Accuracy of i-Scan for Optical Diagnosis of Colonic Polyps: A Meta-Analysis

Chuan-Guo Guo, Rui Ji, Yan-Qing Li*

Department of Gastroenterology, Qilu Hospital, Shandong University, Jinan, Shandong Province, China

* liyanqing@sdu.edu.cn

Abstract

Background

i-Scan is a novel virtual chromoendoscopy system designed to enhance surface and vascular patterns to improve optical diagnostic performance. Numerous prospective studies have been done to evaluate the accuracy of i-Scan in differentiating colonic neoplasms from non-neoplasms. i-Scan could be an effective endoscopic technique for optical diagnosis of colonic polyps.

Objective

Our aim of this study was to perform a meta-analysis of published data to establish the diagnostic accuracy of i-Scan for optical diagnosis of colonic polyps.

Methods

We searched PubMed, Medline, Elsevier ScienceDirect and Cochrane Library databases. We used a bivariate meta-analysis following a random effects model to summarize the data and plotted hierarchical summary receiver-operating characteristic (HSROC) curves. The area under the HSROC curve (AUC) serves as an indicator of the diagnostic accuracy.

Results

The meta-analysis included a total of 925 patients and 2312 polyps. For the overall studies, the area under the HSROC curve was 0.96. The summary sensitivity was 90.4% (95%CI 85%-94.1%) and specificity was 90.9% (95%CI 84.3%-94.9%). In 11 studies predicting polyps histology in real-time, the summary sensitivity and specificity was 91.5% (95%CI 85.7%-95.1%) and 92.1% (95%CI 84.5%-96.1%), respectively, with the AUC of 0.97. For three different diagnostic criteria (Kudo, NICE, others), the sensitivity was 86.3%, 93.0%, 85.0%, respectively and specificity was 84.8%, 94.4%, 91.8%, respectively.

Conclusions

Endoscopic diagnosis with i-Scan has accurate optical diagnostic performance to differentiate neoplastic from non-neoplastic polyps with an area under the HSROC curve exceeding 0.90. Both the sensitivity and specificity for diagnosing colonic polyps are over 90%.
Introduction

Colorectal carcinoma (CRC) is a major public health burden worldwide. Colonoscopy has been widely accepted as the preferred modality for the early detection of CRC. Polypectomy, especially removal of adenomas, could disrupt the polyp-cancer sequence to reduce the incidence and mortality of CRC [1, 2]. However, about 90% of all colonic polyps are smaller than 1 cm in diameter and 80% are diminutive colon polyps (≤ 5 mm), which rarely have malignant potential, and more colonic polyps are identified during colonoscopy as the image resolution of instruments improved [3]. As a consequence, the cost of histological assessment of colorectal polyps has risen, accounting for 30%–50% of all surgical pathology costs [3]. If a sufficiently accurate real-time optical diagnosis of polyps could be made, this may allow the application of a “resect and discard” strategy for neoplastic diminutive colon polyps, and the endoscopists to leave diminutive rectosigmoid hyperplastic polyps in situ [4–6] which have negligible malignant potential [7], to reduce pathology costs.

The clinical application of the “resect and discard” strategy depends to a great extent on the accuracy of endoscopic optical diagnosis in real-time. To improve the accuracy of optical diagnosis of colon polyps, dye-based chromoendoscopy [8, 9], digital image-enhanced endoscopy such as narrow-band imaging (NBI, Olympus, Japan) [10–14], fujinon intelligent color enhancement (FICE, Fujinon, Japan) [15, 16], and image-enhanced endoscopy (i-Scan, Pentax, Japan), have been used in clinical practice. Among the image-enhancing techniques, i-Scan is a novel virtual chromoendoscopy system designed to enhance surface and vascular patterns to improve optical diagnostic performance in vivo [17].

Over the past few years, numerous prospective studies have been done utilizing i-Scan in real-time or post hoc (static images assessment) with different diagnostic criteria to evaluate the accuracy of i-Scan in differentiating colonic neoplasms from non-neoplasms with histology as the reference standard. Our aim of this study was to perform a meta-analysis of published data to establish the overall diagnostic accuracy (sensitivity and specificity) of i-Scan for optical diagnosis of colonic polyps especially in real-time.

Materials and Methods

Search strategy and study selection

Our meta-analysis was done in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (S1 Table.) [18]. We systematically searched the PubMed, Medline, Elsevier ScienceDirect and Cochrane Library databases for all articles associated with i-Scan and colonic polyps published until October 2014. Studies in PubMed were identified with the term i-Scan combined with the MeSH terms colonoscopy, colonic neoplasms or colonic polyps or words beginning with colorect, colon imag or colonoscop. We searched Elsevier ScienceDirect with the terms colon neoplasms or colon polyps and i-Scan with the topics restricted to “colorectal cancer, gastrointestinal, adeno carcinoma, rectal cancer”. Studies in Medline were identified with the terms colon polyps, colon neoplasms and i-Scan. We also searched the Cochrane Library for any systematic review that was relevant to our meta-analysis. Following the initial search, suitable articles on the basis of the titles and abstracts were identified, and then a detailed full text assessment of potentially relevant studies was performed. The reference lists of the relevant articles were checked to avoid missing related studies. Finally, we reviewed the identified studies to assess whether they were eligible according to the inclusion and exclusion criteria. Disagreements between investigators were resolved through discussion.
Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. Studies that used i-Scan prospectively evaluated patients undergoing colonoscopy for screening or surveillance;
2. Diagnostic clinical studies that evaluated the accuracy of i-Scan to make a prediction of polyps histology (neoplastic or non-neoplastic);
3. Studies that compared i-Scan with histology as the reference standard;
4. Studies with available data for constructing 2×2 tables with true positive (TP), false positive (FP), false negative (FN) and true negative (TN); and
5. Studies that were published in English language.

