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Standard of care treatment for stage IVB cervical cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Stage IVB CC is studied with persistent and recurrent CC, but has poorer survival outcomes.
- Standard of care for advanced CC is combination chemotherapy.
- Trials are likely to lead to changes in the standard of care.
- Improving outcomes for the highest risk group, stage IVB CC, will continue to be important.

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ABSTRACT

Objective. Our aim was to perform a systematic review and meta-analysis evaluating the efficacy of standard treatment for stage IVB cervical cancer.

Method. Databases were searched for Phase III trials evaluating stage IVB CC patients according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Systematic review included Phase III trials evaluating first-line treatment of stage IVB cervical cancer (CC). A meta-analysis was pursued for Phase III trials establishing standard of care treatment that included independent analyses of stage IVB, persistent, and recurrent CC.

Results. For the systematic review, 8 studies met inclusion criteria, with a total of 3,161 CC patients analyzed. Of these studies, three met criteria and included suitable data for meta-analysis – GOG 240, KEYNOTE-826, and BEATcc. Of the 1,479 women included in the meta-analysis, 289 (19.5 %) had stage IVB and 1,190 (80.5 %) had persistent or recurrent CC. HR of OS was 0.64 (95 % confidence interval (CI): 0.55–0.75) and 0.85 (95 % CI: 0.64–1.14) for persistent/recurrent and stage IVB CC, respectively. In the test of group differences, *p*-value was insignificant at 0.098.

Conclusion. While trials have assessed outcomes in stage IVB, persistent, and recurrent CC, new treatments demonstrate poorer PFS and OS for stage IVB compared to persistent and recurrent CC. The exact benefit for current standard of care for stage IVB CC could be better defined. Given that stage IVB CC has a different clinical course and treatment history compared to persistent and recurrent disease, stage IVB CC should be analyzed independently in future clinical trials.

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1. Introduction

Cervical cancer (CC) is the fourth most common cancer of women worldwide with an estimated incidence of 604,000 cases and mortality of 342,000 deaths in one year [1]. Although CC incidence and mortality have declined due to increased screening measures against HPV [2], mortality rates continue to remain high for advanced disease [3]. According to the American Cancer Society (ACS), the five-year survival of all stages of CC was 66 % from 2011 to 2017 [3]. New CC diagnoses are estimated at 13,820 cases and deaths at 4,36-cases for 2024, per the National Institute of Health (NIH) [4]. According to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system, the five-year survivability of stage IVB CC estimates 14.7 % [5], markedly lower than the five-year survivability of stage IVA CC, which approximates 24 % [5]. Staging at presentation is the most critical factor for CC prognosis [6].

Stage IV CC is defined as disease that has grown outside the cervix to invade nearby or distant organs [3]. Stage IVA CC is defined as a tumor that has spread to adjacent pelvic organs, such as the bladder or rectum; stage IVB CC is defined as disease that has spread to distant organs beyond the true pelvis [7]. Persistent CC is defined as disease not responsive to treatment, often receiving radiation with or without chemotherapy, while recurrent CC is defined as disease that has returned after a period of remission [7]. Stage IVB CC is studied with persistent and recurrent CC in clinical trials and assigned standard of care along with persistent and recurrent disease. Stage IVB CC may have a different disease course given that most persistent or recurrent disease has been previously treated with chemotherapy, radiation, or surgery, while stage IVB disease has not been previously treated aside from the possibility of palliative intent radiation. Stage IVB CC at diagnosis is an independent poor prognostic factor, often necessitating second or third line therapies [6]. Because the stage IVB population has not been the primary focus of clinical trial enrollment, limitations exist in separating this group for individual analysis.

Standard of care for stage IVB CC not amenable to local treatment is systemic chemotherapy consisting of pembrolizumab, cisplatin, paclitaxel, and bevacizumab [7]. For patients with disease amenable to local treatment, resection with or without individualized radiotherapy followed by adjuvant systemic chemotherapy is recommended (category 2 A recommendation) [7], although the proportion of stage IVB CC patients with disease amenable to local treatment is unclear. Patients for whom resection is an option are not included in clinical trials and thus are not included in this review. Stage IVB CC research has been limited by poor prognosis and survivability, highlighting the importance of this study.

