■ REVIEW

Systematic Review and Meta-Analysis of Diagnostic Accuracy of ^{18}F-FDG PET in Suspected Recurrent Head and Neck Cancer

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Objectives: A meta-analysis of the literature was performed in this article in order to evaluate the diagnostic accuracy of ^{18}F-FDG PET in suspected recurrent head and neck cancer.
Material and methods: A systematic review of the literature was performed using 1987 to 2007 MEDLINE and CANCERLIT databases, applying selection criteria to the studies found. Sensitivity, specificity, positive and negative likelihood ratios, and odds ratio were calculated. The diagnostic accuracy was evaluated with ROC (receive-operating-characteristics) curves.
Results: Nineteen articles were included in the meta-analysis. Sensitivity of ^{18}F-FDG PET was 94%, specificity 80%, and the summary ROC curve showed a good trade-off between sensitivity and specificity.
Conclusions: ^{18}F-FDG PET was useful in patients with suspected recurrence of head and neck cancer, showing a high sensitivity and intermediate-high specificity.

Key words: ^{18}F-FDG PET. Head and neck tumours. Carcinoma of the head and neck. Recurrence. Meta-analysis.

Revisión sistemática y metaanálisis de la eficacia diagnóstica de la PET ^{18}F-FDG en recurrencia tumoral de cánceres de cabeza y cuello
Objetivos: En este trabajo se realizó un metaanálisis de la literatura para evaluar la exactitud diagnóstica de la PET ^{18}F-FDG en la sospecha de recurrencia de cánceres de cabeza y cuello.
Material y métodos: Inicialmente se realizó una búsqueda sistemática de la literatura en las fuentes MEDLINE y CANCERLITE hasta mayo de 2007, aplicando unos criterios de cribado a los estudios hallados. Se calcularon los valores de sensibilidad, especificidad, cocientes de probabilidad positivo y negativo y la *odds ratio* diagnóstica. El rendimiento diagnóstico se valoró mediante curvas ROC *(receive-operating-characteristic)*.
Resultados: Fueron incluidos 19 artículos en el metaanálisis. La sensibilidad de la PET ^{18}F-FDG fue del 94%, la especificidad del 80% y la curva ROC mostró una buena relación entre sensibilidad y especificidad.
Conclusiones: La PET ^{18}F-FDG fue útil en pacientes con sospecha de recurrencia tumoral por cáncer de cabeza y cuello; mostró una sensibilidad alta y una especificidad intermedia-alta.

Palabras clave: ^{18}F-FDG PET. Tumores de cabeza y cuello. Carcinoma de cabeza y cuello. Recurrencia. Metaanálisis.

INTRODUCTION

Many times diagnosing head and neck cancer recurrence is a complex process, even using all the diagnostic techniques within our reach. The changes produced in the tumour tissues following the treatments used (chemotherapy and/or radiotherapy) make evaluation by the traditionally used imaging tests difficult. Use of positron emission tomography (PET) with ^{18}F-FDG as a diagnostic imaging technique (used in Spain since 1995) that measures the tumour metabolism presents an interesting alternative in these situations. In order to know the usefulness of ^{18}F-FDG PET when tumour recurrence is suspected in patients with head and neck cancer we perform this study in which a systematic review of the

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published scientific literature was done, after using selection criteria on the articles found according to evidence based medicine (EBM) regarding quality and relevance, a meta-analysis was done in order to obtain statistical results that allow us to know whether or not ^{18}F-FDG PET proves to be useful in diagnosis head and neck tumour recurrence.

MATERIAL AND METHODS

The method followed in this review and meta-analysis is the following (outlined):

– Bibliography search strategy
– Study screening criteria
– Exclusion criteria
– Methodological quality criteria for diagnostic tests
– Statistical analysis of the relevant results from the selected articles

