Updates on Cervical Cancer

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DECLARATION OF INTERESTS

Nothing to declare

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HPV vaccination

HPV vaccination

Launched in 2006

- In girls and boys from the age of 9 years
- Bivalent vaccine (HPV 16, 18), quadrivalent vaccine (HPV 6, 11), the 2nd generation nonavalent vaccine (HPV 31, 33, 45, 52, 58)

In December 2022, WHO

- For the primary target group aged 9-14 years, as well as those aged 15 years and older, a one- or two-dose schedule (at 0 and 6-12 months)
- Those aged 21 years and older should receive 2 doses
- Immunocompromised patients must receive 3 doses (at 0, 1-2, and 6 months)

Human papillomavirus vaccines: WHO position paper, December 2022. Wkly Epidemiol Rec No 50. 2022;97:645-672. World Health Organization. HPV Dashboard. Accessed December 21, 2024. https:// www. who. int/ teams/ immun izati on-vaccines-and-biologicals/ disea ses/ human -papillomavirus-vaccines-(HPV)/hpv-clearing-house/hpv-dashboard

One-dose HPV vaccine

The longest follow-up study of a prospective cohort for an average period of **12 years**, India

One-dose cohort, 4,949; two-dose cohort, 4980; three-dose cohort, 4348; **quadrivalent vaccine**

Vaccine efficacy against persistent HPV 16/18 infection

- 92.0% (95% CI, 87.0-95.0) in the one-dose arm
- 94.8% (95% CI, 90.0-97.3) in the two-dose arm

Comparable efficacy with one dose compared to two and three doses

No high-grade lesions among vaccinated women vs. eight precancers among the unvaccinated women

JNCI Monogr. 2024;67:317-328.

Screenig program

Global effort to transition to hrHPV-based primary screening

Rolled out in Australia (2017) and the UK (2019)

Also implementing HPV screening nationally or regionally

- Many countries in Europe (Netherlands, Sweden, Türkiye, Finland, and Italy)
- Argentina, Chile, and Mexico

In the process of transition

- Thiland, Japan, and Sri Lanka

Higher initial colposcopy referral rates, but higher detection rates of CIN3+ lesions and CCs

The USTSF, ACOG: cytology Q3y, co-testing Q5y, hrHPV Q5y

Clin Microbiol Infect. 2020;26:579-583

HPV self-collection – core clinical evidence and accuracy

Compared to clinician-collected sample

- Equivalent sensitivity for detecting high-grade cervical lesions
- Marginal specificity drop (approx. 2-4%)
- High (92% positive) agreement in hrHPV detection b/n self-swabs and clinician swabs

CA Cancer J Clin. 2025;76(1):e70047
Lancet Oncol 2014;15:172-83
JAMA Netw Open. 2025;8(5):e2511081

HPV self-collection – guidelines & regulatory approvals

FDA Support

- The FDA has expanded approvals for established molecular tests (Cobas and Onclarity HPV test)
- Australia, Netherlands, Sweden, Denmark, US

Screening Interval

- Routine screening should be repeated in 3 years

The Triage Rule

- Positive self-collected test → follow-up appointment with a clinician is required for cytology (a Pap smear) or a colposcopy

CA Cancer J Clin. 2026 Jan-Feb;76(1):e70041

FIGO staging

Staging of CC

2018 revised FIGO staging

- To allow the option of clinical, radiological, or pathological findings
- The horizontal dimension of a microinvasive lesion is no longer considered
- Tumor size has been stratified further into 3 subgroups: IB1 ≤2cm, IB2 >2 - ≤4cm, and IB3 >4cm
- LN positivity based on positive findings from radiology (IIIC1r) or pathology (IIIC1p)
  - IIIC1 – pelvic nodes (+)
  - IIIC2 – para-aortic nodes (+)
  - Micrometastases – stage IIIC

