^{99m}Tc-Pertechnetate imaging for detection of ectopic gastric mucosa : A systematic review and meta-analysis of the pertinent literature

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Abstract

Background and aims : **^{99m}Tc-pertechnetate scintigraphy has long been used for detection of ectopic gastric mucosa (EGM) in the medical practice and evaluation of children with lower gastrointestinal bleeding. In the current study, we reviewed the available medical literature in this regard.**

Methods : **Medline and SCOPUS were searched for relevant studies. Studies with sample size of at least 5 patients which provided enough numerical data to calculate the sensitivity and/or specificity of ^{99m}Tc-pertechnetate for detection of EGM were included in the systematic review.**

Results : **Overall 40 studies were included in our systematic review. Overall diagnostic indices of the ^{99m}Tc-pertechnetate scintigraphy for EGM diagnosis were : sensitivity 92.1%[95%CI : 90.2-93.8], specificity 95.4%[94.3-96.3], positive likelihood ratio 16.5[9.9-27.5], negative likelihood ratio 0.15[0.1-0.2], diagnostic odds ratio 120.7[73-199]. The pooled sensitivity was higher for studies using H2 blockers as a premedication (92.4% vs. 86.4%), studies using delayed imaging (94.3% vs. 88.4%), children (92.3% vs. 81.8%), and patients with gastrointestinal bleeding (95.3% vs. 75.3%).**

Conclusions : **^{99m}Tc-pertechnetate imaging is a highly accurate diagnostic modality for detection of EGM. This imaging is more accurate in children and patients presenting with gastrointestinal bleeding. Premedication with H2 blockers and delayed imaging can increase the diagnostic accuracy and should be routinely included in the imaging protocol.** (Acta gastroenterol. belg., **2014**, 77, **318-327**).

Key words : ^{99m}Tc-pertechnetate ; ectopic gastric mucosa ; intestinal duplication ; Meckel's diverticulum ; systematic review ; meta-analysis.

Introduction

Ectopic gastric mucosa (EGM) is a pathological tissue which is most commonly located in the Meckel's diverticulum (MD). Other less common possible locations for EGM are the intestinal duplications. EGM is the most common cause of lower gastrointestinal bleeding in children and its rapid and correct diagnosis is vital in this group of patients (1,2).

^{99m}Tc-pertechnetate scintigraphy has long been used for detection of EGM in the medical practice and evaluation of children with lower gastrointestinal bleeding. Despite this widespread use, a wide range of accuracy has been reported in the literature for this imaging technique (3). In addition, there are several variable reported to be associated with the accuracy of ^{99m}Tc-pertechnetate imaging (4).

In the current study, we reviewed the available medical literature on the accuracy of ^{99m}Tc-pertechnetate scintigraphy for EGM detection. We reported the results in a systematic review and meta-analysis format.

Material and methods

The PRISMA guidelines were followed for performing the current systematic review and meta-analysis (http://www.prisma-statement.org).

Search strategy

MEDLINE and SCOPUS were searched with the following keywords to identify the relevant studies without date or language limitation :

("ectopic gastric mucosa" OR Meckel) AND (scintigraphy OR pertechnetate OR "nuclear medicine")

The last search was performed on November 2013. Reference lists of the relevant studies were also searched in order to locate possible missed citations. Articles citing the relevant studies were electronically searched using the "cited by" tools of SCOPUS and Google Scholar.

Inclusion criteria

Studies with the following criteria were included in the systematic review :

1. Sample size of at least 5 patients
2. Providing enough numerical data to calculate the sensitivity and/or specificity of ^{99m}Tc-pertechnetate for detection of EGM.

Retrieved articles were evaluated blindly by two of the authors and in case of any disagreement the opinion of a third author was used to resolve the disagreement. Duplicate publications were discussed and only the most recent or most completely reported studies were included in the systematic review. Quality of the included studies was evaluated using the Oxford Centre for Evidence

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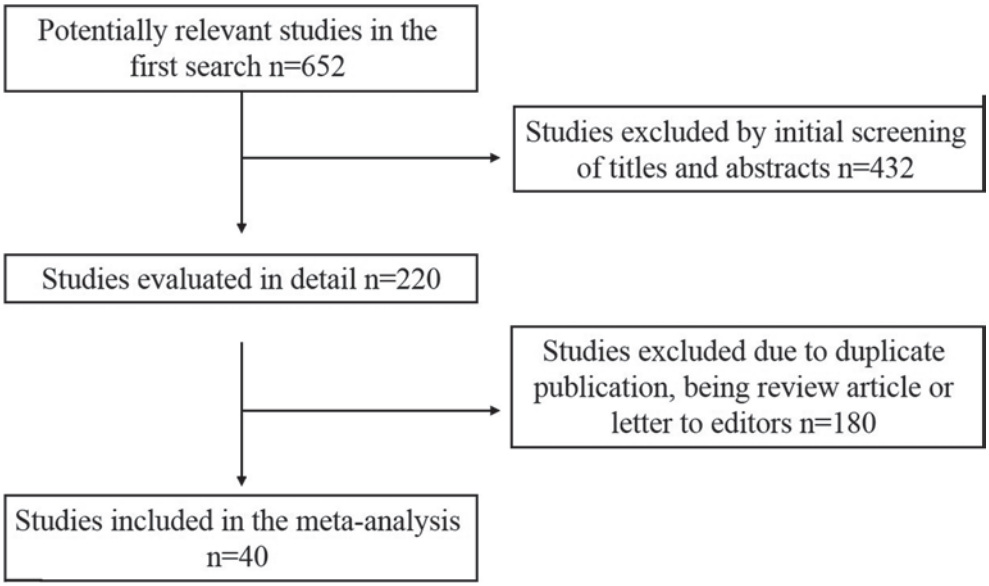

