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Intensified systemic therapy regimens in combination with definitive radiation for treatment of cervical cancer

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Abstract

Definitive standard chemoradiation for locoregionally advanced carcinomas of the uterine cervix includes multimodality therapy consisting of concurrent cisplatin based chemoradiation comprising of external-beam radiotherapy with systemic chemotherapy followed by intracavitary brachytherapy. New developments in radiotherapy, like intensity-modulated radiotherapy (IMRT), which aims to improve tumor control rates and reduce associated toxicity have reopened the discussion regarding the benefit of intensification of concomitant or sequential systemic therapy in the treatment of cervical cancer. Intensification of systemic chemotherapy used in standard chemoradiation for cervical cancer is an attractive approach to improve disease control, but given the concerns regarding toxicity deserves further evaluation to ensure its safe use in patients. This is a review of published and ongoing studies investigating intensification of systemic chemotherapy for locally advanced cervical cancer.

Background

Cervical cancer is the fourth most common malignancy among women globally.¹ In the United States, more than 13,000 women are diagnosed with invasive cervical cancer annually, resulting in more than 4,000 deaths.² Most cervical cancers are of the squamous cell or adenocarcinoma histological subtype³ and therefore will be the main focus of this review. In the vast majority of patients with early stage disease, radical hysterectomy with pelvic lymphadenectomy remains the standard recommendation as a curative treatment option.⁴ The role of postoperative adjuvant therapy in this subset of patients is based on intermediate and/or high risk factors.^{5,6} For locoregionally advanced carcinomas of the

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Author Contributions

All authors contributed in the literature search, creation of the content, and writing and revising of this manuscript.

Ethics Statement

The research presented in this article involved the collection or study of existing data, documents, and records that were publicly available. The research is regarded exempt from Institutional Review Board oversight.

Conflict of Interest Statement

The authors report no conflicts of interest, financial or otherwise, related to the subject matter of the article submitted

uterine cervix the current standard of care includes multimodality therapy consisting of concurrent cisplatin based chemoradiation comprising of external-beam radiotherapy (EBRT) with systemic chemotherapy followed by intracavitary brachytherapy.⁷ The justification for cisplatin based chemoradiation is founded on the principle that tumor radiosensitivity can be enhanced with the addition of systemic chemotherapy and this rationale has been established following a series of randomized trials, evaluating radiotherapy alone versus combined chemoradiation (Table 1).^{7,8}

Defining the Standard of Care: Platinum-based Chemotherapy with Radiation

In the Radiation Therapy Oncology Group (RTOG) 90–01 trial 403 patients with stage IIB to IVA cervical cancer with tumor diameters ≤ 5 cm, or positive pelvic lymph nodes were randomized to extended field radiotherapy (radiotherapy alone) vs. pelvic RT with concomitant fluorouracil and cisplatin (chemoradiation).^{9,10} Pelvic RT patients received 3 cycles of concomitant cisplatin 75 mg/m^2 over 4 hours followed by fluorouracil 4000 mg/m^2 over 96 hours (administered during days 1 through 5 of RT) q 3 weeks. 5-year overall survival (OS) was 58% for radiotherapy alone vs. 73% for chemoradiation ($p = 0.004$). With longer follow-up, an updated publication reported an 8-year OS of 67% (chemoradiation) versus 41% (radiotherapy alone). The study concluded that the addition of fluorouracil and cisplatin to EBRT and brachytherapy improved survival in locally advanced cervical cancer with the greatest effect of adding chemotherapy seen in stage IB to IIB disease (5-year OS: 55% vs. 79%, $p < 0.0001$).

This was followed by the Gynecologic Oncology Group (GOG) 120 trial in which 526 patients with stage IIB, III or IVA cervical cancer without paraaortic lymphadenopathy were randomized to three different concurrent chemotherapy with radiotherapy regimens.¹¹ Concomitant chemotherapy was given with either cisplatin 40 mg/m^2 weekly for 6 weeks (regimen 1), cisplatin 50 mg/m^2 on days 1 and 29, followed by 4 g/m^2 fluorouracil as a 96-hour infusion on day 1 and 29, and 2 g/m^2 hydroxyurea weekly for 6 weeks (regimen 2) or hydroxyurea 3 g/m^2 two times per week for 6 weeks (regimen 3). In all arms, EBRT was delivered from 41 to 51 Gy to the pelvis, plus intracavitary brachytherapy. If intracavitary brachytherapy could not be given, additional EBRT was given for a total of 61.2 Gy. Both regimens that included cisplatin had a higher rate of overall survival than hydroxyurea alone ($p < 0.001$). The conclusion was that concomitant regimens that contain cisplatin improve OS in locally advanced cervical cancer. The updated 10 year long term follow-up was consistent with the original findings reporting an OS of 53% in both cisplatin arms, but only 34% in the hydroxyurea arm ($p < 0.001$).¹²

