Relapsed ovarian cancer - diagnosis using ^{18}F-FDG PET/CT; 4.

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Ovarian cancer is the eighth malignant neoplasm most often diagnosed in women in Brazil and the fifth leading cause of death from cancer in women. According to the National Institute of Cancer (INCA), in 2013, there were 3,283 deaths reported related to ovarian cancer in Brazil. There is an estimated risk of 6.15 cases per 100,000 women in Brazil in 2018[1].

The majority of patients are diagnosed at an advanced stage of the disease (II-IV). The initial staging of ovarian cancer is surgical and involves laparotomy with total hysterectomy, bilateral salpingo-oophorectomy, and peritoneal and lymph node biopsies. The initial treatment usually involves cytoreductive surgery and systemic chemotherapy. Although the rate of response to the initial treatment is high, tumor recurrence is a common problem of patients treated for ovarian cancer. It is estimated that 75% of patients with ovarian cancer have relapses, usually in pelvic/retroperitoneal lymph nodes and in the peritoneum[2]. The initial radiological evaluation of patients suspected of relapse of ovarian cancer is done with computed tomography. The exam has excellent anatomical definition, providing important information about the relationship of tumor lesions with the organs and vascular structures. However, computed tomography has limitations in the evaluation of lymph node disease, since it is based exclusively on morphological criteria, and peritoneal disease due to the difficulty of distinguishing it from non-opacified bowel loops.

The diagnosis of relapse and the anatomical location of the metastatic disease are important to determine the best therapeutic strategy. Patients who undergo cytoreductive surgery after the relapse of ovarian cancer have a better prognosis only when the volume of disease is small and when there are no extra-abdominal metastases[3].

METHODOLOGY

Using the descriptors: patients with ovarian cancer **(P)**, positron emission tomography, computed tomography (PET-CT) with FDG (fludeoxyglucose) **(I)**, computed tomography **(C)**, anatomopathological and/or clinical follow-up **(O)**; a systematic review of the literature was performed, with no time restriction, in the Medline database. A total of 515 studies were retrieved using the following search strategy: Ovarian Neoplasm OR Ovary Neoplasms OR Ovary Neoplasm OR Ovary Cancer OR Ovary Cancers OR Ovarian Cancer OR Ovarian Cancers) AND (PET OR Positron Emission Tomography) AND (FDG OR fluorodeoxyglucose OR fludeoxyglucose). Of these, 9 were selected to answer the clinical questions: What is the diagnostic accuracy of ^{18}F-FDG PET/CT in patients with relapsed epithelial ovarian cancer? Is ^{18}F-FDG PET/CT recommended for patients with relapsed epithelial ovarian cancer?

The risk of bias was assessed using a tool to assess the quality of studies of diagnostic accuracy (QUADAS-2). The global synthesis was elaborated considering the evidence described. Its strength was estimated (Oxford[7]/ GRADE[9]) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate, or weak, or very weak.

RESULTS

What is the diagnostic accuracy of ^{18}F-FDG PET/CT in patients with relapsed epithelial ovarian cancer?

The main population and methodological characteristics for analyzing the quality of the studies are summarized in Table 1 (ANNEX I). The sensitivity and specificity of ^{18}F-FDG PET/CT and computed tomography, the prevalence of tumor relapse, as well as the number of true positives, false positives, false negatives and true negatives for each study are described in Table 2 (ANNEX I).

Of the 474 patients included, 340 (72%) had the relapse of ovarian cancer confirmed by an anatomopathological study or clinical follow-up, while 134 (28%) showed no evidence of relapse.

Using a joint analysis of the selected studies, the characteristics of ^{18}F-FDG PET/CT in the diagnosis of relapsed ovarian cancer were: 91% sensitivity (95% CI 87-93%) (Figure 1 - Annex I); specificity 91% (95% CI 85-95%) (Figure 2 - Annex I); positive likelihood ratio of 6.0 (95% CI 3.5-10.3) (Figure 3 - Annex I); negative likelihood ratio of 0.1 (95% CI 0.05-0.29) (Figure 4 - Annex I); and odds ratio of 56.5 (95% CI 18.8-169.3) (Figure 5 - Annex I).

