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Pre-operative detection of primary colorectal cancer by 18-FDG PET CT: a meta-analysis of 16.824 patients

Flora Badon

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE
pour le
DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
par

BADON, Flora

Présentée et soutenue publiquement le 30 octobre 2020

TITRE DE LA THÈSE

Pre-operative detection of primary colorectal cancer by 18-FDG PET CT: A meta-analysis of 16.824 patients

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A NOTRE PRESIDENT DE THESE

Monsieur le Professeur Denis PEZET

Chef de service de chirurgie digestive et Hépatobiliaire du CHU Clermont-Ferrand.

Merci Monsieur pour votre soutien tout le long de cette formation. Vous savez nous pousser et nous écouter. Faire de nous de bons chirurgiens et de bons médecins. J'espère pouvoir apprendre encore à vos côtés

A NOTRE JURY DE THESE

Monsieur le Professeur Emmanuel BUC,

Parce que oui, Manu, j'aurais pu aller à la poste, mais j'ai choisi la chirurgie. Tu as su me pousser au-delà de mes limites, en étant exigeant tout en restant patient. Je te remercie pour ça et j'espère que tu penses que j'ai fait le bon choix.

Monsieur le Professeur CACHIN

Merci Monsieur, d'avoir accepté de faire partie de ce travail de thèse. J'espère que ce dernier nous permettra de poursuivre ce travail en collaboration avec votre service

Monsieur le Dr GAGNIERE Johan,

Merci Johan pour ton aide dès le début mon de internat et d'avoir facilité mon installation à Clermont . Merci pour ta formation chirurgicale, tant sur le plan théorique que technique au bloc opératoire, et ton aide sur ce travail de thèse

Madame le Docteur SELVY Marie,

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Table des matières :

1. <u>Introduction</u>	p.17
2. <u>Materials and Methods:</u>	p.18
2.2 <i>Literature search</i>	
2.2 <i>Study selection criteria</i>	
2.3 <i>Quality assessment and sensitivity analysis</i>	
2.4 <i>Statistical analyses</i>	
3. <u>Results:</u>	p. 21
3.1 <i>Literature search and selection of studies</i>	
3.2 <i>Study characteristics and methodological quality assessment</i>	
3.3 <i>Diagnostic performance of preoperative CRC detection</i>	
3.4 <i>Sensitivity analysis</i>	
4. <u>Discussion</u>	p.22
5. <u>Conclusion</u>	p. 27
6. <u>Tableaux et Figures</u>	p. 28
7. <u>Bibliographie</u>	p. 35
8. <u>Serment d’Hippocrate</u>	p. 40

Listes Tableaux et Figures :

Table 1 : **Description of the included studies**

Table 2 : **Diagnostic Value of PET- CT in preoperative CRC patients**

Figure 1 : **FLOW CHART**

Figure 2 : **Forrest Plot overall Sensibility**

Figure 3 : **Forrest plot overall Specificity**

Figure 4 : **Fagan diagram with Likelihood Ratio**

Figure 5 : **Aire under curve (AUC) with sensitivity analyses**

Liste des abréviations:

^{18}F -fluorodeoxyglucose : ^{18}F -FDG

CRC: colorectal cancer

CT: computed tomography

FN: False negative

FP: False positive

MRI: Magnetic resonance imagerie

PET: Positron emission tomography

SUV : Standardized Uptake Value

TN: True negative

TNM staging :Tumor, Node, Metastatic

TP: True positive

Pre-operative detection of primary colorectal cancer

by ^{18}F -FDG PET-CT:

A meta-analysis of 16.824 patients

Badon F. MD¹, Pereira B., PhD², Cachin F. MD¹, PHD, Buc E., MD¹, PHD, Pezet D., MD¹, PhD, Gagniere J., PhD¹, Selvy M., MD¹

(1) Department of Digestive Surgery, University Hospital Clermont-Ferrand, Clermont-Ferrand, France

(2) Clinical Research and Innovation Department, University Hospital Clermont-Ferrand, France

Corresponding author:

Marie Selvy

Department of digestive and hepatobiliary surgery Estaing Hospital

CHU Clermont-Ferrand

1, place Lucie-et-Raymond-Aubrac

63003 Clermont-Ferrand Cedex

Tel: +(33)473750594

Fax: +(33)473750459

Email: mselvy@chu-clermontferrand.fr

ORCID: 0000-0001-5897-6434

KEY WORDS: Colorectal cancer, ^{18}F -FDG PET-CT, PET-CT, preoperative diagnostic

ABSTRACT

Background: Accurate preoperative staging of colorectal cancer (CRC) is crucial for providing the optimal therapeutic strategy and evaluating the prognosis. The PET-CT using most frequently the radio-labeled glucose analog ^{18}F -fluorodeoxyglucose (^{18}F -FDG), is an imaging examination used in the staging, evaluation of treatment and therapeutic response or recurrence in many cancers including CRC. We evaluate the diagnostic performance of ^{18}F -FDG PET-CT in the detection of CRC.

Methods: A meta-analysis was conducted based on a search of PubMed, Embase and Cochrane, studies reporting the sensitivity and specificity of PET-CT, from true-positive (TP), false-positive (FP), true negative (TN) and false-negative (FN) and in reference of histological evidence. The QUADAS criteria were used in the qualitative evaluation of the studies.

Results: 29 studies were included in this meta-analysis, with a total of 16. 824 patients. The PET-CT had a sensitivity of 0.51 (95% CI: 0.35-0.66) and a specificity of 0.95 (95% CI: 0.90-0.99). The PET-CT had a positive likelihood ratio of 7.2 (95% CI 5,2-10) and a negative likelihood ratio of 0.55 (95% CI 0,36- 0,84). The sensitivity analysis revealed a sensitivity of 0.49 (95% CI 0.27-0.71) and a specificity of 0.93 (95% CI 0.89-0.96) respectively, which the AUC was 0.9 (95% CI 0.87-0.92).

