



# The role of postoperative radiation after radical hysterectomy for women with early-stage neuroendocrine carcinoma of the cervix: A meta-analysis

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## HIGHLIGHTS

- In patients with neuroendocrine cervical cancer, routine postoperative radiation therapy may reduce pelvic recurrences.
- In patients with neuroendocrine cervical cancer, routine postoperative radiation does not appear to improve overall survival.
- Determining which patients benefit from postoperative radiation therapy is an important next step for improving outcomes.

## ARTICLE INFO

### Article history:

Received 20 November 2022

Received in revised form 29 January 2023

Accepted 30 January 2023

Available online xxxxx

## ABSTRACT

**Introduction.** Neuroendocrine carcinoma of the cervix (NECC) is an aggressive disease with high rates of nodal disease spread even in seemingly cervix-confined disease. Many providers routinely prescribe postoperative radiation therapy in an effort to reduce recurrences despite a lack of supporting studies. The objective of this study was to determine recurrence and mortality in patients with early-stage NECC who had pelvic radiation after radical hysterectomy compared to those who did not receive radiation.

**Methods.** We performed a meta-analysis of 13 unique studies that reported recurrence and/or mortality for patients with early-stage NECC who underwent radical hysterectomy with or without adjuvant radiation therapy.

**Results.** In 5 studies that reported overall recurrence rates, 63 (52.5%) of 120 patients who received postoperative radiation recurred compared to 70 (37.8%) of 185 patients who did not (RR 1.21, 95% CI: 0.85–1.70,  $p = 0.29$ ). In 5 studies that reported pelvic recurrence rates, there were 15 pelvic recurrences (12.5%) in the 120 patients who received postoperative radiation compared to 45 pelvic recurrences (24.3%) in the 185 patients who did not (RR 0.60, 95% CI: 0.34–1.08,  $p = 0.09$ ). In 13 studies that reported mortality rate, there were 138 deaths (34.8%) in 396 patients who received postoperative radiation therapy compared to 223 (35.2%) in 632 patients who did not (RR 1.08, 95% CI: 0.75–1.56,  $p = 0.66$ ).

**Conclusions.** The addition of routine postoperative radiation therapy in all patients with early-stage NECC after radical hysterectomy may reduce pelvic recurrences but does not appear to decrease overall recurrence or death. However, there may still be a role for postoperative radiation therapy in patients with additional high-risk pathologic factors.

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## 1. Introduction

High-grade neuroendocrine carcinoma of the cervix is a rare form of cervical cancer representing <2% of all cervical cancer types [1]. For women with early stage (stages IA1-IB2) high-grade neuroendocrine carcinoma of the cervix, guidelines uniformly recommend radical hysterectomy and lymph node assessment followed by systemic chemotherapy [1–3]. However, those same guidelines do not reach consensus on which patients should receive adjuvant radiation therapy.

As recurrence rates after surgery and chemotherapy are still 50–60%, some centers have routinely given postoperative radiation therapy to all patients with early-stage, high-grade neuroendocrine carcinoma of the cervix regardless of pathologic findings while others utilize radiation only for high-risk factors [2,4]. Multiple studies have shown that post-operative radiation therapy reduces pelvic recurrences [2,4,5]. In 93 patients with stages I-II, high-grade neuroendocrine carcinoma of the cervix who underwent radical hysterectomy, Ishikawa et al. reported a pelvic recurrence rate of 25% for women with early-stage cervical cancer who did not receive postoperative pelvic radiation compared to 16% for those women who did [4]. Similarly, in a study of 110 women with stages I-II, high-grade neuroendocrine carcinoma of the cervix, Chen et al. reported fewer pelvic recurrences in women who received postoperative radiation therapy compared to those who did not (13% vs. 31%) [5]. Finally, in 100 patients with stages IA1-IB2 high-grade neuroendocrine carcinoma of the cervix who underwent radical hysterectomy, Salvo et al. also found decreased pelvic recurrences for those women who underwent postoperative radiation therapy (13% vs 29%) [2]. All of these studies, however, were unable to show that decreasing pelvic recurrences actually translated into a progression free or overall survival benefit.

