Research Article

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Cancer diagnosis via fiber optic reflectance spectroscopy system: a meta-analysis study

Fiber optik yansıma spektroskopi sistemi ile kanser tanısı: Bir meta-analiz çalışması

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Abstract

Background: Reflectance spectroscopy, which is one of spectroscopic techniques, is an optical technique and has the potential to differentiate cancerous tissues from normal tissues. There are several studies which evaluate the diagnostic accuracy of this method in the literature.
Objective: The aim of this study is to assess the sensitivity and specificity of the fiber optic reflectance spectroscopy system in diagnosis of cancerous tissue via meta-analysis.
Materials and methods: In this meta-analysis paper, the literature search was conducted using the "PubMed" database as of 16-August-2018 last date. A total of 30 articles which the pathological evaluation was accepted as the gold standard were included in the meta-analysis, excluding the articles that were out of context and did not contain the required statistics.
Results: Overall sensitivity was 0.82; overall specificity was 0.84 and area under the summary receiver operating characteristic curve was 0.89 in differentiating cancerous from normal tissue by using fiber optic reflectance spectroscopy system. Overall diagnostic odds ratio was obtained as 29.42.
Conclusion: In this study, according to the results of meta-analysis conducted to evaluate the diagnostic accuracy of the fiber optic reflectance spectroscopy high overall sensitivity and specificity values were obtained in the detection of cancerous tissue.

Keywords: Fiber optic reflectance spectroscopy; Meta-analysis; Diagnostic test accuracy; Cancer diagnosis; Sensitivity.

Öz

Giriş: Spektroskopik tekniklerden biri olan yansıma spektroskopisi, optiksel bir teknik olup kanserli dokuları normal dokulardan ayırt etme potansiyeline sahiptir. Literatürde bu yöntemin tanısal doğruluğunu değerlendiren çalışmalar mevcuttur.
Amaç: Bu çalışmanın amacı, meta-analiz yoluyla fiber optik yansıma spektroskopisi sisteminin kanserli doku teşhisindeki duyarlılığını ve seçiciliğini değerlendirmektir.
Gereç ve Yöntem: Bu meta-analiz makalesinde literatür taraması, son olarak 16 Ağustos-2018 tarihi olmak üzere "PubMed" veri tabanı kullanılarak yapılmıştır. Kapsam dışı ve gerekli istatistikleri içermeyen makaleler hariç tutularak, patolojik değerlendirmenin altın standart olarak kabul edildiği toplam 30 çalışma meta-analize dahil edilmiştir.
Bulgular: Fiber optik yansıtma spektroskopi sistemi kullanılarak kanserli dokuların normal dokudan ayırt ediciliğinde genel duyarlılık 0.82, genel seçicilik 0.84 ve özet receiver operating characteristic eğrisi altındaki alan 0.89 olarak belirlendi. Genel tanı odds oranı 29.42 olarak elde edildi.
Sonuç: Bu çalışmada, fiber optik yansıma spektroskopisinin tanısal doğruluğunu değerlendirmek için yapılan meta-analiz sonuçlarına göre, kanserli dokunun saptanmasında yüksek genel duyarlılık ve seçicilik değerleri elde edildi.

Anahtar kelimeler: Fiber optik yansıma spektroskopisi; meta-analiz; tanısal test doğruluğu; kanser tanısı; duyarlılık.

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Introduction

Nowadays besides histopathological evaluation, biomedical tools which based on optical techniques are being developed that can provide real time evaluation and objective results for the diagnosis of cancerous tissues in the clinical practice. Fiber optic reflectance spectroscopy technique is one of these tools and it is very important that the accuracy which is able to differentiate the cancerous and healthy cases correctly (sensitivity and specificity) for diagnosis of cancerous tissues should be high. The interaction of light inner tissue has been used to detect cancer for years and which is quantitatively measuring with improving spectroscopic devices. Because of the scattering properties of tissues, the reflected light is often influenced by changes in morphology in tissue. Since diagnosing of cancerous tissue is very important and when the literature is examined to determine the diagnostic accuracy of biomedical tools, there are many scientific studies which are investigating the accuracy, sensitivity and specificity of the method to diagnose of cancerous tissue.

By using systematic reviews and meta-analysis of the diagnostic accuracy is an important part of the evidence-based medicine and is increasing progressively. There are three main aims of meta-analysis for the accuracy of diagnostic test: (1) obtaining much more valid generalized summary values of the diagnostic accuracy of the test used, (2) providing information about the factors affecting the accuracy of the diagnostic test, (3) defining areas for future studies [1, 2]. The aim of presented study is to assess sensitivity and specificity of fiber optic reflectance spectroscopy technique for diagnosing of cancerous tissue via meta-analysis.