Conclusion: Our meta-analysis suggested the PET-CT could be a promising complementary examination for the detection of preoperative CRC lesions with a good performance and probably more specific way for advanced or preocclusive lesions, beyond its routine use for extension staging.

1. Introduction:

Colorectal cancer (CRC) is the third worldwide cause of cancer mortality (1) and in France, the second in 2018 (2). Accurate preoperative staging of CRC is crucial for providing the optimal therapeutic strategy and evaluating the prognosis. Conventional staging include a colonoscopy and a thoraco-abdomino-pelvic computed tomography (CT)(3) and MRI (Magnetic resonance imagerie) for rectal cancer. A complete overview of the entire colonic tract allow us to identify any synchronous tumour present in 5 to 10% of cases according to the studies (4).

The PET-CT (positron emission tomography), using most frequently the radio-labeled glucose analog ^{18}F -fluorodeoxyglucose (^{18}F -FDG), is an imaging examination used in the diagnosis, staging, evaluation of treatment and therapeutic response in many cancers including colorectal cancer (5). The usefulness of PET-CT, which is non invasive and requires no particular preparation, for the incidental detection of premalignant colonic lesions has been previously reported (6,7). Veit et al (8) had already conducted a study showing that PET-CT could be very useful for staging colorectal cancer patients, focusing on patients with incomplete colonoscopy and those with synchronous small bowel lesions. In addition, several studies have evaluated its ability to detect colorectal lesions (9). In many articles, it has been suggested that PET-CT could be used in the pre-therapeutic diagnosis of patients with CRC and particularly for advanced CRC with potentially metastases (10). For example, some suggest that PET-CT will be the standard preoperative evaluation of the patient with CRC, in the near future (11). At present, it is difficult to conclude this because of the limited number and application of all types of methods to assess the PET-CT value.

The purpose of this meta-analysis was to evaluate the diagnostic performance of ^{18}F -FDG PET-CT in determining preoperative CRC lesions.

2. Materials and Methods:

2.1 Literature search

A comprehensive computerized systematic literature search of the PUBMED, EMBASE and COCHRANE databases was performed to identify relevant published articles on the diagnostic risk of the tumor by ¹⁸F-FDG PET-CT.

We used a search algorithm that was according to a combination of the terms : "colon tumor, colorectal tumor, colorectal cancer" and "positron-emission tomography", "proton magnetic resonance spectroscopic imaging", "tomography, positron emission", "pet", "pets". Keywords could be combined using "AND", except for synonyms, which were combined using "OR". Only articles in English or French were included. The search was updated until January 31, 2020.

A parallel, double blind screening procedure for titles and abstracts was carried out by two reviewers (F.B and M.S). To enhance sensitivity, records were discarded only if both reviewers excluded it at the title/abstract level. Both reviewers performed a full-text analysis of the articles and then went on to make the final selection. Any disagreement was resolved by a third reviewer (JG). This report is structured according to the recommendations of the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis), and the study protocol was registered in the PROSPERO (*in progress*).

2.2 Study selection criteria

Studies, prospective or retrospective, randomized or non-randomized and controlled trials were included if they used (a) ¹⁸F-FDG PET-CT to evaluate patients with or without primary colorectal cancer without surgery or other preoperative treatment; (b) Studies including polyps in dysplasia were retained (c); articles were published in French or English; (d) for per patient

level statistics, sufficient data were presented to extract the true-positive (TP), false-positive (FP), true negative (TN) and false-negative (FN) values; (e) histological evaluation in colonoscopy or surgery were utilized as a reference standard; (f) when data or subsets of data were published in more than one article, the article with the most recent article or the most details was selected; (h) for the quality of the selected studies, we have selected only those with a score greater than or equal to nine out of fourteen, on the QUADAS check list. The non-inclusion criteria were post-surgery follow-up, recurrence follow-up, metastatic disease assessment, re-evaluation after neo-adjuvant treatment, and non-comparative studies (Review articles, case reports, letters, comments, conference, technical description). There are different radio markers, we did not select studies not using 18-FDG PET-CT. Studies prior to 2009 were considered out of date and were not included.

For the analysis of the diagnostic performance of PET-CT, the overall sensitivity and overall specificity of the studies were used as the main analysis. The secondary analysis included sensitivity analysis and likelihood ratio assessments.

2.3 Quality assessment and sensitivity analysis

The quality of the selected studies was analyzed using the QUADAS check list (Quality Assessment of Studies of Diagnostic Accuracy included in Systematic reviews)(12). Only articles where the answer was "yes" on at least nine of the fourteen criteria were included. To undergo accuracy analysis, we extracted data on characteristics of studies, measurements executed and results. For each study, we extracted the following details: first author, year of publication, country of origin, sample size, study design (retrospective, prospective or unknown); included criteria as well as the reasons for exclusions from the analysis. For each study, we extracted the number of TP, FP, TN and FN findings for 18F-FDG PET-CT in diagnosing of primary colorectal cancer. We did a sensitivity analysis from his data

recalculating sensitivity and specificity. We used the derived estimates of sensitivity and specificity and respective variances to construct the area under the curve (AUC).

