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Review Article

The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review

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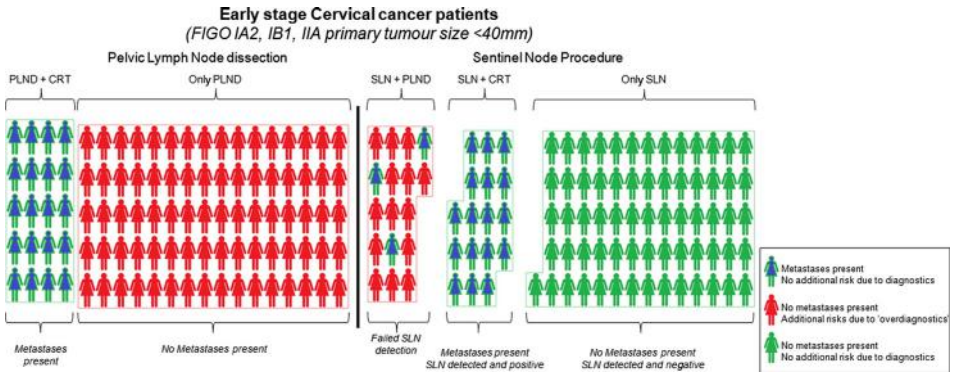
HIGHLIGHTS

- We identified a subgroup in whom a SLN may replace a PLND.
- Ultra staging alone led to a sensitivity of 94%, NPV ranged from 91 to 100%.
- Additional prerequisites led to a sensitivity of 99%, NPV ranged from 97 to 100%.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. Recent reviews on the sentinel lymph node (SLN) procedure in cervical cancer have shown that bilateral SLN detection and ultra staging are safe and superior options compared to a unilateral detection, frozen section and H&E analysis. So far, nobody identified a subgroup of patients in whom a SLN procedure may replace pelvic lymph node dissection (PLND).

Methods. We searched PubMed, Embase, CINAHL and Cochrane from inception up to November 26, 2014. Studies reporting SLN detection, and/or histological outcome of the SLN were included. Methodological quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies tool by two independent reviewers. Data to complete 2 × 2 contingency tables were obtained, and patient-, study- and technique characteristics were extracted. Results were pooled and plotted in forest plots.

Results. Forty-seven studies (4130 patients) were analyzed. Pooled data of diagnostic accuracy on ultra staging (18 studies; 1275 patients) showed a sensitivity of 94% (95% CI 80–99%) and negative predictive values ranging between 91 and 100%. After ultra staging, 19 false negative results remained. Prerequisites such as early FIGO stage (IA2, IB1, IIA primary tumor size <40 mm), no suspicious pre-, and per-operative lymph nodes, and bilateral negative SLNs after ultra staging resulted in 1 remaining false negative result among 1257 patients (0.08%). Pooled data on a combined tracer in early stage cervical cancer patients with primary tumor size <20 mm (6

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studies; 276 patients) resulted in 87% bilateral SLN detection.

Conclusions. Early stage cervical cancer patients (FIGO IA2, IB1, IIA primary tumor size <40 mm) who have no suspicious pre-, and per-operative lymph nodes, and have bilateral negative SLNs after ultra staging, have a residual risk of 0.08% (1/1257) on occult metastases. On the basis of these results we recommend not to perform a full PLND in these patients.

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Contents

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide. With an estimated 266,000 deaths worldwide, it accounts for 7.5% of all female cancer deaths [1]. Pelvic lymph node (PLN) status is an important prognostic factor in cervical cancer, but it is also very important in treatment decisions. The 5-year survival rate decreases from 92% to 64% in case of positive pelvic lymph nodes (PLN), regardless of FIGO stage [2,3]. Guidelines recommend a pelvic lymph node dissection (PLND) in early stage (FIGO IA2, IB1, IIA) cervical cancer in order to detect metastases and adjust treatment accordingly. Only in stage 1A1 disease without lymphovascular space invasion (LVSI) PLND is not recommended because of its low risk of lymph node metastases (<1%) [4]. Lymph node metastases are present in up to 27% in early stage cervical cancer (FIGO stage 1A2–IIA), therefore at least three out of four patients may undergo unnecessary PLND with subsequent risk of significant morbidity and decreased quality of life [2,3,5,6]. A sentinel lymph node (SLN) procedure may detect metastases accurately and may therefore be an attractive alternative to standard PLND.