Int J Gynaecol Obstet. 2019;145:129-135

MIS RH for early-stage CC

Minimally invasive radical hysterectomy

- LACC trial
  - Decreased OS in the MIS group (3/312 vs. 19/319, HR 6.00, 95% CI 1.48-20.3; p=0.004)
  - DFS events were significantly worse in the MIS group (7/312 vs. 27/319, HR 3.74, 95% CI 1.63-8.58; p=0.002)

N Engl J Med. 2018;379:1895-1904

Several ongoing clinical trials – MIS RH (no uterine manipulator, closure of the vagina before colpotomy)

Robotic Approach to Cervical Cancer (RACC) trial (Sweden)

Robotic versus Open Radical Hysterectomy for Early-stage Cervical Cancer (ROCC) trial (GOG-3043)

Laparoscopic Approach to Uterine Cervical Neoplasia (LAUNCH) trial (China)

- LAUNCH 1 trial: 2018 FIGO stages IA1 with LVSI and IA2
- LAUNCH 2 trial: FIGO stages IB1, IB2, and IIA1
- LAUNCH 3 trial: FGIO stages IB3 and IIA2

Int J Gynecol Cancer. 2019;29:1072-1076
Int J Gynecol Cancer. 2025;35:101760
Trials. 2022;23:269

According to the latest international consensus guidelines

Laparotomy is the standard approach for procedures requiring radical parametrectomy (NCCN, ESGO)

Patients must be thoroughly counseled that MIS may correlate with an increased risk of recurrence and lower OS compared to open surgery (NCCN)

MIS may be considered only under strict conditions (ESGO)

- Tumors less than 2cm in size with free margins after conization
- High-volume centers
- Informed consent after a comprehensive discussion regarding current oncologic evidence
- To avoid tumor cell spillage (e.g., avoiding uterine manipulators or using barrier techniques/vaginal cuff closure)

Surgical de-escalation with less radical surgery

Fertility-sparing or less radical surgery for low-risk early-stage CC

Title	Study type	Tumor size & procedures
ConCerv (2021)	Prospective, single-arm, multicenter international cohort (**100 patients**, 9 countries)	Tumor size ≤2cm Conization or SH with pelvic LN assessment
SHAPE (2024)	Phase III, multicenter, randomized controlled, noninferiority trial (**700 patients**, 12 countries)	Tumor size ≤2cm SH with pelvic LN assessment
GOG-278 / NRG-0278 (2025)	Prospective observational multi-institutional cohort study conducted by NRG Oncology / GOG (**224 patients**, 2 countries)	Tumor size ≤2cm Conization or SH with pelvic LN assessment
CONTESSA / NEOCON-F (ongoing, 2022-2026)	Ongoing multi-center, prospective phase II clinical trial (**target 90 patients**, 3 countries)	Tumor size >2cm to ≤4cm 3 cycles of platinum/paclitaxel NACT followed by FSS (conization or simple trachelectomy)

ConCerv trial (2021) & SHAPE trial (2024)

FIGO 2009 stage IA2-IB1;

SCC (any G) or AC (G 1 or 2);

tumor size under 2cm; no LVSI; stromal invasion below 10 mm;

negative imaging for metastasis; and negative cone margins

- Conization or SH with pelvic LN assessment
- Median FU of 36.3 months
- 3 disease recurrence within 2 years of surgery (3.5% cumulative incidence)

FIGO 2009 stages IA2 or IB1 disease;

Diameter ≤2cm;

Stromal invasion <10 mm (LEEP or cone specimen), or < 50% total cervical stromal thickness on MRI;

No evidence of LN metastasis on preoperative imaging

- SH with pelvic LN assessment
- 3-year pelvic recurrence (2.52% in SH vs. 2.17% i n RH; 90% CI 1,62-2.32)
- Urinary retention 4 weeks after surgery:

0.6% in SH vs. 11.0% in RH, p<0.001

Int J Gynecol Cancer. 2021;31(10):1317-1325 / N Engl J Med. 2024;390:819-829

Surgical de-escalation with SLNB

Role of sentinel LN mapping – SENTICOL-2 trial

267 patients with early-stage CC (2009 FIGO stages IA1 with LVSI to IIA1)
Tumor size <40 mm, Surgical morbidity
Median FU 51 months

Two groups	SLN biopsy alone (n=105)	SLNB + PLDN (n=101)	P-value
Lymphatic complications	**31.4%**	**51.5%**	**0.046**
Neurologic symptoms	7.8%	20.6%	0.01
DFS	89.5%	93.1%	0.53
OS	95.2%	96.0%	0.97

Eur J Cancer. 2021;148:307-315

Role of sentinel LN mapping – PHENIX trial

838 patients with early-stage CC (2009 FIGO stages IA1 with LVSI, IA2, IB1, or IIA1, tumor size ≤3 cm)			
Two groups	SLN biopsy alone (n=420)	Full lymphadenectomy (n=418)	P value
3-year DFS	96.9%	94.6%	<0.001 for non-inferiority
Lymphedema	5.2%	19.1%	<0.001
Lymphocyst formation	8.3%	22.0%	<0.001

N Engl J Med. 2025;393:1463-1474

SENTICOL III trial - ongoing

Non-inferiority survival trial	
Target sample size	950 patients
Co-primary endpoints	**3-year DFS** & **health-related QOL**
FIGO stage	2018 FIGO stages IA1 with LVSI up to IB2 and IIA1, **tumor size ≤40 mm**
SENTICOL II vs. III	• Individual institutional evaluation for LNs vs. pathological ultrastaging protocol • Traditional technetium-99 radioactive isotopes + blue dye vs. ICG fluorescence imaging

Int J Gynecol Cancer 2019;29:829-834

Strict size cutoffs for SNLB alone

Larger than 2cm tumor

- Tumor choking effect (To disrupt or compress lymphatic channels)
- Side-specific mapping success rates: 85% (small tumor) to 60-67% (>2cm tumor)
- The risk of pelvic nodal metastasis: 15% to 30% or higher

NCCN

- SNLB can be considered up to 4cm (2018 FIGO stages IB1 and IB2)
- Optimal and safest setting to perform SLNB alone is in tumors less than 2cm

ESGO

- Low-risk, tumor size ≤2cm

Cancers. 2024;16:2541
J Clin Med. 2023;13:27

Pushing late vs. hitting early : chemotherapy timing in LACC

FIGO stage IIB-IVA – OUTBACK vs. INTERLACE trial

Feature	OUTBACK (pushing late)	INTERLACE (hitting early)
Strategy evaluated	Adjuvant chemotherapy (after standard CCRT)	Induction chemotherapy (before standard CCRT)
Chemotherapy regimen	Paclitaxel + carboplatin (4 cycles, every 3 weeks)	Paclitaxel + carboplatin (6 cycles, given weekly)
Sample size	919 patients	500 patients
5-year OS	72% (experimental) vs. 71% (control) → no benefit	80% (experimental) vs. 72% (control) → significant benefit
5-year PFS	63% (experimental) vs. 61% (control) → no benefit	72% (experimental) vs. 64% (control) → significant benefit

Lancet Oncol. 2023;24:468-482
Lancet. 2024;404(10462):1525-1535

Several reasons why OUTBACK trial's strategy failed

22% of randomized patients failed to even start the adjuvant chemotherapy

Delayed attack on distant metastases

- Standard pelvic CCRT takes several months to complete

Higher proportion of patients with lower-stage, better-prognosis disease than originally anticipated (such ad node-positive IB1 and IIA tumor)

PD-L1 expression

Immunohistochemistry for PD-L1 expression

Benefit from immune checkpoint inhibitors (ICIs)

