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Survival differences by race and surgical approach in early-stage operable cervical Cancer

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HIGHLIGHTS

- Black patients are less likely to have minimally invasive surgery; open surgery is superior for cervical cancer.
- OS for Black patients who had open procedures was similar to White patients who had MIS procedures.
- Receipt of guideline-concordant care was significantly lower in Black patients.
- Social Determinants of Health were identified as significantly different among Black patients compared to White patients.
- Patients with private insurance had a higher probability of survival than patients with Medicaid or Medicare coverage.

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ABSTRACT

Objective. To evaluate if the higher rate of open radical hysterectomy in Black patients, prior to the widespread return to open surgical techniques, mitigated survival disparities and to identify other actionable factors to target for systemic change.

Methods. This is a retrospective cohort study including patients from the National Cancer Database with cervical cancer who underwent radical hysterectomy from 2010 to 2018. Patient demographics, clinical characteristics and survival were compared by race and surgical route. Kaplan-Meier plots were constructed. Cox proportional hazards modeling was used to adjust for covariates.

Results. 7201 patients were eligible for inclusion, 687 (9.5%) Black and 4870 (68%) White. We found that 51% of Black patients and 39% of White patients underwent open surgery. Black patients were 10% less likely to receive Guideline Concordant Care (GCC). Those with publicly-funded insurance had a 40% higher hazard of death compared to private insurance (CI 1.19–1.73 $p < 0.001$). Black patients who had open surgery had similar 5-year survival compared to White patients who had MIS surgery (0.90 vs 0.91, NS). After adjusting for potential confounders including age, insurance, nodal status, and lymphovascular space invasion, Black patients who had surgery had a 40% higher hazard for death (HR 1.40 95% CI 1.10–1.79, $p = 0.007$) compared to White patients.

Conclusions. A lower 5 and 10-year survival was seen in Black patients, regardless of surgical approach. Adjustment for significant covariates did not resolve this disparity, confirming that these factors do not fully account racial disparities.

1. Introduction

Due to effective screening and dysplasia treatment, death from cervical cancer has dramatically decreased in American patients. Despite improvements in prevention and early detection, an estimated 4310 U.S. patients will lose their lives to cervical cancer in 2023 [19]. Patients of historically disadvantaged racial and ethnic groups suffer an unequal disease burden compared to White patients. Black patients have been shown to receive human papilloma virus (HPV) testing less frequently, less appropriate colposcopic follow up, and have a higher rate of cervical cancer precursor lesions than their white counterparts [1,20]. These failures have serious ramifications since cancer outcomes are better when cervical cancer is diagnosed in early stages through screening, when most patients are asymptomatic [21].

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Subsequently, Black patients disproportionately experience and die from cervical cancer. It is also important to understand that race is a socially-based construct, and not biologically based, and thus these disparities should be interpreted as ways in which the environmental, interpersonal and inherited aspects of systemic racism impact Black patients [2]. When rate-adjusted for hysterectomy for benign indications, Black patients had an even higher mortality rate at 10.1 per 100,000 compared to 4.7 per 100,000 deaths in White patients [3]. Black patients have consistently been found to have a higher cancer stage at diagnosis, and Black patients' 5- year survival (5YS) is decreased at all stages [22–25]. The disparity in cervical cancer outcomes has been reduced but not resolved in recent decades [26,27]. Previously-identified reasons for some of these disparities include: a lower receipt of adjuvant radiation and disposition to the improper treatment for stage [4,18]. Differences in insurance status and treatment in Black cervical cancer patients have been found to contribute to disparities [28]. Wu et al. developed the concept of Guideline Concordant Care (GCC) to determine the completeness of a patient's evaluation in a standardized fashion, and found that receipt of GCC mitigated the adverse outcomes associated with insurance disparities [28]. Black patients are less likely to receive minimally invasive hysterectomy (MIS), independent of uterine size [29]. Though better examined in benign gynecology, this disparity likely affects the surgical care of Black women with gynecologic malignancies as well. In 2018, patients enrolled in the Laparoscopic Approach to Cervical Cancer (LACC) trial who received MIS for operable cervical cancer were found to have increased mortality compared with those who had an open approach (HR 1.65 for MIS) [5]. Retrospective analyses corroborated this finding, and a practice-changing shift to open surgery was made [6]. The objective of our research was to evaluate if the disparity in survival by race was mitigated by a higher rate of open hysterectomy procedures in Black patients with operable invasive cervical cancer compared to White patients. Secondary outcomes include investigation of the effect of factors including adverse pathologic risk factors, treatment, or social determinants of health (SDoH) on survival.