2.4 Statistical analyses

Statistical analyses were performed using Stata software, Version 15 (StataCorp, College Station, US). Data on the diagnostic performance (true positive, false positive, true negative and false negative results) were combined quantitatively across included studies in order to calculate sensitivity and specificity with 95% confidence intervals based on Wilson score (*Newcombe. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine 17: 857-872. 1998*). A value of 0.5 was added to all cells of studies which included a count of zero to avoid problems in calculations. Random-effects models using the method of DerSimonian and Laird were performed to take into account between and within study variability in which the weight of each study was the single sample size. A test of whether the summary effect measure was equal to the zero was given, as well as a test for heterogeneity, i.e., whether the true effect in all studies was the same. Heterogeneity was also quantified using the I-squared measure (*Higgins et al. Measuring inconsistency in meta-analyses. British Medical Journal 327: 557-560. 2003*). Data were plotted graphically in forest plots. Summary receiver operating characteristic (SROC) curves were constructed to highlight the trade-off between sensitivity and specificity across the included studies. The area under the SROC curves was utilized as a measure of test performance. Likelihood ratios (LR) were also estimated. Higher positive LR and a lower negative LR are usually expected to characterize a clinically useful test. Fagan plot was presented to describe these results. The tests were two-sided with a type I error set at 5%.

3. Results:

3.1 Literature search and selection of studies

The data extraction identified 2171 articles (PUBMED 1961, EMBASE 57 and COCHRANE 153) were yielded of which 924 were removed because their publication date was before 2009. 1124 publications were excluded because they did not respond the inclusion criteria. Among them, 94 articles were excluded owing to following reasons: missing data or off toping. Therefore, 29 eligible studies fulfilled all of the inclusion criteria, were considered for the analysis (13–41). The detailed procedure of study selection was presented in **Figure 1**.

3.2 Study characteristics and methodological quality assessment

There was a total of 16.824 colorectal cancer patient in the 29 included articles. Three studies enrolled patients prospectively while the other 26 studies were retrospective. There were no randomized studies. As the control test, a colonoscopy or surgery with anatomopathological analysis were performed.

For the QUADAS, none of the studies had a total of 14 points. Twelve had a score of 9, nine had a score of 10 and eight had a score of 11. The characteristics of the selected studies were presented in **Table 1**.

3.3 Diagnostic performance of preoperative CRC detection

After retrieving the available data, the overall sensitivity was 0.51 (95% CI: 0.35-0.66, **Figure 2**), on 17 of 29 studies (13,15,19–21,24–29,31,32,35–37,41) and the overall specificity was 0.95 (95% CI: 0.90-0.99, **Figure 3**), on 12 of 29 studies (13,20,21,24,25,27–29,31,36,37,41). The positive likelihood ratio (LR+) was 7,2 (95% CI: 5,2-10) and the negative likelihood (LR-) was 0,55 (95% CI: 0,36-0,84) (**Figure 4**).

3.4 Sensitivity analysis

Of these 29 studies, only 11 studies (13,19,20,24,25,27–29,31,36,41) allowed us to perform sensitivity analyses because we had sufficient data to calculate TP, FP, TN and FN values. The details of these results were presented in **Table 2**.

The sensitivity analysis was 0.49 (95% CI: 0.27-0.71) and the specificity analysis is also consistent with the previous data with 0.93 (95% CI: 0.89-0.96). The area on the curve (AUC) was 0.90 (95% CI: 0.87-0.92, **figure 5**).

4. Discussion:

Our meta-analysis aimed to evaluate the diagnostic performance of specially ^{18}F -FDG PET-CT in the determination of preoperative detection of patients with CRC. The last meta-analysis on this subject (42), was carried out to determine the interest of PET-CT, on preoperative TNM staging (Tumor, Node, Metastatic). Currently, PET-CT is recommended only in pre-operative assessment before metastasectomy and for the evaluation of the suspicious recurrence of CRC (42). We have selected to focus on T, to evaluate its interest even on lesions that were not metastatic at the beginning or at least not known as such and to research for the possibility of finding synchronous lesions. Indeed, the interest of PET-CT has been widely demonstrated for metastatic lesions (10,43). However, some studies have suggested that it may be of interest for advanced and potentially metastatic lesions, where PET-CT would be more efficient than conventional imaging or for pre-occlusive lesions that cannot be fully evaluated by colonoscopy (8,44). We concluded to a overall sensitivity of 51% and a specificity of 94%.

Yasuda et al (45), described the first PET-CT fixation in colonic adenoma and since then, numerous studies have evaluated its ability to detect colorectal lesions (46–49). Our meta-analysis was to date the most important analysis on the performance of preoperative CRC lesion

detection. The interpretation of the ^{18}F -FDG PET-CT was performed qualitatively on most of the studies in regard of QUADA.

The sensitivity of PET-CT, in our study, remained moderate and consistent with the data in the literature (50). Indeed, ^{18}F -FDG PET was found to be more sensitive for adenomas larger than 11 mm and with high-grade dysplasia as in the study by Hirakawa et al. which found that the overall sensitivity for any lesion was 36% but could increase to 85% for lesions larger than 11 mm (20). The literature had established that the larger the lesion, the higher the sensitivity of the PET-CT and Igarashi et al reported that sensitivity increased significantly beyond 10 millimeters and also increased with the degree of neoplasia, from 40.9% for advanced adenomas to 66.7% for T2-T4 cancers (22). However, the specificity was significant with a value of 93 to 95 %, still in line with the results of Hirakawa et al. who found a specificity of 98% for CRC lesions more than 10 millimeters. Similarly, Cipe G et al. reported PET-CT had a precision rate of 90.4% for the staging T (51) and Veit-Haibach et al, reported that precision the T staging rate by PET-CT was 86% (52). Ravizza et al. revealed despite a limited sensitivity, PET-CT was efficient for the detection of CCR adenomas due to higher specificity and PPV (positive predictive value) (9). When compared with the previous meta-analysis, a lower sensitivity and similar specificity was found (42). This can be explained by the fact that the authors grouped in the same category the analysis of detection and staging of the primary lesion, which may have increased the power of the results on detection. Nevertheless, the AUC revealed a good overall ability of PET-CT to highlight a CCR lesion which reinforced the results of the previous Ye et al meta-analysis of 2015, with only one joint study (53). The LR + and LR- also approached the previous results of this meta-analysis and a patient was almost seven times more likely to have a positive PET-CT if he had a CRC lesion, which would make this test interesting in routine clinical practice.

