Short communication

Factors associated with receipt of second-line recurrent or metastatic cervical cancer treatment in the United States: A retrospective administrative claims analysis

Kalyani Sonawane [a,b], Tara Castellano [c], Christina Washington [d], Jie Ting [e], Andy Surinach [f], Carol Kirshner [g], Jagpreet Chhatwal [h], Turgay Ayer [i,j,1], Kathleen Moore [d,1,*]

[a] Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, Charleston, SC, USA
[b] Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA
[c] Louisiana State University, Department of Gynecologic Oncology, New Orleans, LA, USA
[d] Stephenson Cancer Center at the University of Oklahoma HSC, Oklahoma, City, OK, USA
[e] Seagen Inc., Bothell, WA, USA
[f] Genesis Research, Hoboken, NJ, USA
[g] Value Analytics Labs, Boston, MA, USA
[h] Massachusetts General Hospital Institute for Technology Assessment, Harvard Medical School, Boston, MA, USA
[i] Georgia Institute of Technology, Department of Industrial and Systems Engineering, Atlanta, GA, USA
[j] Emory School of Medicine, Atlanta, GA, USA

ARTICLE INFO

ABSTRACT

Purpose: Contemporary, real-world data on eligible patients receiving treatment following progression on first-line (1L) recurrent or metastatic cervical cancer (r/mCC) therapy are needed to inform treatment algorithms and identify potential gaps in the r/mCC care continuum.
Methods: This study estimated the prevalence and predictors of second-line (2L) r/mCC therapy among 1L-treated patients using the 2015–2020 IBM MarketScan® commercial claims database. Women ≥ 18 years diagnosed with cervical cancer and treated with first-line systemic therapies were identified and followed for 12 months from their 1L therapy end date. Women with claims for a new therapy after 60 days but no later than 365 days from the end of 1L treatment were identified as those who progressed and received 2L therapy for r/mCC. Descriptive statistics examined baseline cohort characteristics and multivariable logistic regression model examined the factors associated with receiving 2L treatment.
Results: We identified 384 1L-treated patients with r/mCC with ≥ 12 months of follow-up post-1L treatment. During follow-up, over half (51.0 %) of the 1L-treated r/mCC patients received 2L treatment. Patients from the South and Midwest had a lower likelihood of receiving 2L treatment compared with those living in the Northeast (adjusted odds ratio [aOR] = 0.43; 0.23–0.84) and (aOR = 0.52; 0.28–0.95, respectively). Patients not treated with bevacizumab in 1L were also less likely to receive 2L therapy (aOR = 0.65; 0.43–0.99).
Conclusion: Additional research and targeted outreach efforts are needed to understand geography-, population-, or practice-specific barriers impacting access to 2L therapy among patients with r/mCC.

1. Introduction

An estimated 14,100 women will be diagnosed with invasive cervical cancer in 2022 in the United States (US), with approximately 16 % metastatic at diagnosis, and up to 61 % of patients with earlier stage diagnosis will develop metastatic cervical cancer within the first 2 years of completing treatment (National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, 2022a, 2022b;

* Corresponding author at: Stephenson Cancer Center at the University of Oklahoma HSC, Oklahoma, City, OK, USA. Tel.: +405 271 8707.
E-mail addresses: sonawane@musc.edu (K. Sonawane), tcaste@lsuhsc.edu (T. Castellano), christina-washington@ouhsc.edu (C. Washington), jting@seagen.com (J. Ting), ckirshner@valueanalyticslabs.com (C. Kirshner), JagChhatwal@mgh.harvard.edu (J. Chhatwal), ayer@isye.gatech.edu (T. Ayer), kathleen-moore@ouhsc.edu (K. Moore).
[1] Co-senior authors.

McLachlan et al., 2017; Pfaendler and Tewari, 2016). Although the recurrent or metastatic cervical cancer (r/mCC) setting has been characterized by poor prognosis with limited treatment options, recent approvals offer new treatment options to address the unmet needs for first-line (1L) or second-line or later (2L+) r/mCC patients (National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, 2022a; Marabelle et al., 2020; Colombo et al., 2021; U.S. Food Drug Administration, 2021).

