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Learning curve and factors influencing successful robot-assisted bilateral sentinel lymph node mapping in early-stage cervical cancer: an observational cohort study

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ABSTRACT

Objectives: To evaluate whether a learning curve affects the bilateral sentinel lymph node (SLN) detection in early-stage cervical cancer.

Methods: All patients with FIGO (2018) stage IA1-IB2 or IIA1 cervical cancer who had undergone robot-assisted SLN mapping performed with a combination of preoperative technetium-99m nanocolloids (including preoperative imaging) and intraoperative blue dye were retrospectively included. Risk-adjusted cumulative sum (RA-CUSUM) analysis was used to determine if a learning curve based on bilateral SLN detection existed in this cohort.

Results: A total of 227 cervical cancer patients were included. In 98.2% of patients (223/227) at least one SLN was detected. The bilateral SLN detection rate was 87.2% (198/227). Except for age (OR 1.06 per year, 95%CI 1.02–1.09), no significant risk factors for non-bilateral SLN detection were found (e.g., prior conization, BMI or FIGO stage). The RA-CUSUM analysis showed no clear learning phase during the first procedures and cumulative bilateral detection rate remained at least 80% during the entire inclusion period.

Conclusions: In this single-institution experience, we observed no learning curve affecting robot-assisted SLN mapping using a radiotracer and blue dye in early-stage cervical cancer patients, with stable bilateral detection rates of at least 80% when adhering to a standardized methodology.

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KEYWORDS
Cervical cancer; learning curve; radiotracer; robotic surgery; sentinel lymph node

1. Introduction

Increasingly, sentinel lymph node (SLN) mapping is adopted in early-stage cervical cancer, a minimally invasive approach intended to replace full pelvic lymph node dissection (PLND) to assess lymph node status. Since the cervix is a midline organ with bilateral lymph drainage, bilateral SLN detection is a prerequisite for a high sensitivity and high negative predictive value of SLN mapping [1,2]. Therefore, achieving reliable SLN mapping with high bilateral detection rates by a skilled surgeon is important. Even more now that recent studies showed a surgical learning curve could impact oncological outcomes when adopting new technologies in the treatment of cervical cancer [3–7].

The number of cases needed to consistently perform reliable SLN mapping has been an ongoing topic of discussion in various cancer types. Early studies assessing SLN mapping with a radiotracer and blue dye reported learning curves from 20 to 63 cases in breast cancer and 30 cases in melanoma [8–10]. In gynecologic cancers, the SLN detection rate has shown to increase with time and surgical experience but the exact case number remains undefined [11–13]. Research in endometrial cancer reported a learning curve of 30 cases to achieve an increase in overall detection (i.e., SLN detection in at least one hemipelvis) from 77% to 94% with a radiotracer and blue dye, without reporting the learning curve for bilateral detection [14]. The SLN procedures were part of either laparoscopic or laparotomic treatment. In a cohort of both cervical and endometrial cancer patients treated with robot-assisted surgery, learning curves of 27 cases to achieve 100% overall detection and 48 cases to achieve at least 60% bilateral detection were reported when using indocyanine green (ICG) [15]. A consensus statement from the Society of Gynecologic Oncology (SGO) reviewing SLN mapping in endometrial cancer recommends surgeons to complete at least 20 SLN procedures before abandoning PLND. This statement is based on the breast cancer guidelines and does not specify the mapping technique [16,17]. Overall, results show that the established learning curves for SLN detection seem to vary with tumor type, the method of assessing the learning curve, definition of proficiency, mapping technique used (i.e. radiotracer with blue dye or ICG), surgical approach, and case volume of a center [8,9,11,18]. As SLN mapping is performed increasingly in cervical cancer, while the role of minimally invasive surgery is under debate [19], learning curve assessment of specific mapping techniques is needed.

This article presents the results of a single-institution experience in performing robot-assisted SLN mapping in early-

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stage cervical cancer using a radiotracer combined with blue dye. Our primary aim is to investigate whether a learning curve for performing SLN mapping exists and when surgical proficiency occurs. To establish the learning curve, risk-adjusted cumulative sum analysis is used.

