Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(12) 4885–4897

DOI: 10.1177/0300060518803041
journals.sagepub.com/home/imr
SAGE

Indocyanine green can stand alone in detecting sentinel lymph nodes in cervical cancer

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Abstract

Objectives: The effectiveness of indocyanine green (ICG) dye for detecting sentinel lymph nodes (SLNs) in cervical cancer compared with other tracers is unknown. This study aimed to assess the validity of ICG dye in detecting SLNs in cervical cancer preoperatively.

Methods: We performed a literature search for identifying eligible articles from PubMed database using the search terms "cervical cancer", "sentinel lymph node", "indocyanine green", "blue dyes", "human serum albumin", and "technetium-99 radiocolloid". We performed a meta-analysis. Comparison of the overall, bilateral, and unilateral detection rates of the different tracers was the primary goal. Comparison of the false-negative rate among the tracers was the secondary goal.

Results: Only eight retrospective studies including 661 patients were included. ICG versus combinations of three other tracers showed significantly higher bilateral and unilateral detection rates, but no difference in the overall rate of detecting SLNs. ICG had a higher bilateral detection rate than blue dye and technetium-99. Absorbing human serum albumin into ICG as a lymphatic tracer did not show a difference in detection rate compared with ICG alone.

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Conclusions: ICG is superior and better than other tracers, and absorbing human serum albumin as a lymphatic tracer is not required in patients with cervical cancer.

Keywords
Sentinel lymph node detection, indocyanine green, blue dye, human serum albumin, radiocolloid technetium-99, cervical cancer, tracer

Date received: 20 May 2018; accepted: 3 September 2018

Introduction

Cervical cancer is the most common gynecological cancer in developing countries compared with other gynecological cancers. Bilateral pelvic lymphadenectomy is one of the standard surgical treatments of early-stage cervical cancer.[1,2] The pelvic lymph node involvement rates are only 0% to 4.8% for stage IA, 0% to 17% for IB, 12% to 27% for IIA, and 25% to 29% for IIB.[3,4] Therefore, most patients receive pelvic lymph node dissection on a routine basis if there is no metastasis. This causes many complications, such as lymphedema,[5] nerve injury, bleeding, ureteral injury, sensory loss, and lymph cyst formation.[6] A considerable amount of research has been performed on sentinel lymph node (SLN) detection using safe and effective tracers, especially in clinical use.[7] This detection reduces the morbidity rate because it can show the position of local and regional lymph nodes in patients with cervical cancer. Instead of performing a complete lymphadenectomy, an identified region can be treated after SLN detection.[8] In 2014, SLN mapping was taken into account as an appropriate surgical lymph node assessment in patients with cervical cancer by the National Comprehension Cancer Network guidelines.[9]

The National Cancer Institute defines indocyanine green (ICG) as a cyanine dye, which is used in medical diagnostics to examine cardiac output, hepatic function, liver blood flow, and ophthalmic angiography. This dye has been used and tested for SLN detection not only for various tumors, but also for cervical cancer.[10,11] ICG can be used clinically because of the following reasons: (1) higher signal-to-background ratio, (2) reasonable cost, (3) fewer adverse effects and less toxicity than other tracers, and (4) infrequent allergic reactions.[12] Many studies on cervical cancer have compared the efficacy of ICG dye and the combined vital-radiotracer method with other diagnostic tracers in terms of detection rates.[13] However, some studies have reported lower detection rates of ICG dye compared with other tracers.[14] To clarify these issues, we conducted a quantitative study in the form of a meta-analysis on ICG and other tracers. This study aimed to assess the validity of ICG dye in SLN detection of cervical cancer preoperatively.

Methods

Search strategy

We performed a comprehensive, systematic search in July 2018 using the search terms "cervical cancer", "sentinel lymph node", and "indocyanine green" in the PubMed database. Predefined search terms were used to identify reports on detection of SLNs in patients with cervical cancer using ICG. The selected articles were limited to the English language. Exclusion

criteria were review articles, letters, comments, conference proceedings, unpublished data, and case reports. Only randomized, controlled trials and retrospective studies were included. We analyzed studies in which SLNs were detected by ICG. Some of the articles were excluded because of the following reasons: (1) the focus of injection was not the cervix; (2) the articles were related to endometrial and cervical cancer, not only cervical cancer; and (3) the intervention and outcome did not meet our requirements. No studies using animal models and no research involving human subjects were performed for this study. Therefore, approval for this study was not required.

