Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Survival of Patients With Cervical Cancer at Moi Teaching and Referral Hospital in Eldoret, Western Kenya

Emily Mwaliko (waleghwaem@hotmail.com)
Moi University
Peter Itsura
Moi University
Alfred Keter
Moi Teaching and Referral Hospital
Dirk De Bacquer
Ghent University
Nathan Buziba
Moi University
Hilde Bastiaens
University of Antwerp
Jackie Akinyi
Field coordinator- SBT Population Health AMPATH
Andrew Obala
Moi University
Violet Naanyu
Moi University
Peter Gichangi
Technical University of Mombasa
Marleen Temmerman
Ghent University

Research Article

Keywords: cervical cancer, survival, Kenya

Posted Date: November 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2158838/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

Cervical cancer is a major health burden and the second most common cancer after breast cancer among women in Kenya. Worldwide, cervical cancer constitutes 3.1% of all cancer cases. Mortality rates are greatest in low-income countries owing to a lack of awareness, screening and early-detection programs, and adequate treatment facilities. We aimed to estimate survival rates and determine survival predictors among women with cervical cancer and limited resources in western Kenya.

Methods

We retrospectively reviewed the charts of women diagnosed with cervical cancer in the 2 years from the date of histologic diagnosis. The outcome of interest was 2-year mortality or survival. Kaplan–Meier survival estimates, log-rank tests, and Cox proportional hazards regression were used in the survival analysis.

Results

We included 162 women in this study. The median time from diagnosis to death was 0.8 (interquartile range [IQR] 0.3–1.6) years. The mean age at diagnosis was 50.6 (standard deviation [SD] 12.5) years. Mean parity was 5.9 (SD 2.6). Participants were followed up for 152.6 person-years. Of 162 women, 70 (43.2%) died, with an overall mortality rate of 45.9 deaths per 100 person-years of follow-up. The survival rate was significantly better for women who were managed surgically (0.44 vs. 0.88, $p < 0.001$), those who had medical insurance (0.70 vs. 0.48, $p = 0.007$), and those with early-stage disease at diagnosis (0.88 vs. 0.39, $p < 0.001$). Participants who were diagnosed at a late stage of disease, according to International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging (FIGO stage IIB–IVB), had more than an eight times increased risk of death compared with those who were diagnosed at early stages (I–IIA): hazard ratio (HR) 8.01 (95% confidence interval [CI] 3.65–17.57). Similarly, women who underwent surgical management had an 84% reduced risk of mortality compared with those who were referred for other modes of care: HR 0.16 (95% CI 0.07–0.38).

Conclusion

As described in this study, the survival rate of patients with cervical cancer in Kenya is low. Many women are still diagnosed with cervical cancer when they are at very advanced stages and their likelihood of survival is very low. It is imperative to expand screening for early identification of women with cervical cancer in whom surgery can improve prognosis.

Introduction

Kenya has a high incidence and mortality of cervical cancer. According to estimates from Globocan in 2020, 5236 (19.7%) of all new cancer cases among women in Kenya were cancer of the cervix. Cervical cancer is the leading cause of cancer-related mortality among women. Worldwide, there were 9.2 million new cases of cancer in women in 2020. Of these, 6.5% are cases of cervical cancer (604,127 new cases). Cervical cancer is the leading cause of cancer deaths, followed by breast cancer[1].

In contrast to developed countries, there is a low rate of survival from cervical cancer in low- and middle-income countries, with very high mortality rates in Sub-Saharan Africa. Various factors contribute to the high cervical cancer mortality. One of these is the lack of or low coverage of national screening services. In Kenya, only 14% of women have undergone screening, despite the high rate of awareness about cervical cancer (75%). This lack of screening prevents identification of women at risk and early detection of invasive cancers[2].

More than 90% of women in Kenya with cancer of the cervix are diagnosed at advanced stages, according to the International Federation of Gynecology and Obstetrics staging system (Supplementary file 1), and diagnosis is usually in health facilities that are unable to provide effective treatment. With limited options available for treatment, women mainly receive initial evaluation, symptomatic treatment, and referral[3].

At the time of this study, there was only one public referral hospital in Kenya that offered radiotherapy, Kenyatta National Hospital in the capital city, Nairobi. Access to this hospital is limited for rural residents with low socioeconomic status. Most patients from peripheral hospitals are referred to this one hospital, which has a large backlog of patients. The number of patients who eventually receive radiotherapy can only be speculated, despite the fact that in many cases, women are at stage IIB or above at diagnosis. At the time of this study, three private hospitals were able to offer radiotherapy but at a cost beyond the reach of many patients[4]. The health ministry is in the process of establishing radiotherapy centers at several facilities, including Moi Teaching and Referral Hospital (MTRH) in western Kenya, where this study was undertaken[5].

Late diagnosis is the result of a lack of awareness about cancer and symptom recognition by both patients and health care providers at the primary care level. This, coupled with the time to initiation of radiotherapy, leads to worse outcomes because initiation of radiotherapy can take several months[4].

The aim of the present study was to determine the survival rate and predictors of survival after diagnosis among patients with cervical cancer in western Kenya. More specifically, we estimated the 1- and 2-year survival and predictors of survival after diagnosis among patients with cervical cancer. An understanding of the contribution of late diagnosis, the lag period to initiation of radiotherapy, and their contributions to outcomes has implications for the kind of measures that must be taken to improve policies aimed at reducing cervical cancer incidence and mortality[6,7].

Methods

In this retrospective cohort study, we estimated the time from diagnosis to death among women diagnosed with cervical cancer at MTRH during the study period and those referred from other peripheral hospitals in western Kenya.

The study population included all patients diagnosed with cervical cancer that were either admitted to the ward at MTRH or followed up in the gynecology outpatient clinic or registered in the Eldoret Cancer Registry (ECR), which is also located within the hospital. We identified risk factors in patients' medical charts including age at first pregnancy, multiple sexual partners, smoking, HIV status, post-menopausal status, and contraceptive use. We included the covariates occupation, education level, parity, marital status, and health insurance. Information regarding infection with human papilloma virus was not available. We used age at first pregnancy as a proxy for possible early age of coitarche and occupation as a proxy for socioeconomic status.

Study setting

This study was conducted at the gynecology-oncology ward and gynecology-oncology clinic/follow-up clinic at MTRH in Eldoret, Kenya. MTRH is the second largest public teaching and referral hospital in Kenya and the main referral hospital in western Kenya. It has a catchment of 13 to 15 million people that comprises approximately 40% of the Kenyan population.

The ECR was established in 1999 within MTRH. The ECR includes data on all patients diagnosed with cancer seen at MTRH and thus serves as a hospital-based cancer registry. The ECR also collects data from neighboring facilities that have patients with cancer, so it is also a population-based cancer registry.