This meta-analysis has several limitations. Firstly, only three of the included studies were prospective and there were no double-blind randomized studies. This could be explained that PET-CT remained an expensive examination (54), potentially difficult to access (55) and therefore was not used in routine clinical practice, in this indication. We were not able to collect the majority of FP, FN, TN, TP, this greatly limited the number of studies that could be included in the final analysis. We were unable to use the SUV (Standardized Uptake Value) data we collected. Indeed, the SUV alone should not be used to differentiate between malignant and benign lesions. Indeed, it is well known that knows that the SUV is influenced by several factors, patient as well as technical aspects and procedures (56). Any calculation of a pooled SUV obtained through different studies - acquired with different CT scanners, scan protocols, ¹⁸F-FDG injected activity and patient characteristics - was in our inappropriate analysis. Three studies (19,32,37) suggested that the SUVmax did not offer sufficient sensitivity for the detection of malignancies. However, Hwang et al, described that the SUVmax did not determine the difference between benign and malignant lesions, but that if an SUV was greater than 5, it required colonoscopy (57).

Although the sensitivity of PET-CT who remained limited, its specificity made it an interesting preoperative examination. Engelmann et al demonstrated that PET-CT scanners identify 97-98% of primary tumors, especially T4 tumors (58), which would make this examination all the more interesting in advanced tumors because they have more pre-occlusive and metastatic potential. In case of obstructive CRC that blocks colonoscope passage, it is difficult to examine the colon proximal to the obstruction. CT colonography, used for obstructive CRC, has been shown to have high sensitivity but low PPV for proximal synchronous cancers in obstructive CRC. (59). Hojo et al, reported that the sensitivity for detection of PET-CT synchronous lesions in occlusive lesions was similar to that of the coloscanner without the disadvantage and risk of colonic preparation (60). Recently, Kim et al

found a 100% sensitivity of PET-CT for the detection of CRC synchronous proximal lesions and a negative predictive value (NPV) also of 100% for this type of lesion (44). The major difference between PET-CT and other imaging studies is that PET-CT provides both anatomic and metabolic information about incidental lesions found in the large bowel. The pattern of ¹⁸F-FDG uptake in the large bowel on PET-CT imaging influences the likelihood of malignancy (56). One might even think that PET-CT could, for this type of advanced lesion, assess the extension of potential metastases and thus avoid surgeries not indicated as first-line treatment (61). And, if the PET-CT would be negative in the proximal colon, the surgery would not need to be extensive as there would be little chance of CRC proximal synchronization (44). Unfortunately, we cannot conclude on this because we were not able to do a subgroup analysis for stenotic lesions.

Conclusion:

Our meta-analysis suggested that the PET-CT could be a promising complementary examination for the detection of preoperative CRC lesions with a good performance, and probably more specific way for advanced or preocclusive lesions, beyond its use for extension staging or recidive. Prospective studies for use in routine clinical detection practice will be necessary to confirm its results.

Conclusion

Notre méta-analyse suggère que le PET-CT pourrait être un examen complémentaire prometteur pour la détection des lésions préopératoires du CCR, et probablement de manière plus spécifique pour les lésions avancées ou préocclusives, au-delà de son utilisation courante pour la stadification d'extension.

Son intérêt pour faire partie du bilan standard des lésions coliques gauche pré occlusive, doit cependant faire réaliser une étude randomisée pour confirmer sa non-infériorité face au coloscanner.

Clermont-Ferrand, le 22/09/2020
Pierre CLAVELOU
Doyen - Directeur



Clermont-Ferrand, le 23/09/20
Le Président du Jury

A large, stylized handwritten signature in black ink, positioned below the text "Le Président du Jury".

Table 1: Description of the included studies

Authors	Year	Centers	Study Design	Population	Male	Control tests	Total QUADAS
Lee J. <i>et al.</i>	2009	Australia	R	62	NC	Coloscopy	9
Mori <i>et al.</i>	2010	Japan	R	52	33	Anatomopatolgy	10
Ravizza <i>et al.</i>	2010	Italy	R	92	39	Coloscopy	10
Weston <i>et al.</i>	2010	USA	R	330	NC	Coloscopy	10
Mainenti <i>et al.</i>	2011	Italy	R	34	20	Anatomopatolgy	10
Peng <i>et al.</i>	2011	China	P	136	68	Coloscopy	10
Farquharson <i>et al.</i>	2012	UK	R	24	NC	Coloscopy	9
Hirakawa <i>et al.</i>	2012	Japan	R	492	306	Coloscopy	11
Purandare <i>et al.</i>	2012	India	R	24	15	Coloscopy	9
Treglia <i>et al.</i>	2012	Italy	R	64	41	Coloscopy	9
Cho <i>et al.</i>	2013	Korea	P	241	153	Coloscopy	11
Huang <i>et al.</i>	2013	Taiwan	R	1109	661	Coloscopy	11
Lee C. <i>et al.</i>	2013	Korea	R	195	109	Coloscopy	10
Putora <i>et al.</i>	2013	Switzerland	R	51	NC	Coloscopy	9
Gollub <i>et al.</i>	2014	USA	R	180	88	Coloscopy	9
Minamimoto <i>et al.</i>	2014	Japan	R	1808	1180	Coloscopy	9
Fuertes <i>et al.</i>	2015	Spain	R	27	19	Coloscopy	11
Hwang <i>et al.</i>	2015	Japan	R	614	427	Coloscopy	9
Tianye <i>et al.</i>	2015	USA	R	133	57	Coloscopy	9
Na <i>et al.</i>	2015	Korea	R	306	NC	Coloscopy	9
Sekiguchi <i>et al.</i>	2015	Japan	P	7505	4652	Coloscopy	10
Van Hoej <i>et al.</i>	2015	Netherlands	R	203	116	Coloscopy	9
Kunawudhi <i>et al.</i>	2016	USA	R	157	79	Coloscopy	11
Igarashi <i>et al.</i>	2017	Japan	R	2323	1430	Coloscopy	10
Kim <i>et al.</i>	2017	Korea	R	345	176	Coloscopy	10
Garrido Duran <i>et al.</i>	2018	Spain	R	71	NC	Coloscopy	11
Hojo <i>et al.</i>	2018	Jaen	R	93	60	Coloscopy	11
Valente <i>et al.</i>	2018	USA	R	84	42	Coloscopy	9
Maeda <i>et al.</i>	2019	Japan	R	72	NC	Coloscopy	11