Data extraction

We extracted relevant data by using a standardized data abstraction form. The identity of study investigators and the institution was blinded. A true positive SLN, defined as a positive SLN, was indicated by tracers that dyed SLNs by similar histopathological techniques (hematoxylin and eosin staining, serial sectioning, immunohistochemistry) independent of regional lymph node status. A false-negative SLN was defined as the finding of metastasis, despite an undetected SLN.

The primary goal of the study was to compare the detection rates of the following different mapping tracers: ICG versus combined dyes, ICG versus blue dye (BD), ICG versus ICG:human serum albumin (HSA), and ICG versus technetium-99 (^{99}Tc) dye with BD. We examined overall, bilateral, and unilateral detection rates, and with mapping of at least one SLN per hemipelvis. The effectiveness of all of the dyes was analyzed. The secondary goal was the false-negative rate of SLNs, using different tracers for SLN mapping. Studies were considered false-negative when the SLN was negative with positive non-SLN.

Statistical analysis

The risk ratio (RR) (also called relative risk) and the odds ratio (OR) were considered. Therefore, overall, bilateral, and unilateral detection of SLNs by using different tracers (BD, HSA, and ^{99}Tc) versus ICG was achieved by calculation of the OR or RR. A fixed-effects model was used when heterogeneity between the results was large and a random-effects model was used otherwise. We assumed that effects from each study were the same as "no difference was seen" in the underlying study population, subject selection criteria, and application of tracers.

The chi-square (I^2) test was used to assess statistical heterogeneity between studies. Data from each study were tabulated under an experimental group (ICG dye) and control groups (other dyes, such as BDs, HSA, and ^{99}Tc) and then displayed by forest plots. All statistical analyses were performed using Review Manager (RevMan, version 5.3.5, http://www.cochrane.org) and STATA version 12.0 (College Station, TX, USA). All statistical tests were two-sided and a P value < 0.05 was considered significant.

Results

Overall, 19 studies were selected through the literature search. Among them, three studies were removed as duplicates. Two of the studies were not selected because of different types of cancer (endometrial cancer). Two studies were excluded after evaluation of the title and abstract. A further four studies were excluded successively after full-text evaluation because of a lack of detailed data. Finally, eight studies that included 661 patients were selected (Table 1),[6,15–21] in whom dyes were injected into the cervix at different positions (four quadrants). The reasons for exclusion are as follows: (1) the focus of injection was

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

Authors	Study design	Number of patients	Intervention	Outcome
Schaafsma et al, 2012[15]	Retrospective	18	Surgery: lymphadenectomy Tracer: ICG & HSA Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	Randomized trial showed no advantage of ICG:HSA over ICG alone for the SLN procedure
Imboden et al, 2015[6]	Retrospective	58	Surgery: laparoscopy Tracer: ICG, blue dye, and ^{99}Tc Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	ICG SLN mapping in cervical cancer provided high overall and bilateral detection rates
Buda et al, 2016[16]	Retrospective	144	Surgery: laparoscopy Tracer: ICG, blue dye, and ^{99}Tc Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	Fluorescence SLN mapping with ICG achieved a significantly higher detection rate and bilateral mapping compared with the standard radiocolloid and BD technique
Buda et al, 2016[17]	Retrospective	45	Surgery: lymphadenectomy Tracer: ICG, ^{99}Tc, and blue dye Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	SLN mapping using ICG showed a higher detection rate compared with other modalities. ICG was significantly superior to ^{99}Tc with blue dye regarding the bilateral detection rate
Di Martino et al, 2017[18]	Retrospective	95	Surgery: laparoscopy Tracer: ICG, blue dye, and ^{99}Tc Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	The detection rate and bilateral migration rate on real-time fluorescent SLN mapping were higher with ICG than with ^{99}Tc radiotracer with or without blue dye
Paredes et al, 2017[19]	Retrospective	48	Surgery: laparoscopy Tracer: ICG, blue dye, and ^{99}Tc Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	SLN biopsy with ICG-^{99}Tc-nanocolloid provided bilateral SLN detection in all patients and a higher detection rate than that with blue dye
Salvo et al, 2017[20]	Retrospective	188	Surgery: lymphadenectomy Tracer: ICG, ^{99}Tc, and blue dye Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	SLN biopsy had a high sensitivity and negative predictive value
Buda et al, 2018[21]	Retrospective	65	Surgery: lymphadenectomy Tracer: ICG, ^{99}Tc, and blue dye Position: injected into the cervix alone, and divided into the 3- and 9-o'clock positions	Use of ICG and radiotracer with or without blue dye had no significant effect on the SLN detection rate. Use of the fluorescent dye ICG showed a higher bilateral mapping rate than that with standard techniques