Definition of terms

Median survival time was defined as the point at which half the patients have experienced the event under study and half remain free of the event (in this study, death). *Overall survival time* was defined as the length of time from the date of diagnosis for a disease in patients who are still alive. *Early-stage* cancer of the cervix was defined as stage I–IIA and *late-stage* cervical cancer as stage IIB–IV. The *start date* was defined as the date of diagnosis and the outcome of interest was death. Complete follow-up was achieved when vital status (alive/dead) at the closing date was known for an individual. We used active follow-up methods. Information on deaths was sourced from patients' clinical record files, with repeated scrutiny of the medical records. Additionally, telephone enquiries to patients or relatives/caretakers whose phone number was in the patient file were made. *Censoring* occurred either at death, the closing date of the study, or with loss to follow-up. Loss to follow-up was when patients did not return to the gynecology clinic or could not be contacted and we could not ascertain whether they were still alive after the last known status date. Deaths owing to causes other than cervical cancer complications were not captured in this study. The *index date* was defined as the starting date for calculation of survival, and this was the date of unequivocal diagnosis of cancer by means of

histological diagnosis. The inclusion date was between 1 December 2014 and 30 November 2017. Each patient was followed up for 2 years i.e., up to the closing date of the study (November 2017) or death (date that death was reported) or until they were censored as a result of transfer to another facility, home care, or were lost to follow-up.

Participant selection

In this study, we included women seeking care at MTRH with a histologic diagnosis of cervical cancer between 1 December 2014 to 30 November 2017 and who had a biopsy performed. Patients' charts were retrieved from three sources: first, from charts identified from the ward registers. Every admitted patient is usually registered and the diagnosis noted. The diagnosis is confirmed with a histology report in the chart. If the biopsy is done during admission, the result is followed up through the outpatient gynecology clinic. Second, if the patient is diagnosed in the outpatient gynecology clinic (usually through screening or when presenting with symptoms), they are usually registered in the computer within the gynecology oncology records department. The records clerk therefore retrieved the files containing the information required. Finally, all cancer cases within the region are recorded in the ECR.

File numbers within the registry are harmonized with the follow-up file numbers in the clinics/ward. The histology results were ascertained to be available, and the results recorded. Follow-up information was acquired through admissions in the ward or phone calls, with consent of the patient or relatives for those from other health facilities.

At MTRH, evaluation of each patient starts either in the clinic or, once admitted, in the ward via the emergency room. A history of symptoms of cervical cancer is taken, then a thorough physical examination is done. Pelvic examination including speculum examination is performed. Staging was done clinically per the 2018 FIGO clinical staging (*Supplementary file*).

Survival time was calculated as the time (in months or completed years) between the index date and the date of death, date of loss to follow-up, or the closing date, whichever was earliest. Age at diagnosis was defined as the age in completed years on the index date. Regarding the clinical extent of disease, FIGO staging was used. Histologic grade was not available in all histology reports as some laboratories omitted these data. Whether the patient was diagnosed symptomatically or through screening was noted.

Ethical considerations

The study was approved by Moi University and Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (FAN: IREC 1071) and Ghent University, Commissie voor Medische Ethiek, ONS KENMERK, PA 2011/019. Informed verbal consent was obtained from all patients (or relatives/caretakers).

All records were kept by the research team only and identifiable data were not included in the analysis and discussion.

Statistical analysis

Descriptive statistics such as the mean and standard deviation (SD) were used to summarize age and parity, and the median and interquartile range (IQR) was used to summarize the follow-up time. Frequencies and the corresponding percentages were used to summarize categorical variables such as marital status, occupation, cancer stage, HIV status, use of antiretroviral therapy, and death.

Kaplan–Meier survival curves were used to describe the survival distributions. The survival functions for different groups of participants were compared using the log-rank test. The incidence of death and corresponding 95% confidence interval (CI) were computed for each group of participants. The incidence rates of death for different levels of the categorical variables were compared using a Cox proportional hazards regression model. Two events occurring at the same time (failure/death) were handled using the Breslow test of homogeneity for odds ratios of the strata. The hazard ratio (HR) and corresponding 95% CI were reported.

Data analysis was conducted using Stata version 13 SE (Stata Corp LLC, College Station, TX, USA).

Results

A total of 162 participants were enrolled in the study. Participants' mean age was 50.6 (SD: 12.5) years, with a minimum and maximum of 17.0 and 80.0 years, respectively. Ten percent of participants were aged 35 years or less (Table 1).

Table 1
Sociodemographic characteristics

Variable	Mean (SD) or n (%)
Age (years), mean (SD)	50.6 (12.5)
Range (Min.–Max.)	17.0–80.0
≤35	16 (9.9%)
>35	146 (90.1%)
Median (IQR)	49 (4160)
Range (Min.–Max.)	17.0–80.0
Cohabitation status, n (%)	
Married	109 (67.3%)
Single	19 (11.8%)
Separated	2 (1.2%)
Widowed	20 (12.4%)
Unknown	12 (7.4%)
Occupation, n (%)	
Homemaker	38 (23.5%)
Secular	11 (6.8%)
Trader	39 (24.1%)
Student	7 (4.3%)
Other	67 (41.4%)
Education level, n (%)	
None/Incomplete primary	33 (20.4%)
Completed primary	32 (19.8%)
Secondary	40 (24.7%)
Tertiary	12 (0.4%)
Not indicated	45 (27.8%)
Parity, mean (SD)	5.9 (2.6)
Range (Min.–Max.)	0.0–13.0

SD, standard deviation; IQR, interquartile range.

Variable	Mean (SD) or n (%)
≤5	71 (46.1%)
>5	83 (53.9%)
Median (IQR)	6 (4–8)
Range (Min.–Max.)	0.0–13.0
Health insurance cover, n (%)	
No	81 (50.0%)
Yes	56 (34.6%)
Not indicated	25 (15.4%)
SD, standard deviation; IQR, interquartile range.	

Two-thirds (67.3%) of participants were married, and 23.5% were homemakers. The sample comprised 7.3% students. Up to 40.2% of participants had completed a primary education. The mean parity was 5.9 (SD: 2.6), with a minimum of zero and maximum of 13.0.

Table 2 presents the risk factors for cancer cited in the literature. Of all participants, 26.5% used hormonal and 14.8% used non-hormonal contraceptives. More than half (58.0%) of participants were post-menopausal.

Table 2
Risk factors

Variable	n (%)
Contraceptive use	
None	67 (41.4%)
Hormonal	43 (26.5%)
Non-hormonal	24 (14.8%)
Not indicated	28 (17.3%)
Menopause status	
Pre-menopause	94 (58.0%)
Post-menopause	68 (42.0%)
HIV status	
Unknown	19 (11.7%)
Positive	42 (25.9%)
Negative	101 (62.4%)
HAART[†] use	
No	3 (7.1%)
Yes	30 (71.4%)
Unknown	9 (21.4%)
Smokes cigarettes or chews tobacco	
No	128 (79.0%)
Yes	1 (0.6%)
Not indicated	33 (20.4%)
[†]Among HIV-positive patients.	

HAART, highly active antiretroviral therapy.

Among patients who were HIV positive, 71.4% were on antiretroviral therapy.