The exclusion criteria were as follows:

1. Studies without histology as the reference standard;
2. Studies without complete data for constructing 2×2 tables with true positive (TP), false positive (FP), false negative (FN) and true negative (TN);
3. Studies that overlapped the studies selected;
4. Studies that included patients with inflammatory bowel disease, familial polyposis syndromes, or colorectal cancer; and
5. Studies primarily designed as a retrospective study, review without original data, or meta-analysis.

Data extraction

Two reviewers independently extracted data by using a standardized form designed by our group. If there was inconsistency, the original papers were retrieved and disagreements were resolved by discussion. The data of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) were extracted with the histology as gold standard. We constructed 2×2 tables to record the number of polyps identified as TP (neoplastic polyps predicted to be neoplastic endoscopically), FP (non-neoplastic polyps predicted to be non-neoplastic endoscopically), FN (neoplastic polyps predicted to be non-neoplastic endoscopically), and TN (non-neoplastic polyps predicted to be non-neoplastic endoscopically). In addition, the following data were extracted for each study, if available, first author, publication year, country or area, type of study, number of patients enrolled, patients age, sex ratio, number of polyps, size of polyps, diagnostic criteria, histological reference standard, number of endoscopists, mode of i-Scan and endoscope used. Diagnostic criteria was classified into Kudo pit pattern classification [19, 20] or modified Kudo pit pattern classification (Kudo for short), the Narrow Band Imaging International Colorectal Endoscopic (NICE) classification [21, 22] and other criteria.

Study quality assessment

Two reviewers independently assessed the quality and potential for bias of all studies by using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [23]. There are 4 phases of the QUADAS-2 tool: summarize the review question, produce review-specific guidance, construct a flow diagram, and judge bias and applicability. This tool comprised 4
domains to judge bias and applicability of the studies: patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of risk of bias with signaling questions to help us judge risk of bias. The first 3 domains also had parts to assess in terms of concerns regarding applicability. A study would have an overall judgment of “low risk of bias” or “low concern regarding applicability”, if it was judged as “low” on all domains. In contrast, it would be judged as “risk of bias” or having “concerns regarding applicability”, if it was judged “high” or “unclear” in 1 or more domains.

**Statistical methods**

A bivariate meta-analysis following a random effects model was used to calculate summary estimates of sensitivity and specificity and to plot a hierarchical summary receiver-operating characteristic (HSROC) curve [24, 25]. Positive likelihood ratio and negative likelihood ratio were calculated with the same model. We also calculated 95% confidence intervals (CI) for the summary estimates and likelihood ratios. All studies are presented as a circle and plotted with the HSROC curve. The summary point is represented by a dot which was surrounded by a 95% confidence region. The area under the HSROC curve was calculated.

The heterogeneity of the included studies was also measured. To find the source of heterogeneity, we performed subgroup analyses to assess the effect of assessment methods (histological prediction of colon polyps in real-time or not), diagnostic criteria (Kudo, NICE and others), polyps size (polyps ≤ 10 mm or polyps ≤ 5 mm), published type (full-text or abstracts), polyps number (< 200 and ≥ 200), endoscopists number (≤ 3 and > 3) on summary estimates. Finally, potential publication bias was investigated using Deeks’ funnel plot [26]. We used Stata (version12.1) and MetaDiSc (version1.4) to perform the analyses.

**Results**

**Eligible studies**

Following the initial keyword search, we got 622 citations in total (Fig 1). We excluded 524 citations that were not associated with i-Scan and colonic polyps after removing duplicated citations and screening the titles. 64 articles that did not focus on the endoscopic diagnosis of colonic polyps with i-Scan were excluded after screening the abstracts. One abstract was included after screening the abstracts. Of the 33 articles left for full text review, 23 articles were excluded as they were retrospective studies (n = 4), studies about detection rate of polyps (n = 6), studies without complete data(n = 2), or for other reasons(n = 11). Eventually, 10 full published [27–36] papers and 1 abstract [37] were selected according to the study inclusion criteria and exclusion criteria. 13 eligible studies were identified from the 11 articles. For two articles, Carlos Robles-Medranda et al. [37] and Sung Noh Hong et al. [35], 2 eligible studies were identified from each of them. These studies from one article were performed with different i-Scan mode and met inclusion criteria.

