Analysis of Factors Contributing to the Low Survival of Cervical Cancer Patients Undergoing Radiotherapy in Kenya

Innocent O. Maranga1,2, Lynne Hampson1, Anthony W. Oliver1, Anas Gamal4, Peter Gichangi2, Anselmy Opiyo3, Catharine M. Holland1, Ian N. Hampson1*

1 University of Manchester, Viral Oncology, Research Floor, St Mary’s Hospital, Manchester, United Kingdom, 2 Obstetrics and Gynaecology, University of Nairobi, Nairobi, Kenya, 3 Cancer Treatment Centre, Kenyatta National Hospital, Nairobi, Kenya, 4 Obstetrics and Gynaecology, Mansoura University Hospital, Cairo, Egypt

Abstract

Background: In contrast to the developed nations, invasive cervical cancer (ICC) is the most common women's malignancy in Kenya and many other locations in sub-Saharan Africa. However, studies on survival from this disease in this area of the world are severely restricted by lack of patient follow-up. We now report a prospective cohort study of ICC in Kenyan women analysing factors affecting tumour response and overall survival in patients undergoing radiotherapy.

Methods and Findings: Between 2008 and 2010, 355 patients with histologically confirmed ICC were recruited at the Departments of Gynaecology and Radiotherapy at Kenyatta National Hospital (KNH). Structured questionnaires were completed recording socio-demographics, tumour response and overall survival following treatment with combinations of external beam radiation (EBRT), brachytherapy and adjuvant chemotherapy. Of the 355 patients, 42% (146) were lost to follow-up while 18% (64) died during the two year period. 80.5% of patients presented with advanced stage IIIB disease or above, with only 6.7% of patients receiving optimal combined EBRT, brachytherapy and adjuvant chemotherapy. Kaplan Meier survival curves projected two year survival at <20%.

Conclusion: Cervical cancer is preventable yet poverty, poor education, lack of cancer awareness coupled with an absence of regular screening programs, late patient presentation, sub-optimal diagnosis and treatments are major factors contributing to the alarmingly low survival rate of cervical cancer patients in Kenya. It is concluded that simple cost-effective changes in clinical practice could be introduced which would have a marked impact on patient survival in this setting.

Introduction

Invasive cervical cancer (ICC) is the most common cause of cancer deaths in Africa accounting for 10.4%, which represents one in five of all cancer deaths in African women[1]. Indeed sub-Saharan Africa bears the highest global burden of this fatal yet entirely preventable disease [2]. Global ICC incidence estimates stand at 500,000 cases annually producing 300,000 deaths of which 85% occur in developing countries such as Kenya [3].

The incidence of ICC has plummeted in the developed countries over the last two decades mainly due to the implementation of national screening programs [4]. In these countries screening detects cancers at an early stage in the disease progression and cure rates are high. Equally they have better treatment outcomes for more advanced disease. However, in low resource countries, 80% of cervical cancer cases are very advanced at presentation and treatment outcomes are poor [5]. Indeed in many developing countries the ICC mortality to incidence ratio is high and often exceeds 0.5 [6]. It is a fact that five out of six women with cervical cancer live in developing countries, which possess only 5% of the global resources for cancer control [5]. Thus it is ironic that countries least equipped to treat cervical cancer have the largest burden of this disease [7].

There are few cytology screening programmes with coverage sufficient to have any impact on ICC in developing countries where standard radiotherapy treatment facilities are also severely limited. For most patients, lack of screening and treatment facilities combined with poverty, late presentation, diminished awareness of the preventable nature of ICC and a fatalistic attitude are all contributory factors [8,9,10]. Other concerns are poor follow-up, lack of trained personnel, unaffordable treatments in combination with socio-economic and cultural factors which all operate within an ill-structured health-care system.
In addition, cervical cancer has been classified as an AIDS-defining illness in women with HIV infection which is a recognized prognostic indicator of poor treatment outcome for ICC [11]. Indeed the bulk of global ICC and HIV/AIDS cases are found in developing countries such as Kenya.

Radiation therapy (RT), surgery and adjuvant chemotherapy remain standard treatment options for ICC with RT being the first line treatment although significant numbers of patients fail to respond [3]. Radical surgery and RT are both equally effective for early (1A1 and 2A) disease with the former being the treatment of choice for young women with 1A2, 1B1 or 2A disease. Women with 1A1 disease are treated with cone biopsy or simple hysterectomy whereas chemo-radiotherapy is the treatment of choice for 1B2 disease and above [12].

In the current study we sought to characterise a range of factors which may affect tumour response to various treatment options available to women attending for radiotherapy at Kenyatta National Hospital (KNH). By analysing such factors it may prove possible to implement simple cost-effective changes in practice which may improve the survival of these patients.

