SURVIVAL RATE OF PATIENTS WITH ORBITAL SQUAMOUS CELL CARCINOMA IN KENYATTA NATIONAL HOSPITAL;

A COMPARATIVE RETROSPECTIVE COHORT STUDY

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DECLARATION

I declare that this dissertation is my original work and has not been presented for the award of a degree in any other university.

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee for Cancer Staging
CIN	Conjunctival intraepithelial neoplasia
CIS	Carcinoma-in-situ
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IVCM	In vivo Confocal Microscopy
KNH	Kenyatta National Hospital
OSSN	Ocular surface squamous neoplasia
RCT	Randomised Control Trial
SCC	Squamous cell carcinoma
ToB	Toluidine Blue
UV	Ultraviolet

ABSTRACT

Background: Orbital Squamous cell carcinoma (SCC) is an advanced stage of a spectrum of disease referred to as ocular surface squamous neoplasia (OSSN). Orbital invasion may occur if left untreated or from residual tumour cells after treatment of OSSN. The mainstay of treatment at this stage is exenteration with or without adjuvant radiotherapy. In Kenya most cases of orbital SCC are diagnosed when it is in the late stage. However, there is little evidence that the use of adjuvant radiotherapy in the treatment and management of the disease improves survival of the patients.

Objective: To compare survival rates in patients with orbital SCC who underwent exenteration alone versus those who were prescribed adjuvant radiotherapy post-exenteration at Kenyatta National Hospital (KNH).

Methods: All histologically confirmed exenteration cases of orbital SCC during the period January 2013-December 2016 were included. Cases were identified from the KNH cancer database. Clinical information from medical records was captured in a questionnaire and vital status confirmed from participants or next of kin. The primary outcome measure was to compare one-year survival rates between the treatment groups using the Kaplan-Meier method and correlates of survival were determined using univariate analysis. Statistical Package for Social Scientists (SPSS) Version 22.0 and Stata version 15 were used for analysis.

Results: A total of 56 participants were included, with 14 in the exenteration alone group and 42 in the exenteration plus adjuvant radiotherapy group. Patients who had exenteration alone had a trend to higher survival than exenteration plus radiotherapy both by intention-to-treat (100% vs 55%, p=0.07) and per-protocol (84% vs 77%, p=0.51) but this difference was not statistically significant. Survival probability was affected only by intracranial tumour extension (p=0.01) all other factors assessed including sex, HIV status, ART use, occupation and non-completion of radiotherapy were not statistically significant. Repeat surgery was performed in 7.1% of participants.

Conclusion: There was no difference in survival rates between patients who underwent exenteration alone versus those who underwent exenteration and received adjuvant radiotherapy. Baseline characteristics did not significantly influence survival. Intracranial extension of tumour was the only factor found to negatively influence survival rates. The probability of survival was not negatively affected in those who underwent repeat surgery**.**

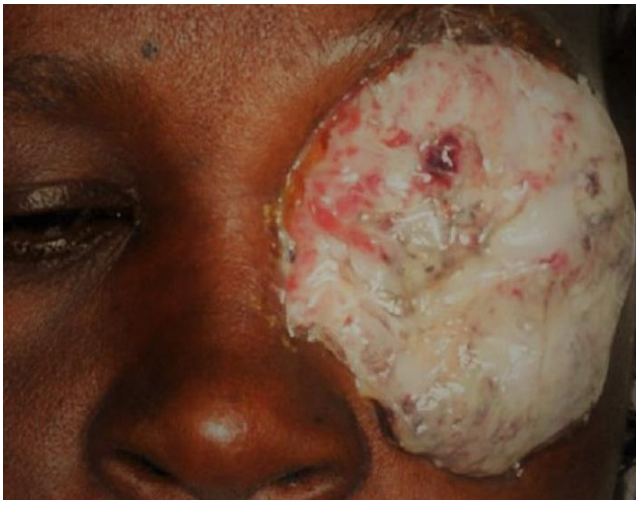
1. INTRODUCTION

1.1.Orbital Squamous Cell Carcinoma

Orbital Squamous cell carcinoma (SCC) is an advanced stage of a spectrum of disease referred to as ocular surface squamous neoplasia (OSSN), which is known to have different degrees of dysplasia on histology(1). It may also arise from lid margin squamous cell carcinoma. In Africa OSSN is reported to be the most common malignancy of the ocular surface and presents in younger individuals as compared to the West where it is reported to present more frequently in the elderly(2). Whereas there are known classifications regarding OSSN histopathological and cancer grading by different authorities, very little has been described for orbital SCC(3,4).

In Kenya most cases of orbital SCC are diagnosed when it is in the late stage.

Figure 1: Orbital Squamous Cell Carcinoma(5)



1.2.Treatment of Orbital SCC

Historically, treatment for orbital SCC has been surgical with or without adjuvant radiotherapy. The main type of surgery that has been conducted is lid or non-lid sparing exenteration, however despite these surgical approaches recurrence rates have still been described as high as 43%, hence adjuvant radiotherapy is therefore given post-surgery(6–10).

2. LITERATURE REVIEW

2.1. How common is Orbital SCC?

OSSN is the most common ocular surface tumor as described in a number of series and can present in the orbital stage (5,11–14). There are few studies describing the incidence of orbital SCC at first presentation. However two case series reported 36% of patients in Nepal and 80% in Zimbabwe presented with orbital SCC(15–17). The difference may have been due to the high HIV prevalence in Zimbabwe (13.3%) compared to Nepal (0.45%)(18,19).

In Kenya, a recent study on orbital SCC, reported an incidence of 81% of participants with a fungating mass at presentation(20). This can be attributed to the fact that the study site was a National referral centre.

2.2.Risk Factors

Current evidence indicates several risk factors associated with OSSN. These include HIV infection, which has also been reported to be associated with more severe OSSN disease compared to the disease seen in HIV negative individuals(14,21). Other factors include ambient solar ultraviolet exposure, allergic conjunctivitis and HPV infection(21–25).

Risk factors for developing orbital squamous cell carcinoma have not been extensively described, however, it is likely due to delays in treatment seeking, as well as delays in management of the disease at health care level(20,26).

2.3.Clinical Manifestations and Histology

In our setting, patients generally present with proptosis or large fungating orbital tumors in more advanced SCC, owing to the delays that have been mentioned earlier(20,26).