The 22C3 pharmDx assay

- FDA approved PD-L1 expression test

Scoring system (combined positive score, CPS)

- The ratio of PD-L1-stained cells (both tumor cells and specific immune cells) to the total number of viable tumor cells, multiplying the result by 100
- CPS ≥1 – PD-L1 positive, eligible for ICI therapy
- CPS ≥10 – higher likelihood of response to ICI

Int J Gynaecol Obstet. 2025 Suppl 1:87-108

PD-L1 expression in different histologic subtypes of CC

Histologic subtype (proportion of cancers)	PD-L1 expression	Therapeutic implications
SCC (75-80%)	Frequently PD-L1 positive (60-80%)	Eligible for pembrolizumab in recurrent/metastatic cases
Adenocarcinoma (15-20%)	Less frequently PD-L1 positive (~20-30%)	May still benefit from ICIs if CPS ≥1
Neuroendocrine tumor (5%)	Often PD-L1 positive	Potential use of ICIs + chemotherapy
HPV-independent gastric type adenocarcinoma	Rarely PD-L1 positive	Limited response to immunotherapy

Int J Gynaecol Obstet. 2025 Suppl 1:87-108

Immunotherapy

Chronological summary of the four landmark phase III immunotherapy trials

Clinical trial (year)	Patient population	Core design	Significance
KEYNOTE-826 (2021)	Persistent, recurrent, or metastatic CC	Pembrolizumab + standard chemotherapy (±bevacizumab)	• PFS ↑, OS ↑ especially in PD-L1 positive tumors (CPS ≥1 and ≥10)
EMPOWER-Cervical 1 (2022)	Persistent, recurrent, or metastatic CC	Cemiplimab monotherapy (IgG4 monoclonal Ab binding to the PD-1 receptor on T-cells)	• First phase III monotherapy success • Efficacy independent of PD-L1 • Improved QOL
CALLA (2022-2023)	Locally advanced CC	Durvalumab (PD-L1 inhibitor) concurrently with standard CCRT and maintenance therapy	• No PFS benefit vs. CCRT alone

Chronological summary of the four landmark phase III immunotherapy trials

Clinical trial (year)	Patient population	Core design	Significance
BEATcc (2023)	Persistent, recurrent, or metastatic CC	Atezolizumab (PD-L1 inhibitor) + paclitaxel + carbo- or cisplatin + bevacizumab	• PFS ↑, OS ↑, regardless of the PD-L1 status
KEYNOTE-A18 (2024)	High-risk locally advanced CC	Pembrolizumab to standard definitive CCRT followed by pembrolizumab maintenance	• PFS ↑, OS ↑ • First IO regimen approved for curative-intent CCRT setting

Locally advance CC – INTERLACE vs. KEYNOTE-A18 trial (1)

Feature	GCIG INTERLACE	KEYNOTE-A18 (ENGOT-cx11)
Core concept	Induction chemotherapy before standard CCRT	Concurrent immunotherapy during CCRT, followed by maintenance
Treatment timelines	6 weeks of weekly chemo upfront (pacli/carbo), then immediate 5 weeks of standard CCRT	Pembro concurrently with CCRT, followed by up to 15 cycles (approx. 2 years) of maintenance
Patient risk profile	Lower-to-intermediate risk LACC (2018 FIGO stage IB3, IIA2, IIB, IIIA, IIIB, or IVA / 2018 FIGO stage IIIC, but node-negative above the the L1/L2 vertebrae, renal vessles)	High-risk LACC (2018 FIGO stage IIIA, IIIB, or IVA / 2018 FIGO stage IIIC1 and IIIC2)

Locally advance CC – INTERLACE vs. KEYNOTE-A18 trial (2)

