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Роль магнитно-резонансной томографии в выявлении злокачественных лёгочных узлов: систематический обзор и метаанализ

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АННОТАЦИЯ

Цель — оценка возможности метода магнитно-резонансной томографии (МРТ) органов грудной клетки для выявления лёгочных узлов, подозрительных в отношении злокачественности, в сравнении с компьютерной томографией (КТ).

Материалы и методы. Проведён поиск в базах данных PubMed и Google Scholar за период до 7 апреля 2021 г. включительно. В соответствии с критериями соответствия были отобраны исследования, в которых проводилась оценка способности МРТ и КТ к выявлению лёгочных узлов, подозрительных в отношении злокачественности. Выбор метода анализа и группировки данных о чувствительности и специфичности выполняли по результатам оценки гетерогенности исследований. Для оценки статистической гетерогенности исследований, включённых в метаанализ, применяли критерий согласия Пирсона x^2 и индекс гетерогенности I^2.

Результаты. По результатам поиска было отобрано 168 работ, в метаанализ вошло 21 исследование. Отобранные работы включали 1188 пациентов. По результатам метаанализа выявлено наличие статистически значимой гетерогенности p <0,00001 по критерию x^2 и индекс гетерогенности I^2=99% для чувствительности и специфичности. В связи с этим для анализа данных использовали метод случайных эффектов. Значения чувствительности для МРТ находились в диапазоне от 70,4 до 100%, специфичности — от 60,6 до 100%.

Заключение. МРТ обладает достаточной чувствительностью и специфичностью для определения злокачественности лёгочных узлов, обнаруженных при КТ-диагностике.

Ключевые слова: магнитно-резонансная томография; лёгочные узлы; рак лёгкого; чувствительность; специфичность.

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Role of chest MRI for the diagnosis of malignant pulmonary nodules: a systematic review and a meta-analysis

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ABSTRACT

AIM: To evaluate the ability of magnetic resonance imaging (MRI) of the chest to detect malignant pulmonary nodules compared to compute tomography (CT).

MATERIALS AND METHODS: We searched the following databases with the final date of search on April 7th, 2021: PubMed, Google Scholar. We selected studies according to the inclusion and exclusion criteria that assessed the detection of malignant lung nodules by MRI and CT and included information about sensitivity and specificity. Method of the analysis and data grouping was chosen with regard to statistical heterogeneity of the studies included in the analysis. We used the x^2 test and I^2 statistic to evaluate the heterogeneity.

RESULTS: We selected 168 articles for the systematic review from the PubMed and Google Scholar databases. We included 21 studies on 1,188 patients in the meta-analysis and revealed statistically significant heterogeneity (p<0,00001 for x^2 test; I^2=99%) for sensitivity and specificity. Hence, we used a random-effect model for further analysis. As a result, values of sensitivity for detection of pulmonary nodules with MRI of 70.4%–100%, specificity — from 60.6% to 100%.

CONCLUSIONS: Thus, MRI has sufficient sensitivity and specificity for detecting malignant pulmonary nodules primarily discovered with CT.

Keywords: MRI; solitary pulmonary nodule; lung cancer; benign; malignant.

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磁共振成像在恶性肺结节检测中的作用 系统回顾和荟萃分析

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简评

目的是评估胸部MRT与CT检测肺结节的可能性，怀疑有恶性肿瘤。

材料与方法。截至 2021 年 4 月 7 日（含） 进行了 PubMed 和 Google Scholar 数据库 根据资格标准，选择了评估 MRI 和 CT 识别可疑恶性肺淋巴结能力的研究。 分析方法的选择和敏感性和特异性数据的分组是根据评估研究异质性的结果进行的。 为了评估荟萃分析中包括的研究的统计异质性，使用了 Pearson χ2 拟合检验和 I2 异质性指数。

结果。根据检索结果，筛选出 168 项研究，21 项研究纳入荟萃分析。 入选作品包括 1188 名患者。 根据 χ^2 标准和异质性指数 I^2 = 99% 的敏感性和特异性，荟萃分析显示存在统计学上显着的异质性 p <0.00001。 对此，采用随机效应的方法对数据进行分析。 MRT 的灵敏度值范围从 70.4 到 100%，特异性 - 从 60.6 到 100%。