P=Prospective, R= Retrospective, NC= not available, Male= absolut value

TABLE 2: Diagnostic Value of PET- CT in preoperative CRC patients

Author	Year	Population	TP	FP	FN	TP	Sensibility	CI 95%	Specificity	CI 95%
Lee J. <i>et al</i>	2009	62	25	7	7	NC	0,78	0,61-0,89	NC	NC
Mori <i>et al</i>	2010	52	12	0	12	13	0,5	0,31-0,69	1	0,77-1
Ravizza <i>et al</i>	2010	92	39	0	118	0	0,25	0,19-0,32	0,5	0,09-0,99
Weston <i>et al</i>	2010	330	38	20	32	240	0,54	0,43-0,64	0,9	NC
Mainenti <i>et al</i>	2011	34	12	3	4	15	0,75	0,51-0,90	0,83	0,61-0,94
Peng <i>et al</i>	2011	136	60	76	NC	NC	NC	NC	NC	NC
Farquharson <i>et al</i>	2012	24	21	3	NC	NC	NC	NC	NC	NC
Hirakawa <i>et al</i>	2012	492	NC	NC	NC	NC	NC	NC	NC	NC
Purandare <i>et al</i>	2012	24	21	3	NC	NC	0,62	NC	NC	NC
Treglia <i>et al</i>	2012	64	31	11	NC	NC	0,77	NC	NC	NC
Cho <i>et al</i>	2013	241	49	46	6	146	0,89	0,78-0,95	0,76	0,70-0,82
Huang <i>et al</i>	2013	1109	6	10	32	1061	0,16	0,07-0,30	0,99	0,98-0,99
Lee C. <i>et al</i>	2013	195	103	87	35	525	0,75	0,67-0,81	0,86	0,83-0,88
Putora <i>et al</i>	2013	51	44	7	38	NC	0,54	0,43-0,64	NC	NC
Gollub <i>et al</i>	2014	180	NC	33	NC	NC	0,74	NC	1	NC
Minamimoto <i>et al</i>	2014	1808	NC	NC	NC	NC	0,63	NC	NC	NC
Fuertes <i>et al</i>	2015	27	18	8	15	NC	0,55	0,38-0,70	NC	NC
Hwang <i>et al</i>	2015	614	10	17	NC	513	0,27	0,18-0,37	0,97	0,96-0,98
Tianye <i>et al</i>	2015	133	10	14	0	109	1,00	0,72-1,00	0,89	0,82-0,93
Na <i>et al</i>	2015	306	49	NC	12	NC	0,8	0,69-0,88	0,83	NC
Sekiguchi <i>et al</i>	2015	7505	47	300	231	44452	0,17	0,13-0,22	0,92	0,88-0,95
Van Hoej <i>et al</i>	2015	203	89	102	NC	NC	NC	NC	NC	NC
Kunawudhi <i>et al</i>	2016	157	21	23	58	526	0,27	0,18-0,37	0,96	0,94-0,97
Igarashi <i>et al</i>	2017	2323	NC	153	NC	NC	NC	NC	NC	NC
Kim <i>et al</i>	2017	345	34	5	NC	NC	NC	NC	NC	NC
Garrido duran <i>et al</i>	2018	71	35	1	NC	NC	NC	NC	NC	NC
Hojo <i>et al</i>	2018	93	18	4	21	50	0,25	0,17-0,36	NC	NC
Valente <i>et al</i>	2018	84	63	21	NC	NC	NC	NC	NC	NC
Maeda <i>et al</i>	2019	72	7	4	6	55	0,54	0,29-0,77	0,93	0,84-0,97

P=Prospectif, R= Retrospectif, NC= not available, (TP=true positive, FP=false positive, FN=false negative, TP=true positive; absolute value), Sensibility / Specificity =percentage