Materials and methods

In this meta-analysis study, the literature search was conducted using the "PubMed" database as of 16 August 2018 last date. As a result of scanning 575 articles have been reached by using the keywords "cancer or dysplasia or hyperplasia", "tissue or patient", "sensitivity", "reflectance or light scatter or fiber optic probe". Of them; all cases involving animal experiments, case reports, reviews, compilations, letters; in the key word and abstract, researches involving image, nanoparticle, drug, confocal microscopy, Raman, laser and fluorescence words which were excluded from the study. The full text of the remaining 54 study has been reviewed. A total of 30 articles which the pathological evaluation was accepted as the gold standard were included in the meta-analysis, excluding the articles that were out of context and did not contain the required statistics [3–32] (Table 1, Figure 1).

Descriptive statistics

Descriptive statistics were obtained as a first step in the accuracy of the diagnostic test meta-analysis. For each study, forest plots were drawn by calculating the sensitivity and specificity values and diagnostic odds ratio (DOR) [2]. DOR is the ratio of odds of the disease in the positive test result to the in the negative test result. DOR takes value from 0 to infinity in which higher values show that the discrimination of the test is good, while the value of 1 indicates that the test does not discriminate between patients with the disease and those without it [33]. In forest plot x-axis shows any descriptive statistics such as sensitivity, specificity with 95% confidence interval, while y-axis includes studies identifier in the Diagnostic Test Accuracy (DTA) meta-analysis. The generic inverse variance method is used to calculate 95% confidence intervals of descriptive statistics [2]. In addition, a summary Receiver Operating Characteristic Curve (ROC) descriptive plot which displays the summary of the individual studies can be obtained [1]. This plot includes 95% confidence region, and the false positive rate appears in x-axis and the sensitivity of the studies appears in y-axis. In addition a summary ROC curve is obtained as a result of meta-analysis [34].

Assessment of heterogeneity

The second step of the DTA meta-analysis is the assessment of heterogeneity which indicates variability across studies [2]. Heterogeneity can come to exist randomly by errors in analytical methodology; and/or by differences in study design, protocol, inclusion and exclusion criteria and diagnostic thresholds [35]. The threshold effect is the most important source of heterogeneity in DTA studies [1]. Studies that evaluate the DTA can use the same test but with different threshold values. Therefore, the accuracy of the diagnostic test depends on the threshold value that classifies the positive and negative test results in the study [2].

From a meta-analytical viewpoint, if studies use different threshold to describe test results, the summary statistics of these studies will also vary depending on the criteria used. Hence, heterogeneity among study results could be observed. There are several ways to determine

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Table 1: Sensitivity, specificity and diagnostic odds ratio (DOR) values with given method and apparatus of selected 30 articles.