These advanced SCC have been described to initially present as either conjunctival or eyelid tumours which subsequently penetrate the corneoscleral lamella into the anterior chamber of the eye or can breach the orbital septum to invade the soft tissues of the orbit, sinuses, and via perineural invasion, spread to the brain(27,28). These tumours have also been known to spread via the lymphatics and blood during the course of the disease(28).

They are therefore considered to be potentially sight-threatening and even life-threatening tumours which require aggressive management.

Histologically certain dysplastic cellular features point towards orbital squamous cell carcinoma such as a high mitotic index, hyperplastic epithelium, bright nucleoli with large nuclei as well as loss of goblet cells and normal cell polarity(29,30).

2.4.Diagnosis

Diagnosis of orbital squamous cell carcinoma remains a challenge in our setting. There are several limiting factors in making a diagnosis. These include no standardized guidelines on making a diagnosis, limited diagnostic tools to be employed as well as delays in systems at the treatment facilities.

We therefore largely rely on clinical judgement coupled with computed tomography scans which may not be always be reliable as several other orbital tumours and inflammatory processes can present in a similar manner as orbital squamous cell carcinoma.

Regarding extent of spread of the tumour, clinicians also rely on clinical judgement based on involvement of the caruncle and forniceal conjunctiva. Orbital extent of disease can be assessed radiologically, as well as bone invasion and perineural spread. Lastly, histological features are used in diagnosis and assessing extent of tumour spread by assessing whether the margins are free of tumour or not. Generally surgeons attempt to excise upto 4mm from the tumour margin "no touch technique"(28). However in some instances intraoperatively, it may be difficult to differentiate normal from cancerous cells, extent of the tumour and site of the orbital invasion especially with larger tumours, which may make it difficult to ensure tumour free margins.

In our era of HIV and its associated comorbidities, patients may present in an atypical manner and this further confuses the clinical picture that clinicians are faced with.

2.5.Treatment

A number of treatment modalities have been described for non-invasive OSSN these include topical 5-flourouracil, topical mitomycin-C as well as subconjunctival interferon-α2b(9,10,31–33). The current standard of treatment in many settings is wide excision of the lesion with 2-4mm margins, followed by long-term monitoring for recurrence(11,28). Reported recurrence rate of OSSN is 15-52%, however, with the modern surgical techniques the recurrence rate can be as low as 5%(9,28,32,34). OSSN has a good prognosis when diagnosed and treated early.

The main goal of surgery is largely to achieve complete removal of the tumor in order to decrease the chances of recurrence(33). However, in our setting where patients present late with orbital disease, the treatment options include radical surgery such as exenteration followed by adjuvant radiotherapy.

2.5.1. Orbital Exenteration

Orbital exenteration (OE) involves the removal of globe and the soft tissues of the orbit. It is a disfiguring procedure which may involve the appendages, eye- lids and, sometimes, a varying amount of surrounding skin and bone(35,36).

OE is largely considered in cases of destructive malignancies such as SCC, intraocular melanomas whereby local control of the tumor would benefit the patient as well as in certain fungal infections as orbital zygormycosis(36)

Several types of OE are performed, they include lid sparing and non- lid sparing; whereby in the latter, the eyelids are also surgically excised. Further classification is based on the amount of orbital tissues removed:

1. Subtotal: The eye and adjacent intraorbital tissues are removed, leaving the periorbita insitu.
2. Total: All intraorbital soft tissues, including periorbita, are removed.
3. Extended: All intraorbital soft tissues are removed, together with adjacent structures (usually bony walls and sinuses)(36).

2.5.2. Radiotherapy

Radiation therapy is routinely used as adjuvant therapy after surgery in orbital squamous cell carcinoma due to the high local recurrence rates (up to 43%) that have been reported in literature(9,10). Ionizing radiation is a highly effective therapeutic modality but it is also harmful to healthy tissues, hence a balance between the dose of radiation and minimizing damage to normal tissues must be achieved(37).

Ionizing radiation can be classified as;

1. Electromagnetic radiation; includes χ-rays and γ-rays. The latter are emitted by radioactive isotopes such as cobalt-60, iridium-192, and iodine-125.

2. Particulate radiation; includes electrons, protons, neutrons, α-particles etc.(37).

Radiotherapy has also been described according to the distance of the source from the target tissue. It includes teletherapy (far), also known as external beam radiotherapy (EBRT), and brachytherapy (near). In EBRT, the most common form is the linear accelerator-derived radiation therapy. Newer techniques include proton, neutron stereotactic radiosurgery, gamma knife and intensity modulated radiation therapy. Whereas brachytherapy involves placing the radioactive source close to or inside the tumour(37,38).

Ionizing radiation damages DNA directly by causing ionization of atoms or indirectly by interaction with water and generation of reactive oxygen species through a number of steps. As our bodies contain 55-60% of water, radiation is most likely to strike water than any other matter. During radiotherapy these reactive oxygen species cause damage to DNA, leading to apoptosis. In the presence of oxygen, permanent damage is caused by double stranded breaks in the DNA(39).

EBRT is delivered in multiple small doses over a number of weeks, this method increases tumor damage by allowing for reoxygenation and cells reorganization in the cell cycle making them more sensitive to the radiotherapy, at the same time allowing normal tissues to regenerate in between the fractions(37).

In our setting, EBRT is the radiotherapy modality available and treatment is usually delivered in multiple small fractions (1.8- 2Gys/day) over a period of weeks (up to 6 weeks to total up to 60 Gys). The treatment duration is also individualized based on the patient's clinical stability, such as hematological parameters within normal range.

There is little evidence on the effectiveness of radiotherapy in the management of orbital SCC. The current clinical practice which includes adjunctive use of radiotherapy is largely based on weak evidence, and this evidence has mainly been obtained from case series and case reports. There have been no randomized clinical trials reported in literature in this field(9,40).

Reports on the radiotherapy management of OSSN in the literature are mostly on strontium 90 therapy for superficial lesions(41,42). Few case series have been published on the use of other radiotherapy modalities including electron external beam treatment.

Similarly in another case report where 2 patients were treated with proton beam therapy without initial surgical excision due to extensive disease preoperatively, tumor regression was reported in both patients successfully(43).

Locally, there have been no studies documented on the effectiveness of radiotherapy in the management of orbital SCC.

The criteria used for OSSN radiotherapy is the same criteria used for head and neck tumors both globally and locally.

Studies reported in literature reported indications that included aggressive histology, recurrent tumor, microscopic perineural invasion, advanced-stage disease, and microscopically positive or "close" margins(44).