Fig. 1. — PRISMA flowchart of the study

Based Medicine Checklist of diagnostic studies (5). Data extraction was done by two authors independently.

Statistical analyses

Sensitivity, specificity, negative and positive likelihood ratios (LR−, LR+), and diagnostic odds ratio (DOR) were calculated for each study and overall results were calculated by pooling the data using the random effects model (DerSimonian and Laird method) (6).

For heterogeneity evaluation, the Cochran Q test was used and significance level was set at P = 0.05. For quantifying the heterogeneity, inconsistency index (I^2 index) was used. Threshold effect was evaluated by correlation between sensitivity and specificity of the included studies. Summary receiver operating characteristics curve (sROC curve) and area under the curve (AUC) calculations as well as Q^* value were used to summarize the overall performance (7).

Publication bias was graphically evaluated using funnel plots. Funnel plot asymmetry was also tested statistically using the Egger's regression intercept (8). Duval and Tweedie's method was used for quantifying possible publication bias and its possible importance (9). Comprehensive Meta-Analysis Version 2 (Biostat, Inc. Englewood NJ, US) and Meta-DiSc version 1.4 (Madrid University, Madrid, Spain) were used for all statistical analyses (10).

Results

Figure 1 shows the literature search results (PRISMA flowchart). Overall 40 studies were included in our systematic review (11-50). Four studies had duplicate information and were excluded accordingly (51-54). Three article were in Italian, eight were in Chinese, one in Turkish and the remainder were in English.

Table 1 shows the characteristic as well as the quality assessment of the included studies. Overall diagnostic indices of the ^{99m}Tc-pertechnetate scintigraphy for EGM diagnosis were : sensitivity 92.1%[95%CI : 90.2-93.8), specificity 95.4%[94.3-96.3), positive likelihood ratio (LR+) 16.5[9.9-27.5), negative likelihood ratio (LR-) 0.15[0.1-0.2), diagnostic odds ratio (DOR) 120.7[73-199). sROC curve showed an AUC of 0.97, and Q^* of 0.92. Figure 2 shows the forest plots and sROC of overall sensitivity and specificity pooling. Threshold analysis showed a Spearman correlation coefficient of 0.035 (p = 0.8) between Logit of true positive and false positive rates.

Figure 3 shows the funnel plots of overall sensitivity and specificity pooling. For sensitivity pooling, Egger's regression intercept was 1.33 (p = 0.03). After trimming 14 studies by trim and fill method, adjusted pooled sensitivity decreased by 8.6%. For specificity pooling, Egger's regression intercept was 1.67(p = 0.005). After trimming 11 studies by trim and fill method (in order to achieve a symmetrical funnel plot), adjusted pooled specificity decreased by 2.3%.

As shown in table 1, three studies used old rectilinear imaging instruments (15,18,20). Excluding these three studies (only studies using modern gamma camera remained in the meta-analysis) we found the following pooled indices : sensitivity 92.4%[90.4-94), specificity 96.2%[95.1-97), LR+ 17.3[10.9-27.4), LR-0.15[0.09-0.24), DOR 133.5[78.8-226).

Table 2 shows the subgroup analyses of our systematic review regarding patients' age, presenting symptoms, premedication, and use of delayed imaging.

Table 1. — **The use of pentagastrin contributed to the conversion from a negative to a positive result in only one of the four scans. Repetition of the scan was of benefit in two of the eight patients, one scan with and one without pentagastrin. Cimetidine was administered during one false-negative scan.**