Despite the above findings, a 2008 meta-analysis suggested that non-platinum based approaches may be equally effective in concomitant chemoradiation regimens.^{13,14} The study reviewed thirteen randomized controlled trials that compared chemoradiation vs. the same radiotherapy. The analysis revealed a 6% improvement in 5-year survival (from 60% to 66%) with chemoradiation (hazard ratio (HR) = 0.81, $p < 0.001$). Notably, there was a significant survival benefit for trials that used either platinum-based (HR = 0.83, $p = 0.017$)

or non-platinum-based (HR = 0.77, p = 0.009) chemoradiotherapy. This meta-analysis not only validated the use of chemoradiation, but suggested that the benefit associated with chemoradiotherapy may not be contingent on the use of platinum based chemotherapy. Additionally, this meta-analysis reported a lower hazard rate for trials that included chemotherapy after chemoradiation (aka Outback chemotherapy). This question is being addressed in the ongoing ANZGOG 0902 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01414608) identifier: [NCT01414608](https://clinicaltrials.gov/ct2/show/study/NCT01414608)).

The addition of chemotherapy to radiation results in considerably more short term toxicity when compared to radiation alone but does not appear to increase the risk of long term toxicity. A Cochrane meta-analysis comparing concomitant chemoradiation vs radiotherapy which included 24 randomized trials and 4,921 women treated throughout the 1980s and 1990s demonstrated significantly greater acute hematological and gastrointestinal toxicity associated with chemoradiation.¹⁵ These short term toxicities which included neutropenia, nausea, vomiting, and diarrhea can increase the risk of treatment delays which are known to decrease survival.^{16,17} The previously discussed meta-analysis that evaluated 1,243 women undergoing chemoradiation or the same radiotherapy reported a grade 3 or 4 late complication rate of 8% in patient who received radiotherapy vs. 10% in those who received chemoradiation.¹³ The major reported sites of serious late toxicity included the vagina, bowel and bladder.

Advanced techniques in radiotherapy, like intensity-modulated radiotherapy (IMRT), have the potential to limit the toxicity of radiation therapy and potentially permit the use of more intensified systemic therapy regimens. The benefits of IMRT are discussed in the accompanying article from Dr. Charles Kunos and colleagues.

Intensified Systemic Therapy Concurrent with Radiation

One strategy to intensify the systemic component of concomitant chemoradiation is to increase the dose of cisplatin delivered at each treatment. The large magnitude of the benefit to cisplatin on the 90–01 trials using the q 3 week approach where patients received cisplatin 75 mg/m² over 4 hours followed by fluorouracil 4000 mg/m² over 96 hours, administered during days 1 through 5 of RT, q 3 weeks for 3 cycles¹⁰ suggests that increasing the dose of platinum given in each treatment may be a key intervention. To test this, the tri-weekly cisplatin-based chemoradiation approach is being investigated in the tri-weekly cisplatin-based chemoradiation for locally advanced cervical cancer (TACO) Trial/KGOG 1027 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01561586) identifier: [NCT01561586](https://clinicaltrials.gov/ct2/show/study/NCT01561586)). In this study patients with stage IB2, IIB to IVA cervical cancer are being randomized to cisplatin 40 mg/m² qwk for 6 weeks plus concurrent radiation therapy versus cisplatin 75 mg/m² q 3 weeks × 3 cycles plus concurrent radiation therapy.