SLN detection is a standard of care diagnostic procedure for several other tumors like breast, penile, skin and vulvar cancer. It is used as an alternative to a full lymph node dissection in case of a negative SLN [7–9]. The ability to safely predict absence and presence of metastases and therefore replace a full pelvic lymph node dissection will depend on both the detection rate (DR) and the diagnostic accuracy of the SLN procedure. In cervical cancer, there is ongoing debate with regard to whether detection should be bilateral or per pelvis side in order to omit PLND on either side, whether a single tracer or a double tracer (dye and/or radioisotope) should be used, and whether or not the SLN should undergo ultra staging. FIGO stage and tumor size appeared to be important factors influencing both the diagnostic accuracy and detection rate [10–12]. Furthermore, recent reviews on the sentinel lymph node (SLN) procedure in cervical cancer have shown that bilateral SLN detection and ultra staging are safe and superior options compared to a unilateral detection, frozen section and H&E analysis [13,14]. So far, nobody identified a subgroup of patients with clear and applicable criteria in whom a SLN procedure may replace pelvic lymph node dissection (PLND). This appears to preclude the SLN procedure from becoming an alternative to standard pelvic lymph node dissection in early stage cervical cancer patients.

The aim of this diagnostic review therefore is to assess which technique or combination of techniques yields the highest detection rate and diagnostic accuracy for SLN analysis, and to study whether it is possible to identify a subgroup of early cervical cancer patients in which a SLN procedure is a safe alternative to PLND.

2. Materials and methods

2.1. Data sources and searches

We systematically searched Medline, EMBASE, Cochrane Library and CINAHL from inception up to November 26, 2014 for studies on SLN procedure in patients with cervical cancer. The search query combined synonyms for 'cervical cancer' with synonyms for 'sentinel node procedure' (see Supplementary material 1 for the complete search strategy). We also performed a reference and related article search. Duplicate articles were manually filtered using the bibliographic database of EndNote [15].

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2.2. Study selection

We included studies reporting results on SLN detection, and/or comparing histological outcome of the SLN to the non-sentinel lymph nodes from the pelvic lymph node dissection and their respective techniques in patients with early stage uterine cervical cancer. We excluded studies reporting <40 patients to bypass learning curve effects. Two reviewers (C.T. and C.d.G.) independently assessed eligibility of identified papers. Any disagreements were resolved by discussion with a third reviewer (M.M.R.).

2.3. Data extraction and quality assessment

We reviewed the included studies in duplicate and extracted; study population, number of included patients, year of publication, FIGO-stage, tumor size, surgical procedure, SLN identification methods and results, histological processing and results, and number of patients with SLN and non-SLN metastasis.

We assessed the risk of bias and the applicability at study cohort level using the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [16] scoring system. This is a validated tool for assessment of the methodological quality and applicability of diagnostic accuracy studies. Four domains are scored: (1) patient selection, which describes the method for patient selection and the patients included; (2) index test, which describes the test being studied and how it was conducted and interpreted; (3) reference standard, which describes the reference standard used and how it was conducted and interpreted; and (4) flow and timing, which describes the flow of patient inclusion and exclusion and the interval between the index test and the reference standard. The quality assessment was performed by two independent reviewers (C.T. and C.d.G.). Any disagreements were resolved by discussion with a third reviewer (M.M.R.).