Methods

The study was carried out between March 2008 and February 2010 where 355 consecutive patients with histologically verified ICC were recruited and followed up at KNH Departments of Radiotherapy and Gynecology. KNH is the University of Nairobi’s teaching and referral hospital with a 2000 bed capacity. The Departments of Obstetrics and Gynecology and Radiotherapy make up the largest ICC treatment centre in Kenya receiving patients from all over the country. Following recruitment a structured questionnaire was completed detailing the patients’ socio-demographics, obstetric and gynaecological history and sexual history. Questionnaires were available in English (universal medium of teaching and communication in Kenya), Swahili (national language) or in local dialect as applicable. Patient visits and management were as per hospital protocol including: pre-radiation assessment, marking for external beam radiotherapy (EBRT), EBRT for ~25 sessions and scheduled appointments. Pre-radiation assessment is standardized in the unit and entails complete physical examination, tests for haemoglobin, urea & electrolyte levels, chest x-ray, intravenous urogram (IVU) and examination under anesthesia for clinical staging according to the International Federation of Gynecology and Obstetrics 1995 (FIGO) system (see Table 1). Other radiological investigations like MRI, CT-Scan and ultra-sound scans were not routine due to cost implications. Thos who had low haemoglobin were transfused to at least 10 g/dL before commencing EBRT. The Unit cost-implications. Those who had low haemoglobin were transfused to at least 10 g/dL before commencing EBRT.

Statistical analysis

The main outcome measures were pelvic tumour control at 4–7 months from the last day of EBRT and overall survival following this or, where available, either brachytherapy or adjuvant chemotherapy. Data were entered and analyzed using SPSS version 16.0 (SPSS inc. Chicago, Illinois, USA). Comparison of means and proportion was done using Pearson’s Chi-square tests, Fishers exact test and Student t-test where appropriate. Odds ratio (OR), adjusted OR (AOR) and the 95% Confidence intervals (CI) were used to measure strengths of associations.

Relative risk (RR) in univariate analysis and adjusted relative risk (ARR) on multivariate analysis were also computed. Cox regression multivariate analysis was used to estimate the hazard of pelvic tumor, while Kaplan-Meier statistical methods were used to calculate survival curves. A p-value (two-tailed test) of 0.05 was considered statistically significant. The study was approved by the Kenyatta National Hospital’s Ethics and Research Committee (KNHREC), the University of Nairobi and the University of Manchester. All patients gave informed written consent to participate in this study.

Results

Age Distribution

The mean age was 49 (Range 21–94 years) with 28.2% of women aged between 40 and 49 yrs. The peak age for ICC incidence was 47 although this was 37 for HIV+ve Women.

Awareness of Cervical Screening Procedures

Only 126 (35.5%) of patients with ICC had heard of a cervical screening. Similarly, only 54 (15.3%) patients had ever had a cervical smear; of which 9 never received their results.

HIV Status and Whether in Receipt of Highly Active Antiretroviral Therapy (HAART)

Out of 355 patients, 189 (53.2%) had a HIV test prior to starting radiotherapy of which 52 (27.5%) were HIV+ve, while 137 (72.5%) were negative. Of the HIV+ve’s 27 (52.0%) were on concurrent chemo/radiotherapy (CCRT) and those eligible were admitted. The qualifying criteria for chemotherapy included functional renal status, a haemoglobin level >10 g/dL and a sufficiently stable clinical condition to withstand treatment related complications. Chemotherapeutic agents used were cisplatin 50 mg/M2 on day one and 5fluorouracil 1000 mg/m2 IV on days 1–4 with a repeat cycle every 21 days. Following this treatment, patients were referred to neighbouring countries for brachytherapy since the equipment available at KNH was non-functional during this study.

As part of the standard Unit protocol, during the follow up visits, patients’ symptoms were noted and a physical examination carried out using pelvic bimanual examination to assess tumour response to treatment. Any additional investigations such as ultrasound scans, CT-scans, X-rays, MRI, and biopsy were optional due to cost implications. Thus, for the current study, tumor control was primarily documented by physical examination [13,14] which was verified histologically whenever possible. Additionally, acute toxicity was documented using the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) Radiation Toxicity Grading [15]. Acute toxicity was defined as adverse events occurring during treatment and up to 90 days after completion of chemotherapy or radiotherapy.
highly active antiretroviral therapy (HAART) whilst 25 (48.0%) were not.

Haemoglobin (Hb) Status
At diagnosis 43.5% of patients had Hb >10 g/dL, while 33.8% had between 8–10 g/dL and 22.7% had Hb <8 g/dL. 37.0% of patients received a blood transfusion during the study period.

Histological Type and Staging
The most prevalent histological type of ICC was squamous cell carcinoma (SCC) (89.9%), followed by adenocarcinoma (AC) (5.6%). Two patients had anaplastic carcinoma, and another two had sarcoma of the cervix. Among those with SCC, most had moderately differentiated SCC (39.2%), with 32.0% and 21.3% having poorly differentiated and well differentiated disease respectively (Table 2). At the time of diagnosis the majority of patients (80.5%) presented with stage 2B disease or above as shown in Figure 1.