2. Patients and methods

2.1. Patient selection

This observational cohort was derived from the departmental treatment outcome register for robot-assisted laparoscopy, created for continuous quality review of the provided care at our tertiary referral center. Included in this study were patients diagnosed with FIGO 2009/2018 stage IA1 (with lymph-vascular space invasion (LVSI)) to IB1 (FIGO 2009) or IB2 (FIGO 2018), or IIA1 cervical cancer who were consecutively treated with robot-assisted laparoscopy including an SLN mapping procedure with technetium-99m (^{99m}Tc) nanocolloid and blue dye (between September 2009 and May 2021) [20,21]. Tumor extent (and FIGO staging) was partly based on MRI findings. Excluded were patients who were younger than 18 years old, were treated with neoadjuvant chemotherapy (EORTC 55,994 or NCT04016389) or who objected against the reuse of their health care data (recorded in their medical record) for scientific research. All procedures were part of standard clinical care, for which informed consent was obtained. This study was approved by the Institutional Review Board. Requirements for consent were waived for the use of these pseudonymized retrospective data.

2.2. Sentinel lymph node mapping

We have previously reported on the SLN mapping technique that was used during the inclusion period [22]. To summarize, one day prior to surgery (with an 18–20 h interval to surgery; long protocol) or the morning of surgery (4–6 h interval to surgery; short protocol) a total dose of 240 MBq ^{99m}Tc-nanocolloid (General Electric Healthcare, Eindhoven, The Netherlands) was injected into four quadrants of the cervix. Ninety minutes post-injection either planar lymphoscintigraphy (Forte gamma camera, Philips Healthcare, Best, The Netherlands) until March 2011 or SPECT/CT (Symbia T16, Siemens, Erlangen, Germany) was performed. All scans were preoperatively reviewed by nuclear medicine physicians.

Intraoperatively, a total dose of 4 mL patent blue dye (Blue Patenté V, Guerbet Group, Roissy, France) was injected into four quadrants of the cervix using a prepositioned injection system (as reported in our previous publication [22]). Reports of preoperative imaging were consulted before the start of SLN mapping to indicate the expected SLN station. Simultaneously with the visual aid of blue dye, a laparoscopic gamma probe (Europrobe 3 Coelioscopique, Euromedical Instruments, Le Chesnay, France) was used for the intraoperative detection of SLNs.

Sentinel lymph nodes were defined as the first lymph node(s) of each pelvic side to receive afferent lymphatic drainage from the primary cervical tumor, identified intraoperatively with either a gamma probe or blue color, and preferably both. After each SLN mapping procedure full pelvic lymph node dissection (PLND) was performed, according to European guidelines [23]. In some cases with small tumors (i.e., FIGO IA1 with LVSI) and on an individualized basis, PLND was omitted in shared decision with the patient. In cases with tumor-positive SLNs at frozen section analysis, chemoradiation substituted radical hysterectomy. Histopathological assessment of the excised SLNs was performed according to the previously described protocol [24].

All robot-assisted procedures were performed at a tertiary referral center by a surgical team consisting of two gynecological oncologists at the same time (surgeon A and B from inception to 2017, surgeon B and C from 2017 to 2021) using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA, type S until 2010, Si until 2018, and X or Xi since 2018 onwards). From the introduction of a novice surgeon in 2017 (surgeon C), an experienced proctor (surgeon B) was present during 22 cases before the novice performed a SLN mapping procedure alone. During the inclusion period, robot-assisted surgery was the standard modality. No SLN mapping procedures were performed in endometrial cancer patients (as this was and is not considered standard-of-care in the Dutch guidelines), nor did we participate in any trial regarding SLN mapping or was there any prior SLN experience with ^{99m}Tc-nanocolloid that could have contributed to the learning curve. Before introducing ^{99m}Tc-nanocolloid with preoperative imaging, 11 robot-assisted SLN mapping procedures were performed with blue dye only.

2.3. Data collection

Clinical, surgical, and histopathological data in our register were collected from institutional medical records including: age at diagnosis, body mass index (BMI, in kg/m^2), clinical FIGO stage (following the 2009 guidelines from inception to February 2019; following 2018 guidelines from February 2019 onwards), medical history, prior conization or large loop excision of transformation zone (LLETZ), tumor diameter (clinically), type of procedure, year of surgery, tumor histology and size, preoperative and intraoperative overall SLN detection rate (defined as at least one SLN detected) and bilateral SLN detection rate (defined as at least one SLN detected in each pelvic side), SLN count, lymph node tumor status (positive tumor status was defined as macrometastasis (≥2 mm) or micrometastasis (0.2–2 mm), and oncological outcome. Adverse events following SLN mapping were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [25].