Whereas in our setting majority of our patients present with more aggressive disease and in some instances advanced disease with fungating tumors requiring more radical surgeries including lid or non-lid sparing exenteration and subsequent radiotherapy(40).

Currently the criteria used in KNH is based on clinical and imaging findings and grading of the tumor whether it invades the orbit and adjacent structures, intra-operative criteria include, remnant tumor at the base, bony erosion by the tumor and/or suspicious margins on exenteration and histological criteria includes tumors that are poorly differentiated or undifferentiated. This criteria has not been standardized as guidelines and hence, it is largely surgeon dependent.

2.6.Prognosis

OSSN can progress to orbital disease if not treated early or if remnant tumour cells are present post-excision. Studies have described multiple delays in patients seeking treatment for their eye condition and even when they reach the treatment facility, there are further delays in instituting patient management(20,26). Other factors which may contribute to progression of OSSN to orbital SCC include difficulties in making a diagnosis due to use of clinical judgement in the absence of histopathological support. This may arise when patients are unfit for surgical procedures due to poor clinical status at presentation, bearing in mind that majority are persons living with HIV.

High cost of treatment can lead to delays in receiving treatment and hence increasing the likelihood of further progression of disease. Prior to 2016, patients had to pay for surgical and radiological

procedures out of pocket at Kenyatta National Hospital(45). These delays have been found to be unfavourable for patients' treatment success.

Once orbital extension has occurred, the treatment of choice shifts to exenteration which in itself is an extremely disfiguring and debilitating surgery(45). Often times patients require reconstructive surgery at a later date in order to cover the defect left(46,47).

The psychosocial impact on the patients is usually not factored in the management preoperatively, as at that point the primary goal is to prevent further spread or extension of tumour by achieving complete resection of the tumour. However, this soon after changes when patients are now faced with the reality of the disfiguring surgical procedure(48).

Further to this, patients would also likely require to have radiotherapy conducted based on the initial clinical presentation such as caruncle and forniceal involvement, radiological findings pre-operatively, histopathological results as well as surgeons intraoperative findings.

Post-exenteration patients are expected to continue with their normal daily activities, yet they have multiple psychosocial issues to deal with, including devastating functional, aesthetic and psychological losses(48).

Studies have described factors such as very large lesions, incomplete excision, histopathologic features such as poor differentiation and delayed diagnosis being associated with poor prognosis(49). Recurrence rates have been shown to range from 16.6% to 43%(7,8,14,50) and the highest reported at 67%(10), with recurrence rates higher in HIV positive patients. A higher malignancy grade has also been noted in HIV positive patients compared to their HIV negative counterparts(14,51).

However, there is little evidence in literature informing on survival correlates when comparing patients who underwent exenteration alone versus those who received adjuvant radiotherapy following exenteration. Graue et.al reported a small case series of 8 patients in which no radiotherapy related deaths were reported(52). We therefore set out to determine and compare the survival rates of patients presenting with orbital SCC at Kenyatta National Hospital who underwent exenteration alone versus those who received adjuvant radiotherapy.

3. PROBLEM STATEMENT

In Kenya, orbital SCC is one of the most common ocular tumors causing blindness and debilitation. Surgery and radiotherapy are the mainstay of treatment in our setup, however there is little evidence that the use of adjuvant radiotherapy in the treatment and management of the disease improves survival of the patients.

Most patients we see in KNH with orbital SCC have advanced large tumors, HIV infection and its attendant comorbidities which would affect survival.

4. JUSTIFICATION

Orbital SCC results in blindness and even death. Kenya has a high HIV prevalence and due to straddling the equator the prevalence of disease is notably high.

Currently the only public hospital that provides radiotherapy services in Kenya is the Kenyatta National Hospital (KNH).

There is a knowledge gap on the effectiveness of radiotherapy as adjuvant therapy. Since there are no randomized control trials (RCT) in this area, then there are no clear criteria for treatment allocation to either radical surgical management alone- exenteration, or exenteration plus adjuvant radiotherapy.

The high cost of treatment and longer hospital stays during radiotherapy would be interpreted better with information about the survival of the recipients. Survival information is also important to help patients make decisions about therapy and currently there is none. As no other studies of this kind had been undertaken in our setting, this study was the first of its kind and hence will be instrumental in providing key baseline information for the policy makers in setting up treatment guidelines.

Conducting an RCT would be ideal, however a retrospective cohort study is faster and cheaper to conduct hence providing baseline information for whether an RCT may or may not be needed.

5. OBJECTIVES

The main objective of this study was to determine the survival rates of patients with orbital squamous cell carcinoma managed at Kenyatta National Hospital.

5.1.Primary Objective

1. To determine the survival rates of patients by treatment group (those who underwent exenteration alone, those who were prescribed adjuvant radiotherapy post-exenteration).

5.2.Secondary Objectives

1. To describe the survival rates of patients by sex, HIV status, CD4 level, ART use, occupation, radiological findings, histopathology, exenteration method, and surgical findings – residual tumor or not.
2. To determine the correlates of survival in patients with orbital squamous cell carcinoma.
3. To determine the proportion of patients who needed repeat surgery.

6. MATERIALS AND METHODS

6.1.Study Design

The study design was a retrospective cohort study.

6.2.Study Area

The study took place at Kenyatta National Hospital. This is a public tertiary, referral hospital which is the largest hospital in the country and the biggest referral hospital in East Africa. Kenyatta National Hospital is also a teaching hospital of the University of Nairobi, College of Health Sciences. KNH is the only public hospital in Kenya that offers radiotherapy.

The catchment area was Kenya and the East African region. On average, annually there have been 76 confirmed cases of orbital SCC at KNH with 22 referred to the radiotherapy department for adjuvant therapy. Most ophthalmologists refer cases of orbital SCC to KNH mainly because of the presumed need for radiotherapy.

Figure 2: Map of East Africa showing location of KNH

6.3.Study Period

The study was conducted from September 2018- March 2019. Data for the period January 2013 - December 2016 was retrieved.

6.4.Study Population

All histologically confirmed cases of orbital SCC who met the inclusion criteria and had undergone exenteration with or without post-exenteration radiotherapy presenting at Kenyatta National Hospital.