Table 1. FIGO staging system for cervical carcinoma prior to the 2009 revision.

| Stage | Findings |
|-------|----------|
| IA    | Micro-invasive carcinoma. |
| IB    | Macroscopic Invasive cancer confined to the cervix |
| IIA   | Tumour extending to upper third of vagina but not to the parametrium. |
| IIB   | Tumour extending to the parametrium. |
| IIIA  | Tumour involving the lower third vagina with no extension to the pelvic side wall |
| IIIB  | Tumour involving pelvic side wall and/or hydronephrosis or non-functioning kidney |
| IV A  | Tumour involving adjacent pelvic organs i.e. bladder or rectum. |
| IV B  | Extra-pelvic spread, e.g. metastasis to the liver, lungs etc |

All patients in this study were assessed using the same pre-2009 staging system. doi:10.1371/journal.pone.0078411.t001

Figure 1. FIGO staging of disease at diagnosis. The numbers of patients is shown above each bar (n = 355) of which the majority (80.5%) presented late at stage 2B and above. doi:10.1371/journal.pone.0078411.g001

Table 2. Histological types of disease (n = 355).

| Histological diagnosis     | Frequency | %   |
|----------------------------|-----------|-----|
| SCC                        | 318       | 89.5|
| Well Differentiated        | 68        | 19.3|
| Moderate                   | 124       | 34.2|
| Poorly                     | 102       | 28.6|
| Keratinizing               | 14        | 3.9 |
| Large Cell non-keratinizing| 9         | 2.5 |
| Small cell                 | 1         | 0.3 |
| Anaplastic Carcinoma       | 2         | 0.6 |
| Adenocarcinoma             | 20        | 5.6 |
| Mixed Sq.                  | 13        | 3.7 |
| Sarcoma of Cervix          | 2         | 0.6 |

Squamous cell carcinoma was the commonest histological type with 89.5%, while adenocarcinomas accounted for 5.6%. doi:10.1371/journal.pone.0078411.t002
Follow-Up

During the 2 year period out of the initial 355 patients, 146 (41.1%) patients were lost to follow-up. Of these 146 patients: 31 had a complete course of EBRT without any other treatments; 86 received partial courses of EBRT alone; 10 received a combination of partial EBRT and chemotherapy; 3 received partial chemotherapy alone; none had brachytherapy, while 16 received no definitive treatment at all. Therefore, among the 355 patients, 240 completed EBRT only.

Of those where follow up was available (n = 209), this had a mean duration of 16.8 months following commencement of treatment with a range of between 6 and 30 months. Out of these, 121 (57.9%) were diagnosed as having progressive disease while 64 (30.6%) patients died during the follow-up period. All the followed up patients received ~25 sessions of EBRT (2 Gy per session) although 67% of them also received additional adjuvant therapies such as external boost radiotherapy (48.6%), brachytherapy (11.4%), chemotherapy (25.7%) and 37.9% used traditional herbal remedies. Only 6.7% of patients received the recommended treatment of combined EBRT, brachytherapy and chemotherapy with the majority receiving only EBRT (Table 3). The criterion for chemotherapy was met by 42% whereas 36% were ineligible and with the majority receiving only EBRT (Table 3). The criterion for chemotherapy was met by 42% whereas 36% were ineligible and with the majority receiving only EBRT (Table 3).

All patients had a pelvic bimanual examination to assess tumour response to treatment. Additional investigations done in this regard were as follows: 26.8% had ultrasound scans, 21.1% had X-rays, 16.2% had CT-scan, 1.0% had secondary biopsies, while only one patient had a radio-isotope examination (bone scan). None had MRI.

Tumour Response

There was a significant association between the treatment options the patient received, the tumour response and subsequent overall survival (p<0.014 and 0.001 respectively) (Table 3). Patients who received optimal treatment of combined EBRT, brachytherapy and adjuvant chemotherapy had improved tumour control and better survival. Conversely, survival was significantly influenced by the observed tumour response to treatment when evaluated at 4–7 months following the initial 25 sessions of EBRT (P<0.001).

Although CCRT produced more cases of grade 3–4 overall acute toxicity than EBRT alone, the difference was not statistically significant. However, combined EBRT, brachytherapy and chemotherapy had significantly higher gastrointestinal grade 3–4 acute toxicity than EBRT alone (p<0.04) (Table 4). No deaths occurred directly due to acute treatment toxicity.

Comparison of histological diagnosis versus disease progression indicated that, those with poorly differentiated SCC were almost twice as likely to progress (OR = 2.0 (0.8–4.9) and 2.5 times more likely to die than those with well differentiated SCC. Indeed overall patient survival was clearly influenced by both histological diagnosis (p<0.046) and FIGO disease stage (p<0.001) (Table 5).

Kaplan Meier Survival Curves

Among those who died, the mean time to death after the onset of treatment was 15.1 months while the median survival was 15.0 months as shown by Kaplan Meier curves (Figure 2). Median survival for FIGO Stage I was 21 months while stages II, III, and IV were 18, 15 and 11 months respectively. At less than 20% the reported two year survival rate is very low.

Discussion

The most important finding from this study was the low overall survival rates across all ICC FIGO stages among patients undergoing treatment at the main cancer referral centre in Kenya. To our knowledge, this is the first such investigation carried out in this geographical location. Another important finding was the low level of awareness of the importance of cervical cancer screening and equally disappointing were the low numbers of previous cervical smears carried out in the study population.