**Study characteristics**

The main characteristics of the included studies were listed in Table 1. The 13 studies [27–37] included a total of 925 patients and 2312 polyps. 51.4% of all polyps were neoplastic verified by histology—the range was from 3.28% to 78.67%. One of the studies did not present information of patients [34]. Three studies [29, 32, 36] were performed in Germany, three [33, 35] in South Korea, two [37] in Ecuador, and each of Italy [31], Netherlands [34], Taiwan [28], UK [30], and USA [27] had one. In 11 studies [27–31, 33, 35–37] the endoscopic diagnosis of polyp was performed in real-time. However, two [32,34] were performed by reading static images.
which were collected from consecutively enrolled patients. For the diagnostic criteria to predict polyp histology, Kudo pit pattern classification or modified Kudo pit pattern classification was used in six studies [27–29, 32, 35], Narrow Band Imaging International Colorectal Endoscopic (NICE) classification in three [31, 37], and other criteria in four [30, 33, 34, 36]. Six studies [27–28, 30, 33–34, 36] analyzed the small polyps (≤ 10 mm in size). The diminutive polyps (≤ 5 mm in size) were analyzed in two studies [33, 36].

**Quality assessment**

The quality of the included studies according to the QUADAS-2 tool was summarized and displayed graphically (Figs 2 and 3). In general, the included 13 studies met most of the quality criteria. However, in some studies it was not clear whether histologists were blinded to the endoscopic diagnosis that may induce bias.
| Study (year)       | Study no. | Country or Area | Study type | Assessment methods | Diagnostic criteria | Endoscopists number | No. of Patients | No. of polyps | No. of neoplasms/No. of non-neoplasms | Mean size of polyps, mm (range or ±SD) |
|-------------------|-----------|-----------------|------------|--------------------|---------------------|---------------------|----------------|--------------|------------------------------------------|----------------------------------------|
| Basford et al (2014)[30] | 1         | UK              | Prospective | Real time          | Adapted N.A.C.      | 1                   | 84             | 209          | 134/75                                    | 4.2 (±2.2)                             |
| Bouwens et al (2013)[34] | 2         | Netherlands     | Prospective | Static image       | ICE-classification  | 1 operator 11 raters| N              | 550          | 396/154                                  | - (<10)                                |
| Carlos et al (2013)*[37] | 3         | Ecuador         | Prospective | Real time          | NICE                | 3                   | 72             | 122          | 20/102                                   | -                                     |
| Carlos et al (2013)*[37] | 4         | Ecuador         | Prospective | Real time          | NICE                | 3                   | 72             | 122          | 20/102                                   | -                                     |
| Chan et al (2012)[27] | 5         | USA             | Prospective | Real time          | Kudo                | 2                   | 43             | 103          | 54/49                                    | 3.7(2–8)                               |
| Han et al (2012)[28]  | 6         | Taiwan          | Prospective | Real time          | Kudo                | 5                   | 54             | 101          | 57/44                                    | 4.2(1–9)                               |
| Hoffman et al (2010)[36] | 7         | Germany         | Prospective | Real time          | Mucosal pattern and vascular pattern* | 3 | 69 | 335 | 11/324 | - (≤5) |
| Hoffman et al (2010)[29] | 8         | Germany         | Prospective, randomized | Real time | Kudo and vascular pattern | 6 | 100 | 145 | 82/63 | 5.6 (±6.8) |
| Hong et al (2012)**[35] | 9         | South Korea     | Prospective, randomized | Real time | Modified Kudo and vascular pattern | 3 | 115 | 116 | 71/45 | - |
| Hong et al (2012)**[35] | 10        | South Korea     | Prospective, randomized | Real time | Modified Kudo and vascular pattern | 3 | 118 | 109 | 74/35 | - |
| Lee et al (2011)[33]  | 11        | South Korea     | Prospective | Real time          | Mucosal pattern and vascular pattern | 1 | 72 | 140 | 74/66 | - (≤5) |
| Neumann et al (2013)[32] | 12        | Germany         | Prospective | Static image       | Kudo                | 4                   | 48             | 110          | 77/33                                    | 4(2–20)                                |
| Pigó et al (2012)[31] | 13        | Italy           | Prospective | Real time          | NICE                | 1                   | 78             | 150          | 118/32                                   | 6.8 (±5.5)                             |

* These two studies were identified from one literature.  
** These two studies were identified from one literature.  
* This study did not describe their diagnostic criteria in detail.

N.A.C., a previously described classification system developed on the base of characterization of colonic polyps using FICE; ICE-classification, i-Scan classification for endoscopic diagnosis which is a simple classification built upon Kudo classification and NICE classification; NICE, Narrow Band Imaging International Colorectal Endoscopic Classification; N, not mentioned.

doi:10.1371/journal.pone.0126237.t001
Diagnostic performance of i-Scan diagnosis

Meta-analysis of all 13 studies showed that the summary sensitivity of i-Scan to predict polyps histology was 90.4% (95%CI 85%-94.1%), and specificity was 90.9% (95%CI 84.3%-94.9%). The summary positive likelihood ratio (LR+) and negative positive likelihood ratio (LR-) was 9.94 (95%CI 5.49–17.98) and 0.10 (95%CI 0.06–0.17), respectively. The area under the HSROC curve (AUC) was 0.96 (95%CI 0.94–0.97) (Fig 4) indicating highly accurate optical diagnostic performance of i-Scan.