2.4. Statistical analysis

The primary outcome of interest was the learning curve to obtain surgical proficiency in SLN mapping, based on bilateral SLN detection rate. Bilateral detection rate is defined as intraoperative detection of at least one SLN on both sides of the hemipelvis. Secondary outcomes of interest were oncological outcomes (i.e., overall survival and disease-free survival), risk factors related to non-bilateral SLN mapping and cumulative bilateral SLN detection rate. Other clinical relevant outcome

like false-negativity and sensitivity of SLN mapping, and anatomical location and count of SLNs were described in a previous publication [24].

To assess the learning curve, risk-adjusted cumulative sum (RA-CUSUM) analysis was used, following the methodology described in our previous publication [3]. Surgical failure was defined as non-bilateral SLN detection (i.e., either unilateral SLN detection or complete mapping failure). The extent to which the curve move was determined by the difference between the observed and predicted probability of non-bilateral detection of each subject. To model the predicted probability of each individual, logistic regression was performed using predefined variables considered to be risk factors for non-bilateral detection based on the previous literature [18]. We limited this model to three degrees of freedom to prevent overfitting. Variables yielding a *p*-value of less than 0.05 by univariate analysis were entered into a multivariate logistic regression model. Different models were tested and the best performing model, based on likelihood ratio test, was chosen for further analysis. Details of the RA-CUSUM functions are provided in supplementary Appendix S1.

Survival curves were estimated using Kaplan-Meier method and differences between groups were compared using log-rank test. Overall survival was defined as the time interval between diagnosis and death of any cause. Disease-free survival was defined as time interval between diagnosis and disease recurrence, detected clinically, by imaging, or histopathological biopsy. For the cumulative bilateral detection rate, the number of cases with bilateral detection was divided by the serial number of procedures performed.

The continuous data were compared using the t-test or Mann – Whitney U-test as appropriate. Categorical data were reported as proportions and compared between groups using chi-square test or Fisher's exact test as appropriate. Statistical tests were two-sided with a significance set at $p < 0.05$, with confidence intervals (CI) at the 95% level.

Analyses were performed using the Statistical Package for the Social Sciences version 26.0.0.1 (SPSS; International Business Machines, Armonk, NY, USA), RStudio version 1.3.1093 (RStudio: Integrated Development Environment for R, PBC, Boston, MA, USA) and Microsoft Excel 2016 (Microsoft, Redmond, WA, USA).

3. Results

3.1. Cohort

In total, 227 cervical cancer patients who underwent robot-assisted SLN mapping were enrolled between September 2009 and May 2021. Baseline characteristics of the study population are summarized in Table 1. The majority of patients was staged as FIGO 2009/2018 1B1 or FIGO 2018 IB2 (in total 87.2%) and 67.0% was diagnosed with squamous cell carcinoma of the cervix. In total, 92.5% the patients underwent full PLND. The combination of ^{99m}Tc-nanocolloid and blue dye yielded an overall detection rate of 98.2% and a bilateral detection rate of 87.2%. In 1.8% (4/227) patients complete mapping failure occurred. Three patients developed adverse events related to blue dye injection for which they received parenteral intervention: two grade 3 allergic reactions (urticaria $n = 1$, anaphylaxis with rapid response to intervention = 1) and one grade 4 allergic reaction (anaphylactic shock $n = 1$).

Table 2 shows the characteristics of the population divided into two groups: patients with successful bilateral detection intraoperatively versus patients with non-bilateral detection intraoperatively. Median age differed significantly between the two groups: a median of 38 years when successful bilateral detection occurred versus a median of 50 years when bilateral detection failed ($p < 0.001$). Other baseline characteristics were not significantly different between the groups. Regarding oncological outcomes, the proportion of lymph node metastasis was higher in patients with non-bilateral mapping: 24.1% in the non-bilateral group versus 14.1% positive lymph nodes in the bilateral detection group ($p = 0.17$). Patients with successful bilateral detection had a 5-year overall survival of 91.1% while patients with non-bilateral mapping had a 5-year overall survival of 81.0% ($p = 0.12$). Patients with successful bilateral mapping had a 5-year disease-free survival of 86.7% while patients with non-bilateral mapping had a 5-year disease-free survival of 73.2% ($p = 0.054$).