In 2018, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab as monotherapy for previously treated patients with r/mCC whose tumors express PD-L1 (Marabelle et al., 2020). In 2021, pembrolizumab received full approval for use in combination with chemotherapy +/- bevacizumab for patients with PD-L1 expression in the 1L r/mCC setting (Colombo et al., 2021). Also in 2021; tisotumab vedotin-tftv, an antibody-drug conjugate targeting tissue factor, was granted accelerated approval for treatment of patients with r/mCC with disease progression on or after chemotherapy (U.S. Food Drug Administration, 2021).

As the r/mCC treatment landscape continues to evolve, quantifying the proportion of patients needing 2L therapy and the predictors of 2L therapy uptake will help inform treatment algorithms, identify potential gaps in the care continuum, and provide insights into underlying drivers of r/mCC treatment continuity for future research. Data on these aspects of r/mCC treatment are so far limited. Therefore, the objective of this study was to determine the prevalence and predictors of 2L therapy among 1L treated patients with r/mCC.

2. Methods

We analyzed the 2015–2020 IBM MarketScan® commercial claims database. The database comprises member enrollment information consisting of demographic variables such as age, sex, geographic location (identified as four census regions, Northeast, Midwest, South, or West), and health plan enrollment/disenrollment dates, as well as medical and prescription drug claims. We utilized a previously-validated claims-based algorithm to identify patients with r/mCC (Musa et al., 2022). Briefly, a cohort design was used; we identified women ≥ 18 years with one or more inpatient claim or two outpatient claims with a diagnosis for malignant neoplasm of the cervix (identified by the International Classification of Diseases 9th and 10th Revisions, Clinical Modification Codes, 180.XX and C53.XX), followed by utilization of one or more systemic therapy indicative of 1L r/mCC treatment. Therapies that included concomitant radiation therapy or surgery within 60 days were excluded. The last recorded date of 1L treatment was assigned as the index date for each patient. Continuous enrollment criteria of a minimum 3-month pre-index and 12-month post-index were applied (Fig. 1). Women with claims for a new therapy after 60 days but no later than 365 days from the end of 1L treatment were identified as those who received subsequent r/mCC therapy.

We used descriptive statistics to examine the baseline characteristics of the final analytical cohort. A multivariable logistic regression model examined the factors associated with receiving 2L treatment. All analyses were performed using SAS®, Cary, NC. *P*-value was tested at 0.05.

3. Results

A total of 1080 patients with 1L-treated r/mCC were identified, of whom 384 met the study criteria (Fig. 2). The cohort comprised women with a mean age of 54.5 years, largely enrolled in a non-health maintenance organization health plan (88.8 %), and most women had no comorbid conditions (55.0 %). Approximately 40 % of these women were previously treated with bevacizumab (Table 1).

Post-1L treatment, 196 (51.0 %) patients initiated a subsequent therapy within a median duration of 122 days from the end date of 1L therapy. The baseline characteristics of patients who received 2L therapy were generally similar to those who did not receive 2L therapy (Table 2). The geographic location of the patient and prior exposure to bevacizumab were significant predictors of receiving 2L therapy (Table 3). Specifically, patients from the South (adjusted odds ratio [aOR] = 0.43 [0.23–0.84]) and Midwest (aOR = 0.52 [0.28–0.95]) regions had a lower likelihood of receiving 2L treatment after 1L therapy compared with those living in the Northeast. Women without prior bevacizumab treatment were also less likely to receive subsequent therapy (aOR = 0.65 [0.43–0.99]). Age, type of health plan, and comorbidity score were not associated with the likelihood of receipt of 2L therapy.

4. Discussion

Our finding that nearly half of 1L-treated patients with r/mCC received 2L therapy is consistent with a recent study that followed patients with r/mCC from 2014 to 2020 in the US Oncology Network, reporting that 48 % of 1L-treated patients received 2L therapy (Alholm et al., 2022). To our knowledge, these are the only two studies so far that estimated real-world receipt of 2L therapy and its predictors among contemporary patients with r/mCC. Collectively, these data provide highlight potential gaps in the r/mCC care continuum.