Another approach to intensify systemic therapy given with chemoradiation is to add additional concurrent chemotherapy agents. This was seen with the use of fluorouracil in RTOG 90–01 and although fluorouracil's associated toxicity has limited its use in practice,¹⁸ other classic chemotherapy agents or molecular targeting agents have been considered. Duenas-Gonzales et al. randomized 515 patients with stage IIB to IVA cervical cancer to

cisplatin 40 mg/m² and gemcitabine 125 mg/m² qwk for 6 weeks with concurrent EBRT of 50.4 Gy in 28 fractions followed by brachytherapy of 30 to 35 Gy in 96 hours, and then 2 cycles of adjuvant cisplatin on day 1 and gemcitabine 1000 mg/m² on days 1 and 8 q 3 weeks (arm A) vs. cisplatin 40 mg/m² and concurrent EBRT followed by brachytherapy (arm B).¹⁹ The study showed an improved 3-year PFS (74.4% vs. 65%; $p = 0.029$), an improved time to progressive disease ($p = 0.001$), and an improved OS (HR = 0.68, $p = 0.022$) with gemcitabine plus cisplatin chemoradiation followed by brachytherapy but with a higher toxicity (grade 3/4 toxicities 86.5% (arm A) vs. 46.3% (arm B); including two deaths possibly related to the treatment toxicity of arm A). The concern for toxicity has limited the adoption of this regimen in the United States.

Given that vascular endothelial growth factor (VEGF) expression is a known significant independent prognostic factor in cervical cancer patients treated with radiotherapy²⁰ and that the addition of the VEGF inhibitor bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer is associated with an improvement in OS,²¹ its role as an intensifying option in curative-intent chemoradiation for cervical cancer has recently been explored. In the phase II trial RTOG-0417, forty nine patients with stage IIB to IIIB (or IB-IIA with histologically proven pelvic nodal metastases or IIA > 5 cm) cervical cancer were treated with once-weekly cisplatin (40 mg/m²) chemotherapy, standard pelvic radiation therapy/brachytherapy and bevacizumab 10 mg/m² (every 2 weeks, 6 cycles)²². The 3-year OS was 81.3% (95% confidence interval [CI], 67.2%–89.8%) and the study concluded that bevacizumab in combination with standard pelvic chemoradiation therapy for locally advanced cervical cancer showed promising results and may warrant further investigation. Despite this, there are no ongoing randomized trial comparing chemoradiation with bevacizumab with platinum based chemotherapy.

In a phase I study, sorafenib, another potent tyrosine kinase inhibitor of VEGF, was evaluated in 13 patients with cervical cancer receiving conventional chemoradiation administered with curative intent²³. Patients received sorafenib for 7 days before the start of radiation therapy and concurrent cisplatin. Patients were treated with EBRT and concurrent weekly cisplatin chemotherapy followed by intracavitary brachytherapy. EBRT was delivered with a planned dose of 45–50 Gy. Chemotherapy consisted of cisplatin administered weekly during EBRT at a dose of 40 mg/m²tumor, with a maximum dose of 70 mg. EBRT was followed in most patients by brachytherapy. 12 patients had an initial complete response. Tumor perfusion/permeability was measured using dynamic contrast-enhanced magnetic resonance (DCE MR) and tumor oxygen partial pressure measured directly with a needle electrode. The 4-year actuarial survival was 85%, but sorafenib alone produced a decline in tumor perfusion/permeability and an increase in hypoxia, which resulted in the trial being permanently closed to new patient enrollment. The authors concluded that because sorafenib increases tumor hypoxia, there is concern that its use may impair rather than improve disease control when given concurrently with standard chemoradiation.

An ongoing targeted therapy study includes a randomized phase III trial of standard chemoradiation with and without concurrent triapine (a ribonucleotide reductase inhibitor necessary for DNA synthesis) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02466971) identifier: [NCT02466971](https://clinicaltrials.gov/ct2/show/study/NCT02466971)). Eligibility

criteria includes those with stage IB2 (> 5 cm), II, IIIB, or IVA cervical cancer. The primary end point is PFS.