2. Methods

This was a retrospective cohort study abstracting data from the 2022 National Cancer Database (NCDB) Participant Use File (PUF) [7]. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB contains clinical oncology information from 1500 CoC-accredited facilities nationwide, including patient demographics, treatment, and outcomes information documented by local tumor registrars. The NCDB PUF captures 70% of new cancer cases nationwide and 10% of case abstracts are reviewed by NCDB site surveyors to maintain accuracy [7]. This study was granted exemption through the University of Texas at Austin Institutional Review Board. In the NCDB, *race and ethnicity are collected from electronic medical records (EMR), billing records, or self-reported.*

The NCDB was queried for all patients with a new diagnosis of cervical cancer between January 1, 2010 and December 31, 2018. Patients with stages IA1 with positive lymphvascular space invasion (+LVSI), IA2, and IB disease who had undergone radical hysterectomy between 2010 and 2018 were included in this study. All histologies and tumor sizes were included; histologies were categorized into squamous, adenocarcinoma, and "other." If tumor size was not documented, it was extrapolated from the T category of the Tumor, Node, Metastasis (TNM) clinical staging variable as defined by the American Joint Committee on Cancer (AJCC), 8th Edition [30]. Clinical stage was assigned as previously published using clinical TNM stage group if available, followed by the Site-Specific Factor 1 International Federation of Gynecology and Obstetrics (FIGO) criteria, and finally by AJCC TNM pathologic stage group if neither clinical stage group nor FIGO stage were available [30]. All codes for radical hysterectomy were included, including modified and extended radical hysterectomy. Patients who had no documented staging information, were missing surgical approach, received neoadjuvant treatment, did not pursue treatment at the facility of diagnosis, were missing months between diagnosis and last contact, or for whom cervical cancer was not their primary diagnosis, were excluded (Fig. 1).

A guideline-concordant care (GCC) variable was constructed and defined by completeness of documentation of the following: histology, invasive pathology, regional lymph node evaluation, staging (clinical or TNM), tumor size, LVSI, and completion of adjuvant treatment in <60 days. If all the above items were present, a "yes" was assigned, and if any were missing, a "no" was assigned. A second validating GCC variable using Wu et al.'s definition was also used [28].

Demographic and clinical factors were summarized and compared by patient race using Pearson's x2 tests. Kaplan-Meier curves stratified by race and surgical route were constructed. Unadjusted hazard ratios and relative risks were calculated between surgical approach and race to define a baseline comparator prior to the inclusion of covariates in the model. Cox proportional hazards regression was used to calculate crude adjusted hazard ratios (HR) to assess associations between race and survival. Any variable that had a p-value of 0.0–0.20 or less in unadjusted analysis or that was known to be a potential confounder was considered during variable selection for the adjusted model. Model fit was assessed using likelihood ratio tests. Tests of Schoenfeld residuals were used to assess the assumption of proportional hazards for each variable and globally. The final model controlled for surgical approach, nodal status, Charlson-Deyo score, LVSI, and insurance type. Age category, tumor size, and histology were included as stratifying variables due to non-proportional hazards of these variables over time. Not included in the final model were stage, nodes examined, nodes positive, guideline-concordant care, income, education, geographic location, and facility type. All analyses were conducted using R version 4.2.2 using the *survminer* and *survival* packages.

3. Results

The screened cohort included 12,240 patients (8232 non-Hispanic White, 1271 non-Hispanic Black, 1789 Hispanic, 948 Other). A total of 7201 operable stage IA1 + LVSI, IA2, and IB2 cancer patients were eligible for inclusion in this study, of whom 687 were non-Hispanic Black, 4870 were non-Hispanic White, and 1058 were Hispanic. Demographic and clinical characteristics of all patients are compared in Table 1.