Stage IVB CC is not frequently independently analyzed for outcomes, as most trials analyze the combination of stage IVB, persistent, and recurrent disease. Furthermore, stage IVB, recurrent, and persistent CC have different clinical course and treatment histories, confounding the true effects observed in clinical trials. It is difficult to ascertain whether stage IVB clear best practices can be concluded from literature to date. The poor prognosis for stage IVB CC elicits the question: how can standard of care for stage IVB CC be refined to improve patient outcomes? The objective of this systematic review is to summarize the current literature and health disparities in the treatment of stage IVB disease.

2. Methods

This systematic review was completed via the PRISMA 2020 guidelines [10] using a search for literature pertaining to stage IVB CC on two databases, PubMed and Embase, with the following MeSH terms: ((cervical cancer) AND (stage IVB)). There were 1224 articles identified including clinical trials, randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Inclusion criteria included Phase III clinical trials assessing first-line treatment of stage IVB CC in the last twenty years (2004–2024). Only literature in English was included. Of the articles identified, 7 met inclusion criteria. One well-known phase III trial, KEYNOTE-826, did not fit our search criteria; however, due to relevance and impact, we elected to include this in our analysis, leaving 8 articles for review (Fig. 1).

Meta-analysis inclusion criteria included Phase III trials establishing standard of care that evaluated an investigational versus standard treatment with independent analyses of stage IVB, persistent, and recurrent CC. Meta-analysis was performed using the random effects model of DerSimonian and Laird, evaluating the effect size of HRs for OS in stage IVB, persistent, and recurrent CC. Risk of bias and quality assessment were performed using the ROBINS-I and GRADE tools, respectively.

3. Results

3.1. Systematic review

For the systematic review, 7 studies met inclusion criteria and an 8th was added due to relevance and impact, with a total of 3161 CC patients analyzed (Table 1). Given the rare clinical situation of stage IVB CC, primary literature has been limited. Stage IVB CC presents a challenge for clinical research due to low survivability, with average PFS of about 10.4 months and OS at 24 months around 53 % for the current standard of care regimen [11], making this an important and urgent question to study.

In 2004, a Phase III trial established that cisplatin with paclitaxel was superior to cisplatin alone for response rate and PFS in the treatment of squamous cell carcinoma of the cervix [8]. The exact number of stage IVB patients included in the study was not stated and the majority of all patients had prior radiation therapy (91.5 % of study population) [8]. In 2005, GOG 179 (stage IVB = 59; 20.1 % of study population) found that cisplatin plus topotecan was superior to cisplatin alone in the treatment of recurrent, persistent, and metastatic CC [9]. There was no independent analysis for stage IVB patients [9].

In 2009, GOG 204 (stage IVB = 74; 17.1 % of study population) assessed multiple chemotherapy agents for stage IVB, recurrent, or persistent CC in a phase III trial [10]. Patients were randomly assigned to one of four chemotherapy groups: paclitaxel and cisplatin, vinorelbine and cisplatin, gemcitabine and cisplatin, or topotecan and cisplatin. Results showed that the cisplatin/paclitaxel arm was noninferior to the other groups in terms of OS, but had a preferable side-effect profile [10]. For stage IVB disease, the HR for PFS was 0.63 (95 % CI: 0.38–1.06) in comparison to recurrent disease (progression-free interval (PFI) of 0–5.9 months) and 0.70 (95 % CI: 0.49–1.01) in comparison to persistent disease [10]. The HR for stage IVB OS was 0.82 (95 % CI:

