

CLINICAL DETERMINANTS OF SURVIVAL FROM STAGE IB CERVICAL CANCER IN AN INNER-CITY HOSPITAL

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This study reviewed a high-risk population of inner-city women with FIGO (International Federation of Gynecologists and Obstetricians) stage Ib cervical cancer diagnosed and treated at a single institution between 1986 and 1993. The patient age at diagnosis averaged 49 years, and most of the patients were black (83%). Squamous carcinomas predominated (75%). Radiotherapy was the most frequent treatment modality (49%), followed by surgery (38%) and combined radiation/surgery (13%). The Kaplan-Meier estimated 4-year survival for all patients completing treatment was 81%. Increased survival was significantly associated with therapy. The Kaplan-Meier estimated survival at 26 months (the time of the last death in radiotherapy patients) was 66% for radiotherapy patients and 100% for those treated with surgery. Radiotherapy patients differed from surgery patients in age, tumor size, and pelvic lymph node status, indicating that treatment selection bias could explain the observed difference in survival. Age, race, histology, and cervical lesion size were not significantly associated with survival. (*J Natl Med Assoc.* 1998;90:303-308.)

Key words: cervical cancer ♦ blacks
♦ urban hospitals

Cervical cancer survival and treatment are highly dependent on clinical stage. Stage Ia disease is usually treated surgically and has a favorable prognosis. Stages II and III have less favorable survival rates and are, with few exceptions, treated with radiotherapy. Treatment options for stage Ib cervical cancer include radiotherapy, surgery, or a combination of both. Treatment selection criteria and the relationship between treatment type and outcome for stage

Ib patients are poorly defined.^{1,2} Factors such as age,³ tumor size,^{4,5} histologic type,^{6,7} and nodal status^{6,7} have all been reported to influence treatment selection decisions and prognosis for stage Ib patients.

Treatment selection for patients with cervical cancer is complicated by marked regional and racial differences in survival. An estimated 15,700 new cases were diagnosed in the United States in 1996, resulting in 4900 deaths.⁸ The highest mean annual cervical cancer death rates occur in Georgia and the surrounding southeastern states (5.2 per 100,000 compared with 3.3 in the general population).⁹ While it is likely that much of this difference in survival is due to more advanced disease at diagnosis, reflecting a lack of access to effective screening programs, there are little data on the distribution of prognostic factors within this population.¹⁰ Currently half of newly diagnosed cervical cancers are stage I. This proportion should increase with improvements in screening, so that treatment selection for patients with stage

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Ib cancers will become an increasingly important issue.

This study examined the clinical and pathologic determinants of survival from stage Ib cervical cancer in an urban medically indigent population diagnosed and treated at Grady Memorial Hospital and Clinics (GMHC), Atlanta, Georgia. Economic, racial, and social factors combined to place the study population at high risk for cervical cancer incidence and treatment failure. The prognostic influence of primary tumor size, histology, age, and lymph node status were examined in this high-risk population as part of an ongoing molecular epidemiology study of cervical cancer.

MATERIALS AND METHODS

Study Population

The study population included all women with FIGO (International Federation of Gynecologists and Obstetricians) stage Ib¹¹ cervical cancer diagnosed and treated at GMHC from January 1, 1986, through December 31, 1993. Grady Memorial Hospital and Clinics is a large, inner-city, public, tertiary-care hospital serving Fulton and DeKalb counties in Atlanta, Georgia. Patients diagnosed from 1986 through 1991 were identified by using the GMHC section of the Atlanta Surveillance, Epidemiology, and End Results (SEER) program, and patients diagnosed during 1992 and 1993 were identified by monitoring all visits to the gynecologic oncology and radiation oncology inpatient and outpatient services.

Clinical Data Collection

Clinical data were obtained by reviewing each patient's complete hospital record. These records included the inpatient chart (operative summaries, discharge summaries, pathology, and other consultations), outpatient clinic charts (staging, treatment, and follow-up), and the central computerized GMHC records system (pathology/radiology reports, discharge summaries, operative notes, and other medical admissions).

Information recorded included race, age at diagnosis, FIGO clinical stage, tumor histology, date of diagnosis, specifics of treatment, date of failure, site of failure, date of last follow-up, clinical status, and vital status (alive or dead) at last follow-up through December 1995. All surgical pathology slides and reports relating to each patient's diagnosis and treatment of cervical cancer were reviewed by one of the

authors (E.R.U.) to confirm histologic diagnosis.

Complete study protocols were approved by the Emory University and Centers for Disease Control and Prevention Human Subjects Committees. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of the study.