Figure 6 (annex I) corresponds to the ^{18}F-FDG PET/CT performance compared to the reference standard (anatomopathological) in the diagnosis of relapsed ovarian cancer. In the figure, 3 curves can be observed, of which only the central corresponds to the SROC curve (summary receiver-operating characteristic), while the others correspond to the CI of 95%. The area below the curve [area under the curve (AUC)] totals 0.94 (SE=0.02), indicating that, in a random sample, the diagnostic test has the capacity to distinguish the majority of individuals considered cases and non-cases. In this analysis, we identified that the highest common value between sensitivity and specificity (Q* index) was 0.88 (SE=0.03).

Is ^{18}F-FDG PET/CT recommended for patients with relapsed epithelial ovarian cancer?

There is no direct evidence of reduction of clinical events with the use of ^{18}F-FDG PET/CT in patients with relapsed ovarian cancer. In the absence of direct evidence of the effectiveness of the method, we compared the diagnostic accuracy with conventional imaging (computed tomography) and analyzed the change in clinical management determined by the use of PET/CT in patients with suspected relapsed ovarian cancer.

The joint analysis of the selected studies suggests that ^{18}F-FDG PET/CT is more sensitive and more specific than computed tomography for relapsed ovarian cancer: sensitivity 91% (95% CI 87-93%) vs. 84% (95% CI 79-89%) ($p<0.001$) and specificity 91% (95% CI 85-95%) vs. 65% (95% CI 53-76%) ($p<0.001$). The SROC curves (Figures 6 and 7 - Annex II) illustrate a significantly greater diagnostic accuracy of ^{18}F-FDG PET/CT (AUC=0.94; SE=0.02) compared to computed tomography (AUC=0.84; SE=0.03).

Fulham et al[4] included 90 patients with suspected relapsed epithelial ovarian cancer in a Australian prospective and multicenter study with a follow-up of 12 months. ^{18}F-FDG PET/CT was superior to computed tomography in detecting lymph node, peritoneal and subcapsular hepatic metastases. The use of PET/CT changed management in 59% (95% CI 49-69%) of patients. Of patients who were candidates for surgery before the PET/CT, 54% (95% CI 37-70%)

avoided it; chemotherapy was added to the treatment of 16% (95% CI 9-24%) and avoided in 13% (95% CI 8-22%).

Hillner et al[5] evaluated the rate of change of therapy in patients who underwent ^{18}F-FDG PET/CT for suspected relapsed ovarian cancer in the NOPR (National Oncology PET Registry). Of the 2,160 PET/CT examinations included, there was a change in the intention-to-treat in 44% of cases (95% CI 42-47%).

The Fulham et al[4] and Hillner et al[5] studies suggest that ^{18}F-FDG PET/CT changes the clinical management of a significant proportion of patients due to increased sensitivity, mainly due to the contraindication of cytoreductive surgery. The detection of extra-abdominal metastases or sites of diseases anatomically inaccessible avoids the morbidity and mortality associated with the invasive procedure. Although there is no evidence in the literature of an improvement in the quality of life of patients who have cytoreductive surgery replaced by other treatments, there is a consensus among physicians that the potential benefits of surgery do not outweigh the risks in patients with disseminated disease.

The majority of ovarian cancer patients present with high serum levels of the tumor marker CA-125. CA-125 has a high sensitivity in the detection of ovarian cancer recurrence. Its plasma concentration generally increases months before the disease manifests itself clinically. It is not uncommon to find patients with high CA-125 levels and normal computed tomography. In this scenario, the use of ^{18}F-FDG PET/CT can be considered due to its greater sensitivity as compared to computed tomography.

A multicenter clinical study[6] randomized 529 patients to start chemotherapy based on increased CA-125 levels only (group that started the treatment early) or on clinical/symptomatic relapse (group that started the treatment late). After a median follow-up of 57 months, there was no difference in overall survival between the groups [HR 0.98 (95% CI 0.8-1.2)], which puts into question whether it is useful to have an early confirmation of tumor relapse by imaging (computed tomography or ^{18}F-FDG PET/CT) in patients who are not candidates for cytoreductive surgery. New systemic therapies for ovarian cancer have been developed over the last decade, such as PARP inhibitors (poly ADP-ribose polymerase) and angiogenesis inhibitors. However, it is still unkown whether early start of systemic therapies can reduce clinical events in patients with recurrent ovarian cancer.

