Economic and humanistic outcomes associated with treatment of recurrent or metastatic cervical cancer: a literature review



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INTRODUCTION

- Cervical cancer is the third leading cause of cancer deaths in women aged 15 to 44 years in the US.¹ The 5-year survival rate in the US is only 17.2% in women diagnosed with metastatic disease²
- According to the National Comprehensive Cancer Network guidelines, cisplatin (or carboplatin) plus paclitaxel plus bevacizumab is the preferred regimen for first-line treatment of recurrent or metastatic disease. The preferred second-line therapy is pembrolizumab for PD-L1-positive or microsatellite instability-high/mismatch repair-deficient tumors. For patients without these biomarkers, bevacizumab or non-platinum based chemotherapy is recommended³
- The objective of this review is to summarize the economic and humanistic burden associated with the treatment of patients with recurrent or metastatic cervical cancer

METHODS

- A systematic literature review was conducted in MEDLINE and Embase® (January 2010-April 2020) of any published studies
- The following criteria were used:

Table 1. Key Inclusion Criteria

Population	Patients with recurrent/metastatic cervical cancer		
Interventions	Regimens (any line) containing topotecan, bevacizumab, pembrolizumab, and novel therapies in development		
Comparison	Any comparator		
Outcomes	Patient-reported outcomes (PROs) and humanistic outcomes, cost, or healthcare resource utilization		
Study design	design Clinical trials, observational studies, economic models		

RESULTS

Search results and study characteristics

- 1,471 abstracts were screened; 73 were related to the interventions of interest, including 12 that included outcomes of interest
- 12 publications were included:
- 11 regarding metastatic/recurrent disease
- 1 regarding metastatic disease
- Line of therapy was not reported for most publications; only 1 study specifically focused on first-line treatment, and 1 specifically focused on second-line treatment
- In studies that reported age, over 50% of patients were between 40 and 59 years old
- Outcomes were assessed as follows:
- 4 reported humanistic outcomes
- 7 reported economic outcomes (6 in the US; 1 in the UK)
- 1 reported healthcare resource use outcomes (Republic of Korea)

Humanistic outcomes (Table 2)

- The following interventions were studied:
- Topotecan plus cisplatin (n=2)
 Bevacizumah plus chemotherapy (n=1)
- Bevacizumab plus chemotherapy (n=1)
- Cediranib plus chemotherapy (n=1)

- The following instruments were used to assess PROs:
- Functional Assessment of Cancer Therapy-Cervix (FACT-Cx; n=3)
- Brief Pain Inventory (n=3)
- Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Nx; n=2)
- European Organisation for Research and the Treatment of Cancer (EORTC) QLQ-C30 (n=1)
- Patients had impaired physical, emotional, social, and functional well-being and experienced mild to moderate pain before treatment⁴⁻⁶
- The FACT-Cx Trial Outcome Index (TOI) score ranged from 67 to 78 (possible score ranged from 0 to 116, with higher scores indicating improved outcomes)^{5,6}
- No difference was found in overall quality of life, neurotoxicity score, or pain outcomes between treatments⁴⁻⁷
- Cediranib plus chemotherapy was associated with a worse diarrhea score on EORTC QLQ-C30 compared with chemotherapy alone in patients who were not previously treated⁷
- Pretreatment FACT-Cx physical well-being was significantly associated with survival in patients with recurrent, metastatic, and persistent cervical cancer⁵

Economic outcomes (Table 3)

- Cisplatin plus paclitaxel (CP) was found to be cost-effective or dominant in 1 UK (incremental cost per quality-adjusted life-year [QALY]=£17,974)⁸ and 2 US analyses (cost per QALY=\$13,654 or dominant)^{9,10} for the treatment of recurrent and advanced cervical cancer compared with other chemotherapy regimens
- **CP dominated all other examined regimens** (cisplatin, cisplatin plus topotecan [CT], cisplatin plus gemcitabine [GC], or cisplatin plus vinorelbine [CV]) in 1 US analysis⁹ and was cost-effective compared with cisplatin alone in another US study (incremental cost per QALY=\$13,654)¹⁰
- Drug cost for topotecan plus cisplatin accounted for one-third of the total cost of treatment in the US; cost for adverse event (AE) management accounted for the majority of the total cost⁹
- The addition of bevacizumab to standard chemotherapy provided a modest health benefit (≈4 additional months in overall survival) but was not considered cost-effective (incremental cost per life-year ranged from \$157,941 to \$280,380)¹¹⁻¹³
- The American Society of Clinical Oncology (ASCO) Value Framework suggested that adding bevacizumab to chemotherapy as a second-line therapy provided a modest net health benefit but was associated with a significantly higher cost¹⁴