Table 3 presents the clinical characteristics of included patients with cancer. The main histological diagnosis was squamous cell carcinoma, observed in 135 (83.3%) patients, and two-thirds (68.5%) of participants were diagnosed at a late cancer stage.

Table 3
Patients' clinical characteristics

Variable	n (%)
Method of diagnosis	
Through symptoms	120 (74.1%)
Screening	29 (17.9%)
Not indicated	13 (8.0%)
Diagnosis	
Squamous cell carcinoma	135 (83.3%)
Adenocarcinoma	14 (8.6%)
Adenosquamous carcinoma	2 (1.2%)
Clinical diagnosis with VE	8 (4.9%)
CIS	2 (1.2%)
Not indicated	1 (0.6%)
Stage of cancer	
Early	51 (31.5%)
Late	111 (68.5%)
Management	
Referred for radiotherapy/palliative care/chemotherapy	125 (77.2%)
Surgery	37 (22.8%)
VE, vaginal examination; CIS, carcinoma in situ.	

Table 4 presents results regarding outcome. In total, 45.1% of participants died, and the median time of follow-up was 21 months (IQR: 1.2, 2.0 years).

Table 4
Patient outcomes

Variable	n (%) or median (IQR)
Survival status, n (%)	
Alive	89 (54.9%)
Dead	70 (43.2%)
Time from diagnosis to death (years), median (IQR)	0.8 (0.3, 1.6)
Range (Min.–Max.)	0.03–2.0
IQR, interquartile range.	

The total follow-up time was 152.6 person-years, and total number of deaths was 70. This gives an overall incidence rate of death of 45.9 (95% CI: 36.3, 58.0) per 100 person-years of follow-up.

Table 5
Survival probabilities at specific time points

Time (years)	Beginning total	Deaths	Survival probability (95% CI)
0.5	105	29	0.79 (0.71, 0.85)
1	72	29	0.58 (0.48, 0.65)
1.5	51	9	0.49 (0.40, 0.57)
2.0	28	3	0.45 (0.36, 0.54)
CI, confidence interval.			

At 1 year, the survival probability of participants was 58.0% (95% CI: 48.0%, 65.0%) and at 2 years, 45.0% (95% CI: 36.0%, 54.0%) were alive (85% of women with stages I–IIA and 43% in women with stages IIB or more) (Table 5). The median (95% CI) survival time was 1.50 (0.92, 2.09) years and the mean (95% CI) overall survival time was 1.29 (1.16, 1.41) years.

We explored the survival function of participants according to the key variables of interest. The findings are shown in Figs. 1–4.

The data show that participants who were pre-menopausal had better survival rates than who were post-menopausal (p = 0.039).

Participants who had health insurance cover had significantly longer survival than those who did not have health insurance (p = 0.007). Up to 70.0% of patients who had health insurance cover were still alive at 1 year compared with 48.0% of those who did not have health insurance cover.

Participants diagnosed at an early stage of disease had better survival than those who were diagnosed in late stages ($p < 0.001$). For women in stages I–IIA, the median survival time could not be determined because follow-up was too short to identify a median. The mean (95% CI) survival time was 1.75 (1.61, 1.92) years. For women in stages above IIA, the median (95% CI) survival was 0.85 (0.57, 1.11) years. The mean (95% CI) survival time was 1.02 (0.87, 1.18) years. The probability of surviving 10 months after a late-stage diagnosis was 0.5.

Participants who were referred for radiotherapy, palliative care, or chemotherapy had poorer survival than those who were treated surgically ($p < 0.001$).

Table 6
Incidence and hazard ratio of death

Variable	Deaths (%)	FUP time (y)	Incidence (95% CI) ¥	Hazard ratio (95% CI)
Age (years)				
≤35	4 (25.0)	17.6	22.8 (8.5, 60.7)	Reference group
>35	66 (45.2)	135.0	48.9 (38.4, 62.2)	2.01 (0.73, 5.50)
Education				
Primary/none	31 (47.7)	56.9	54.5 (38.3, 77.5)	Reference group
Secondary/tertiary	24 (46.2)	54.0	44.4 (29.8, 66.3)	0.87 (0.51, 1.48)
Not indicated	15 (33.3)	41.6	36.0 (21.7, 59.7)	0.70 (0.38, 1.30)
Cohabitation status				
No§	20 (48.8)	43.0	46.5 (30.0, 72.2)	Reference group
Yes	47 (43.1)	97.6	48.1 (36.2, 64.1)	0.98 (0.58, 1.65)
Not indicated	3 (25.0)	12.0	25.1 (8.1, 77.8)	0.50 (0.15, 1.70)
Menopausal status				
Pre-menopausal	35 (37.2)	96.0	36.5 (26.2, 50.8)	Reference group
Post-menopausal	35 (51.5)	56.6	61.9 (44.4, 86.2)	**1.63 (1.02, 2.61)**
Parity				
≤5	30 (42.3)	70.7	42.4 (29.7, 60.7)	Reference group
>5	37 (44.6)	72.2	51.2 (37.1, 70.7)	1.17 (0.73, 1.90)
Insurance cover				
No	43 (53.1)	69.0	62.3 (46.2, 84.0)	Reference group
Yes	18 (32.1)	65.4	27.5 (17.4, 43.7)	**0.47 (0.27, 0.82)**
Not indicated	9 (36.0)	18.2	49.4 (25.7, 95.0)	0.78 (0.38, 1.59)
History of contraceptives use				
None	27 (40.3)	59.1	45.7 (31.3, 66.6)	Reference group
Hormonal	15 (34.9)	43.4	34.6 (20.8, 57.4)	0.78 (0.42, 1.47)
Non-hormonal	15 (62.5)	22.8	65.7 (39.6, 109.0)	1.49 (0.79, 2.80)

Variable	Deaths (%)	FUP time (y)	Incidence (95% CI) ¥	Hazard ratio (95% CI)
Not indicated	13 (46.4)	27.3	47.7 (27.7, 82.1)	1.00 (0.51, 1.93)
HIV status				
Negative	41 (40.6)	95.6	42.9 (31.6, 58.3)	Reference group
Positive	17 (40.5)	41.6	40.8 (25.4, 65.7)	0.95 (0.54, 1.67)
Unknown	12 (63.2)	15.4	78.1 (44.4, 137.6)	1.73 (0.91, 3.30)
HAART use†				
No	1 (33.3)	2.7	36.9 (5.2, 262.3)	Reference group
Yes	13 (43.3)	31.3	41.5 (24.1, 71.5)	1.09 (0.14, 8.32)
Not Indicated	3 (33.3)	7.6	39.3 (12.7, 121.9)	1.13 (0.12, 10.99)
Initial consultation‡				
Symptoms	54 (45.0)	109.8	49.2 (37.7, 64.2)	Reference group
Screening	8 (27.6)	36.1	22.2 (11.1, 44.3)	**0.47 (0.22, 0.98)**
Not indicated	8 (61.5)	6.6	120.6 (60.3, 241.1)	**2.51 (1.19, 5.27)**
Stage of cancer				
Early	7 (13.7)	74.3	9.4 (4.5, 19.8)	Reference group
Late	63 (56.8)	78.3	80.5 (62.9, 103.1)	**8.01 (3.65, 17.57)**
Management				
Referred	64 (51.2)	95.4	67.1 (52.5, 85.7)	Reference group
Surgery	6 (16.2)	57.1	10.5 (4.7, 23.4)	**0.16 (0.07, 0.38)**

¥ Incidence was calculated per 100 person-years of follow-up. §Single, separated, and widowed. †Among HIV-positive patients. ‡ Individuals seeking health care.

