cancers

Systematic Review

Sentinel Lymph Node Biopsy Alone Versus Sentinel Lymph Node Biopsy with Systematic Pelvic Lymphadenectomy in Early-Stage Cervical Cancer—A Systematic Review and Meta-Analysis

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Simple Summary

Whether extensive removal of pelvic lymph nodes can be safely avoided in early-stage cervical cancer remains debated. Sentinel lymph node biopsy examines the first lymph nodes to which cancer is likely to spread and may allow less extensive surgery. We reviewed 11 studies involving 3842 patients to compare cancer outcomes after sentinel lymph node biopsy alone or combined with systematic pelvic lymph node removal. The estimated proportion of patients alive without disease at three years was 95% after sentinel lymph node biopsy alone and 93% after additional pelvic lymph node removal, with no statistically significant difference. Deaths were uncommon and generally comparable between groups. The randomized trial provides the clearest evidence that additional pelvic lymph node removal can be omitted in patients who meet its eligibility criteria. Other studies also reported high three-year survival after sentinel node biopsy alone, but many enrolled women with smaller tumors or favorable lymph node findings. These differences help explain why the results are most applicable to patients selected in a similar way.

Abstract

Background/Objectives: Despite the widespread use of sentinel lymph node biopsy, in cervical cancer the omission of systematic lymphadenectomy is still debatable. We aimed to compare oncologic outcomes of sentinel lymph node biopsy without or with pelvic lymphadenectomy in patients operated for early-stage cervical cancer. Methods: MEDLINE, Embase, CENTRAL, Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov were searched from inception to 30 October 2025. Randomized and observational studies including patients with invasive cervical cancer undergoing sentinel biopsy alone or sentinel biopsy plus pelvic lymphadenectomy were eligible. Study selection and data extraction were performed in compliance with PRISMA 2020 and Cochrane recommendations. Pooled data was evaluated using a random-effects model. Risk of bias was assessed using ROBINS-I and RoB 2. Three-year disease-free survival, recurrence outcomes and prognostic factors of recurrence were analyzed.

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Results: Eleven studies, involving 3842 patients with early-stage cervical cancer, were included. A total of 1818 patients underwent sentinel lymph node biopsy alone and 2024 underwent systematic pelvic lymphadenectomy. Pooled 3-year disease-free survival across all cohorts was 94% (95% CI, 92–95%), while it was 95% (95% CI, 92–96%) in the sentinel lymph node-only group and 93% (95% CI, 92–95%) in the pelvic lymphadenectomy group (p = 0.246). Recurrence and mortality were summarized descriptively across studies. In PHENIX-I, retroperitoneal nodal recurrence occurred in 0/420 patients assigned to SLND alone and 9/418 assigned to additional PLND. In exploratory meta-regression, the cohort proportion of grade 3 tumors was associated with 3-year DFS. Conclusions: Three-year DFS was high with both nodal strategies. PHENIX-I supports omission of pelvic lymphadenectomy in trial-eligible patients with negative sentinel nodes on frozen sections, with lower postoperative lymphatic morbidity. Differences in patient selection limit interpretation of the recurrence and mortality proportions across studies.

Keywords: cervical cancer; sentinel node biopsy; lymphadenectomy; surgical de-escalation

1. Introduction

Cervical cancer poses a significant global health burden, particularly in resource-limited regions, where cervical cancer represents the most common gynecologic malignancy [1]. Surgical management including pelvic lymphadenectomy (PLND) has been the cornerstone of treatment for early-stage disease for more than a century [2,3]. However, this approach carries substantial morbidity, including lymphedema of various severity, lymphocyst formation, vascular and neural injury, venous thromboembolism, and prolonged operative duration [2,4]. Furthermore, many early-stage cervical cancer patients who are eligible for surgical treatment are node-negative according to imaging results, and the majority of these do not show lymphonodal involvement in the final pathological results. This raises concerns that systematic lymphadenectomy may represent overtreatment in a significant proportion of cases [5].

Sentinel lymph node biopsy (SLND) has emerged as a less invasive alternative, precisely identifying and removing only the closest lymph nodes of the afferent lymphatic chain, the nodes at highest risk for metastasis [6]. This technique utilizes cervical injection of tracers such as technetium-99m (Tc), blue dye (BD), indocyanine green (ICG), or their combination [7]. Numerous studies validated the diagnostic accuracy of SLND in cervical cancer, with pooled detection rates of 95%, and sensitivity approaching 95–97% when bilateral mapping is achieved [8–11]. The technique allows for ultrastaging with serial sectioning and immunohistochemistry. Due to the potential detection of micrometastases or even isolated tumor cells (ITC) that would be missed by routine pathologic examination, high-risk patients who might otherwise go unrecognized can be identified [12–14].

Despite these well-documented advantages, clinical practice guidelines have not reached consensus on whether and when lymphadenectomy should be replaced by SLND alone [2]. Current guidelines list SLN mapping as an acceptable alternative to pelvic lymphadenectomy for early-stage cervical cancer, with the best detection rates in tumors <2 cm [3,7]. Previous systematic reviews have examined survival after sentinel lymph node biopsy alone in early-stage cervical cancer [15]. The subsequent publication of PHENIX-I, which randomized patients to sentinel lymph node biopsy alone or additional pelvic lymphadenectomy, and the final results of SENTIX, a prospective single-arm study,

expanded the evidence available for this question [2,5]. We synthesized oncologic outcomes at a common 3-year landmark and examined how the estimates varied with follow-up duration and the availability of a within-study comparator. Our objective was to clarify what the randomized and observational evidence each contribute to decisions about omitting systematic pelvic lymphadenectomy. We performed a systematic review and compared the disease-free survival and recurrence tendencies in patients undergoing surgical treatment for cervical cancer with sentinel lymph node biopsy (SLND) with or without systematic lymphadenectomy, to determine whether data available in the literature supports the omission of lymphadenectomy in these patients.

2. Materials and Methods

This systematic review was prospectively registered on PROSPERO (CRD420251180289) on 30 September 2025 [16]. Reporting followed PRISMA 2020 guidelines [17] and the Cochrane Handbook Version 6.5 [18]. The PRISMA checklist can be found in the Supplementary Materials (Supplementary Tables S3 and S4).

2.1. Eligibility Criteria

Observational studies and randomized controlled trials were included using the following PICO framework:

P: Female patients with invasive cervical cancer undergoing
sentinel lymph node biopsy (SLND);
I: SLND only;
C: SLND plus systematic pelvic lymphadenectomy;
O: 3-year disease-free survival (primary outcome).

2.2. Search Strategy

Six databases (MEDLINE, Embase, CENTRAL, Cochrane, Web of Science, Scopus) and ClinicalTrials.gov were searched from inception to October 30, 2025, using the following keywords: (cervi*) AND (cancer OR malign* OR tumo* OR neoplas* OR carcinoma OR adenocarcinoma) AND (surger* OR treat OR management OR therap*) AND (senti*). No language or other restrictions were applied.

2.3. Study Selection

After duplicate removal using EndNote X9 (Clarivate Analytics), two independent reviewers (R.T., M.P.) screened titles/abstracts and full texts via Rayyan.ai. Of 3350 screened articles, 3321 were excluded at title/abstract and 20 at full-text review. Ten additional articles were identified from reference lists, of which 8 were excluded. Eleven studies were included in the final analysis. Inter-reviewer agreement was substantial (Cohen's $\kappa = 0.85$ and 0.87 for each screening stage); disagreements were resolved by a third reviewer (N.B.) (Figure 1).