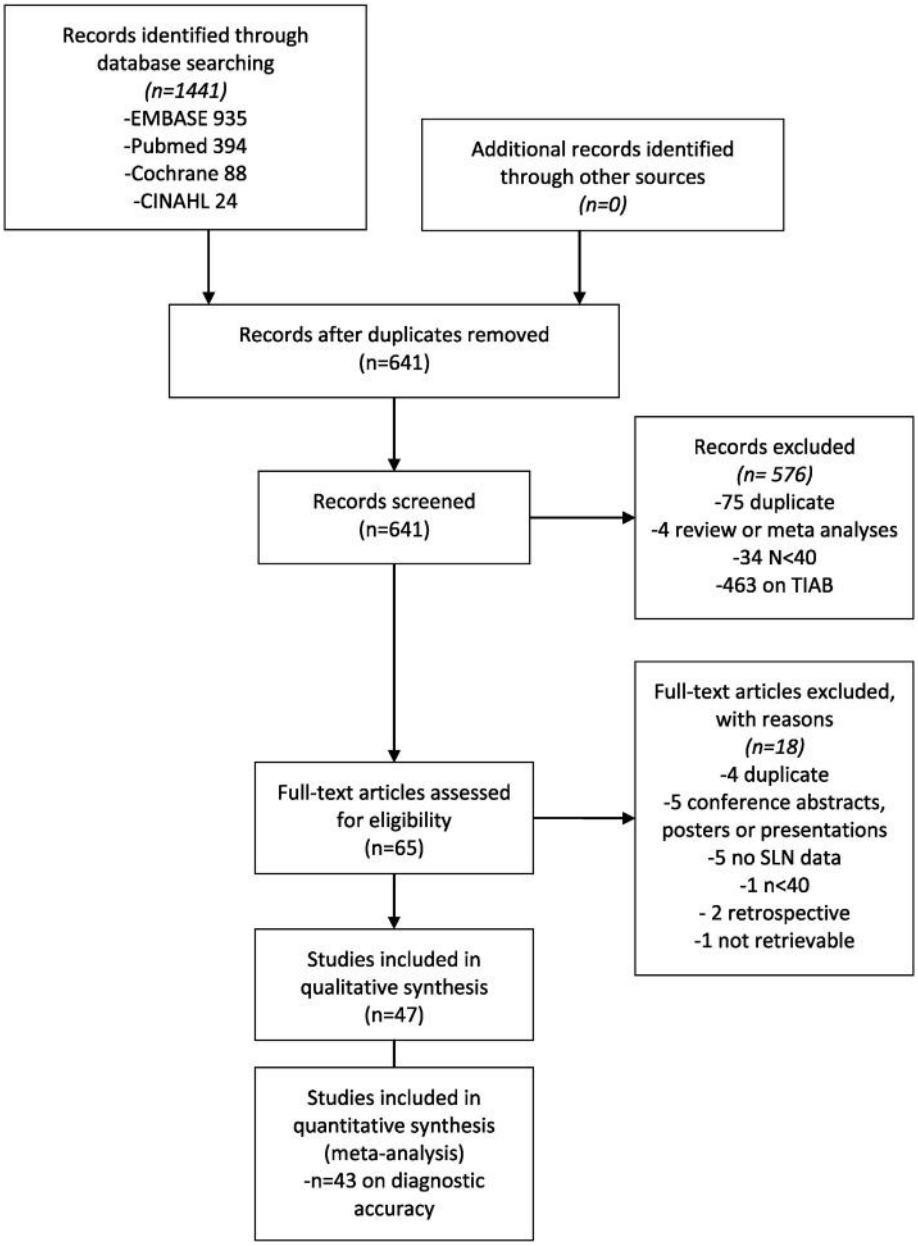

Fig. 1. PRISMA flow diagram. No legend applicable.

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2.4. Data synthesis and analysis

Data from each study were summarized in 2 × 2 tables of true positive, true negative, and false negative values to calculate sensitivity and negative predictive value. False positive results are impossible by definition. Therefore specificity and positive predictive value are always 1.0 and not shown. Authors of studies that did not report all sufficient data were asked to provide additional information. To graphically display the sensitivity and specificity measurements at study level, we used RevMan 5 [17]. We drew forest plots to show variation and to explore heterogeneity for sensitivity. Primary outcomes are pooled estimates of sensitivity with 95% confidence intervals (CIs). We used the Metadas tool [18] within the statistical software package SAS [19] to perform a random effects bivariate logit regression analysis.

2.5. Subgroup analyses

Subgroup analysis on SLN detection and histological SLN analysis was performed on the respective techniques; dye and/or radio-isotope and frozen section analysis, or H&E analyses or ultra staging, respectively. Detection rate and diagnostic accuracy per technique were

Table 1
Characteristics of included studies.