CI, confidence interval; FUP, follow-up.

Table 6 presents the total number of deaths and corresponding proportions, total follow-up time, incidence rate, and HR of death for each level of the categorical variables.

Table 7
Unadjusted and adjusted risk factors

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Age (years)		
≤35	Reference group	Reference group
>35	2.01 (0.73, 5.50)	1.12 (0.40, 3.15)
Insurance cover		
No	Reference group	Reference group
Yes	**0.47 (0.27, 0.82)**	0.64 (0.37, 1.12)
Not indicated	0.78 (0.38, 1.59)	0.68 (0.32, 1.42)
HIV status		
Negative	Reference group	Reference group
Positive	0.95 (0.54, 1.67)	1.39 (0.73, 2.66)
Unknown	1.73 (0.91, 3.30)	1.14 (0.64, 2.04)
Stage of cancer		
Early	Reference group	Reference group
Late	**8.01 (3.65, 17.57)**	**5.20 (2.28, 11.87)**
Management		
Referred	Reference group	Reference group
Surgery	**0.16 (0.07, 0.38)**	**0.36 (0.15, 0.90)**

CI, confidence interval.

The adjusted model (Table 7) shows that participants who were diagnosed at a late stage of disease had a more than five times increased risk of death compared with those who were diagnosed at an early stage: HR 5.20 (95% CI 2.28, 11.87). Similarly, the adjusted effect of disease management showed that surgical management was associated with a 64% lower risk of mortality compared with referral: HR 0.36 (95% CI 0.15, 0.90).

There was no evidence of a difference in the survival rate between participants who had a secondary or tertiary education level and those who had a primary education, did not complete primary education, or those with no education at all (p = 0.526).

There was no difference in the survival distribution of participants who were HIV positive compared with that of those who did not have HIV infection (p = 0.859). The rate of survival for those who were HIV positive was similar to the survival rate among patients who were HIV negative at 1 year and 2 years.

Discussion

This was a retrospective cohort study conducted at a national tertiary hospital in Kenya. In this study, we reviewed the charts of 162 patients. Each recruited patient was to be followed up for a total of 2 years. In this study, 68.5% of participants presented with advanced stages of cervical cancer, which is consistent with other studies in low-income countries[8–11]. In most cases, the diagnosis was made following symptomatic presentation. This indicates the lack of screening and urgent need for earlier diagnosis of cervical cancer. The late presentations also reflect delayed diagnosis owing to limited accessibility or availability of oncology services, especially in rural areas[12].

In this study, we found that the 1- and 2-year survival probability was 58% and 45%, respectively. The overall incidence of death was 45.9 per 100 person-years. In most of these cases (80%), the patient died within the first year after diagnosis. The 1-year survival was used as a proxy for early diagnosis and is also indicative of the cancer stage at diagnosis. The 1-year survival for patients with stage IIA and below was 88%. The probability of surviving 10 months after diagnosis was 0.5 for those with stage IIB and above. Compared with the 5-year survival in developed countries, this finding further confirms that most women were diagnosed late and effective treatment was not available[13].

In this study, we categorized patients into those with early (stage IIA and below) and late (above stage IIB) stage disease. In total, 32% of patients presented in an early stage. Late presentation is consistent with other studies done in Africa[8–10]. All these studies highlight the challenge posed by late presentation in terms of survival in Kenya and in Africa as a whole. In our study, the 1-year survival rate for those diagnosed with early-stage cervical cancer were 88% compared with 39% for those diagnosed in a late stage.

We analyzed the survival rate according to mode of management after diagnosis. Patients either had surgery or were referred for radiotherapy or palliative care. Those who underwent surgery had better survival than those who were referred. In Nigeria, Musa and colleagues reported the potential benefit of surgery[10]. In this study, women who were referred had 1- and 2-year survival rates of 44% versus 89% and 31% versus 82% compared with those who underwent surgery. Although the extent of surgery and surgical complications in terms of survival benefit are controversial, surgical management is clinically important. Health systems in Sub-Saharan Africa are overwhelmed with many competing priorities, and referral options for many patients are often limited. Additionally, many patients may not even present for chemo- or radiation therapy owing to a lack of finances and choose traditional medications instead. Cancer survival after treatment reflects the availability and accessibility of cancer health services in the region.

Ginsberg and colleagues showed that the costs of a treatment approach alone are higher than those for an approach that combines prevention, early detection, and treatment. However, primary prevention using vaccines is not widespread and screening in this region is sporadic at best, with low coverage[14]. Therefore, with early diagnosis—which is the aim—surgery is reasonable in this context.

In our predictive model, we also analyzed other factors associated with mortality, including age at diagnosis, HIV status, use of highly active antiretroviral therapy (HAART), and whether diagnosis was based on symptoms or was incidental during screening. A Swedish study found that women diagnosed with cervical cancer at age 65 years or above had more advanced disease compared with younger women[15]. This was mainly owing to being left out of the screening program, and the prognosis was poor in the older women. This can be assumed to be the case in our context, where no screening program is in place. However, the groups in our study did not show a significant difference in HR values. In this study, we compared women who were age 35 years or more with those younger than 35 years (16 participants); the incidence rate of death was higher in the older group, although this was not significant. This is similar to a study by Pelkofski and colleagues who concluded that, on its own, age at diagnosis for women under age 35 years does not infer a worse prognosis[16]. Our finding may be because there were few study participants under 35 years of age in our cohort, making it difficult to detect a difference (there was only one participant aged 17 years who was censored alive at 2 years). We cannot say from this study whether cervical cancer is more aggressive in women under 35 years of age because we obtained the opposite result.

Age at first sexual encounter and age at first full-term pregnancy have been shown to be risk factors for cervical cancer[17]. As a proxy in this study, we used parity, assuming that higher parity indicated a lower age at first pregnancy. We also assumed that higher parity indicated a more advanced cancer stage at diagnosis. However, we found no difference in the incidence rate of death between participants with parity of 5 or less and those with parity more than 5. The age of participants in this study was similar to that among participants in a study in Ethiopia where more participants were over age 35 years[18].

As expected, patients who were diagnosed through screening had a reduced mortality rate. Most had an early stage of disease and were therefore more likely to be surgically managed. This finding highlights the rationale for early detection and for women to undergo regular screening for cervical cancer.

In a study in Malawi that discussed the relationship of HIV with pre-invasive lesions and cervical cancer, the incidence of cervical cancer was not found to be different between HIV-positive and HIV-negative participants. However, the incidence of precancerous lesions was increased in the HIV-positive group. Survival for HIV-infected patients in Botswana was reported to be lower than that in HIV-negative patients[19,20].