3.2. Learning curve

To be able to adjust for individual risks in RA-CUSUM analysis, multiple-risk models were fitted using logistic regression. Table 2 shows the outcomes of univariate analysis in which only age appeared significantly related to non-bilateral detection (OR 1.06 per year, 95% CI 1.02–1.09). The model with age as a continuous variable, rather than a categorical variable, fitted the data best. The probabilities from a model containing age were used in further RA-CUSUM analysis.

Figure 1 shows the RA-CUSUM chart. In the first procedures no learning curve is observed, which would be indicated by a peak in the chart. Later on, from procedure number 64 to 70, a peak is observed indicating an increase in non-bilateral SLN detection. The specific cases ($n = 6$) contributing to this peak were analyzed: five patients with unilateral SLN detection intraoperatively and one patient with complete mapping failure intraoperatively. Of these six patients, two were aged above 50 years old, all had BMI below 30 kg/m^2, four had previous conization/LLETZ, all had tumor size less than 20 mm at physical examination, and none of the patients had tumor-positive lymph nodes in pelvic lymph node dissection. None of these six patients developed a recurrence within the received follow-up time. Another, smaller, peak is observed at the end of the RA-CUSUM chart starting at procedure number 176. At this point, in a range of 21 procedures, seven procedures resulted in an intraoperative unilateral detection only. A novice was introduced to the surgical team at procedure number 135, without visibly impacting the RA-CUSUM chart.

As a sensitivity analysis, a multivariate model based on previous literature was fitted including age (<50 vs 50–70 vs ≥ 70), BMI (<18.5 vs 18.5–25 vs 25–30 vs ≥ 30), and tumor size (<20 mm vs ≥20 mm) [18]. Herein, only age contributed significantly ($p < 0.001$ for category 50–70). The RA-CUSUM

Table 1. Baseline characteristics of study population ($n = 227$).

		n	%
Age, median (range)	39 (23–81)		
BMI, median (range)	23.7 (17.3–41.8)		
FIGO stage 2009	IA1/IA2	12	6.6
	IB1	165	91.2
	IIA1	4	2.2
	Total	181	100.0
FIGO stage 2018	IA1/IA2	9	19.6
	IB1	22	47.8
	IB2	11	23.9
	IIA1	4	8.7
	Total	46	100.0
Histology	Squamous cell carcinoma	152	67.0
	Adenocarcinoma	61	26.9
	Other	14	6.2
Grade[a]	I	49	22.4
	II	105	47.9
	III	65	29.7
LVSI	No	121	54.3
	Yes	102	45.7
Prior LLETZ or conization	No	97	42.7
	Yes	130	57.3
Type of nodal assessment	PLND + SLN	210	92.5
	SLN only	17	7.5
Preoperative imaging	Lymphoscintigraphy	31	13.7
	SPECT/CT	196	86.3
SLN procedure success (intraoperatively)	Complete mapping failure	4	1.8
	Left unilateral detection	13	5.7
	Right unilateral detection	12	5.3
	Bilateral detection	198	87.2
Lymph node status	Tumor negative	192	84.6
	Tumor positive	35	15.4
Adjuvant therapy	No	172	75.8
	Yes	55	24.2
	Radiotherapy	*23*	*10.1*
	Chemoradiation	*32*	*14.1*

Percentages may not total 100 because of rounding.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymph-vascular space invasion; LLETZ, large loop excision of the transformation zone; PLND, pelvic lymph node dissection; SLN, sentinel lymph node; SPECT/CT, single photon emission computed tomography with X-ray computed tomography.
[a]8 missings.

