UCLA
UCLA Previously Published Works

Title

Current opinions: updates on the changing landscape in the management of cervical cancer

Permalink

https://escholarship.org/uc/item/2z54664v

Journal

Current Opinion in Obstetrics & Gynecology, 37(1)

ISSN

1040-872X

Authors

Venkat, Puja S
Smick, Alexandra H
Salani, Ritu

Publication Date

2025-02-01

DOI

10.1097/gco.0000000000000999

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Current opinions: updates on the changing landscape in the management of cervical cancer

Puja S. Venkat[a,b], *Alexandra H. Smick*[c] *and Ritu Salani*[b,c]

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

Purpose of review
To review the recent updates in the management of cervical cancer across all stages of the disease.

Recent findings
After decades of minor advances, the landscape in cervical cancer is now rapidly changing. Recent studies have reported across the cervical cancer spectrum and on different therapeutic modalities. First, less radical surgery in the assessment and management of patients with early-stage, low-risk disease has been shown to be a safe option with reduced morbidity. The role of checkpoint inhibitor therapy in combination with chemotherapy and radiation has demonstrated improved survival outcomes, moving immunotherapy to earlier lines of therapy. The options for systemic therapy continue to include checkpoint inhibitors as well as treatment with antibody drug conjugates (ADCs) in the recurrent setting. Additional research continues to focus on targeting biomarkers in this disease.

Summary
In this paper, we will review the practice-changing trials impacting early stage, locally advanced, and recurrent cervical cancer patients. Despite advances, the limited survival for these patients continues to highlight the need for access to preventive healthcare (vaccine/cytology) and clinical trials to continue to make advances.

Keywords
cervical cancer, chemoradiation, pembrolizumab, radical hysterectomy, tisotumab vedotin

INTRODUCTION

Though the highest impact is in the developing world, cervical cancer continues to have a significant impact globally with an estimated 604 127 cases and 341 831 deaths in 2020 [1]. As the median age for patients with cervical cancer is 50 [2], studies have emphasized the need to focus on improving or maintaining survival outcomes while enhancing quality of life and reducing morbidity. Recently, trials have resulted that have accomplished these goals for cervical cancer patients. In this review, we will focus on new updates in the management of patients with cervical cancer across the spectrum of the disease.

Surgical management

Standard of care for early-stage cervical cancer (stage IA1 to IB2) is hysterectomy with or without lymph node evaluation and ovarian conservation depending on stage and patient risk factors. Since 2018, advanced imaging can now be used for staging purposes [3]. Fertility-preservation is considered an option for early-stage disease at low risk of recurrence (tumor $\leq$2 cm, no lymph node metastasis) including cold knife conization and trachelectomy. Results from recent trials have shifted surgical practice towards an open approach and less radical surgery given equivalent oncologic outcomes and improved quality of life (QoL).

Prior to 2018, treatment of early-stage cervical cancer was largely with minimally invasive surgery (MIS). The LACC trial was a phase 3 noninferiority trial that compared MIS to open abdominal radical hysterectomy in patients with IA1 (with LVSI), IA2, or IB1 cervical cancer. The updated final analysis was published in 2024 and showed a 4.5-year disease-free survival (DFS) and overall survival (OS) favoring

[a]Department of Radiation Oncology, University of California Los Angeles, [b]Jonsson Comprehensive Cancer Center, University of California and [c]Department of Obstetrics and Gynecology, University of California Los Angeles, Los Angeles, California, USA

Correspondence to Ritu Salani, MD, MBA, David Geffen School of Medicine at UCLA, PO Box 951740, Los Angeles, CA 90095, USA. Tel: +1 310 794 3639; e-mail: rsalani@mednet.ucla.edu

Curr Opin Obstet Gynecol 2024, 36:000–000

DOI:10.1097/GCO.0000000000000999

1040-872X Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

KEY POINTS

- Simple hysterectomy is not inferior to radical hysterectomy in early-stage, low risk cervical cancer.
- Sentinel lymph node mapping has acceptable sensitivity and negative predictive value for lymph node metastases in early-stage cervical cancer.
- The addition of concurrent and maintenance pembrolizumab to chemoradiation (CRT) for high-risk, locally advanced cervical cancer resulted in improved progression free survival and overall survival.
- Platinum-based chemotherapy, bevacizumab, and pembrolizumab should be considered standard of care for programmed death ligand 1 (PD-L1) positive disease.
- Tisotumab vedotin demonstrated improved survival outcomes in the recurrent setting when compared to single agent chemotherapy.
- Trastuzumab deruxtecan is an option for patients whose tumors have 3+ human epidermal growth factor receptor 2 (HER2) expression on immunohistochemistry.