No	Study	Year	Sample size (Case/Control)	Cancer type	Measurement	Apparatus				SENS	SPEC	DOR
						Spectrometer	LS	FD	FG			
1	Bailey	2017	28/28	Oral Cavity	In-vivo	PI Acton SpectraPRO SP-2356	TH	Each 100 μm	Multiple (11)	0.986	0.988	5865.00
2	Turhan	2016	73/22	Larynx	Ex-vivo	USB2000	TH	100 μm	Single	0.845	0.978	244.57
3	Lay	2016	32/153	Prostate	Ex-vivo	USB2000+	TH	Each 100 μm	Multiple (2)	0.894	0.938	128.20
4	Denkçeken	2016	12/83	Lymph	Ex-vivo	USB2000	TH	100 μm	Single	0.962	0.958	575.00
5	Werahera	2016	78/109	Prostate	Ex-vivo	PMT	XA	–	Multiple (8)	0.690	0.732	6.07
6	Morgan	2016	11/22	Prostate	Ex-vivo	USB2000+	TH	Each 200 μm	Multiple (2)	0.792	0.848	21.17
7	Sircan	2015	12/12	Prostate	Ex-vivo	USB2000	TH	100 μm 200 μm 400 μm	Single Single Single	0.962	0.577	34.09
8	Mutyal	2015	9/20	Pancreas	In-vivo	USB2000+	TH	50 μm (D1) 60 μm (LS) 70 μm (D2) 160 μm (D3)	Multiple (4)	0.750	0.833	15.00
9	Hu	2014	51/198	Head and Neck	In-vivo	USB4000	TH	Each 400 μm	Multiple (2)	0.683	0.817	9.58
10	Tabrizi	2014	17/150	Cervix	In-vivo	AVASPEC-2048-USB2	TH	800 μm	Single	0.639	0.679	3.74
11	Rosen	2014	66/127	Thyroid	Ex-vivo	S2000	TH	Each 200 μm	Multiple (2)	0.813	0.848	24.26
12	Baykara	2014	14/31	Prostate	Ex-vivo	USB2000	TH	100 μm	Single	0.833	0.953	101.67
13	Evers	2013	435/393	Liver	Ex-vivo	DU420A-BRDD	TH	Each 200 μm	Multiple (3)	0.942	0.940	253.80
14	Evers	2013	241/480	Breast	Ex-vivo	DU420A-BRDD	TH	Each 200 μm	Multiple (3)	0.899	0.878	64.12
15	Denkçeken	2013	16/89	Cervix	Ex-vivo	USB2000	TH	100 μm	Single	0.912	0.461	8.84
16	Evers	2012	18/14	Lung	Ex-vivo	DU420A-BRDD	TH	Each 200 μm	Multiple (3)	0.763	0.833	16.11
17	Garcia	2012	30/377	Skin	In-vivo	CCD camera	TH	100 μm (3, LS) 200 μm (12, D)	Multiple (15)	0.952	0.933	271.86
18	Upile	2012	510/147	Skin	In-vivo	CCD	XA	400 μm (LS) 200 μm (D)	Multiple (2)	0.778	0.801	14.07
19	Canpolat	2011	15/13	Skin	In-vivo, Ex-vivo	USB2000	TH	100 μm	Single	0.844	0.821	24.84
20	Suh	2011	15/21	Thyroid	Ex-vivo	S2000	XA	200 μm (LS) 200 μm (D)	Multiple (2)	0.719	0.932	34.93
21	Tery	2011	13/159	Barrett's Esophagus	In-vivo	SP 2150i	LED	400 μm (LS) 400 μm (D)	Multiple (2)	0.964	0.841	142.41
22	Lin	2010	27/32	Brain	In-vivo	USB2000	TH	300 μm (LS) 300 μm (6, D)	Multiple (7)	0.946	0.652	33.03
23	Zysk	2009	18/40	Breast	In-vivo	SU1024LE-1.7T1-0500	NIR Laser Diode	200 μm	Single	0.605	0.598	2.28
24	Mourant	2009	58/80	Cervix	In-vivo	CCD	TH	200 μm (2, LS) 200 μm (4, D)	Multiple (6)	0.771	0.685	7.34
25	Roy	2008	10/86	Colon	Ex-vivo	CCD	XA	–	–	0.591	0.925	17.89

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Table 1 (continued)

No	Study	Year	Sample size (Case/Control)	Cancer type	Measurement	Apparatus				SENS	SPEC	DOR
						Spectrometer	LS	FD	FG			
26	Nieman	2008	22/13	Oral Cavity	In-vivo	PAD	XA	200 µm (LS) 200 µm (2, D)	Multiple (3)	0.848	0.607	8.61
27	Turzhitsky	2008	44/159	Pancreas	Ex-vivo	CCD	XA	–	–	0.722	0.891	21.17
28	Liu	2007	19/32	Pancreas	Ex-vivo	CCD	XA	–	–	0.925	0.894	103.95
29	Palmer	2006	17/24	Breast	Ex-vivo	PMT	XA	Each 200 µm	Multiple (31)	0.806	0.900	37.29
30	Wallace	2000	12/52	Barrett's Esophagus	In-vivo	–	XA	200 µm (LS) 200 µm (6, D)	Multiple (7)	0.885	0.896	66.21

CCD, Charge coupled device; D, detector; FD, fiber diameter; FG, fiber geometry; LS, light source; NIR, near-infrared; SENS, sensitivity; SPEC, specificity; PAD, photodiode array detector; PMT, photomultiplier tube; TH, tungsten halogen; XA, xenon arc.