Search Strategy

We started with a systematic literature search that was done by 2 researchers, by access to the MEDLINE and SilverPlatter medical databases. The next step was to search for articles up to May 2007 without setting a start date since all published articles regarding the topic were included since they began. The following search words were used[2]: *(deoxyglucose OR desoxy-glucose OR fluorodeoxyglucose OR fludeoxyglucose OR fdg OR 18fdg OR f-18-dg OR fluoro-2-deoxy-d-glucose OR 2fluoro-2deoxyglucose OR fluoro-d-glucose OR PET OR Positron Emission Tomography) AND (head and neck cancer OR recurrent head and neck cancer OR recurrent carcinoma of the head and neck OR recurrent squamous cell carcinoma of the head and neck)* A large number of articles were found as a result of this search. At the Hospital de Móstoles (Madrid) a manual search was done of the magazines that had articles related to the topic. Also, through the article search service provided by that library, articles that were not available at that health centre were obtained from libraries in different hospitals and universities, both in Spain as in other countries. Recent conference and seminar information summaries were also reviewed, as well as abstracts presented at conferences that may have been published in such scientific magazines. By the same method, at the School of Medicine of the Universidad Complutense de Madrid and the Data Processing Centre, unpublished literature and bibliography were obtained: doctoral theses, doctoral works, etc.

Study Screening Criteria

First of all those works that did not have a title, in spite of their key search words, that was completely in-tune with the topic of this study. Generally speaking, the screening criteria took into account: *a)* patient characteristics (for example, age, gender, etc); *b)* pathological characteristics; *c)* technological aspects; *d)* methodological issues (for example, number of patients, follow-up duration, study design, etc); *e)* results measured; and *f)* publication types. The inclusion criteria set in the first preliminary phase were:

1. Studies published in any language, both complete articles published in quality magazines (meaning that they are cited by the Science Citation Index (SCI) or included in the MEDLINE database) as well as abstracts presented at conferences and that were published as such.
2. Studies providing primary data.
3. Studies with at least 12 ill patients.
4. Studies that evaluated the effectiveness and utility of ^{18}F-FDG PET in diagnosing suspected head and neck tumour recurrence.
5. Included the use of fluorodeoxyglucose (FDG) as a radiotherapy drug.
6. Included the use of dedicated PET cameras.
7. Specification of the reference trial used (pathological anatomy and/or clinical follow-up).

The exclusion criteria set in the first preliminary phase were:

1. Reviews.
2. Other radiotherapy drugs that were not FDG.
3. Duplicate articles or those phased out by subsequent studies (with the same level of hierarchy and with the same intent) from the same institution.
4. Dual-head coincidence gamma cameras (because they offer less diagnostic exactness and detection ability).
5. Articles that presented only one case.
6. Articles that included not enough information to be able to judge the: procedure protocol followed to obtain images, whether or not the analysis was visual or semi-quantitative, and clear statistical results regarding sensitivity and specificity.

After this first phase the researchers (JAPP, MNCM, and JLCD) contrasted the results obtained and gave their individual opinions regarding whether or not the inclusion criteria was applicable regarding the studies available in the literature. Once the literature was organized, the available references were once again researched regarding their relevance and the entire document was carefully analyzed. Then some studies were excluded (secondary exclusion) because they were not considered relevant or because their methods were deficient.

The conference abstracts were included only when the sensitivity and specificity objectives, methods, and results of the study were clear. These studies were included in the sensitivity and specificity analysis but not in the methodological quality analysis.

During a second step the quality of the selected works was critically evaluated.

Methodological Quality Criteria for Diagnostic Tests

The modified methodological quality criteria for diagnostic tests from Huebner, Gould, Owens et al[5] and Delgado's et al[6] were applied in order to analyze the selected articles.

These criteria comprised seven aspects: *a)* a description of the study design and patient selection criteria; *b)* characteristics of the population that was finally studied; *c)* indications for performing a ^{18}F-FDG PET; *d)* details of

Table 1. Methodological Quality Criteria for Diagnostic Imaging Tests[a]