Our results demonstrate there is a significant association between the kind of treatment options that the patient received and overall survival (p<0.001). As expected, patients who received optimal combined therapies had better tumour control and improved overall survival. A number of women reported the use of traditional herbs although these were not standardized and there was no difference in treatment outcomes between those who used these and those who did not.

In spite of previous clinical trials which showed up to 30% improvement in overall survival of patients treated with CCRT [16,17,18], due to cost implications, relatively few patients actually received this treatment despite this being prescribed. Not surprisingly, those who did receive CCRT had better overall survival than those who received EBRT alone. In our study those patients who were given chemotherapy received mainly cisplatin and 5-fluorouracil since the addition of both these agents has been shown to significantly improve the survival rate of women with locally advanced ICC without increasing the rate of late complications.

Table 3. Correlation of treatment options with tumour control and overall survival.

| Therapy combinations | Total | Tumour control at 4–7months | Survival (No./%) |
|----------------------|-------|-----------------------------|------------------|
|                      | No./% | No Lesion | Residual | Alive | Dead |
| 1. EBRT alone        | 78(37.3) | 65 (40.1) | 13 (27.7) | 49 (62.8) | 29 (37.2) |
| 1+ External boost    | 47(22.5) | 28 (17.3) | 19 (40.4) | 24 (51.0) | 23 (49.0) |
| 1+ Brachy            | 18(8.6) | 15 (9.3) | 3 (6.4) | 14 (77.8) | 4 (22.2) |
| 1+ chemo             | 52(24.9) | 41(28.3) | 11 (23.4) | 45 (86.5) | 7 (13.5) |
| 1+ brachy + chemo    | 14(6.7) | 13 (8.0) | 1 (2.1) | 13 (92.8) | 1 (7.1) |
| Total/ p-value       | 209(100) | p<0.014 | p<0.001 |

Most patients received only the initial EBRT (37.8%), while 24.9% and 8.6% got additional chemotherapy and brachytherapy respectively. Only 6.7% of patients received combined treatment of EBRT, brachytherapy and chemotherapy. The kind of treatment options the patient received seemed to significantly affect tumour response and overall patient survival as shown here. On adjusting for age and HIV status through multivariate cox proportional hazards regression analysis and multinomial logistic regression, this statistical significance was maintained.

doi:10.1371/journal.pone.0078411.t003
treatment-related side effects [19]. However, it should be noted that our interpretations of treatment efficacy are limited by the low frequency of followed up patients, limited duration of follow-up and the small number of cases receiving adequate treatment. In a retrospective analysis of management outcomes of 3,892 cases of locally advanced ICC’s in Chennai India it was shown that treatment with EBRT alone produced the lowest 5-year disease free survival (DFS) (37%). Surprisingly use of CCRT produced little improvement in DFS (41%) although inclusion of brachytherapy with EBRT significantly enhanced this (58%, p<0.001). However, the combination of CCRT with brachytherapy resulted in the best DFS (69%), irrespective of disease stage. These findings clearly indicate that current best practice for locally-advanced ICC should be CCRT which includes brachytherapy [20] and there are many studies which support the benefits of CCRT for the management of ICC [21,22,23].

Table 4. Acute toxicity (grade 3–4) following various treatment modalities (N = 209).

| Variable          | All Patients | EBRT alone | EBRT + Chemo | EBRT + Brachy + Chemo | P-value |
|-------------------|--------------|------------|-------------|-----------------------|---------|
|                   | (n = 209)    | (n = 125/59.8%) | (n = 52/24.9%) | (n = 18/8.6%) | (n = 14/6.7%) |         |
| Overall toxicity  | 73/34.9%     | 39/31.2%   | 19/36.5%    | 8/44.4%               | 7/50.0% | 0.56    |
| Gastro-intestinal | 50/23.9%     | 26/20.8%   | 14/26.9%    | 4/22.2%               | 6/42.9% | 0.04    |
| Skin toxicity     | 34/16.3%     | 17/13.6%   | 9/17.3%     | 5/27.8%               | 3/21.4% | 0.39    |
| Genito-urinary    | 25/12.0%     | 11/9%      | 9/17%       | 3/16%                 | 2/14%   | 0.18    |

Incidence of acute toxicity (grade 3–4) following various treatment modalities (N = 209). Although chemoradiation had higher cases of grade 3–4 overall toxicity than EBRT alone, the difference was not statistically significant. However, combined EBRT, brachytherapy and chemotherapy had significantly higher gastrointestinal grade 3–4 toxicity than EBRT alone (p<0.04).

doi:10.1371/journal.pone.0078411.t004

Table 5. Correlation of FIGO staging and histological diagnosis with survival.