ICG, indocyanine green; HAS, human serum albumin; SLN, sentinel lymph node; ^{99}Tc, technetium-99

other than the cervix; (2) the results were from combining two cancers, endometrial and cervical cancer, rather than from only cervical cancer; (3) the intervention and outcome differed from our requirements; and (4) exclusion was due to different bias within the studies. The PRISMA flow chart summarizes the process (Figure 1). An experimental group and control group were studied. The experimental group included female patients in whom ICG alone was injected into the cervix. The control group included female patients in whom different dyes, such as combinations of HSA, BDs, and ^{99}Tc, were injected into the cervix. Although tracers were injected in the same number of female patients, the detection rate was measured separately. In the selected studies, SLN detection with different tracers was compared with reference to bilateral, overall, and unilateral detection rates.

ICG versus combined dyes

When ICG was compared with BDs, including isosulfan blue, ^{99}Tc, and HSA, for SLN detection, there was no difference in the overall detection rate (OR 1.64; 95% confidence interval [CI]: 0.82–3.29; $P = 0.17$, fixed-effect model; Figure 2a). The bilateral detection rate with ICG for detection of SLNs showed obvious superiority compared with a combination of tracers (OR 4.49; 95% CI: 1.36–14.77; $P = 0.01$, random-effects model; Figure 2b). Similarly, the unilateral detection rate was significantly higher with ICG than with a combination of different tracers (OR 0.22; 95% CI: 0.07–0.70; $P = 0.01$, random-effects model; Figure 2c). Therefore, ICG showed better bilateral and unilateral detection rates than did a combination of different tracers.

ICG versus BDs

When ICG was compared with BDs for detecting SLNs in patients with cervical cancer, the pooled analysis data did not show such a remarkable change in the overall detection rate between these two dyes (OR 5.69; 95% CI: 0.25–128.50; $P = 0.27$, random-effects model; Figure 3a). The bilateral detection rate appeared to be greater for ICG than for BD (OR 12.09; 95%CI: 0.52–280.40; $P = 0.12$ fixed-effect model; Figure 3b). The unilateral detection rate also appeared to be greater for ICG than for BD (OR 0.08; 95% CI: 0.00–1.92; $P = 0.12$, fixed-effect model; Figure 3c). Although there were no significant differences in the bilateral and unilateral rates, we concluded that ICG was better than BD because it appeared to show a better detection rate. This finding proved that ICG could stand alone and was superior to BD.

ICG versus a combination of ICG and HSA

When ICG was compared with ICG:HSA for SLN detection, the pooled analysis data showed a non-significant higher overall detection rate with ICG (OR 0.25; 95% CI: 0.02–3.04; $P = 0.28$, fixed-effect model; Figure 4a). The bilateral detection rate was not different between ICG and ICG:HSA (OR 1.60; 95%CI: 0.24–10.81; $P = 0.63$, random-effects model; Figure 4b). The unilateral detection rate was also not different between ICG and ICG:HSA (OR 0.10; 95% CI: 0.00–2.23; $P = 0.14$, fixed-effect model; Figure 4c). Therefore, HSA appeared to be unnecessary because there was no change in the results.