It is unknown why studies have not shown improved survival in patients with high-grade neuroendocrine carcinoma of the cervix who receive postoperative radiation. Is it because each of these retrospective studies are relatively small and therefore do not have enough power to detect a difference in survival? Or is there truly no difference in survival due to the high rate of extrapelvic, distant recurrences outside the radiation field? Due to the rarity of this disease, prospective trials are likely impossible and large retrospective or population-based studies difficult. For those reasons, we undertook a meta-analysis of published studies of women with early-stage, high-grade neuroendocrine carcinoma of the cervix to compare outcomes in those patients who underwent postoperative radiation therapy to those who did not.

## 2. Methods

We performed a literature search using the Pubmed database published from 1978 to 2021 on May 1, 2021 to May 1, 2022 for articles regarding early-stage, high-grade neuroendocrine carcinoma of the cervix and adjuvant therapies after a radical hysterectomy. Specifically, any study related to early-stage, high-grade neuroendocrine carcinoma and metrics involving survival, recurrence, treatment choice, staging, were all taken into account. Our database search included terms neuroendocrine (“neuroendocrine”, “small cell”, “large cell”, “neurosecretory systems”), cervical cancer (“uterine cervical neoplasm”, “cervical neoplasm”, “cervical carcinoma”, “malignant neoplasm of cervix”), adjuvant therapy (“adjuvant chemotherapy”, “adjuvant concurrent chemoradiation therapy”, “adjuvant radiation therapy”, “therapeutics”, “treatment”), and prognosis (“progression free survival”, “overall survival”, “recurrence”, “mortality”, “death”). Search restrictions were limited to English only articles and no geographic limitations were placed.

We included systematic literature reviews, retrospective cohort studies, SEER studies, case series with a sample size  $\geq 3$ , studies that included early-stage, high-grade neuroendocrine cervical carcinoma patients, studies that provided information with mean follow up, overall recurrence, distant recurrence, local recurrence, overall survival, status post radical hysterectomy status, post-operative adjuvant therapies

including chemotherapy, concurrent chemoradiation therapy, radiation therapy, or no therapy. Exclusion criteria were as follows: older studies with data points included in more recent studies as to prevent duplicate data, case studies and case series with a sample size  $\geq 3$  due to high probability of publication bias, and studies that did not include post-operative radiation therapy as a metric of interest.

Single investigator data extraction was performed using a form, which included study sample size, total patients who had undergone radical hysterectomy for early-stage, high-grade neuroendocrine cervical carcinoma, post-operative adjuvant therapies including chemotherapy or no therapy that was categorized as “no post-op RT”, post-operative adjuvant radiation therapy categorized as “post-op RT” that included concurrent chemoradiation therapy, chemotherapy followed by radiation therapy, number of patients deceased by the end of the study, number of patients with recurrence with further delineation by locoregional or distant recurrence. Patient level data were verified from published data available for each study and included confirmed pathologic diagnosis of early-stage neuroendocrine carcinoma of the cervix, having undergone radical hysterectomy, and whether or not post-operative radiation therapy was administered. Studies that reported recurrence data were validated for site of recurrence after completion of primary treatment, which was further delineated by inside (local) or outside (distant) the pelvis, or both. Studies were not included in the recurrence meta-analysis if recurrence patterns or rates were not reported in the study.

We performed a meta-analysis of studies that reported recurrence and/or mortality for patients with early-stage, high-grade neuroendocrine cervical carcinoma who underwent radical hysterectomy with or without adjuvant radiation therapy. Dichotomous data eligible were compared as relative risk (RR) with its 95% confidence interval (CI). The relative risk was weighted and pooled by Mantel-Haenszel models to evaluate for post-operative radiation therapy survival and recurrence in this meta-analysis. Heterogeneity analysis was assessed by  $I^2$ , whereby 0–25% represented insignificant heterogeneity, 25% to  $\leq 50\%$  was low heterogeneity, and  $> 50\%$  was high heterogeneity. Random-effects model was chosen for analysis. Forest plots were generated using the RevMan 5.3 software.

## 3. Results

Thirteen unique studies met inclusion criteria. The reported median follow-up time for all of the studies was 25.5 months. There were 3 studies that did not have a median follow-up period reported. (Table 1).