Criterion 1: description of the study design and patient selection criteria
1. Study design
2. Patient selection criteria
3. Patient exclusion from the final study
Criterion 2: population characteristics
1. Age average, range, and gender
2. Concurrent diseases
3. Diabetes mellitus
4. Location of the recurrence
5. Special characteristics of the institution
Criterion 3: patient situation that leads to a PET being performed
1. Reasons for using the PET
2. Reasons for using the PET and correlation with the results
3. Spread of the disease, specified per patient
Criterion 4: details of the technology used during the study and characteristics of the image readings
1. Image techniques used in the study and resolution
2. Patient preparation
3. Fasting for at least 4 hours
4. Glucose levels prior to the FDG injection
5. Urinary catheter (with or without furosemide and IV hydration)
6. Correction of attenuation
7. Image meshing
8. Explanation of the general characteristics of the interpreting parties
9. Definition of a positive PET-FDG and a negative PET-FDG
10. Visual or semi-quantitative analysis
11. Additional scans
Criterion 5: confirmation of the final diagnosis
1. Final confirmation
2. Association between the specific PET findings and the final confirmation
3. Histopathological confirmation
4. Non-histopathological confirmation
5. Unconfirmed patients due to missing follow-ups
Criterion 6: sensitivity and specificity information
1. Description of PV, PF, NV, NF
2. Qualitative explanation of PF and NF
3. Specific area studied by the FDG-PET
4. Localization of the recurrence by FDG-PET
5. Confidence intervals
6. Erroneous findings of the FDG-PET
7. Information on patients and corresponding lesions
Criterion 7: information about changes in patient management
1. FDG-PET directly changes the management
2. FDG-PET is used to decide initial treatment
3. FDG-PET is used to decide the final treatment
4. 2 + 3 are both used
5. A correct or incorrect FDG-PET directly changes management of the patient
6. Increase or decrease in the stratification by the FDG-PET
7. FDG-PET in the patient management algorithm

[a]Adapted from Gould, Huebner, Owens, and Delgado.

the technological aspects and image interpretations; *e)* final diagnostic confirmation; *f)* sensitivity and specificity information; and *g)* information about changes in the way the patient is managed.

Table 1 shows the methodological quality criteria and the different aspects they include. A 4-point rating system was set-up that will allow us to evaluate compliance with each criterion and aspect: adequate (A), partial (P), non-referred (N), or non-applicable (N/A), all of which refers to the degree of exhaustiveness with which the article presented that aspect of the study. An "A" rating means that the aspect was described sufficiently and is in agreement with what we consider to be ideal. A "P" rating means a partial description of the aspect or partial compliance with the methodological section. An "N" rating is assigned when there is no reference to that aspect or it is not described at all in spite of the fact that it is considered relevant for the study's aims. Finally, a "N/A" rating was assigned when a study did not deal with the aspect of our criteria. It is important to clarify that the results of this analysis do not reflect the trustworthiness of the results presented, but instead the amount of available information and compliance with one of the methodological guides that we use as the ideal standard.

At least 2 experienced ^{18}F-FDG PET researchers (JAPP and MNCM) independently performed the methodological quality criteria compliance analysis. For those cases in which there was not 100% agreement among the researchers, a third researcher (JLCD) performed an analysis in order to reach a consensus.[7] The analysis of the studies by the researchers was not done blindly regarding authors, years, magazines, results, or name of the institutions.

In those studies that were finally selected for the meta-analysis, 2 types of studies or subgroups were set in order to assess heterogeneity factors. In the first subgroup classification was done, on one hand, of the studies in which ^{18}F-FDG PET was requested when recurrence was suspected, based on the physical finding and/or conventional imaging methods (type A), in comparison with those articles in which ^{18}F-FDG PET was done systematically during follow-up of patients with head and neck carcinomas, but without recurrence being evidently suspected (type B). The second subgroup was established in function of the analysis of the ^{18}F-FDG PET interpretation, taking into account if this was just visual (type I) or visual and semi-quantitative with an SUV (standardized uptake value) measurement (type II).

Statistical Analysis

In those studies of diagnostic test evaluation, each study is summarized according to the indices that describe the validity of the test. These are sensitivity, specificity, positive and negative probability ratios, and diagnostic odds ratio.

The sensitivity and specificity confidence intervals were calculated by the exact method for binomial ratios. The homogeneity of the positive and negative probability ratios and the diagnostic odds ratio was contrasted with Cochran's Q test. The probability and diagnostic odds ratios were grouped according to the DerSimonian Laird method (random effects model) in order to incorporate the variation between studies.

Table 2. Population Data Taken From the Articles Selected for the Meta-Analysis

Authors	*Total Patients, No.*	*Studied Patients, No.*	*PET, No.*	*Range Age*	*Mean Age*	*Males, %*	*Females, %*
Rege et al[9]	60	17	17	23-75	58	79	21
Anzai et al[10]	12	12	12	48-80	63	83	17
Greven et al[11]	31	31	31				
Fischbein et al[12]	44	35	36	30-82	59		
Chia-Hung et al[13]	36	36	36	18-67	44.7	66.6	33.3
Farber et al[14]	28	28	28				
Hanasono et al[15]	84	34	34				
Nowak et al[16]	71	30	26		61 (10)	69	31
Lowe et al[17]	44	30	30				
Lonneux et al[18]	44	44	44	39-80	57.5 (10.7)	88.6	11.4
Di Martino et al[19]	50	13	13		60.5	2	28
Li et al[20]	43	43	43				
Kresnik et al[21]	54	15	15		61.3	76	24
Wong et al[22]	143	143	181	13-91	59	67.8	32.2
Tsai et al[23]	28	28	28		48.9	78.5	21.5
Pasamontes et al[24]	30	30	34	15-76	58	73.3	26.7
Álvarez et al[25]	60	60	60	37-83	55	80	20
Cermik et al[26]	50	37	48	28-89	58	58.3	41.7
Total	912	666	716	13-91	56.8	74.4	25.6