ICG versus ^{99}Tc dye combined with BD

When ICG was compared with ^{99}Tc combined with BD for SLN detection, the overall detection rate was not significantly different between them; however, this result was considered meaningful (OR 1.70; 95% CI: 0.74–3.90; $P = 0.21$, fixed-effect model; Figure 5a). The bilateral

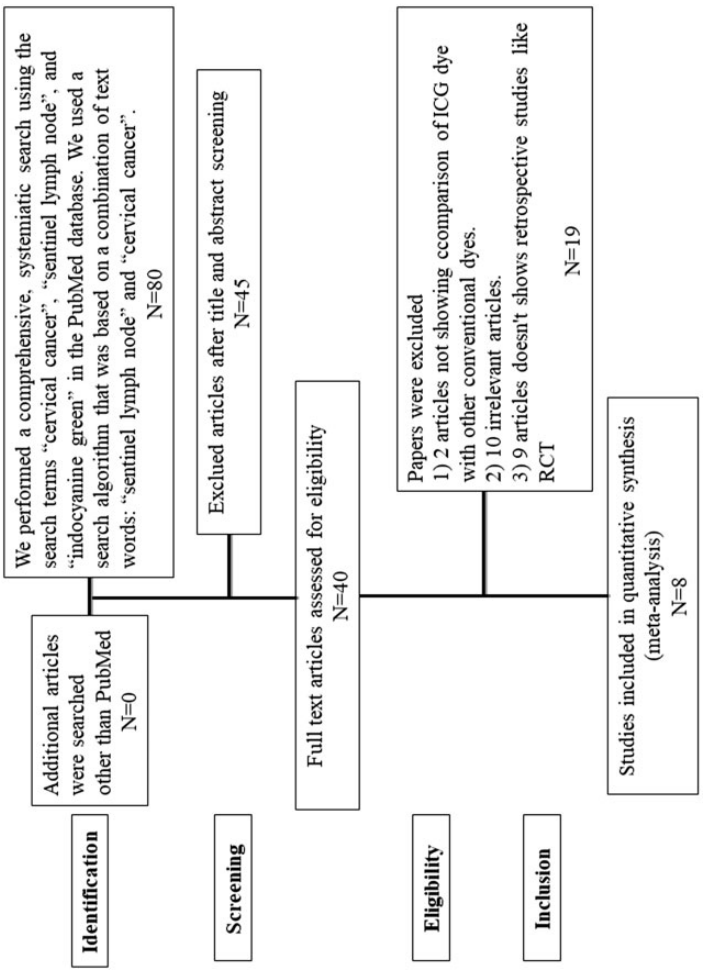

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow chart

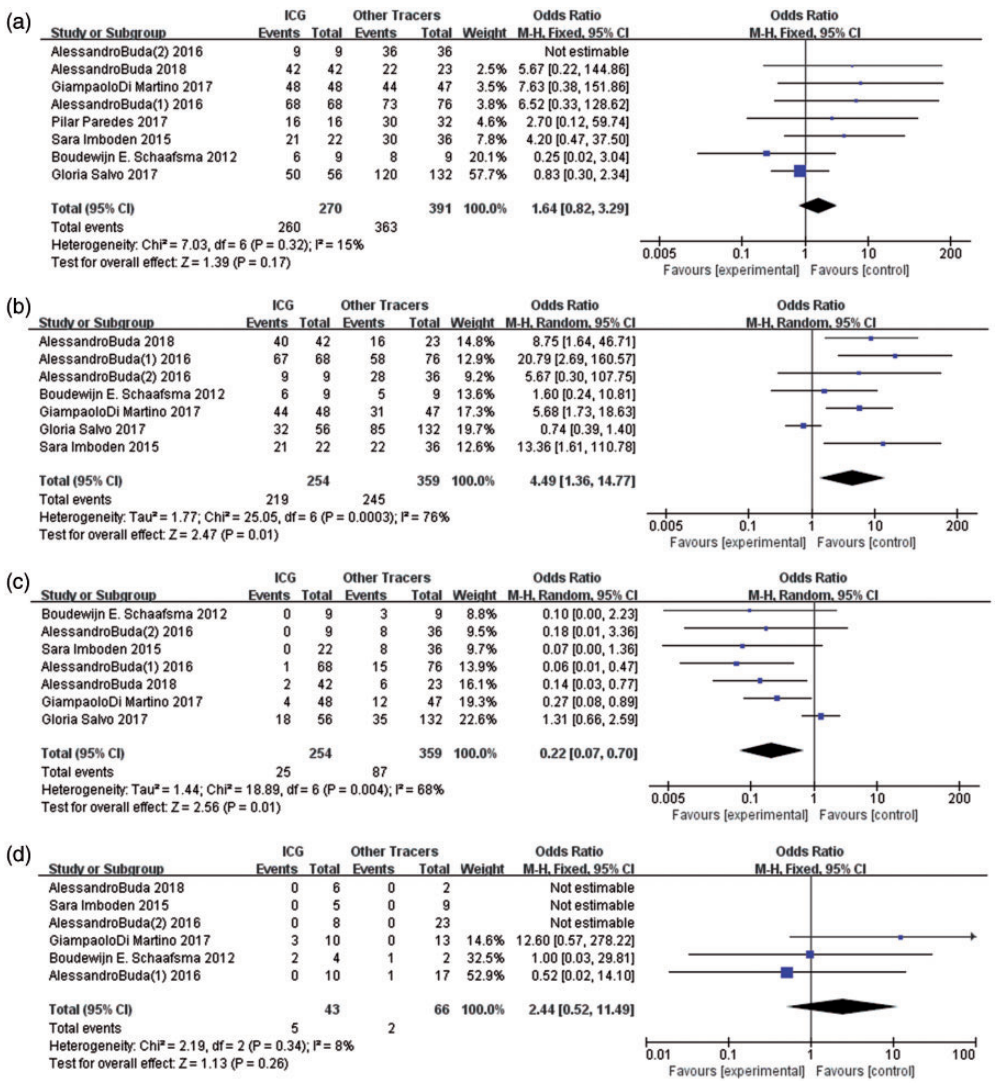

Figure 2. Detection rate of ICG versus other tracers. (a) Overall detection rate of ICG versus other tracers; (b) bilateral detection rate of ICG versus other tracers; (c) unilateral detection rate of ICG versus other tracers; (d) false-negative rate of ICG versus other tracers. ICG, indocyanine green

detection rate appeared to be much higher for ICG than for ^{99}Tc combined with BD, but this was nonsignificant (OR 4.71; 95% CI: 0.93–23.95; $P = 0.06$, random-effects model; Figure 5b). The unilateral detection rate for ICG was much higher than that for ^{99}Tc combined with BD, but this was still considered nonsignificant (OR 0.27; 95% CI: 0.06–1.10; $P = 0.07$, random-effects model; Figure 5c). With regard to all detection rates, ICG alone had the same role, and even appeared to be better, than using ^{99}Tc combined with BD. Therefore, ICG appeared to be superior to ^{99}Tc with BD in detecting SLNs in patients with cervical cancer because of higher detection rates.