6.5.Sample Size

Sample size was derived using the calculations for survival analysis. This estimate was based on a comparison of survival in the two main treatment groups. We hypothesized and had observed anecdotally that patients who were prescribed radiotherapy were more likely to have more severe disease and hence poorer prognosis for survival than those treated by exenteration alone. We also knew from existing data that HIV vs non-HIV mortality ratio in Kenya in 2015 was 4.35 (95%CI, 3.67-5.15)(53).

Therefore, using Stata version 15 we obtained the following:

. **power exponential, hratio (2.5) effect (hratio)**

Estimated sample sizes for two-sample comparison of survivor functions
Exponential test, hazard difference, conditional
Ho: h2 = h1 versus Ha: h2! = h1
Study parameters:
alpha = 0.0500
power = 0.8000
delta = 2.5000 (hazard ratio)
Survival information:
hratio = 2.5000
Estimated sample sizes:
N =46

6.6.Inclusion Criteria

1. All patients ≥18 years of age with histological confirmation of SCC who underwent exenteration with or without adjuvant radiotherapy.

6.7.Exclusion Criteria

1. Patients missing or incomplete records.

6.8.Data collection procedure

Kenyatta National Hospital has a cancer registry database, and this is where records of orbital SCC were initially identified from. The KNH eye clinic records officer was the contact person, and they retrieved the medical records for data extraction by the PI. Clinical information about the patient's surgery, histology and details of radiotherapy and other medical care was obtained from these medical records.

Overall survival time of interest was defined as the period from the date of exenteration surgery to being alive one year after or the date of death from any cause (all-cause mortality) for patients who died. Attrition was defined as participants whose vital status could not be determined 1-year post exenteration after all methods of contact had been exhausted.

Any missing information was then crosschecked with information in the KNH theatres and radiotherapy department. Information about the radiological features was abstracted from the medical record above, as well as any corresponding information from the radiology department of KNH.

Vital status information was obtained using the contact information from the patients file. Participants or their next of kin were contacted to determine the participant's vital status Appendix 2 and 3).

6.9.Data Storage

All data was handled with confidentiality and the principal investigator always stored the questionnaires in a locked cabinet and kept the key. Data stored on computer was password protected.

6.10. Statistical Analysis

Coding of questionnaires was performed, and data entered into Microsoft Excel 2010 database. Statistical Package for Social Scientists (SPSS) Version 22.0 and Stata version 15 was used to statistically analyze the coded data.

The primary outcome measure was to compare survival rates between the treatment groups

The survival rates were analyzed with the Kaplan-Meier method. Multivariate analysis was performed with Cox regression analysis, using Cox's proportional hazard model to adjust for confounding factors which may have influenced the survival rate. The one-year survival rate of the study population was calculated with a 95% confidence interval.

The secondary outcomes were to describe the survival rates in different socioeconomic groups; the correlates of survival and compare the proportions that needed repeat surgery. To determine the correlates of survival we conducted univariate and multivariate analysis. Univariate analysis was used compare basic characteristics of the groups and was performed using the Pearson's chi-squared test and the independent two-sample *t*-test. Variables that were associated with the outcome on the initial univariate analyses at a level of $P < 0.05$ were included in the multivariate analysis model and those with $P<0.20$ retained in the model. The likelihood ratio test was used to determine the significance of associations. Multivariable logistic regression analysis was used to adjust for confounding factors and estimate odds ratios (ORs) and 95% confidence intervals (CIs). A summary description of numbers and proportions has been used describe the participants that needed repeat surgery in the groups. The data collected was analyzed and presented in tables and figures as illustrated below.

6.11. Ethical Considerations

Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi ethics and research board. Approval to undertake the study in KNH was also obtained. Confidentiality was maintained throughout the study period while handling patient information and data collected.

7. RESULTS

7.1. Sociodemographic Characteristics

Table 1: Demographic Characteristics of the two Main Treatment Arms

Indicator	Level	Exenteration alone	Exenteration + Radiotherapy
	N= 56	**14**	**42**
Age (yrs.)	**Median (IQR)**	43.5 (35.8-52.8)	47.5 (38.2-54.2)
Gender	**Female**	4(28.6%)	23(54.8%)
	Male	10(71.4%)	19(45.2%)
HIV results	**Positive**	12(85.7%)	27(64.3%)
	Negative	1(7.1%)	4(9.5%)
	Missing HIV result	1(7.1%)	11(26.2%)
CD4 Count	**Median (IQR)**	241 (141.5-298.5)	265 (87.5-350.5)
ART use	**ART use**	11(91.7%)	18(66.7%)
	No ART use	0(0.0%)	5(18.5%)
	Missing ART use	1(8.3%)	4(14.8%)
Duration on ART (years)	**Median (IQR)**	2 (1.0-3.8)	2 (1.0-5.0)
Follow-up till death (months)	**Median (IQR)**	-	6.1 (5-8.3)
Occupation	**Outdoors**	12(85.7%)	32(76.2%)
	Indoors	2(14.3%)	9(21.4%)

One participant in the exenteration plus radiotherapy arm did not have a documented occupation.