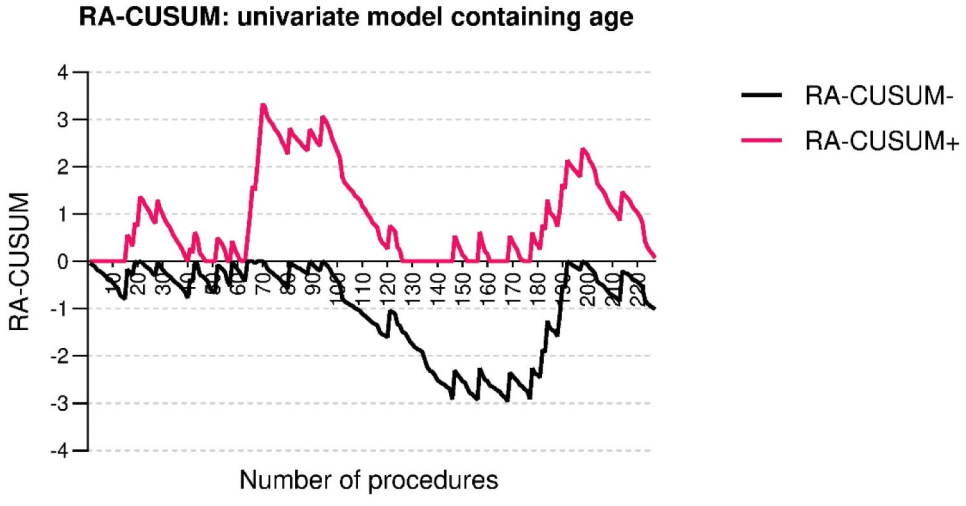

Figure 1. Learning curve of robot-assisted sentinel lymph node mapping procedures ($n = 227$) with ^{99m}Tc-nanocolloid and blue dye.

The x-axis indicates the number of SLN procedures performed. The y-axis indicates the cumulative sum of surgical success and failure (here: non-bilateral detection) adjusted for the probabilities from the risk model. The RA-CUSUM+ (red) is designed to detect a decrease in surgical performance (odds of non-bilateral detection = 2). The RA-CUSUM- (black) is designed to detect an increase in surgical performance (odds of non-bilateral detection = 0.5). Both curves move upward for surgical failure and downward for surgical success.

Table 2. Baseline characteristics of the two groups and univariate analysis of factors associated with non-bilateral detection.

		Successful bilateral mapping n = 198	Non-bilateral mapping n = 29	p^a	OR univariate analysis	p
Age	Median (IQR)	38 (31 to 46)	50 (37 to 58)	<0.001	1.06 (1.02–1.09)	<0.001
BMI	Median (IQR)	23.6 (21.3 to 26.3)	23.7 (21.7 to 26.5)	0.724	1.00 (0.91–1.09)	0.993
Parity	0	71 (35.9)	12 (41.4)	0.680		
	≥1	127 (64.1)	17 (58.6)		0.79 (0.36–1.79)	0.565
Prior abdominal surgery	No	148 (74.7)	21 (72.4)	0.821		
	Yes	50 (25.3)	8 (27.6)		1.13 (0.45–2.62)	0.788
FIGO 2009 stage[b]	IA1/IA2	12 (7.5)	0 (0.0)	0.518	*NA*	
	IB1	144 (90.6)	21 (95.5)			
	IIA1	3 (1.9)	1 (4.5)			
FIGO 2018 stage[c]	IA1/IA2	8 (20.5)	1 (14.3)	1.000	*NA*	
	IB1	18 (46.2)	4 (57.1)			
	IB2	9 (23.1)	2 (28.6)			
	IIA1	4 (10.3)	0 (0.0)			
Histology	Squamouscell carcinoma	129 (65.2)	23 (79.3)	0.220		
	Adenocarcinoma	57 (28.8)	4 (13.8)		0.39 (0.11–1.08)	0.099
	Other	12 (6.1)	2 (6.9)		0.93 (0.14–3.73)	0.933
LVSI[d]	No	102 (52.6)	19 (65.5)	0.233		
	Yes	92 (47.4)	10 (34.5)		0.58 (0.25–1.29)	0.196
Prior conization or LLETZ	No	83 (41.9)	14 (48.3)	0.551		
	Yes	115 (58.1)	15 (51.7)		0.77 (0.35–1.70)	0.519
Clinical tumor size[e]	<20 mm	136 (68.7)	17 (58.6)	0.294	1.55 (0.70–3.44)	0.283
	≥20 mm	62 (31.3)	12 (41.4)			
Preoperative imaging	Lymphoscintigraphy	27 (13.6)	4 (13.8)	1.000		
	SPECT/CT	171 (86.4)	25 (86.2)		0.99 (0.35–3.54)	0.982
Year of surgery	2009 – 2012	49 (24.7)	7 (24.1)	1.000		
	2013 – 2017	81 (40.9)	12 (41.4)		1.04 (0.39–2.95)	0.943
	2017 – 2021	68 (34.3)	10 (34.5)		1.03 (0.37–3.01)	0.956
Lymph node status	Negative	170 (85.9)	22 (75.9)	0.172		
	Positive	28 (14.1)	7 (24.1)		1.93 (0.71–4.77)	0.170