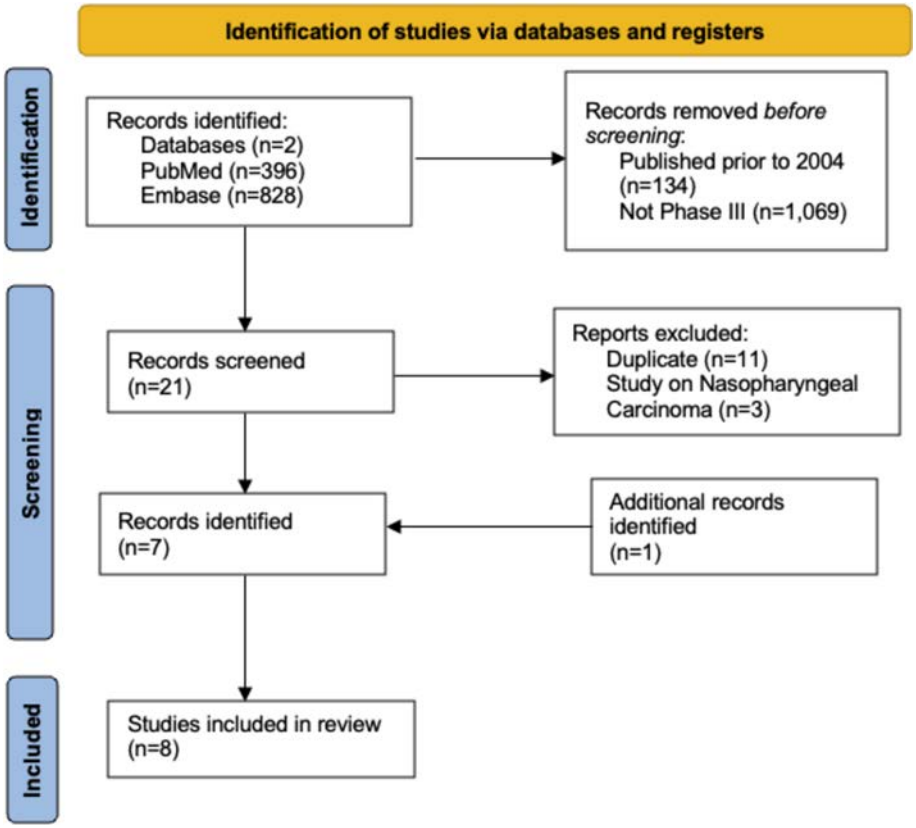


Fig. 1. PRISMA flow diagram.

Table 1
Total studies included for systematic review.

Author/Year	Stages CC Evaluated	Study Total	Total stage IVB	Primary Objective	Intervention	Results
Moore et al., 2004 [8]	Recurrent, persistent, metastatic	264	Did not include	To determine if cisplatin plus paclitaxel improved survival compared with cisplatin alone.	Paclitaxel 135 mg/m^2	Cisplatin and paclitaxel was superior to cisplatin alone for response rate and PFS with sustained quality of life.
Long et al., 2005 [9]	Recurrent, persistent, metastatic	293	$n = 59$; 20.1 % of study population	To determine whether survival is improved with combination chemotherapy compared to cisplatin alone.	Cisplatin 50 mg/m^2 plus topotecan 0.75 mg/m^2; or methotrexate 30 mg/m^2 vinblastine 3 mg/m^2 doxorubicin 30 mg/m^2 and cisplatin 70 mg/m^2	Combination chemotherapy showed a survival advantage over cisplatin alone.
Monk et al., 2009 [10]	Recurrent, persistent, metastatic	513	$n = 74$; 17.1 % of study population	Assess toxicity/efficacy of cisplatin doublet combinations in recurrent, persistent, and metastatic cervical cancer.	Cis 50 mg/m^2; vinorelbine 30 mg/m^2 plus Cis 50 mg/m^2; gemcitabine 1000 mg/m^2 plus Cis 50 mg/m^2; or topotecan 0.75 mg/m^2 plus Cis 50 mg/m^2	Doublets were not superior to cisplatin alone in terms of OS. PFS and OS favored cisplatin alone.
Tewari et al., 2014 [11]	Recurrent, persistent, metastatic	452	$n = 76$; 16.8 % of study population	To evaluate the effectiveness of bevacizumab and nonplatinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.	Bevacizumab 15 mg/kg	Bevacizumab in addition to combination chemotherapy significantly improved overall survival.
Kitagawa et al., 2015 [12]	Recurrent, persistent, metastatic	253	Did not include	To evaluate the clinical benefits of carboplatin-based rather than cisplatin-based chemotherapy.	Carboplatin AUC 5 mg/mL/min	Carboplatin was noninferior to cisplatin for patients who had not received platinum agents before.
Aoki et al., 2018 [13]	Recurrent, persistent, metastatic	364	$n = 43$; 11.8 % of study population	To evaluate the effects of S-1 plus cisplatin vs cisplatin alone as a first-line chemotherapy in patients with recurrent, persistent, or metastatic CC	S-1 80–120 mg	S-1 did not show superiority over cisplatin alone in OS but significantly improved PFS in patients with stage IVB, recurrent, and persistent CC.
Colombo et al., 2021 [14]	Recurrent, persistent, metastatic	612	$n = 123$; 19.9 % of study population	To assess the benefit of adding pembrolizumab to chemotherapy with or without bevacizumab.	Pembrolizumab 200 mg	PFS and OS were significantly longer with pembrolizumab than placebo for patients with persistent, recurrent, or metastatic cervical cancer receiving chemotherapy with or without bevacizumab.
Oaknin et al., 2024 [15]	Recurrent, persistent, metastatic	410	$n = 90$; 21.9 % of study population	To evaluate the addition of atezolizumab standard therapy for metastatic or recurrent cervical cancer.	Atezolizumab 1200 mg	Atezolizumab significantly improved OS and PFS compared to standard therapy for recurrent, persistent, and metastatic CC patients.