In this study, patients who were HIV positive had a non-significantly lower incidence of death compared with HIV-negative participants. We postulate that at this referral center, which has facilities for follow-up of all patients with HIV including regular screening (integrated services, which have been shown to be feasible with a reduction in loss to follow-up), early diagnosis was probably facilitated in patients with HIV as opposed to HIV-negative patients who must seek and pay for screening themselves. When a patient with cervical cancer is HIV positive, the prognosis will depend on the stage at diagnosis. Previous studies have shown greater toxicity in patients with HIV undergoing chemo- or radiotherapy[21,22]. A study in Zambia demonstrated no significant difference with regard to major acute reactions between HIV-

positive patients taking HAART and HIV-negative ones[23]. A study in Brazil found no association between HIV infection and an initial treatment response or early mortality; however, relapse after attaining a complete response and late mortality were increased[24]. In our study, there was no evidence of an association between the use of HAART and a reduction in cervical cancer mortality among HIV-positive patients.

We found no difference among our participants who used hormonal contraceptives in terms of the incident rate of death[25]. Survival among women who were premenopausal was better than in those who were postmenopausal. This is expected from the data because we had more older women and women with a late stage at diagnosis.

We also analyzed factors associated with loss to follow-up, including education level, marital status, and whether the patient had medical insurance. These factors are known to increase the delay in presentation for diagnosis[26]. Poverty leads to lower education levels and lower socioeconomic status, which in turn lead to low levels of symptom awareness. In this study, we examined the HRs of women with and those without health insurance (paid by the participant as part of health care in Kenya). Participants who had insurance had lower HRs for death and follow-up time compared with those who did not. Demands and priorities on finances as well as the fear of a cancer diagnosis, have been reported in qualitative studies as reasons for late presentation for diagnosis[27]. Cohabitation status differentials in cervical cancer incidence may reflect differences in socioeconomic status, especially in cases where women do not own or inherit wealth from their fathers or husbands. This is within the context of behavioral factors, social networks, and social support characteristics. To some extent, these are risk factors for cervical cancer and influence survival, specifically the ability of the patient to pay for the cost of treatment after referral. As has been noted previously, health systems in Sub-Saharan Africa are overwhelmed with many competing priorities. Additionally, poverty in most areas' limits patients' choices in terms of seeking care, and most individuals in this region do not have health insurance[28,29].

Limitations

Although we obtained information regarding the date of diagnosis and recommended treatment, collecting information during follow-up was difficult. Some information provided by telephone proved to be inaccurate and some relatives of our patients were reluctant or refused to cooperate in divulging information. The size of the sample was small, which may have limited the statistical power. The small cohort did not allow us to conduct analyses such as regarding the effect of HIV/HAART status, surgery versus chemoradiation, hormonal versus non-hormonal contraceptive use, and different age categories.

At the time of the study, HPV testing was not available; however, 1 in 10 women have been screened for cervical cancer in the past 5 years. There are three radiotherapy units per 10,000 women in Kenya and these are located in referral hospitals in large cities (as of 2021). A national screening program exists as well as an HPV vaccination program for girls. The HPV vaccination program was introduced in 2019 and 1 in 10 girls have received the final vaccination dose, with 16% coverage in 2020. As of 2021, there were

three radiotherapy units per 10,000 patients with cancer and 1 for brachytherapy, with most cancer services concentrated in urban areas. There are now six new public centers with radiotherapy facilities in Kenya[30]

Conclusion

The predictors of death among women diagnosed with cervical cancer in MTRH were stage at diagnosis, mode of management, and having health insurance. The overall incidence of death was 45.9 per 100 person-years of follow-up, and the 1- and 2-year survival was 57% and 45%, respectively.

The poor survival of women in our study can be attributed to a lack of screening and early diagnosis, leading to late stage of disease at diagnosis. Access to radiotherapy services is difficult for patients as there is only one public facility in Kenya. Improvement in basic cancer services the country is required for diagnostic, surgery radio/chemotherapy, palliative care, and appropriate follow-up after diagnosis and treatment. This is urgent considering it will be many years before primary prevention and screening finally achieve the set goals.

Abbreviations

HAART: highly active antiretroviral therapy

HR: hazard ratio

CI; confidence interval

IQR: interquartile range

SD: standard deviation

MTRH: Moi Teaching and Referral Hospital

FIGO: International Federation of Gynecology and Obstetrics

Declarations

Ethics approval and consent to participate: Approval for the study was granted by Moi University School of Medicine Institutional Research and Ethics Committee (IREC) -FAN: IREC 1071, and Ghent University, Commissie voor Medische Ethiek, ONS KENMERK, PA 2011/019. Human data collection was done in accordance with relevant applicable guidelines and regulations. Informed verbal consent was obtained from all patients (or relatives/caretakers).

Availability of data and material: The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Conflict of interest: The authors declare that they have no competing interests.

Consent for publication: Not applicable.

Funding: This study was supported by the VLIR-UOS PROGRAM, Moi University. Reference: ZIUS2012APO17, ZIUS2013APO17, ZIUS2014APO17, ZIUS2015APO17, ZIUS2016APO17, Serial number: 2012-157. The funding body had no role in the design of the study, data collection, analysis and interpretation of the data, or writing of the manuscript.

Authors' contributions: EM: conception and design, development of methodology, acquisition of data, analysis and interpretation of data, and writing of article. MT, HB, PI and VN: concept design and review proposal writing. EM, JA, NB and AO: data collection. EM, AK, and DDB: Data analysis and interpretation. AK, MT, PI, PG, HB, DDB, VN and EM: read and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Acknowledgments

We thank the record clerks at the Oncology Centre MTRH, Cancer Registry Eldoret, Oncology Ward, and outpatient clinic. We also thank Jack Odunga, Research Assistant, Department of Reproductive Health at Moi University. We thank Analisa Avila, MPH, ELS, of Edanz (www.edanz.com/ac) for editing a draft of this manuscript.