We principally performed subgroup analysis for studies with histology prediction of polyps in real-time, and studies using different criteria. The subgroup of histology prediction in real-time composed of 11 studies enrolling 1652 polyps. In the 11 studies, the summary sensitivity and specificity was 91.5% (95%CI 85.7%-95.1%) and 92.1% (95%CI 84.5%-96.1%), respectively. The LR+ and LR- was 11.6 (95%CI 5.61–23.81) and 0.09 (95%CI 0.05–0.16), respectively. The AUC was 0.97 (95%CI 0.95–0.98) (Fig 5) indicating a high accuracy of i-Scan to differentiate neoplastic and non-neoplastic polyps in real-time. In the 6 studies (684 polyps) in which histology prediction was performed with Kudo or modified Kudo classification, sensitivity and specificity was 86.3% (95%CI 82.7%-89.5%) and 84.8% (95%CI 79.9%-88.8%), respectively. For the 3 studies (394 polyps) using NICE, the sensitivity and specificity was 93.0% (95%CI 87.9%-96.5%) and 94.4% (95%CI 90.6%-97.0%), respectively. In 4 studies (1234 polyps) with other criteria, the sensitivity and specificity was 85.0% (95%CI 82.0%-87.8%) and 91.8% (95%CI 89.3%-93.8%), respectively. For these three groups with different criteria, of which the data were not plotted in a HSROC curve, we just calculated summary estimates of them. For the sub-group analysis of small polyps (≤ 10 mm) in six studies (1438 polyps), sensitivity and specificity was 89.3% (95%CI 79.5%-94.7%) and 88.3% (95%CI 80.7%-93.2%), respectively, with AUC of 0.95(0.92–0.96). The sensitivity and specificity of diagnosis of diminutive polyps...
The main results were shown in Table 2.

Test for heterogeneity

The heterogeneity, however, was presented in the overall studies with Q of 5.001 (Chi-square, \( p = 0.041 \)) and \( I^2 \) (I-square) of 60% indicating a high heterogeneity in the overall studies. There was no threshold effect inducing heterogeneity (Spearman’s coefficient: -0.322, \( p = 0.284 \)). Then we performed subgroup analyses to find the source of heterogeneity to assess the effect of assessment methods (real-time or not), diagnostic criteria (Kudo, NICE and others), and polyps size (polyps \( \leq 10 \text{ mm} \) or polyps \( \leq 5 \text{ mm} \)) on summary estimates. The mode of i-Scan was varied in most studies, so we did not analyze it. This may be one of the sources of heterogeneity. For the subgroup of real-time, the \( I^2 \) (I-square) was 44% indicating a moderate heterogeneity. For the subgroup of small polyps (\( \leq 10 \text{ mm} \)), the \( I^2 \) (I-square) was 25% indicating a mild heterogeneity.

Publication bias estimate

We used Deeks’ funnel plot [26] to assess the potential publication bias of the overall studies. A slope coefficient of 12.8 (\( p = 0.533 \)) in the Deeks’ funnel plot (Fig 6) asymmetry test indicates a symmetrical funnel shape and suggests that publication bias is absent.
Discussion

This meta-analysis summarized the available evidence regarding the accuracy of i-Scan for optical diagnosis of colonic polyps. The overall results of this meta-analysis indicated that i-Scan had accurate optical diagnosis performance, with an area under the hierarchical summary receiver-operating characteristic (HSROC) curve of 0.96. For i-Scan predicting polyps histology in real-time, it also showed a high accuracy with an area under the HSROC curve of 0.97. Endoscopy with i-Scan correctly diagnosed 91.5% of neoplasms and 92.1% of non-neoplastic polyps in real-time. Comparing with narrow band imaging, i-Scan has a similar sensitivity (91.5% vs 91%) and a higher specificity (92.1% vs 82.6%) to differentiate neoplastic from non-neoplastic colonic polyps in real-time according to a meta-analysis of Sarah K McGill et al. [38]. Similarly, comparing with fujinon intelligent color enhancement (FICE), i-Scan has a similar sensitivity (91.5% vs 91.8%) and a higher specificity (92.1% vs 83.5%) to differentiate neoplastic from non-neoplastic colonic polyps in real-time according to a meta-analysis of Linda K Wanders et al. [39]. Our findings may be explained by the fact that i-Scan is generally integrated with high-definition colonoscopy, and high-definition colonoscopy could have better performance than standard definition colonoscopy in detecting polyps [40]. However, some studies included in the above two meta-analyses were based on standard definition colonoscopies [41–45].