In the descriptive analysis, the majority of variables examined differed significantly by race: Black patients had more open surgery than White patients (51% vs 39%):Black patients were more likely than White patients to have died (13% vs 9%), to have a Charlson-Deyo score of 1 or more (20.4% vs 13.6%), have larger tumors (<2 cm; 37% vs 42%), and have government insurance or be uninsured (government 43% vs 30% and uninsured 7.7% vs 3.2%). Black patients were also more likely to live in neighborhoods with a high proportion of low-income households (<$40,227 median household income; 39% vs 13%), and lower educational status (>17.6% neighborhood percentage without high school degree 40% vs 15%), to receive care from a facility in a southern US region (33% vs 23%), and to be treated at an academic/training facility (35% vs 27%). Additionally, the rate of GCC for Black v White patients was 10% lower (41% vs 51%) with similar results by Wu et al.'s stricter definition at (35% vs 45%). Receipt of chemotherapy and radiation was similar in both groups. Black patients had a higher rate of undocumented tumor size (17% vs 12%) and undocumented or unknown lymph node status (3.6% vs 2.2%). The median follow-up time was 4.82 years (IQR 4.07) for Black patients and 4.87 (IQR 4.06) years for White patients.

Figure 2 shows Kaplan-Meier survival curves by surgical approach and race. Black patients have the lowest overall survival regardless of surgical approach, followed by White, then Hispanic patients. Figure 3 shows survival by race alone. The unadjusted relative risk (RR) for