Study	Year	Number of patients	Prevalence in study	Prevalence after detection	Stage	Approach (open/scopic)	Detection technique	Overall DR	Bilateral DR	Hemi pelvis DR	Histological analysis
Malur [20]	2001	50	20%	n.a.	Ia1–IIB, IV	Both	Tc + Dye	78%	n.a.	n.a.	H&E
Dargent [21]	2003	70	n.a.	15%	IA1–IIB	Unknown	Tc + Dye	90%	n.a.	90%	H&E/IHC
Plante [22]	2003	70	17%	18%	IA1–IIA	Scopic	Tc + Dye	87%	60%	74%	FS/H&E/IHC
Basta [23]	2005	52	n.a.	36%	IA2–IIB	Unknown	Tc + Dye	96%	n.a.	n.a.	IHC
Di Stefano [24]	2005	50	20%	22%	IA2–IIA	Open	Dye	90%	54%	72%	FS/H&E/IHC
Rob [25]	2005	183	26%	26%	IA1–IIA	Both	Tc + Dye	100%	54%	77%	FS/H&E/IHC
Roca [26]	2005	40	20%	23%	IA2–IIA	Both	Tc + Dye	87%	75%	81%	H&E/IHC
Silva [27]	2005	56	10%	10%	IA2–IIA	Open	Tc + Dye	100%	n.a.	n.a.	H&E/IHC
Frumovitz [28]	2006	50	n.a.	38%	IA2–IB1	Open	Tc	93%	38%	65%	H&E/IHC
Marnitz [29]	2006	151	n.a.	19%	IA1–IV	Both	Tc + Dye	94%	60%	77%	unclear
Schwendinger [30]	2006	47	28%	26%	IA1–IIB	Open	Dye	83%	n.a.	n.a.	FS/H&E/IHC
Wydra [31]	2006	100	n.a.	26%	IB1–IIA	Unknown	Tc + Dye	84%	66%	75%	FS/H&E/IHC
Altgassen [32]	2007	60	n.a.	27%	IA1–IIB	Open	Dye	93%	n.a.	n.a.	FS
Coutant [33]	2007	67	n.a.	28%	IA1–IIB	Scopic	Tc + Dye	85%	39%	62%	Giemsa/H&E/IHC
Daraï [34]	2007	54	28%	29%	IA1–IB1, IIA–IIB	Scopic	Tc + Dye	83%	n.a.	n.a.	Giemsa/H&E/IHC
Hauspy [35]	2007	39 (42)	8%	8%	A1–IB1, IIA	Both	Tc + Dye	97%	72%	85%	FS/H&E/IHC
Seok Lee [36]	2007	57	19%	19%	IB1–IIA	Unknown	Tc + Dye	100%	n.a.	n.a.	FS
Seong [37]	2007	89	24%	22%	IA2–IIB	Both	Dye	57%	n.a.	n.a.	FS/H&E
Yuan [38]	2007	81	20%	19%	IB1–IIA	Unknown	Dye	83%	56%	69%	H&E/IHC
Altgassen [39]	2008	590	n.a.	20%	IA1–IV	Both	Tc + Dye	90%	36%	52%	H&E
Bats [40]	2008	71	n.a.	29%	IA2–IIB	Scopic	Tc + B Dye	91%	35%	58%	Giemsa/H&E/IHC
Diaz-Feijoo [41]	2008	50	8%	8%	IA2–IIA	Both	Tc + B Dye	100%	n.a.	n.a.	H&E/IHC
Euscher [42]	2008	n.a.	n.a.	33%	IA1-IB2	Unknown	Unclear	n.a.	n.a.	n.a.	H&E/IHC
Rob [43]	2008	40	15%	15%	IA1–IB1	Scopic	Unclear	100%	90%	95%	FS/H&E/IHC
Strnad [44]	2008	158	n.a.	16%	IA2–IB1	Both	Tc + Dye	99%	90%	94%	FS/H&E/IHC
Cibula [45]	2009	44	52%	62%	IB1–IIB	Scopic	Tc + Dye	77%	59%	68%	FS/H&E/IHC
Gortzak [46]	2009	n.a.	n.a.	17%	IB1–IIA	Unknown	Dye	n.a.	n.a.	n.a.	FS/H&E/IHC
Pazin [47]	2009	50	42%	43%	IB1–IIA	Unknown	Dye	92%	38%	65%	unclear
Pluta [48]	2009	60	8%	8%	IA1–IB1	Scopic	Tc + Dye	100%	88%	94%	FS/H&E/IHC
vd Lande [49]	2009	58	22%	21%	IB1–IIA	Scopic	Tc + Dye	97%	n.a.	n.a.	FS/H&E/IHC
Vieira [50]	2009	56	20%	13%	IA1–IIA	Unknown	Tc + Dye	84%	54%	69%	FS/H&E
Yamashita [51]	2009	58	n.a.	10%	IA1–IIIB	Both	Tc + Dye	86%	n.a.	n.a.	FS/H&E
Zarganis [52]	2009	40	20%	15%	IA1–IIB	Unknown	Tc + Dye	85%	35%	60%	H&E/IHC
Darlin [53]	2010	105	19%	19%	IA1–IIA	Both	Tc	90%	59%	74%	FS/H&E/IHC
Fotiou [54]	2010	45	22%	21%	IA2–IB1, IIA	Open	Tc + Dye	87%	42%	64%	H&E/IHC
Ogawa [55]	2010	82	18%	17%	IA1–IIB	Unknown	Tc	88%	66%	77%	H&E/IHC
Cormier [56]	2011	122	20%	21%	IA1–IIA	Both	Tc + Dye	93%	75%	84%	H&E/IHC
Diaz [57]	2011	81	n.a.	34%	IA1–IIB	Unknown	Tc + Dye	95%	72%	83%	H&E/IHC
Du [58]	2011	68	12%	13%	IA2–IB1	Open	Tc	94%	41%	68%	FS/H&E/IHC
Kato [59]	2011	50	14%	n.a.	IA2–IB1	unknown	Tc	94%	72%	83%	FS/H&E/IHC
Roy [60]	2011	211	16%	15%	IA1–IIA	Scopic	Tc + Dye	99%	86%	92%	FS/H&E/IHC
Bats [61]/Lecuru [12]	2012	139	19%	15%	IA1–IB1	Scopic	Tc + Dye	98%	75%	86%	H&E/IHC
Devaja [62]	2012	86	n.a.	11%	IA1–IB1, IIA	Both	Tc + Dye	98%	n.a.	n.a.	H&E/IHC
Klat [63]	2012	204	n.a.	n.a.	IA2–IB2	unknown	Tc + Dye	94%	n.a.	n.a.	IHC
Hoogendam [64]	2013	62	n.a.	22%	IA1–IIA	Scopic	Tc + Dye	94%	87%	90%	Unclear
Freitas [10]	2014	57	16%	19%	IA2-IIA	unknown	Tc + Dye	82%	49%	66%	H&E/IHC
Klapdor [65]	2014	51	n.a.	n.a.	IA1–IV	Both	Tc + Dye	94%	80%	87%	FS/H&E