0.47–1.45) in comparison to recurrent disease (PFI interval of 0–5.9 months) and 0.91 (95 % CI: 0.61–1.35) in comparison to persistent disease [10].

GOG 240 (stage IVB = 76; 16.8 % of study population) established that adding bevacizumab to standard chemotherapy regimens resulted in improved OS in patients with stage IVB, persistent, or recurrent CC, implementing bevacizumab as a current standard of care for these patient populations [11]. OS was 17 months in the treatment arm vs 13.3 months in the control arm for metastatic, recurrent, and persistent disease [11]. The HR for OS was 0.71 (98 % confidence interval (CI): 0.54–0.95; $p = 0.004$). For stage IVB disease, the HR for OS was 0.89 (95 % CI: 0.46–1.71), although this was not statistically significant [11]. This finding revolutionized the clinical standard of care for advanced CC, as previously few treatment agents were efficacious in conjunction with standard chemotherapy.

JCOG0505 evaluated the clinical benefits of carboplatin-based versus cisplatin-based chemotherapy and found that carboplatin was noninferior to cisplatin for patients who had not received platinum agents before [12]. In patients who had not undergone previous treatment with cisplatin, OS was inferior when treated with paclitaxel and carboplatin, suggesting that cisplatin should remain the standard drug for patients not receiving prior platinum agents [12]. However, this finding suggests that carboplatin may be an option for those with recurrent or persistent disease after initial treatment with cisplatin. The number of stage IVB CC patients was not stated and there was no independent analysis for stage IVB. In a Phase III trial (stage IVB = 43; 11.8 % of study population) evaluating the effects of S-1, an oral fluoropyrimidine-based anticancer agent, plus cisplatin versus cisplatin alone as a first-line chemotherapy for patients with recurrent, persistent, and metastatic CC, S-1 did not show superiority over cisplatin alone for OS [13]. However, S-1 showed significant improvement in PFS for patients with stage IVB, recurrent, and persistent CC [13].