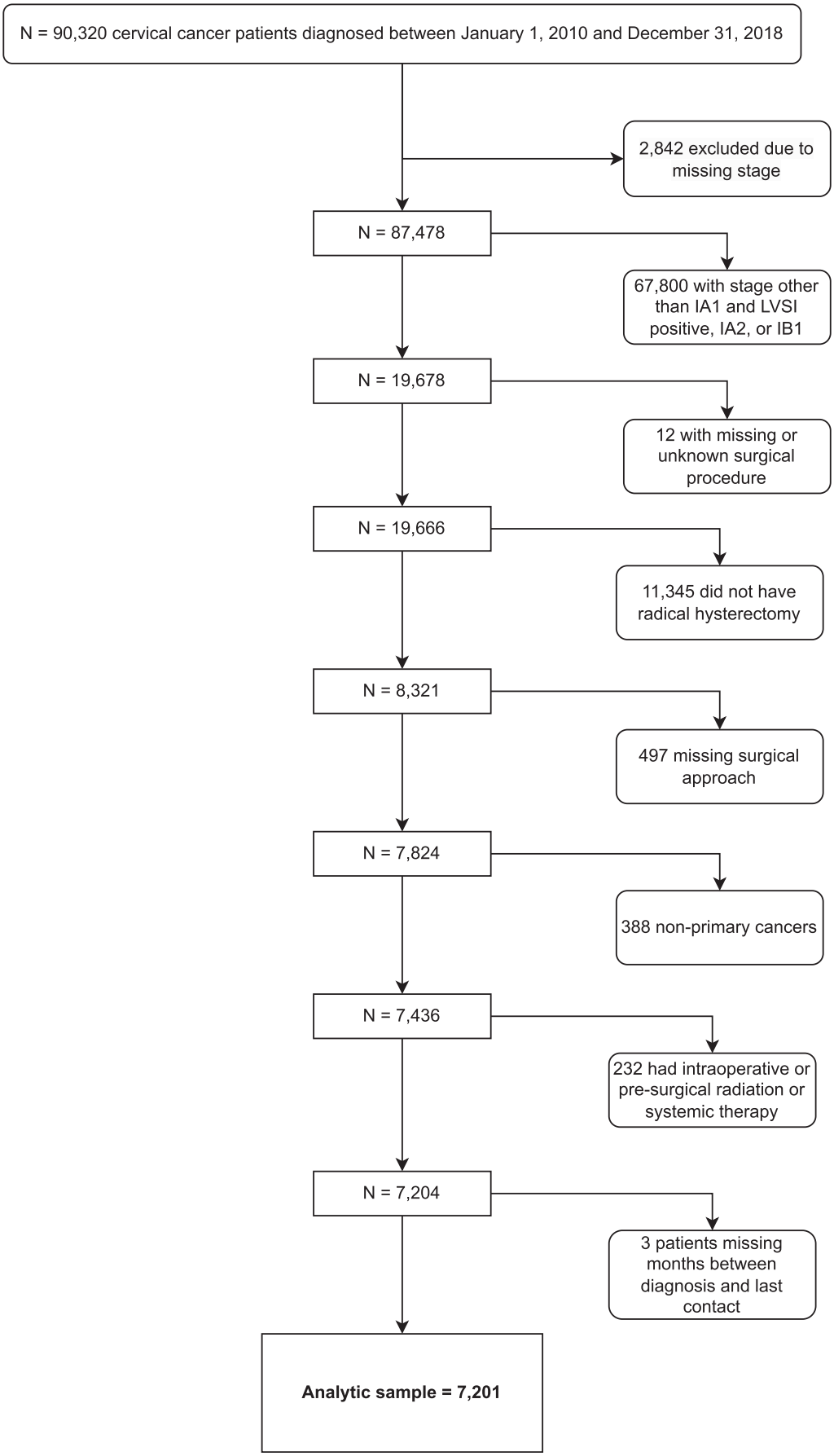

Fig. 1. Study Inclusion/Exclusion Diagram.

Table 1
Study subject characteristics and demographics. MIS = minimally invasive surgery.

Patient demographics.						
Characteristic	Overall, $N = 7201$[1]	WHITE, NH, $N = 4870$[1]	BLACK, NH, $N = 687$[1]	HISPANIC, $N = 1058$[1]	OTHER, NH, $N = 586$[1]	p-value[2]
Vital Status						<0.001
Alive	6596 (92%)	4433 (91%)	601 (87%)	1010 (95%)	552 (94%)	
Dead	605 (8.4%)	437 (9.0%)	86 (13%)	48 (4.5%)	34 (5.8%)	
Surgical approach						<0.001
OPEN/NOS	2943 (41%)	1875 (39%)	348 (51%)	481 (45%)	239 (41%)	
MIS	4258 (59%)	2995 (61%)	339 (49%)	577 (55%)	347 (59%)	
Tumor size						<0.001
<2 cm	2982 (41%)	2064 (42%)	251 (37%)	408 (39%)	259 (44%)	
>4 cm	493 (6.8%)	356 (7.3%)	48 (7.0%)	58 (5.5%)	31 (5.3%)	
2–4 cm	2785 (39%)	1865 (38%)	272 (40%)	437 (41%)	211 (36%)	
UNKNOWN	941 (13%)	585 (12%)	116 (17%)	155 (15%)	85 (15%)	
Stage at diagnosis						0.3
1A1 + LVSI	194 (2.7%)	142 (2.9%)	12 (1.7%)	30 (2.8%)	10 (1.7%)	
1A2	869 (12%)	578 (12%)	93 (14%)	131 (12%)	67 (11%)	
1B1	6138 (85%)	4150 (85%)	582 (85%)	897 (85%)	509 (87%)	
Histology						<0.001
Adenocarcinoma	2951 (41%)	2181 (45%)	149 (22%)	395 (37%)	226 (39%)	
Other	247 (3.4%)	165 (3.4%)	19 (2.8%)	38 (3.6%)	25 (4.3%)	
Squamous	4003 (56%)	2524 (52%)	519 (76%)	625 (59%)	335 (57%)	
Nodes examined						0.13
Yes	7043 (98%)	4768 (98%)	664 (97%)	1034 (98%)	577 (98%)	
No or NA/Unknown	158 (2.2%)	102 (2.1%)	23 (3.3%)	24 (2.3%)	9 (1.5%)	
Nodes positive						0.2
No	6370 (88%)	4318 (89%)	605 (88%)	927 (88%)	520 (89%)	
Yes	667 (9.3%)	446 (9.2%)	57 (8.3%)	107 (10%)	57 (9.7%)	
Charlson-Deyo score						<0.001
0	6221 (86%)	4221 (87%)	549 (80%)	951 (90%)	500 (85%)	
1	779 (11%)	523 (11%)	101 (15%)	84 (7.9%)	71 (12%)	
2+	201 (2.8%)	126 (2.6%)	37 (5.4%)	23 (2.2%)	15 (2.6%)	
Insurance type						<0.001
Private	4352 (60%)	3235 (66%)	336 (49%)	440 (42%)	341 (58%)	
Government	2396 (33%)	1477 (30%)	298 (43%)	410 (39%)	211 (36%)	