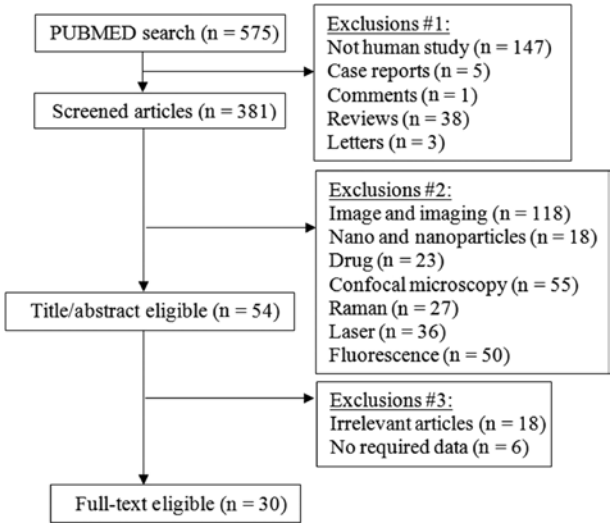


Figure 1: The flow diagram for study selection.

if the threshold effect exists or not. One of these is to examine the forest graphics plotted for sensitivity and specificity. If there is a threshold effect, it will show a descending order of specificity values versus ascending order of sensitivity values. Therefore, the overall view of the coupled forest plot will have a "V" or an "inverted-V" shape. It can be assessed by linear correlation between sensitivity and false positive rate. If linear correlation exists between these two statistics, with a correlation coefficient of 0.6 or higher, it can be regarded as the threshold effect is present. Another way exploring threshold effect is to overview the summary ROC curve plot. In the existence of threshold effect, circles in the plot will have a curvilinear distribution in the ROC space from the left lower part to the right upper part, which shows also convexity to the left upper corner of the plot. Consequently, if existence of a threshold effect is confirmed, using bivariate model or Hierarchical Summary ROC (HSROC) model is appropriate to summarize diagnostic accuracy [2, 34].

Cochran's Q test as or Higgins' I^2 statistic are generally used in assessing heterogeneity in the meta-analysis of interventional studies. For Q test a p value less than 0.10 or 0.20 or for I^2 statistic greater than 50% are accepted to indicate heterogeneity among the study results conventionally. In DTA studies, these statistics should be interpreted with caution because they do not consider a threshold effect. According to the Cochran Handbook for Systematic Reviews of Diagnostic Test Accuracy, the use of these statistics for the assessment of heterogeneity is not recommended in meta-analysis of DTA [2, 36].

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Assessment of publication bias

As in other meta-analysis studies in DTA meta-analysis, publication bias is an important threat to the validity of the study results and it should be examined absolutely [1]. In order to evaluate the publication bias in DTA meta-analysis, Deeks's funnel plot is used instead of the Begg or Egger tests used in meta-analysis of other study types. In this plot, x-axis shows the natural logarithm of the DOR, while y-axis shows the inverse of the square root of the effective sample size [37, 38]. Linear regression of lnDOR against the inverse of the square root of the effective sample size, weighting by the effective sample size, is evaluated. The effective sample size is obtained as $(4 \times ND \times D)/(ND + D)$, in which "ND" is non-diseased group and "D" is diseased group [37].

Selection of appropriate model

At the end of all these steps, meta-analysis is applied by selecting the most appropriate method. For example, if there is no heterogeneity between studies, the use of fixed-effects model is recommended. When data are heterogeneous random-effects meta-analysis methods are recommended, which focus on obtaining an estimate of the average accuracy of the test, and describing the variability in the effect. It is presumed that heterogeneity exist so random-effects models are fitted by default in DTA reviews [39]. It has been proposed to decide which random-effects model should be used by considering whether there is a threshold effect [1]. If studies have reported different threshold values for test positivity, a hierarchical summary ROC model is proposed. If similar threshold values are reported the use of bivariate model meta-analysis is recommended [1].

In this study, a meta-analysis was performed to evaluate the sensitivity and specificity of a diagnosis method by using "mada" package in the R program [40]. Forest plots of sensitivity and specificity were obtained using true positive, false negative, false positive and true negative numbers. DORs were calculated and plotted by forest plot. A summary ROC curve plot was used to assess whether the threshold effect exists or not. Deeks' funnel plot and test were used to assess the publication bias. SPSS 23v. was used for plotting Deek's funnel plot [41]. Bivariate random-effects model was used for DTA meta-analysis and overall values of sensitivity, specificity and DOR were obtained.

Results

Descriptive statistics

Forest plots of sensitivity and specificity values of 30 studies are given in Figure 2A and B. Forest plot of DOR is given in Figure 2C. Overall DOR was obtained as 29.42 (95% confidence interval: 17.19-50.37).

Assessment of heterogeneity

To assess threshold effect which is the most probable source of heterogeneity in DTA meta-analysis summary ROC curve plot was used given in Figure 3A.