First author	Country/ Language	Presenting symptoms	Dose (MBq)/Imaging technique/ Premedication	Total cases/FN/TP/ FP/TN	Age/Gender(F-M)	FP and/or FN reasons	Quality assessment according to CEBM					
							Consecutive recruitment	Gold standard/follow up duration	Blind independent evaluation of the tests	Retro-spective/ prospective	Enough explanation of the tests	Level of evidence
Rosenthal 1972	Canada/ English	AP ; RB ; An ; MS	200/GC ; 3h/-	45/4/4/0/37	Children/n-a	n-a	No	Surgery ; FU/n-a	No	R	Yes	4
Leonidas 1975	US/English	RB ; AP	3.7/kg/GC ; 45 min/-	13/1/3/0/9	Children (1d to 16 y)/ 7-6	n-a	Yes	Surgery ; FU/n-a	No	R	Yes	4
Ho 1975	US/English	RB	7.4/kg/GC ; 30 min/-	21 (20 patients)/0/4/3/14	Children (5w to 15 y)/ 5-15	FP : Duodenal ulcer	Yes	Surgery ; FU/n-a	No	R	Yes	4
Adiseshan 1976	Australia/ English	RB ; AP ; An ; MS	5.5/kg/GC ; 30 min/-	30/0/4/0/26	Mixed (6 w to 64 y)/n-a	n-a	No	Surgery ; FU/n-a	No	R	Yes	4
Berquist 1976	US/English	n-a	200 adult ; 120 children/RL ; 15 min/-	44/1/8/1/34	Mixed (2 m to 80 y)/n-a	FN : small amount of EGM	No	Surgery ; other abnormalities with previous diagnosis (11 patients)/n-a	Yes	R	Yes	3
Schussheim 1977	US/English	RB ; AP	5.55/kg/GC ; 60-90 min/-	70/0/5/0/65	Children/n-a	n-a	No	Surgery ; FU/n-a	No	R	Yes	4
Gelfand 1978	US/English	RB ; AP	1.5-5.5/kg/GC ; 1 h	58 (3 uninterpretable scans)/2/7/2/44	Children (2 m-19 y)/n-a	FN : small amount of EGM	Yes	Surgery ; FU/n-a	No	R	Yes	4
Seitz 1978	Germany/ English	RB	111-185/RL ; 1 h/-	42/0/6/15/21	Mixed/n-a	FP : Neurinoma of jejunum ; Carcinoma of sigmoid colon ; Colitis ; Polyp of sigmoid colon.	Yes	Surgery ; FU/n-a	No	R	Yes	4
Yamaguchi 1978	Japan/ English	RB	n-a/n-a/-	15/0/12/3/0	Mixed (infants to 21 y)/n-a	n-a	n-a	Surgery/n-a	Yes	R	No	2
Sfakianakis 1982	US/English	RB ; AP ; An	1.8/kg/RL(57) ; GC(87) ; 1 h/-	RL : 57/4/5/2/46 GC : 87/1/11/1/74	Children (3 adults)/n-a	FP : Misinterpretation of urine or duodenal activity ; colitis FN : Barium enema before study ; small amount of EGM	n-a	Surgery ; FU/1-8 y	No	R	Yes	4
Cooney 1982	US/English	RB ; AP ; MS	27-37/kg/GC ; 60 min and 24 h delayed if needed/-	265/2/11/12/240	Children (3 d to 17 y)/ 94-176	FN : small amount of EGM FP : Small bowel duplication ; intussusception ; bowel perforation ; pelvic kidney ; meningomyelocele	n-a	Surgery ; FU/n-a	No	R	Yes	4
Fries 1984	Sweden/ English	RB ; An	n-a/GC ; -/-	22/3/9/0/10	Children/n-a	FN : small amount of EGM ; fibrosis	n-a	Surgery/-	No	R	Yes	4
Vane 1987	US/English	RB	n-a/GC ; -/-	10/1/9/-/-	n-a/n-a	n-a	No	Surgery/-	Yes	R	No	3
Brophy 1989	US/English	RB	n-a/GC ; -/n-a	6/1/5/-/-	Children/n-a	n-a	No	Surgery/-	Yes	R	No	3
Valenza 1990	Italy/Italian	RB	n-a/GC ; -/n-a	27/0/7/0/20	Children/n-a	Meckel's diverticulum without EGM was negative on scintigraphy	n-a	Surgery ; FU/-	No	R	No	4
Adalat 1993	Turkey/ Turkish	n-a	n-a/GC ; 1h/n-a	15/0/5/0/10	Mixed (2 m-25 y)/5-16	n-a	n-a	Surgery ; FU/n-a	No	R	No	4
Whitaker 1993	UK/ English	RB	400/GC ; 1h/-	50/2/2/3/43	Mixed/n-a	FP : Duodenitis and ulcer FN ; a Meckel's and ileal polyp with EGM ; the reason not known	No	Surgery ; FU/n-a	No	R	Yes	4
Kong 1994	Taiwan/ English	RB	n-a/GC ; -/Cimetidine given to some patients	101/8/39/2/52	Children/n-a	FN : Severe bleeding FP : Telangectasis	Yes	Surgery ; FU/n-a	No	R	No	4
Yao 1994	China/ Chinese	RB	n-a/GC ; -/n-a	17/1/9/0/7	Children/n-a	n-a	n-a	Surgery ; FU/n-a	No	n-a	No	4