We found that geography is an important predictor in the receipt of 2L treatment. Due to data limitations, however, it was not possible to capture geographic-level factors contributing to a lower likelihood of receiving 2L r/mCC treatment for patients living in the South and the Midwest, compared with those in the Northeast. Previous studies have pointed to a high correlation between treatment discontinuation and/or interruption due to longer travel times, lack of gynecologic oncology workforce, and suboptimal treatment with patients' area of residence and distance from the care facility (Barrington et al., 2016; Temkin et al., 2015; Ricci et al., 2017; Hung et al., 2020). Southern and Midwestern states were reported to have fewer gynecological oncologists and fewer National Cancer Institute (NCI)-designated cancer centers compared with the Northeast (Alimena et al., 2021). Spees et al. also
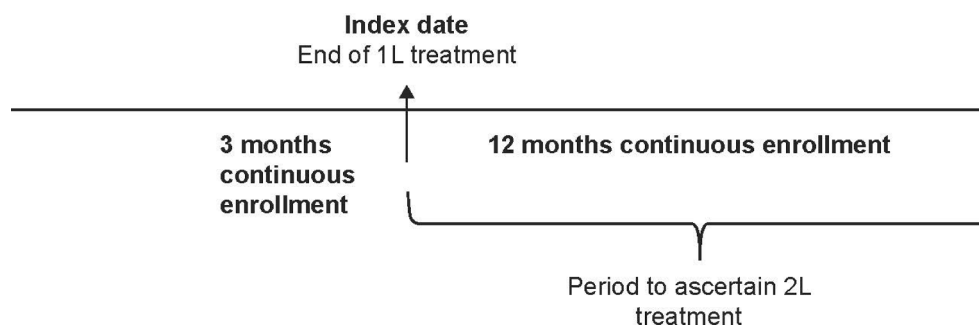

Fig. 1. Study design.
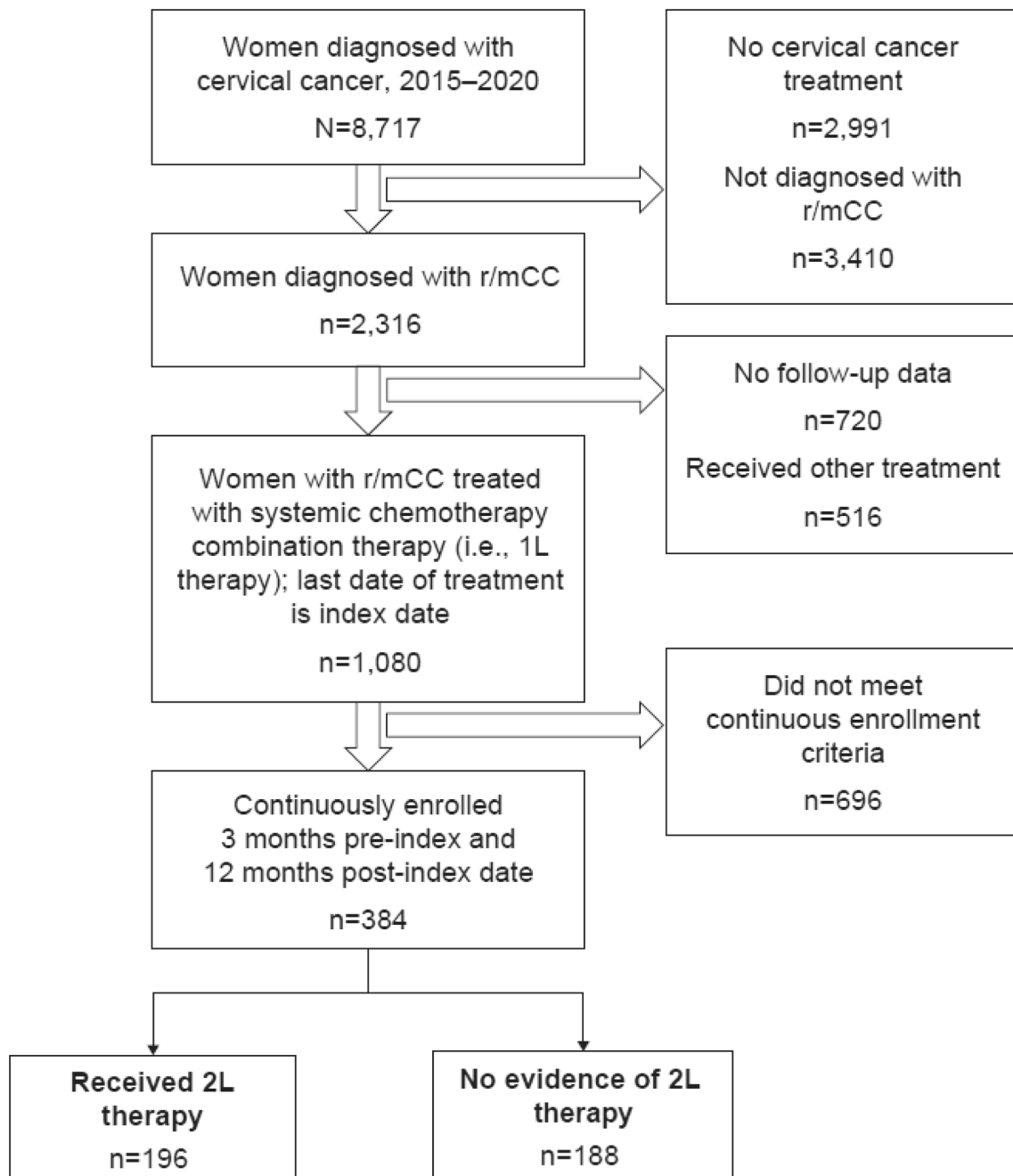1L, first-line; 2L, second-line.