In order to assess the diagnostic test performance based on the results of the studies analyzed we developed a summary ROC curve in the way described by Moses et al.[8] To explore sources of heterogeneity in the studies (meta-regression) the Moses-Shapiro-Littenberg method was used adding co-variables to the model.

RESULTS

Using the previously described search strategy a total of 1729 articles were found, from October 1967 to May 2007.

However, the first publication mentioning positron emission tomography appears in May 1987. This is why we eliminated articles published before that date, which were 47 in total. This way the total number of bibliographic references included in the review was left at 1682.

Then those articles that did not meet the abovementioned requirements were discarded, which is why 18 articles[9-26] were finally left for definitive evaluation. Only one conference abstract[27] met all the inclusion criteria.

All these 18 articles were from the MEDLINE search and in every case referred to patients who were diagnosed and treated for head and neck carcinoma and who, when faced with the suspicion of recurrence, underwent a positron emission tomography.

Characteristics of the Studied Population (Table 2)

Among all the articles selected a total of 912 patients were recorded, and of these, 666 were finally studied in the meta-analysis. These 666 patients underwent 716 PET studies.

The age range of the entire population studied was 13-91, with a mean age of 56.8. Of these 74.4% were male and 25.6% were female.

Methodological Quality Analysis

The methodological quality analysis of the studies did not include the conference abstract,[26] since the entire article was not available (because it was not a publication) its results were only taken into account for the statistical analysis. For those articles selected the percentages of the A, P, and N ratings given to each article were calculated. The interval of A rating fulfilment for each article was 45.2%-89.3%, with an average of 63.6%.

The average percent of P rating fulfilment for each article was 16.8% with a range of 3.4%-39.3%. The average fulfilment for N ratings of each article was 17.8%, with a range of 3.6%-29.4%. Compliance with the methodological quality guides for each article were considered to be high when the percent of A ratings was above 70%, acceptable when it was between 50% and 70%, and low when it was below 50%. When results were obtained from each one of the criterions, of the 18 selected articles, it was found that criteria 1, 3, and 5 showed a generally high fulfilment rate (>70%). Criterion