RECOMMENDATION

The meta-analysis of studies selected shows good diagnostic accuracy of ^{18}F-FDG PET/CT for detecting relapsed ovarian cancer with high sensitivity. We recommend the use of ^{18}F-FDG PET/CT in patients with relapsed ovarian cancer when the findings of computed tomography do not contraindicate cytoreductive surgery (grade of recommendation and strength of the evidence B). The presence of multifocal disease or extra-abdominal metastasis on ^{18}F-FDG PET/CT, a frequent finding, can avoid surgery and reduce the morbidity and mortality associated with the invasive procedure. Confirmation of exclusively intra-abdominal disease by ^{18}F-FDG PET/CT supports the recommendation of cytoreductive surgery.

APPENDIX I

TABLE 01. TABLE OF CHARACTERISTICS

Author/Year	Disease	Population (N)	Test (T)	Gold Standard (P)	Comparison	Time interval (T→P)
Tawakol 2016	Any relapse	111	PET/CT	Anatomopathological or clinical follow-up	Computed tomography	≥ 6 months
Hynninen 2013	Peritoneal	41	PET/CT	Anatomopathological	Computed tomography	Up to 2 weeks
Signorelli 2013	Pelvic/Aortic lymph node	68	PET/CT	Anatomopathological	_	Not available
Risum 2009	Any relapse	60	PET/CT	Anatomopathological or clinical follow-up	Computed tomography	3 months
Sebastian 2008	Any relapse	53	PET/CT	Clinical follow-up	Computed tomography	≥ 4 months
Mangili 2007	Any relapse	32	PET/CT	Anatomopathological or clinical follow-up	Computed tomography	Not available
Simcock 2006	Any relapse	56	PET/CT	Anatomopathological or clinical follow-up	_	6 months
Sironi 2004	Pelvic/ Abdominal relapse	31	PET/CT	Anatomopathological	_	3-11 days
Bristow 2003	Relapse ≥ 1 cm	22	PET/CT	Anatomopathological	_	Up to 30 days

T→P=time interval between the test and the gold standard (anatomopathological or clinical follow-up) / PET/CT=positron emission tomography/computed tomography

TABLE 02. RESULTS

Author/Year	Sensitivity	Specificity	True +	False +	False -	True -
PET X Anatomopathological						
Tawakol 2016	0.959	0.923	93	3	4	36
Hynninen 2013	0.912	0.857	31	1	3	6
Signorelli 2013	0.833	0.982	10	1	2	55
Risum 2009	0.976	0.9	41	1	1	9
Sebastian 2008	0.974	0.8	37	3	1	12
Mangili 2007	0.897	0.667	26	1	3	2
Simcock 2006	0.868	0.667	46	1	7	2
Sironi 2004	0.529	0.857	9	2	8	12
Bristow 2003	0.833	0.75	15	1	3	3
PET x CT						
Tawakol 2016	0.835	0.59	81	16	16	23
Hynninen 2013	0.794	0.714	27	2	7	5
Risum 2009	0.976	0.9	41	1	1	9
Sebastian 2008	0.921	0.8	35	6	3	9
Mangili 2007	0.645	1	20	0	11	1

PET: positron emission tomography; CT: computed tomography

TABLE 05: TABLE OF BIASES.

Author/Year	Patient selection			
	Questions			Risk of bias
	Were the patients consecutive or random?	Was case-control avoided?	Were unnecessary exclusions avoided?	Did the selection of patients introduce a bias?
Tawakol 2016	Yes	Yes	No	☹
Hynninen 2013	Yes	Yes	Yes	☺
Signorelli 2013	Yes	Yes	Yes	☺
Risum 2009	Yes	Yes	Yes	☺
Sebastian 2008	Yes	Yes	No	☹
Mangili 2007	Yes	Yes	Yes	☺
Simcock 2006	Yes	Yes	Yes	☺
Sironi 2004	Yes	Yes	Yes	☺
Bristow 2003	Yes	Yes	Yes	☺

PET/CT = positron emission tomography/computed tomography. /. ☺= low risk; ☹= high risk