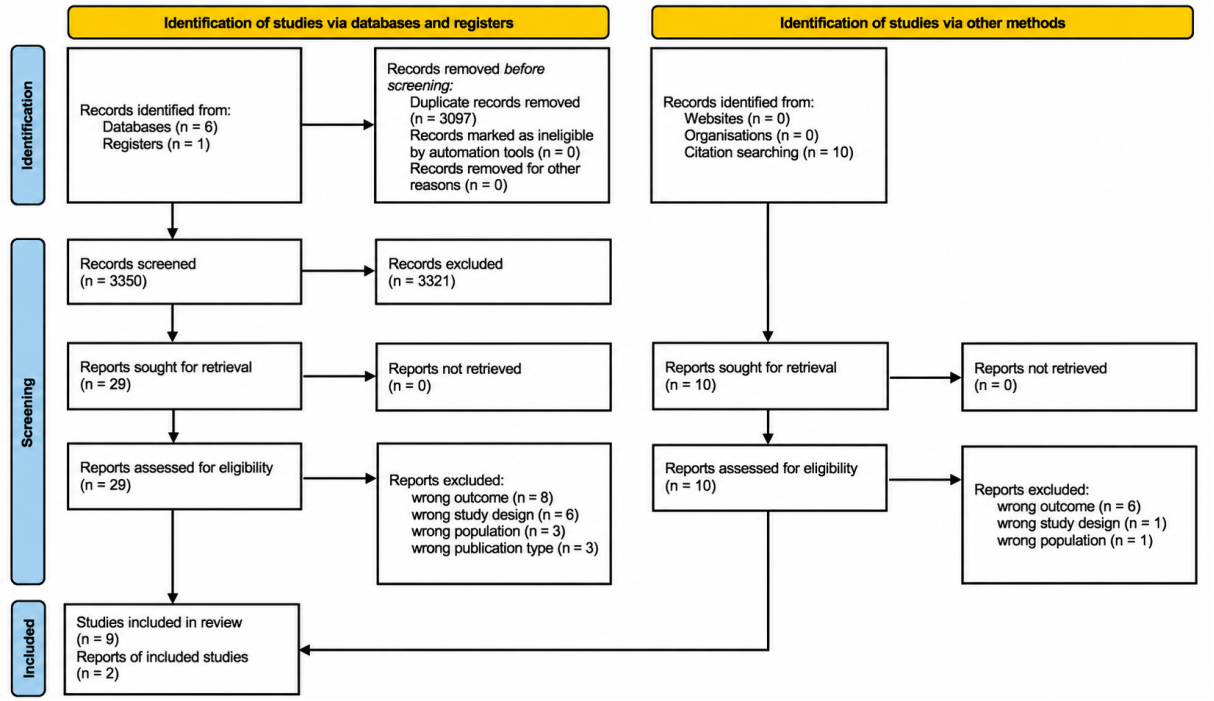

Figure 1. PRISMA 2020 flow diagram summarizing the study selection process for the systematic review.

2.4. Data Extraction

Two reviewers (R.T., M.P.) independently extracted data into Microsoft Excel for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA)., including author, publication year, study design, study period, intervention, age, BMI, histology, stage, tracer type, surgical approach, follow-up duration, recurrence, death, and survival data.

For each cohort, we recorded the median follow-up, whether follow-up was reported for the treatment arm or the whole study, the endpoint used by the investigators, and the source of the 36-month estimate. We extracted the published numerical estimate when available and otherwise used the published Kaplan–Meier curve when the relevant treatment group and endpoint could be identified at 36 months. We recorded the number at risk at 36 months when available. Supplementary Table S5 summarizes these details by study.

2.5. Risk of Bias and Quality of Evidence

Risk of bias was assessed independently by two reviewers (R.T., M.P.) using RoB 2 for randomized trials and ROBINS-I for non-randomized studies [17], with disagreements resolved by a third reviewer (N.B.). Visualization was performed using Robvis [19]. Evidence certainty was evaluated using the GRADE framework via GRADEpro GDT software (McMaster University, Hamilton, ON, Canada; developed by Evidence Prime; web-based version, accessed 10 March 2026) [20].

2.6. Publication Bias

We assessed small-study effects separately for SLND and PLND by plotting each cohort's logit-transformed 3-year DFS estimate against its standard error. Each study contributed at most one cohort to each plot. For Egger's test, we regressed the standardized estimate on its precision and used a two-sided t test of the intercept. We applied the Duval–Tweedie trim-and-fill method with the L_0 estimator and random-effect pooling. We examined both directions of asymmetry and report the number of imputed cohorts and the resulting pooled estimates. Because fewer than ten studies contributed to either group,

we interpreted these analyses as exploratory. All analyses were conducted in R (version 4.4.2).

2.7. Statistical Analysis

Pooled effect estimates were reported as proportions with their 95% confidence intervals. The degree of heterogeneity was quantified using the I^2 statistic, the τ^2 (between-study variance) and Cochran's Q test; a random effect model, based on the DerSimonian and Laird method, was implemented to account for between-study variability. The subgroup difference was assessed using the $\chi 2$ test for interaction. Meta-regression analysis was performed to investigate potential differences in outcome based on study-level population characteristics.

We repeated the analysis of 3-year DFS after excluding studies judged to be at serious risk of bias and retaining randomized or prospectively assembled cohorts with an identifiable 36-month estimate for the relevant treatment arm. We pooled absolute DFS across the eligible arms. For observational comparisons, we also recorded the factors used to select patients for each nodal strategy and whether the investigators used matching or multivariable adjustment (Supplementary Table S6).

Recurrence and mortality outcomes were summarized descriptively by treatment group using the reported event counts and denominators. We did not conduct study-level comparative meta-analyses for these outcomes; therefore, no pooled odds ratio or hazard ratio, inferential *p* value, or heterogeneity statistic was estimated. These descriptive summaries were not interpreted as estimates of a treatment effect.

In a post hoc sensitivity analysis, we repeated the subgroup analysis after restricting it to cohorts with a reported median follow-up of at least 36 months. We used arm-specific follow-up when available and the overall study median when only that value was reported. Eligibility was assessed separately for each arm. Cohorts with unknown median follow-up were excluded. We then repeated the restricted analysis after correcting discrepancies identified in the source reports and excluding cohorts without a verifiable treatment-specific 36-month estimate. We pooled logit-transformed proportions using inverse-variance random-effect models with restricted maximum likelihood estimation of between-cohort variance. For curve-derived estimates represented as counts relative to the baseline cohort size, the sampling variance was approximate.

In a further post hoc analysis, we stratified SLND cohorts according to whether the same study also reported a PLND comparator. We estimated pooled 3-year survival separately for SLND arms of comparative studies and for single-arm SLND cohorts using logit-transformed proportions and a random-effect model with restricted maximum likelihood estimation. We compared the two SLND strata using a test for subgroup differences and reported heterogeneity within each stratum. We also summarized the PLND arms of the comparative studies. Surgical approach was examined using the cohort-level proportion of patients undergoing open surgery. Tracer use was summarized descriptively because cohorts using multiple tracers generally reported survival for the cohort as a whole.

3. Results

3.1. Study Inclusion

A literature search identified 6447 records. After duplicate removal, 3350 articles were screened; 3321 were excluded at title and abstract review. Eleven studies met eligibility criteria and were included.

3.2. Risk of Bias of Included Studies

Most included studies were retrospective cohorts with serious risk of bias; prospective cohorts carried moderate risk. The sole randomized controlled trial (PHENIX-I) had low risk of bias. RoB 2 was applied to the RCT and ROBINS-I to all other studies (Supplementary Figures S1–S4).

3.3. Study Characteristics and Patient Population

Eleven studies encompassing 3842 patients with early-stage cervical cancer were included: 1818 (47.3%) underwent SLND only and 2024 (52.7%) underwent SLND plus pelvic lymphadenectomy (PLND). Median age ranged from 34 to 51 years. Squamous cell carcinoma predominated (67.4%), followed by adenocarcinoma (28.4%); other histotypes comprised 4%. Most patients had FIGO 2009 stage IB1 disease (45–85%), with tumors predominantly 2 cm (40–78%). Tracers varied, primarily Tc+BD or ICG (Table 1).

Reported median follow-up ranged from 13 to 83.5 months. Follow-up differed substantially between treatment arms in two studies: 13 versus 59 months in Gortzak-Uzan et al. [4] and 32 versus 59 months in Lennox and Covens [21], for SLND and PLND, respectively. Devaja et al. reported a median of 53 months for the whole cohort and 28 months in the description of patients managed according to the protocol [21]. Supplementary Table S5 presents follow-up alongside the source of each 36-month estimate (Table 1).

Table 1. Basic characteristics of studies.