McCulley 1996	South Africa/ English	RB ; AP ; An ; MS	4/kg/GC ; 1 h/-	77/3/7/3/64(49 RB ; 15 others)	Children (2 m-10 y)/35-42	FP : Polyp FN : MD with active bleeding	Yes	Surgery ; FU/n-a	No	R	Yes	4
Zhao 1997	China/ Chinese	RB	n-a/GC ; n-a/n-a	26/2/12/1/11	Children/n-a	n-a	n-a	Surgery ; FU/n-a	No	n-a	No	4
Rampin 1998	Italy/Italian	RB ; AP	37-180/GC ; n-a/H2 Blocker	28/0/10/0/18	Mixed (8 m-80y)/11-17	n-a	n-a	Surgery ; FU/12 months	No	n-a	Yes	4
Swaniker 1999	US/English	RB ; MS	n-a/GC ; n-a/inconsistent use of pentagastrin or H2 blocker[1]	171(165 patients)/16 (in 10 patients)/14/1/140	Children (birth to 18 y)/n-a	FN : the age of FN cases was higher than those with TP and TN results	Yes	Surgery ; FU/n-a	Yes	R	No	2
Dell'Erba 2000	Italy/Italian	RB ; AP	18-150/GC ; 75 min/ H2 blocker	54/1/11/14/28	Mixed ((5 mon-68 y)/19-35	FP : 6 enteritis, 3 entrocolitis, 2 nonspecific colitis, 1 tumor, 1 uterine, 2 renal system	n-a	Surgery ; FU/n-a	No	P	Yes	4
Poulsen 2000	Denmark/ English	RB ; AP	3/kg/GC ; 1 h/n-a	55/1/2/2/50	Children (below 16)26-27	FP : Possible ongoing intestinal bleeding	n-a	Surgery ; FU/n-a	No	R	Yes	4
Howarth 2002	Australia/ English	RB	250/GC ; n-a/n-a	11/0/0/0/11	Adults (30-86 y)/n-a	n-a	n-a	Surgery ; FU/n-a	Yes	R	Yes	3
Song 2002	China/ Chinese	RB	7.4/kg/GC ; 1h/n-a	141/1/54/5/81	Children (6 days-7 years)/33-108	FP : congenital Megacolon, cavernous hemangioma of the small intestine and intestinal telangiectasia	n-a	Surgery ; FU/n-a	No	R	Yes	4
Peng 2003	China/ Chinese	RB	n-a/GC ; 1 h/n-a	44/3/29/1/11	Children/n-a	n-a	n-a	Surgery ; FU/n-a	No	n-a	No	4
Rerksuppaphol 2004	Australia/ English	RB	n-a/GC ; n-a/H2 blocker	8/3(1 with H2 blocker)/5(7 with H2 blocker)/n-a/n-a	Children (0.1-17.7 y)/n-a	FN : possible low dose of H2 blocker	No	Surgery/n-a	Yes	R	No	3
Varcoe 2004	Australia/ English	RB ; MS	n-a/GC ; n-a/n-a	8/5/2/0/1	Mixed (1 day-92 years)/n-a	n-a	No	Surgery/n-a	Yes	R	No	3
Chen 2005	China/ Chinese	RB	n-a/GC ; n-a/n-a	94/1/31/1/61	Children/n-a	FP : Jejunal sub-mucosal vascular malformation	n-a	Surgery ; FU/n-a	No	R	No	4
Kumar 2005	India/ English	RB	3.7/kg/GC ; 1 h and delayed imaging if negative/-	11/3(0 with delayed imaging)/8(11 with delayed imaging)/n-a/n-a	Children/n-a	FN : duplications	No	Surgery/n-a	Yes	R	Yes	3
Yang 2006	China/ Chinese	RB	n-a/GC ; n-a/n-a	22/1/18/0/3	Children/n-a	n-a	Yes	Laparoscopic surgery/ n-a	Yes	R	No	2
Guo 2007	China/ Chinese	RB	n-a/GC ; 30 min/n-a	57/3/37/2/15	Children/n-a	n-a	n-a	Surgery ; FU/n-a	No	R	No	4
Dolezal 2008	Czech Republic/ English	RB	100-185/GC ; 20 min ; SPECT in selected patients/H2 Blocker	79/0/3/0/76	Children (1-17 y)/39-40	n-a	n-a	Surgery ; FU/n-a	No	R	Yes	4
Mittal 2008	India/ English	RB ; AP	37-148/GC ; 30 min/-	107/0/16/3/86	Children (5 days-11 y)/28-79	FP : Colonic perforation : 2 MD with Pancreatic mucosa : 1	n-a	Surgery ; FU/n-a	No	R	Yes	4
Kiratli 2009	Turkey/ English	n-a	3.7/kg/GC ; 40 min ; delayed/H2 blocker	50/0/11/2/37	Children (7m-12 y)/n-a	FP : Regional enteritis : 1 Calyceal/activity : 1 ; Perforated appendix : 1	n-a	Surgery ; FU/n-a	No	R	Yes	4
Jia 2009	China/ Chinese	RB	18.5/kg/GC ; 1 h/n-a	486/3/423/0/63	Children (mean 13 y) /232-254	FN : small amount of EGM	n-a	Surgery ; FU/n-a	No	R	Yes	4
Sinha 2013	UK/ English	RB ; MS	150/GC ; delayed and SPECT/ H2 blocker	183/1/17/5/160	Children (median 3 y)/n-a	FP : Tubular duplication ; Intussusception ; Small bowel mucosa in MD	n-a	Surgery ; Endoscopy ; FU/median 2 y	No	R	Yes	4
Woo 2013	Hong Kong/ English	RB ; AP ; MS	370 for adults ; adjusted for children/GC ; 1 h/H2 blocker	105/1/6/2/96	Mixed (62 children ; 42 adults ; mean age 17.6 y)/40-65	FP : Local ileitis, uterine blush	Yes	Surgery ; FU/n-a	No	R	Yes	4