References

1. Globocan 2018: Estimated cancer incidence, mortality and prevalence worldwide December 2020. International Agency for Research on Cancer. World Health Organization. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed on 21 July 2022
2. Kenya Demographic and Health Survey 2014, Central Bureau of Statistics Kenya. Ministry of Health Nairobi, Kenya National AIDS Control Council Nairobi, Kenya Kenya Medical Research Institute Nairobi, Kenya National Council for Population and Development Nairobi, Kenya. The DHS Program, ICF International, Rockville, Maryland, USA. December 2015
3. Were EO, Buziba NG. Presentation and health care seeking behaviour pf patients with cervical cancer seen at Moi Teaching and Referral Hospital, Eldoret, Kenya. East Afr Med J 2001: 78: 55–59. DOI 10.4314/eamj.v78i2.9088
4. Were E, Nyaberi Z, Buziba N. Perception of risk and barriers to cervical cancer screening at Moi Teaching and Referral hospital (MTRH), Eldoret. Kenya. Afr Health Sci 2011; 11: 58–64
5. Ministry of Health, Kenya. National Cancer Control Strategy 2017–2022 Nairobi, June 2017. www.health.go.ke Accessed on 18 August 2020
6. Compton CC, Byrd BR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. AJCC Cancer Staging Atlas: A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and

Handbook. Cancer Survival Analysis, p.23. DOI 10.1007/978-1-4614-2080-4_2

7. Swaminathan R, Brenner H. Statistical methods for cancer survival analysis IARC Sci Publ 2011; 162: 7–13
8. Gondos A, Brenner H, Wabinga H, Parkin DM. Cancer survival in Kampala, Uganda. Br J Cancer 2005; 92: 1808–1812
9. Msyamboza KP, Manda G, Tembo B, Thambo C, Chitete L, Mindiera C, Finch I, Hamling K. Cancer survival in Malawi: a retrospective cohort study. Pan Afr Med J 2014; 19: 234. DOI 10.11604/pamj.2014.19.234.4675
10. Musa J, Nankat J, Achenbach CJ, Shambe IH, Taiwo BO, Barnabas Mandong B Cervical cancer survival in a resource limited setting-North Central Nigeria. Infect Agents Cancer 2016; 11: 15. DOI 10.1186/s13027-016-0062-0
11. Chokunonga E, Ramanakumar AV, Nyakabau AM, Borok MZ, Chirenje ZM. Survival of cervix cancer patients in Harare, Zimbabwe 1995-1997. Int J Cancer 2004; 109: 274–277
12. Whitaker KL, Smith CF, Winstanley K, Wardle J. What prompts help-seeking for cancer 'alarm' symptoms? A primary care-based survey. Br J Cancer 2016; 114: 334–339. DOI 10.1038/bjc.2015.445
13. Corner J, Brindle L. The influence of social processes on the timing of cancer diagnosis: a research agenda. J Epidemiol Community Health 2011; 65: 477–482. DOI 10.1136/jech.2008.084285
14. Ginsburg OM. Breast and cervical cancer control in low and middle-income countries: Human rights meet sound health policy. J Cancer Policy 2013; 1: e35– DOI 10.1016/j.jcpo.2013.07.002
15. Darlin L, Borgfeldt C, Widen E, Kannisto P. Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. Anticancer Res 2014; 34: 5147–5152
16. Pelkofski E, Stine J, Wages NA, Gehrig PA, Kim KH, Cantrell LA. Cervical cancer in women aged 35 years and younger. Clin Ther 2016; 38: 459– DOI 10.1016/j.clinthera.2016.01.024
17. Louie KS, de Sanjose, Diaz M, Castellsague X, Herrero R, Meijer CJ, Shah K, et al. Early age ant first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer 2009; 100: 1191–1197
18. Ameya G, Yerakly F. Characteristics of cervical disease among symptomatic women with histopathological sample at Hawassa University referral hospital, Southern Ethiopia. Womens Health 2017; 17: 91. DOI 10.1186/s12905-017-0444-5
19. Chirenje ZM. HIV and cancer of the cervix. **Best Pract Res Clin Obstet Gynaecol** 2005; 19: 269– DOI 10.1016/j.bpobgyn.2004.10.002
20. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, et al. HIV infection and survival among women with cervical cancer. J Clin Oncol 2016; 34: 3749–3757
21. Sigfrid L, Murphy G, Haldane V, Chuah FLH, Ong SE, Cervero-Licera F, et al. Integrating cervical cancer with HIV healthcare services: A systematic review. PLoS ONE 2017; 12: e0181156. DOI

10.1371/journal.pone.0181156

22. Ghebre RG, Grover S, Xue MJ, Chuang LT, Simonds H. Cervical cancer control in HIV-infected women: Past, present and future. Gynecol Oncol Rep 2017; 21: 101–108
23. Mdletshe S, Munkupa H, Lishimpi K. Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia. South Afr J Gynaecol Oncol 2016; 8: 37– DOI 10.1080/20742835.2016.1239356
24. Ferreira MP, Coghill AE, Chaves CB, Bergmann A, Thuler LC, Soares EA, Ruth M. Outcomes of cervical cancer among HIV-infected and HIV-uninfected women treated at the Brazilian National Institute of Cancer. AIDS 2017; 31: 523– DOI 10.1097/QAD.0000000000001367
25. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptive: collaborative reanalysis of individual data for 16573 women with cervical cancer and 35509 women without cervical cancer from 2 epidemiological studies. Lancet 2007; 370: 1609–1621
26. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. Br J Cancer 2009; 101: S92–S101
27. de Nooijer I, Lechner L, de Vries H. Help seeking behaviour for cancer symptoms: perception of patients and general practitioners. Psychooncology 2001; 10: 469–478. DOI 10.1002/pon.535
28. Randal TC, Ghebre R. Challenges in prevention and care delivery for women with cervical cancer in Sub-Saharan Africa. Front Oncol 2016; 6: 160. DOI 10.3389/fonc.2016.00160
29. Clegg LX, Marsha E, Reichman ME, Miller BA, Hankey B, Singh GK, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control. 2009; 20: 4174–4135. DOI 10.1007/s10552-008-9256-0
30. Kenya Cervical Cancer Profile. https://cdn.who.int/media/docs/default-source/country-profiles/cervical-cancer/cervical-cancer-ken-2021-country-profile-en.pdf?sfvrsn=5af61b0b_38&download=true. Accessed on 21 July 2022