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LLETZ, large loop excision of the transformation zone; LVSI, lymph-vascular space invasion; PLND, pelvic lymph node dissection; SPECT/CT, single photon emission computed tomography with X-ray computed tomography.
[a]Fisher's exact test and Mann-Whitney U test were used for categorical data and median values, respectively.
[b]46 missings; [c]181 missings; [d]4 missings; [e]Tumor size reported during physical examination. When previous conization/LLETZ was performed clinical tumor size was assumed to be <20 mm.

plot constructed with the probabilities of the multivariate model showed identical charts (not shown).

Figure 2 shows the cumulative bilateral detection at every procedure during the entire inclusion period. From the beginning, intraoperative bilateral detection rate remained between 80% and 100%. The lowest intraoperative bilateral detection rate in this cohort, at 80%, was observed at 70 procedures, after which the intraoperative bilateral detection increased again and stabilized around 87% until the end.

The number of SLNs excised during surgery remained stable over the years (no significant association with linear regression) with a median of two SLNs (range 1–5).

4. Discussion

To the best of our knowledge, we are the first to assess the learning curve of robot-assisted SLN mapping with ^{99m}Tc-nanocolloid and blue dye in early-stage cervical cancer patients. Our results suggest no institutional learning curve is present when performing robot-assisted SLN mapping procedures with ^{99m}Tc-nanocolloid and blue dye when adhering to a standardized methodology. A pronounced peak halfway in the learning curve chart, indicating a short period of less satisfying SLN detection rates, could not be explained from the data. Over the entire period, the cumulative bilateral detection remained at least 80%. In this cohort, only age was a significant risk factor associated to non-bilateral SLN detection with an OR of 1.06 for each year of increase in age (95% CI 1.02–1.09). A non-significant lower 5-year disease-free survival was observed in the subgroup of patients with non-bilateral detection (73.2% versus 86.7% in the bilateral detection group, $p = 0.054$). Prior work already showed that percentage of false-negative SLN in this cohort is low (negative predictive value of 99.4% in the case of bilateral mapping) and, therefore, could not be used as an endpoint to assess a learning curve [24].

This study had several strengths and limitations. To assess the learning curve for bilateral SLN detection, we used RA-CUSUM analysis, which is considered the reference standard for studying surgical learning curves [26]. We focused on bilateral detection as this is a prerequisite for reliable nodal assessment by SLN mapping. To acquire a homogenous population and limit variables affecting the learning curve as much as possible, we excluded patients in whom other SLN methods than the combined approach of a radiotracer and blue dye were used. This study is limited by its retrospective single-institution design. Another limitation is that surgeons participating in this study had performed 11 robot-assisted SLN procedures with blue dye only before inception of SLN mapping with the combined approach. The acquired robot-assisted skills and anatomical understanding of the various lymph node stations could have contributed to identifying SLNs effectively from the start with the combined approach, although this impact would be relatively small since the length of reported learning curves in the previous literature is much longer than 11 cases.

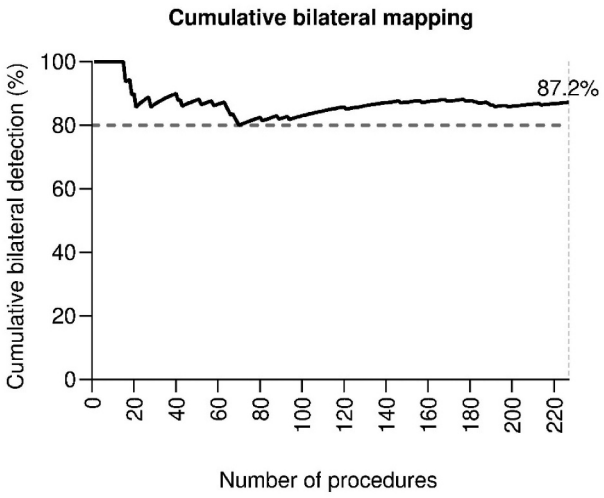

Figure 2. Cumulative bilateral detection rate with ^{99m}Tc-nanocolloid and blue dye.