Most recently, pembrolizumab has been added to stage IVB CC treatment, as KEYNOTE-826 (stage IVB = 123; 19.9 % of study population) found that adding pembrolizumab to chemotherapy for patients with stage IVB, persistent, or recurrent cervical cancer significantly improved survival outcomes [14]. When analyzed by stage, stage IVB disease had a HR of 0.92 (95 % CI: 0.64–1.30) for PFS and 0.84 (95 % CI: 0.56–1.26) for OS [14]. The HR was 0.58 (95 % CI: 0.45–0.75) for PFS and 0.61 (95 % CI: 0.46–0.80) for OS for patients with persistent and recurrent disease [14]. The HR was 0.91 (95 % CI: 0.63–1.30) for PFS and 0.88 (95 % CI: 0.58–1.35) for OS for stage IVB CC patients with PD-L1 expression greater than or equal to one [11] (Figs. 2&3). The HR was 0.77 (95 % CI: 0.47–1.26) for PFS and 0.77 (95 % CI: 0.47–1.26) for OS for stage IVB patients with PD-L1 greater than or equal to 10 [14]. It is noteworthy that the HR of PFS and OS were the same for stage IVB patients with PD-L1 greater than or equal to 10, perhaps speaking to the mortality of the disease. In both GOG 240 and KEYNOTE-826, the HR for PFS and OS were higher in the newly diagnosed metastatic subgroup, suggesting that bevacizumab and pembrolizumab are less effective for stage IVB CC compared to recurrent and persistent disease [11,14]. The mechanism of this remains unclear, although it is plausible there is a higher disease burden stage IVB CC versus persistent/recurrent disease.

The phase III BEATcc trial (stage IVB = 90; 21.9 % of study population) evaluated the addition of atezolizumab to cisplatin/paclitaxel and bevacizumab for stage IVB, metastatic, and recurrent CC patients [15]. The addition of atezolizumab significantly improved OS and PFS compared to standard therapy for recurrent, persistent, and metastatic CC patients, with HRs of 0.68 (95 % CI: 0.52–0.88; $p = 0.0046$) and 0.62 (95 % CI: 0.49–0.78; $p < 0.0001$), respectively [15]. Given dramatically low survivability of this patient population, the potential benefit of immunotherapy is significant. Efficacious chemotherapy and immunotherapy agents for stage IVB CC remain an area of unmet need.

3.2. Meta analysis

Of the 7 trials analyzed, three met criteria and included suitable data for meta-analysis – GOG 240, KEYNOTE-826, and BEATcc. Of the 1479 women included in the meta-analysis, 356 had stage IVB and 1132 had persistent or recurrent CC. HR of OS was 0.64 (95 % CI: 0.55–0.75) and 0.85 (95 % CI: 0.64–1.14) for persistent/recurrent and stage IVB CC, respectively. In the test of group differences, p-value was insignificant at 0.098 (Fig. 2). Given that the CI surpassed one for stage IVB CC, the exact benefit of current standard of care for stage IVB could be better defined.

4. Health disparities

Existing health disparities are magnified in CC. The NIH quotes an overall five-year survival rate of 91.6 % for localized CC, 58.6 % for