Five studies reported recurrence data for early stage, high-grade neuroendocrine carcinoma who underwent postoperative radiation therapy versus those that did not. The total recurrence for the postoperative radiation therapy group was 63 (52.5%) of 120 patients and 70 (37.8%) of 185 patients for the no postoperative radiation therapy

**Table 1**  
Median follow up in months for the unique studies included in the meta-analysis.

Study	Median follow-up (months)
Collinet 2000 [11]	10
Boruta 2001 [12]	26.5
Sato 2003 [13]	16
Lee, J 2007 [14]	44
Tian 2011 [15]	24.5
Lin 2012 [16]	21
McCann 2013 [17]	27
Intaraphet 2014 [18]	not reported
Chen 2015 [5]	51
Xie 2017 [19]	20.6
Ishikawa 2018 [4]	not reported
Salvo 2021 [2]	38.5
Dong 2021 [20]	not reported
Total	25.5

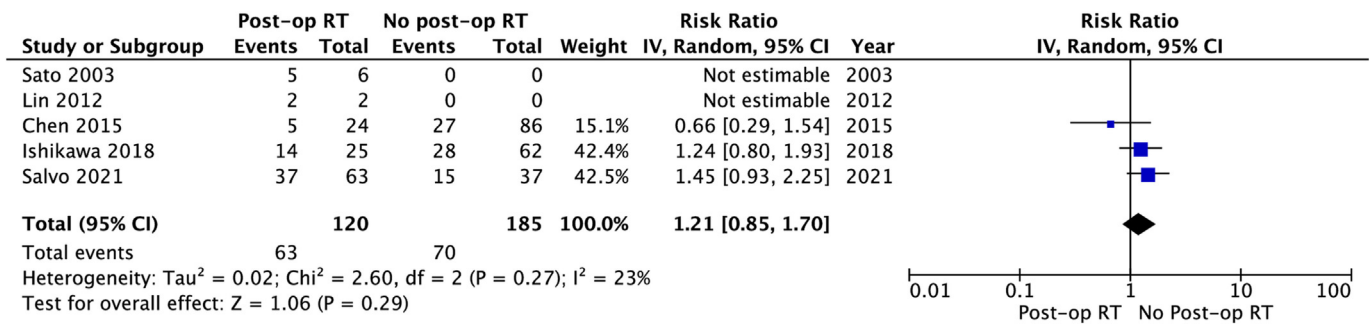


Fig. 1. Number of recurrences, weight of study, and summative relative risk for total recurrence.

group. The total recurrence relative risk (RR) was 1.21 (95% CI: 0.85–1.70, *p* = 0.29). The I<sup>2</sup> was 23%, reflected as insignificant heterogeneity between studies (Fig. 1).

The same 5 studies were analyzed for pelvic recurrence only. There were 15 pelvic recurrences (12.5%) in the 120 patients who received postoperative radiation therapy compared to 45 pelvic recurrences (24.3%) in the 185 patients who did not (RR 0.60, 95% CI: 0.34–1.08, *p* = 0.09). The I<sup>2</sup> was 0%, reflected as insignificant heterogeneity between studies. (Fig. 2).

Evaluating those patients who had distant recurrence only, there were 40 (33.3%) of 120 patients who received postoperative radiation therapy with distant recurrence. For those who did not receive postoperative radiation therapy, 17 (9.2%) of 185 patients had distant recurrence (RR 2.47, 95% CI: 1.28–4.76, *p* = 0.007). The I<sup>2</sup> was 24%, reflected as insignificant heterogeneity between studies (Fig. 3).

There were 8 patients who received postoperative radiation therapy who had both pelvic and distant recurrences (6.7%) of the 120 patients compared to 7 pelvic recurrences (3.8%) in the 185 patients who did not (RR 0.87, 95% CI: 0.30–2.49, *p* = 0.79). The I<sup>2</sup> was 0%, reflected as insignificant heterogeneity between studies (Fig. 4).

All thirteen studies reported mortality data for women with early-stage, high-grade neuroendocrine carcinoma who received postoperative

radiation therapy versus those who have not. There were 138 deaths (34.8%) in 396 patients who received postoperative radiation therapy compared to 223 (35.2%) in 632 patients who did not (RR 1.08, 95% CI: 0.75–1.56, *p* = 0.66). The I<sup>2</sup> was 71%, reflected as high heterogeneity between studies (Fig. 5).