Uninsured	453 (6.3%)	158 (3.2%)	53 (7.7%)	208 (20%)	34 (5.8%)	
Lymph vascular invasion						0.054
No	4223 (59%)	2843 (58%)	430 (63%)	602 (57%)	348 (59%)	
Yes	2336 (32%)	1598 (33%)	212 (31%)	351 (33%)	175 (30%)	
Received guideline-concordant care						<0.001
Yes	3455 (48%)	2478 (51%)	282 (41%)	425 (40%)	270 (46%)	
No	3746 (52%)	2392 (49%)	405 (59%)	633 (60%)	316 (54%)	
Received guideline-concordant care (Wu et al. criteria)						<0.001
Yes	3053 (42%)	2199 (45%)	249 (36%)	370 (35%)	235 (40%)	
No	4148 (58%)	2671 (55%)	438 (64%)	688 (65%)	351 (60%)	
Neighborhood median household income quartiles						<0.001
≥$63,333	2109 (29%)	1548 (32%)	111 (16%)	223 (21%)	227 (39%)	
$40,227–$50,353	1416 (20%)	975 (20%)	134 (20%)	221 (21%)	86 (15%)	
$50,354–$63,332	1490 (21%)	1052 (22%)	87 (13%)	219 (21%)	132 (23%)	
<$40,227	1254 (17%)	625 (13%)	271 (39%)	283 (27%)	75 (13%)	
Not Available	932 (13%)	670 (14%)	84 (12%)	112 (11%)	66 (11%)	
Neighborhood percentage without high school degree						<0.001
≥17.6%	1685 (23%)	711 (15%)	278 (40%)	537 (51%)	159 (27%)	
<6.3%	1337 (19%)	1096 (23%)	41 (6.0%)	81 (7.7%)	119 (20%)	
10.9%–17.5%	1606 (22%)	1122 (23%)	180 (26%)	191 (18%)	113 (19%)	
6.3%–10.8%	1652 (23%)	1280 (26%)	104 (15%)	139 (13%)	129 (22%)	
Not Available	921 (13%)	661 (14%)	84 (12%)	110 (10%)	66 (11%)	
Facility location						<0.001
Midwest	1128 (16%)	925 (19%)	97 (14%)	57 (5.4%)	49 (8.4%)	
Northeast	816 (11%)	536 (11%)	81 (12%)	102 (9.6%)	97 (17%)	
South/Southeast	1690 (23%)	1106 (23%)	227 (33%)	257 (24%)	100 (17%)	
West	982 (14%)	563 (12%)	29 (4.2%)	210 (20%)	180 (31%)	
Facility type						<0.001
Academic/Research Program	2149 (30%)	1339 (27%)	241 (35%)	353 (33%)	216 (37%)	
Community Cancer Program	73 (1.0%)	43 (0.9%)	5 (0.7%)	16 (1.5%)	9 (1.5%)	
Comprehensive Community Cancer Program	1467 (20%)	1079 (22%)	97 (14%)	170 (16%)	121 (21%)	
Integrated Network Cancer Program	927 (13%)	669 (14%)	91 (13%)	87 (8.2%)	80 (14%)	
Not Available	2585 (36%)	1740 (36%)	253 (37%)	432 (41%)	160 (27%)	