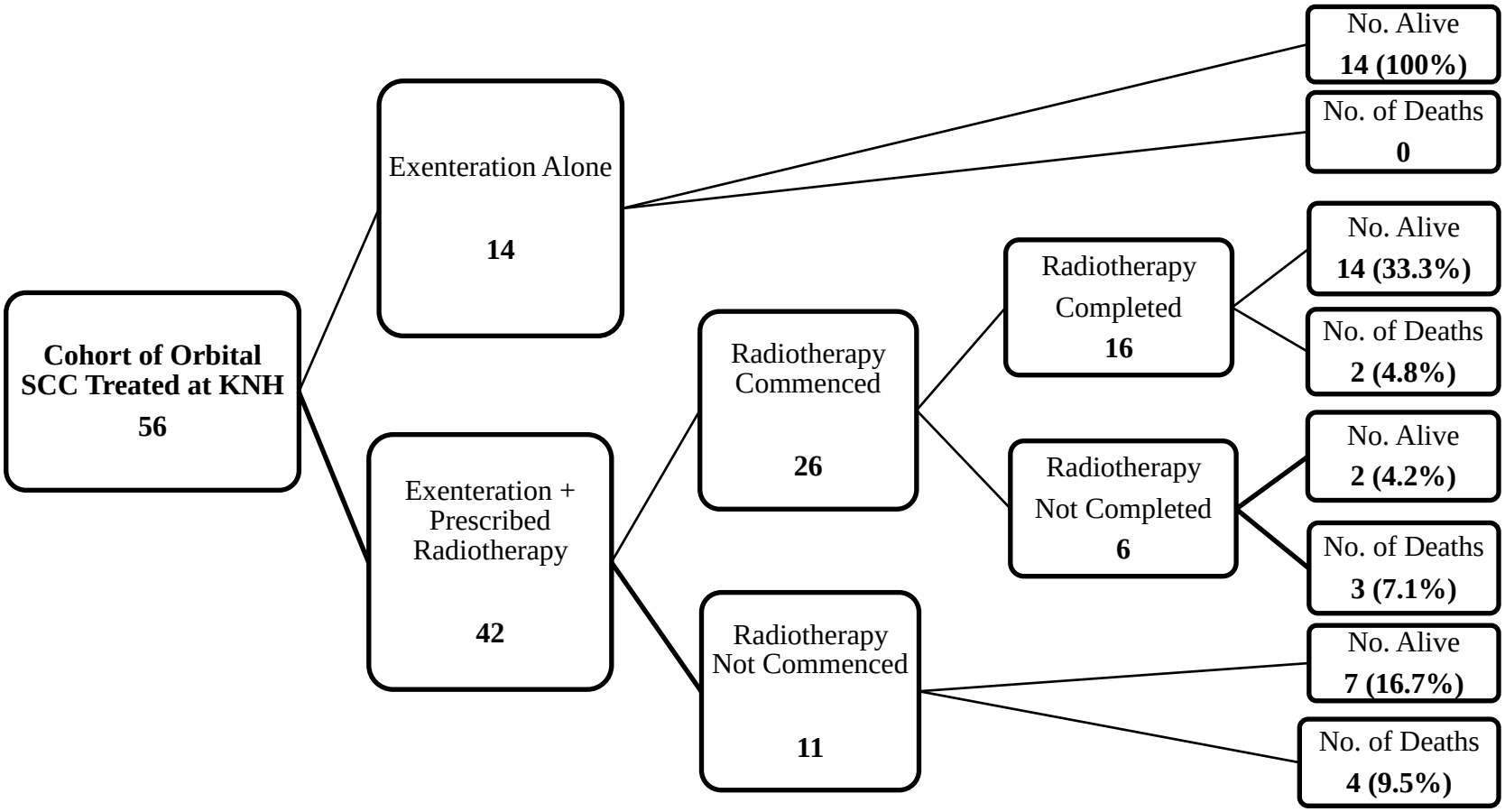
Table 2: Demographic Characteristics of the Exenteration Plus Radiotherapy Sub-Groups

Indicator	Level	Exenteration + Radiotherapy Completed	Exenteration + Radiotherapy not Completed	Exenteration + Radiotherapy not commenced	Exenteration + Radiotherapy (Incomplete Radiotherapy data)
	N= 42	**16**	**6**	**11**	**9**
Age (yrs.)	**Median (IQR)**	48.5 (38.2-55.8)	44.5 (41.0-48.8)	47 (33.0-57.5)	48 (40.0-51.0)
Sex	**Female**	6(37.5%)	4(66.7%)	6(54.6%)	7(77.8%)
	Male	10(62.5%)	2(33.3%)	5(45.5%)	2(22.2%)
HIV results	**Positive**	11(68.8%)	4(66.7%)	6(54.6%)	6(66.7%)
	Negative	1(6.2%)	0(0.0%)	2(18.2%)	1(11.1%)
	Missing HIV result	4(25.0%)	2(33.3%)	3(27.3%)	2(22.2%)
CD4 Count	**Median (IQR)**	327 (290.0-357)	199 (142.0-609.0)	108 (73.0-166)	90 (64.5-295.0)
ART use	**ART use**	8(72.7%)	2(50.0%)	6(100%)	2(33.3%)
	No ART use	3(27.3%)	1(25.0%)	0(0.0%)	1(16.7%)
	Missing ART use	0(0.0%)	1(25.0%)	0(0.0%)	3(50.0%)
Duration on ART (years)	**Median (IQR)**	2.5 (1.4-4.2)	4.5 (2.8-6.2)	1.2 (1.0-1.6)	1.2 (1.0-1.6)

Follow-up till death (months)	**Median (IQR)**	5.9 (5.4-6.3)	5.6 (4.8-5.9)	8.4 (6.3-8.9)	8.4 (6.3-8.9)
Occupation	**Outdoors**	11(68.8%)	4(66.7%)	9(81.8%)	8(88.9%)
	Indoors	5(31.3%)	2(33.3%)	1(9.1%)	1(11.1%)