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

open surgery [DFS: 96% open vs. 85% MIS; 95% confidence interval (CI), –15.8 to –6.3; $P = .95$; OS: 96.2% open vs. 90.6% MIS; 90% CI, 1.32–5.59; $P = 0.007$] [4▪▪]. Since the results of this study were published, the trend has moved towards open abdominal surgery for early-stage cervical cancer. However, criticisms of the LACC trial have included the use of uterine manipulators and no standard system for tumor containment [5]. The ROCC trial is a phase 3, randomized controlled trial (RCT), currently enrolling patients to compare MIS (robot-assisted) to open abdominal radical hysterectomy with standardized procedures intended to reduce the risk of peritoneal contamination [6].

Surgical advances in early-stage cervical cancer also include a trend towards simple hysterectomy. The CONCERV trial was a prospective single-arm study of patients with stage IA2 to IB1 cervical cancer who underwent simple hysterectomy with lymph node assessment after cold knife cone with negative margins (Table 1). Results demonstrated a 2-year recurrence rate of 3.5% (95% CI, 0.9–9.0) [7]. This was followed by the SHAPE trial, a prospective RCT published in 2024, which compared simple hysterectomy to radical hysterectomy (both with lymph node assessment) in patients with IA2 to IB1 cervical cancer (Table 1). Results showed a similar 3-year pelvic recurrence rate between the two surgical routes (2.17% radical vs. 2.53% simple; 90% CI, −1.62 to 2.32). QoL outcomes demonstrated lower rates of urinary incontinence (UI) and urinary retention (UR) in the simple hysterectomy cohort (UI: 4.7% simple vs. 11% radical; $P = 0.048$; UR: 0.6% simple vs. 9.9% radical; $P < 0.001$) [8▪▪]. Simple hysterectomy is now frequently adopted in this patient population given similar recurrence rates and improved QoL outcomes. However, radical hysterectomy may still be offered in patients with IB1 (with extensive stromal invasion) or IB2 cervical cancer.

Complete pelvic lymph node dissection (PLND) in early-stage cervical cancer is also being challenged with the study of sentinel lymph node (SLN) mapping. The goal of SLN is to maintain equivalent detection rates of metastatic disease while decreasing surgical morbidity. The SENTICOL-1 study evaluated the sensitivity and negative predictive (NPV) of SLN mapping compared to complete PLND in early-stage cervical cancer and found that SLN mapping had a

Table 1. Comparison of trial designs for the CONCERV and SHAPE studies [7,8▪▪]

Study criteria	CONCERV trial (2021)	SHAPE trial (2024)
Study type	Prospective, single arm	Phase 3 RCT
Stage	IA2 to IB1	IA2 to IB1
Histology	squamous cell (any grade) or adenocarcinoma (grade 1 or 2 only) histology	squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma
Tumor size	<2 cm	≤2 cm
LVSI allowed	No	Yes
Depth of invasion	<10 mm	<10 mm or < 50% cervical stromal tissue on MRI
Metastatic disease	Imaging must be negative	Imaging must be negative
Cone margins	Negative	Positive allowed
Primary outcome	2-year incidence of recurrence	Pelvic recurrence at 3 years

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

sensitivity of 92% (95% CI, 74–99) and NPV of 98.2% (95% CI, 74–99) [9]. The SENTICOL-2 study then followed up on the surgical morbidity and QoL outcomes of this cohort and showed a decrease in lymphatic morbidity and nerve injury in the SLN mapping group [10]. We are still awaiting results from the SENTICOL-3 study to validate the DFS and QoL results [11].

Radiation therapy in the management of cervical cancer

Radiation plays a critical role in treating early stage and locally advanced cervical cancer (LACC). For early-stage disease, radiation is used in the adjuvant setting with recommendations based on pathologic intermediate or high-risk factors (Table 2). For patients with ≥2 intermediate risk factors current recommendation is for adjuvant radiation alone [12]. However, the pending GOG 0263 trial is investigating if the addition of concurrent cisplatin to adjuvant radiation will result in survival benefits in this intermediate risk group. For patients with high-risk features following surgery, standard of care is chemoradiation (CRT) [13]. In the RCT RTOG/GOG 0724, the role of adjuvant systemic therapy following CRT was evaluated in patients with high-risk factors after surgery for early-stage disease [14▪]. The results demonstrated no benefit in DFS or OS with carboplatin and paclitaxel following CRT. This echoes the OUTBACK trial, which demonstrated no benefit to the addition of adjuvant chemotherapy to CRT and brachytherapy (BT) in LACC [15].