Author	Intervention	Total Number of	Age	BMI	Age	Histology			Histologic Grade				FIGO Stage						LV	Tumor Size		Tracer Type			Surgical Approach			Media
			Years		Years	S %	A %	O %	G %	G %	G %	N %	I %	I %	I %	I %	II %	II %	II %	SI %	< %	> %	B %	I %	N %	O %	M %	C %	Months
Tu et al. [2]	SNL	420	48	23	48	73.1	23.6	3.3	8.1	6.9	29.5	15.5	0.5	4.3	84.5	-	10.7	-	-	-	6.0	40.0	84.5	14.8	0.7	37.4	62.6	-	62.8
	PLN	418	49	23	49	72.5	24.4	3.1	9.6	45.9	28.9	15.6	0.7	5.7	82.8	-	10.8	58.9	41.1	85.4	13.9	0.7	39.5	60.5	32.5	67.5	32.5	-	
Cibula et al. [5]	SNL	594	44	_	44	66.0	31.0	3.0	27.0	50.0	23.0	-	5.0	6.0	52.0	25.0	2.0	2.0	6.0	29.0	-	-	31.0	29.0	-	36.0	64.0	-	47.0
Balaya et al. [22]	SNL	87	44	23	44	63.2	33.3	3.4	56.1	29.8	14.0	-	-	10.3	78.2	6.9	3.4	1.2	-	-	90.2	9.8	100.	-	-	4.6	95.4	-	53.0
	PLN	172	43	24	43	69.2	27.9	2.9	39.3	41.0	19.7	-	-	9.9	72.1	12.8	2.3	81.5	18.5	1.0	-	-	7.6	92.4	-			-	46.0
Tanaka et al. [23]	SNL	52	46	_	46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.	-	-	-	100.	-	42.0
	PLN	52	45	_	45	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.0	-	-	0.0	100.	-	0.0	-	-	
Devaja et al. [24]	SNL	103	36	27	36	67.0	25.2	7.8	4.8	70.8	24.4	-	16.5	14.5	69.0	-	-	-	-	-	100.	-	100.	-	-	27.2	69.9	-	28.0
Gortzak-Uzan et al. [4]	SNL	81	38	_	38	42.0	42.0	16.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.	-	-		-	-	13.0
	PLN	218	41	_	41	47.0	42.0	11.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	59.0
Ting et al.[25]	SNL	33	51	50	51	61.0	33.0	6.0	3.0	42.0	33.0	21.0	-	6.0	-	-	6.0	-	-	58.0	27.0	72.0	-	100.	-	97.0	3.0	-	-
	PLN	74	52	25	52	65.0	28.0	7.0	7.0	51.0	26.0	16.0	-	16.0	-	-	7.0	-	-	66.0	46.0	53.0	-	100.	-	89.0	11.0	-	-
Yahata et al. [26]	SNLD	181	34	-	34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.0	-	-	-	-	-	83.5
Niikura et al. [27]	SNL	23	39	- -	39	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.	-	-	100.	-	-	49.0
	PLN	12				-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.	-	-	
Togami et al. [28]	SNL	134	40	21.7 -	40	72.0	-	6.0	-	-	-	-	-	17.0	80.0	1.0	-	2.0	-	-	-	-	-	100.	-				57.5
	PLN	4				-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	56.0	44.0	-	

https://doi.org/10.3390/cancers18233818

Lennox et al. [21]	SNL	110	35	_	35	71.3	28.7	0.0	-	-	-	-	-	59.1	40.9	-	-	-	-	26.4	-	-	-	-	-	0.0	70.9	29.1	32.0
	PLN	1078	40	_	40	71.7	25.6	27.0	-	-	-	-	-	9.5	-	90.5	-	-	-	37.1	-	-	-	-	-	75.1	20.9	0.0	59.0

https://doi.org/10.3390/cancers18233818

3.4. Recurrence Outcomes

Table 2 summarizes recurrences by study, treatment group, and anatomical site. In the randomized PHENIX-I trial, no retroperitoneal nodal recurrences occurred among 420 patients assigned to SLND alone, compared with nine (2.2%) among 418 assigned to additional PLND [2]. Across studies, differences in patient selection, follow-up duration, and reporting of recurrence sites limited comparison of the aggregate proportions. Vaginal stump recurrence predominated in the SLND cohort, while distant recurrence was most common in the PLND group, though this difference was not statistically significant. Retroperitoneal nodal recurrence rates were similar between groups (10.5% vs. 10.1%; p = 0.91) (Table 2).

Table 2. Data on recurrence according to studies.

Author	Intervention	Total Number of Patients	Any	Vaginal Stump	Retroperitoneal Nodal			Pelvic, Non- Vaginal Stump	Abdominal	Distant Site	Multiple Sites	Missing Data	Death from Cervical Cancer		Death from Other Causes		Death from Any Cause	
					All	Pelvic	Paraaortic						No	%	No	%	No	%
Tu et al. [2]	SNLD	420	16	7						9			6	1.4	3	0.7	9	2.1
	SLN+PLND	418	26	4	9	3	1	5	10	3	17	10	1	16	3.8	1	0.2	17	4.1
Cibula et al. [5].	SNLD	594	54	25	5	4	1			16		13		19	3.2	2	0.3	21	3.5
Balaya et al. [22]	SNLD	87	10	3	3	3					4			5	5.7			5	5.7
	SLN+PLND	172	11	5	1		1					5		4	2.3	1	0.6	5	2.9
Tanaka et al. [23]	SNLD	52																	
	SLN+PLND	52	4	1	1	1					2								
Devaja et al. [24].	SNLD	103	3	2					1					1	1.0			1	1.0
Gortzak-Uzan et al. [4].	SNLD	81	5		1	1			3		1								
	SLN+PLND	218	16		4	4			7		3	2							
Ting et al. [25].	SNLD	33	2																
	SLN+PLND	74	17											14	19.0				
Yahata et al. [26].	SNLD	181	4		1			1	1		2			1	0.6				
Niikura et al. [27].	SNLD	23	3	1							2								
	SLN+PLND	12												1	8.3				
Togami et al. [28].	SNLD	134	4	2	1	1					1			3	2.2				
	SLN+PLND	4																	
Lennox et al. [21].	SNLD	110	4	2					1				1						

SLN+PLND	1078	75		36	3.3

The four PLND patients reported by Togami et al. [26] had no available outcome data and were excluded from the corresponding outcome analyses.

3.5. Mortality

Disease-specific and all-cause mortality were summarized descriptively from the available study reports. The reported group proportions should not be interpreted as comparative treatment effects because they were not estimated using a study-level meta-analytic model and were not adjusted for between-study differences or potential confounding. No inferential *p* value or heterogeneity statistic was calculated for these outcomes. Accordingly, the available data do not establish a mortality advantage for either approach (Table 2).

3.6. Disease-Free Survival

Several studies reported outcomes beyond 36 months, but the available data were insufficient for a pooled five-year DFS analysis. The reported endpoints also differed. For example, Yahata et al. reported five-year progression-free survival of 98.8%, whereas Togami et al. reported five-year recurrence-free survival of 97.0% for the entire surgical cohort [26,28]. These findings provide descriptive information on longer-term outcomes. At 60 months, disease-free survival ranged from 85.9 to 100% for SLND versus 75.5–94.9% for PLND. The largest study (Tu et al., $n = 838$) showed comparable 5-year disease-free survival (96.3% vs. 93.6%) [2]. Cibula et al. ($n = 594$) reported 5-year disease-free survival of 89.8% in the SLND cohort [5]. Tanaka et al. ($n = 104$) demonstrated 100% disease-free survival at 60 months in the SLND group versus 90.6% in the PLND group [23]. Ting et al. showed superior SLND outcomes (87.6% vs. 75.5%) [25]. Balaya et al. reported 5-year disease-free survival of 85.9% for SNLD versus 94.9% for PLND ($n = 259$) [22].

Studies of SLND-only cohorts without direct PLND comparison also showed favorable results: Yahata et al. reported 98.8% disease-free survival at 60 months ($n = 181$) [26], Togami et al. 97.0% ($n = 134$) [28], and Devaja et al. 97.1% at 48 months ($n = 103$) [24].

3.7. Three-Year Disease-Free Survival

Pooled analysis of 18 cohorts (3842 patients) yielded an overall 3-year disease-free survival of 94% (95% CI 0.92–0.95; $I^2 = 58.9\%$, $p = 0.0008$) (Figure 2). The SLND subgroup had a pooled 3-year disease-free survival of 95% (95% CI 0.92–0.96; $I^2 = 58.7\%$; range 88–100%), while the PLND subgroup had a pooled 3-year disease-free survival of 93% (95% CI 0.89–0.95; $I^2 = 62.0\%$; range 82–97%).