#### 4. Discussion

As recurrence rates are high even for patients with early stage high grade neuroendocrine cervical cancer, it has been common practice for providers to prescribe postoperative radiation therapy in addition to surgery and chemotherapy in an effort to provide adequate disease control and improve survival. This meta-analysis showed that although the addition of postoperative radiation therapy likely decreases pelvic recurrences, there was no associated improvements in overall survival. These findings call into question the utility of routine postoperative radiation therapy in all women with early-stage high grade neuroendocrine cervical cancer after radical hysterectomy.

In this meta-analysis, the addition of postoperative radiation therapy decreased pelvic recurrence rate by 40% which approached statistical significance (*p* = 0.09). Salvo et al. [2] reported that patients who received adjuvant radiation therapy were 62% less likely to have

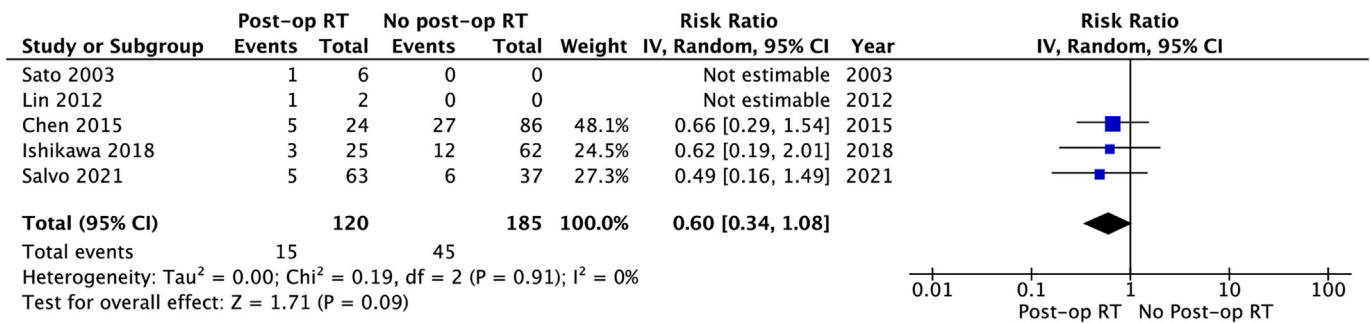


Fig. 2. Number of recurrences, weight of study, and summative relative risk for pelvic recurrence only.

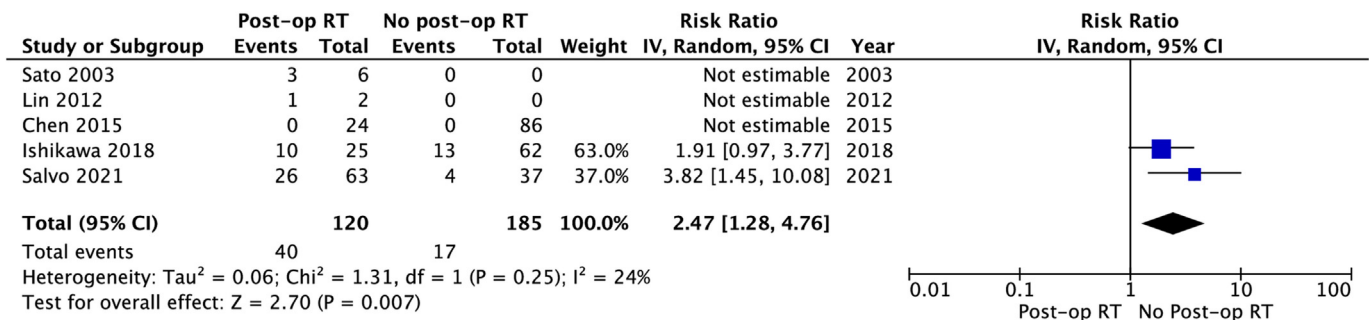


Fig. 3. Number of recurrences, weight of study, and summative relative risk for distant recurrence only.