DR; detection rate.
Dye; any dye.
FS; frozen section analysis.
Giemsa; giemsa staining and analysis.
H&E; hematoxylin and eosin stain and analysis.
ICH; ultrastaging comprising of serial sectioning and/or immunohistochemistry.
n.a.; not available.
Open; laparotomy.
Scopic; laparoscopy.
Tc; technetium or any other radioisotope.

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analyzed on subgroups for a tumor size smaller than 40 mm and 20 mm in early stage cervical cancer patients.

3. Results

3.1. Literature search

Fig. 1 provides an overview of the literature search and study selection. Our search yielded 641 unique records, of which 65 remained after screening titles and abstracts. The full-text of these studies was reviewed for eligibility. Nineteen studies were excluded for reporting <40 patients (1), were duplicate (4), retrospective (2), not retrievable (1), not peer-reviewed (5), or presented no data on SLN detection and diagnostic accuracy (5). Finally, 47 studies (4130 patients) were included.

3.2. Study characteristics

Table 1 summarizes the characteristics of the included studies. Study population ranged from 40 to 590 patients, with a mean of 88 patients.

3.3. Methodological quality

Overall quality of studies was moderate (Fig. S1). Specific information on selection methods, index test and reference test were not provided in 19, 23 and, 24 studies, respectively. A high risk of bias in patient selection, index test, reference test, and flow and timing was present in 5, 8, 4 and 9 studies, respectively. Patients were excluded from analysis without a clear reason, detection technique and/or histological process of the SLN as well as the reference analysis were changed, and studies were often not blinded. Since we could extract data on technique level and perform relevant subgroup analyses, applicability was of less concern.

3.4. Diagnostic accuracy

Overall diagnostic accuracy was assessable in 43 studies. Four studies [21,59,63,65] were excluded for not reporting diagnostic accuracy per patient, only reporting false negative outcomes, and only reporting diagnostic accuracy for the entire study population, respectively [21,59,63,65]. Prevalence of metastases after SLN detection was 21% (710/3426).

Pooled sensitivity and NPV are shown in Table 2. Ultra staging resulted in a sensitivity of 94% and a NPV range of 91–100% compared to a sensitivity of 68% and NPV range of 59–100% from frozen section and/or H&E analysis. This was due to correctly detecting metastases with ultra staging in 75/94 false negative (FN) patients on frozen section and/or H&E analysis. Of these 75 patients, 26 had isolated tumor cells, 44 micro metastases and 5 had macro metastases.

Ultra staging alone resulted in a FN outcome in 19 out of 1275 patients. Therefore the risk of under treatment on ultra staging, i.e. not detecting pelvic lymph node metastases due to false negative SLN results and leaving out a full pelvic lymph node dissection, is 1.5%.

Further investigation of the19 patients with FN results showed that 18 cases could have been prevented by adding additional criteria as a prerequisite to ultra staging. These criteria are bilateral SLN detection (9/18), early FIGO stages IA2, IB1, IIA cervical cancer (6/18), no suspicious lymph nodes during either pre-operative imaging or surgery (2/18), and primary tumor size <40 mm (1/18). If we applied these criteria, only one FN result remained in a stage IB1 patient who had bilateral negative SLNs, tumor size <40 mm, and no suspicious lymph nodes during either pre-operative imaging or surgery (Fig. 2). Application of abovementioned criteria would decrease the chance of under treatment from 1.5% (19/1275) to 0.08% (1/1257).

Table 2
Diagnostic accuracy per technique.