| Staging       | Alive n/% | Dead n/% | P-value |
|---------------|------------|----------|---------|
| 1A (2)        | 1 (50.0)   | 1 (50.0) |         |
| 1B (13)       | 10 (76.9)  | 3 (23.1) |         |
| IIA (19)      | 16 (84.2)  | 3 (15.8) |         |
| IIB (69)      | 59 (85.5)  | 10 (14.5) | 0.001   |
| IIIA (35)     | 21 (60.0)  | 14 (40.0) |         |
| IIIB (50)     | 33 (66.0)  | 17 (34.0) |         |
| IV A (13)     | 4 (30.8)   | 9 (69.2)  |         |
| IV B (8)      | 1 (12.5)   | 7 (87.5)  |         |
| Total         | 145 (69.4) | 64 (30.6) |         |
| HPE (SCC) results |          |          |         |
| Well Differentiated | 37 (27.6) | 7 (12.3) |         |
| Moderately     | 56 (41.8)  | 30 (52.6) |         |
| Poorly         | 36 (26.9)  | 19 (33.3) | 0.046   |
| Keratinizing   | 2 (1.5)    | 1 (1.8)   |         |
| Large non-Keratinizing | 3 (2.2) | 0 (0.0) |         |
| Total          | 134 (70.2) | 57 (29.8) |         |

Patients with poorly differentiated SCC were more than 2.5 times likely to die as compared to those with well differentiated SCC, while those with more advanced disease staging had as expected, higher death rates (p<0.046, and 0.001 respectively). Even after adjusting for age and HIV status using multivariate cox proportional hazards regression analysis and multinominal logistic regression, the disease stage was significantly associated with overall survival.

doi:10.1371/journal.pone.0078411.t005
Figure 2. Kaplan Meir Survival Curves. (A). Overall median survival of 15.0 months; (B) Stratified median survival based on FIGO staging, whereby, stage I was 21 months with stages II, III, and IV having 18, 15 and 11 months respectively. 
doi:10.1371/journal.pone.0078411.g002
empowerment of practitioners needs to be combined with provision of the necessary infrastructure to ensure one-stop screening and treatment where VIA or VILI is used to inform the decision for immediate cryotherapy or LEEP. This should ensure cost-effective access to preventive and early treatment of premalignant cervical lesions. In addition there is also a need to establish an effective referral systems from primary health centres to regional/national centres for specialist management of invasive cancer. Furthermore, it is clear that increased investment in capacity building and infrastructure will facilitate decentralised management of ICC to regional centres which should alleviate the congestion at single national referral hospitals to reduce the waiting time between diagnosis to treatment.

Concerning the influence of ICC staging and histology, our results showed that, the majority of patients (80.5%) presented with advanced stage 2B or above (Figure 1) and is consistent with previous studies carried on in Africa where >80–90% of women present with late stage disease [33,34]. However, this does not explain the low overall survival observed in the current study. For example, developed countries have reported 5 year overall ICC survival rates of approximately 68% [12,35,36]. Indeed 80–90% of women with stage I and 50–65% with stage II ICC are still living 5 years after treatment. Furthermore, 25 to 35% of women with stage III and 15% of those with stage IV cancer have >5 year survival [35]. Additionally, in the US, Brookfield et al (2009) found an overall median survival in 5367 ICC patients of 43 months. However, this was lower at 28.8 months in African Americans when compared to 47.1 months in Caucasians (p<0.001) [37]. In our study, the median survival was extremely low at 15.1 months. This clearly indicates that early detection is not the only reason for higher survival among patients in developed countries since improved treatment outcomes are seen across all FIGO stages of the disease. The explanation for this poor survival in African locations is not clear although it is possible this could be related to inaccurate clinical staging.

Clinical examination (CE) was the mainstay of assessing initial staging and response to treatment in our study. Although various investigations were requested to supplement CE, few patients could afford these additional tests which were: ultra-sound (27%), X-Ray (21%) and CT (6%). In our study no patient had MRI due lack of availability and high cost. Nevertheless, the correlation between CE and MRI has been reported as good in early stage disease although this worsens with advanced local disease [38]. Kodaira T, et al (2003) also found that MRI provides improved diagnostic information over FIGO stage for patients with bulky disease and yet this is still a good prognostic factor for patients with non-bulky disease (volume <50 cc)[39]. However, for ICC patients selected for non-surgical treatment, radiological assessment of tumor size and lymph node status does provide valuable prognostic information over and above FIGO staging alone [40]. Thus it is possible that the poor treatment outcome reported in our study could have been due to ‘under-staging’ where women had more advanced disease than was diagnosed. Undoubtedly, another contributory factor was that it took an average of 2–3 months from diagnosis to commencement of treatment for most cases. Indeed, 21% were initiated within one month, 44% within 2 months, 31% within 3 months while 4% did not commence treatment until the 4th month after diagnosis. The reasons for these ranged from socio-economics, difficulties with travelling, inability to gain admission to crowded hospital oncology wards and queues of patients awaiting treatment with the single radiotherapy machine at KNH.

Although lymph node (LN) status is undeniably the most important prognostic indicator, FIGO staging is most often used in low resource settings [41]. However, this has an error rate of approximately 25% in stage I and II disease and 65–90% in stage III and IV disease [41] which undoubtedly contributes to the differences in survival observed between patients who are ascribed the same disease stage. For example, in stage IB disease, the survival rate is 85%–95% for patients with negative nodes at surgery and 45%–55% for those with positive nodes [42]. Thus it is clear that these errors are most likely due to under-staging since it is difficult to accurately measure the extra-cervical spread of disease [41]. This has prompted the increased use of CT and MRI in the developed world. Even though LN involvement is the single most important prognostic factor for ICC [40], in resource poor countries such as Kenya, CE is still most commonly used. In order to improve this, it may be possible to change referral procedures to decrease the long waiting time between diagnosis and commencement of treatment since this may reduce the risk of progression of ICC to less treatable stages.

