99m}Tc-MIBI [23, 24].

Immunoscintigraphic methods using ^{99m}Tc- labelled monoclonal antibody (MAb) fragments such as anti-CEA MAb [25] did not show promising results for the diagnosis of abdominal malignancies, and so far no other radiopharmaceutical is available for intra-abdominal tumor scintigraphy, except those expressing vasoactive intestinal peptide or somatotstatin [26].

In conclusion, pre-scintigraphic morphine administration successfully inhibits background activity, improving intra-abdominal ^{99m}Tc-MIBI imaging of adenocarcinomas. The dose of morphine used for this investigation was effective and well tolerated. However, unspecific localized tracer accumulation in the bowel, led to high amount of false positive results. For abdominal adenocarcinomas ^{99m}Tc-MIBI-imaging shows limited sensitivity and poor specificity, in contrast to tumor locatized in other body locations. In comparison with endoscopy its use in the gastrointestinal tract for the diagnosis of adenocarcinomas, remains poor due to high rates of incorrect tracer accumulation.

Bibliography

1. Bond JH. Update on colorectal polyps: management and follow-up surveillance. *Endoscopy* 2003; 35: S35-S40.
2. Pickhardt PJ, Choi JR, Hwang I, et al. CT virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003; 349: 2189-2198.
3. Pickhardt PJ. CT colonography (virtual colonoscopy) for primary colorectal screening: challenges facing clinical implementation. *Abdom Imaging* 2005; 30: 1-4.
4. Ajaj W, Lauenstein TC, Pelster G, et al. MR colonography in patients with incomplete conventional colonoscopy. *Radiology* 2005; 234: 452-459.
5. Jadvar H, Fischman AJ. Evaluation of pancreatic carcinoma with FDG PET. *Abdom Imaging* 2001; 26: 254-259.
6. Stahl A, Wieder H, Wester HJ, et al. PET/CT molecular imaging in abdominal oncology. *Abdom Imaging* 2004; 29: 388-397.
7. Zhang X, Liu X, He ZX, et al. Long-term prognostic value of exercise 99mTc-MIBI SPET myocardial perfusion imaging in patients after percutaneous coronary intervention. *Eur J Nucl Med Mol Imaging* 2004; 31: 655-662.

8. Obwegeser R, Berghammer P, Rodrigues M, et al. A head-to-head comparison between technetium-99m-tetrofosmin and technetium-99m-MIBI scintigraphy to evaluate suspicious breast lesions. *Eur J Nucl Med* 1999; 26: 1553-1559.
9. Maurea S, Acampa W, Varrella P, et al. ^{99m}Tc -sestamibi imaging in the diagnostic assessment of patients with lymphomas: comparison with clinical and radiological evaluation. *Clin Nucl Med* 1998; 23: 283-290.
10. Amano S, Inoue T, Tomiyoshi K, et al. In vivo comparison of PET and SPECT radiopharmaceuticals in detecting breast cancer. *J Nucl Med* 1998; 39: 1424-1427.
11. Mekmandarov S, Sandbank J, Cohen M, et al. Technetium-99m-MIBI scintimammography in palpable and nonpalpable breast lesions. *J Nucl Med* 1998; 39: 86-91.
12. Kosuda S, Yokoyama H, Katayama M, et al. Technetium-99m-tetrofosmin and technetium-99m-sestamibi imaging of multiple metastases from differentiated thyroid carcinoma. *Eur J Nucl Med* 1995; 22: 1218-1220.
13. Aigner RM, Fueger GF, Nicoletti R. Parathyroid scintigraphy: comparison of technetium-99m methoxyisobutyilisonitrile and technetium-99m tetrofosmin studies. *Eur J Nucl Med* 1996; 23: 693-696.
14. Kao CH, Chang-Lai SP, Chieng PU, Yen TC. Technetium-99m-methoxyisobutylisonitrile chest imaging of small cell lung carcinoma: relation to patient prognosis and chemotherapy response – a preliminary report. *Cancer* 1998; 83: 64-68.
15. Soderlund V, Jonsson C, Bauer HC, et al. Comparison of technetium-99m-MIBI and technetium-99m-tetrofosmin uptake by musculoskeletal sarcomas. *J Nucl Med* 1997; 38: 682-686.
16. Krolicki L, Cwikla JB, Timorek A, et al. Technetium-99m MIBI imaging in diagnosis of pelvic and abdominal masses in patients with suspected gynaecological malignancy. *Nucl Med Rev Cent East Eur* 2002; 5: 131-137.
17. Helm JF, Venu RP, Geenen JE, et al. Effects of morphine on the human sphincter of Oddi. *Gut* 1988; 29: 1402-1407.
18. Cabana MD, Alavi A, Berlin JA, et al. Morphine-augmented hepatobiliary scintigraphy: a meta-analysis. *Nucl Med Commun* 1995; 16: 1068-1071.
19. World Medical Association General Assembly. World Medical Association Declaration of Helsinik: ethical priniciples for medical research involving human subjects. *J Int Bioethique* 2004; 15:124-129.
20. Wang H, Maurea S, Mainolfi C, et al. ^{99m}Tc-MIBI scintigraphy in patients with lung cancer. Comparison with CT and fluorine-18 FDG PET imaging. *Clin Nucl Med* 1997; 22: 243-249.
21. Minai OA, Raja S, Mehta AC, et al. Role of ^{99m}Tc-MIBI in the evaluation of single pulmonary nodules: a preliminary report. *Thorax* 2000; 55: 60-62.
22. Prats E, Banzo J, Merono E, et al. ^{99m}Tc-MIBI scintimammography as a complement of the mammography in patients with suspected breast cancer. A multicenter experience. *Breast* 2001; 10: 109-116.
23. Hurwitz GA. Increased extra-cardiac background uptake on immediate and delayed post-stress images with ^{99m}Tc sestamibi: determinants, independence, and significance of counts in lung, abdomen and myocardium. *Nucl Med Commun* 2000; 21: 887-895.
24. Weinmann P, Moretti JL. Metoclopramide has no effect on abdominal activity of sestamibi in myocardial SPET. *Nucl Med Commun* 1999; 20: 623-625.
25. Fuster D, Maurel J, Muxi A, et al. Is there a role for ^{99m}Tc-anti-CEA monoclonal antibody imaging in the diagnosis of recurrent colorectal carcinoma? *Q J Nucl Med* 2003; 47: 109-115.
26. Gabriel M, Hausler F, Bale R, et al. Image fusion analysis of ^{99m}Tc-HYNIC-Tyr^3-octreotide SPECT and diagnostic CT using an immobilisation device with external markers in patients with endocrine tumors. *Eur J Nucl Med* 2005; 32: 1440-1451.