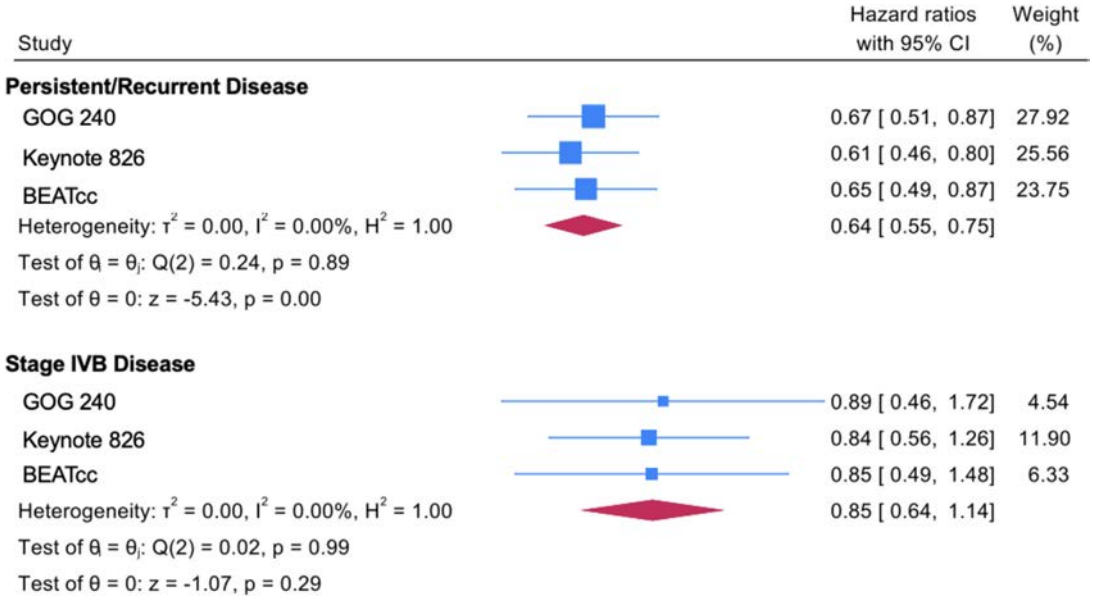


Fig. 2. Hazard ratio and 95 % confidence interval of overall survival for patients with stage IVB and persistent/recurrent CC, respectively, in meta-analysis of GOG 240, Keynote 826, and BEATcc.

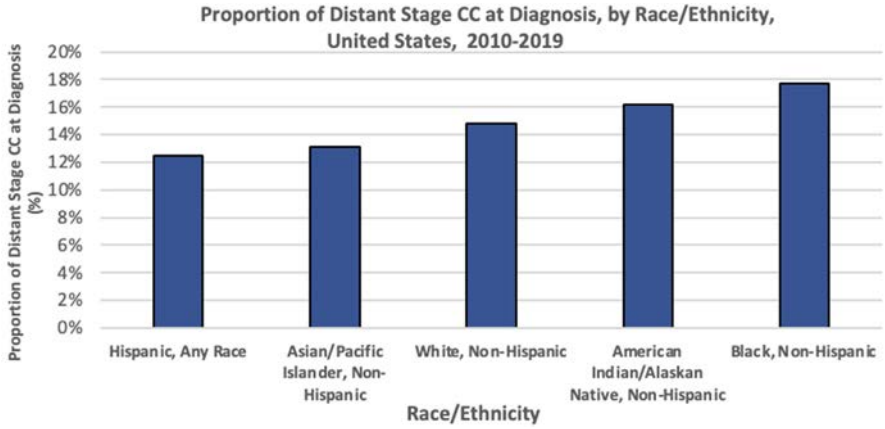


Fig. 3. Proportion of distant CC patients at diagnosis by race, including Hispanic, Asian/Pacific Islander, White, American Indian/Alaskan Native, and Black populations [32] (2022).

regional CC, and 17.4 % for distant CC [16]. The overall stage distribution for new CC cases was 44.2 % localized, 34.4 % regional, 15.0 % distant, and 6.5 % unstaged in 2022 [17]. When examined by race and ethnicity, Hispanic patients of any race had 12.5 % new distant CC diagnoses, Asian/Pacific Islander, Non-Hispanic patients had 13.1 % new distant CC diagnoses, White, Non-Hispanic patients had 14.8 % new distant CC diagnoses, American Indian and Alaskan Native, Non-Hispanic patients had 16.2 % new distant CC diagnoses, and Black, Non-Hispanic patients had 17.7 % new distant CC diagnoses from 2010 to 2019 [17] (Fig. 3). Given that CC prevention relies heavily on access to routine screening, patients with limited access are more likely to present with advanced CC [18,19]. Systemic inequities have limited the ability of minority and marginalized communities to obtain healthcare coverage [20]. History of sexual trauma amongst advanced CC patients warrants exploration, as the trigger of a pelvic exam could prevent victims of sexual violence from seeking routine gynecologic healthcare and CC screening.

5. Future directions and conclusions

Clinical trials and literature to date have evidenced standard of care treatments for advanced CC overall; however, stage IVB CC is often overlooked and assigned standard of care in conjunction with recurrent and persistent CC, showing a clear problem for patients presenting at this stage. In a meta-analysis of GOG 240, KEYNOTE-826, and BEATcc, HR of OS was higher for stage IVB CC compared to persistent and recurrent disease and the CI surpassed one. The exact benefit of current standard of care for stage IVB could be better defined. There are disproportionately poor outcomes for stage IVB CC patients. These poor outcomes, in conjunction with lack of research on stage IVB CC patients alone, elicit a call to action: future studies should independently analyze stage IVB CC patients with the goal of refining current treatment methods. To define the current standard of care for stage IVB disease, previous Phase III trials that have not independently analyzed stage IVB CC should review this data to elucidate the effect of specific treatment agents for this population.