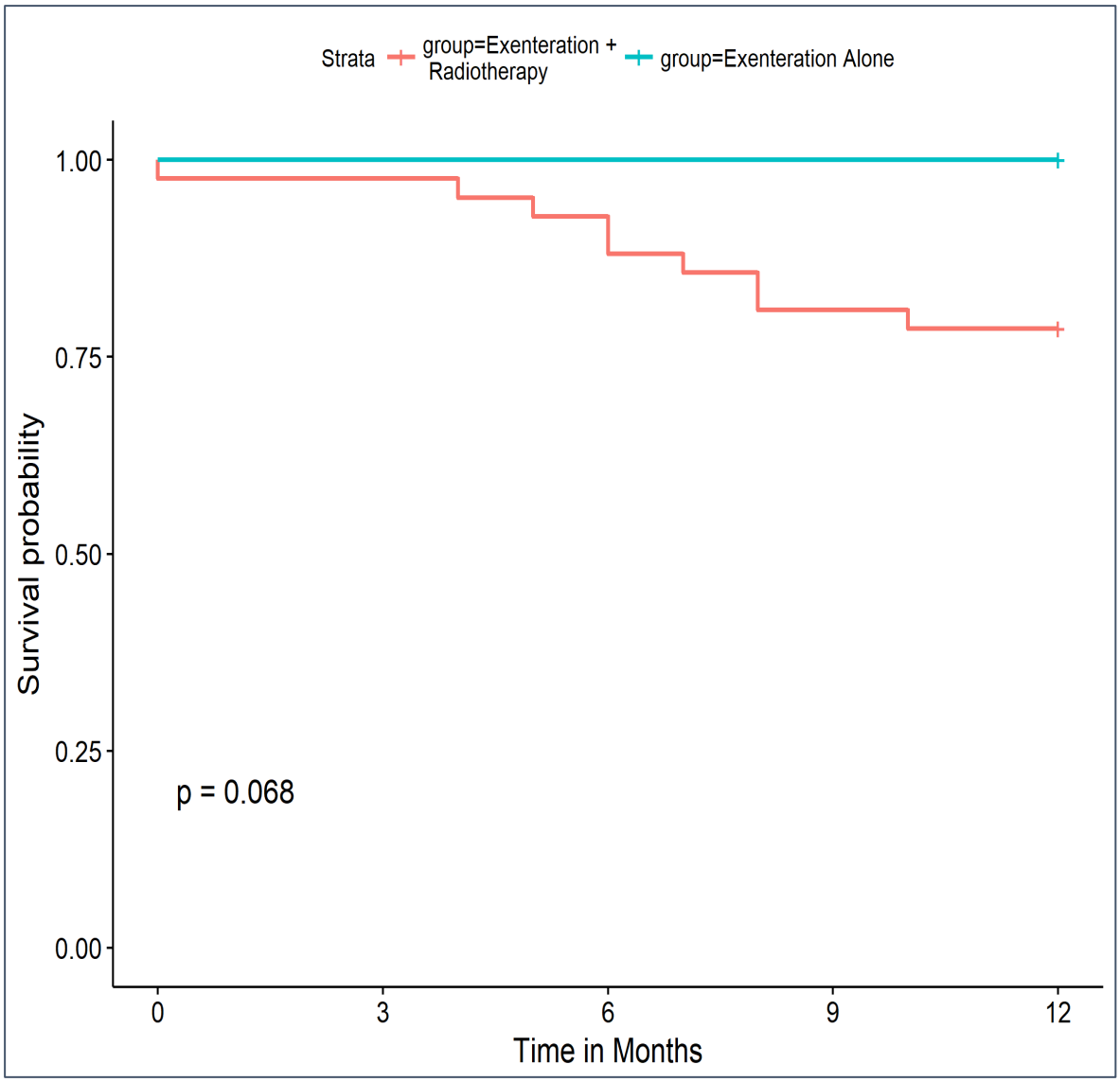
7.2.Intention to Treat Analysis

Figure 3: Intention-To-Treat Flow Diagram



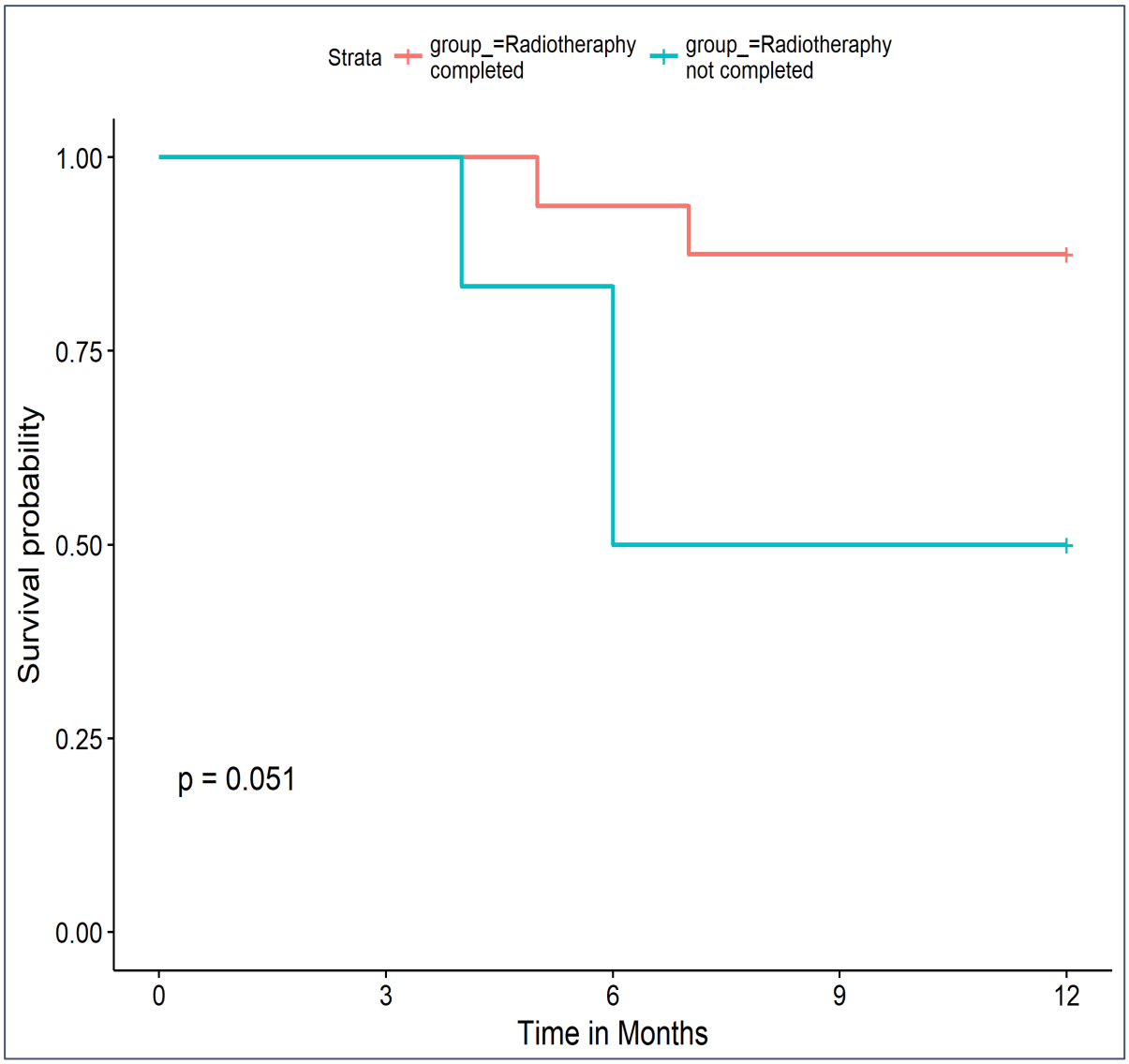
A total of 9 participants had incomplete radiotherapy records. In 5 of these participants documentation of radiotherapy commencement was not available and in 4 participants, completion of radiotherapy dose was not documented, but all were alive 1 year post exenteration. One participant was lost-to-follow-up (LTFU) in the “Radiotherapy not completed” arm

Figure 4: Kaplan Meier Survival Probability Exenteration Alone vs Exenteration Plus Radiotherapy Arm



The above figure shows that the patients who had exenteration alone had a trend to higher survival than exenteration plus radiotherapy but this difference was not statistically significant.