Fig. 2. Study sample flow.
1L, first-line; 2L, second-line; r/mCC, recurrent or metastatic cervical cancer.

reported that travel time of ≥15 miles from residence is associated with a nearly 30 % higher risk of lack of timely cervical cancer treatment (Spees et al., 2019). It is possible that patients with r/mCC in our study who live in the South or the Midwest experienced these barriers, which decreased their likelihood of receiving 2L treatment. More granular patient- and geography-level indicators of healthcare access are needed to better understand drivers of geographic disparities in r/mCC treatment.

Patients without prior exposure to bevacizumab were also less likely to receive 2L treatment for r/mCC. Previous reports have suggested that factors associated with the likelihood of receiving 2L r/mCC treatment were similar to those predicting survival, including prior bevacizumab exposure (other factors cited included disease stage, histology, metastases, tumor size, and tumor burden) (Tewari et al., 2014; Kim et al.,

2012; Chen et al., 2021; Kato et al., 2021; Zhang et al., 2018; Endo et al., 2015; Rose et al., 2015), although we were unable to directly assess such an association due to data limitations. Future studies should seek to understand patient characteristics or other factors influencing bevacizumab inclusion in a patient's treatment.

Our study findings should be interpreted within the context of study limitations. Claims databases do not contain information on pathology, biomarkers, and qualitative indicators pertaining to treatment; therefore, our model does not account for these factors. Patients who may have initiated a subsequent line of therapy beyond the 12-month follow-up duration study were not captured in our analysis. Finally, our cohort was derived from a nationwide sample of women enrolled in a commercial health plan, which precludes generalizability to uninsured patients and patients enrolled under public health insurance plans.

K. Sonawane et al.

Gynecologic Oncology Reports 44 (2022) 101121

Table 1
Demographic characteristics of 1L-treated patients with r/mCC.

Characteristics	N	Percent
Total	384	100.0
Age at Index, years, mean (SD)	54.52	11.38
Index year		
2015	100	26.0
2016	78	20.3
2017	82	21.4
2018	68	17.7
2019	56	14.6
Region		
Northeast	62	16.2
Midwest	93	24.2
South	183	47.7
West	46	12.0
1L contains bevacizumab	155	40.4
Charlson Comorbidity Score, mean (SD)	0.82	1.23
CCI categories		
0	211	55.0
1	97	25.3
2	40	10.4
3+	36	9.4
Baseline comorbidities		
Myocardial infarction	8	2.1
Congestive heart failure	8	2.1
Peripheral vascular disease	23	6.0
Dementia	1	0.3
Chronic pulmonary disease	45	11.7
Rheumatic disease	5	1.3
Peptic ulcer disease	3	0.8
Liver disease	50	13.0
Diabetes without complications	58	15.1
Diabetes with complications	16	4.2
Paralysis	2	0.5
Renal disease	29	7.6
AIDS	1	0.3

1L, first-line; AIDS, acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; HMO, health maintenance organization; r/mCC, recurrent or metastatic cervical cancer.