Healthcare resource use outcomes (Table 4)

- The total number of emergency department visits due to an AE was similar between regimens with and without bevacizumab¹⁵
- Differences were observed between regimens in number of emergency department visits related to urinary tract infection and neutropenic fever¹⁵

Table 2. Summary of PROs

NR, not reported; RCT, randomized clinical trial.

		Patient group (sample size), age, and race	Outcome		
Chase 2012 ⁴ (recurrent, metastatic, and persistent) Post hoc analysis of multiple studies	Stage IV: 13.5% Recurrent/persistent: 85.7% Unknown: 0.7% Line of therapy: NR	Topotecan + cisplatin In Study 179 (n=141) In Study 204 (n=109) Age: NR Race: NR	Baseline, mean (SD), Study 179, Study 204: FACT-Cx physical well-being (0=worst outcomes; 28=best outcomes) 17.80 (6.11), 18.93 (6.63) FACT-Cx emotional well-being (0=worst outcomes; 24= best outcomes) 14.17 (5.06), 15.03 (5.51) FACT-Cx social well-being (0=worst outcomes; 28=best outcomes) 21.61 (5.57), 21.84 (5.53) FACT-Cx functional well-being (0=worst outcomes; 28=best outcomes) 14.51 (6.63), 15.75 (7.54) FACT-Cx cervical cancer subscale (0=worst outcomes; 60=best outcomes) 39.27 (8.14), 32.98 (8.03) Brief Pain Inventory worst pain (0=best outcomes, 10=worst outcomes) 4.94 (3.50), 3.66 (3.37) Association of overall survival and FACT-Cx baseline score, adjusted hazard ratio: FACT-Cx physical well-being 0.963 (95% CI, 0.951-0.975; p<0.001) FACT-Cx emotional well-being 1.006 (95% CI, 0.992-1.020; p=0.052) FACT-Cx social well-being 0.994 (95% CI, 0.980-1.008; p=0.043) FACT-Cx functional well-being 0.997 (95% CI, 0.981-1.012; p=0.68) FACT-Cx cervical cancer subscale 0.991 (95% CI, 0.979-1.004; p=0.16) Brief Pain Inventory worst pain (0=worst outcomes, 10=best outcomes) 1.002 (95% CI, 0.973-1.031; p=0.91)		
Cella 2010 ⁵ (recurrent and metastatic) RCT	Stage IVB: 18.8% Recurrent/persistent: 81.2% Line of therapy: NR	Topotecan + cisplatin (n=96) vs paclitaxel + cisplatin (n=86) Topotecan + cisplatin: Age, y: ≤39 (8%), 40-49 (30%), 50-59 (40%), 60-69 (13%), ≥70 (9%) Race: Asian (2%), Black (15%), other (9%), White (74%) Paclitaxel + cisplatin: Age, y: ≤39 (7%), 40-49 (22%), 50-59 (33%), 60-69 (27%), ≥70 (12%) Race: Asian (5%), Black (19%), other (3%), White (73%)	Pre-cycle 1 vs 9 months post cycle 1, mean (SD): • FACT-Cx TOI (0=worst outcomes; 116=best outcomes) Topotecan + cisplatin: 