	Studies	TP	FN	TN	Total	Pooled sensitivity (95% CI)	Range NPV
Overall	43	544	156	2620	3320	81% (47–95%)	59–100%
FS or H&E	18	176	94	1005	1275	68% (38–88%)	59–100%
Ultra staging		251	19	1005	1275	94% (80–99%)	91–100%
Proposed criteria		251	1	1005	1257	99% (98–100%)[a]	97–100%

CI; confidence interval.
TP; true positive i.e. a tumor positive SLN regardless of remaining pelvic lymph nodes status.
FN; false negative i.e. a tumor negative SLN with metastasis present in remaining pelvic lymph nodes.
TN; true negative i.e. a tumor negative SLN and no metastasis present in remaining pelvic lymph nodes.
[a] Assessed if it were a single study.

3.5. Detection rate

A SLN procedure was performed in 47 studies including 4130 patients; the overall detection rate could be assessed in 44 studies including 3931 patients. Three studies were excluded, two [42,46] did not report the number of patients in whom a SLN procedure was performed and one [21] only reported a detection rate per side [21,42,46]. Overall detection rate differed per approach (Table S1). Detection rates were 91%, 74% and 60% using an 'at least one SLN', a 'per hemi pelvis', and a 'bilateral SLN' approach, respectively.

3.6. Subgroup analysis

Table 3 shows the subgroup analysis on detection rate per technique, i.e. a dye or an isotope tracer, and a combined tracer. Compared to the overall detection rates (Table S1), a higher detection rate in early stage cervical cancer patients was achieved in both the 'at least one SLN' and 'bilateral SLN' detection using a combined tracer, 94% versus 91% and 72% versus 60%, respectively. This analyses was unfortunately not possible for the 'per hemi pelvis' approach.

Subgroup analysis on tumor size and technique within the 'bilateral SLN' approach showed that bilateral detection rate was highest (87%) when a combined tracer was used in early stage patients with a tumor size <20 mm (Fig. 3).

3.7. Detecting a SLN due to a combined tracer

In 10 studies it was explicitly reported that a combined tracer resulted in detecting either an only dyed, or only radioactive SLN in 133 SLNs out of the 653 SLNs detected by those studies. Thus a combined tracer detects 20% (133/653) SLNs which might not have been detected when either a dye or isotope alone was used.

3.8. Anaphylactic reactions

The presence or absence of anaphylactic reactions due to a dye tracer was explicitly reported in 10 studies, with anaphylactic reaction in 0.6% (8/1302 patients). Of these, at least four were serious leading to resuscitations and/or ICU admittance, three had mild allergic reactions e.g. blue hives leading to postponing surgery, or only canceling the SLN procedure and one reaction was unexplained.

3.9. Standard PLND compared to a SLN procedure as diagnostic tool

We compared current standard PLND guidelines to implementing a SLN procedure as a diagnostic tool in all early stage cervical cancer patients of this diagnostic review (Fig. S2). Both scenarios use pelvic lymph node status as reference. Current guidelines would advise a

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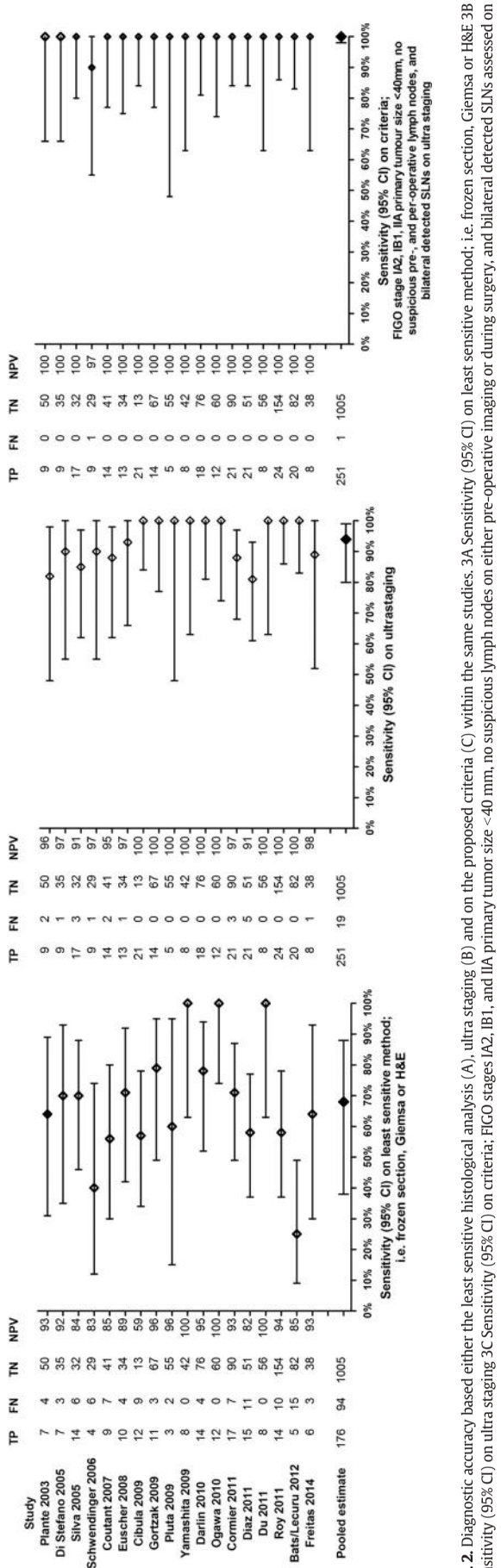