Fig 5. Hierarchical summary receiver-operating characteristic (HSROC) curve for the diagnostic performance of i-Scan to predict colonic polyps histology in real-time. The size of the blue circles indicates the number of polyps in the individual studies. The summary sensitivity and specificity is shown with a dark red square and the 95% confidence region is plotted in short lines. The AUC was 0.97 (95%CI 0.95–0.98).

doi:10.1371/journal.pone.0126237.g005
The criteria adopted for predicting colonic polyps histology when performing optical diagnosis of colonic polyps with i-Scan varied in the included studies. As to subgroups with different diagnostic criteria, Narrow Band Imaging International Colorectal Endoscopic (NICE) classification showed higher sensitivity and specificity (93% and 94.4% respectively) than the other two criteria. However, we were not sure if the difference was statistically significant, because of the overlapped 95% confidence interval. Only three studies with NICE as criteria were included. NICE had shown high accurate diagnosis of colonic lesions, whereas it was designed

| Study group | No. of studies (no. of polyps) | Sens (95%CI) | Spec (95%CI) | LR+ (95%CI) | LR- (95%CI) | Area under HSROC curve (95%CI) |
|-------------|-------------------------------|--------------|-------------|-------------|-------------|-------------------------------|
| ALL         | 13 (2312)                     | 90.4 (85.0–94.1) | 90.9 (84.3–94.9) | 9.94 (5.49–17.98) | 0.10 (0.06–0.17) | 0.96 (0.94–0.97) |
| Real-time   | 11 (1652)                     | 91.5 (85.7–95.1) | 92.1 (84.5–96.1) | 11.6 (5.61–23.81) | 0.09 (0.05–0.16) | 0.97 (0.95–0.98) |

| Criteria    | Sens (95%CI) | Spec (95%CI) | LR+ (95%CI) | LR- (95%CI) | Area under HSROC curve (95%CI) |
|-------------|--------------|-------------|-------------|-------------|--------------------------------|
| Kudo        | 86.3 (82.7–89.5) | 84.8 (79.9–88.8) | 5.00 (2.69–9.30) | 0.17 (0.10–0.30) * |
| NICE        | 93.0 (87.9–96.5) | 94.4 (90.6–97.0) | 11.59 (3.18–42.28) | 0.11 (0.05–0.25) * |
| Others      | 85.0 (82.0–87.8) | 91.8 (89.3–93.8) | 9.31 (4.97–17.45) | 0.10 (0.03–0.35) * |

| Size         | Sens (95%CI) | Spec (95%CI) | LR+ (95%CI) | LR- (95%CI) | Area under HSROC curve (95%CI) |
|--------------|--------------|-------------|-------------|-------------|-------------------------------|
| Polyps ≤10mm | 89.3 (79.5–94.7) | 88.3 (80.7–93.2) | 7.62 (4.31–13.5) | 0.12 (0.06–0.25) | 0.95 (0.92–0.96) |
| Polyps ≤5mm  | 92.9 (85.3–97.4) | 94.4 (91.6–96.4) | 11.9 (3.20–44.29) | 0.10 (0.03–0.30) * |

* These four groups were not plotted in a HSROC curve.

The criteria adopted for predicting colonic polyps histology when performing optical diagnosis of colonic polyps with i-Scan varied in the included studies. As to subgroups with different diagnostic criteria, Narrow Band Imaging International Colorectal Endoscopic (NICE) classification showed higher sensitivity and specificity (93% and 94.4% respectively) than the other two criteria. However, we were not sure if the difference was statistically significant, because of the overlapped 95% confidence interval. Only three studies with NICE as criteria were included. NICE had shown high accurate diagnosis of colonic lesions, whereas it was designed...
on the basis of NBI characters [21, 22]. So more studies need to be done to make sure if it is suitable to i-Scan. More studies included in the meta-analysis adopted Kudo pit pattern classification or modified Kudo pit pattern classification as their diagnostic criteria showing sensitivity of 86.3% and specificity of 84.8%. Kudo pit pattern classification, however, was designed only on the pit pattern of colonic lesions [19, 20]. One included study adopted N.A.C. as the diagnostic criteria, which was a classification system developed on the basis of characterization of colonic polyps using FICE [46]. Both of these criteria are not specialized for i-Scan. While only three studies [33, 34, 36] were performed using their own criteria adjusted to the characters of i-Scan. To internationally standardize the i-Scan observation criteria, a simple effective classification system is required. Further studies validating a specific polyp classification system specialized for i-Scan may be necessary. In this way, i-Scan will be more widely applied in clinical practice.