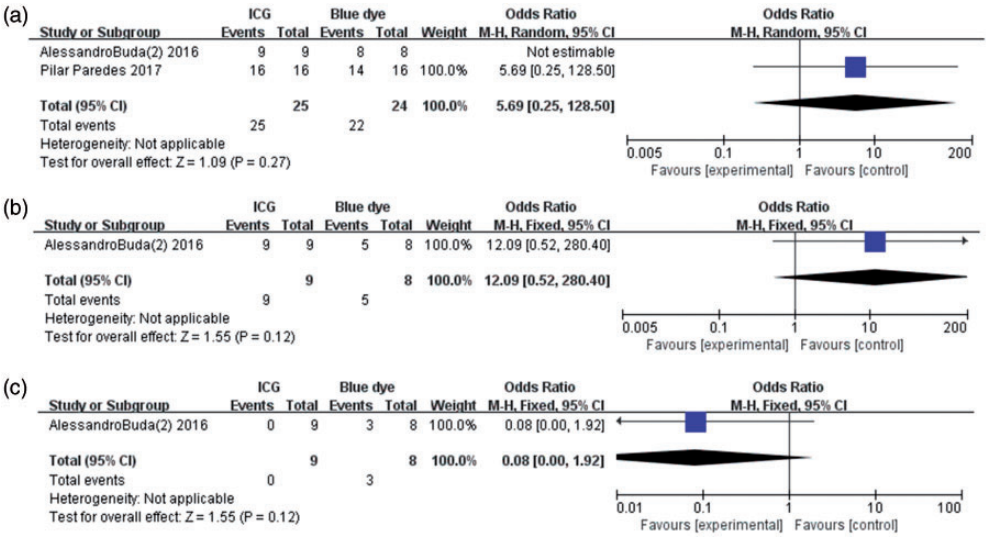

Figure 3. Detection rate of ICG versus blue dyes. (a) Overall detection rate for ICG versus blue dyes; (b) bilateral detection rate for ICG versus blue dyes; (c) unilateral detection rate for ICG versus blue dyes. ICG, indocyanine green

False-negative rates

When ICG was compared with BDs, including isosulfan blue, ^{99}Tc, and HSA for SLN mapping, the pooled analysis data showed no difference in false-negative rates between the two groups (OR 2.44; 95% CI: 0.52–11.49; $P = 0.26$, fixed-effect model; Figure 2d). ICG alone compared with other dyes also showed no difference in false-negative rates (Figure 4d, Figure 5d).

Discussion

When SLN detection algorithms are adopted for cervical cancer as proposed by the Memorial Sloan Kettering Cancer Center, higher overall and bilateral detection rates lead to a lower number of side-specific lymphadenectomies on non-mapping hemi-pelvises.[16] This reduces lymphadenectomy-related surgical morbidity, which has been reported to be as high as 20%,[22] and other common complications. The most commonly used tracers are ICG, BDs, and ^{99}Tc in detecting SLNs in cervical cancer.[4,17,23] HSA is absorbed with ICG to make it more effective. Currently, overall SLN mapping of the pelvis is adequate, with detection rates of 80%.[24] However, for patients with cervical cancer, this mapping is not as effective for SLNs that are located along the internal or external iliac nodal basin.[25] We evaluated unilateral, bilateral, and overall detection rates of SLNs in cervical cancer.

The clinical effectiveness of ICG has been evaluated for SLN identification in gynecological malignancies, either by the laparoscopic approach or by using a robotic platform.[24] An extensive study that used ICG in gynecologic cancers was recently published by Jewell et al.[24] The optimal bilateral mapping of ICG alone was 79% (156/197) and it was 77% (23/30) for ICG and BD. These authors concluded that ICG has a high bilateral detection rate and appears to offer an advantage over using