PRISMA 2009 Flow Diagram

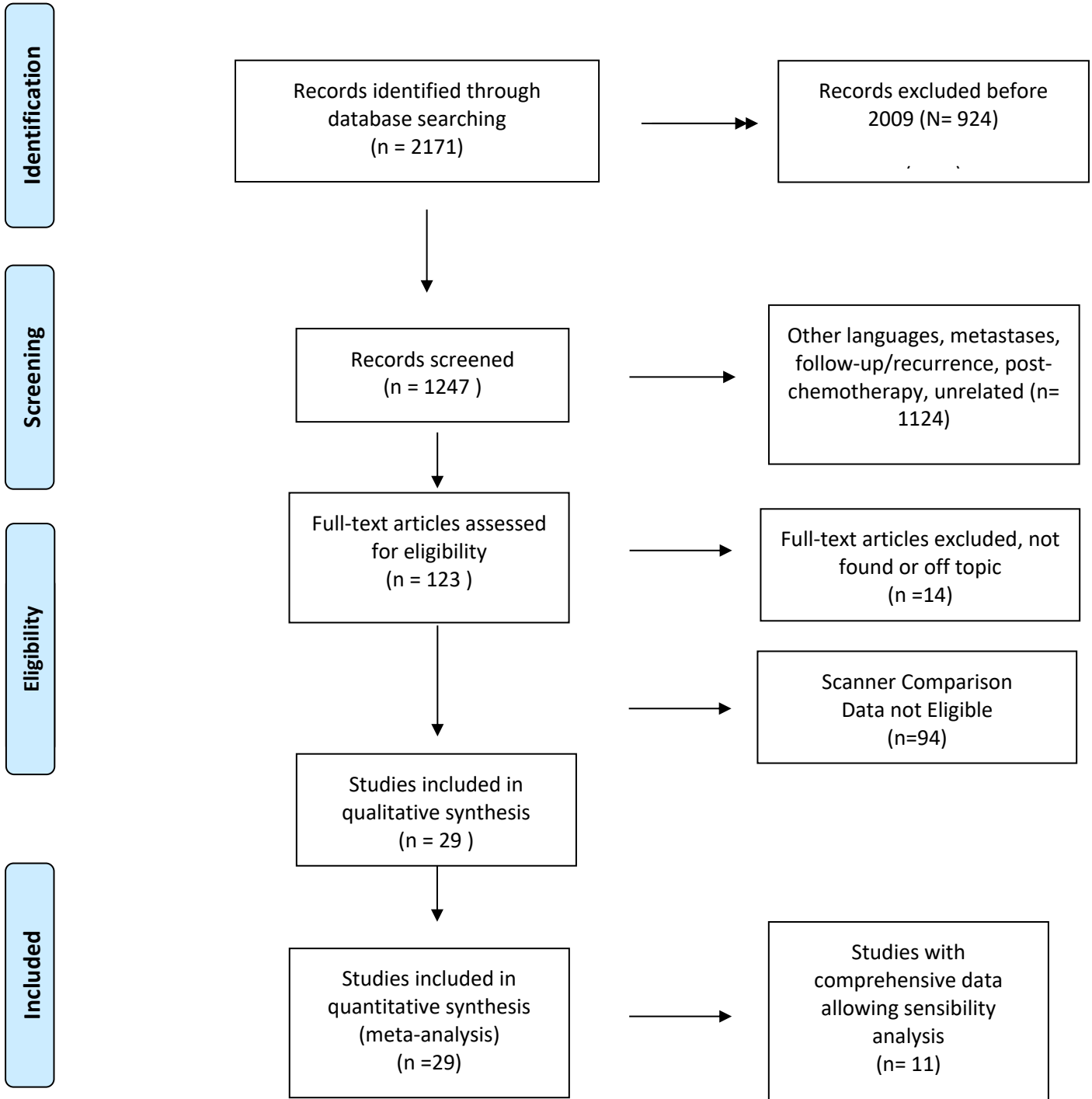


Figure 1: FLOW CHART

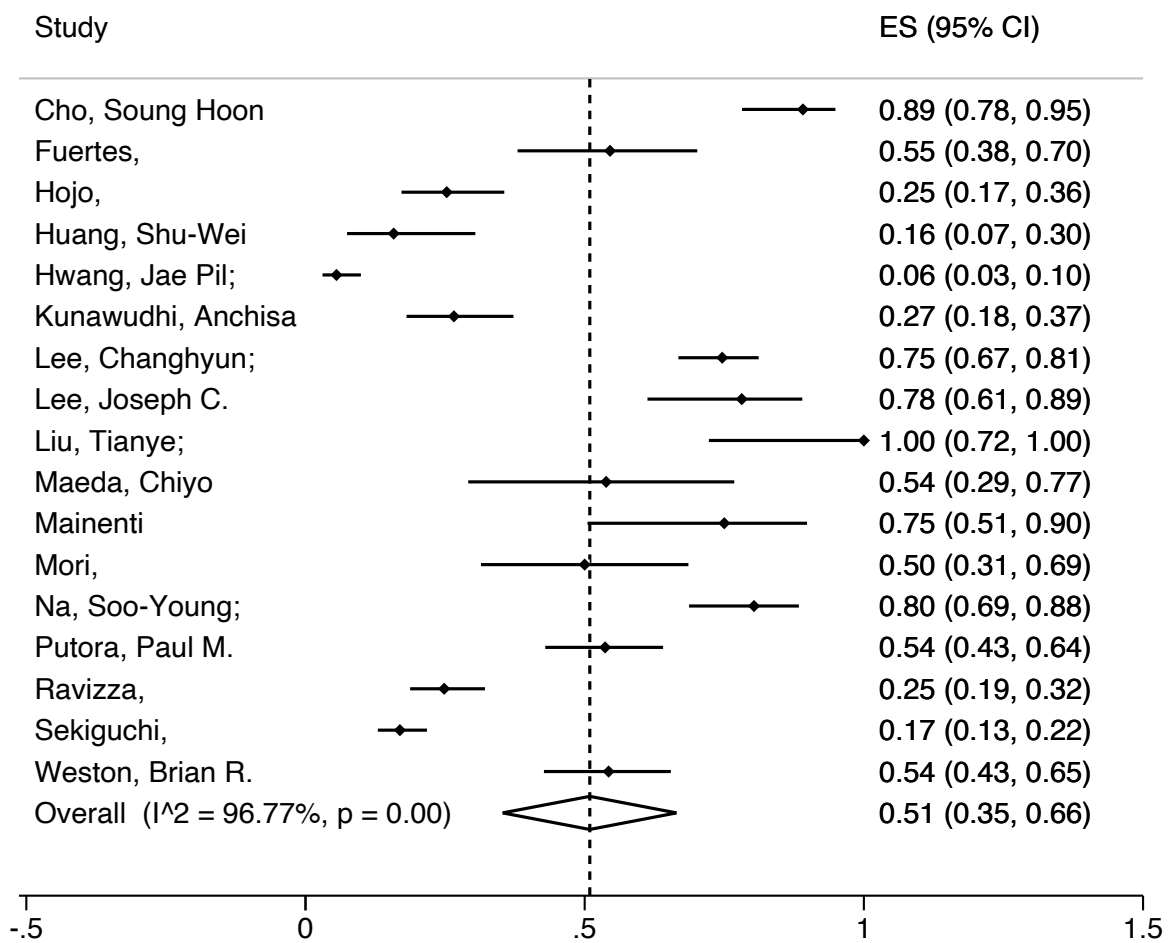


Figure 2 : Forrest Plot overall Sensibility

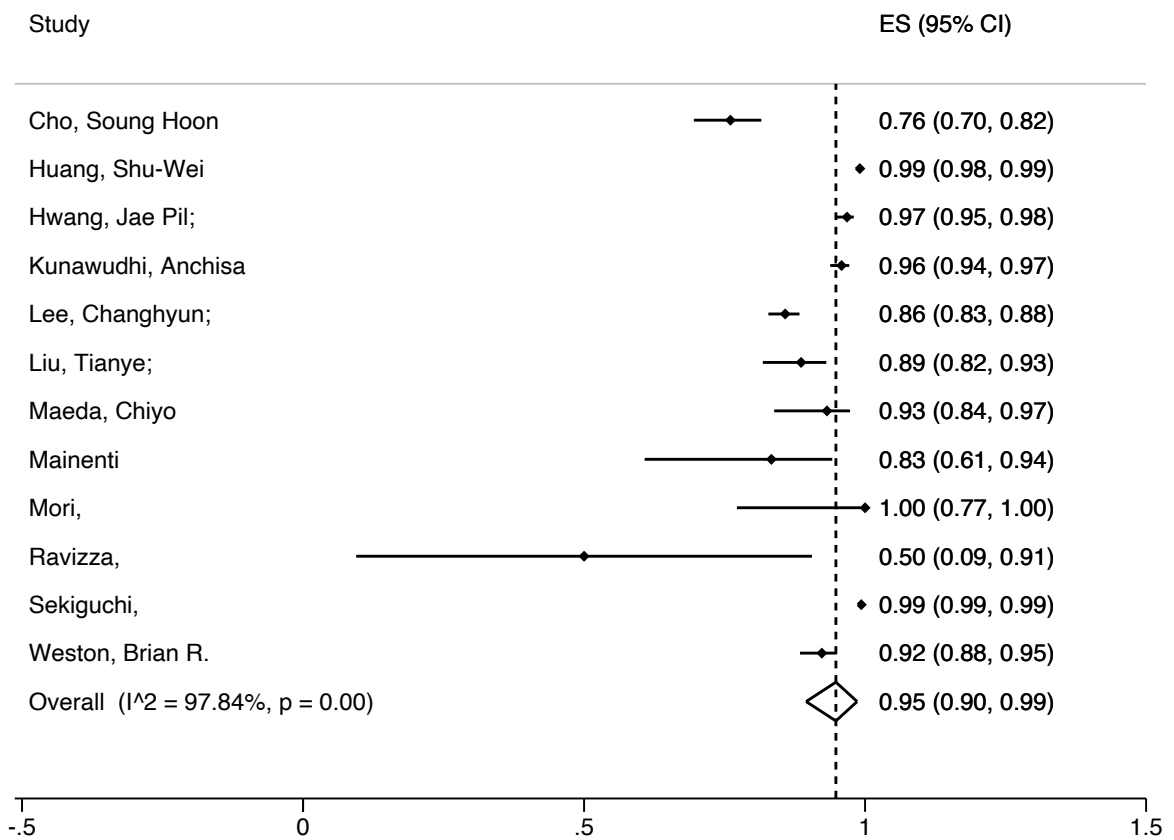