[1] n (%).
[2] Pearson's Chi-squared test.

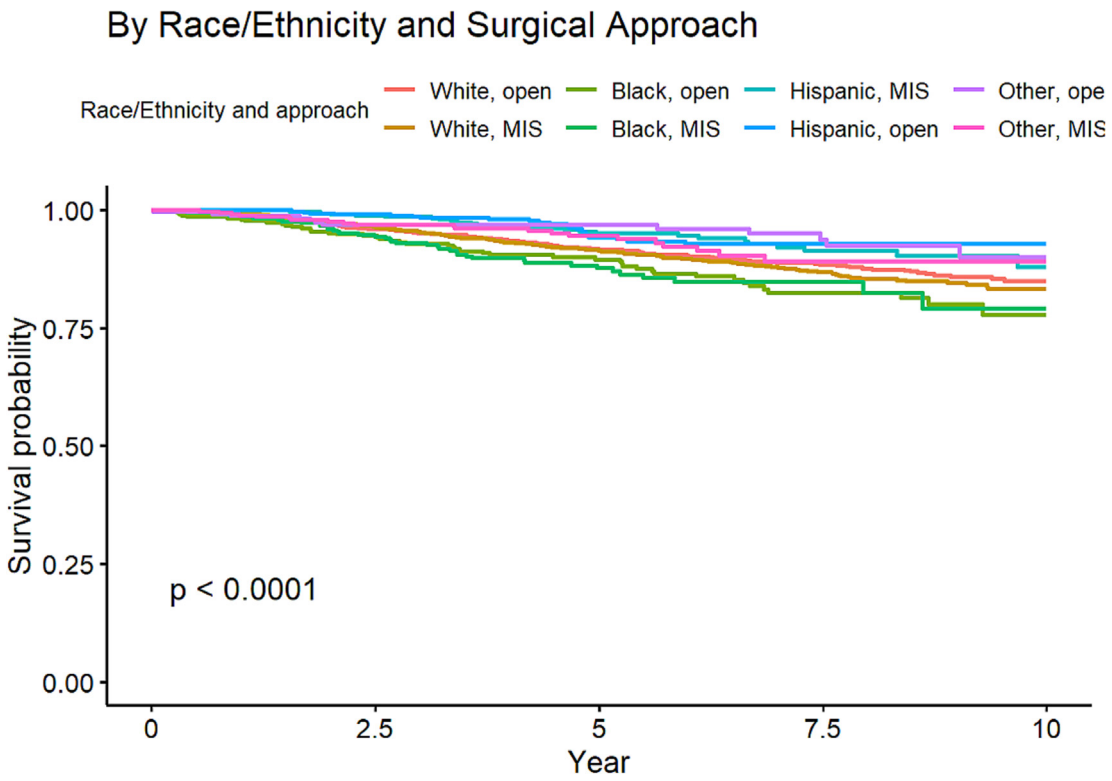

Fig. 2. Kaplan-Meier plot of survival probability following radical hysterectomy for Black and White patients, stratified by open and minimally invasive surgery. Not adjusted for clinical and other demographic variables.Use the "Insert Citation" button to add citations to this document.

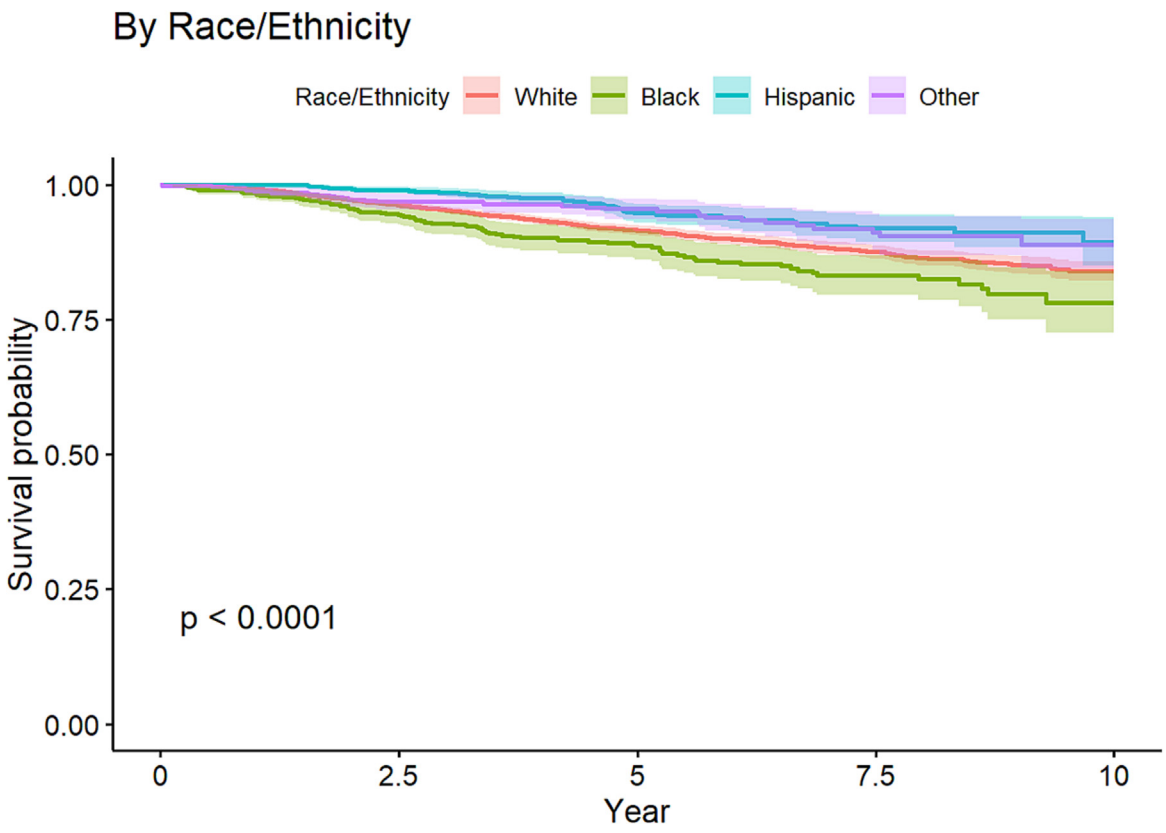

Fig. 3. Kaplan-Meier plot of overall survival by race in our entire cohort.