The size of polyps is always related to pathological grade and endoscopy accuracy and diminutive colon polyps (< 5 mm) rarely have malignant potential [7]. In our study, i-Scan showed accurate optical diagnostic performance for optical diagnosis of small and diminutive polyps. For the sub-group analysis of small polyps (< 10 mm), sensitivity and specificity of i-Scan was 89.3% and 88.3%, respectively. The sensitivity and specificity for diminutive polyps (< 5 mm) was 92.9% and 94.4%, respectively. i-Scan seemed have better diagnostic performance for diminutive polyps numerically. However, we were not sure if the difference was statistically significant, because of the overlapped 95% confidence interval.

i-Scan could combine 6 digital chromoendoscopic post-processing settings (v, p, e, b, g and c) called tone enhancement (TE) with different levels of contrast enhancement (CE) and surface enhancement (SE) resulting in diverse combinations [17]. TE is designed to enhance minute surface structures and subtle changes in color and evaluate the lesions in detail. SE and CE can improve identification of lesions without markedly reducing the brightness of images and altering the color tone. Each mode can be used along or combined with other modes to get operators preferred images. There are 3 established modes combinations (i-Scan 1, 2 and 3) currently available presented in the instrument. The combination of multiple modes can provide operator preferred images. We are not sure which one is the most suitable combination of modes for optical diagnosis of colonic polyps. Carlos Robles-Medranda et al. [37] established 3 new i-Scan setting (NIS) modes measuring their effectiveness for the real-time histological prediction of colonic polyps and found that their NIS modes were effective for histological prediction of colonic polyps in real-time. More studies need to be done to establish a general accepted setting specifically for histological prediction of colonic polyps.

In our study, we analyzed accuracy of i-Scan in the diagnosis of colonic polyps in real-time. This is the first meta-analysis assessing the performance of different diagnostic criteria for predicting colonic polyps histology with i-Scan. We performed the analyses using a bivariate meta-analysis following a random effects model to calculate overall estimates of sensitivity and specificity, allowing more intra- and inter-study variability than a fixed-effect model [47]. This model allows researchers to avoid misleading conclusions.

Nonetheless, the main limitation to our study is that various i-Scan modes and different diagnostic criteria were adopted when performing optical diagnosis with i-Scan. The non-uniform diagnostic criteria may restrict the application of i-Scan. Though we performed subgroup analyses, such as real time, diagnostic criteria, polyp size, it is not comprehensive. In most studies, it is not clear whether the endoscopic diagnoses of polyps were performed with high confidence. Not all of the included studies provided the information of polyps location, polyps morphology and proportion of exact pathological type. The incomplete information restricts further analyses. The relatively high heterogeneity presented across the 13 included studies is also the limitation of this study. Though the heterogeneity was reduced in subgroup analyses,
moderate heterogeneity was still present in some subgroup analyses. The relative percentage of neoplasia to non-neoplastic fluctuates between 78.67% and 3.28% indicating non-uniformity of all studies. The discrepancy in the included studies may be caused by diverse target population, such as American, Asian and European, and the population composition of the individual studies. For 1 article and 1 abstract in the study, two studies were identified from each of them. The two studies from one literature may have potential impropriety, though there is no obvious change in the results as the analysis being repeated after removing one of them. The above situation may induce heterogeneity.

Conclusions
Endoscopic diagnosis with i-Scan is an accurate optical diagnosis technique to differentiate neoplastic from non-neoplastic polyps, with an area under the hierarchical summary receiver-operating characteristic (HSROC) curve exceeding 0.90. Both the sensitivity and specificity for diagnosing colonic polyps are over 90%.

Supporting Information
S1 Table. PRISMA checklist. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Every section of the meta-analysis is noted in the PRISMA checklist.

Acknowledgments
This study was funded by National Natural Science Foundation of China (grant number 81330012, 81300284) and the Shandong Province Science and Technology Commitee (grant number 2013GSF11833). We are grateful to Lixiang Li and Yuhui Zhang for the revision and polish of the manuscript.

Author Contributions
Conceived and designed the experiments: CGG YQL. Performed the experiments: RJ CGG. Analyzed the data: RJ CGG. Contributed reagents/materials/analysis tools: CGG. Wrote the paper: CGG. Revised the article: YQL RJ.

References
1. Hewett DG. Colonoscopic polypectomy: current techniques and controversies. Gastroenterol Clin North Am. 2013; 42(3): 443–458. doi: 10.1016/j.glc.2013.05.015 PubMed PMID: 23931853.
2. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colono

scopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012; 366 (8): 687–696. doi:10.1056/NEJMoa1100370 PubMed PMID: 22356322.
3. Rex DK. Reducing costs of colon polyp management. Lancet Oncol. 2009; 10(12): 1135–1136. doi:
10.1016/s1470-2045(09)70342-0 PubMed PMID: 19910251.
4. Ignjatovic A, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Ressect and Discard; DISCARD trial): a prospective cohort study. Lancet Oncol. 2009; 10(12): 1171–1178. doi: 10.1016/s1470-2045
(09)70329-8 PubMed PMID: 19910250.
5. Hassan C, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. Clin Gastroenterol Hepatol. 2010; 8(10): 865–869, 9.e1-3. doi: 10.1016/j.cgh.2010.05.018 PubMed PMID: 20621680.
6. Rex DK, Kahi C, O'Brien M, Levin TR, Pohl H, Rastogi A, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time
endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc. 2011; 73(3): 419–422. doi: 10.1016/j.gie.2011.01.023 PubMed PMID: 21353837.

7. Gupta N, Bansal A, Rao D, Early DS, Jonnalagadda S, Wani SB, et al. Prevalence of advanced histological features in diminutive and small colon polyps. Gastrointest Endosc. 2012; 75(5): 1022–1030. doi: 10.1016/j.gie.2012.01.020 PubMed PMID: 22405698.