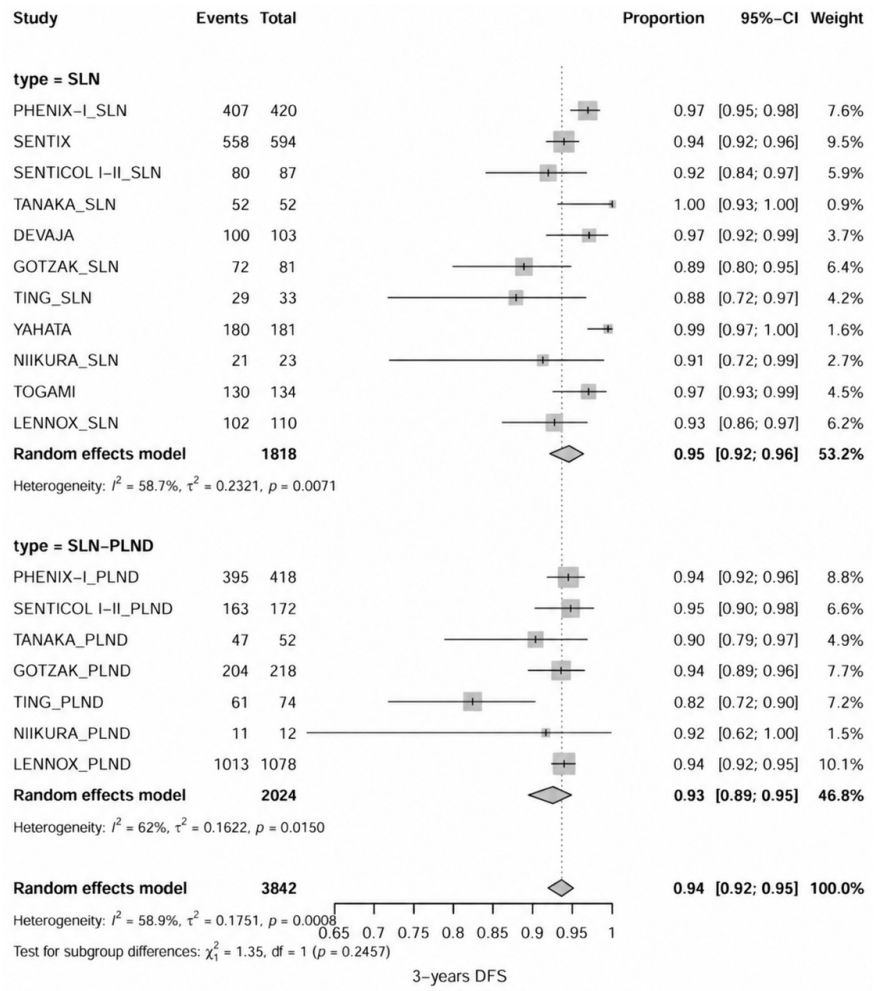

Figure 2. Forest plot of the 3-year disease free survival reported by the 11 involved studies.

The subgroup test compared pooled survival proportions across nodal strategies. Because the contributing cohorts differed in design and patient selection, this comparison provides a descriptive summary of outcomes and does not estimate the effect of omitting PLND (Supplementary Table S2).

In the exploratory analysis by study design, pooled 3-year survival after SLND was 93.3% (95% CI, 88.9–96.0%; I^2 = 65.2%) in six studies with a PLND comparator and 97.0% (95% CI, 88.5–99.3%; I^2 = 79.4%) in three single-arm studies. The test for a difference between these two SLND strata yielded p = 0.281. In the PLND arms of the six comparative studies, pooled 3-year survival was 92.8% (95% CI, 89.6–95.1%; I^2 = 66.8%). Heterogeneity persisted in each stratum.

Restriction to cohorts with documented median follow-up of at least 36 months retained eight SLND cohorts (1594 patients) and six PLND cohorts (1950 patients). Using the original Figure 2 inputs, the pooled 3-year estimates were 95.8% (95% CI, 93.6–97.3%) and 94.0% (95% CI, 92.8–94.9%), respectively (p for subgroup difference = 0.117). After correcting the SENTIX and Tanaka estimates and excluding the Niikura and Togami cohorts, six SLND cohorts (1437 patients) and five PLND cohorts (1938 patients) remained [5,23,27,28]. The corresponding estimates were 96.1% (95% CI, 92.5–98.0%) and 94.1% (95% CI, 92.9–95.0%), respectively (p = 0.228).

In the sensitivity analysis restricted to the randomized trial and eligible prospective cohorts, five treatment arms from three studies contributed 1691 patients: PHENIX-I (n = 838), SENTIX (n = 594), and the post hoc analysis of the prospectively assembled SENTICOL I–II cohorts (n = 259) [2,5,22]. Pooled 3-year DFS across these arms was 94.3% (95%

CI, 92.1–96.0%; $I^2 = 60.8\%$). Niikura et al. did not contribute to the revised analysis because treatment-specific 36-month DFS estimates could not be verified [27]. The pooled estimate summarizes absolute DFS across both nodal strategies (Supplementary Figure S6).

3.8. Meta-Regression Analysis of Prognostic Factors

Table 3 presents univariable and multivariable meta-regression results examining associations between study-level covariates and treatment outcomes.

Table 3. Study-level meta-regression analyses for 3-year disease-free survival.

Covariate	Univariable Meta-Regression β (95% CI)	*p* Value	Meta-Regression Adjusted for Surgical Subgroup * β (95% CI)	*p* Value	Subgroup Interaction (TYPE) β (95% CI)	*p* Value
Age (years)	−0.0021 (−0.005; 0.0010)	0.19	−0.0014 (−0.0043; 0.0015)	0.35	−0.0229 (−0.0535; 0.0077)	0.14
Squamous cell carcinoma (%)	0.0225 (−0.1265; 0.1715)	0.77	0.0188 (−0.117; 0.1546)	0.78	−0.0267 (−0.0569; 0.0035)	0.08
Grade 3 tumors (%)	0.3193 (0.0550; 0.5837)	0.018	0.3233 (0.0492; 0.5975)	0.021	−0.0160 (−0.0435; 0. 0115)	0.25
FIGO stage IA–IB (%)	0.0333 (−0.0546; 0.1212)	0.46	0.0286 (−0.0511; 0.1083)	0.48	−0.0317 (−0.0641; 0.0006)	0.055
Tumor size (%)	−0.0943 (−0.2054; 0.0169)	0.10	−0.0775 (−0.1942; 0.0392)	0.19	−0.0233 (−0.0644; 0.0198)	0.30
Open surgery (%)	−0.0396 (−0.0886; 0.0093)	0.11	−0.0205 (−0.0843; 0.0432)	0.53	−0.0210 (−0.0614; 0.0194)	0.31
LVSI (%)	−0.0878 (−0.1858; 0.0102)	0.08	−0.0806 (−0.1775; 0.0162)	0.10	−0.0154 (−0.0444; 0.0135)	0.30

* Adjusted models include surgical approach as a subgroup variable (sentinel lymph node biopsy alone versus sentinel lymph node biopsy plus pelvic lymph node dissection). β coefficients represent study-level random-effect meta-regression estimates for 3-year disease-free survival. Age is expressed in years; all other covariates represent the percentage of patients within each study presenting the specified characteristic. The subgroup interaction (TYPE) term tests for effect modification by surgical approach. Statistically significant associations are shown in bold.

3.8.1. Univariable Meta-Regression

In univariable meta-regression, studies with a higher proportion of grade 3 tumors had higher estimated 3-year DFS (β = 0.3193, 95% CI 0.0550 to 0.5837, $p = 0.018$). This was the only covariate significantly associated with 3-year DFS. The estimated coefficients for lymphovascular space invasion (LVSI) prevalence ($p = 0.08$), tumor size ($p = 0.10$), and the proportion of patients undergoing open surgery ($p = 0.11$) were negative, but all three 95% confidence intervals included zero. Age ($p = 0.19$), the proportion of patients with squamous cell carcinoma ($p = 0.77$), and the proportion with FIGO stage IA–IB disease ($p = 0.46$) also showed no statistically significant association with 3-year DFS.

3.8.2. Multivariable Meta-Regression Adjusted for Surgical Subgroup

After adjustment for nodal staging strategy (sentinel lymph node biopsy alone or with pelvic lymphadenectomy), cohorts with a higher proportion of grade 3 tumors had higher estimated 3-year DFS (β = 0.3233, 95% CI 0.0492 to 0.5975, $p = 0.021$). The coefficient was similar to the univariable estimate (β = 0.3193). None of the other covariates showed a statistically significant association with 3-year DFS after adjustment for nodal staging strategy (Table 3). For surgical approach, the association between the cohort-level

proportion of open procedures and 3-year survival was uncertain in both the univariable analysis ($p = 0.11$) and the model adjusted for nodal strategy ($p = 0.53$).