Neoadjuvant chemotherapy prior to chemoradiation

The role of neoadjuvant chemotherapy prior to surgery or chemoradiation has been tested in a variety of trials across multiple decades (Table 1). A phase II single arm study which included 43 patients with stage IB2 to IIIB cervical cancer investigated carboplatin AUC 6 and paclitaxel 175 mg/m² over 3 hours q 3 weeks × 3 cycles followed by a radical hysterectomy and adjuvant chemoradiation with cisplatin 40 mg/m² qwk × 6 cycles and concurrent EBRT, mean dose 49.3 Gy, and brachytherapy with 32 Gy.²⁴ Overall the neoadjuvant regimen was well tolerated and 41 of 43 patients underwent a radical hysterectomy. Response, based on pathology, was a complete response (CR) in 17%, near CR in 20%, 12% with positive surgical margins, and 20% with positive pelvic lymph nodes. The study concluded that triple modality with neoadjuvant chemotherapy followed by radical hysterectomy and concurrent adjuvant chemoradiation was a highly active treatment for locally advanced cervical carcinoma with acceptable toxicity. In a another single-center, phase III, randomized controlled trial Gupta et al. evaluated the efficacy and toxicity of neoadjuvant chemotherapy followed by radical surgery versus standard concurrent cisplatin-based chemoradiation in patients with locally advanced squamous cervical cancer.²⁵ Patients were randomly assigned to receive either three cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin once every 3 weeks followed by radical hysterectomy, or standard radiotherapy with concomitant cisplatin once every week for 5 weeks. Patients in the neoadjuvant group received postoperative adjuvant radiation or concomitant chemotherapy and radiotherapy as indicated. The 5-year disease-free survival (DFS) in the neoadjuvant chemotherapy plus surgery group was significantly lower (69.3% compared with 76.7% in the concomitant chemoradiation group, (HR, 1.38; 95% CI, 1.02 to 1.87; p = 0.038). 5-year OS in the neoadjuvant chemotherapy plus surgery group compared with the concomitant chemoradiation group was 75.4% and 74.7%, respectively (HR, 1.025; 95% CI, 0.752 to 1.398; p = 0.87). There was no difference in delayed rectal and bladder toxicities at 24 months between the two groups, whereas vaginal toxicity occurred at a lower rate in the neoadjuvant chemotherapy plus surgery group (12.0% v 25.6% in the concomitant chemoradiation group; p < 0.001). The conclusion was that cisplatin-based concomitant chemoradiation resulted in superior DFS compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer. Interestingly, a post hoc analysis that included patient in the neoadjuvant chemotherapy plus surgery group who were able to undergo surgery suggested that patients who received adjuvant radiation or concomitant chemoradiation had inferior DFS compared to patients who did not (HR, 1.69; 95% CI, 1.02 to 2.80; p = 0.04) which demonstrates that patients with treatment responsive disease, predictably are more likely to remain disease-free. This is supported by a second post hoc analysis that showed DFS in patients who were unable to undergo surgery, and who crossed over to concomitant chemoradiation was inferior compared with patients who could undergo surgery (HR, 1.49; 95% CI, 0.94 to 2.38; p = 0.089).

In another recently published phase II trial, patients with stage IIB to IVA cervical cancer were randomly assigned to either three cycles of neoadjuvant chemotherapy with cisplatin

and gemcitabine followed by standard chemoradiation with weekly cisplatin plus pelvic radiotherapy or to standard chemoradiation alone. The primary end point was 3-year PFS.²⁶ Neoadjuvant chemotherapy was associated with an inferior PFS, with 3-year PFS rates of 40.9% vs. 60.4% in the standard chemoradiation arm (HR, 1.84; 95% CI, 1.04 to 3.26; $p = 0.033$). Neoadjuvant chemotherapy also was associated with a lower OS (3-year OS rate, 60.7% vs. 86.8%; HR, 2.79; 95% CI, 1.29 to 6.01; $p = 0.006$). The study concluded that the addition of neoadjuvant chemotherapy, consisting of cisplatin and gemcitabine, when compared to standard chemoradiation, is not superior and is possibly inferior to chemoradiation alone for the treatment of locally advanced cervical cancer.