8. Fu KI, Sano Y, Kato S, Fuji T, Nagashima F, Yoshino T, et al. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. Endoscopy. 2004; 36(12): 1089–1093. doi: 10.1055/s-2004-826039 PubMed PMID: 15578300.

9. De Palma GD, Rega M, Masone S, Persico M, Siciliano S, Addeo P, et al. Conventional colonoscopy and magnified chromoendoscopy for the endoscopic histological prediction of diminutive colorectal polyps: a single operator study. World J Gastroenterol. 2006; 12(15): 2402–2405. PubMed PMID: 16688833.

10. Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology. 2007; 133(1): 42–47. doi: 10.1053/j.gastro.2007.04.029 PubMed PMID: 17631129.

11. Uraoka T, Saito Y, Matsuda T, Sano Y, Ikehara H, Mashimo Y, et al. Detectability of colorectal neoplastic lesions using a narrow-band imaging system: a pilot study. J Gastroenterol Hepatol. 2008; 23(12): 1810–1815. doi: 10.1111/j.1440-1746.2008.05635.x PubMed PMID: 19032454.

12. Adler A, Aschenbeck J, Yenerim T, Mayr M, Aminalai A, Drossel R, et al. Narrow-band versus white-light high definition television endoscopic imaging for screening colonoscopy: a prospective randomized trial. Gastroenterology. 2009; 136(2): 410–416.e1; quiz 715. doi: 10.1053/j.gastro.2008.10.022 PubMed PMID: 19014944.

13. Kaltenbach T, Friedland S, Soetikno R. A randomised tandem colonoscopy trial of narrow band imaging versus white light examination to compare neoplasia miss rates. Gut. 2008; 57(10): 1406–1012. doi: 10.1136/gut.2007.137984 PubMed PMID: 19523025.

14. Rastogi A, Keighley J, Singh V, Callahan P, Bansal A, Wani S, et al. High accuracy of narrow band imaging without magnification for the real-time characterization of polyp histology and its comparison with high-definition white light colonoscopy: a prospective study. Am J Gastroenterol. 2009; 104(10): 2422–2430. doi: 10.1038/ajg.2009.403 PubMed PMID: 19584829.

15. Chung SJ, Kim D, Song H, Park MJ, Kim YS, Kim JS, et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. Gastrointest Endosc. 2010; 72(1): 136–142. doi: 10.1016/j.gie.2010.01.055 PubMed PMID: 20493487.

16. Longcroft-Wheaton GR, Higgins B, Bhandari P. Flexible spectral imaging color enhancement versus conventional colonoscopy to compare adenoma miss rates. Gastrointest Endosc. 2011; 74(5): 1022–1027. doi: 10.1016/j.gie.2011.01.023 PubMed PMID: 21353837.

17. Kodashima S, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. World J Gastroenterol. 2010; 16(9): 1043–1049. doi: 10.3748/wjg.v16.i9.1043 PubMed PMID: 20205272.

18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. J Clin Epidemiol. 2015; 4(10): 1. doi: 10.1016/j.amepi.2015.08.004 PubMed PMID: 25554246.

19. Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic (NICE) classification. Gastrointest Endosc. 2013; 78(4): 422. doi: 10.1016/j.gie.2013.04.018 PubMed PMID: 23910062.

20. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155(8): 529–536. doi: 10.7326/0003-4819-155-8-201110180-00009 PubMed PMID: 22007046.
24. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005; 58(10): 982–990. doi: 10.1016/j.jclinepi.2005.02.022 PubMed PMID: 16168343.

25. Wang F, Gatsonis CA. Hierarchical models for ROC curve summary measures: design and analysis of multi-reader, multi-modality studies of medical tests. Stat Med. 2008; 27(2): 243–256. doi: 10.1002/sim.2828 PubMed PMID: 17340598.

26. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005; 58(9): 882–893. doi: 10.1016/j.jclinepi.2005.01.016 PubMed PMID: 16085191.

27. Chan JL, Lin L, Feiler M, Wolf AI, Cardona DM, Gellad ZF. Comparative effectiveness of i-SCAN and high-definition white light characterizing small colonic polyps. World J Gastroenterol. 2012; 18(41): 5905–5911. doi: 10.3748/wjg.v18.i41.5905 PubMed PMID: 23139606.

28. Han ML, Lee YC, Chen CC, Fang YJ, Lee JY, Lin TL, et al. Computer-generated surface and tone enhancements to distinguish neoplastic from non-neoplastic colon polyps less than 1 cm in diameter. Int J Colorectal Dis. 2012; 27(3): 337–344. doi: 10.1007/s00384-011-1319-0 PubMed PMID: 22006490.

29. Hoffmann A, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S, et al. High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial. Endoscopy. 2010; 42(10): 827–833. doi: 10.1055/s-0030-1255713 PubMed PMID: 20803419.