Statistical Analysis

Associations were tested between rows and columns in 2×2 or $R \times C$ contingency tables using Fisher's exact test.^{12,13} To compare continuous variables, such as age, the nonparametric Wilcoxon rank sum test was used.¹⁴ Survival times were calculated from the date of staging. Kaplan-Meier plots were used to illustrate survival distributions for patient subgroups,¹⁵ and the generalized Wilcoxon rank sum statistic¹⁶ was used to test the equality of survival curves. The Wilcoxon rank sum test is more sensitive than the log rank test to detect differences in early deaths and uses data better with heavy censoring. The term "nonsignificant" indicates a significance level $>.05$. All significance tests were two-sided and exact *P* values¹⁷ were calculated. Analyses were performed using SAS (SAS Institute Corp, Cary, North Carolina) and StatXact (Cytel Software Corp, Cambridge, North Carolina) software.

RESULTS

Patient Population

A total of 48 women were diagnosed with FIGO stage Ib cervical cancer during the study period. Three patients failed to complete treatment at GMHC and were excluded from treatment-specific analyses. Of these, one was lost to follow-up and was excluded from survival analyses.

Patients ranged in age from 25 to 88 years (mean: 49 years; median: 46 years). Forty (83%) patients were black and the remainder white. Black patients were not significantly older (mean: 50 years; median: 48 years) than white patients (mean: 44 years; median: 38 years). Thirty-six (75%) patients had squamous cell carcinomas, 10 (21%) had adenosquamous or adenocarcinomas, and 2 (4%) had undifferentiated cancers.

Lymph Node Evaluation

Although lymph node evaluation is not used to determine FIGO clinical staging, 43 (90%) patients had information on pelvic or para-aortic lymph node status. Thirty-four (70.8%) of these patients had

computed tomography (CT) scans of the abdomen and pelvis. Of the patients evaluated by CT, 15 also had histopathologic examination of pelvic nodes. Histopathologic lymph node examination also was performed on an additional 9 patients without CT scans. Five (21%) of the 24 patients with histopathologic nodal evaluations had pelvic node metastases. Para-aortic involvement was not documented in any patient at the time of diagnosis.

Treatment

Of the 45 patients completing treatment at GMHC, 22 (49%) underwent curative radiotherapy, 17 (38%) underwent surgery, and 6 (13%) patients underwent both surgery and radiotherapy. Radiotherapy patients began treatment from 1 to 125 days after staging (mean: 26 days; median: 21 days). One patient with recurrent malignant lymphoma diagnosed synchronously with cervical cancer had a 125-day delay in onset of radiotherapy while undergoing multi-agent chemotherapy.

The treatment duration for external beam and intracavitary radiotherapy was 37 to 97 days (mean: 65; median: 62). All radiotherapy patients received external beam irradiation. External beam irradiation was delivered using either Cobalt 60, a 4-MV linear accelerator, or an 18- to 25-MV linear accelerator. All but one of the radiotherapy patients had one or two intracavitary brachytherapy insertions. The one exception was a patient who died of brain metastases during external beam radiotherapy and prior to intracavitary radiotherapy. Cesium 137 in Fletcher-Suit-Delclos afterloading intrauterine tandem and vaginal ovoids were used in all but one intracavitary radiotherapy; the exception being one patient who had high-dose rate applications using Iridium 192 afterloading sources. The radiotherapy combined total dose from external beam radiotherapy and intracavitary radiotherapy for those patients completing all planned treatment ranged from 63.9 to 100.8 Gy.

Sixteen (94%) of the women treated surgically underwent radical hysterectomies, and one underwent simple hysterectomy. Two of 5 patients treated with combined surgery and curative radiation therapy underwent radical hysterectomies followed by external beam radiotherapy and vaginal irradiation, which was done with Delclos vaginal domed cylinders or ovoids. These patients had deep cervical stromal invasion and close or positive surgical margins. The other 3 patients underwent preoperative

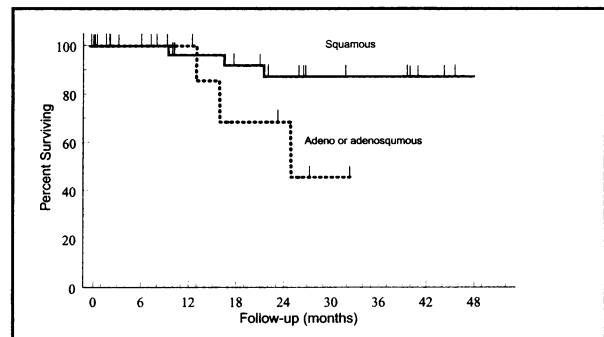


Figure. Kaplan-Meier estimated survival for radiotherapy versus surgery patients.

external beam radiotherapy and intracavitary radiotherapy followed by radical (2) or simple (1) hysterectomy. These patients had maximum primary tumor dimensions of at least 4 cm.