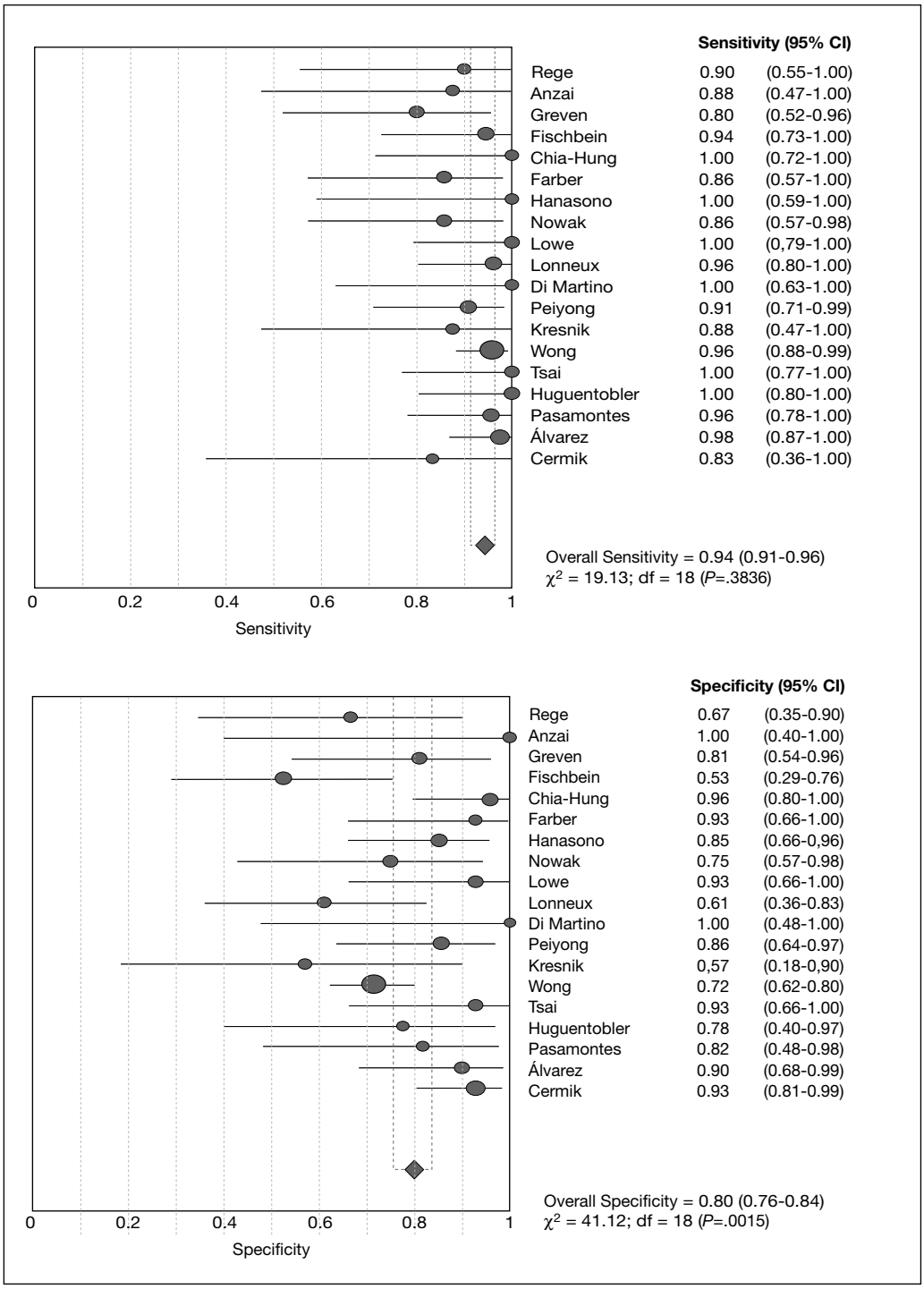

Figure 1. Sensitivity and specificity results in the studies selected for the meta-analysis of the literature.

1 (description of the study design and sample selection criteria) showed the highest rate of fulfilment (91.3%); criterion 3 (patient situation that leads to a ^{18}F-FDG PET being done) showed a fulfilment rate of 86.05%; and criterion 5 (confirmation of the final diagnosis), was at 88.8%. For the rest of the criteria the fulfilment rate was between 30.5% and 72.8%.

It stands out that the criterion that was least mentioned in all the articles was 2 (characteristics of the population finally studied), with an N rating of 56.9%. On another note, criterion 7, which refers to the information regarding the changes in how the patient was managed after undergoing the ^{18}F-FDG PET, was the one that had the most N/A ratings, at 72.2%.

Values Obtained From the Meta-Analysis

The global sensitivity of the ^{18}F-FDG PET in the 19 studies included in the meta-analysis was 94% (95% confidence interval, 91-96) with a range between 80 and 100. The global specificity was 80% (95% confidence interval, 76-84) with a