The prospect of concurrent systemic chemotherapy with radiation has been explored retrospectively. Systemic chemotherapy in conjunction with radiation followed by adjuvant chemotherapy could perhaps simultaneously treat local and distant disease, a current challenge in advanced CC. Retrospective analysis of radiotherapy for stage IVB CC has demonstrated safety and efficacy [21–26] (Table 2).

A Phase III trial recently established tisotumab vedotin monotherapy as superior to investigator's choice chemotherapy for patients with recurrent, persistent, or metastatic CC who showed disease progression after first-line combination therapy [27]. Tisotumab vedotin has been FDA-approved for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [27]. A Phase II trial also recently showed efficacy for fam-trastuzumab deruxtecan in the treatment of cervical cancer that is IHC 3 + [28]. This has also been FDA-approved. Another Phase I/II trial showed promise with the treatment combination of nivolumab plus ipilimumab for the treatment of recurrent or metastatic CC [29].

It is evident that with such poor prognosis, stage IV CC patients present with greater social and psychological needs. Existing health disparities are magnified in the gynecologic oncology landscape, as access to screening and routine healthcare are paramount to preventing advanced CC. Historically marginalized racial minorities present most frequently with stage IV CC [17]. The intersectional inequity of one's identity as a historically marginalized minority and as a patient with late stage CC is notably grim. Further research should explore specific systemic barriers and mechanisms by which racial minorities present with stage IVB CC at higher rates.

Recurrent, persistent, and metastatic CC are studied in tandem despite different treatment history and survival outcomes. Poor survival outcomes limit stage IVB research while highlighting the importance of this review and the need for further research. Given the difference in treatment history, clinical course, and survival outcomes for persistent, recurrent, and stage IVB CC, it is imperative that future research analyze stage IVB disease independently. Unfortunately, this depends upon the survivability of those with stage IVB CC, and ultimately, improved survivability depends upon research outcomes.

Table 2
Retrospective Analysis of Addition of Radiation Therapy for Advanced Metastatic Cervical Cancer.

Author	Journal	Year	n	Study type	Results
Perkins [21]	Gyn Oncol	2020	126	Multi-institutional	41.6 OS vs 17.6 months, no major AEs
Zighelboim [22]	Radiat Med	2006	24	Single institutional	OS 44 % @ 3 yr, 22 % at 5 yr
Ning [23]	Gyn Oncol	2018	38	Single institutional	Median OS 51 months
Kim [24]	IJROBP	2012	25	Single institutional	OS 49 % @ 3 yr
Wang [25]	JAMA Oncol	2018	3169	NCDB	14.4 vs 10.2 months, HR 0.65
Venigalla [26]	PRO	2018	2838	NCDB	RT:19.2 vs 10.1 mo OS

(Stage IVB) by Lead Author, Journal, Year, Sample Size (n), Study Type, and Results.

6. Limitations

This review is limited by the search criteria, as only including Phase III trials limited the scope of data evaluated. There are certainly more studies that have evaluated treatment outcomes for stage IVB CC compared to persistent and recurrent disease; however, our objective was to evaluate the differences in outcomes amongst stage IVB, persistent, and recurrent disease for first-line standard of care regimens. There is one Phase II trial and one second-line Phase III trial that have been FDA-approved, shown above in the discussion. Our search criteria also missed a key trial that was ultimately included in the study, KEYNOTE-826, highlighting another limitation of this review and meta-analysis. This analysis is also limited by the landscape of CC research, as many trials study stage IVB (which is often radiation naive) with recurrent or persistent disease (which has been radiated). Stage IVB CC research is limited by the high mortality of the disease.

CRediT authorship contribution statement

Kyra S. Hunsberger: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Krishnansu S. Tewari:** Data curation. **Bradley J. Monk:** Conceptualization. **Dana M. Chase:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

There are no conflicts of interest for this systematic review and meta-analysis.

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