Figure 5: Kaplan Meier Survival Probability Radiotherapy Completed vs Radiotherapy Not Completed Arm

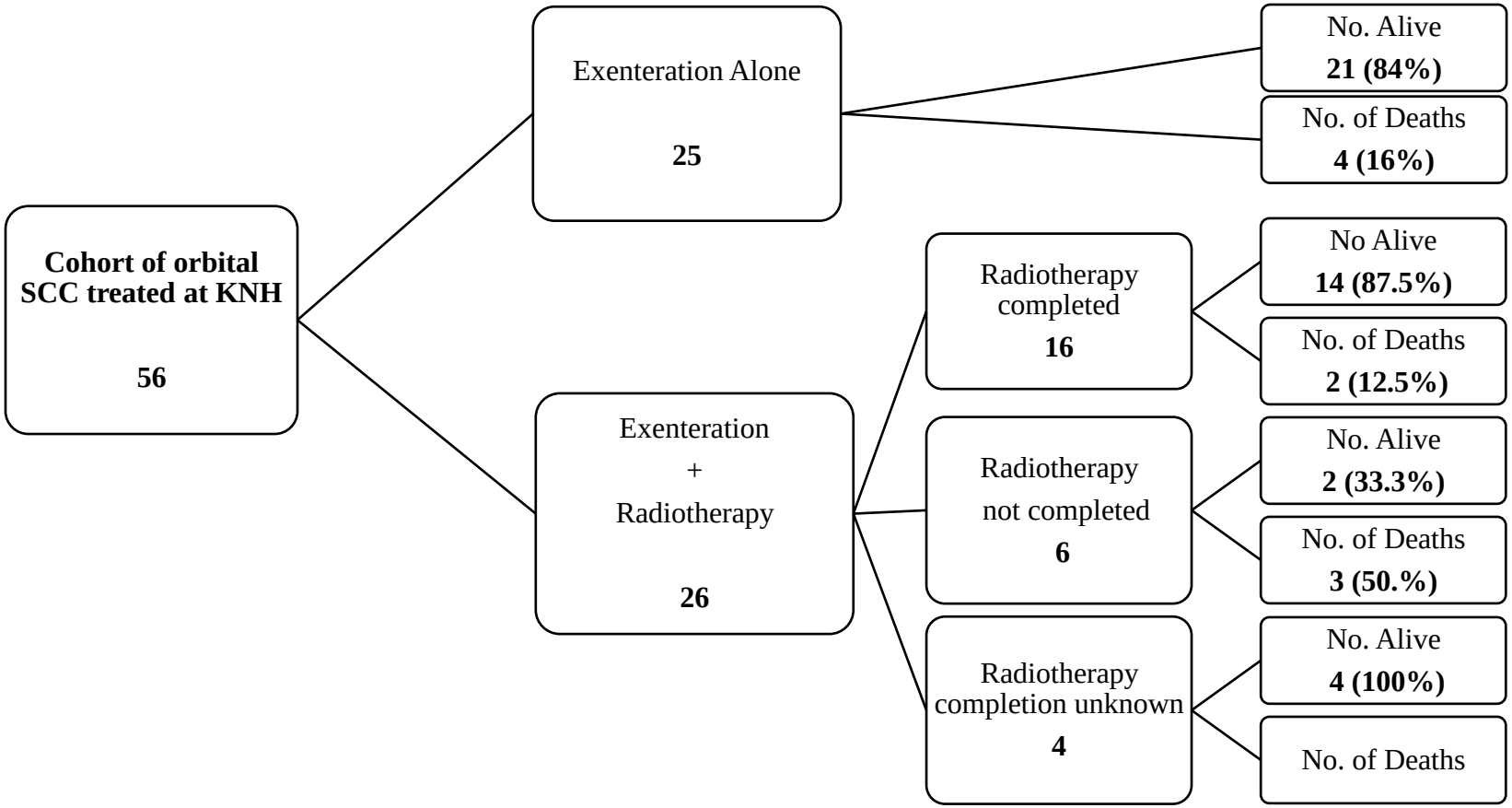


In the figure above, participants who completed radiotherapy had a survival probability of 87.5% whereas it was 50% in those who did not complete radiotherapy.