结论。因此，MRI 具有足够的敏感性和特异性来确定 CT 诊断中发现的肺淋巴结的恶性程度。

关键词：磁共振成像； 肺结节； 肺癌; 灵敏度; 特异性。

引用本文

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BACKGROUND

The solitary pulmonary nodule (SPN) is a single, delimited, rounded lesion with a diameter of <3 cm [1, 2]. SPN is completely surrounded by unchanged pulmonary tissue and is unrelated to atelectasis, the root of the lung, or mediastinum. This mass could be caused by benign processes such as hamartoma, infectious lesions, granulomatous inflammation, or malignant processes (primary lung cancer, metastatic disease, or lymphoma). Malignancy of nodules is assumed until proven otherwise [2].

Currently, computed tomography (CT) is the gold standard for assessing SPN and monitoring patients who are at risk of cancer [3]. CT, despite its many advantages, has a major disadvantage: high radiation exposure, which certainly increases in dynamic monitoring. With the development and improvement of hardware and software, the search for new alternative visualization methods becomes evident. Over the last two decades, research into the potential use of magnetic resonance imaging (MRI) for the diagnosis of chest diseases has resulted in a separate research area devoted to SPN detection by MRI. The advantage of MRI is the lack of ionizing radiation exposure and the optional quantitative assessment of the revealed changes even without the use of contrast agents.

The aim of the study was to compare the capabilities of chest MRI to standard CT for detecting malignant SPN.

METHODS

This work was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard [4].

Study type

Inclusion criteria:

- (I) Prospective case-control studies, retrospective case-control studies, prospective cohort studies, and retrospective cohort studies;
- (II) Studies that included a description of the use of MRI to detect malignant SPN;
- (III) CT as the reference method; and
- (IV) Availability of sensitivity and specificity data.

Exclusion criteria:

- (I) The full text of the paper was not available.
- (II) The study did not involve humans.
- (III) The study involved children.
- (IV) Case reports, case series studies, systematic reviews, and meta-analyses.
- (V) Combination of positron emission tomography (PET) and CT (PET/CT) or PET and MRI (PET/MRI); contrast-enhanced studies.
- (VI) Involvement of patients with pulmonary tuberculosis and other inflammatory lung diseases.

Participants

Patients over 18 years of age.

The review excluded patients for whom diagnostic data could not be obtained using standard reference methods (standard chest CT).

Interventions

Studies that assessed the ability of MRI and standard CT to detect SPN suspicious for malignancy.

Results

Primary results: numerical values of lung MRI sensitivity and specificity to assess the detection of malignant SPN.

Secondary results: identification of the most optimal MR pulse sequences.

Sources of information

The databases PubMed and Google Scholar were searched until April 7, 2021.

Search

Since PubMed takes approximately a month to assign the term MeSH to a published paper, two types of queries were used in the PubMed database, that is, MeSH library terms and keywords to search among recent articles:

"Magnetic Resonance imaging" [Mesh] or "MRI" and "Computed tomography" or "CT" and "Lung neoplasms" [Mesh] or "Solitary Pulmonary Nodule" [Mesh] and "Sensitivity" and "Specificity";

"Lung MRI" or "chest MRI" and "Computed tomography" or "CT" and "lung cancer" or "Solitary Pulmonary Nodule".

The query "MRI, CT, lung cancer, specificity, sensitivity" was used to search in the Google Scholar database.

Data collection and data items

Using the Google Spreadsheet service, a data extraction table was created. The authors had simultaneous and unrestricted access to the document. The following data was extracted from the selected papers by two researchers (O.Yu. Panina and Ye.A. Grik): title of the article, journal (or service for posting preprints), publication date, DOI, MRI protocol, MRI magnetic induction value, types of lesions revealed, sensitivity, specificity, and standard deviation for MRI and CT. After calculating the sensitivity and specificity indicators for each pulse sequence (PS) separately, the most effective values were included in the meta-analysis.

Three other researchers (E.S. Akhmad, Yu.N. Vasilyeva, and Yu.A. Vasilyev) verified the extracted data. All disagreements were resolved through discussion among the authors.