Our results differ from reported learning curves of SLN mapping in other studies in gynecological cancers so far. In 2003, Plante et al. already reported their experience with conventional laparoscopic SLN detection using either blue dye only or combined with a radiotracer in 70 cervical cancer patients [11]. Their results showed that bilateral detection increased from 51% to 93% after 55 cases, suggesting a learning curve effect. However, the major increase in bilateral detection could, at least partly, be attributed to the addition of a radiotracer in a subgroup of 29 patients, which already increased the bilateral detection rate from 55% to 72%. The addition of a radiotracer followed by preoperative lymphoscintigraphy seemed to contribute valuable information regarding the SLN location after intracervical injection, which involves multiple possible SLN stations within the inner pelvis. In 2009, Khoury et al. reported their experience with and laparotomic and laparoscopic SLN procedures in endometrial cancer patients. They found a single surgeon's learning curve of 30 SLN procedures based on an increase in overall detection from 77% to 94% after 30 cases [14]. Bilateral detection rate was not reported. Further limitations encompassed unclear cutoff selection and heterogeneity in the methodology in terms of injection (71% cervix versus 29% cervix and uterine fundus) and tracer use (36% blue dye only versus 64% ^{99m}Tc sulfur colloid and blue dye).

A variety of learning curves are also reported for SLN mapping with the more recently adopted fluorescent tracer ICG. Bedýnska et al., studying a population of 32 patients with cervical or endometrial cancer who underwent laparotomy or conventional laparoscopy, reported a learning curve of 17 cases after which the bilateral detection of SLNs increased from 53% (9/17) to 100% (15/15) [12]. It remained unclear how the cutoff of 17 cases was established and whether the high detection rate was maintained after the reported 15 cases of the second group. Another single-center study stated at least 27 cases were needed to achieve proficient robot-assisted SLN mapping with ICG in a total of 80 patients with cervical or endometrial cancer, without defining proficient mapping [15]. Their results showed that even 48 cases were needed to reach a minimal bilateral detection of 60%. The reported learning curve was based on cumulative sum (CUSUM) analysis, without specifying the parameters needed for this analysis. Surgeons participating in this study had already performed more than 100 robot-assisted procedures when they started with SLN mapping.

Several reasons might explain the differences between our results and the results of previous studies. First, from the moment of introducing SLN mapping with ^{99m}Tc-nanocolloid and blue dye at our institution, the bilateral detection rate was high, which makes a possible learning curve less pronounced. Second, rather than randomly dividing the cohort based on year of surgery or percentage of cases performed, we used RA-CUSUM analysis. A RA-CUSUM has an additional value in its individual risk adjustment, required to assess and adjust for heterogeneous patient cohorts, compared to standard CUSUM analysis wherein parameters are set based on the literature. Third, in the aforementioned studies, preoperative imaging of SLNs was not possible (in case of using ICG) or only performed in a part of the population. Our results suggest that preoperative lymphoscintigraphy or SPECT/CT, performed on all patients in this study, could have guided the surgeon more effectively toward the SLN location during surgery. Having access to preoperative imaging showing the number and locations of SLNs can be valuable for intraoperative guidance. Results from a retrospective analysis on SLN mapping with ICG substantiate that this technique is associated with removing more SLNs, which likely include second echelons lymph nodes, especially with limited surgical experience [27]. Therefore, instead of omitting the combined approach and adopting ICG only, a hybrid ^{99m}Tc-ICG tracer providing the opportunity of preoperative imaging might be considered. Lastly, the different surgical modalities used for SLN mapping in prior studies (in which laparotomic and laparoscopic procedures are combined), could have contributed to differences in learning curves.

The question remains if the described learning curves for SLN mapping are mainly constituted by the surgical experience or by the tracer technique used, or a combination of the two. Since its inception, the SLN mapping technique has evolved and it is possible that with different SLN mapping techniques different learning curves exist. Large prospective studies in breast cancer patients showed that not only surgeon experience but also tracer technique (i.e. blue dye only versus radiotracer with blue dye) significantly contributed to the detection rate [9,28]. Sentinel lymph node mapping, especially when using the combined method, is eminently a multidisciplinary procedure, such that a possible learning curve reflects the combined experience of colleagues in nuclear medicine, radiology, pathology, and the operating room [29].