Overall Survival and Treatment-Specific Survival

Eight (17%) of the patients have died, and the Kaplan-Meier estimated 4-year survival of stage Ib cervical cancer patients who received treatment was 81%. Six deaths occurred between 10 and 26 months and the last death was at 52 months after diagnosis. Seven (87.5%) deaths occurred in women receiving radiotherapy, and 1 death occurred in a woman treated by preoperative radiotherapy and surgery who died of cervical cancer 52 months following treatment. Estimated survival at 26 months, when the last death for radiotherapy patients occurred, was 66% for women treated with radiotherapy and 100% among those treated with surgery ($P=.04$). (Figure).

Follow-up of the 39 surviving patients varied from 1 to 103 months (mean: 36 months; median: 34 months). Surviving women treated surgically underwent follow-up for a significantly shorter time (mean: 24 months; median: 23 months) than those treated with radiotherapy (mean: 48 months; median: 41 months) ($P=.01$, Wilcoxon).

The Table summarizes characteristics of patients according to treatment modality. Women treated with radiotherapy were significantly older than those treated with surgery ($P=.04$). Patients with cervical lesions >3 cm in diameter were significantly more likely to be treated with radiotherapy than surgery ($P=.04$). Histopathologic lymph node metas-

Table. Comparison of Surgery, Radiotherapy, and Combined Therapy Patients

	No (%) Radiotherapy (n=22)	No. (%) Surgery (n=17)	No. (%) Combined (n=6)
Mean /median age (years)*	56/56	45/43	37/37
Lesion size†			
<3 cm	6 (27.3)	10 (58.8)	2 (33.0)
3 to 6 cm	12 (50.0)	6 (35.3)	3 (50.0)
>6 cm	3 (12.5)	0	1 (20.0)
Not determined	1 (4.2)	1 (5.9)	0 (0)
Pathologic lymph node evaluations (no. positive/total no.)‡§			
Pelvic	3/3 (100)	0/17 (0)	1/3 (33.3)
Para-aortic	0/3 (0)	0/14 (0)	
Histology			
Squamous	15 (71.4)	14 (82.4)	4 (67.0)
Adenocarcinoma/adenosquamous	6 (28.6)	3 (17.6)	2 (33.0)
Race			
Black	19 (86.4)	15 (88.2)	3 (50.0)
White	3 (13.6)	2 (11.8)	3 (50.0)

* $P=.04$ (Wilcoxon) for radiotherapy versus surgery.
† $\chi^2=4.26$ and $P=.04$ for radiotherapy versus surgery.
‡One additional patient not completing radiotherapy had histopathologic pelvic node metastasis.

tases were all identified in radiotherapy patients ($P=.001$). While only 3 (13.6%) of 22 radiotherapy patients had histopathologic lymph node sampling, all 3 patients had positive nodes. One additional patient had pelvic lymph node metastases and was subsequently lost to follow-up. All patients treated with hysterectomy alone had pelvic or pelvic and para-aortic lymph-node sampling and none had metastases. Two of 5 patients treated with combined surgery and radiotherapy had pelvic lymph-node sampling; 1 had metastatic disease. There was no significant correlation between treatment and histology or race.

Other Findings

Because all but one death occurred in patients treated with radiotherapy, age, tumor size, histology, and pelvic node involvement were analyzed as possible predictors of survival in this group of patients. No significant associations were identified.

For all treatment modalities combined, survival was worse among patients with adenocarcinomas or adenosquamous carcinomas than for those with squamous carcinomas (62% versus 80%); this difference was not statistically significant ($P=.08$). There was no significant association between histology and

the variables of age, tumor size, and node involvement. Women who died were slightly older (mean: 54 years; median: 54 years) than those who survived (mean: 48 years; median: 46 years) ($P=.44$, Wilcoxon). Kaplan-Meier survival estimates were not significantly different for women older or younger than 50 years (80% versus 68%), women with cervical lesions larger or smaller than 3 cm (68% versus 77%), or black women compared with whites (72% versus 86%).

DISCUSSION

The incidence of cervical cancer in black women of lower socioeconomic status is more than twice that of white women. Cervical cancer is the fourth most common cancer in black women, and the age-adjusted survival is only 57%. Despite the disproportionate impact of cervical cancer on minorities, few studies have been directed specifically at this high-risk population. This study focused on an urban, medically indigent, primarily minority population diagnosed and treated at one institution to evaluate clinical factors influencing survival in women with stage Ib cervical cancer. Of the variables analyzed, only treatment was shown to have significant impact on survival.