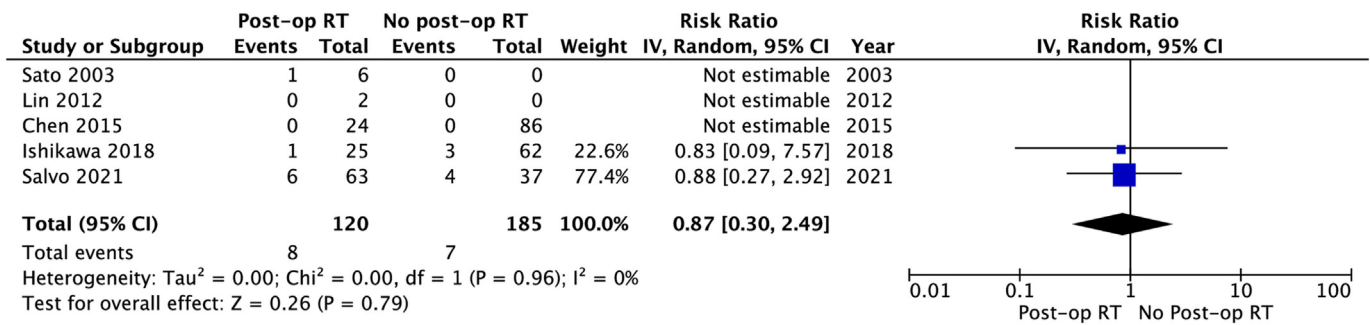


Fig. 4. Number of recurrences, weight of study, and summative relative risk for both pelvic and distant recurrences.

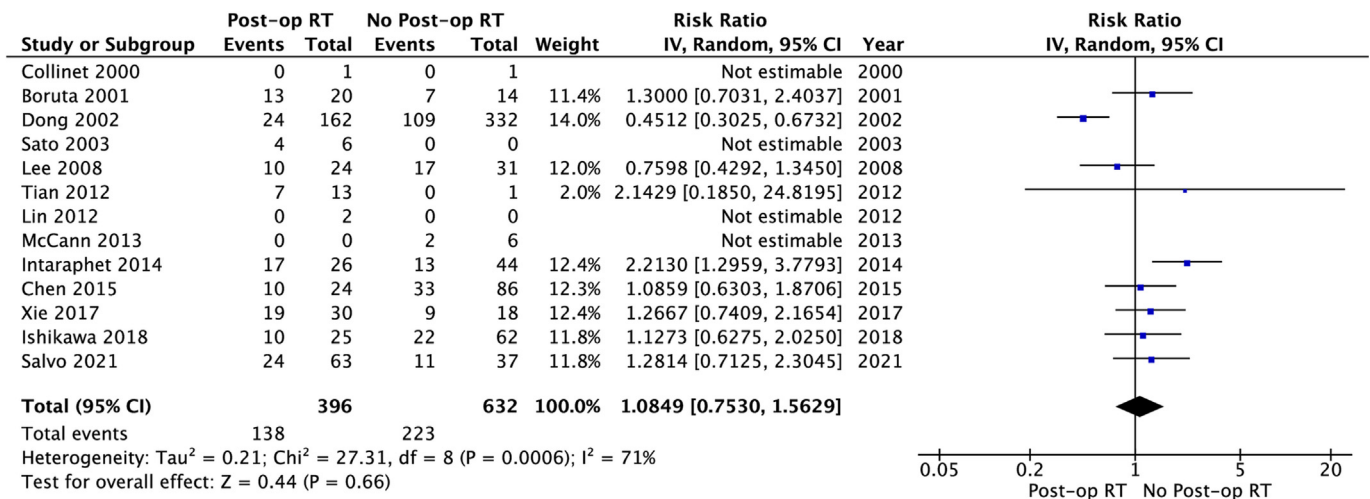


Fig. 5. Number of deaths, weight of study, and summative relative risk for mortality for those who received post-operative radiation therapy versus those who have not.

locoregional recurrence independent of distant recurrence. However, the authors of that study likewise failed to show an overall survival benefit with a median survival of identical 53 months in both the group that received postoperative radiation therapy and the one who did not. Although our study also supports improved locoregional disease control with postoperative radiation therapy, we likewise found no improvement in overall survival. This lack of survival benefit is likely due to high rates of distant recurrences despite improved locoregional control.

Interestingly, this meta-analysis showed that patients who underwent postoperative radiation therapy had significantly higher rate of recurrences at distant sites than those who did not. However, this meta-analysis did not account for the use of chemotherapy in patients after surgery. As patients who recur have a distant component to their recurrence 75% of the time, the addition of chemotherapy after surgery is mandatory [2]. Cohen et al. showed the addition postoperative chemotherapy reduced recurrence by 38% when compared to those who had surgery without chemotherapy [6]. Pei et al. likewise showed that patients with early-stage high-grade neuroendocrine cervical cancer who did not receive chemotherapy after surgery were 5.4 more times likely to recur than those who received at least 5 cycles of platinum and etoposide after surgery [7].