3.9. Subgroup Analyses

The interaction between the proportion of open procedures and nodal strategy was imprecisely estimated ($p = 0.31$). The aggregate data therefore provide limited information about whether the effect of omitting PLND differs between open and minimally invasive surgery. Borderline trends were observed for FIGO stage IA–IB (interaction $p = 0.055$) and squamous cell carcinoma histology (interaction $p = 0.08$). All remaining interaction terms had p-values >0.10 (Table 3).

PHENIX-I reported 3-year DFS by surgical approach. Among patients undergoing laparoscopic surgery, 3-year DFS was 97.3% after SLND alone and 93.6% after SLND plus PLND (HR for recurrence or death 0.40, 95% CI 0.18–0.92), with 8 and 19 events during follow-up, respectively. Among patients undergoing open surgery, 3-year DFS was 96.1% and 96.3%, respectively (HR 1.25, 95% CI 0.45–3.44), with eight and seven events. The trial presented the subgroup estimates without a formal test of interaction in its subgroup figure [2].

Postoperative Morbidity Reported in Individual Trials

In PHENIX-I, patients undergoing SLND alone had lower rates of lymphocyst formation (8.3% vs. 22.0%), lymphedema (5.2% vs. 19.1%), paresthesia (4.0% vs. 8.4%), and pain (2.6% vs. 7.9%) than patients undergoing SLND plus PLND (all $p < 0.01$) [2]. The SENTICOL-2 morbidity report also found lower rates of lymphatic morbidity (31.4% vs. 51.5%, $p = 0.0046$) and postoperative neurological symptoms (7.8% vs. 20.6%, $p = 0.01$) after SLND alone .

3.10. Certainty of Evidence

Evidence certainty for all outcomes was rated moderate per the GRADE framework, indicating that further research may refine effect estimates but is unlikely to change overall conclusions substantially (Supplementary Table S1).

3.11. Small-Study Effects and Publication Bias

In the SLND funnel plot, the two least precise cohorts had higher 3-year DFS estimates than the pooled estimate. The six PLND cohorts showed no clear pattern of asymmetry (Supplementary Figure S5). Egger's intercept test yielded $t(7) = 1.33$ ($p = 0.227$) for SLND and $t(4) = -0.79$ ($p = 0.472$) for PLND. On the lower-DFS side, trim-and-fill imputed two SLND cohorts and one PLND cohort, shifting pooled 3-year DFS from 94.3% to 93.3% and from 92.8% to 92.4%, respectively. On the higher-DFS side, the method imputed no cohorts in either group. The small number of studies and the heterogeneity of the contributing cohorts limit inference about publication bias.

4. Discussion

4.1. Principal Findings

This systematic review and meta-analysis of 11 studies comprising 3846 patients with early-stage cervical cancer demonstrates that SLND alone is non-inferior to PLND with respect to DFS, with pooled 3-year DFS rates of 95% versus 93%, respectively ($p = 0.25$). Recurrence and mortality were summarized descriptively and do not establish an oncologic advantage for either surgical approach. The non-significant subgroup comparison for 3-year disease-free survival should not be interpreted as proof of equivalence or non-inferiority [29]. Three-year survival estimates were high after both nodal strategies.

Among SLND cohorts, the pooled estimate was higher in single-arm studies than in studies with a PLND comparator, although the estimate for single-arm studies was imprecise. For the clinical question of omitting PLND, the strongest direct evidence came from PHENIX-I, which met its prespecified non-inferiority criterion for 3-year DFS [2]. The observational cohorts provide additional information about outcomes in selected patients, but differences in selection and treatment limit their contribution to a comparative effect estimate.

The lower crude proportions of recurrence and disease-specific death observed after SLND may partly reflect the selection of patients with more favorable disease. In some cohorts, smaller tumors, reassuring imaging findings, or negative intraoperative sentinel nodes increased the likelihood that lymphadenectomy would be omitted. Conversely, suspicious nodes or positive frozen sections prompted further dissection. These pathways could produce lower recurrence and mortality in the SLND group even if the extent of nodal surgery had no effect on either outcome. The magnitude of this bias cannot be estimated from the aggregate event counts [2].

Previous meta-analyses have compared survival after sentinel lymph node biopsy and pelvic lymphadenectomy, including a recent synthesis addressing both oncologic outcomes and surgical morbidity. Our analysis adds an assessment of how study design affects the interpretation of absolute 3-year outcomes. Among patients undergoing sentinel lymph node biopsy alone, pooled 3-year survival was 93.3% in studies with a pelvic lymphadenectomy comparator and 97.0% in single-arm studies. The difference was imprecise (p = 0.281), and heterogeneity persisted within both groups. These findings illustrate the limits of using favorable outcomes from selected single-arm cohorts to infer the effect of omitting pelvic lymphadenectomy. For that inference, the within-trial comparison from PHENIX-I remains the most informative evidence [2].

4.2. The Interaction Between Surgical Approach and Lymphadenectomy

In a prespecified subgroup analysis of PHENIX-I, 3-year DFS after SLND alone versus SLND plus PLND was 97.3% versus 93.6% among patients undergoing laparoscopic surgery (HR for recurrence or death, 0.40, 95% CI 0.18–0.92) and 96.1% versus 96.3% among those undergoing open surgery (HR 1.25, 95% CI 0.45–3.44) [2]. During follow-up, there were eight versus nineteen events in the laparoscopic subgroup and eight versus seven in the open subgroup. Surgical approach was one of several subgroup variables examined. Given the small event counts and multiple comparisons, chance remains a plausible explanation for the difference between the point estimates. The trial reported separate subgroup estimates without a formal test of interaction in Figure 2 [2].

These findings raise the hypothesis that surgical approach might modify the effect of nodal strategy on DFS. The pelvic and abdominal recurrence pattern observed in LACC makes this a clinically relevant question [30]. However, LACC randomized the route of radical hysterectomy and did not isolate the contribution of lymphadenectomy [31]. Neither trial measured changes in lymphatic drainage, regional immune function, or the tumor microenvironment that could explain the recurrence pattern. Whether the effect of nodal strategy differs by surgical approach remains uncertain

4.3. The Role of Ultrastaging in Sentinel Biopsy

A critical advantage of sentinel biopsy over routine lymphadenectomy is the ability to perform ultrastaging with serial sectioning and immunohistochemistry, which significantly increases the detection of micrometastases and isolated tumor cells that would be missed by standard assessment [7–9,12,30,32,33]. In the SENTICOL study, 39.1% of patients with positive nodes had metastases detected only by immunohistochemistry, and 17% of involved sentinel nodes were located in unexpected drainage areas outside of

routine field [30]. The SCCAN collaborative study demonstrated that 5-year DFS was 96.0% in patients who underwent SLND+PLND versus 92.0% in those who underwent lymphadenectomy alone ($p = 0.024$), suggesting that ultrastaging identifies additional patients who benefit from adjuvant therapy [2,13].

Although no universal protocol exists [2,7,32], studies have shown that ultrastaging detects metastases in an additional 20–40% of cases compared to routine processing, with sensitivity approaching 96–97% [8,9,11,33]. This enhanced pathologic assessment allows for more accurate risk stratification and tailored adjuvant therapy, explaining the better outcomes observed in the SLND groups [8,12,13,33].

4.4. Morbidity Reduction with Sentinel-Only Approach

The morbidity benefits of omitting complete lymphadenectomy were substantial and consistent across studies. In PHENIX-I, the SLND group had significantly lower rates of lymphocyst (8.3% vs. 22.0%), lymphedema (5.2% vs. 19.1%), paresthesia (4.0% vs. 8.4%), and pain (2.6% vs. 7.9%) compared to the PLND group (all $p < 0.01$) [2]. Similarly, the SENTICOL-2 trial demonstrated significantly lower lymphatic morbidity with SLND (31.4%) compared to PLND (51.5%) ($p = 0.0046$), as well as fewer postoperative neurological symptoms (7.8% vs. 20.6%, $p = 0.01$) [34]. These findings are particularly important given that lymphedema affects up to 47% of patients following pelvic lymphadenectomy and represents a chronic, debilitating complication that significantly impacts quality of life [35–37].

The reduction in surgical morbidity translates to shorter operative duration, less blood loss, and faster recovery without compromising oncologic outcomes [2,29].