Fig. 2. Diagnostic accuracy based either the least sensitive histological analysis (A), ultra staging (B) and on the proposed criteria (C) within the same studies. 3A Sensitivity (95% CI) on least sensitive method; i.e. frozen section, Giemsa or H&E 3B Sensitivity (95% CI) on ultra staging 3C Sensitivity (95% CI) on criteria; FIGO stages IA2, IB1, and IIA primary tumor size <40 mm, no suspicious lymph nodes on either pre-operative imaging or during surgery, and bilateral detected SLNs assessed on ultra staging.

Table 3
Overall and bilateral detection rate per technique.

	At least one SLN				Bilateral detection			
	Studies	Total patients	Number detected	DR (95% CI)	Studies	Total patients	Number detected	DR (95% CI)
Overall	44	3931	3584	91% (90–92)	31	3026	1816	60% (58–62)
Per technique								
Dye tracer	11	594	502	85% (81–87)	8	349	194	56% (50–61)
Isotope tracer	7	336	299	89% (85–92)	4	256	139	54% (48–60)
Dye or isotope tracer	18	930	801	86% (84–88)	12	605	333	55% (51–59)
Dye and isotope tracer	32	2539	2379	94% (93–95)	18	1274	916	72% (69–74)

SLN; sentinel lymph node.
DR; detection rate.

PLND in all patients compared to 17% after a SLN procedure due to a failed SLN procedure; i.e. no bilateral SLN detection and/or anaphylactic reaction. A SLN procedure may result in 0.6% having an anaphylactic reaction whenever a dye tracer is used. Although 17% underwent a PLND due to a failed SLN detection, only 14% received 'overdiagnostics', as 3% had pelvic metastases present, justifying the PLND in retrospect. The 17% patients with a true positive SLN should be treated with concurrent chemoradiotherapy (CRT) according to current guidelines [4].

The standard PLND scenario resulted in a justified-, under-, and over-diagnostics in 20%, 0%, and 80% compared to 85.92%, 0.08%, and 14% after a SLN procedure, respectively.

4. Discussion

This diagnostic review shows that a SLN procedure may replace a full pelvic lymph node dissection in patients with early stage cervical cancer (IA2, IB1, IIA primary tumor size <40 mm) with bilateral negative SLNs after ultra staging and without suspicious lymph nodes during either pre-operative imaging or surgery, as a SLN procedure will reduce the PLND over treatment rate from 80 to 10% with an acceptable risk on occult metastases of only 0.08%.

The major strength of this diagnostic review is that as far as we are aware, it is the first study defining a subgroup of patients with clear and applicable criteria in whom it is safe to omit a full pelvic lymph node. Furthermore, our results are also in agreement with other reviews which also showed that bilateral sentinel node detection and ultra staging are safer and superior compared to unilateral detection, frozen section, and H&E analysis. The other reviews did, however, not quantify this superiority. We also found that FIGO stage and tumor size are important factors influencing both the diagnostic accuracy and detection rate [13,14]. Furthermore, all analyses were performed according to the safest option, i.e. overestimating risks and underestimating positive results. For example, only Pluta [48] could be included based on the criteria of; only early stage cervical cancer patients (FIGO stages IA2, IB1, and IIA with primary tumor <40 mm) and bilateral detected SLNs assessed on ultra staging. We however, decided to exclude results on patient level, which resulted in 18 studies (1157 patients) with a lower sensitivity and NPV compared to Pluta [48], 99.6% versus 100%, and 99.9% versus 100%, respectively. Furthermore, the risk of 0.6% on anaphylactic reactions due to a dye tracer may be overestimated since it is based on 10 studies that explicitly mention either the presence or absence of adverse reactions, out of 40 studies using a dye tracer.