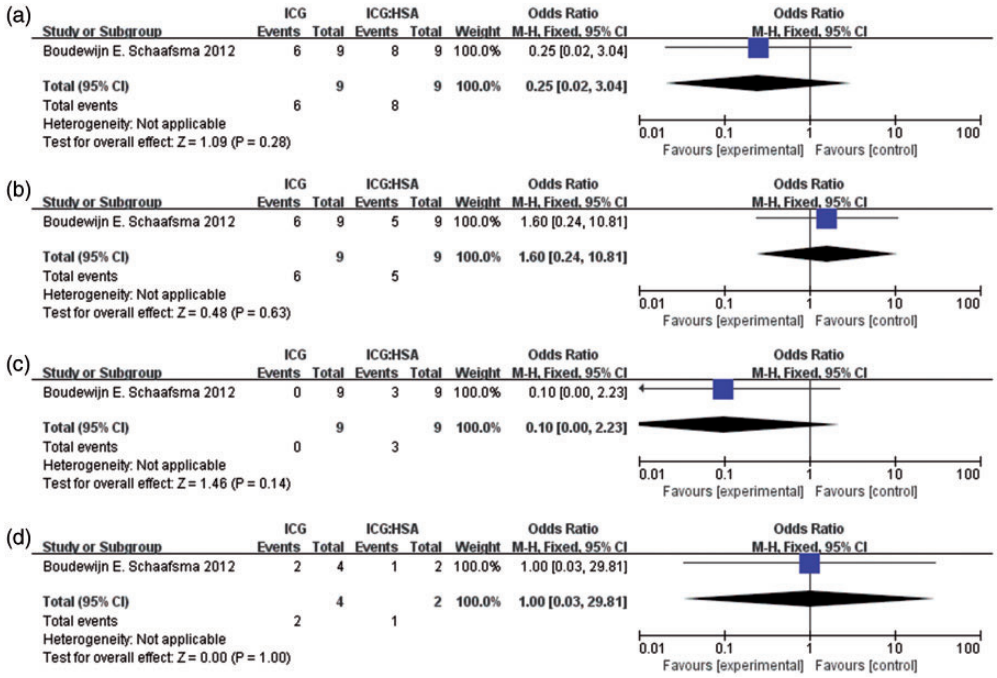

Figure 4. Detection rate of ICG versus ICG:HSA. (a) Overall detection rate for ICG versus ICG:HSA; (b) bilateral detection rate for ICG versus ICG:HSA; (c) unilateral detection rate for ICG versus ICG:HSA; (d) false-negative rate for ICG versus ICG:HSA (not applicable). ICG, indocyanine green; HAS, human serum albumin

BD alone.[16,26] The outcome in our meta-analysis also supports this finding. According to the National Comprehension Cancer Network guidelines, evaluation of SLNs in early-stage cervical cancer remains unclear because of a poor detection rate and low negative predictive value with radiocolloid and BD techniques.[25] However, our outcome showed significant detection rates, especially bilaterally, in evaluating SLNs with ICG over other tracers. Therefore, ICG is superior preoperatively among patients with cervical cancer because of its high detection rate, higher signal-to-background ratio, cheaper cost, fewer adverse effects, and less toxicity compared with other tracers. Understanding of identification of SLNs among patients with cervical cancer is growing rapidly, but several questions remain unanswered.[27]

Several studies have reported the combined use of green dyes and BDs for detecting SLNs.[19,20] After performing our meta-analysis, we did not find any advantage in using BDs and ICG together or BDs over ICG. Therefore, we suggest discontinuing the use of BDs in conjunction with ICG because ICG dye alone can simplify SLN identification. We also evaluated HSA with ICG. This is because preclinical studies indicated that adsorption of ICG in HSA increases the fluorescent intensity and the hydrodynamic diameter, thereby providing improved detection and better retention in SLNs.[28] However, our study showed that ICG:HSA performed as well as ICG