Despite limitations, our study points to clear contributors of eligible patients not receiving 2L r/mCC therapy. Taken together, results suggest that the difference across the US in proportion of patients receiving subsequent therapy are likely influenced by both local- and patient-level factors. Further investigation into these relationships will help in understanding more clearly drivers of treatment and health disparities in r/mCC.

Funding

This study was funded by Seagen Inc.

CRediT authorship contribution statement

Kalyani Sonawane: Conceptualization, Methodology, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Tara Castellano:** Conceptualization, Methodology, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Christina Washington:** Methodology, Validation, Writing – review & editing. **Jie Ting:** Conceptualization, Methodology, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Andy Surinach:** Investigation, Data curation, Data analysis, Writing – review & editing. **Carol Kirshner:** Investigation, Data curation, Data analysis, Writing – review & editing. **Jagpreet Chhatwal:** Conceptualization, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Turgay Ayer:** Conceptualization, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Kathleen Moore:** Conceptualization, Methodology, Investigation, Supervision, Validation, Writing – original

Table 2
Baseline characteristics of 1L treated patients with r/mCC with and without 2L therapy during follow-up.

Characteristics	Total	Received 2L		Did Not Receive 2L		P-value
		N	Percent	N	Percent	
Total	384	196	100.0	188	100.0	
Age at index, years						0.85
Mean (SD)	54.52	54.63	10.65	54.41	12.13	
Index year						0.32
2015	100	57	29.1	43	22.9	
2016	78	40	20.4	38	20.2	
2017	82	45	23.0	37	19.7	
2018	68	30	15.3	38	20.2	
2019	56	24	12.2	32	17.0	
Region						0.08
Northeast	62	40	20.4	22	11.7	
Midwest	93	41	20.9	52	27.7	
South	183	90	45.9	93	49.5	
West	46	25	12.8	21	11.2	
Index line contains bevacizumab						0.08
No	229	108	55.1	121	64.4	
Yes	155	88	44.9	67	35.6	
Providers seen in 60 days prior to index						
Oncologist	180	90	45.9	90	47.9	0.76
Gynecologist	122	64	32.7	58	30.9	0.74
Others	193	97	49.5	96	51.1	0.76
Charlson Comorbidity Score						0.66
Mean (SD)	0.82	0.79	1.22	0.85	1.24	
CCI categories						0.74
0	211	112	57.1	99	52.7	
1	97	47	24.0	50	26.6	
2	40	18	9.2	22	11.7	
3+	36	19	9.7	17	9.0	
Baseline comorbidities						
Myocardial infarction	8	5	2.6	3	1.6	0.72
Congestive heart failure	8	4	2.0	4	2.1	1.00
Peripheral vascular disease	23	10	5.1	13	6.9	0.52
Cerebrovascular diseases	13	5	2.6	8	4.3	0.41
Dementia	1	0	0.0	1	0.5	0.49
Chronic pulmonary disease	45	24	12.2	21	11.2	0.75
Rheumatic disease	5	4	2.0	1	0.5	0.37
Peptic ulcer disease	3	1	0.5	2	1.1	0.62
Mild liver disease	50	28	14.3	22	11.7	0.54
Diabetes without complications	58	28	14.3	30	16.0	0.67
Diabetes with complications	16	7	3.6	9	4.8	0.62
Paralysis	2	1	0.5	1	0.5	1.00
Renal disease	29	12	6.1	17	9.0	0.34
AIDS	1	1	0.5	0	0.0	1.00

1L, first-line; 2L, second-line; AIDS, acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; HMO, health maintenance organization; r/mCC, recurrent or metastatic cervical cancer.

draft, Writing – review & editing.