RB : rectal bleeding ; AP : abdominal pain ; An : anemia ; MS : miscellaneous ; FN : false negative ; TP : true positive ; FP : false positive ; TN : true negative.

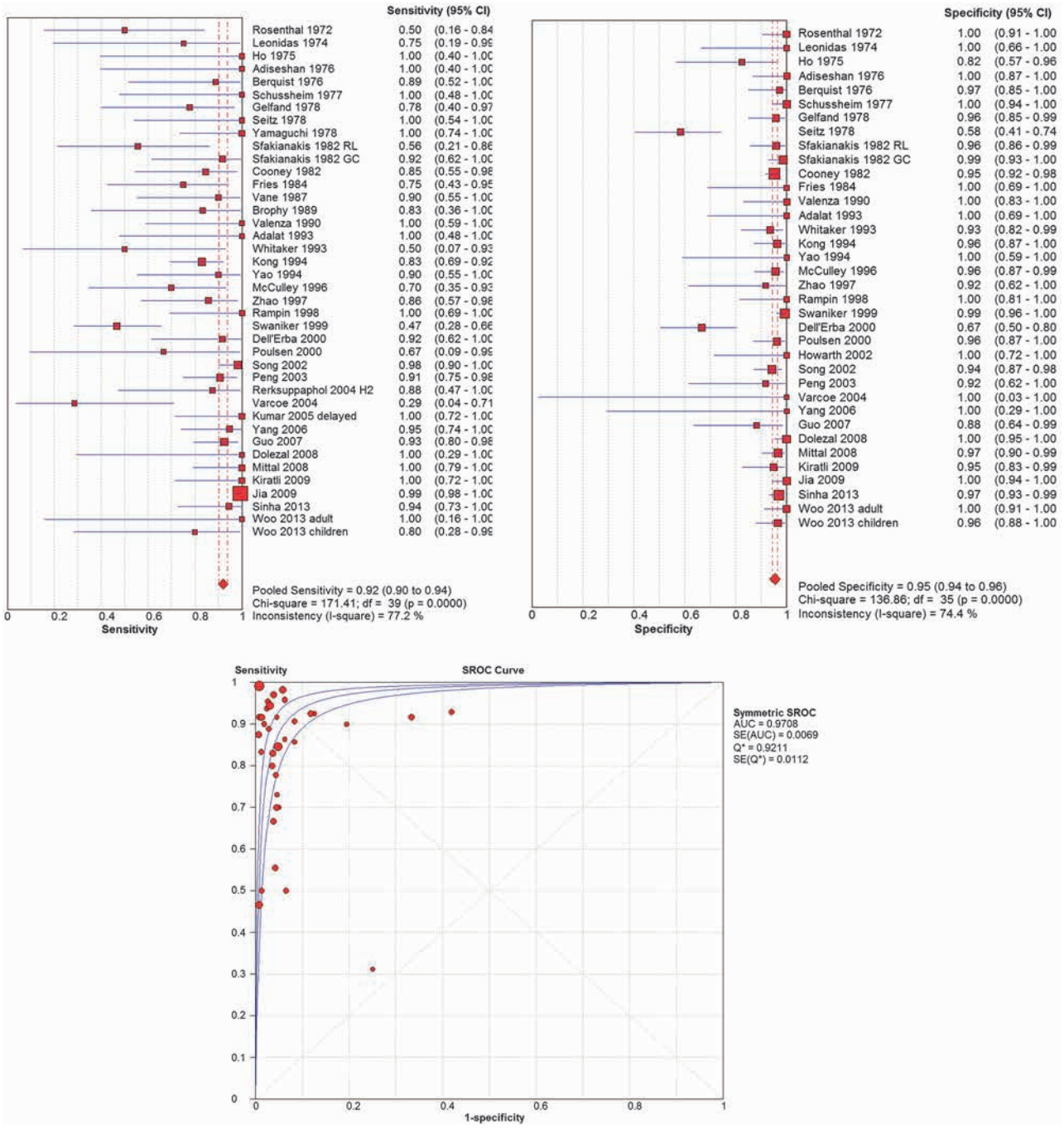

Fig. 2. — Forest plots of sensitivity and specificity pooling as well as the SROC curve of the study

Discussion

^{99m}Tc-pertechnetate scintigraphy is considered as an integral part of gastrointestinal bleeding workup in pediatric patients. The main indication of this imaging modality is diagnosis of EGM in the intestinal tract. The EGM will concentrate ^{99m}Tc-pertechnetate just as normal gastric mucosa does. This is the principle on which ^{99m}Tc-pertechnetate imaging is based.