Though radiation is the backbone for LACC, recent trials have evaluated how systemic therapies can be used to improve outcomes. The KEYNOTE A-18/ENGOT-cx11/ GOG-3047 trial evaluated the addition of pembrolizumab, a PD-1 inhibitor, given concurrently and as a maintenance strategy to standard CRT and BT [16▪▪]. This RCT enrolled over 1000 patients from 176 centers and 30 countries. Patients had high risk advanced disease with either FIGO 2014 IB2-IIB node positive or stage III-IVA disease (approximating to FIGO 2018 IIIA–IVA). At the prespecified interim analysis, a statistically significant improvement in progression-free survival (PFS) was seen with the addition of pembrolizumab to standard therapy. PFS at 24 months was 68% in the pembrolizumab-CRT group vs. 57% in the placebo-CRT group with a hazard ratio (HR) for disease progression or death of 0.70 (95% CI 0.55–0.89, $P = 0.0020$). Though the OS at 24 months did not reach statistical significance at the first analysis (87% pembrolizumab-CRT arm vs. 81% placebo-CRT arm, the sponsor Merck has stated that at the second prespecified interim analysis, a statistically significant OS benefit was seen with the addition of pembrolizumab [17].

The Gynecologic Cancer InterGroup INTERLACE trial took a different approach investigating the benefit of induction chemotherapy to CRT [18]. INTERLACE randomized 500 patients to neoadjuvant dose dense weekly paclitaxel plus carboplatin for 6 weeks followed by CRT compared to standard CRT alone. FIGO 2008 Stage IB1 node positive, IB2, II, IIIB, and IVA stages were eligible (approximating to stage IB3–IVA excepting stage IIIA or IIIC2). After a median follow-up of 64 months, the induction chemotherapy arm demonstrated a statistically significant improvement in PFS (73% vs. 64% at 5 years, HR = 0.65; 95% CI = 0.46–0.91, $P = 0.013$) and OS (80% vs. 72% at 5 years, HR = 0.61, 95% CI = 0.4–0.91, $P = 0.04$).

Comparing these trials, KEYNOTE A18 enrolled >1000 patients from 2020 to 2022 while INTERLACE enrolled 500 patients from 2012 to 2022. It is important to note that radiation techniques have changed dramatically over the extended time frame of INTERLACE and may have impacted results. Furthermore, KEYNOTE A18 enrolled patients with more advanced disease (FIGO 2018 IIIA–IVA) while INTERLACE enrolled a wider and more favorable range of stages (FIGO 2018 IB3-IVA excluding IIIA and IIIC2). Is induction chemotherapy worth the added toxicity in earlier stage disease? Will it play a role in cases where pembrolizumab may not be available or accessible to patients? Finally, KEYNOTE A18 enrolled patients from 30 different countries while INTERLACE enrolled almost exclusively from the United Kingdom and Mexico. This leads to the question are the INTERLACE results applicable globally? We eagerly anticipate publication of the INTERLACE data and OS data from KEYNOTE A18 to allow in depth comparison of these two practice-changing clinical trials.

Advances in radiation technologies are also changing the landscape of adjuvant pelvic radiotherapy for gynecologic malignancies. RTOG 1203 randomized cervical and uterine cancer patients to adjuvant 4-field radiotherapy or intensity modulated radiotherapy (IMRT) demonstrating improved

Table 2. Pathologic risk factors indicating adjuvant treatment in early-stage cervical cancer [12,13]

Intermediate-risk factors	High-risk factors
Tumor >4 cm	Parametrial involvement
>1/3 cervical stromal invasion	Pelvic lymph node involvement
Lymphovascular space invasion	Positive margin

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

quality of life with IMRT, cementing IMRT as standard of care for adjuvant gynecologic pelvic radiotherapy [19]. More recently, the prospective Phase 1/2, nonrandomized SPARTACUS trial evaluated the safety of adjuvant stereotactic hypofractionated radiation to the pelvis for uterine cancers. This study demonstrated acceptable short-term toxicity with long term data forthcoming [20]. Though we should be cautious in extrapolating endometrial cancer data to cervical cancer due to differences in surgery and radiation fields, the technique is promising, and future studies including hypofractionated radiation are warranted for cervical cancer.