Declaration of Competing Interest

Kalyani Sonawane has received consulting fees from, and has held a leadership role with Value Analytics Labs; Jie Ting is an employee of, and holds stock in Seagen Inc.; Andy Surinach is an employee of Genesis Research, which received consulting fees from Seagen Inc. in connection with this study; Jagpreet Chhatwal received funding from Seagen Inc. in connection with this study, and has received consulting fees and honoria from Novo Nordisk, and Bayer; Turgay Ayer received funding from

4

Table 3
Likelihood of receipt of 2L treatment among 1L treated patients with r/mCC.

Effect	Odds Ratio*	95 % Confidence Limits		P-value
Age	1.01	0.99	1.04	0.33
Region				
South versus Northeast	0.43	0.23	0.84	0.03
Midwest versus Northeast	0.52	0.28	0.95	0.01
West versus Northeast	0.64	0.29	1.40	0.26
Plan type (Non-HMO vs HMO)	1.23	0.64	2.38	0.53
Group type (Medicare vs. commercial)	0.79	0.35	1.75	0.55
Bevacizumab history (No vs Yes)	0.65	0.43	0.99	0.04
Charlson Comorbidity Index	0.96	0.81	1.14	0.65

1L, first-line; 2L, second-line; HMO, health maintenance organization; r/mCC, recurrent or metastatic cervical cancer.
*Odds ratio and 95% confidence limits for multivariable logistic regression model simultaneously adjusted for age, region, plan type, group type, bevacizumab treatment history, and comorbidity index.

References

Alholm, Z., He, D., Ting, J., Zhang, Y.J., Sudharshan, L., Leong, T., Coleman, R.L., Monk, B.J., 2022. Real-world treatment drop-off among recurrent or metastatic cervical cancer patients: a US community oncology-based analysis. Gynecol. Oncol. 166 (3), 567–575.

Alimena, S., Davis, M., Pelletier, A., Terry, K., King, M., Feldman, S., 2021. Regional variation in access to oncologic care and racial disparities among cervical cancer patients. Gynecol. Oncol. 162, S261.

Barrington, D.A., Dilley, S.E., Landers, E.E., Thomas, E.D., Boone, J.D., Straughn, J.M., et al., 2016. Distance from a Comprehensive Cancer Center: a proxy for poor cervical cancer outcomes? Gynecol. Oncol. 143, 617–621.

National Cancer Institute: Surveillance, Epidemiology, and End Results Program (SEER*Explorer), Cervix Uteri Cancer Stage Distribution of SEER Incidence Cases, 2008-2017, https://seer.cancer.gov/statistics-network/explorer/application.html (Accessed January, 2022).

National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, Cancer Stat Facts: Cervical Cancer, https://seer.cancer.gov/statfacts/html/cervix.html (Accessed August 11, 2022).

Chen, H.-H., Meng, W.-Y., Li, R.-Z., Wang, Q.-Y., Wang, Y.-W., Pan, H.-D., et al., 2021. Potential prognostic factors in progression-free survival for patients with cervical cancer. BMC Cancer 21, 531.

Colombo, N., Dubot, C., Lorusso, D., Caceres, M.V., Hasegawa, K., Shapira-Frommer, R., Tewari, K.S., Salman, P., Hoyos Usta, E., Yañez, E., Gümüş, M., Olivera Hurtado de Mendoza, M., Samouëlian, V., Castonguay, V., Arkhipov, A., Toker, S., Li, K., Keefe, S.M., Monk, B.J., 2021. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N. Engl. J. Med. 385 (20), 1856–1867.

Endo, D., Todo, Y., Okamoto, K., Minobe, S., Kato, H., Nishiyama, N., 2015. Prognostic factors for patients with cervical cancer treated with concurrent chemoradiotherapy: a retrospective analysis in a Japanese cohort. J. Gynecol. Oncol. 26, 12–18.

Hung, P., Deng, S., Zahnd, W.E., Adams, S.A., Olatosi, B., Crouch, E.L., et al., 2020. Geographic disparities in residential proximity to colorectal and cervical cancer care providers. Cancer 126, 1068–1076.