4.5. Meta-Regression Analysis and Prognostic Factors

The meta-regression analysis revealed an unexpected finding: the proportion of grade 3 tumors within a study was positively associated with 3-year DFS ($\beta = 0.32$, 95% CI 0.05–0.60; $p = 0.018$), indicating higher DFS rates in studies with more G3 tumors. This counterintuitive result likely reflects selection bias and confounding, as studies with higher proportions of G3 tumors may have applied more stringent inclusion criteria, more aggressive adjuvant therapy protocols, or more intensive surveillance. The higher probability of the earlier recognition of micrometastases or ITCs in these G3 tumors further supports this relation. Alternatively, this may represent an ecological fallacy where study-level associations do not reflect individual-level relationships. Notably, no significant associations were observed for age, histologic subtype, FIGO stage, tumor size, surgical approach, or LVSI in the meta-regression, suggesting that the benefits of SLND approach are consistent across diverse patient populations.

4.6. Strengths and Limitations

This study has several important strengths enhancing the validity and clinical relevance of its findings. This meta-analysis includes a large, contemporary patient population. The inclusion of both prospective and retrospective cohorts, including high-quality datasets such as the PHENIX-I [2] randomized controlled trial and the SENTIX prospective study [5], ensures that the analysis reflects real-world clinical practice while incorporating the highest level of available evidence.

Furthermore, the study was conducted according to rigorous methodological standards. The protocol was prospectively registered in PROSPERO, and the review adhered to PRISMA 2020 guidelines and Cochrane recommendations, minimizing the risk of reporting bias and enhancing transparency and reproducibility. Dual independent screening, data extraction, and risk-of-bias assessment further strengthen the internal validity of the analysis.

Finally, this study addresses a highly relevant and unresolved clinical question with direct implications for surgical decision-making and guideline development. By synthesizing the most recent evidence, including data from newly published trials, it provides timely support for the ongoing paradigm shift toward de-escalation of surgical radicality in early-stage cervical cancer.

Several limitations need consideration. First, only one randomized controlled trial (PHENIX-I) was included, with the remaining studies being observational cohorts. Heterogeneity persisted after stratification by study design. Eligibility for SLND alone could depend on successful bilateral mapping, intraoperative nodal findings, tumor characteristics, and institutional practice. These selection criteria could produce differences in baseline recurrence risk between nodal strategies, particularly in studies using historical comparators. Tracer choice and mapping protocols could influence which patients qualified for SLND alone. Differences in pathological ultrastaging could also alter the detection of low-volume nodal disease and, together with institutional thresholds for adjuvant therapy, affect subsequent treatment. The available aggregate data did not permit estimation of the independent contribution of these factors. Median follow-up varied across cohorts, and several reports did not provide the number at risk at 36 months. A Kaplan–Meier estimate can extend beyond the median follow-up when patients remain under observation, but its precision depends on the risk set and censoring at that landmark. The restricted analyses addressed variation in follow-up duration. Differences in endpoint definitions, approximate variances for curve-derived estimates, and insufficient data for a pooled five-year analysis limit conclusions about the magnitude and durability of any difference between surgical approaches. Third, the mechanisms underlying the paradoxical increase in retroperitoneal nodal recurrence with complete lymphadenectomy remain speculative and require further investigation [2].

Last, the influence of patient selection was evident in several comparative studies. In Tanaka et al., the SLND group had smaller tumors than the PLND group (median 12 versus 20 mm) and fewer patients with nodal metastases (1/52 versus 9/52) [23]. In Lennox and Covens, the PLND cohort included patients treated in an earlier period and had more advanced disease and more frequent lymphovascular space invasion [27]. The crude hazard ratio for recurrence after SLND versus PLND was 0.75 (95% CI, 0.27–2.05), compared with 1.82 (95% CI, 0.62–5.40) after multivariable adjustment [27]. Balaya et al. also reported an imprecise adjusted association with DFS (HR 1.78, 95% CI, 0.71–4.46) [22]. Gortzak-Uzan et al. matched patients on tumor size, histology, depth of invasion, and lymphovascular invasion [4]. These methods address measured differences, although residual confounding remains plausible. Study-specific selection criteria and adjustment methods are summarized in Supplementary Table S6.

The assessment of small-study effects was limited by the small number of studies within each nodal strategy and by the inclusion of both single-arm and comparative studies in the SLND group. Differences in patient selection or study design could generate funnel plot asymmetry. In addition, the standard error of a logit-transformed survival proportion depends partly on the estimated proportion itself. Consequently, the non-significant Egger tests and modest trim-and-fill shifts leave selective reporting unresolved.

4.7. Clinical Implications and Future Directions

These findings have immediate clinical implications. Sentinel biopsy alone should be considered the new standard of care for early-stage cervical cancer in patients with successful bilateral sentinel mapping, as recommended by updated NCCN guidelines [7]. The sentinel mapping algorithm must be rigorously followed, including side-specific lymphadenectomy when mapping fails and removal of any suspicious nodes regardless of

mapping status [7]. Ultrastaging of sentinel nodes should be performed routinely to maximize detection of low-volume metastases [7,8].

The PHENIX-I subgroup findings do not justify choosing the extent of nodal surgery on the basis of a minimally invasive approach alone. Future studies should prespecify a test of interaction between surgical approach and nodal strategy and accrue sufficient recurrence events to estimate that interaction precisely [2,33,35,38].

Future research should focus on elucidating the biological mechanisms by which complete lymphadenectomy may promote recurrence, including studies of lymphatic drainage patterns, regional immunity, and tumor microenvironment alterations [2,39–41]. Several ongoing trials will provide additional high-quality evidence regarding the role of sentinel biopsy and optimal surgical approaches. The ongoing SENTICOL-III trial is designated to answer this question, while the RACC, ROCC and LASH trials will evaluate this aspect as secondary end-points [36,42–44]. Investigation of molecular markers and imaging techniques to improve preoperative lymph node assessment may further refine patient selection for conservative surgical approaches [33].

5. Conclusions

Pooled 3-year DFS was 95% after sentinel lymph node biopsy alone and 93% after biopsy plus pelvic lymphadenectomy ($p = 0.246$ for the subgroup comparison). Differences in study design and patient selection limit interpretation of this comparison. Crude recurrence proportions were 5.8% and 7.3%, respectively, and disease-specific mortality was 1.9% and 3.5%. These unadjusted figures cannot establish whether omitting lymphadenectomy reduces recurrence or mortality. In PHENIX-I, sentinel lymph node biopsy alone met the prespecified non-inferiority criterion for 3-year DFS and reduced postoperative lymphatic morbidity [2]. This trial supports omission of systematic pelvic lymphadenectomy in patients who meet its eligibility criteria and have negative sentinel nodes on intraoperative frozen sections. Available data were insufficient to pool 5-year DFS.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers18233818/s1: Figure S1. Risk of bias evaluations for cohort studies (ROBINS-I); Figure S2. Risk of bias evaluations for cohort studies; Figure S3. Risk of bias evaluations (ROB-2); Figure S4. Risk of bias evaluation for randomized controlled trial; Table S1: Assessment of Certainty; Figure S5. Funnel plots assessing publication bias for 3-year disease-free survival; Table S2. Leave-one-out sensitivity analysis of pooled 3-year disease-free survival; Figure S6. Sensitivity analysis excluding studies at serious risk of bias; Table S3. PRISMA Checklist; Table S4. PRISMA Abstract Checklist; Table S5. Follow-up and source of the 36-month estimate; Table S6. Patient selection and control of confounding in the included studies.