Frontline systemic therapy

The first line management for recurrent, persistent, or metastatic cervical cancer (m/rCC) is platinum-based chemotherapy. Since 2014, the incorporation of bevacizumab to chemotherapy has demonstrated an improvement in objective response rates (ORR) and survival outcomes and was adopted as the standard of care for most patients. However, some patients may not be candidates for the addition of bevacizumab due to extensive pelvic disease burden or adverse events like hypertension, thromboembolic events, and gastrointestinal fistula formation [21].

KEYNOTE-826 introduced immune checkpoint inhibitors (ICI) to the frontline setting in 2021. This phase 3 RCT evaluated the addition of pembrolizumab to platinum-based chemotherapy ± bevacizumab. Results showed that programmed death ligand 1 (PD-L1) positive patients with a combined positive score (CPS) $\geq$1, which is defined as the proportion of PD-L1 staining cells to the total number of viable tumor cells, had improved PFS and OS with the addition of pembrolizumab (PFS 10.4 months pembrolizumab vs. 8.2 months placebo, HR 0.62, 95% CI, 0.50–0.77, $P < 0.001$; 24 month OS 53% pembrolizumab vs. 41.7% placebo, HR 0.64, 95% CI, 0.50–0.81, $P < 0.001$) [22].

There has been interest in exploring other ICIs in the frontline setting. BEATcc is a phase 3 RCT that looked at the addition of atezolizumab (a PD-L1 inhibitor) to platinum-based chemotherapy and bevacizumab in patients with m/rCC. Unlike KEYNOTE-826, bevacizumab was required in BEATcc, potentially excluding patients with higher-risk disease. The results showed a PFS and OS benefit with the addition of atezolizumab to chemotherapy (PFS 13.7 months atezolizumab vs. 10.4 months placebo, HR = 0.62, 95% CI 0.49–0.78, $P < 0.0001$; OS 32.1 months atezolizumab vs. 22.8 months placebo, HR 0.68, 95% CI 0.52–0.88, $P = 0.0046$) [23▪]. Outcomes based on PD-L1 status have not yet been reported and this regimen is not FDA approved at the time of this report. Future directions for the frontline treatment of m/rCC include better understanding the efficacy of ICI in patients with prior ICI exposure, particularly with the recent impact of the KEYNOTE A18 study [16▪▪].

Management of recurrent cervical cancer

Prior to the study of chemotherapy vs. cemiplimab, a PD-1 inhibitor, in the 2022 EMPOWER Cervical-1/GOG 3016/ENGOT cx-9 study, there was a paucity of phase 3 trials in second line or beyond in cervical cancer [24]. Based on the impact of ICI in m/rCC, there has been continued efforts to further enhance the role of immunotherapy in patients with recurrent cervical cancer. Recently, the role of dual immune blockade using atezolizumab ± tiragolumab was evaluated in 171 patients with m/rCC with PD-L1 expression in their tumors in the SKYSCRAPER-04 trial. The objective response rate was 15.6% for atezolizumab, comparable to that of other PD-1/PD-L1 inhibitors in this setting. Unfortunately, there was only a nominal increase in overall response rate (ORR) to 19.0% with the addition of tiragolumab and the combination did not significantly improve outcomes [25]. Further studies of immunotherapy combinations are being explored but will need to account for earlier ICI exposure [16▪▪,22].

Another interesting area of exploration is the study of antibody drug conjugates (ADC). Tisotumab vedotin (TV), is an ADC targeting tissue factor, and has demonstrated some exciting results. Based on the phase 2 data from InnovaTV204, TV had an ORR of 24% in the second- or third-line setting and quickly became a standard option for patients [26]. In 2023, the results of the confirmatory phase 3 trial, InnovaTV301, resulted. This trial randomized patients with 1–2 prior systemic therapies to TV or single agent chemotherapy (pemetrexed, topotecan, vinorelbine, irinotecan, gemcitabine) [27▪▪]. In the TV arm, a PFS benefit (4.2 months vs. 2.9 months; HR 0.67) and an OS advantage (11.5 vs. 9.5 months; HR 0.70) were reported. Notably, ORR was 17.8% in the TV arm and 5.2% for the chemotherapy regimens. Of importance to highlight is that approximately 25% of patients received prior immunotherapy in this trial prior to enrollment, representing the current treatment landscape. Additionally, there were no new reported safety signals and ocular toxicity, peripheral neuropathy and bleeding remain adverse events of special interest [27▪▪]. These data place TV as the second line therapy option for patients with recurrent cervical cancer.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