30. Basford PJ, Longcroft-Wheaton G, Higgins B, Bhandari P. High-definition endoscopy with i-Scan for evaluation of small colon polyps: the HiSCOPE study. Gastrointest Endosc. 2014; 79(1): 111–118. doi: 10.1016/j.gie.2013.06.013 PubMed PMID: 23871094.

31. Pigo F, Bertani H, Manno M, Mirante V, Caruso A, Barbera C, et al. i-Scan high-definition white light endoscopy and colorectal polyps: prediction of histology, interobserver and intraobserver agreement. Int J Colorectal Dis. 2013; 28(3): 399–406. doi: 10.1007/s00384-012-1583-7 PubMed PMID: 23014976.

32. Neumann H, Vieth M, Fry LC, Gunther C, Atreya R, Neurath MF, et al. Learning curve of virtual chromoendoscopy for the prediction of hyperplastic and adenomatous colorectal lesions: a prospective 2-center study. Gastrointest Endosc. 2013; 78(1): 115–120. doi: 10.1016/j.gie.2012.02.001 PubMed PMID: 23528656.

33. Lee CK, Lee SH, Hwangbo Y. Narrow-band imaging versus I-Scan for the real-time histological prediction of diminutive colonic polyps: a prospective comparative study by using the simple unified endoscopic classification. Gastrointest Endosc. 2011; 74(3): 603–609. doi: 10.1016/j.gie.2011.04.049 PubMed PMID: 21762907.

34. Bouwens MW, de Ridder R, Masclere AA, Driessen A, Riedl RG, Winkens B, et al. Optical diagnosis of colorectal polyps using high-definition i-scan: an educational experience. World J Gastroenterol. 2013; 19(27): 4334–4343. doi: 10.3748/wjg.v19.i27.4334 PubMed PMID: 23985144.

35. Hong SN, Choe WH, Lee JH, Kim SI, Kim JH, Lee TY, et al. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. Gastrointest Endosc. 2012; 75(5): 1011–1021.e2. doi: 10.1016/j.gie.2011.11.040 PubMed PMID: 22381530.

36. Hoffmann A, Kogel C, Goetz M, Tresch A, Mudter J, Biesterfeld S, et al. Recognition and characterization of small colonic neoplasia with high-definition i-scan is as precise as chromoendoscopy. Dig Liver Dis. 2010; 42(1): 45–50. doi: 10.1016/j.dld.2009.04.005 PubMed PMID: 19473893.

37. Robles-Medranda C, Valle RSD, Lukashok HP, Abarca F, Robles-Jara C. Mo1662 Pentax i-SCAN With Electronic Magnification for the Real-Time Histological Prediction of Colonic Polyps: A Prospective Study Using a New Digital Chromoendoscopy Setting. Gastrointest Endosc. 2013; 77(suppl 5a): AB463.

38. McGill SK, Evangelou E, Ioannidis JP, Soetikno RM, Kalttenbach T. Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics. Gut. 2015; 64(3): 344–347. doi: 10.1136/gutjnl-2014-308065 PubMed PMID: 25450564.

39. Sanders KO, East JE, Uitentuis SE, Ang MMGL, Dekker E. Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis. Lancet Oncol. 2013; 14: 1337–1347. doi: 10.1016/S1470-2045(13) 70509-6 PubMed PMID: 2439209.

40. Tribonias G, Theodoropoulou A, Konstantinidis K, Vardas E, Karmiris K, Chronis N, et al. Comparison of standard vs high-definition, wide-angle colonoscopy for polypl detection: a randomized controlled trial. Colorectal Dis. 2010; 12(10 Online): e260–266. doi: 10.1111/j.1463-1318.2009.02145.x PubMed PMID: 19930146.

41. Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and
nonneoplastic colonic polyps. Am J Gastroenterol. 2006; 101(12): 2711–2716. doi:10.1111/j.1572-0241.2006.00932.x PubMed PMID: 17227517.

42. Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, et al. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut. 2007; 56(3): 373–379. doi:10.1136/gut.2006.099614 PubMed PMID: 17005766.

43. Liu YX, Huang LY, Bian XP, Cui J, Xu N, Wu CR. Fuji Intelligent Chromo Endoscopy and staining technique for the diagnosis of colon tumor. Chin Med J (Engl). 2008; 121(11): 977–982. PubMed PMID: 18706244.

44. Pohl J, Nguyen-Tat M, Pech O, May A, Rabenstein T, Ell C. Computed virtual chromoendoscopy for classification of small colorectal lesions: a prospective comparative study. Am J Gastroenterol. 2008; 103(3): 562–569. doi:10.1111/j.1572-0241.2007.01670.x PubMed PMID: 18070234.

45. Pohl J, Lotterer E, Balzer C, Sackmann M, Schmidt KD, Gossner L, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multi-centre trial. Gut. 2009; 58(1): 73–78. doi:10.1136/gut.2008.153601 PubMed PMID: 18838485.

46. Longcroft-Wheaton GR, Bhandari P. Characterisation colonic polyps using fice without optical magnification: a new classification system (N.A.C.). Gut. 2012; 65(supp 2): A329–A330.

47. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001; 20(19): 2865–2884. PubMed PMID: 11568945.