68.1 (19.2) vs 70.9 (17.9) Paclitaxel + cisplatin: 66.6 (17.6) vs 71.9 (16.6) • FACT/GOG-Nx (0=worst outcomes; 16=best outcomes) Topotecan + cisplatin: 14.1 (3.5) vs 13.1 (3.5) Paclitaxel + cisplatin: 14.4 (2.9) vs 11.1 (5.2) • Brief Pain Inventory worst pain (0=best outcomes; 10=worst outcomes) Topotecan + cisplatin: 3.6 (3.3) vs 2.9 (2.7) Paclitaxel + cisplatin: 4.0 (2.8) vs 3.6 (3.3) There was no difference between the groups in any of the outcomes.		
Penson 2015 ⁶ (recurrent, metastatic, and persistent) RCT	Cancer grade/stage: NR No previous chemotherapy for recurrence was allowed, and no previous paclitaxel or topotecan with prior radiation was permitted.	Chemotherapy + bevacizumab (n=196) vs chemotherapy alone (n=194) Chemotherapy + bevacizumab: Age, y: ≤ 39 (12%), $40-49$ (28%), $50-59$ (34%), $60-69$ (18%), ≥ 70 (8%) Race: Asian (6%), Black (16%), other (4%), White (74%) Chemotherapy alone: Age, y: ≤ 39 (10%), $40-49$ (35%), $50-59$ (25%), $60-69$ (21%), ≥ 70 (9%) Race: Asian (3%), Black (11%), other (6%), White (80%)	 Baseline vs 9 months post cycle 1, mean (SE): FACT-Cx TOI (0=worst outcomes; 116=best outcomes) Chemotherapy: 77.9 (1.2) vs 74.5 (1.4) Chemotherapy + bevacizumab: 75.8 (1.2) vs 72.7 (1.6) Difference across all time points was 1.2 points lower with bevacizumab (98.75% CI, -4.1 to 1.7; p=0.30). FACT/GOG-Ntx (0=worst outcomes; 16=best outcomes) Chemotherapy: 12.16 (NR) vs 8.78 (NR) Chemotherapy + bevacizumab: 11.87 (NR) vs 8.92 (NR) Difference across all time points was 0.23 points lower with bevacizumab (98.75% CI, -1.19 to 1.64; p=0.69). Brief Pain Inventory worst pain (0=best outcomes; 10=worst outcomes) Chemotherapy: 5.38 (NR) vs 4.69 (NR) Chemotherapy + bevacizumab: 5.37 (NR) vs 5.09 (NR) Odds of experiencing pain over study period were similar. 		
Symonds 2015 ⁷ (recurrent and metastatic) Clinical trial	Stage IVB: 100% First line	Chemotherapy + cediranib (n=34) vs chemotherapy (n=35) Chemotherapy + cediranib: Age, y: median, 44 (interquartile range, 37-60) Chemotherapy: Age, y: median, 44 (interquartile range, 34-53) Race: NR	 Mean standardized adjusted area under the curve over 12 months: EORTC QLQ-C30 (higher scores indicating better outcomes) -11.1 (95% CI, -20.8 to -7.4) vs -5.4 (95% CI, -13.1 to -1.0); p=0.50 Quality of life associated with diarrhea Difference between groups: 18 (95% CI, 5-37; p=0.030); worse with cediranib 		