Author/Year	Test (PET/CT)			Gold Standard		
	Questions		Risk of bias	Questions		Risk of bias
	Was the PET interpreted without the knowledge of the outcome of the gold standard?	If a threshold was used, was it predetermined?	Is it possible that the interpretation of the PET introduced a bias?	Did the gold standard supposedly correctly classify the presence/absence of the disease?	Was the gold standard conducted/interpreted without knowledge of the PET results?	Is it possible that the conduct or interpretation of the gold standard introduced a bias?
Tawakol 2016	No	No	☹	Yes	No	☹
Hynninen 2013	Yes	No	☹	Yes	No	☹
Signorelli 2013	Yes	No	☹	Yes	Yes	☺
Risum 2009	No	No	☹	Yes	No	☹
Sebastian 2008	Yes	No	☹	Yes	No	☹
Mangili 2007	No	No	☹	Yes	No	☹
Simcock 2006	Yes	No	☹	Yes	No	☹
Sironi 2004	Yes	No	☹	Yes	No	☹
Bristow 2003	Yes	No	☹	Yes	No	☹

PET/CT = positron emission tomography/computed tomography. /. ☺= low risk; ☹= high risk

FIGURE 01: SENSITIVITY

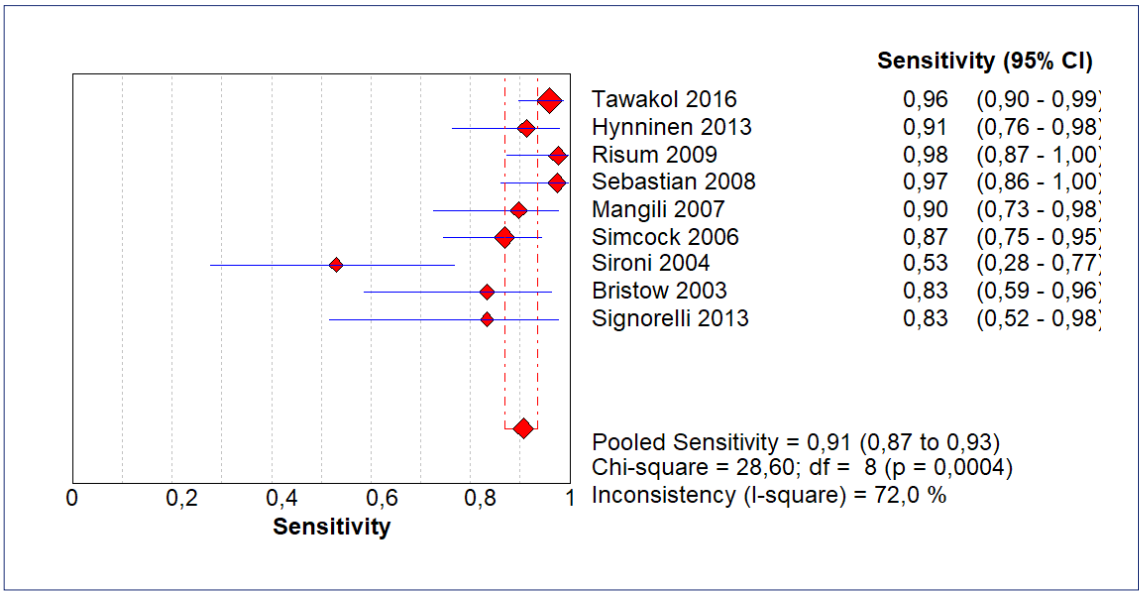


FIGURE 02: SPECIFICITY

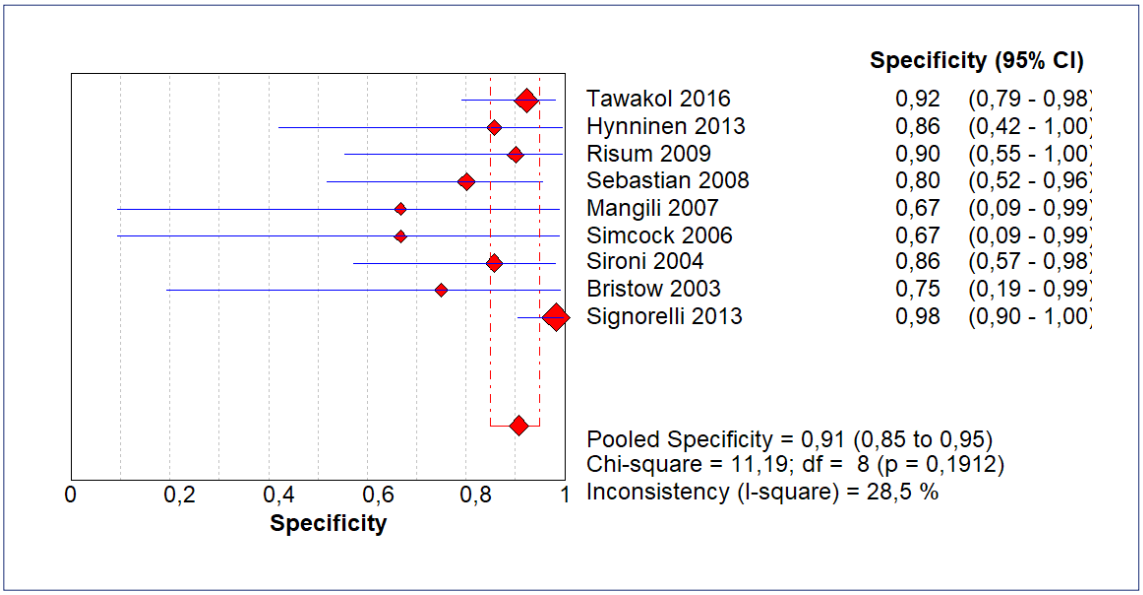


FIGURE 03: POSITIVE LIKELIHOOD RATIO

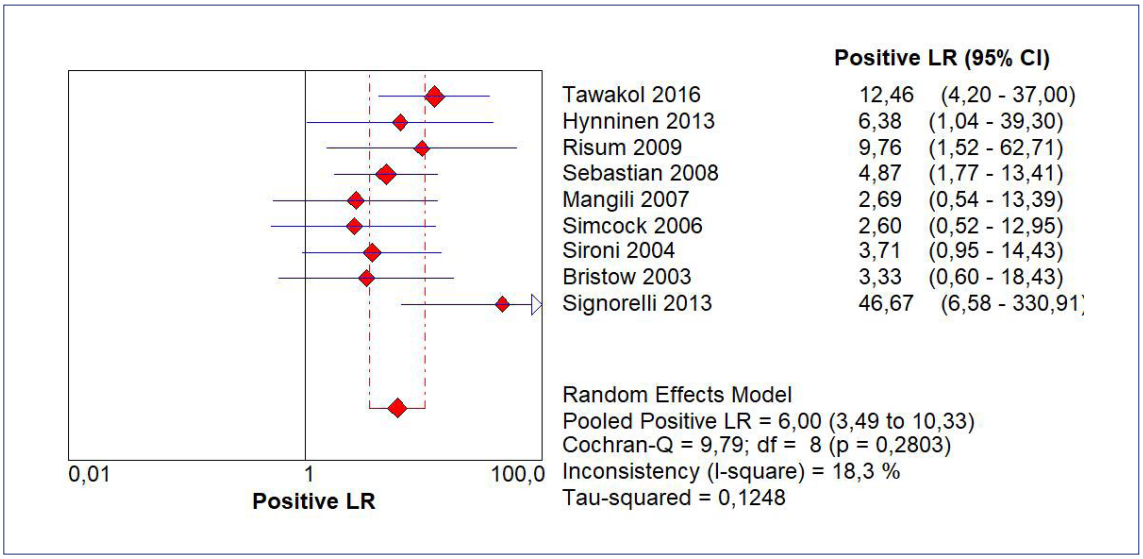
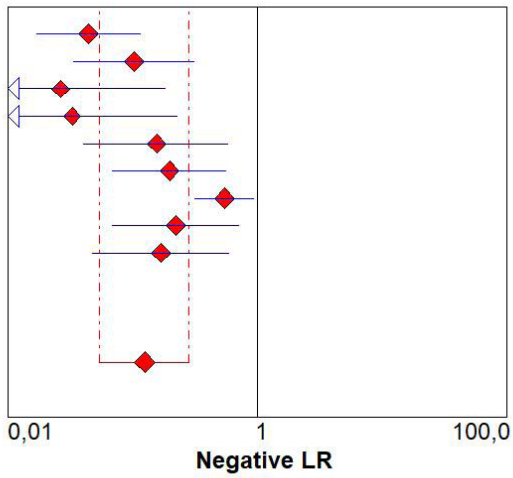