Concerning treatment related toxicity, our study showed that although CCRT had higher cases of grade 3–4 overall toxicity than EBRT alone, the difference was not statistically significant. However, combined CCRT and brachytherapy, not surprisingly, had significantly higher gastrointestinal grade 3–4 toxicity than EBRT alone (p<0.04). There was no significant difference in genitourinary and skin toxicities from any of the treatment combinations. Therefore use of CCRT for the treatment of locally advanced ICC is feasible and produced acceptable toxicity. EBRT was well tolerated and all patients completed the whole course. These findings are consistent with previous studies which showed that non-haematological grade 3 and 4 toxicities were considerably more common in the CCRT groups than the EBRT groups [43]. Furthermore gastrointestinal toxicity was twice as common in women randomised to CCRT (P<0.001), with 8% of these patients suffering severe or life threatening adverse events. In the current study, we did not assess haematological toxicity.

Our results showed there was a high incidence of anaemia in our patients with 37% requiring blood transfusion during the course of their treatment. Given that tumour hypoxia is a well known predictor of response to RT treatment this scenario could also have contributed to the poor outcomes. Iron deficiency and tumor bleeding are common causes of anemia in ICC [44] which are treated with either transfusion and/or erythropoietin prior to treatment. Indeed many investigators have demonstrated tumour hypoxia has a negative impact on the ability of RT to influence loco-regional control of tumours [45,46,47] and hypoxic tumour cells are also known to be more resistant to chemotherapy. Thus, hypoxia plays a key role in tumour prognosis since it enhances therapy resistance and also promotes the development of more malignant phenotypes [48].

Concerning the impact of HIV status on survival from ICC, in our patient cohort, 27.5% of those tested were positive for HIV and had poorer survival when compared to HIV-ve women and yet, surprisingly, this did not achieve statistical significance. A similar investigation carried out in the same institution between 1989 and 1998 found a HIV prevalence of 15% and concluded that the prevalence in ICC patients was comparable to that found in the general population at the time.[49]. However, in the USA, cervical cancer has been reported to be the most common malignancy among women with AIDS [50]. Indeed based on data from the CDC, the incidence of cervical cancer is approximately 900 per 100,000 in women with AIDS, as compared with about 10 per 100,000 in the general population [51]. These data indicate that not only are women with HIV more likely to develop ICC, but also the course of the disease may be worsened by the presence of the virus. Moreover, HIV-positive women with ICC are more
likely to be diagnosed at a later stage, have a poorer response to therapy and have a higher rates of recurrence than HIV negative women [11]. Furthermore, ICC is known to progress rapidly in HIV positive women [32,53]. In addition previous work has shown that HIV infection is also associated with increased risk of multisystem radiation-related toxicity; treatment interruptions and locoregional failure following EBRT [11]. In our study, since 46.8% of women had unknown HIV status it is possible that some of these could have been HIV+ve which could contribute to the observed poor outcomes. Interestingly, current HIV prevalence in Kenya is 8.0% among women in the general population [54].

Obtaining follow up data is a massive problem in African locations and of the initial 355 patients enrolled in our study, 146 (41.1%) patients were lost to follow-up which is typical for comparable geographical locations. It is most likely that financial considerations were the driving force behind this level of attrition since a study carried out in Nigeria showed that of 95 ICC patients referred for RT, only 19% (n = 18) actually underwent the procedure whilst the remaining 81% (n = 77) did not attend due to lack of funds [55]. It is also very significant that all the patients that underwent RT were in the upper social class and used approximately 30% of their annual income for the treatment. Thus, our study further serves to emphasize the difficulties encountered in ensuring patients receive adequate and timely diagnosis, staging, treatment and follow-up in this area of the world.

It is very clear that the magnitude of the cancer burden in many low resource countries is poorly understood owing to lack of monitoring systems to assess cancer incidence, survival and mortality. Therefore the current study aims to raise awareness of the scale of this problem for ICC in Kenya. Cancer diagnosis and care services are woefully inadequate in low- and middle-income countries with late-stage presentation being a common feature that results in less potential for cure and more need for symptom management [56]. And yet palliative care services are also grossly inadequate in such countries, with many cancer patients dying unnecessarily painful deaths.