Risk of bias in selected studies

The authors used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) checklist [5], which is recommended by the Agency for Healthcare Research and Quality (Cochrane Collaboration, US) for systematic reviews. Each of

the selected papers was assessed based on four domains: patient selection, index test, reference test, and patient flow. For a detailed description of each domain and the judgment of the criteria used, see the *Cochrane Handbook for Systematic Reviews of Interventions* [6].

Statistical analysis

The selection of method for analyzing and grouping sensitivity and specificity data (random- or fixed-effects model) was performed according to the results of the study heterogeneity assessment. The x^2 criterion and I^2 heterogeneity index were used to assess the statistical heterogeneity of the studies included in the meta-analysis. In the studies, statistically significant heterogeneity corresponds to $p < 0.10$ in the x^2 criterion and $I > 40\%$. Moreover, meta-analysis was performed using the RevMan 5.4.1 software package.

RESULTS

Based on search results in the PubMed and Google Scholar databases, 168 selected papers were imported into the Mendeley Reference Manager software library. Following a second check for inclusion and exclusion criteria and text review, 33 papers remained (Fig. 1).

A text review of the remaining 33 papers [7–38] revealed that two studies performed contrast-enhanced CT [23, 24], which is not an appropriate type of intervention. Furthermore, the sensitivity and specificity data for CT were completely absent in ten papers [20–22, 25–29, 31, 32], so these studies were excluded. The meta-analysis included papers in which a low-dose CT was used as a control study [9, 10, 16] rather than an exclusion criterion. Thus, the meta-analysis included 21 studies (see Fig. 1).

The selected studies included 1188 patients and contained information on lung MRI and CT scans. Sensitivity data for MRI and CT were presented in all papers; however, specificity rates were not reported in three articles [8, 16, 30]. The majority of the studies were performed on tomographs with magnetic field induction of 1.5 T (Table. 1).

Risk of bias

Eleven studies adequately reported the index test and reference test data [7, 8, 10–13, 15–18, 33]. The primary sources of errors were the index test (MRI) and its interpretation (Fig. 2). Some studies lacked complete data to assess the risk of bias, for example, whether the index test results were interpreted without knowing the results of the reference test, or whether interpretation of the reference test was impossible without knowing the results of the index test. Moreover, the risk of bias was characteristic of studies that were more likely to be published if an effect was found as opposed to those that did not. However, participants in all studies met the protocol criteria for this review.

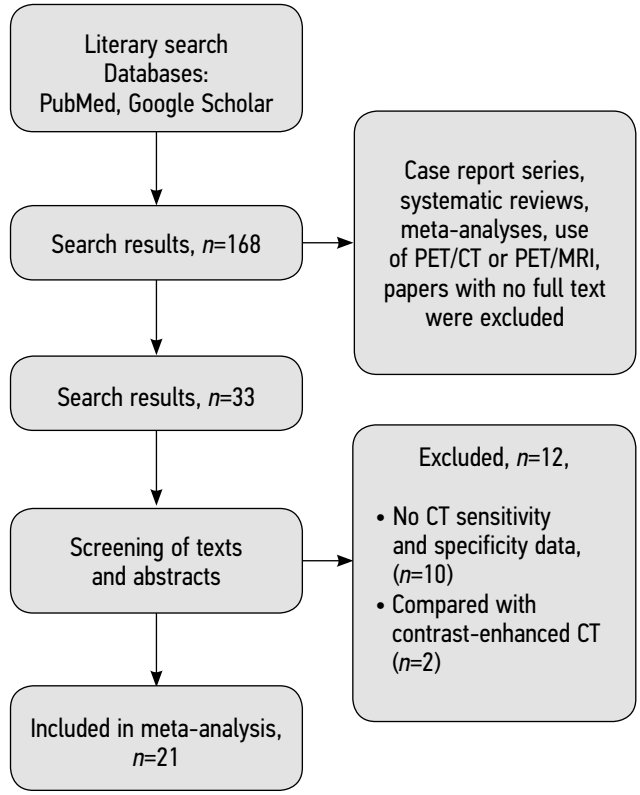

Fig. 1. Flow diagram

The meta-analysis revealed statistically significant heterogeneity ($p < 0.00001$) using the x^2 criterion and the heterogeneity index ($I^2=99\%$) for sensitivity and specificity. In this case, the random-effects method was used to analyze the data.