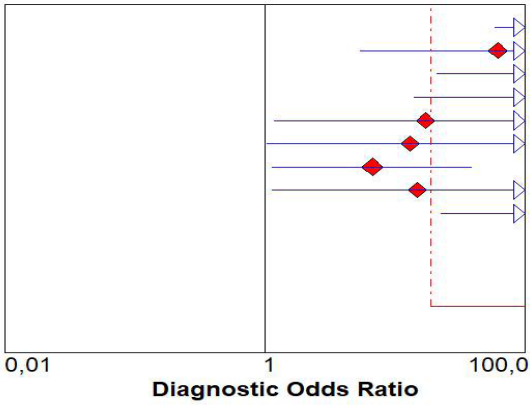
FIGURE 04: NEGATIVE LIKELIHOOD RATIO



	Negative LR (95% CI
Tawakol 2016	0,04 (0,02 - 0,12)
Hynninen 2013	0,10 (0,03 - 0,32)
Risum 2009	0,03 (0,00 - 0,19)
Sebastian 2008	0,03 (0,00 - 0,23)
Mangili 2007	0,16 (0,04 - 0,59)
Simcock 2006	0,20 (0,07 - 0,57)
Sironi 2004	0,55 (0,32 - 0,95)
Bristow 2003	0,22 (0,07 - 0,72)
Signorelli 2013	0,17 (0,05 - 0,60)

Random Effects Model
Pooled Negative LR = 0,12 (0,05 to 0,29)
Cochran-Q = 38,84; df = 8 (p = 0,0000)
Inconsistency (I-square) = 79,4 %
Tau-squared = 1,1868

FIGURE 05: ODDS RATIO



	Diagnostic OR (95% CI)
Tawakol 2016	279,00 (59,48 - 1.308,73)
Hynninen 2013	62,00 (5,48 - 701,54)
Risum 2009	369,00 (21,04 - 6.470,25)
Sebastian 2008	148,00 (14,04 - 1.559,61)
Mangili 2007	17,33 (1,19 - 253,19)
Simcock 2006	13,14 (1,05 - 164,78)
Sironi 2004	6,75 (1,14 - 39,80)
Bristow 2003	15,00 (1,14 - 198,04)
Signorelli 2013	275,00 (22,73 - 3.327,60)

Random Effects Model
Pooled Diagnostic Odds Ratio = 56,46 (18,83 to 169,28)
Cochran-Q = 16,53; df = 8 (p = 0,0354)
Inconsistency (I-square) = 51,6 %
Tau-squared = 1,4147

FIGURE 06: ^{18}F-FDG PET/CT PERFORMANCE COMPARED TO THE REFERENCE STANDARD (COMPUTED TOMOGRAPHY)