When the plot is viewed, studies do not show curvilinear distribution and is not also convex to the left upper corner of the plot. Besides, the linear correlation between sensitivities and false positive rates of the studies was assessed and no statistically significant correlation was found between them ($r = -0.141$; $p = 0.457$). These two results indicate that there is no threshold effect between studies.

Assessment of publication bias

Deek's funnel plot which assesses the publication bias is given in Figure 3B.

As a result of the weighted regression test for the asymmetry of the Deek's funnel plot p value was obtained as 0.636. It is concluded that the studies are asymmetric.

Appropriate model

As a result of the absence of threshold effect, the bivariate random-effects model is used to obtain the general values of sensitivity and specificity. Overall sensitivity value was found as 0.82 (95% confidence interval: 0.78–0.86); overall specificity value was found as 0.84 (95% confidence interval: 0.79–0.88). Area under the summary ROC curve was obtained as 0.89.

Discussion and conclusion

Fiber optic spectroscopy techniques have the potential to become an important biomedical optical tool for cancer diagnosis. Recently, significant improvement has been made in the discriminating abilities of these techniques between normal and cancer of various human tissues. The progression of cancer is correlated with important changes

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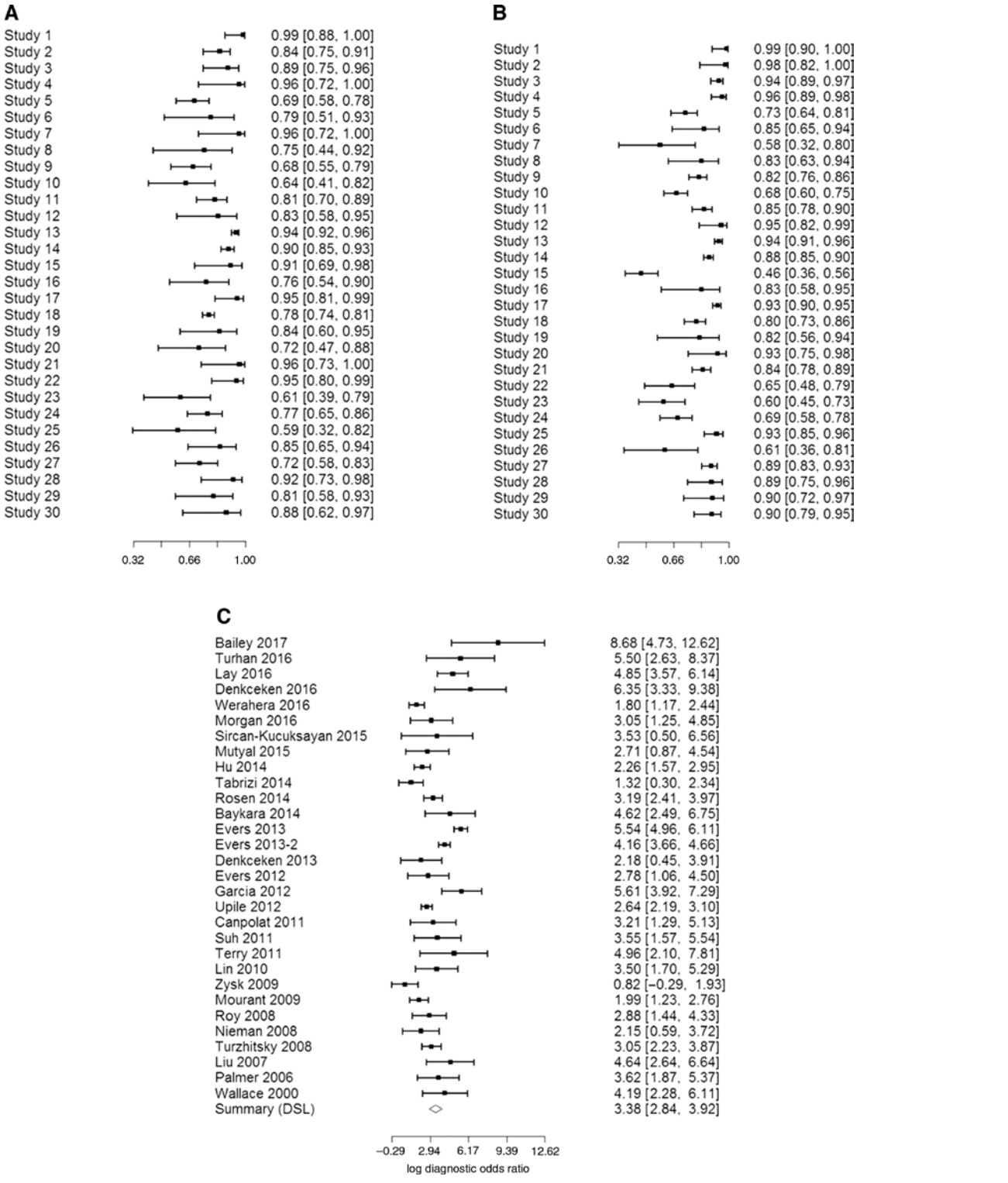