Figure 3 : Forrest plot overall Specificity

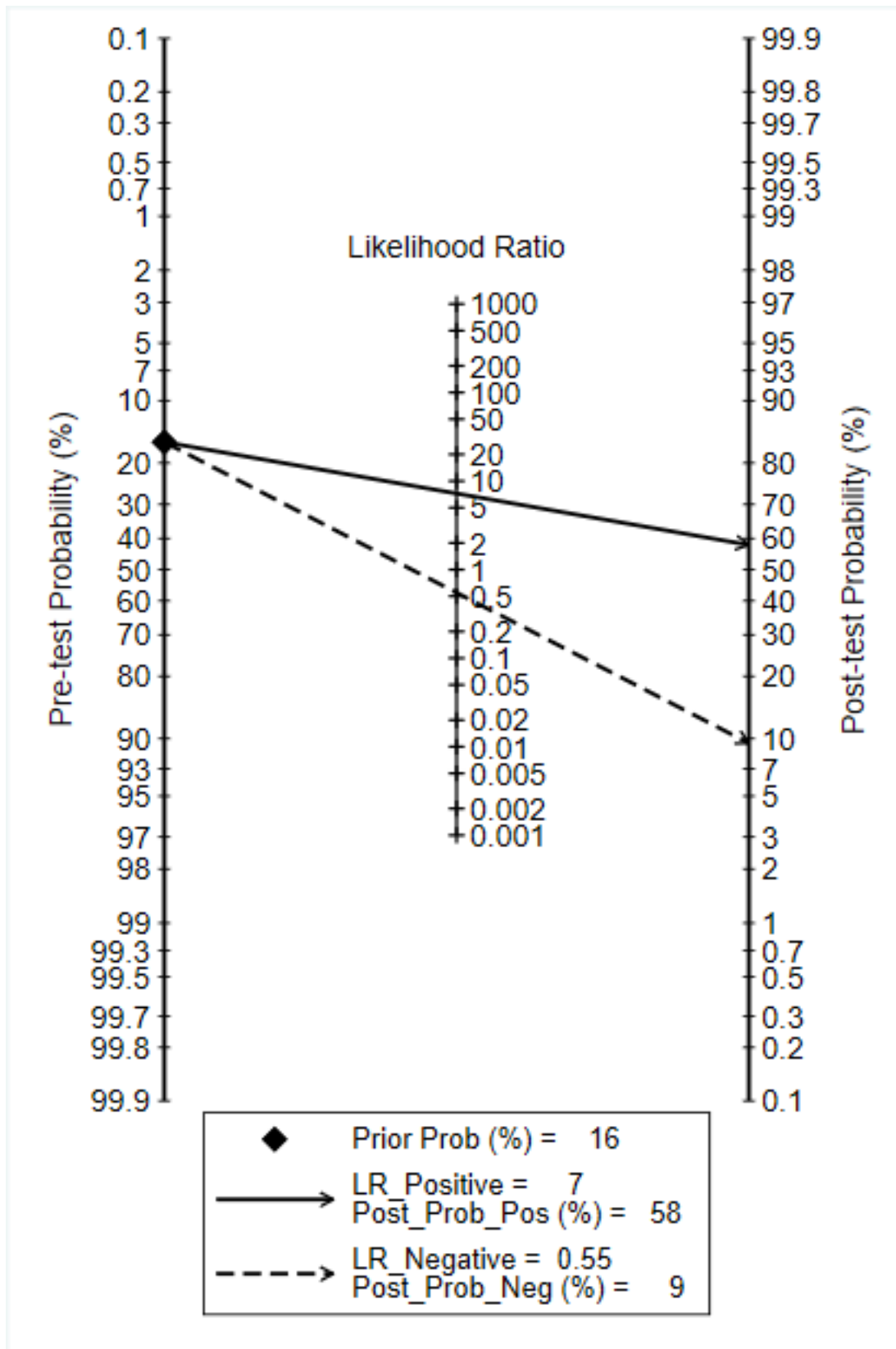


Figure 4 : Fagan diagram with Likelihood Ratio

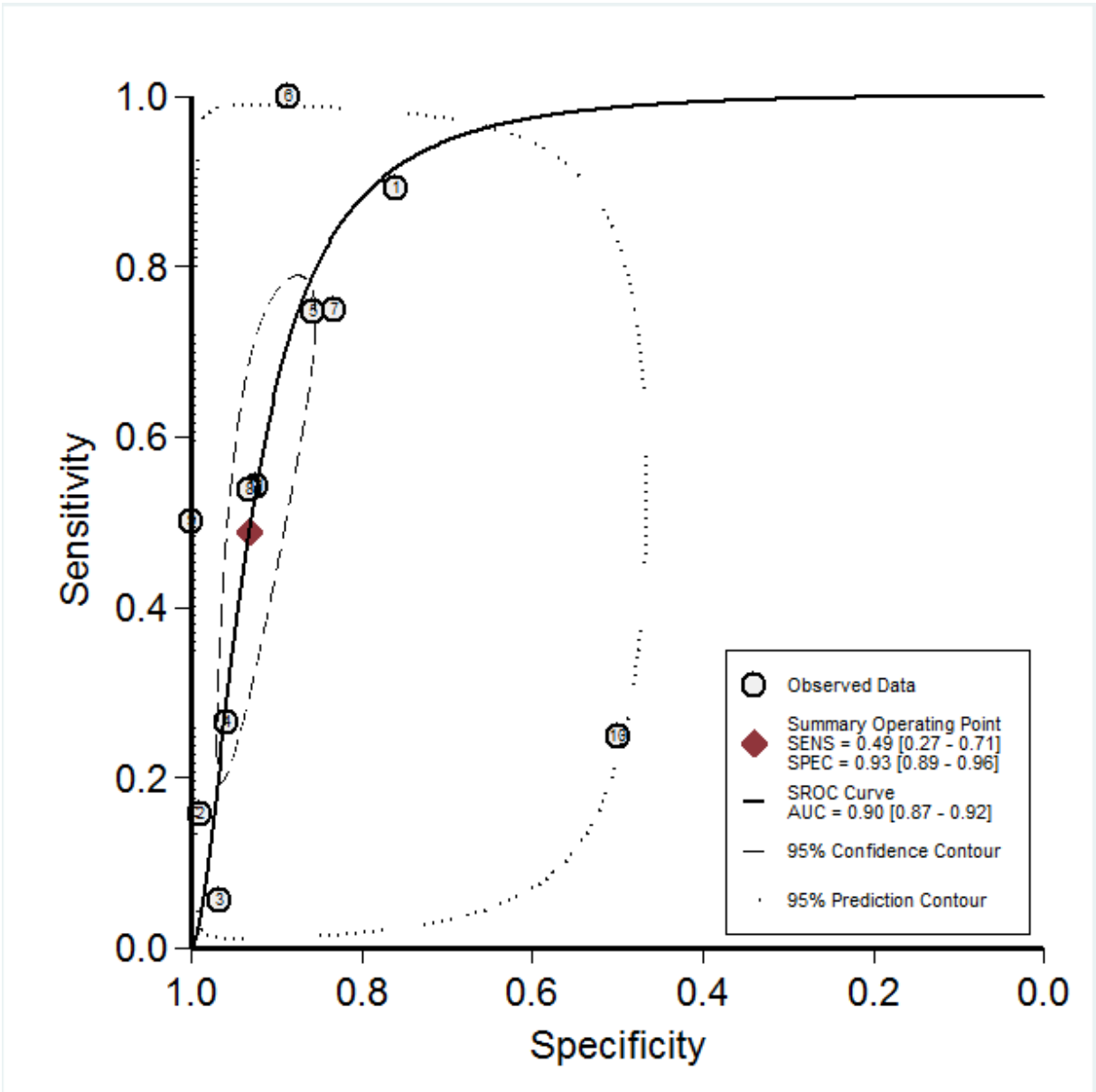


Figure 5: Aire under curve (AUC) with sensitivity analyses

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(Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Nom, Prénom

Signature

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque

Nom, Prénom

Signature