Figures

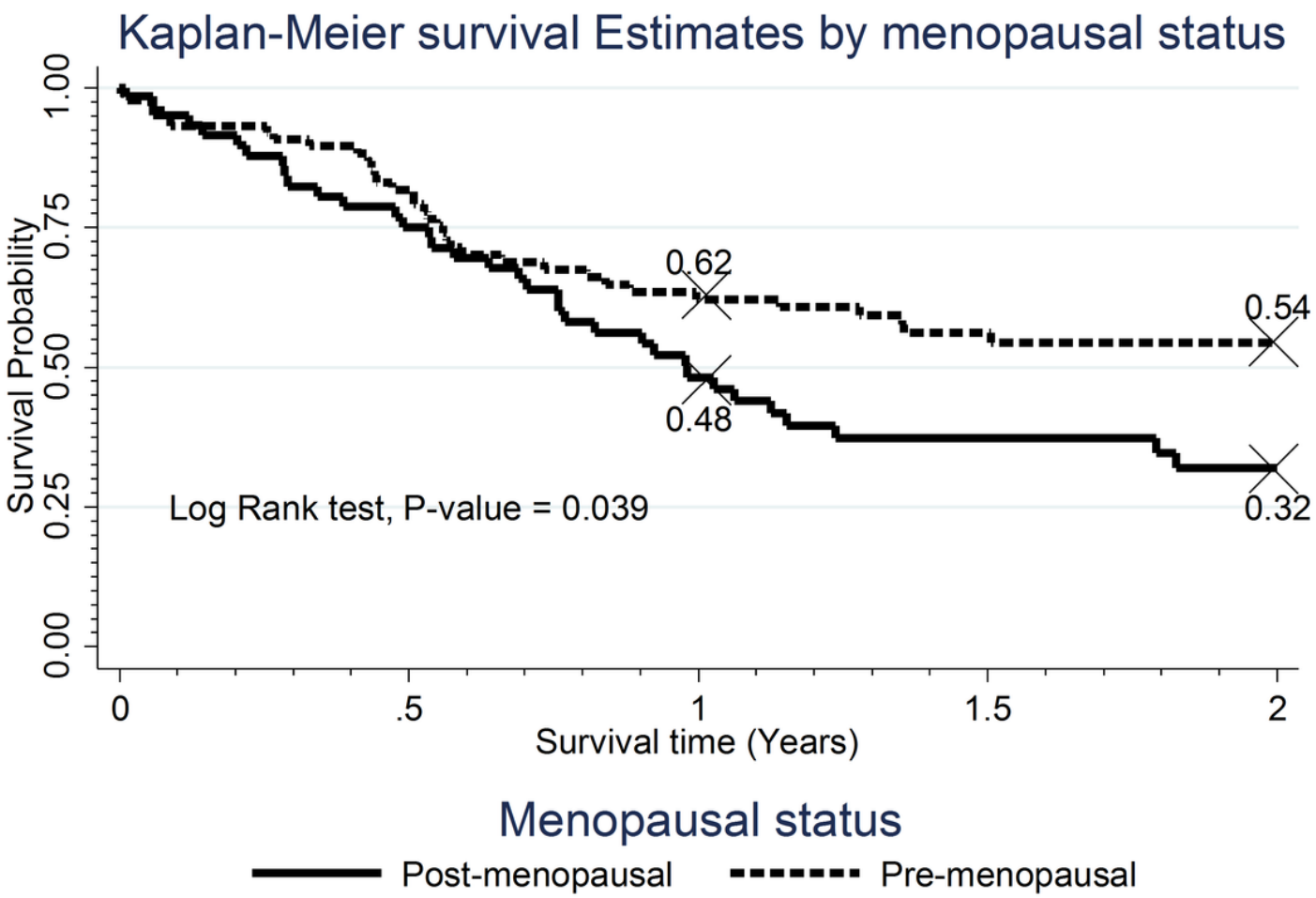

Figure 1

Survival rate according to menopausal status

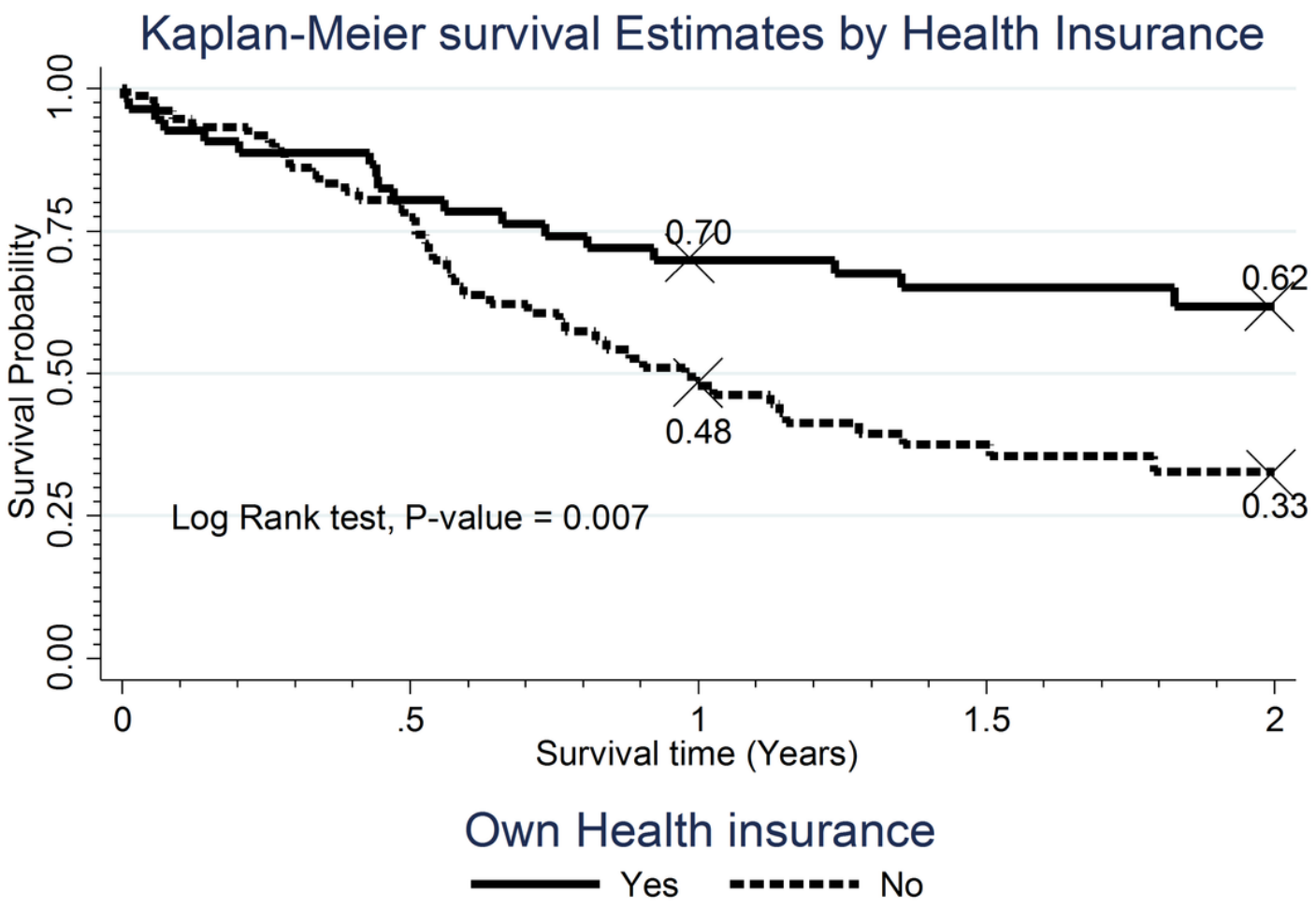

Figure 2

Survival rate according to health insurance cover

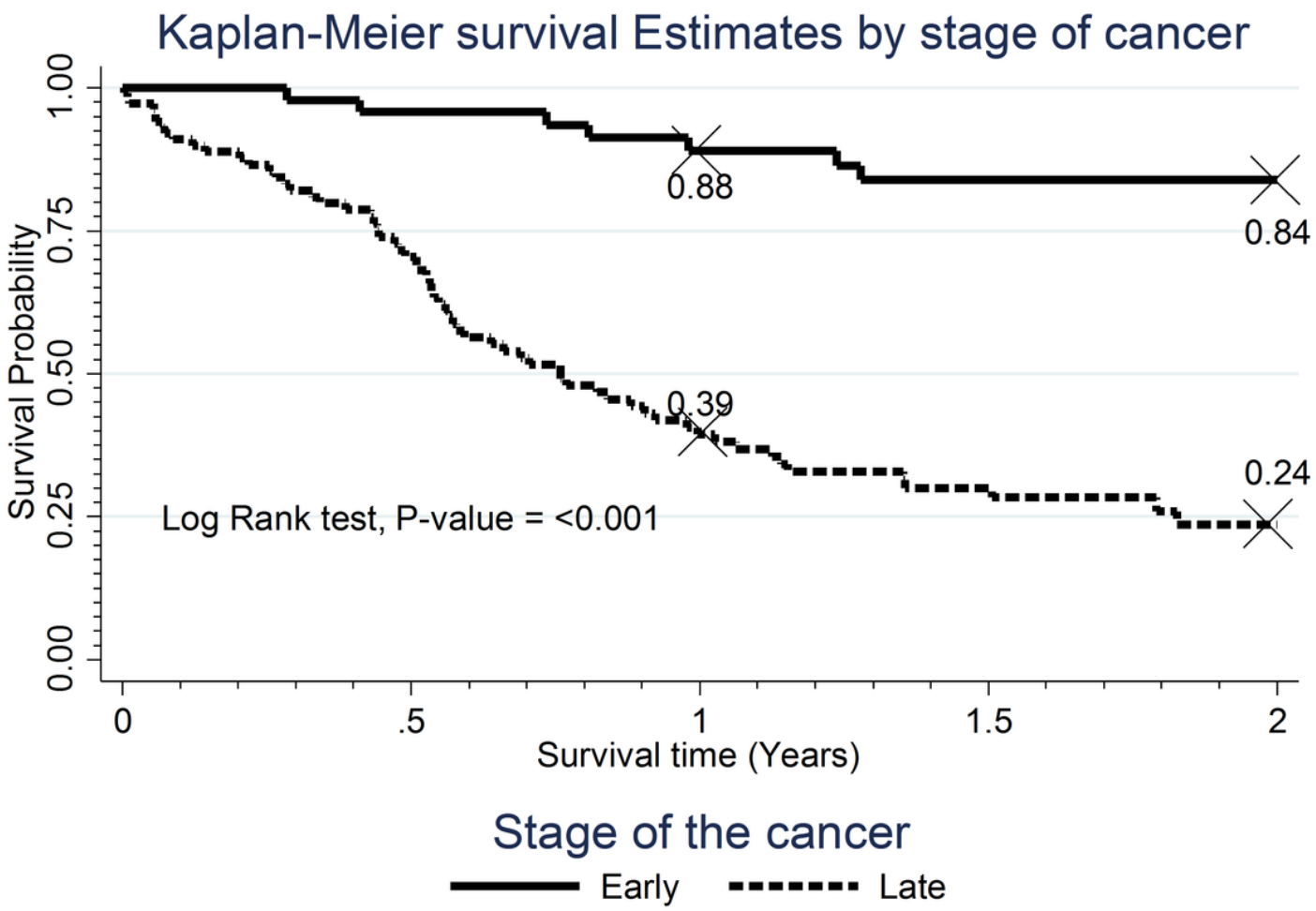