EGM can occur in various locations in the gastrointestinal tract. Meckel's diverticulum is the main location of EGM as about 25% contain EGM and are prone to gastrointestinal bleeding (55). It is worth mentioning that Meckel's diverticula without EGM are usually without symptoms. Even symptomatic Meckel's diverticula without EGM cannot be localized by ^{99m}Tc-pertechnetate imaging (56). Unfortunately medical literature is very inconsistent in the reporting of ^{99m}Tc-pertechnetate scintigraphy diagnostic studies. There are many studies reporting the accuracy of ^{99m}Tc-pertechnetate imaging for detection of Meckel's diverticulum regardless of EGM presence which can underestimate the sensitivity

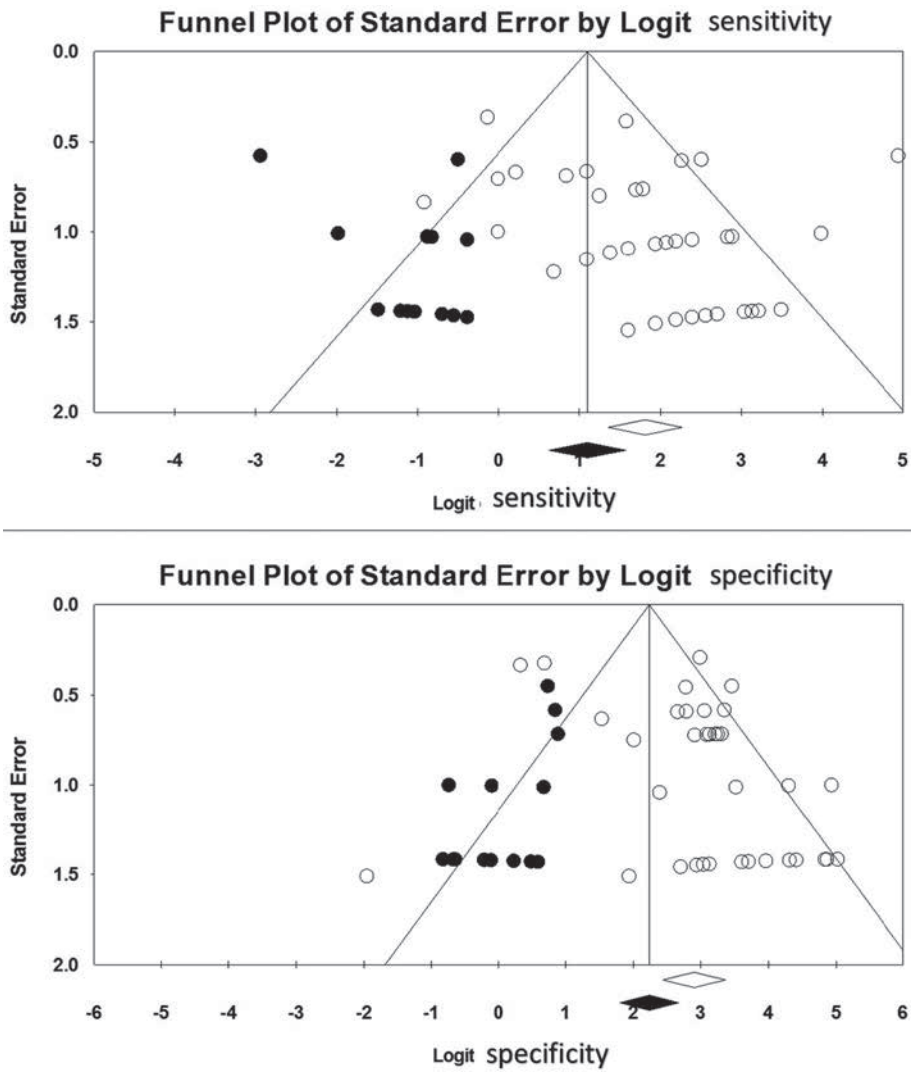

Fig. 3. — Funnel plots of sensitivity and specificity pooling

of ^{99m}Tc-pertechnetate scintigraphy. Many Meckel's diverticula do not contain EGM and ^{99}Tc-pertechnetate imaging would be invariably negative in these cases. This is the main reason of inconsistent and very heterogeneous reports in the literature as sensitivity of ^{99m}Tc-pertechnetate scintigraphy for diagnosis of Meckel's diverticulum is in a wide range of 20-100% (55). To overcome this shortcoming, in the current systematic review we only included studies reporting the accuracy of ^{99m}Tc-pertecnetate imaging for EGM diagnosis. Furthermore we explored the factors associated with its diagnostic performance.