death in Black patients who had open surgery compared to white patients who had MIS surgery was 1.3 (CI 0.941–1.80, $p = 0.0115$). The unadjusted RR for Black patients compared to White patients who had open surgery was 1.45 (CI 1.075–1.98, p 0.0154) and for Black patients to White patients with MIS surgery was 1.33 (0.5681–1.8096, $p = 0.0789$). When comparing Black patients with open surgery to White patients with MIS surgery, the 5Y survival was 0.90 compared to 0.91, NS). In Cox regression models, the unadjusted hazard of death for Black patients was 1.44 (1.14–1.81 $p = 0.002$). This hazard ratio remained similar after adjusting for potential confounders (HR 1.40 (95% CI 1.02–1.79 $p = 0.007$). Adjusted hazard ratios are shown in Table 2. When adjusted for confounders significantly associated with death in our comparative analysis, the HR for death for MIS compared with open surgery was 1.21 (1.02–1.43, $p = 0.026$). Mortality risk increased with LVSI (HR: 1.38, CI 1.15–1.67, p = 0.002), node positivity (HR 1.81 CI 1.45–2.25, $p < 0.001$), Charlson-Deyo score (HR 1.57 for 2+ CI 1.08–2.29 $p = 0.018$), and government insurance (1.43 CI 1.19–1.73 p < 0.001) (see Table 2).

4. Discussion

This research used a national cancer database to examine survival outcomes by race following surgical treatment for early cervical cancer. We identified that Black patients with operable cervical cancer had a decreased 5 and 10-year survival, regardless of surgical route, even when compared to White patients who underwent less-optimal MIS for cervical cancer. The increased rate of open surgery in Black patients did not resolve the survival disparity, but outcomes in Black patients who received the more optimal surgical approach were similar to White patients who received an inferior one. This study is consistent with current literature reporting open surgery's superiority to MIS. [5,6] As stated in a collective statement by the American College of Obstetrics and Gynecology and the Society of Gynecologic Oncology, "recognizing that race is a social construct, not biologically based, is important to understanding that racism, not race, impacts health care, health, and health outcomes." [31] It is, therefore, critical to recognize that other sources of these disparities, such as environmental and social factors exist and should be investigated.

Table 2
Adjusted cox proportional hazards model[1].

Characteristic	HR[1]	95% CI[2]	p-value
Surgical approach			
OPEN/NOS	–	–	
MIS	1.21	1.02, 1.43	0.026
Race/Ethnicity			
WHITE, NH	–	–	
BLACK, NH	1.40	1.10, 1.79	0.007
HISPANIC	0.52	0.38, 0.71	<0.001
OTHER, NH	0.62	0.43, 0.89	0.009
Charlson-Deyo score			
0	–	–	
1	1.32	1.05, 1.67	0.019
2+	1.57	1.08, 2.29	0.018
Lymph vascular invasion			
No	–	–	
Unknown	1.00	0.71, 1.39	>0.9
Yes	1.38	1.15, 1.67	<0.001
Nodes positive			
No	–	–	
N/A or Unknown	1.02	0.57, 1.80	>0.9
Yes	1.81	1.45, 2.25	<0.001
Insurance type			
Private	–	–	
Government	1.43	1.19, 1.73	<0.001
Uninsured	1.12	0.77, 1.63	0.6

[1] Age category, tumor size, and histology were included as stratifying variables.
[2] HR = Hazard Ratio, CI = Confidence Interval.