Recently, the single-arm, open-labeled phase 2 trial, DESTINY PanTumor02 basket trial evaluated the role of trastuzumab deruxtecan (TDXd), in patients with recurrent cancer with human epidermal growth factor receptor 2 (HER2) expression 2+ or 3+ on immunohistochemistry (IHC)[28]. The ORR was 50% in the entire cervical cancer cohort (n = 40) and 75% in patients with IHC 3+ tumors ($n = 8$). Impressively, the median PFS in those with IHC 3+ tumors had not been reached after 14 months of follow up. It is important to recognize that IHC 3+ in cervical cancer may be an uncommon finding, with current prevalence reported between 4–11% [29]. However, to date, testing has not been consistent or standardized; but with routine testing, the true prevalence of HER2 expression in cervical cancers will be elucidated. Regardless, based on these provocative results and pending the results of additional studies, TDXd received accelerated approval in patients with solid tumors, including m/rCC that have 3+ IHC expression of HER2.

Despite advances, new studies are ongoing or in development to continue to capitalize on targets in cervical cancer. Areas of interest include the use of tumor infiltrating lymphocytes (TILs) therapy and HPV 16 vaccine targets as well as the role of ADCs targeting TROP2 and NECTIN4, both of which are highly expressed in cervical cancer.

CONCLUSION

Recent advances continue to change the landscape of cervical cancer. Less radical surgery has been shown to have comparable oncologic outcomes in select patients with early-stage cervical cancer and the role of SLN mapping is more widely accepted. In the locally advanced setting, the addition of pembrolizumab to CRT and BT has received FDA approval in patients with FIGO 2014 stage III and IV cervical cancer. The role of pembrolizumab (or atezolizumab) in the m/rCC setting is the standard but may need to be reassessed in those with prior ICI therapy. Lastly, recent FDA approvals have impacted the second line setting with new options including tisotumab vedotin and trastuzumab deruxtecan for select patients. Though survival rates have improved over time, clinical trials in all stages of cervical cancer remain a high priority.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Singh D, Vignat J, Lorenzoni V, *et al.* Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health 2023; 11:e197–e206.
2. https://www.cdc.gov/cancer/hpv/diagnosis-by-age.html.
3. Bhatla N, Berek JS, Cuello Fredes M, *et al.* Revised FIGO staging for carcinoma of the cervix uteri [published correction appears in Int J Gynaecol Obstet. 2019;147:279–80. doi:10.1002/ijgo.12969]. Int J Gynaecol Obstet. 2019;145:129–35.
4. ■■ Ramirez PT, Robledo KP, Frumovitz M, *et al.* LACC trial: final analysis on overall survival comparing open versus minimally invasive radical hysterectomy for early-stage cervical cancer. J Clin Oncol 2024; 42:2741–2746.

The results of this clinical trial are largely responsible for shifting the standard of care from MIS hysterectomy to open approach hysterectomy for early-stage cervical cancer.

5. Di Donato V, Bogani G, Casarin J, *et al.* Ten-year outcomes following laparoscopic and open abdominal radical hysterectomy for "low-risk" early-stage cervical cancer: a propensity-score based analysis. Gynecol Oncol 2023; 174:49–54.
6. Kristin Leigh Bixel *et al.* ROCC/GOG-3043: a randomized noninferiority trial of robotic versus open radical hysterectomy for early-stage cervical cancer. JCO 2022;40:TPS5605–TPS5605.
7. Schmeler KM, Pareja R, Lopez Blanco A, *et al.* ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer 2021; 31:1317–1325.
8. ■■ Plante M, Kwon JS, Ferguson S, *et al.* Simple versus radical hysterectomy in women with low-risk cervical cancer. N Engl J Med 2024; 390:819–829.

The results of this clinical trial have shifted practice towards simple hysterectomy with lymph node evaluation in patients with stage IA2 to IB1 cervical cancer.