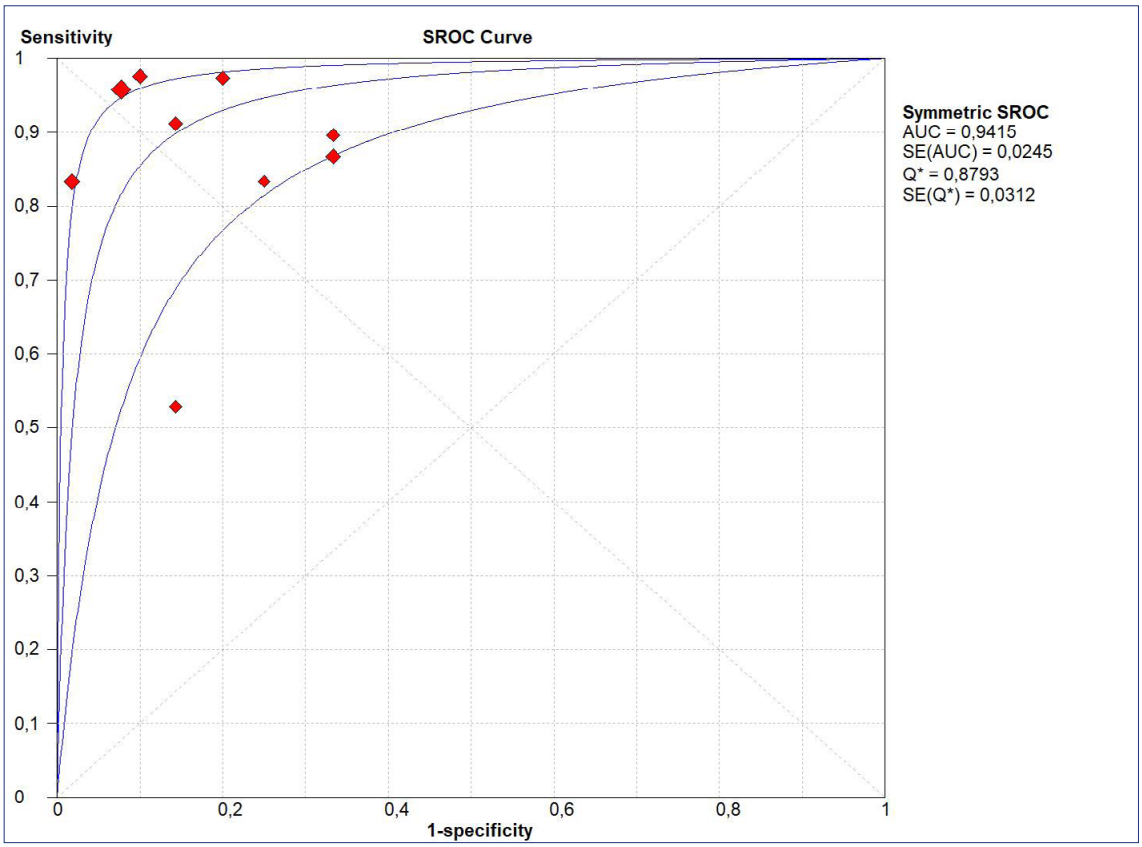
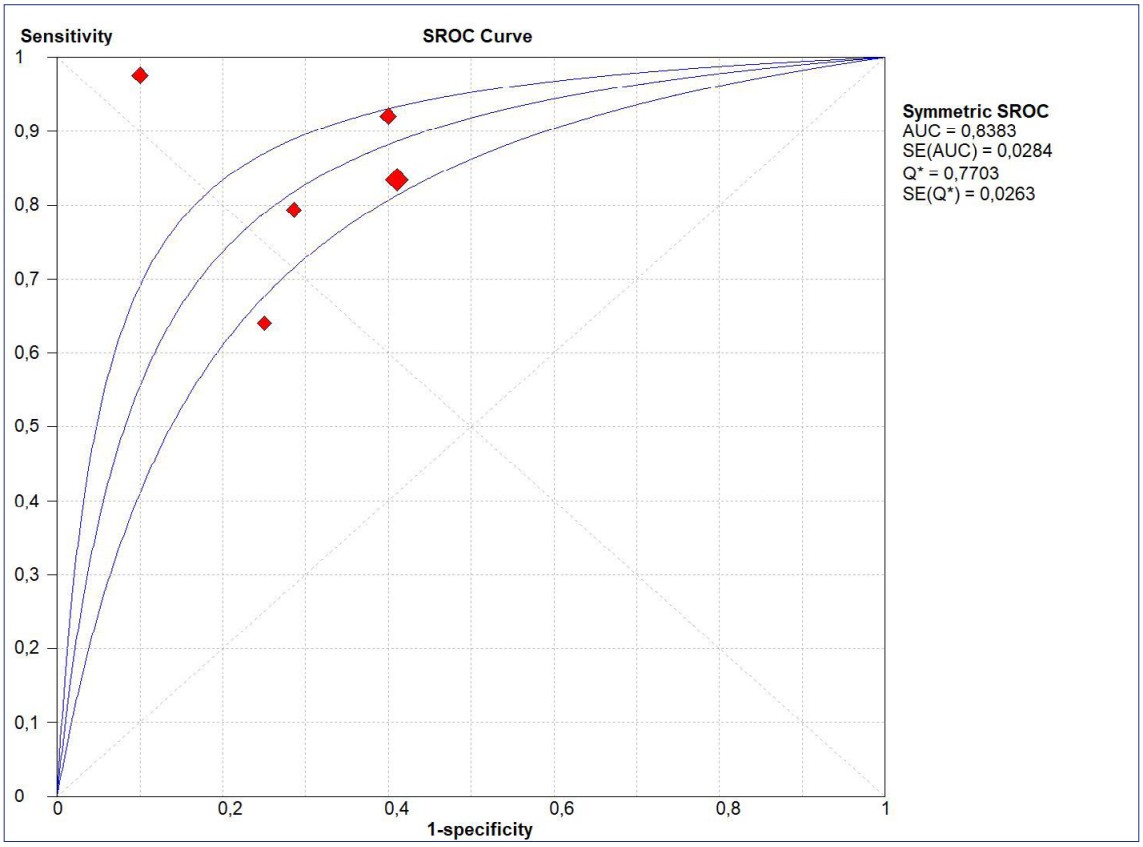


FIGURE 07: DIAGNOSTIC ACCURACY OF COMPUTED TOMOGRAPHY



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