Women with stage Ib cervical cancer treated with radiotherapy had significantly poorer survival rates than those treated with surgery (66% versus 100%; $P=.04$). This finding is similar to the FIGO report of 5-year survival rates of 98% for surgically treated stage Ib cervical carcinomas and 68% for patients treated with irradiation.¹¹ In contrast, both prospective^{2,18} and retrospective^{1,19-21} studies of stage Ib patients treated by either surgery or radiotherapy have reported virtually identical survival rates. It is difficult to compare such studies because they involved selected patients who were evaluated and treated at different centers during different eras. One study excluded from randomization all patients >70 years of age or in poor health,¹⁸ while another excluded women with "severe medical disease limiting chances of 5 or more year survival."²²

While the study reported here followed a defined group of patients treated at a single institution, treatment selection criteria were not formalized during the time of this study. Bias in treatment selection criteria clearly can influence treatment-specific survival. Radiotherapy patients were significantly older, had larger tumors, and were more likely to have pelvic node metastases than surgery patients (Table). In three instances, patients originally scheduled for surgical treatment were reassigned to radiotherapy when pelvic metastases were identified during intraoperative pathology consultation. The combination of these independent determinants of survival could explain the poorer survival of radiotherapy patients.

In addition to treatment selection bias, the impact of social and economic factors on response to radiotherapy should be considered. Radiotherapy equipment used during the early part of the study was marginally adequate because of low beam energy. For effective radiotherapy, the patient also requires extensive social service support to ensure compliance and completion of therapy in a timely fashion. In a public hospital setting, those patients assigned to radiotherapy would benefit from more intensive social service intervention.

Pathologic lymph node status was not significantly associated with overall survival. This finding conflicts with other studies that have demonstrated poorer survivals for patients with lymph node metastases.^{5,22,23} The fact that clinical staging is not altered by the presence of nodal metastasis represents a known artifact of the FIGO system, and patients with pelvic node metastases in reality have

demonstrated disease progression. The most likely explanation for the lack of association in this study is that lymph node evaluations were not performed systematically. While all surgery patients had pelvic nodes examined histologically, this was true for only 17% of radiotherapy patients. In the absence of histologic examination, the actual incidence of lymph node metastasis is undoubtedly underestimated in the radiotherapy patients.

Other clinical variables not found to be associated with survival were tumor size, histology, and age. These conclusions must be tempered by the small number of patients, which limits the statistical power of the study. In addition, no difference in survival by race was identified in this study, although the small number of white patients limits the ability to conclude that such a difference does not potentially exist.

CONCLUSION

Within the limits of this study, there appeared to be no difference in treatment selection. These findings, as well as SEER analyses, suggest that any differences in observed survivals for blacks and whites are the result of imbalances in other prognostic factors.²²

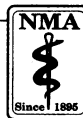
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Social Support Among African-American Adults With Diabetes, Part 1: Theoretical Framework

Marvella E. Ford, Barbara C. Tilley, and Patricia E. McDonald

Diabetes mellitus affects African Americans in disproportionate numbers relative to whites. Proper management of this disease is critical because of the increased morbidity and mortality associated with poor diabetes management. The role of social support in promoting diabetes management and improved glycemic control among African Americans is a little-explored area. This article, the first in a two-part series, provides a theoretical framework for examining the relationship between social support and glycemic control among African-American adults.

A Characterization of Older AIDS Patients in Maryland

Anthony K. Wutsh, Julia Hidalgo, Walter Rhee, and Joseph Bareta

This retrospective study evaluated Maryland acquired immunodeficiency syndrome (AIDS) patients who were ≥ 50 years at the time of AIDS diagnosis. All patients diagnosed between January 1987 and June 1996 who were ≥ 50 years were included in the cohort. A total of 610 male (82.7%) and 128 female (17.3%) AIDS patients aged ≥ 50 were identified. The most common mode of human immunodeficiency syndrome (HIV) transmission was male-to-male sexual contact (34.7%). Additionally, 146 (19.8%) patients contracted HIV through blood transfusions, 93 (12.1%) were infected through heterosexual contact, and the remaining 109 (14.8%) had unknown risk factors.

Data from this preliminary study demonstrate that an alarming percentage of AIDS patients (approximately 10%) in Maryland are aged ≥ 50 . Sexual contact, either male-to-male or heterosexual transmission, was the route of transmission for nearly 47% of this patient population. However, few research projects, educational programs, or public health initiatives are specifically targeted to this patient population. The increasing life expectancy of AIDS patients as well as the advent of new drug treatments highlight the need for further research to investigate the diagnosis and treatment of AIDS and HIV infection among older patients.