Feature	GCIG INTERLACE	KEYNOTE-A18 (ENGOT-cx11)
Primary results	• 5-year OS increased to 80% (vs. 72% with CCRT alone) • Reduced systemic relapses	• 3-year OS improved to 82.6% • 33% reduction in risk of death
Core conceptual breakthroughs	Dose-dense 6-week window without a significant delay in definitive local pelvic radiation	Capitalizing on the abscopal effect (RT destroy cancer cells, releasing tumor antigens → tumor microenvironment into an immune reactive state)
When to prefer	• Stage I-II disease with pelvic nodes but no para-aortic extensions • Low-resource settings	• High-risk, bulky, or advanced node-positive disease • Highly constrained by the premium cost

Locally advance CC – CALLA vs. KEYNOTE-A18 trial

Feature	CALLA	KEYNOTE-A18 (ENGOT-cx11)
Immunotherapy agent	**Durvalumab** (Anti-PD-L1)	**Pembrolizumab** (Anti-PD-1)
Patient population	Lower percentage of advanced stage III disease and higher percentage of patients with no nodal involvement	Higher-risk population (approx. 85% node-positive) and over 55% advanced stage III-IVA disease
Eligibility criteria	≥1 involved lymph node ≥1.0 cm	≥2 involved lymph nodes ≥1.5 cm
Treatment duration	Up to ≈ 24 weeks (concurrently with CCRT)	Up to ≈ 2 years (concurrent + adjuvant maintenance)
Key findings	No statistically significant improvement in PFS	Significant improvement in PFS and OS

Several reasons why CALLA trial failed

High quality and performance of the control group

- IMRT & image-guided brachytherapy

Patient cohort and baseline risk difference

- Patients with lower overall baseline risk profile (vs. KEYNOTE-A18)

Mechanism of action: PD-1 vs. PD-L1

- Pembrolizumab (PD-1 inhibitor) and durvalumab (PD-L1 inhibitor) target different parts of the same pathway
- Complete prevention PD-1 (from binding to both PD-L1 and PD-L2) vs. only block the PD-1/PD-L1 interaction

Metastatic or recurrent settings - immunotherapy

KEYNOTE-826

617 persistent, recurrent, or metastatic CC

PD-L1 status

- 88.8% (n=548) CPS ≥1, 51.4% (n=317) CPS ≥10

Pembrolizumab + chemo ± bevacizumab (308 patients) vs.

Placebo + chemo ± bevacizumab (309 patients)

75% SCC, 21% AC, 5% ASC

KEYNOTE-826 – key findings & safety

OS (CPS ≥1): 28.6 vs. 16.5 months (HR 0.60)

OS (all-comers): 26.4 vs. 16.8 months (HR 0.63)

PFS significantly improved: 10.4 vs. 8.2 months (HR 0.62)

Grade ≥3 adverse events: 82.4% (pembro) vs. 75.4% (placebo)

- Anemia, neutropenia, & hypertension

Immune-mediate AEs: 34.5% (pembro) vs. 16.5% (placebo)

- Grade 3-5 imAEs: 12.1% (pembro) vs. 2.9% (placebo)
- Hypothyroidism (19.2% vs. 10.0%), hyperthyroidism (8.5% vs. 3.2%), colitis (5.2% vs. 1.6%)

EMPOWER Cervical-1

Drug design & regimen

- Cemiplimab – human IgG4 anti-PD-1 monoclonal antibody
  - 350 mg every 3 weeks, up to 96 weeks

Control arm

- Single-agent chemotherapy (pemetrexed, vinorelbine, gemcitabine, irinotecan, or topotecan)

Patient population

- Recurrent or metastatic CC that progressed during or after standard first-line platinum-based chemotherapy
- 608 patients randomized (304 in the cemiplimab vs. 304 in the chemotherapy)
  - 472 SCC (77.8%), 136 AC (22.2%)
- Regardless of baseline PD-L1 expression

EMPOWER Cervical-1 - Key findings

OS (total population)

- Median OS of 12.0 months vs. 8.5 months with chemotherapy (HR: 0.67; p<0.00001, 33% reduction in risk of death)