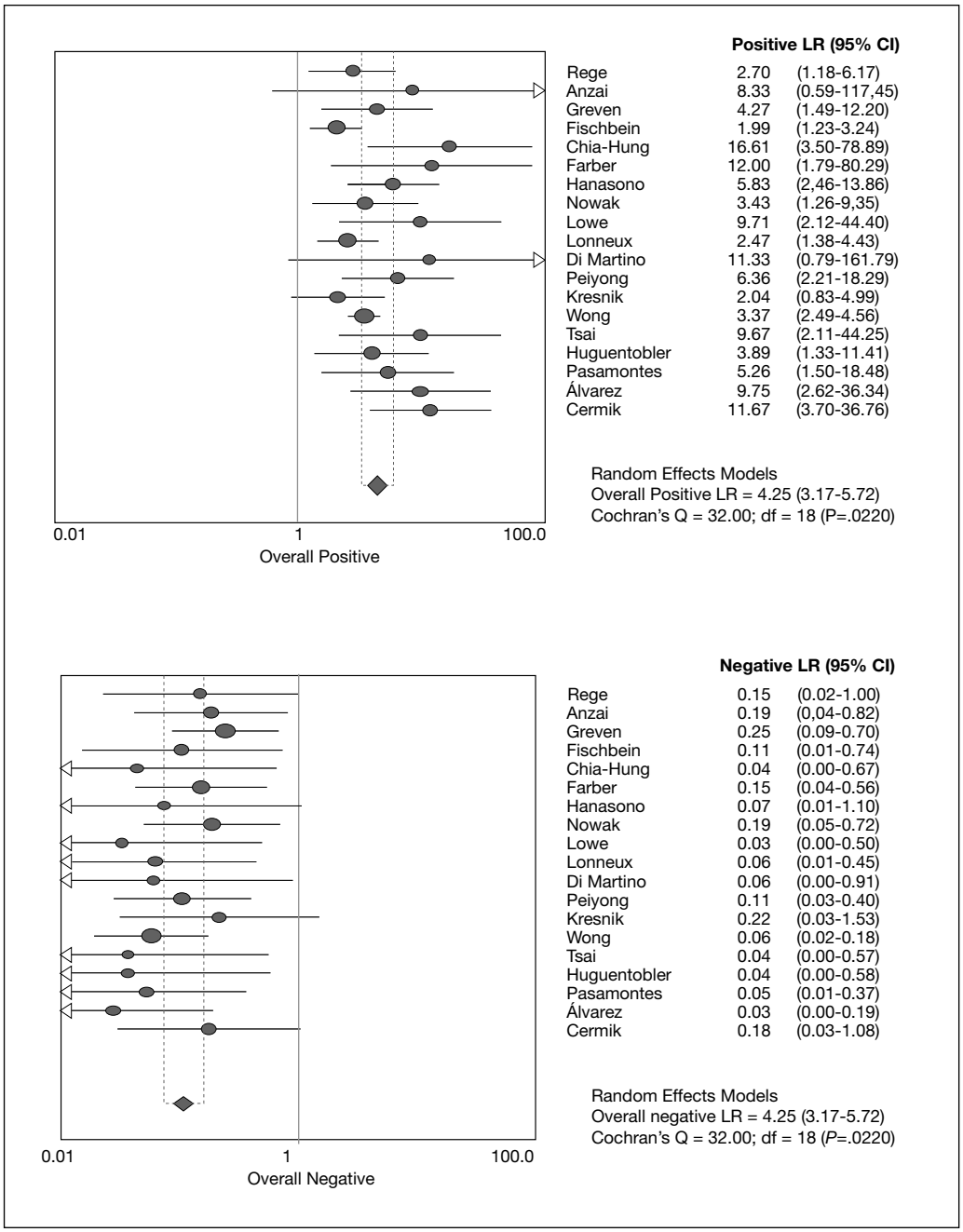

Figure 2. Positive and negative LR results of the meta-analysis studies.

range between 53 and 100. While evaluating the heterogeneity, both for the sensitivity and the specificity of the different studies, the χ^2 test showed a *P*=.383 for the sensitivity and a *P*=.001 for the specificity (Figure 1). Therefore, if we consider that there is heterogeneity when *P*<.05, this implies that, regarding sensitivity, there was global homogeneity among the studies and therefore the results could be used to reach a global sensitivity estimation. This was different with the specificity, where we got a *P*<.05 and therefore it showed that there was heterogeneity among the studies. Factors or subgroups were established (type I/II and A/B, found in the Materials and Methods section) within the articles analyzed to see if these could justify that heterogeneity.

This way, while performing the meta-regression (using the inverse variance weight) it was proven that those subgroups did not show a statistically significant difference, for which they did not influence the lack of homogeneity. A *P*=.33 value was obtained for the I/II subgroup and a *P*=.87 value was obtained for the A/B subgroup. In both cases, since *P*>.05, no significance was shown. The same thing occurred with the methodological quality analysis of the studies, where it turned out that this did not influence the heterogeneity (*P*=.03). A diagnostic odds ratio was calculated as a diagnostic test performance measurement tool. A global value of 51.68 (95% CI, 30.34-88.05) was obtained. The positive LR was 4.25 (95% CI, 3.17-5.72) and shows that a positive ^{18}F-FDG PET result leads to small