Table 3. Summary of economic outcomes

Author, year (population), and country	Patient group, line of therapy, age, and race	Time frame	Cost	Effectiveness	Incremental cost-effectivenes ratio
Paton 2010 ⁸ (recurrent and advanced) UK	CT vs cisplatin Line of therapy: NR Age: NR Race: NR	Lifetime	Total cost: NR	 Life-months: Licensed population: 12.9 vs 9.9 Naive population: 15.1 vs 11.1 Sustained cisplatin-free interval population: 9.5 vs 7.9 	 Incremental cost per QALY (201 cost): Licensed population: £17,97 Naive population: £10,928 Sustained cisplatin-free interval population: £32,463
McKim 2016 ⁹ (recurrent, advanced, and persistent) US	CT Cisplatin CP GC CV Line of therapy: NR Age: NR Race NR	Lifetime	Total cost for 6 cycles, including drug, drug administration, and AE cost (2012 US\$): CT: \$24,147 (drug cost=\$7,480) Cisplatin: \$14,573 (drug cost=\$95) CP: \$13,250 (drug cost=\$489) GC: \$33,559 (drug cost=\$18,306) CV: \$22,956 (drug cost=\$1,637)	Life-years: CT: 0.85 Cisplatin: 0.54 CP: 1.1 GC: 0.86 CV: 0.83	CP dominated all other regimen
Geisler 2012 ¹⁰ (recurrent, advanced, and persistent) US	CP vs cisplatin CT vs cisplatin Line of therapy: NR Age: NR Race: NR	Lifetime	Total cost, including drug, drug administration, and AE cost (2011 US\$): Cisplatin: \$34,908 CP: \$36,978 CT: \$49,071	Life-months: Cisplatin: 6.5 CP: 9.7 CT: 9.4	Incremental cost per QALY: CP vs cisplatin: \$13,654 CT vs cisplatin: \$152,327
Minion 2015 ¹¹ (recurrent, metastatic, and persistent) US	Chemotherapy + bevacizumab vs chemotherapy alone Line of therapy: NR Age: NR Race: NR	5 years	Total drug cost (2013 US\$): \$79,844 vs \$6,053	Life-months: 18.5 vs 15	Incremental cost per life-year: \$252,996
Schroeder 2014 ¹² (recurrent, persistent, and advanced) Abstract only US	Chemotherapy + bevacizumab vs chemotherapy alone Line of therapy: NR Age: NR Race: NR	Lifetime	Total drug cost (US\$, year NR): \$88,550 vs \$2,100	Life-months: 17 vs 13.3	Incremental cost per life-year: \$280,380
Minion 2013 ¹³ (recurrent, metastatic, and persistent) Abstract only US	Chemotherapy + bevacizumab vs chemotherapy alone Line of therapy: NR Age, median (all patients), y: 47 Race: NR	Lifetime	Total incremental cost (2013 US\$): \$48,330; bevacizumab drug cost was the driver Cost per AE: • Hypertension: grade 2, \$116; grade 3, \$357 • Thromboembolism: grade ≥3, \$3,947 • Bleeding: grade 3, \$333; grade 4, \$1,988	NR	Incremental cost per life-year: \$157,941
Smith 2017 ¹⁴ (recurrent and metastatic) Abstract only	Bevacizumab Second line Age: NR Race: NR	Not applicable	Using the ASCO Value Framework, the net health benefit for bevacizumab vs standard chemotherapy was 25.0 at an incremental cost of \$57,477. The actual cost of bevacizumab in DrugAbacus was \$10,948/month. Using \$108,000 per life-year, the DrugAbacus price was \$9,529/month. If the cost per life-year was \$132,000, the DrugAbacus price increased to \$11,647/month, higher than the actual cost.		

AE, adverse event; **ASCO**, American Society of Clinical Oncology; **CP**, cisplatin + paclitaxel; **CT**, cisplatin + topotecan; **CV**, cisplatin + vinorelbine; **GC**, cisplatin + gemcitabine; **NR**, not reported; **QALY**, quality-adjusted life-year; **UK**, United Kingdom; **US**, United States.

Table 4. Summary of healthcare resource use outcomes

Author, year (population), and country	Patient group (sample size), line of therapy, age, and race	Resource use outcome
Choi 2020 ¹⁵ (recurrent and advanced) Republic of Korea	Paclitaxel + cisplatin + ifosfamide (n=92; 38% first line) vs paclitaxel + cisplatin + bevacizumab (n=71; 96% first line) Line of therapy: NR Paclitaxel + cisplatin + ifosfamide: Age, mean±SD, y: 48.0±11.6 Paclitaxel + cisplatin + bevacizumab: Age, mean±SD, y: 49.9±9.8 Race: NR	Number of patients with emergency department visit due to AEs, n (% 25 (28%) vs 22 (31%); p=0.606 Number of emergency department visits due to AEs, n: All AEs: 40 vs 41; p=0.485 Due to urinary tract infection: 4 vs 14; p=0.029 Due to neutropenic fever: 15 vs 1; p=0.015

AE, adverse event; **NR**, not reported; **SD**, standard deviation.

CONCLUSIONS

- PRO and economic data in patients with recurrent/metastatic cervical cancer were limited
- CP therapy was cost-effective compared with other chemotherapies, while chemotherapy plus
- bevacizumab was not cost-effective despite being recommended as first-line therapy
 Patients had impaired physical, emotional, social, and functional well-being and experienced mild to moderate pain; these outcomes were not improved by treatment with topotecan,
- bevacizumab, or cediranib
- AEs related to treatment could negatively affect PROs, and AE management was costly
 The addition of bevacizumab to chemotherapy offered modest incremental clinical benefits at high incremental costs
- There was no PRO or economic evidence related to pembrolizumab in patients with recurrent/ metastatic cervical cancer
- Novel therapies that can improve survival as well as economic and humanistic outcomes in patients with recurrent/metastatic cervical cancer are needed

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DISCLOSURES

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