Diagnostic accuracy of chest MRI

In each of the 21 studies, MRI was compared to the reference method. Sensitivity for MRI ranged from 70.4% to 100%, while the specificity ranged from 60.6% to 100% (Fig. 3). The mean MRI sensitivity was 88.3%, while the mean MRI specificity was 71.3%. In studies where the standard deviation parameters for sensitivity and specificity were not specified, the calculation was performed by estimating the values of the indicators [40].

Table 2 shows the characteristics that were included in the meta-analysis of studies with the highest sensitivity and specificity values for MRI, which are comparable to CT.

DISCUSSION

The results of this meta-analysis show that MRI has lower mean specificity and sensitivity when compared to CT. In the majority of studies included in the meta-analysis, the sensitivity and specificity of chest CT for detecting SPN was 100%. Since CT was used as a reference test, only three studies had lower rates. For chest MRI, 5 of the 21 studies had 100% sensitivity, and only 2 studies had 100% sensitivity and specificity.

Table 1. Characteristics of studies included in the meta-analysis

No.	Studies	Year	Magnetic field induction, T	MRI model and manufacturer	MRI PS
1	Both [7]	2005	1,5	Magnetom Vision, Siemens	VIBE, HASTE, T2TSE
2	Bruegel [8]	2007	1,5	Magnetom Sonata, Siemens	STIR
3	Chang [19]	2015	1,5	Intera Achieva, Philips	SS-TSE-HF
4	Cieszanowski [30]	2016	1,5	Magnetom Avanto, Siemens	T2TSE, T2-STIR, T2-HASTE
5	Dewes [33]	2016	3,0	Magnetom Prisma, Siemens	CAIPIRINHA-VIBE
6	Fatihoğlu [34]	2019	1,5	Magnetom Aera, Siemens	DWI (ADC)
7	Heye [35]	2012	1,5	Avanto, Siemens	VIBE, HASTE
8	Huang [39]	2020	1,5	Magnetom Aera, Siemens	UTE free-breathing
9	Koo [36]	2019	3,0	Magnetom Skyra, Siemens	T2FSE
10	Koyama [37]	2008	1,5	Intera, Philips	STIR
11	Koyama [38]	2015	1,5	Achieva, Philips	DWI (ADC)
12	Meier-Schroers [9]	2016	1,5	Ingenia, Philips	T2FSE
13	Meier-Schroers [10]	2019	1,5	Ingenia, Philips	T2STIR
14	Ohno [11]	2017	3,0	Vantage Titan, Canon Medical Systme	UTE
15	Regier [12]	2011	1,5	Achieva, Philips	DWI (ADC)
16	Satoh [13]	2008	1,5	Intera NovoDual, Philips	DWI (ADC)
17	Schaefer [14]	2006	1,0	Magnetom Expert, Siemens	PDWI
18	Schroeder [15]	2005	1,5	Magnetom Sonata, Siemens	HASTE
19	Sommer [16]	2014	1,5	Magnetom Avanto, Siemens	HASTE
20	Vogt [17]	2004	1,5	Magnetom Sonata, Siemens	HASTE
21	Yi [18]	2007	3,0	Achieva, Philips	T1WI 3D TFE*