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Abbreviations

The following abbreviations are used in this manuscript:

BD	Blue dye
BMI	Body mass index
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
FIGO	International Federation of Gynecology and Obstetrics
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEpro GDT	GRADEpro Guideline Development Tool
HR	Hazard ratio
ICG	Indocyanine green
ITC	Isolated tumor cells
LACC	Laparoscopic Approach to Cervical Cancer (trial)
LASH	LAcc & SHape (clinical trial)
MEDLINE	Medical Literature Analysis and Retrieval System Online
PHENIX-I	PHENIX trial, sentinel lymph node-negative cohort
PICO	Population, Intervention, Comparator, Outcome
PLND	Pelvic lymphadenectomy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RACC	Robot-assisted Approach to Cervical Cancer (trial)
RoB 2	Risk of Bias 2
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
ROCC	Robotic versus Open Surgery for Early-Stage Cervical Cancer (trial)
SCCAN	Surveillance in Cervical CANcer (collaborative study)
SENTICOL	Ganglion Sentinelle dans le Cancer du Col (clinical study)
SENTIX	SENTIX prospective multicenter cervical cancer sentinel lymph node study
SLN	Sentinel lymph node
SLND	Sentinel lymph node dissection

References

1. Kalas, N.; Szabó, V.; Vida, B.; Tóth, Z.; Lőczi, L.; Sebők, B.; Merkely, P.; Lintner, B.; Ács, N.; Keszthelyi, A.; et al. The Platelet-to-Lymphocyte Ratio (PLR) as a Non-Invasive Biomarker for Cervical Malignancy in Conization Patients. *Life* **2025**, *15*, 971. https://doi.org/10.3390/life15060971.
2. Tu, H.; Huang, H.; Li, Y.; Chen, X.; Wang, C.; Zheng, M.; Zhang, Y.; Zhao, W.; Feng, Y.; Wan, T.; et al. Sentinel-Lymph-Node Biopsy Alone or with Lymphadenectomy in Cervical Cancer. *N. Engl. J. Med.* **2025**, *393*, 1463–1474. https://doi.org/10.1056/nejmoa2506267.
3. Cibula, D.; Raspollini, M.R.; Planchamp, F.; Centeno, C.; Chargari, C.; Felix, A.; Fischerová, D.; Jahnn-Kuch, D.; Joly, F.; Kohler, C.; et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer—Update 2023*. *Int. J. Gynecol. Cancer* **2023**, *33*, 649–666. https://doi.org/10.1136/ijgc-2023-004429.
4. Gortzak-Uzan, L.; Jimenez, W.; Nofech-Mozes, S.; Ismiil, N.; Khalifa, M.; Dubé, V.; Rosen, B.; Murphy, J.; Laframboise, S.; Covens, A. Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: Is it time to change the gold standard? *Gynecol. Oncol.* **2010**, *116*, 28–32. https://doi.org/10.1016/j.ygyno.2009.10.049.
5. Cibula, D.; Marnitz, S.; Jarkovský, J.; Kocián, R.; Dundr, P.; Klát, J.; Zapardiel, I.; Arencibia, O.; Landoni, F.; Presl, J.; et al. Sentinel lymph node biopsy without systematic pelvic lymphadenectomy in females with early-stage cervical cancer: Final outcome of the SENTIX prospective, single-arm, noninferiority, international trial. *Nat. Cancer* **2025**, *6*, 1585–1594. https://doi.org/10.1038/s43018-025-01016-y.
6. Vida, B.; Lintner, B.; Veres, D.S.; Várbíró, S.; Merkely, P.; Lőczi, L.; Ács, N.; Tóth, R.; Keszthelyi, M. Assessing the comparative efficacy of sentinel lymph node detection techniques in vulvar cancer: A systematic review and meta-analysis. *Am. J. Obstet. Gynecol.* **2025**, *233*, 363–379.e9. https://doi.org/10.1016/j.ajog.2025.04.052.
7. NCCN. *NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer*; NCCN: Plymouth Meeting, PA, USA, 2026.
8. Mathevet, P.; Guani, B.; Ciobanu, A.; Lamarche, E.M.; Boutitie, F.; Balaya, V.; Lecuru, F. Histopathologic Validation of the Sentinel Node Technique for Early-Stage Cervical Cancer Patients. *Ann. Surg. Oncol.* **2020**, *28*, 3629–3635. https://doi.org/10.1245/s10434-020-09328-2.

9. Salvo, G.; Ramirez, P.T.; Levenback, C.F.; Munsell, M.F.; Euscher, E.D.; Soliman, P.T.; Frumovitz, M. Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. *Gynecol. Oncol.* **2017**, *145*, 96–101. https://doi.org/10.1016/j.ygyno.2017.02.005.
10. Sponholtz, S.E.; Mogensen, O.; Hildebrandt, M.G.; Schledermann, D.; Parner, E.; Markauskas, A.; Frøding, L.P.; Fuglsang, K.; Vilstrup, M.H.; Bjørnholt, S.M.; et al. Sentinel lymph node mapping in early-stage cervical cancer—A national prospective multicenter study (SENTIREC trial). *Gynecol. Oncol.* **2021**, *162*, 546–554. https://doi.org/10.1016/j.ygyno.2021.06.018.
11. Lécuru, F.; Mathevet, P.; Querleu, D.; Leblanc, E.; Morice, P.; Daraï, E.; Marret, H.; Magaud, L.; Gillaizeau, F.; Chatellier, G.; et al. Bilateral Negative Sentinel Nodes Accurately Predict Absence of Lymph Node Metastasis in Early Cervical Cancer: Results of the SENTICOL Study. *J. Clin. Oncol.* **2011**, *29*, 1686–1691. https://doi.org/10.1200/jco.2010.32.0432.
12. Alonso-Espías, M.; Gracia, M.; Zapardiel, I. Benefits of sentinel node detection in cervical cancer. *Curr. Opin. Oncol.* **2024**, *36*, 397–405. https://doi.org/10.1097/cco.0000000000001063.
13. Bizzarri, N.; Querleu, D.; Ramirez, P.T.; Dostálek, L.; van Lonkhuijzen, L.R.W.; Giannarelli, D.; Lopez, A.; Salehi, S.; Ayhan, A.; Kim, S.H.; et al. Survival associated with the use of sentinel lymph node in addition to lymphadenectomy in early-stage cervical cancer treated with surgery alone: A sub-analysis of the Surveillance in Cervical CANcer (SCCAN) collaborative study. *Eur. J. Cancer* **2024**, *211*, 114310. https://doi.org/10.1016/j.ejca.2024.114310.
14. Lecuru, F.R.; McCormack, M.; Hillemanns, P.; Anota, A.; Leitao, M.; Mathevet, P.; Zweemer, R.; Fujiwara, K.; Zanagnolo, V.; Eriksson, A.G.Z.; et al. SENTICOL III: An international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study. *Int. J. Gynecol. Cancer* **2019**, *29*, 829–834. https://doi.org/10.1136/ijgc-2019-000332.
15. Mauro, J.; Viveros-Carreño, D.; Vizzielli, G.; De Ponti, E.; Fanfani, F.; Ramirez, P.T.; Buda, A. Survival after sentinel node biopsy alone in early-stage cervical cancer: A systematic review. *Int. J. Gynecol. Cancer* **2023**, *33*, 1370–1375. https://doi.org/10.1136/ijgc-2023-004692.
16. PROSPERO Registration:: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251180289 (accessed on: 03 March 2026.
17. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement : An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. https://doi.org/10.1136/bmj.n71.
18. Higgins, J.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.; Welch, V.; Flemyng, E. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions Version 6.5 (Updated August 2024)*; Cochrane: London, UK, 2024.
19. McGuinness, L.A.; Higgins, J.P.T. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res. Synth. Methods* **2021**, *12*, 55–61. https://doi.org/10.1002/jrsm.1411.
20. Schünemann, H.J.; Oxman, A.D.; Brozek, J.; Glasziou, P.; Jaeschke, R.; Vist, G.E.; Williams, J.W., Jr.; Kunz, R.; Craig, J.; Montori, V.M.; et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* **2008**, *336*, 1106–1110. https://doi.org/10.1136/bmj.39500.677199.ae.
21. Lennox, G.K.; Covens, A. Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer? *Gynecol. Oncol.* **2017**, *144*, 16–20. https://doi.org/10.1016/j.ygyno.2016.08.337.
22. Balaya, V.; Guani, B.; Morice, P.; Querleu, D.; Fourchotte, V.; Leblanc, E.; Daraï, E.; Baron, M.; Marret, H.; Levêque, J.; et al. Long-term oncological safety of sentinel lymph node biopsy in early-stage cervical cancer: A post-hoc analysis of SENTICOL I and SENTICOL II cohorts. *Gynecol. Oncol.* **2022**, *164*, 53–61. https://doi.org/10.1016/j.ygyno.2021.10.074.
23. Tanaka, T.; Nishie, R.; Murakami, H.; Tsuchihashi, H.; Toji, A.; Ueda, S.; Morita, N.; Hashida, S.; Terada, S.; Maruoka, H.; et al. Oncologic Outcomes of Patients with Early-Stage Cervical Cancer after Minimally Invasive Radical Hysterectomy and Sentinel Lymph Node Biopsy. *J. Clin. Med.* **2024**, *13*, 3981. https://doi.org/10.3390/jcm13133981.
24. Devaja, O.; Papadopoulos, A.J.; Bharathan, R.; Montalto, S.A.; Coutts, M.; Tan, A.; Corrigan, A.; Perovic, M.; Lalami, S.Z.R. Sentinel lymph node biopsy alone in the management of early cervical carcinoma. *Int. J. Gynecol. Cancer* **2022**, *32*, 15–20. https://doi.org/10.1136/ijgc-2019-001082.
25. Ting, W.-H.; Chen, H.-H.; Hsieh, S.-W.; Wei, M.-C.; Hsiao, S.-M. Comparison of clinical outcomes in women with surgically treated early primary cervical cancer: Lymphadenectomy vs sentinel lymph node biopsy. *J. Chin. Med. Assoc.* **2024**, *88*, 238–245. https://doi.org/10.1097/jcma.0000000000001169.
26. Yahata, H.; Kodama, K.; Okugawa, K.; Hachisuga, K.; Yasutake, N.; Maenohara, S.; Yagi, H.; Yasunaga, M.; Ohgami, T.; Onoyama, I.; et al. Long-term follow up after sentinel node biopsy alone for early-stage cervical cancer. *Gynecol. Oncol.* **2022**, *165*, 149–154. https://doi.org/10.1016/j.ygyno.2022.01.031.