Overall pooled diagnostic indices were high (sensitivity 92.1% and specificity 95.4%) demonstrating the high accuracy of this scintigraphy method. However, there are numerous causes for getting false positive and false negative scans (Table 1). Medical literature is rich of case reports of false positive ^{99m}Tc-pertechnetate scintigraphy. Many gastrointestinal and non-gastrointestinal pathologies have been associated with false positive results which can be divided into three broad categories : hyperemia of the bowel (peptic ulcer, regional enteritis, etc), vascular masses (hemangioma, uterine blush, etc), and urinary tract abnormalities (3,4,57). False negative scans can also occur. Necrosis of the diverticulum, insufficient EGM, active bleeding during scanning, obstruction of the diverticular outlet, superimposition of physiological activity on the EGM, and previous barium studies have been reported as the main reasons (3,4).

Factors influencing the accuracy of ^{99m}Tc-pertechnetate imaging

As shown in forest plots (Fig. 2), the heterogeneity of the included studies was high (I^2 indices of 72% and 74% for sensitivity and specificity pooling). In order to explain this heterogeneity we evaluated possible variables associated with accuracy of the ^{99m}Tc-pertechnetate scintigraphy.

Table 2. — **Subgroup analyses of the systematic review**

		Sensitivity (%)	I^2 index (%)	Specificity (%)	I^2 index (%)	LR+	I^2 index (%)	LR-	I^2 index (%)	DOR	I^2 index (%)
Age	Children	92.3[90.3-94]	80	96.7[95.7-97.5]	33.2	17.6[13.6-22.9]	0	0.15[0.09-0.24]	79	135[81.6-223]	12
	Adults	81.8[48.2-97.7]	59	97.2[92.1-99.4]	42.7	14[4-48.8]	6.5	0.3[0.08-1]	28	61.4[6.6-571]	26.6
	Mixed	88.3[77.4-95.2]	72.3	81[74-86.8]	88	5.8[2-16.6]	82	0.16[0.04-0.7]	71	51.7[8.8-303]	47.5
Presenting symptoms	Rectal bleeding only	95.3[93.5-96.7]	67.3	94.7[92.8-96.2]	76	15.5[6.9-34.6]	82	0.12[0.07-0.21]	66.7	130.8[62.5-274]	30
	Any symptom	75.3[68-81.7]	72.8	95.8[94.4-96.9]	74	17.6[8.5-36.5]	80	0.26[0.15-0.45]	70.5	94.3[44.5-200]	27.5
Premedication	H2 blocker	94.2[85.8-98.4]	0	94.7[92.2-96.6]	87.7	21.5[5.7-81.5]	87	0.1[0.04-0.24]	0	193.4[59.5-629]	12.8
	No premedication	86.4[81.2-90.7]	65.7	94.7[93.1-96]	77.3	15.8[7.6-32.7]	82	0.21[0.12-0.36]	58	100[50.2-199]	15.1
Imaging protocol	No delayed imaging	88.4[84-92]	49.7	94[92.4-95.4]	81.2	15.1[8.1-28.3]	81	0.18[0.12-0.3]	48.8	95[54-167.2]	2.4
	Delayed imaging	94.3[84.3-98.8]	28	95.8[93.6-97.5]	0	20.3[12.8-32]	0	0.1[0.04-0.27]	0	210[63-697]	0

Non patient-related variables

1. Threshold effect

The criteria of positivity can be implicitly or explicitly different among the included studies. This can be a major source of heterogeneity is the systematic reviews of diagnostic studies.

The correlation between sensitivity and specificity (as a marker of threshold effect) was small ($r = 0.035$) and statistically not statistically ($p = 0.8$) which shows minimal threshold effect in our systematic review. SROC analysis also supported the above-mentioned results (Fig. 2) as the AUC was 0.97 and Q* was 0.92. It seems that threshold effect was not an important source of heterogeneity in our systematic review and our results are robust for different thresholds of scan positivity.

2. Imaging instrument

Several early studies reported the results of ^{99m}Tc-pertechnetate imaging using the rectilinear imaging device. By the advent of gamma camera, rectilinear technology became obsolete. In order to explore the effect of imaging instrument on the accuracy of ^{99m}Tc-pertechnetate imaging, we performed sensitivity analysis by excluding rectilinear studies. The new results were slightly higher than the original results (0.3% and 0.8% increase in pooled sensitivity and specificity respectively). It seems that superior technology of gamma camera over rectilinear scanners increased the accuracy of ^{99m}Tc-pertechnetate imaging for detection of EGM.

3. Imaging protocol (delayed images vs. dynamic imaging only)

Although the classic criteria of positive ^{99m}Tc-pertechnetate scan is an abnormal area of activity in the abdomen which corresponds to the appearance time and activity of the stomach, delayed appearance of EGM has been reported in many studies (21,42,58). Kumar *et al*. in a 2005 study showed that a variety of scintigraphic patterns could be found in patients with EGM depending on the location and size of the abnormal tissue. They reported three thoracic duplication cysts with EGM which were only apparent on the delayed ^{99m}Tc-pertechnetate images. Kumar *et al*. attributed this finding to the small amount of activity in the duplication cyst which needs time to become visible (42).