Note. MRI PS: pulse sequences of magnetic resonance imaging

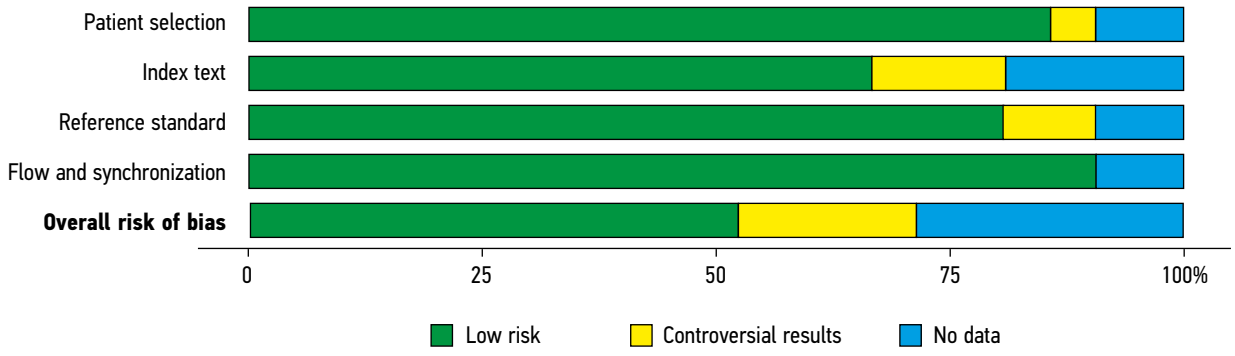

Fig. 2. Histogram of the risk of bias

When the results of the meta-analysis were examined, high sensitivity rates were observed in studies that calculated overall sensitivity and specificity rates for the entire MR protocol rather than separately for each PS (see Table 2). This phenomenon demonstrates the peculiarity of the meta-analysis for MRI as a method in which the signal characteristics are assessed in conjunction with the scanning protocol. These examples may indicate a lack of research into MRI capabilities in the differential diagnosis of SPN, the need for studies of current PS, and the careful tuning of routine PS on a tomograph. This approach will allow for greater MRI efficiency in detecting SPN and studying their characteristics, which is especially important in lung cancer diagnosis.

Lung cancer continues to be the leading cause of death worldwide, including in the Russian Federation, and it is a serious social and economic problem [41, 42]. The presence of cancer among detected SPN ranges from 10% to 70% [2]. In some countries, low-dose CT is performed in high-risk groups as part of screening.

Currently, the coverage of the screening program remains low, and the criteria for inclusion of patients are limited to ensure its economic viability. Thus, many patients will still be diagnosed after the onset of symptoms, rather than at an early stage of disease development and at a high cost of misdiagnosis [41]. Furthermore, radiologists and clinicians continue to face difficulties in monitoring and managing ambiguous SPN. Accordingly, only a comprehensive approach is always used for diagnosis, patient routing, and selection of optimal management and treatment strategies [43].

This meta-analysis revealed an alternative approach for assessing SPN that are suspicious for cancer. In addition, the emphasis was on standard studies that did not make use of contrast enhancement.

Limitations

There were several limitations to this study. For various reasons, the meta-analysis included data with lesions larger than 6 mm. First, nodule sizes greater than 6 mm are the most common in selected studies; second, nodules smaller than 6 mm have a fairly low risk of malignancy according to recent data from Fleischner Society [3]. In addition, the meta-analysis did not compare MRI with histologic data, which could be considered a limitation of the study.

CONCLUSIONS

MRI has the sensitivity and specificity needed for additional diagnosis of SPN that are suspicious for malignancy