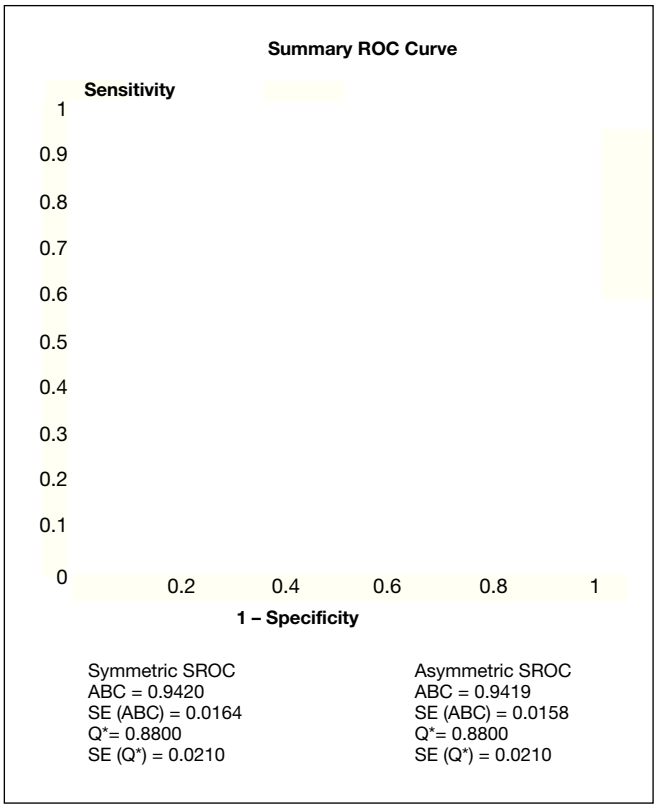

Figure 3. Summary ROC curve. The threshold used in most of the studies favoured sensitivity over specificity since most of the studies are situated at the top of the diagram.

changes in the pre-test probability. However, the negative LR was 0.11 (95% CI, 0.07-0.16) and shows that when the ^{18}F-FDG PET was negative it lead to moderate changes in the pre-test probability (Figure 2). The summary ROC curve shows a good link between the sensitivity and the specificity. This means that the variation or compensation between the sensitivity and the specificity was adequate, as the test threshold was changed (Figure 3).

DISCUSSION

The homogeneity observed in the sensitivity (and in its 95% CI) of the different types of studies lead to a global or joint effect being reached.[28] However, in the specificity, if heterogeneity among the studies appeared (*P*=.001), which may be justified by an elevated pre-test probability of tumour recurrence among the patients studied in the selected articles.

The best summary of the results of the studies is a ROC curve. The ROC curve obtained in the meta-analysis of the literature showed a good trade-off between sensitivity and specificity. A useful statistical piece of information, when studies are grouped together by the ROC curve, is the area under the curve (ABC), which summarizes the diagnostic performance in just 1 number. So that the perfect tests have an ABC close to 1 and the useless ones, close to 0.5. The ABC of our curve was 0.94, which is very close to 1, which means that we could state that the ^{18}F-FDG PET has a high diagnostic performance rate in diagnosing a suspected head and neck tumour recurrence. The diagnostic odds ratio showed that there is a significant positive link between tumour recurrence and a positive ^{18}F-FDG PET result, versus a negative result, which means that its contribution to diagnosis was significant. The positive LR showed small probability changes from pre-test to post-test, while a negative LR showed moderated changes. The results obtained mean that an ^{18}F-FDG PET may be useful in patients who are suspected of having a head and neck tumour recurrence. The ^{18}F-FDG PET presented an intermediate-high specificity and a high sensitivity, which shows that there are very little false negatives. This is something that is very important in managing oncology patients and may point to its usefulness in the initial phases of the diagnostic process.

The meta-analysis of the studies published on ^{18}F-FDG PET, in patients that are suspected of having head and neck tumour recurrence, provided the following conclusions:

In the first place, the methodological quality was high and the differences in quality of the studies were not correlated with the differences it their results.

In second place, there was homogeneity among the different types of studies seen, regarding the sensitivity, positive probability ratio, negative probability ratio, and the diagnostic odds ratio, which is why the results may be grouped together for a global or joint estimation.

In third place the specificity did present heterogeneity among studies, due to the high pre-test probability of recurring disease.

In fourth and last place, the diagnostic performance of the ^{18}F-FDG PET in diagnosing head and neck tumour recurrence suspicions, shown by the summary ROC curve, was high due the ABC being very close to 1.

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