Our systematic review also showed that studies which used delayed imaging had higher sensitivity and specificity than those without delayed imaging. This shows that delayed imaging can be very helpful in the diagnosis of EGM and should be included in the routine imaging protocol of nuclear medicine departments.

4. Premedication

Pharmacological intervention before ^{99m}Tc-pertechnetate imaging has long be considered for increasing the accuracy of EGM detection. H2 blockers, pentagastrin, and glucagon have all been used as premedication. H2 blockers can decrease the secretion of ^{99m}Tc-pertechnetate in the EGM which can increase the intensity of uptake and visibility of the lesions. Pentagastrin can increase the acid output and ^{99m}Tc-pertechnetate uptake of the stomach and EGM. Finally glucagon can decrease bowel movement and prevent dilution of ^{99m}Tc-pertechnetate in the EGM location (59,60).

The effect of premedication on ^{99m}Tc-pertechnetate imaging accuracy is mostly anecdotal in the medical literature and thus far no compelling evidence could be find in the literature for its benefit. Efficacy of pentagastrin premedication has been shown in few case reports (61,62), however Imaeda *et al*. reported a case in which the initial scintigraphy was normal despite a positive second scintigraphy without pentagastrin (63). Among the studies included in our systematic review only Swaniker *et al*. study reported the efficacy of pentagastrin stimulation. They reported eight false negative patients, four had second scans with pentagastrin and four without. The use of pentagastrin contributed to the conversion from a negative to a positive result in only one of the four scans (33).

None of the included studies in our systematic review reported the efficacy of glucagon. Again only anecdotal reports in the literature exist in this regard. Emamian *et al*. reported a case of inconclusive ^{99m}Tc-pertechnetate scintigraphy which was clearly positive after glucagon stimulation on the second scintigraphy. They showed that the higher target to background ratio is the main reason of better scan results with the glucagon (64).

For H2 blockers, our systematic review provided more conclusive evidence. Pooled sensitivity was higher in the studies used H2 blocker before scintigraphy (92.4% vs. 86.4%) without any change in pooled specificity.

To sum up, it seems that routine use of H2 blockers before ^{99m}Tc-pertechnetate scintigraphy can increase the sensitivity of EGM detection and can be recommended. On the other hand, there is not enough evidence to support other types of pre-medication.

Patient related variables

1. Age

Age of the patients at the imaging time is an important variable which can affect the accuracy of ^{99m}Tc-pertechnetate imaging. Our results showed the highest sensitivity in children (less than 18 years old) and the lowest in the studies with patients older than 18 years old (92.3% vs. 81.8%). This shows that the negative predictive value of ^{99m}Tc-pertechnetate scintigraphy is relatively low in the adult population and negative scans does not preclude the diagnosis of possible EGM.

The reason of the lower sensitivity is relatively smaller volume of EGM in the adult population compared to the children (65-67).

2. Presenting symptom

The pooled sensitivity of ^{99m}Tc-pertechnetate imaging for EGM diagnosis was higher in patients with gastrointestinal bleeding as compared to those with other

symptoms (obstruction, abdominal pain, etc) : 95.3% vs. 75.3%. This is an important finding and is due to smaller amount of EGM in patients without gastrointestinal bleeding (65,68).

Study limitations

1. Quality of the included studies

The diagnostic studies included in our systematic review mostly had methodological flaws which can decrease the validity of our results. As shown in Table 1, in 30 studies the results of the ^{99m}Tc-pertechnetate imaging influenced the decision to perform the surgery which invariably put the studies in the level 4 category evidence hierarchy. Only 7 studies were of level 3 and 3 were of level 2 of evidence.

The gold standard itself is another limitation of our study. Most of the studies included in our systematic review used a combination of surgery and follow up as diagnostic gold standard and the vast majority didn't report the mean duration of follow up. As short follow up can spuriously increase the sensitivity estimation, results of our pooled sensitivity can be overestimated and the readers should be aware of this limitation.

The low quality of the included studies can result in overestimation of diagnostic accuracy in our systematic review and the readers should be aware of this fact. This can be considered the main limitation of our study.

2. Publication bias

We evaluated the publication bias using funnel plots and as shown in figure 3, funnel plots of sensitivity and specificity pooling were asymmetric which denotes the possible publication bias. Egger's test also showed that the above-mentioned asymmetry was statistically significant too.

In order to quantify the possible publication bias, trim and fill method was used which showed a decreased of 8.6% in sensitivity and 2.3% in specificity after adjustment of the funnel plots for possible publication bias.

Altogether, publication bias ; if present, can change the results of our systematic review. This is especially true for sensitivity pooling.

Conclusion

^{99m}Tc-pertechnetate imaging is a highly accurate diagnostic modality for detection of EGM. This imaging is more accurate in children and patients presenting with gastrointestinal bleeding. Premedication with H2 blockers and delayed imaging can increased the diagnostic accuracy and should be routinely included in the imaging protocol.

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