Some clinical and demographic factors were disproportionately elevated in Black patients and were associated with an increased hazard of death. Adjustment for these factors did not attenuate the survival disparity experienced by Black patients (unadjusted HR 1.44 and adjusted HR 1.40), demonstrating that factor effects not included in our model worsened outcomes for Black patients. The variables we did examine and were statistically significant merit attention due to their importance in prognosis and treatment planning. We found that Black patients were 9% less likely to receive GCC. Guideline adherence has been associated with significantly improved outcomes for all patients, possibly by bias reduction via standardization [32]. Despite this information, studies have found that only 47% of early cervical cancer patients receive GCC, yielding inferior survival outcomes as seen here [28,32]. GCC outcomes in cervical cancer compare to published outcomes in lung cancer, with lower OS in racial groups who do not receive the standard of care [8]. A comparable study in patients with ovarian cancer showed analogous poor outcomes when GCC was not followed, with stark disparities seen between between Black and White patients [9]. Clinical trial enrollment, with strict adherence to protocols, has shown equalization of outcomes between Black and White patients and reduced disparities in survival [32]. Electronic medical record (EMR) reminders have previously proven beneficial in reminding physicians about clinical trial eligibility, and may be an effective method to aid in care standardization, including documentation of tumor size, stage, and nodal evaluation [10,33]. Benchmarking GCC via the EMR can improve disparities in cancer survival, and allow provider targeting for improvement [33]. However, GCC is unlikely to correct all disparities due to their multifactorial etiology. We believe that future investigations could focus on the standardization of care via a checklist and patient navigation. An example checklist is presented in Appendix A.

Discrimination permeates care in a variety of ways. Identification of interpersonal bias among health care providers starts with awareness, followed by conversations and teaching [10]. Systemic racism and adverse SDoH affect both medicine and our entire society, which in turn affects our patients' health [10]. Sources of adverse outcomes may include neighborhood segregation, employment opportunities, and poor investment in housing and schools. Necessary improvements also include increased access to healthy foods and active lifestyles, enabled by the creation of safe spaces and recreational options [10]. These investments drive population health [33]. Community partnerships, outreach, and positive media will build towards better survival through education, trust, and economic support [11]. Additionally, universal patient screening for social services needs has been shown to improve patient receipt of resources [10].

Insurance status also creates personal, logistical, and systemic obstacles [10]. In our study, Black patients were more likely to have government-funded insurance, which was associated with a higher hazard of death. Poor reimbursement from government-funded insurance is one of many mediators of poor outcomes and inequitable care [10,12,16,33]. Poor reimbursement of brachytherapy leading to decreased brachytherapy access is a notable example of funding-related limitations of quality cervical cancer care [13,14]. Affordability of all levels of treatment could be accomplished with a national insurance overhaul or via improved reimbursement within plans available through commercial or government insurance. Universal network inclusion of gynecologists and gynecologic oncologists would also improve access. To eliminate cost barriers, out-of-pocket costs for secondary and tertiary prevention could be reduced or eliminated [15]. Additional research can include health services and implementation research, clinical trials, basic and translational research, and prevention research.

Strengths of this study include a large sample size, a long length of follow-up, and national data from a cancer-specific database. We were also able to include SDoH factors that play heavily into disease outcomes. Limitations in our study are related to the database as well as the sociocultural context of race. The NCDB can only compile

information from Committee on Cancer-accredited facilities, and therefore this was not a population-based sample, was dependent on information available in the EMR, and analysis was limited to available variables. We recognize that survival disparities are multifactorial and there is a lack of data on certain SDoH such as neighborhood and environment, as well as genetic and molecular components of cervical cancer. We also recognize the complexity of the applied racial categorizations as highly simplified, which leads to overgeneralization and can disregard the interactions between ancestry and environment-related epigenetic changes that admix with SDoH [32].

In conclusion, this study demonstrated that the risk of mortality for Black patients undergoing surgical management of operable cervical cancer was higher than that for White patients. Despite more commonly receiving an open surgical approach for radical hysterectomy, the 5-year and 10-year survival remained lower than that of White patients following either open or minimally invasive surgery. While this study provided insight into some explanatory factors, the persistent elevation of the hazard ratio in our adjusted model indicates that known modifiers of mortality do not mitigate these racial disparities and further investigation is needed.

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CRediT authorship contribution statement

Rebekah Summey: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization. **Mchelle Benoit**: Methodology, Formal Analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing. **M. Yvette Williams-Brown**: Conceptualization, Methodology, Resource Acquisition, Data Curation, Writing - Review & Editing, Supervision.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.10.015.

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