Previously, several risk factors for failed bilateral SLN detection have been described in other cohorts of cervical cancer patients. Risk factors reported from analysis on the combined SENTICOL I and SENTICOL II dataset were age ≥ 70 years, BMI ≥ 30 kg/m2, tumor size ≥ 20 mm, and yearly institutional volume of <5 cases. Recent results of the multicenter SENTIX trial ($n = 391$) showed that, in multivariate analysis, higher age, and lower number of cases per site were significantly associated with non-bilateral detection (both $p < 0.01$) [30]. In our single-institution cohort all these potential risk factors, except for case volume, were assessed, but only an increase in age was significantly associated with

bilateral detection failure. The hypothesis behind age being an important and independent risk factor is that lymphatic draining declines over time due to lymphatic channels becoming enlarged, hyperpermeable and less contractile, and the reduced production of lymphangiogenic factors [31–33].

Remarkable is the difference in proportion of lymph node metastases between the groups: 24.1% in the non-bilateral group versus 14.1% positive lymph nodes in the bilateral detection group. Although lymph node metastases showed no significant association with bilateral detection rate in this study or other large cervical cancer studies (SENTICOL I & II and SENTIX trial [18,30]), previous studies in breast cancer showed that the risk of SLN nonvisualization was significantly higher when nodal metastases were present ($p < 0.001$) [34,35]. The failed detection could be explained by infiltrating tumor cells blocking tracer passage through lymph vessels and nodes. Nonetheless, the higher proportion of lymph node metastases and lower disease-free survival in the non-bilateral group stresses the importance of reliable SLN mapping with high bilateral detection rates. How to ascertain this when implementing SLN mapping?

In 2013, Mansel et al. published the results of New Start, a structured, validated, multidisciplinary training program in SLN mapping in breast cancer to ensure safe and competent practice across the United Kingdom [36]. Their most striking finding was that a combination of a standard injection protocol (in this case using a radiotracer and blue dye) with structured multidisciplinary training could diminish learning curves for SLN naïve surgeons performing their first 30 consecutive SLN procedures. Another study in breast cancer suggested that performing SLN procedures on a phantom is a valuable teaching tool for surgeons to become familiar with using a gamma probe to localize SLNs intraoperatively, and could help to shorten the learning curve [37]. Before starting the SLN mapping technique in cervical cancer, our institution had extensive experience with the tracer technique in other tumor types like vulvar cancer and breast cancer, which laid the foundation for the standardized SLN protocol used in this study. Based on our results, we could not establish a learning curve or suggest a minimal number of cases to be performed under supervision. However, our results add to the current literature by indicating that a multidisciplinary team dedicated to a standardized SLN mapping technique in – what is considered – high volumes will lead to stable and high bilateral detection without an evident learning phase. More research is needed on structured learning programs for (robot-assisted) SLN procedures, following the example of breast cancer studies.

5. Conclusion

In this single-institution experience, we observed no evident learning curve to achieve bilateral SLN detection in early-stage cervical cancer patients. Stable bilateral detection rates above 80% are feasible when SLN procedures are performed by a dedicated multidisciplinary team experienced in using a radiotracer and blue dye in a standardized approach. Besides increasing age, no other patient factors were found association with bilateral SLN detection failure. More research on structured training programs can be beneficial when widely adopting the SLN mapping concept in cervical cancer.

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Declaration of interest

RPZ is a proctor for robot-assisted surgery in gynecological oncology on behalf of Intuitive Surgical Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Data availability statement

The data that support the findings of this study are available from the corresponding author, IGTB, upon reasonable request.

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Author contributions

IGTB: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Visualization. JPH: Conceptualization, Methodology, Validation, Writing – Review & Editing. AJATB: Validation, Writing – Review & Editing. BdK: Validation, Writing – Review & Editing. CGG: Conceptualization, Methodology, Validation, Writing – Review & Editing. RPZ: Conceptualization, Methodology, Validation, Writing – Review & Editing, Supervision.

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