These studies demonstrate that neoadjuvant chemotherapy prior to chemoradiation does not improve outcomes. This may be because chemotherapy selects for more resistant tumor clones which may be difficult to control with radiotherapy. Previous studies have described the accelerated repopulation of tumor clonogens occurring around the fourth week of radiation treatment.²⁷ Neoadjuvant chemotherapy before chemoradiation may precipitate a regenerative response in the tumor and prevent local control by radiotherapy.²⁸ This implies that neoadjuvant chemotherapy, not only delays administration of definitive radiation, but may also increase radioresistance by causing the accelerated repopulation of resistant tumor clones. Another theory suggest that tumors express specific mutations that may explain differences in treatment response. For example, in locally advanced rectal cancer, studies suggest that unique sub-clones within tumors may harbor mutations which contribute to variation in response to neoadjuvant chemoradiotherapy.²⁹ Neoadjuvant chemotherapy has also been investigated as a fertility sparing approach. Tesfai et al. recently reported on a retrospective analysis of 19 women who were treated with neoadjuvant chemotherapy for cervical tumors >2 cm.³⁰ Mean clinical tumor size was 4.4 cm (range 3.5–6.0). Chemotherapy consisted of six weekly cycles of cisplatin (70 mg/m²) and paclitaxel (70 mg/m²). In 74% (15 of 19) of patients fertility was successfully preserved. In the four women in whom fertility preservation failed, one did not meet the criteria for fertility-sparing surgery and three patients had intra- or post-operative indications for adjuvant therapy. Three of the 19 patients (15.7%) had a relapse leading to two death. The authors concluded that neoadjuvant chemotherapy followed by fertility-sparing surgery may be a feasible and safe option in select women with cervical tumors greater than 2 cm.

Recent advances in imaging and molecular profiling techniques have the potential to improve both disease characterization and outcomes in women with cervical cancer. Ultimately these approaches may make it possible to identify which patients have highly sensitive tumors which may benefit from single modality treatment thus minimizing toxicity. However, currently, concurrent chemoradiation is the recommended approach for all patients.

Outback Chemotherapy following Chemoradiation

The Adjuvant Chemotherapy Following Chemoradiation as Primary Treatment for Locally Advanced Cervical Cancer Compared to Chemoradiation Alone (OUTBACK) (ANZGOG0902/GOG0274/RTOG1174; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01414608) identifier: NCT01414608) trial is a phase III randomized study exploring adjuvant chemotherapy following chemoradiation as

a primary treatment for locally advanced cervical cancer compared to chemoradiation alone. The trial is designed to determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemoradiation improves OS.³¹ Inclusion criteria includes women with stage IB, IIA, IIB, IIIB, and IVA cervical cancer. Patient are randomized to cisplatin IV q wk for 5 cycles, EBRT q daily for 5 days for 5 weeks, then high-dose rate, pulsed dose rate, or low-dose rate intracavitary brachytherapy vs. standard chemoradiation (EBRT and brachy) as in arm 1 followed by 4 cycles of adjuvant chemotherapy with paclitaxel over 3 hours and carboplatin over 1 hour on day 1 q 3 weeks for 4 cycles. This trial should provide a more definitive answer for the role of systemic adjuvant chemotherapy for locally advanced cervical cancer, but questions will likely remain with regard to who might truly benefit from this maintenance therapy in order to prevent local relapse and distant failures. There may be a subset of high risk patients for whom there is a role for adjuvant chemotherapy, such as those with positive paratotic nodes, those with adenocarcinoma or adenosquamous histologies, or a role for persistent biomarkers, like residual HPV DNA.

Conclusion

Multimodality therapy consisting of concurrent chemoradiation comprising of EBRT with systemic chemotherapy followed by intracavitary brachytherapy remains the standard of care for locally advanced cervical cancer. Neoadjuvant chemotherapy when compared to standard chemoradiation for locally advanced cervical cancer offer little benefit. The ongoing substitution of IMRT and the individualization of both external-beam radiotherapy and brachytherapy reduces toxicity through the relative sparing of normal tissues and leads to improved local tumor control. Intensification of systemic chemotherapy used in standard chemoradiation for cervical cancer is an attractive approach to improve disease control, but given the concerns regarding toxicity deserves further evaluation to ensure its safe use in patients. Ongoing trials will provide insight into the overall benefit of systemic adjuvant chemotherapy for locally advanced cervical cancer.

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Table 1.