Kato, M.K., Tanase, Y., Uno, M., Ishikawa, M., Kato, T., 2021. Brain metastases from uterine cervical and endometrial cancer. Cancers (Basel) 13 (3), 519.

Kim, T.-E., Park, B.-J., Kwack, H.-S., Kwon, J.-Y., Kim, J.-H., Yoon, S.-C., 2012. Outcomes and prognostic factors of cervical cancer after concurrent chemoradiation. J. Obstet. Gynaecol. Res. 38, 1315–1320.

Marabelle, A., Le, D.T., Ascierto, P.A., Di Giacomo, A.M., De Jesus-Acosta, A., Delord, J. P., et al., 2020. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J. Clin. Oncol. 38, 1–10.

McLachlan, J., Boussios, S., Okines, A., Glaessgen, D., Bodlar, S., Kalaitzaki, R., Taylor, A., Lalondrelle, S., Gore, M., Kaye, S., Banerjee, S., 2017. The impact of systemic therapy beyond first-line treatment for advanced cervical cancer. Clin. Oncol. (R. Coll Radiol.) 29 (3), 153–160.

Musa, F.B., Brouwer, E., Ting, J., Schwartz, N.R.M., Surinach, A., Bloudek, L., Ramsey, S. D., 2022. Trends in treatment patterns and costs of care among patients with advanced stage cervical cancer. Gynecol. Oncol. 164 (3), 645–650.

Pfaendler, K.S., Tewari, K.S., 2016. Changing paradigms in the systemic treatment of advanced cervical cancer. Am. J. Obstet. Gynecol. 214 (1), 22–30.

Ricci, S., Tergas, A.I., Long Roche, K., Fairbairn, M.G., Levinson, K.L., Dowdy, S.C., Bristow, R.E., Lopez, M., Slaughter, K., Moore, K., Fader, A.N., 2017. Geographic disparities in the distribution of the U.S. gynecologic oncology workforce: a Society of Gynecologic Oncology study. Gynecol. Oncol. Rep. 22, 100–104.

Rose, P.G., Java, J., Whitney, C.W., Stehman, F.B., Lanciano, P., Thomas, G.M., DiSilvestro, P.A., 2015. Nomograms Predicting Progression-Free Survival, Overall Survival, and Pelvic Recurrence in Locally Advanced Cervical Cancer Developed From an Analysis of Identifiable Prognostic Factors in Patients From NRG Oncology/Gynecologic Oncology Group Randomized Trials of Chemoradiotherapy. J. Clin. Oncol. 33 (19), 2136–2142.

Spees, L.P., Brewster, W.R., Varia, M.A., Weinberger, M., Baggett, C., Zhou, X., et al., 2019. Examining urban and rural differences in how distance to care influences the initiation and completion of treatment among insured cervical cancer patients. Cancer Epidemiol. Biomarkers & Prev. 28 (5), 882–889.

Temkin, S.M., Fleming, S.A., Amrane, S., Schluterman, N., Terplan, M., 2015. Geographic disparities amongst patients with gynecologic malignancies at an urban NCI-designated cancer center. Gynecol. Oncol. 137 (3), 497–502.

Tewari, K.S., Sill, M.W., Long, H.J., Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., Oaknin, A., Reid, T.J., Leitao, M.M., Michael, H.E., Monk, B.J., 2014. Improved survival with bevacizumab in advanced cervical cancer. N. Engl. J. Med. 370 (8), 734–743.

U.S. Food & Drug Administration, 2021. FDA grants accelerated approval to tisotumab vedotin-tftv for recurrent or metastatic cervical cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer (Accessed August 11, 2022).

Zhang, Y., Guo, X., Wang, G., Ma, W., Liu, R., Han, X., Li, L., Baklaushev, V.P., Bryukhovetskiy, A.S., Wang, W., Wang, X., Zhang, C., 2018. Real-world study of the incidence, risk factors, and prognostic factors associated with bone metastases in women with uterine cervical cancer using surveillance, epidemiology, and end results (SEER) data analysis. Med. Sci. Monit. 24, 6387–6397.