A potential physiologic mechanism may actually promote distant recurrences in patients who receive radiation after surgery. Animal studies in large cell neuroendocrine lung cancer models have shown increased metastatic events after local irradiation. Those authors theorized that the local effects of radiation on blood vessels may promote an environment conducive to tumor cell attachment and migration

into systemic circulation [8]. In contrast, radiation therapy has also been shown to have an abscopal effect whereby localized radiation therapy could induce an anti-tumoral response throughout the body outside the radiation field [9]. However, it is difficult to deduce which mechanism may be favored as no similar translational or animal studies in high-grade neuroendocrine cervical carcinoma of the cervix specimens have been performed.

Strengths of this study was incorporating multiple different studies from various institutions to generate a large sample size from a niche population. To our knowledge, our study was the first to compile an analysis of women with early stage, high-grade neuroendocrine cervical carcinoma comparing radical hysterectomy with adjunct postoperative radiation therapy to those who did not receive postoperative radiation therapy. Weaknesses of this study are those inherent to the meta-analysis methodology and include the variegated modes of reporting. We used differing observational studies including case series, retrospective cohort studies, and SEER data that could have contributed heterogeneity, especially with the mortality analysis. Another weakness is that this meta-analysis of retrospective studies is that for those centers that do not routinely utilize postoperative radiation therapy, the group that did receive radiation likely had other high-risk factors that concerned their oncology team who thereby then recommended postoperative radiation. Furthermore, most of the studies included in the meta-analysis are derived from tertiary cancer centers that may potentiate higher level of cancer related care, which may interfere with the external validity of this study. The specific patient level data in regards to frequency, type, and plan of radiation therapy administered, as well

as patients lost to follow-up were not verifiable. However, all studies included in the meta-analysis have shown a very low number of patients lost to follow-up given the long accrual period of patients due to the rarity of the disease. There is no way to account for these confounding factors in this study. Unfortunately, due to the rarity of this disease, no prospective studies have been performed nor is there likely to ever be one performed. For that reason, this meta-analysis may be the best data available for evaluating postoperative radiation therapy in women with early-stage high-grade neuroendocrine cervical cancer.

In conclusion, we found that in patients with early stage, high-grade neuroendocrine cervical cancer who undergo radical hysterectomy, the addition of postoperative radiation therapy trends toward decreasing pelvic recurrences but does not improve overall survival likely due to the high rate of distant, extra-pelvic recurrences in both groups. Our findings call into question the routine use of postoperative radiation therapy for all patients with early stage, high-grade neuroendocrine cervical cancer after surgery. For women with surgical stage I high grade neuroendocrine cervical cancer, there are no known matrices that predict high rates of pelvic recurrences as are commonly used for triaging patients with adenocarcinoma or squamous carcinoma to postoperative radiation (i.e. “Sedlis Criteria [10]”). We now plan to perform a large study to review pathologic factors of radical hysterectomy specimens that may predict a high-risk of recurrence in order to define a high-risk group of women with surgical stage I, high-grade neuroendocrine cervical cancer who would benefit for postoperative radiation therapy.

## Funding

Small/Large Cell Carcinoma of the Cervix: Sisters United.

## CRedit authorship contribution statement

**Catherine Kim:** Methodology, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Gloria Salvo:** Conceptualization, Data curation, Resources, Writing – original draft, Writing – review & editing. **Mitsuya Ishikawa:** Data curation, Resources, Writing – original draft, Writing – review & editing. **Tze-Chien Chen:** Data curation, Resources, Writing – original draft, Writing – review & editing. **Anuja Jhingran:** Conceptualization, Writing – original draft, Writing – review & editing. **Priya Bhosale:** Writing – original draft, Writing – review & editing. **Preetha Ramalingam:** Writing – original draft, Writing – review & editing. **Michael Frumovitz:** Conceptualization, Methodology, Formal analysis, Data curation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

## Declaration of Competing Interest

Michael Frumovitz receives research funding from AkesoBio and GlaxoSmithKline and serves on speaker and advisory boards for Stryker. All other authors have no disclosures.

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