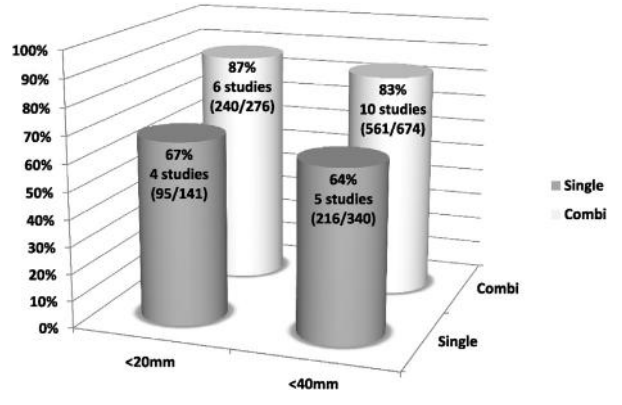

Fig. 3. Bilateral detection rate in early stage cervical cancer per technique and tumor size n. a.

This diagnostic review also has two major limitations. First, lymph nodes other than the SLN were not analyzed on ultra staging, whereas ultra staging has the highest diagnostic accuracy. Analyzing these non-sentinel lymph nodes similarly to ultra staging might reveal occult metastases. This may decrease both the diagnostic accuracy and the validity of the SLN concept in general. However, we couldn't find any other study that analyzed the results of ultra staging for SLN's and non-sentinel lymph nodes in a similar way, neither in cervical cancer nor in any other tumor type.

Second, we could only exclude patients who did not comply with the proposed criteria on stage, size, suspicion of metastases, and bilateral detection rate and had false negative results since details regarding these criteria were only reported for FN results. This has probably resulted in an underestimation of the FN rate. However, at least 92% (1157/1257) of all true positive and true negative patients on ultra staging need to be excluded before the risk on occult metastases would exceed 1%.

Diagnostic accuracy is the single most important aspect of any SLN procedure. In general, it should be as high as possible in order to be a safe alternative to standard lymph node dissection. The detection rate should also be as high as possible since it depicts the proportion in which a SLN procedure might prevent a PLND. However, an increase in detection rate should never lead to a decrease in diagnostic accuracy.

Ultra staging led to the highest diagnostic accuracy by detecting SLN metastases in 80% (75/94) of early stage cervical cancer patients in whom the SLN was deemed negative on FS and/or H&E analysis. Recent reports also showed clinical relevance of removing low volume disease including isolated tumor cells which are primarily detected through ultra staging. [66] We therefore believe that ultra staging is the best option for SLN analysis in early stage cervical cancer patients.

Bilateral SLN detection yielded a lower detection rate (60%) compared to 'at least one SLN' (91%), or 'per hemi pelvis' (74%) approach. However, bilateral detection is superior since it results in the highest diagnostic accuracy through a superior reduction of false negative results. Therefore bilateral detection should be a prerequisite. We advise to perform a full pelvic lymph node dissection whenever the SLN is not bilaterally detected, A side-specific LND is an alternative option which will lead to a residual false negative risk of 0.4% (data not shown) instead of 0.08% (1/1257).

Detection rates were higher when using a combined tracer technique. This higher detection rate could be due to a combined tracer detecting 20% (133/653) SLN's that were either only dyed or radioactive during surgery. These SLN's might have been missed when either a dye or isotope was used alone. We did not include studies on

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fluorescent probes such as indocyanine green as they did not meet our inclusion criteria. So far, no evidence is available showing that fluorescent dye alone may perform as well as a combined tracer, without the risk of anaphylaxis. However, if a bilateral sentinel lymph node is detected with a single fluorescent probe, its diagnostic accuracy is probably equivalent.

Subgroup analyses in patients with early stage disease showed a bilateral detection rate of 87% and 83% in patients with a tumor diameter of <20 mm and <40 mm when using a double tracer technique.

Thus, an acceptable bilateral detection rate with a low false negative rate may be achieved when using a double tracer technique in early stage cervical cancer patients with at least <40 mm primary tumor size.

Diagnostic accuracy was highest with an estimated sensitivity of 99.6% (95% CI: 98–100%) and 99.9% NPV when the following criteria were met as prerequisites; bilateral SLN detection, no suspicious lymph nodes on pre-operative imaging or during surgery, and a primary tumor diameter of <40 mm. These criteria reduce the residual risk on occult metastases to 0.08% (1/1257). In contrast, in melanoma, breast and vulvar cancer a residual risk of 3%, 0–10% and 2% on occult metastasis has been used as an acceptable cut-off point to abandon full lymph node dissection [67–71].

5. Conclusion

Early stage cervical cancer patients (FIGO stages IA2, IB1, and IIA primary tumor size <40 mm) who have no suspicious lymph nodes on either pre-operative imaging or during surgery, and have bilateral negative SLNs after ultra staging, have a residual risk of 0.08% on occult metastases. On the basis of these results we recommend not to perform a full PLND in these patients.

Declaration of interests

There are no conflicts of interests.

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