9. Lécuru F, Mathevet P, Querleu D, *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.
10. Mathevet P, Lécuru F, Uzan C, *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.
11. Lecuru FR, McCormack M, Hillemanns P, *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.
12. Sedlis A, Bundy BN, Rotman MZ, *et al.* A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999; 73:177–183.
13. Peters WA, Liu PY, Barrett RJ, *et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18:1606–1613.
14. ■ Anuja J. Adjuvant chemotherapy following concurrent chemoradiation (CRT) in patients with high-risk early-stage cervical carcinoma following radical hysterectomy: Results of NRG oncology/RTOG 0724/GOG-0724. J Clin Oncol 2024; 42(Suppl):5504–5514.

The results of this study led to the discontinuation of adjuvant platinum-base chemotherapy after radiation for locally advanced cervical cancer (publication pending).

15. Mileshkin LR, Moore KN, Barnes EH, *et al.* Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomized, phase 3 trial. Lancet Oncol 2023; 24:468–482.
16. ■■ Lorusso D, Xiang Y, Hasegawa K, *et al.* Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. Lancet. 2024 Mar 20 [cited 2024 Mar 21]; Available at: https://www.sciencedirect.com/science/article/pii/S0140673624003179?via%3Dihub.

The results of this study led to the addition of concurrent and maintenance pembrolizumab to CRT for patients with high-risk, locally advanced cervical cancer.

17. Merck. Merck's KEYTRUDA® (pembrolizumab) plus chemoradiotherapy (CRT) significantly improved overall survival (OS) versus CRT alone in patients with newly diagnosed high-risk locally advanced cervical cancer. Merck Press Release, 15 March 2024. Available at: https://www.merck.com/news/mercks-keytruda-pembrolizumab-plus-chemoradiotherapy-crt-significantly-improved-overall-survival-os-versus-crt-alone-in-patients-with-newly-diagnosed-high-risk-locally-advanced-ce/ [Accessed 8 April 2024].

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

18. McCormack M, Dolores Gallardo Rincón. Eminowicz G, *et al.* LBA8 A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: the GCIG INTERLACE trial. Ann Oncol 2023; 34:S1276–S1286.
19. Klopp AH, Yeung AR, Deshmukh S, *et al.* Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology–RTOG 1203. J Clin Oncol 2018; 36:2538–2544.
20. Leung E, Gladwish AP, Davidson M, *et al.* Quality-of-life outcomes and toxic effects among patients with cancers of the uterus treated with stereotactic pelvic adjuvant radiation therapy. JAMA Oncol 2022; 8:853.
21. Tewari KS, Sill MW, Penson RT, *et al.* Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017; 390:1654–1663.
22. Monk BJ, Colombo N, Tewari KS, *et al.* First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. J Clin Oncol 2023; 41:5505–5511.
23. ■ Oaknin A, Gladieff L, Martínez-García J, *et al.* Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet 2024; 403:31–43.

This trial identified an opportunity to treat recurrent, persistent, metastatic cervical cancer with immunotherapy regardless of biomarker status, however it does not yet have FDA approval.

24. Tewari KS, Monk BJ, Vergote I, *et al.* Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022; 386:544–555.
25. Salani R, McCormack M, Kim Y-M, *et al.* A noncomparative, randomized, phase II trial of atezolizumab or atezolizumab plus tiragolumab for programmed death-ligand 1-positive recurrent cervical cancer (SKYSCRAPER-04). Int J Gynecol Cancer 2024; 34:1140–1148.
26. Coleman RL, Lorusso D, Gennigens C, *et al.* Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021; 22:609–619.
27. ■■ Vergote I, Gonzalez-Martin A, Fujiwara K, *et al.* Tisotumab vedotin as second- or third-line therapy for recurrent cervical cancer. N Engl J Med 2024; 91:44–55.

This trial established TV as the standard option for patients with recurrent cervical cancer.

28. Meric-Bernstam F, Makker V, Oaknin A, *et al.* Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol 2024; 42:47–58.
29. Makkar V. Efficacy and safety of trastuzumab deruxtecan in patients with HER2expressing solid tumors: biomarker and subgroup analyses from the cervical, endometrial, and ovarian cancer cohorts of the DESTINY-PanTumor02 study. Abstract presented at the 2024 Society of Gynecologic Oncology Annual Meeting.

Downloaded from http://journals.lww.com/co-obgyn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/09/2024

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.