Significant survival improvement in SCC (median OS 11.1 vs. 8.8 months; HR, 0.73)

OS advantage was maintained even in patients with PD-L1 expression <1%

Grade ≥3 adverse events occurred in 45% of the cemiplimab vs. 53.4% of the chemotherapy arm

BEATcc

- Patient population
  - 410 patients with metastatic (IVB), persistent, or recurrent CCs
  - Not amenable to curative surgery or radiation
  - No prior systemic therapy for metastatic/recurrent disease
  - Regardless of PD-L1 status
- Control arm
  - Paclitaxel + cis/carboplatin + bevacizumab (n=204)
- Experimental arm
  - Standard chemotherapy + bevacizumab + atezolizumab (1200 mg Q3W) (n=206)

BEATcc – key findings

- OS
  - Median OS, 32.1 months vs. 22.8 months (HR, 0.68; 95% CI, 0.52-0.88; p=0.046)
  - Reduced risk of death by 32%
- PFS
  - Median PFS, 13.7 months vs. 10.4 months (HR, 0.62; 95% CI, 0.49-0.78; p<0.0001)
  - Reduced risk of progression by 38%
- Efficacy demonstrated independently of PD-L1 expression
- Manageable safety

Metastatic or recurrent settings - ADC

InnovaTV 301 phase 3 clinical trial

Tisotumab vedotin

- Binding to tissue factor on cancer cells, entering the cell, and releasing a toxic payload called MMAE to kill the cell

Tisotumab vedotin (2.0 mg/kg IV every 3 weeks)

- 253 patients

Investigator's choice chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed)

- 249 patients

Recurrent or metastatic CC (316 SCC, 63%; 161 AC, 32%, 25 ASC, 5%)

- Disease progression during or after 1-2 prior systemic regimens (including a chemotherapy doublet ± bevacizumab and/or anti-PD-1/PD-L1 therapy)

InnovaTV 301 – key findings & safety

OS, **11.5 months** vs. 9.5 months

- 30% reduction; HR, 0.70; p=0.0038

PFS, **4.2 months** vs. 2.9 months

- 33% reduction; HR, 0.67; p<0.0001

ORR, 17.8% vs. 5.2%

- OR, 4.0; p<0.0001

Manageable adverse events including ocular toxicity, peripheral neuropathy, and hemorrhage (mild epistaxis)

Rare pneumonitis, Stevens-Johnson SD

Summary (1)

MIS for early-stage CC

- Open abdominal RH is the preferred gold standard for early-stage CC, while MIS is restricted or discouraged due to lower survival and higher recurrence rates, except for highly selected low-risk early cases in specialized centers

Summary (2)

Surgical de-escalation

- Less radical surgery (such as simple hysterectomy) is safe and effective for low-risk, early-stage CC patients, minimizing complications and preserving QOL without compromising survival
- SLNB alone is a safe alternative to pelvic lymphadenectomy for early-stage CC, providing similar 3-year DFS while reducing postoperative morbidity

Summary (3)

Locally advanced cervical cancer

- When considering the addition of novel systemic therapies (pembro concurrently or induction chemo) to standard CCRT in LACC, clinicians should evaluate four primary pillars; LN status (specifically para-aortic nodes), FIGO stage, patient comorbidities, and financial/regulatory accessibility

Summary (4)

Recurrent or metastatic CCs

- Incorporating ICIs into first- and second-line regimens significantly prolongs both PFS and OS compared to standard chemotherapy alone

ADCs

- ADCs as a new standard of care by significantly improving OS in previously treated recurrent or metastatic CC, paving the way for ADCs to expand into first-line combination settings

Korean Society of
Gynecologic Oncology

2026년
대한부인종양학회 하계학술대회
제20차 젊은의사 워크숍
제9차 분과전문의 연수강좌
제1차 부인종양간호사 연수강좌
& 카데바 워크숍

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