In our study very few women received the optimal recommended treatment and therefore it is perhaps not surprising that the outcomes are so poor even for women with stage 1 disease. What are the barriers to providing full treatment? The main obstacle is that patients have to pay and simply can not afford it. Since the health system funding in Kenya is unlikely to change, it is suggested that implementation of a workable screening programme combined with a system for treating women with early-stage abnormal smears should be considered as a viable option. Clearly prevention is far preferable and much cheaper than the previously discussed treatment options for ICC. However, this is not straightforward! Any type of screening service will have to be quality controlled, there must be adequate coverage and this must be accompanied by an educational programme to encourage women to attend. Cultural barriers, erroneous beliefs and misconceptions must be addressed which are common problems in many developing nations. What factors has the present study identified which could improve survival of women who currently develop ICC in Kenya? It is very clear that there is a great need for a standardized system of follow-up which focuses mainly on the actual care that women are getting. One suggestion would be to standardise diagnostic and follow-up investigations making these simpler which would cut costs and potentially reduce the lead-time from diagnosis to commencement of treatment. For example, given that so few women are able to get the recommended pre-treatment imaging (CT/MRI), it may prove more effective for all women to get EUA with biopsy and X-ray to check for hydronephrosis which will then form the basis of treatment decisions. Since the majority of women are self-funding and have limited resources it makes sense to use these monies for the most important treatment-associated costs. This, should, in turn, increase the numbers able to complete the treatment program.

Unlike the situation in the majority of developed countries it is important to identify and prioritize which resources address healthcare needs most effectively and to consider alternative approaches in countries like Kenya. Therefore, given the challenges in implementing organised screening programs, the value of implementing HPV vaccination (i.e. in 9–13 year old girls) cannot be over emphasized since this will eventually build a cohort of women at very low risk of cervical cancer. Prophylactic HPV vaccines as a primary intervention against ICC may be used as part of the WHO’s widespread Expanded Program of Immunization (EPI) i.e. childhood vaccination program in developing countries [57]. Additionally, there is now an opportunity to implement this approach in Sub Saharan Africa with the assistance of GAVI which will clearly help establish the necessary capacity and infrastructure. Indeed such partnerships will ensure increased access to immunization for children in poorer countries where cost is obviously a major issue although, in the long term, this approach may prove to be the most cost-effective.

In summary, more studies of this type are needed to strengthen ICC as a public health priority in Sub Saharan Africa since publicizing the extent of this problem may help to drive implementation of some of the potentially life saving changes discussed.

Acknowledgments

Our gratitude goes to Alex Mwaniki of the University of Nairobi and Christopher Roberts of University of Manchester for their invaluable input in statistical analysis.

Author Contributions

Conceived and designed the experiments: IOM PG AO CMH LH AG INH. Performed the experiments: IOM AO INH. Analyzed the data: IOM Roberts of University of Manchester for their invaluable input in statistical analysis.

References

1. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, et al. (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 348: 518–527.
2. WHO (2004) The global burden of disease: 2004 update - Annex A; WHO; 2004 Deaths and DALYS 2004 Annex tables. Available at https://extranet.who.int/iris/restricted/bitstream/10663/43942/1/9789241563710-eng.pdf Accessed 4th October 2013.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, et al. (2008) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893–2917.
4. Pisani P, Bray F, Parkin DM (2002) Estimates of the worldwide prevalence of cancer for 25 sites in the adult population. Int J Cancer 97: 72–81.
5. WHO (1996) Cervical cancer control in developing countries: memorandum from a WHO meeting. Bull World Health Organ 74: 345–351.
6. WHO (2007) Cancer Incidence in Five Continents. In: Curado MP EB, Shin HR, StormH, Ferlay J, Haanen M, Boyle P, Lyon: IARC Scientific Publications.
7. Kirchner HC, Hoskins W, Small W Jr, Thomas GM, Trimble EL (2010) The development of priority cervical cancer trials: a Gynecologic Cancer InterGroup report. Int J Gynecol Cancer 20: 1092–1100.
8. Aniebue PN, Aniebue UU (2010) Awareness and practice of cervical cancer screening among female undergraduate students in a Nigerian university. J Cancer Educ 25: 106–108.
9. Anorlu RI (2008) Cervical cancer: the sub-Saharan African perspective. Reprod Health Matters 16: 41–49.
32. Louie KS, de Sanjose S, Mayaud P (2009) Epidemiology and prevention of HIV-positive women in southeastern Nigeria. Medscape J Med 11: 19.

31. Gichangi P, Bwayo J, Estambale B, Rogo K, Njogu E, et al. (2006) HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. Gynecol Oncol 100: 403–411.

30. Watkins MM, Gabali C, Winkleby M, Gaona E, Lebaron S (2002) Barriers to cervical cancer counselling and screening at the outpatient clinics in Nigeria. J Obstet Gynaecol 29: 754–756.

29. Claeys P, Gonzalez C, Gonzalez M, Page H, Bello RE, et al. (2002) An ethnographic study of cervical cancer and practice about cervical cancer and Pap smear testing among patients at Kenyatta National Hospital, Nairobi, Kenya. Int J Gynecol Cancer 13: 827–838.

28. Spence AR, Goggin P, Franco EL (2007) Process of care failures in invasive cervical cancer: 12-Year survival after radiotherapy. Int J Gynecol Cancer 16: 1313–1318.

27. Gichangi P, Estambale B, Bwayo J, Rogo K, Njuguna E, et al. (2006) HIV and attitudes of female patients admitted at Muhimbili National Hospital, Dar es Salaam, East Africa Med J 73: 575–578.