Figure 3

Survival rate according to cancer stage

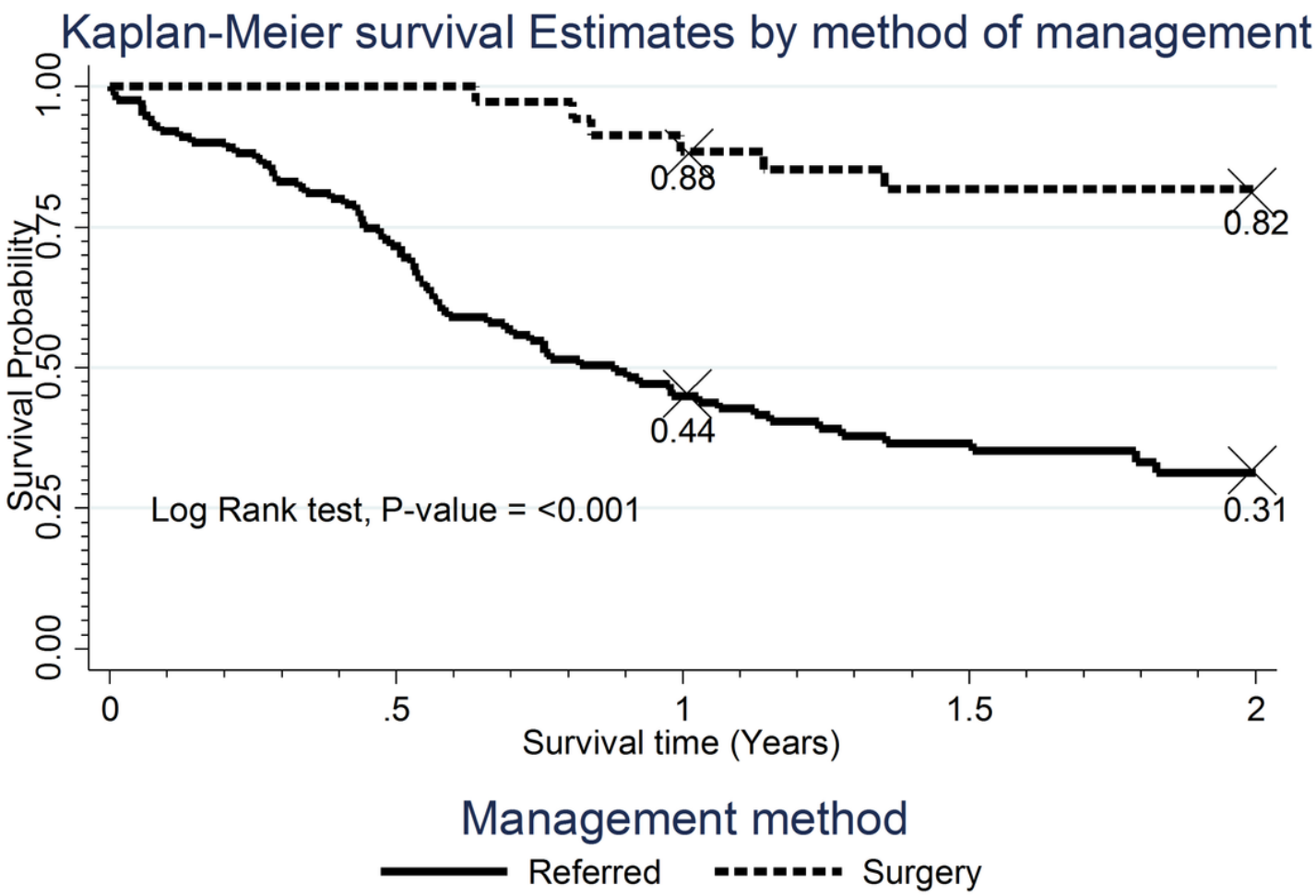

Figure 4

Survival rate according to mode of cancer management

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Article3Supplementaryfile.docx