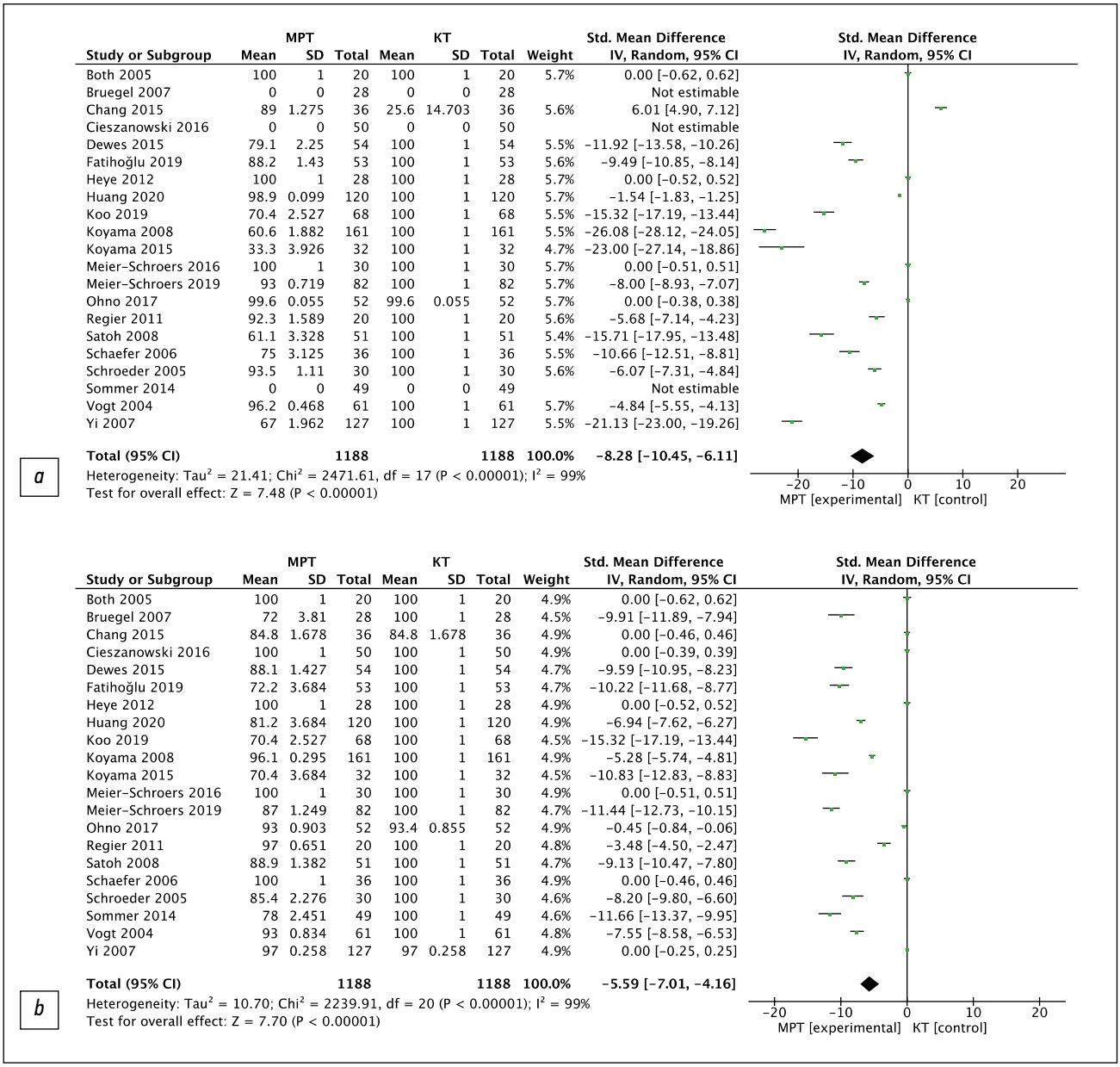

Fig. 3. Forest plot of grouped data for specificity (*a*) and sensitivity (*b*) [40]

Note. SMD: standardized mean difference; CI: confidence interval

Table 2. Characteristics of studies with the highest sensitivity and specificity values

No.	Author, year of study	Sensitivity (general index)	Specificity (general index)	MRI PS	Magnetic field induction, T
1	Both, 2005 [7]	100	100	VIBE, HASTE, T2TSE	1,5
2	Cieszanowski, 2016 [30]	100	-	T2TSE, T2-STIR, T2-HASTE	1,5
3	Meier-Schroers, 2016 [9]	100	100	T2FSE	1,5
4	Regier, 2011 [12]	97	92,3	DWI (ADC)	1,5
5	Heye, 2012 [35]	100	100	VIBE, HASTE	1,5
6	Schaefer, 2006 [14]	100	75	PDWI	1,5

Note. MRI PS: pulse sequences of magnetic resonance imaging

and revealed by CT. The mean MRI sensitivity was 88.3%, while the mean MRI specificity was 71.3%.

MRI is a non-ionizing imaging method that can be used as an additional technique in the evaluation of various PS while resolving controversial cases.

Further research into the most efficient PS, the feasibility of contrast enhancement, and new technological solutions for high-quality diagnostics of SPN is necessary.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. Yury A. Vasilev — research concept, writing the manuscript, analysis and expert assessment of research results; Olga Yu. Panina — research concept, search for publications, processing of the results, writing the manuscript; Evgeniia A. Grik — search for publications, processing of the results, Kate A. Akhmad — processing of the results, systematization and final editing of the review; Yulia N. Vasileva — analysis and expert assessment of research results, systematization and final editing of the review. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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