26. Gichangi P, Estambale B, Bwayo J, Rogo K, Njuguna E, et al. (2006) HIV and attitudes of female patients admitted at Muhimbili National Hospital, Dar es Salaam, East Africa Med J 73: 575–578.

25. Gatun JL, Kigula-Mugambe JB (2007) Treatment outcomes of cervical cancer in Sub-Saharan Africa. Radiother Oncol 83: 94–96.

24. Gatune JL, Nyamongo IK (2005) An ethnographic study of cervical cancer among women in rural Kenya: is there a folk causal model? Int J Gynecol Cancer 15: 1049–1059.

23. Vale CL, Tierney JF, Davidson SE, Drinkwater KJ, Symonds P (2010) Substantial improvement in UK cervical cancer survival with chemoradiotherapy: results of a Royal College of Radiologists’ audit. Clin Oncol (R Coll Radiol) 22: 590–601.

22. Kesic V (2006) Management of cervical cancer. Eur J Surg Oncol 32: 832–837.

21. Pearcey R, Miao Q, Kong W, Zhang-Salomons J, Mackillop WJ (2007) Impact of chemoradiotherapy in the treatment of cervical cancer in Sub-Saharan Africa. Radiother Oncol 83: 94–96.

20. Shanta V, Selvakumary G, Swaminathan R, Shanthiselvam P (1991) Cervical cancer as an AIDS-defining illness. Obstet Gynecol 77: 217–218.

19. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, et al. (2004) Pelvic irradiation with concurrent weekly cisplatin and radiotherapy for cervical carcinoma: results of a Royal College of Radiologists’ audit. Clin Oncol (R Coll Radiol) 22: 590–601.

18. Berclaz G, Gerber E, Beer K, Aebi S, Greiner R, et al. (2002) Process of care failures in invasive cervical cancer: 12-Year survival after radiotherapy. Int J Gynecol Cancer 16: 1313–1318.

17. Gatune JL, Nyamongo IK (2005) An ethnographic study of cervical cancer and practice about cervical cancer and Pap smear testing among patients at Kenyatta National Hospital, Nairobi, Kenya. Int J Gynecol Cancer 13: 827–838.

16. Gichangi P, Estambale B, Bwayo J, Rogo K, Njuguna E, et al. (2006) HIV and attitudes of female patients admitted at Muhimbili National Hospital, Dar es Salaam, East Africa Med J 73: 575–578.

15. Cox J (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31: 1341–1346.

14. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, et al. (1999) A comprehensive review. Trop Med Int Health 14: 1287–1302.

13. Samant R, Kobeleva S, Choan E, Balaraj K, Tien Le, et al. (2010) Evaluating the adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 32: 1301–1307.

12. Samant R, Kobeleva S, Choaan E, Balaraj K, Tien Le, et al. (2010) Evaluating the adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 32: 1301–1307.

11. Gichangi P, Bwayo J, Estambale B, Rogo K, Njuguna E, et al. (2006) HIV and attitudes of female patients admitted at Muhimbili National Hospital, Dar es Salaam, East Africa Med J 73: 575–578.

10. Dim CC, Dim NR, Ezegeui HU, Ireme AC (2009) An unmet cancer screening need of HIV-positive women in southern Nigeria. Medscape J Med 11: 19.

9. Gichangi P, Bwayo J, Estambale B, Rogo K, Njuguna E, et al. (2006) HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. Gynecol Oncol 100: 403–411.

8. Samant R, Kobeleva S, Choaan E, Balaraj K, Tien Le, et al. (2010) Evaluating the adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 32: 1301–1307.

7. Sedli A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, et al. (1999) A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol 73: 177–183.

6. Gichangi P, Estambale B, Bwayo J, Rogo K, Ojwang S, et al. (2003) Knowledge and practice about cervical cancer and Pap smear testing among patients at Kenyatta National Hospital, Nairobi, Kenya. Int J Gynecol Cancer 13: 827–838.

5. Gatune JL, Nyamongo IK (2005) An ethnographic study of cervical cancer among women in rural Kenya: is there a folk causal model? Int J Gynecol Cancer 15: 1049–1059.

4. Gichangi P, Estambale B, Bwayo J, Rogo K, Ojwang S, et al. (2003) Knowledge and practice about cervical cancer and Pap smear testing among patients at Kenyatta National Hospital, Nairobi, Kenya. Int J Gynecol Cancer 13: 827–833.

3. Dim CC, Nwaqua UI, Ezegeui HU, Dim NR (2009) The need to incorporate routine cervical cancer counselling and screening in the management of women at the outpatient clinics in Nigeria. J Obstet Gynaecol 29: 734–736.

2. Spence AR, Goggin P, Franco EL (2007) Process of care failures in invasive cervical cancer: systematic review and meta-analysis. Prev Med 45: 93–106.

1. Claeys P, Gonzalez C, Gonzalez M, Page H, Hannel B, et al. (2001) Determinants of cervical cancer screening in a poor area: results of a population-based survey in Rivas, Nicaragua. Trop Med Int Health 7: 935–941.