27. Niikura, H.; Okamoto, S.; Otsuki, T.; Yoshinaga, K.; Utsunomiya, H.; Nagase, S.; Takano, T.; Ito, K.; Watanabe, M.; Yaegashi, N. Prospective Study of Sentinel Lymph Node Biopsy Without Further Pelvic Lymphadenectomy in Patients With Sentinel Lymph Node-Negative Cervical Cancer. *Int. J. Gynecol. Cancer* **2012**, *22*, 1244–1250. https://doi.org/10.1097/igc.0b013e318263f06a.
28. Togami, S.; Furuzono, N.; Mizuno, M.; Yanazume, S.; Kobayashi, H. Long-term outcomes of sentinel lymph node navigation surgery for early-stage cervical cancer. *Int. J. Clin. Oncol.* **2024**, *29*, 1740–1745. https://doi.org/10.1007/s10147-024-02605-0.
29. Tu, H.; Huang, H.; Xian, B.; Li, J.; Wang, P.; Zhao, W.; Chen, X.; Xie, X.; Wang, C.; Kong, B.; et al. Sentinel lymph node biopsy versus pelvic lymphadenectomy in early-stage cervical cancer: A multi-center randomized trial (PHENIX/CSEM 010). *Int. J. Gynecol. Cancer* **2020**, *30*, 1829–1833. https://doi.org/10.1136/ijgc-2020-001857.
30. Bats, A.-S.; Mathevet, P.; Buenerd, A.; Orliaguet, I.; Mery, E.; Zerdoud, S.; Le Frère-Belda, M.-A.; Froissart, M.; Querleu, D.; Martinez, A.; et al. The Sentinel Node Technique Detects Unexpected Drainage Pathways and Allows Nodal Ultrastaging in Early Cervical Cancer: Insights from the Multicenter Prospective SENTICOL Study. *Ann. Surg. Oncol.* **2012**, *20*, 413–422. https://doi.org/10.1245/s10434-012-2597-7.
31. Frumovitz, M.; Obermair, A.; Coleman, R.L.; Pareja, R.; Lopez, A.; Ribero, R.; Isla, D.; Rendon, G.; Bernardini, M.Q.; Buda, A.; et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): A secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol.* **2020**, *21*, 851–860. https://doi.org/10.1016/s1470-2045(20)30081-4.
32. Euscher, E.D.; Malpica, A.; Atkinson, E.N.; Levenback, C.F.; Frumovitz, M.; Deavers, M.T. Ultrastaging Improves Detection of Metastases in Sentinel Lymph Nodes of Uterine Cervix Squamous Cell Carcinoma. *Am. J. Surg. Pathol.* **2008**, *32*, 1336–1343. https://doi.org/10.1097/pas.0b013e31816ecfe4.
33. Margioula-Siarkou, C.; Almperis, A.; Gullo, G.; Almperi, E.-A.; Margioula-Siarkou, G.; Nixarlidou, E.; Mponiou, K.; Papakotoulas, P.; Sardeli, C.; Guyon, F.; et al. Sentinel Lymph Node Staging in Early-Stage Cervical Cancer: A Comprehensive Review. *J. Clin. Med.* **2023**, *13*, 27. https://doi.org/10.3390/jcm13010027.
34. Mathevet, P.; Lécuru, F.; Uzan, C.; Boutitie, F.; Magaud, L.; Guyon, F.; Querleu, D.; Fourchotte, V.; Baron, M.; Bats, A.-S.; et al. Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: Results of a multicentre randomised trial (SENTICOL-2). *Eur. J. Cancer* **2021**, *148*, 307–315. https://doi.org/10.1016/j.ejca.2021.02.009.
35. Tewari, K.S. Cervical Cancer. *N. Engl. J. Med.* **2025**, *392*, 56–71. https://doi.org/10.1056/nejmra2404457.
36. Cohen, P.A.; Jhingran, A.; Oaknin, A.; Denny, L. Cervical cancer. *Lancet* **2019**, *393*, 169–182. https://doi.org/10.1016/s0140-6736(18)32470-x.
37. Jing, H.; Xiuhong, W.; Ying, Y.; Xiyun, C.; Deping, L.; Changmei, S.; Qi, W.; Tao, P.; Yiyun, P. Complications of radical hysterectomy with pelvic lymph node dissection for cervical cancer: A 10-year single-centre clinical observational study. *BMC Cancer* **2022**, *22*, 1286. https://doi.org/10.1186/s12885-022-10395-9.
38. Ramirez, P.T.; Frumovitz, M.; Pareja, R.; Lopez, A.; Vieira, M.; Ribeiro, M.; Buda, A.; Yan, X.; Shuzhong, Y.; Chetty, N.; et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N. Engl. J. Med.* **2018**, *379*, 1895–1904. https://doi.org/10.1056/NEJMoa1806395.
39. Panici, P.B.; Basile, S.; Angioli, R. Pelvic and aortic lymphadenectomy in cervical cancer: The standardization of surgical procedure and its clinical impact. *Gynecol. Oncol.* **2009**, *113*, 284–290. https://doi.org/10.1016/j.ygyno.2008.12.014.
40. Höckel, M.; Horn, L.-C.; Tetsch, E.; Einenkel, J. Pattern analysis of regional spread and therapeutic lymph node dissection in cervical cancer based on ontogenetic anatomy. *Gynecol. Oncol.* **2012**, *125*, 168–174. https://doi.org/10.1016/j.ygyno.2011.12.419.
41. Höckel, M.; Wolf, B.; Schmidt, K.; Mende, M.; Aktas, B.; Kimmig, R.; Dornhöfer, N.; Horn, L.-C. Surgical resection based on ontogenetic cancer field theory for cervical cancer: Mature results from a single-centre, prospective, observational, cohort study. *Lancet Oncol.* **2019**, *20*, 1316–1326. https://doi.org/10.1016/s1470-2045(19)30389-4.
42. Leitao, M.M.; Bixel, K.L.; Chase, D.M.; Quick, A.; McCormick, C.; Black, D.; Lim, P.C.; Eskander, R.N.; Gotlieb, W.H.; LoCoco, S.; et al. ROCC/GOG-3043: A randomized controlled trial of robotic versus open surgery for early-stage cervical cancer. *Int. J. Gynecol. Cancer* **2025**, *35*, 101760. https://doi.org/10.1016/j.ijgc.2025.101760.
43. Bizzarri, N.; Querleu, D.; Ramirez, P.T.; Plante, M.; Giannarelli, D.; Falconer, H.; Abu-Rustum, N.R.; Cibula, D.; Martinez, A.; Laas, E.; et al. Minimally invasive simple hysterectomy in low-risk cervical cancer: A single-arm trial with stopping rules (ENGOT-cx23/MITO/LASH trial). *Int. J. Gynecol. Cancer* **2025**, *35*, 101818. https://doi.org/10.1016/j.ijgc.2025.101818.
44. Falconer, H.; Palsdottir, K.; Stalberg, K.; Dahm-Kähler, P.; Ottander, U.; Lundin, E.S.; Wijk, L.; Kimmig, R.; Jensen, P.T.; Zahl Eriksson, A.G.; et al. Robot-assisted approach to cervical cancer (RACC): An international multi-center, open-label randomized controlled trial. *Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc.* **2019**, *29*, 1072–1076. https://doi.org/10.1136/ijgc-2019-000558.

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