Clinical Trials of Concurrent Chemoradiation, Neoadjuvant Chemotherapy, and Adjuvant Chemotherapy for Locally Advanced Cervical Cancer

Trial	Participants	Intervention	Results	Comments
Trials of concurrent chemoradiation for locally advanced cervical cancer				
Morris et al./RTOG 90-01 ^{9,10}	Stage IIB-IVA; IB-IIA with lesions greater than or equal to 5 cm and/or pelvic lymph node metastasis (N = 403)	WPRT plus EFRT 45 Gy vs. WPRT 45 Gy plus two cycles CDDP 75 mg/m ² plus 5FU 4,000 mg given on days 1–5 and days 22–26 of WPRT	Median f/u 43 months: 58% OS vs. 73% OS p = 0.004	The addition of fluorouracil and cisplatin to EBRT and brachytherapy improved survival in locally advanced cervical cancer with the greatest effect in stage IB to IIB disease
Rose et al./GOG-120 ¹¹	Stage IIB, III, IVA with negative PA nodes (N=526)	WPRT 40.8–51.0 Gy plus CDDP 50 mg/m ² day 1, 29 plus 96-hour 5FU 4 g/m ² day 1, 29 plus oral HU 2 g/m ² twice weekly for 6 weeks vs. WPRT 40.8–51.0 Gy plus CDDP 40 mg/m ² weekly x 6 vs. Oral HU 3 g/m ² twice weekly for 6 weeks	OS RR, 0.58; 95% CI, 0.41 to 0.81; P = 0.002; PFS RR, 0.55; 95% CI, 0.4 to 0.75; p < 0.001 vs. OS RR, 0.61; 95% CI, 0.44 to 0.85; P = .004; PFS RR, 0.57, 95% CI, 0.42 to 0.78; p < 0.001 vs. reference	Concomitant regimens of that contain cisplatin improve OS in locally advanced cervical cancer
Trials of adjuvant chemoradiation for locally advanced cervical cancer				
Whitney et al./GOG-85 (SWOG 8695) ³²	Stage IIB, III, IVA; all patients required to have negative peritoneal cytology and negative PA nodes (N=368)	WPRT 40.8 Gy (IIB), 51.0 Gy (III, IVA) plus CDDP 50 mg/m ² day 1, 29 plus 5FU 1,000 mg/m ² days 2–5, days 30–33 vs. Oral HU 80 mg/kg twice weekly for 5–6 weeks	RR progression/death, 0.79; 90% CI, 0.62 to 0.95; p = 0.033 vs. reference	The combination of 5-FU and cisplatin with RT offers patients better PFS and overall survival than hydroxyurea
Dueñas-Gonzalez et al. ¹⁹	Stage IIB to IVA (N=515)	WPRT 50.4 Gy with CDDP 40 mg/m ² + Gemcitabine 125 mg/m ² weekly x 6 followed by BT 30–35 Gy and adjuvant CDDP 50 mg/m ² day 1 plus gemcitabine 1,000 mg/m ² day 1, 8 every 21 days x 2 vs. WPRT 50.4 Gy with CDDP 40 mg/m ² weekly x 6 followed by BT 30–35 Gy	3-year PFS, 74.4%; p = 0.029 vs. 3-year PFS, 65.0%	Improved 3-year PFS, an improved time to progressive disease, and an improved OS with gemcitabine plus cisplatin chemoradiation followed by brachytherapy
Schefter et al./RTOG-0417 ²²	Stage IIB to IIIB (or IB-IIA with histologically proven pelvic nodal metastases or IIA > 5 cm) (N=49)	WPRT with CDDP 40 mg/m ² weekly 3 6 plus bevacizumab 10 mg/kg every 2 weeks x 3 cycles with chemoradiation	The 3-year OS was 81.3% (95% CI, 67.2%–89.8%)	Bevacizumab in combination with standard pelvic chemoradiation therapy for locally advanced cervical cancer showed promising results and may warrant further investigation.
Trials of neoadjuvant chemotherapy for locally advanced cervical cancer				
Dueñas-Gonzalez et al. ²⁴	Stage IB2 to IIIB (N=43)	NACT Carboplatin AUC 6 and paclitaxel 175 mg/m ² over 3 hours q 3 weeks x 3 cycles followed by a radical hysterectomy and adjuvant chemoradiation with cisplatin 40 mg/m ² qwk x 6 cycles and concurrent EBRT and brachytherapy	Complete response (CR) in 17%, near CR in 20%, 12% with positive surgical margins, and 20% with positive pelvic lymph nodes	Triple modality with neoadjuvant chemotherapy followed by radical hysterectomy and concurrent adjuvant chemoradiation was a highly active treatment for locally advanced cervical carcinoma