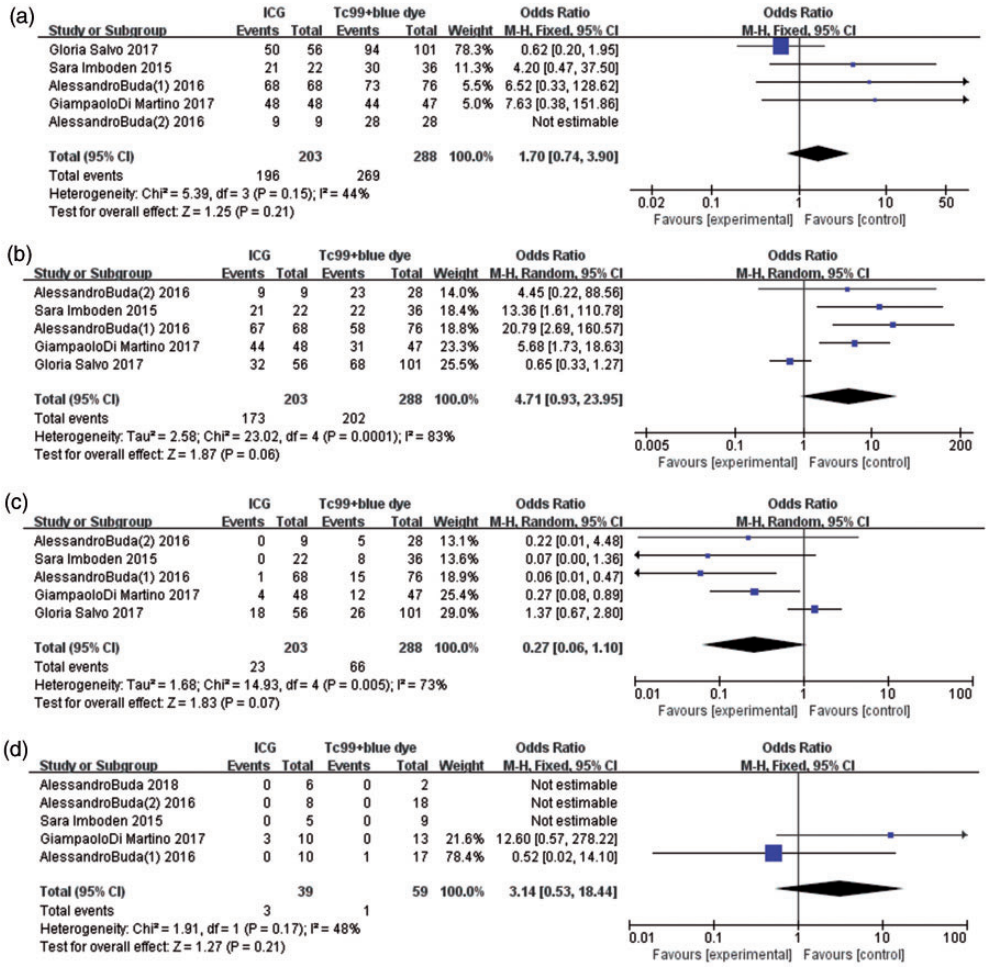

Figure 5. Detection rate of ICG vs. ^{99}Tc combined with blue dyes. (a) Overall detection rate for ICG versus ^{99}Tc combined with blue dyes; (b) bilateral detection rate for ICG versus ^{99}Tc combined with blue dyes; (c) unilateral detection rate for ICG versus ^{99}Tc combined with blue dyes; (d) false-negative detection rate for ICG versus ^{99}Tc combined with blue dyes. ICG, indocyanine green; ^{99}Tc, technetium-99

alone, with no remarkable changes or differences. This finding is in accordance with a previous study in which no difference was found between the use of ICG:HSA and ICG alone in SLN mapping in patients with cervical cancer,[15] but using ICG alone has advantages in early-stage cervical cancer. Therefore, we conclude that the use of ICG:HSA is clinically unnecessary. Besides the advantages of ICG, it also has some disadvantages. ICG rapidly binds to proteins that are present in lymphatic fluid. Four clinical studies, including our study, justified the use of ICG at different anatomical locations (breast cancer, cervical cancer, and vulvar cancer) and at different times, from injection to imaging.[29,30]

ICG has some practical advantages, which include avoiding radiation exposure to patients and staff, and the need for fewer personnel because more staff are no longer required. Additionally, ICG dye is injected

while patients are under anesthesia, which avoids painful administration of radiocolloid preoperatively. Finally, use of ICG appears to be useful during a surgical procedure after SLN detection, allowing the surgeon to complete the procedure without staining the operative field, which occasionally occurs with BD. This is particularly useful in the case of obese patients, when bleeding covers the retroperitoneal fat and obscures the SLN, and BD extensively stains the operative field.[17]

Our meta-analysis had a large sample size and showed better results for ICG compared with other tracers. Therefore, our study can help gynecological oncologists in detection of SLNs using ICG in patients with cervical cancer. Optimization of detection techniques and rates, with the goal of convenience, safety, and lower cost, is important as accuracy rates continue to be assessed.

Acknowledgement

The authors are grateful to Mrs. Juan Li for collecting data.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was partly funded by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AHCR2014-007), the Key Research and Development Project of Shaanxi Provincial Science and Technology Department (2017ZDXM-SF-068), the Natural Foundation of Shaanxi Province (2017ZDJC-11), a grant from the National Natural Science Foundation of China (81472823), and the Shaanxi Provincial Collaborative Technology Innovation Project (2017XT-026).

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