Figure 2: Forest plots of sensitivity and specificity values.
(A) Forest plot representing sensitivity values of all studies separately, (B) forest plot representing specificity values of all studies separately, (C) forest plot representing diagnostic odds ratio (DOR) values of all studies separately.

in tissue organization, composition and cellular morphology which can be detected by fiber optic reflectance spectroscopy technique, therefore specifying this optical technique as a tool in discriminating between normal and cancerous tissue. When examining discrimination accuracy of the published articles which are involving fiber

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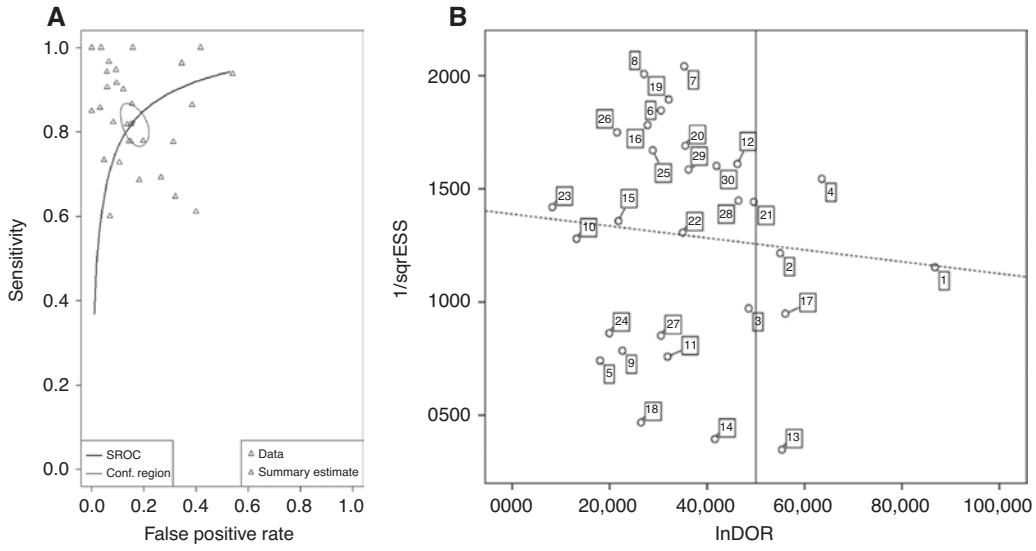


Figure 3: Threshold effect and publication bias.
(A) Summary ROC curve plot representing the threshold effect, (B) Deek's funnel plot representing the publication bias.

optic reflectance spectroscopy and human tissues, sensitivity and specificity values differed from 59.1 to 98.6% and from 46.1 to 98.8%, respectively as shown in Table 1.

In this study, according to results of meta-analysis conducted to evaluate the diagnostic accuracy of the fiber optic reflectance spectroscopy high overall sensitivity and specificity values were obtained in detection of cancerous tissue. After scientific article database search 30 articles were included in the study [3–32].

Heterogeneity and publication bias have been examined to decide which model is appropriate. It was resulted that there was no threshold effect and publication bias. Although fixed-effects model is feasible under these circumstances, it was decided to apply random-effects model in the direction of the Cochrane handbook proposal as well as considering the existence of other sources of heterogeneity [2, 39].

As a result of the study, the overall DOR was found to be large enough to say that the test was discriminatory. High overall sensitivity and specificity values show a high detection potential of fiber optic reflectance spectroscopy for cancerous tissue.

The need for DTA meta-analysis has greatly increased in recent years with the increasing interest of evidence-based medicine and statistical methodology of it is continuously improving. Conducting a high level of evidence-based study, such as meta-analysis, of a diagnostic test by using the scientific studies in the literature will lead to more reliable results for that test.

Conflict of interest statement: There is no a potential conflict of interest between the authors and others.

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