Trial	Participants	Intervention	Results	Comments
Gupta et al. ²⁵	Stage IB2, IIA, IIB (N=633)	NACT carboplatin AUC 5–6 plus paclitaxel 175 mg/m ² every 21 days x 3 followed by RH-nodes with or without adjuvant WPRT or chemoradiation vs. WPRT 40 Gy with CDDP 40 mg/m ² weekly x 5 plus BT (30 Gy LDR, 35 Gy HDR)	DFS, 69.3% vs. DFS, 76.7%	Cisplatin-based concomitant chemoradiation resulted in superior DFS compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer.
Da Costa et al. ²⁶	Stage IIB to IVA (N=107)	NACT cisplatin 50 mg/m ² on day 1 and gemcitabine 1,000 mg/m ² on day 1 and day 8 every 3 weeks for 3 cycles followed by weekly cisplatin 40 mg/m ² for 6 weeks concurrent with EBRT 45–50.4 Gy followed by BT 28–30Gy vs. Weekly cisplatin 40 mg/m ² for 6 weeks concurrent EBRT 45–50.4 Gy followed by BT 28–30Gy	NACT 3-year PFS rates of 40.9% vs. 60.4% in the standard chemoradiation arm (HR, 1.84; 95% CI, 1.04 to 3.26; p = 0.033). NACT 3-year OS rate, 60.7% vs. 86.8%; HR, 2.79; 95% CI, 1.29 to 6.01; p = 0.006	The addition of neoadjuvant chemotherapy consisting of cisplatin and gemcitabine when compared to standard chemoradiation is not superior and is possibly inferior to chemoradiation alone
Critical Trails Ongoing				
TACO Trial/KGOG 1027	Stage IB2, IIB to IVA	Cisplatin 40 mg/m ² qwk for 6 weeks plus concurrent radiation therapy vs. Cisplatin 75 mg/m ² q 3 weeks x 3 cycles plus concurrent radiation therapy		Currently testing the tri-weekly cisplatin-based chemoradiation approach.
Outback (ANZGOG0902/ GOG0274/ RTOG1174)	Stage IB, IIA, IIB, IIIB, and IVA	Cisplatin IV qwk x 5 cycles, EBRT q daily x 5 days x 5 weeks, then high-dose rate, pulsed dose rate, or low-dose rate intracavitary brachytherapy vs. EBRT and BT (as in arm 1) followed by 4 cycles of adjuvant chemotherapy with paclitaxel over 3 hours and carboplatin over 1 hour on day 1 q 3 weeks for 4 cycles		This trial should provide a more definitive answer for the role of systemic adjuvant chemotherapy for locally advanced cervical cancer.
NCT02466971	Stage IB2 (> 5 cm), II, IIIB, or IVA	IV Triapine over 2 hours on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, and 33 and Cisplatin IV on days 2, 9, 16, 23, 30, (and day 36 or 37 at the treating physician's discretion). Patients then undergo EBRT (either conventional RT or IMRT) QD 5 days a week for 25 fractions followed by LDR or HDR brachytherapy according to institution's standards. vs. Cisplatin IV on days 2, 9, 16, 23, 30, (and day 36 or 37 at the treating physician's discretion). Patients then undergo EBRT (either conventional RT or IMRT) QD 5 days a week for 25 fractions followed by LDR or HDR brachytherapy according to institution's standards		Triapine is a ribonucleotide reductase inhibitor necessary for DNA synthesis. Stops the growth of tumor cells by blocking this specific enzyme which is needed for cell growth.

Abbreviations: 5-FU, fluorouracil; AE, adverse events; AUC, area under the concentration-time curve; BT, brachytherapy; CDDP, cisplatin; DF, distant failure; DFS, disease-free survival; EFRT, extended-field radiation therapy; f/u, follow-up; G, grade; GOG, Gynecologic Oncology Group; HDR, high dose rate; HR, hazard ratio; HU, hydroxyurea; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiation therapy; IV, intravenous; LDR, low dose rate; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; pts, patients; RH-nodes, radical hysterectomy with pelvic lymphadenectomy; RR, relative risk; RTOG, Radiation Therapy Oncology Group; s/p, status post or after; WPRT, whole-pelvic radiation therapy.

* All studies are randomized phase III trials except Dueñas-Gonzalez et al.²⁴ and Schefter et al./RTOG-0417²² which are phase II.