7.3. Per Protocol Analysis

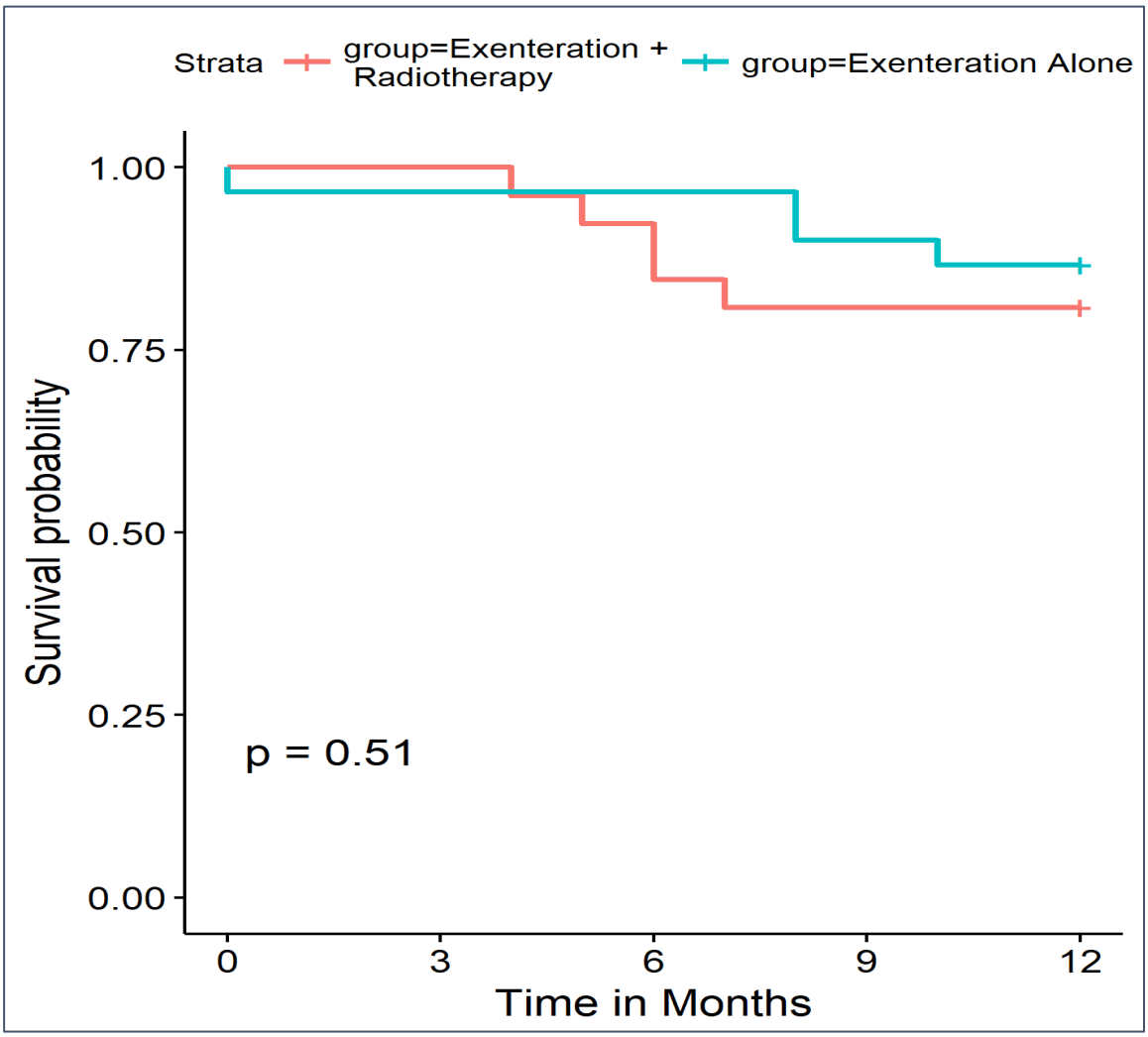
Per protocol analysis was conducted because there were 11 participants who were prescribed radiotherapy but did not receive it. They were therefore analyzed as part of the exenteration alone group in this per protocol analysis.

Figure 6: Per Protocol Analysis Flow Diagram



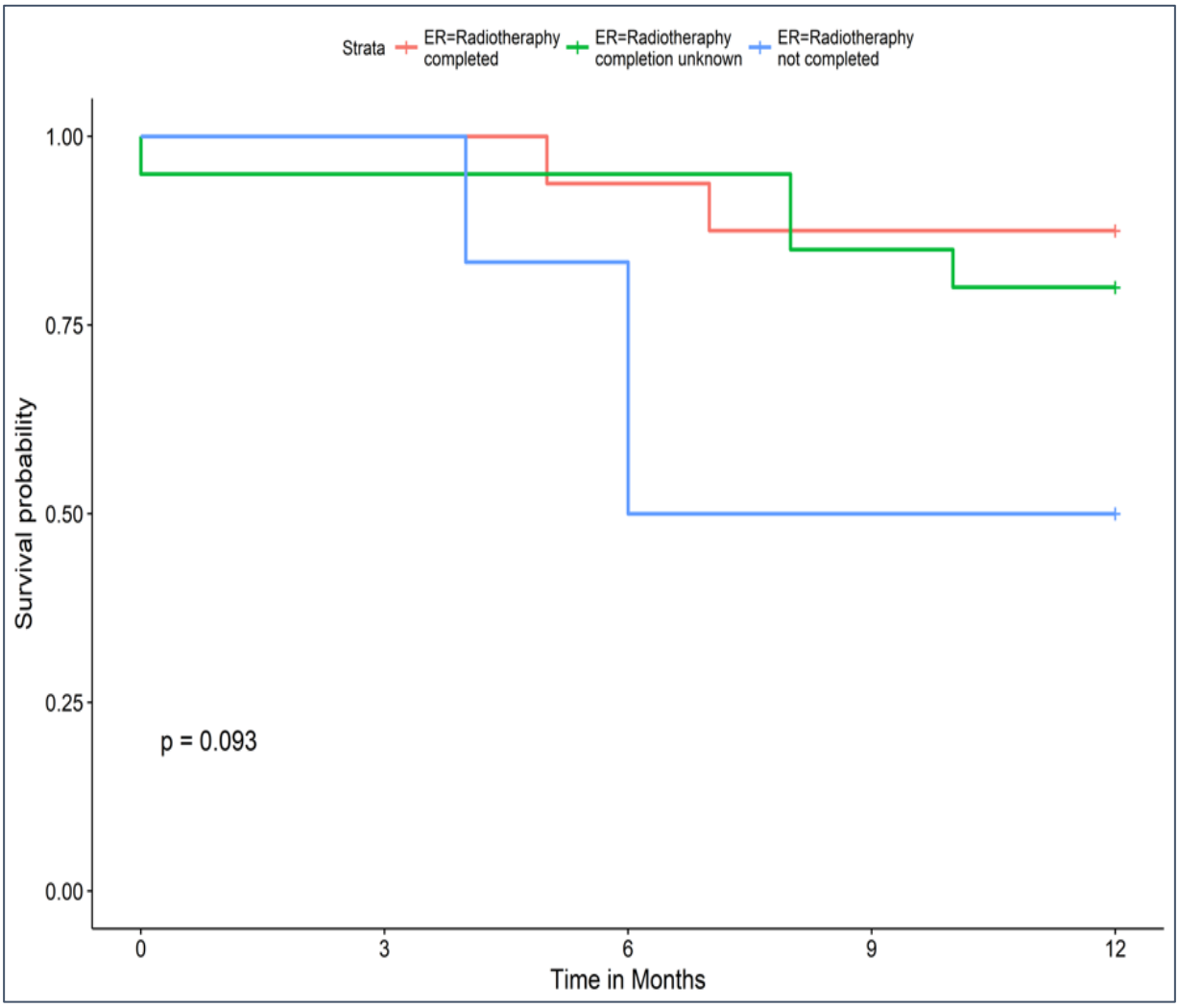
In 5 participants who were prescribed radiotherapy, it was not documented whether they commenced radiotherapy or not.

Figure 7: Kaplan Meier Survival Probability Exenteration Alone vs Exenteration Plus Radiotherapy Arm



In the per protocol analysis, there was no difference in survival probability in the main treatment arms (p= 0.51).

Figure 8: Kaplan Meier Survival Probability Exenteration Plus Radiotherapy Sub-Groups

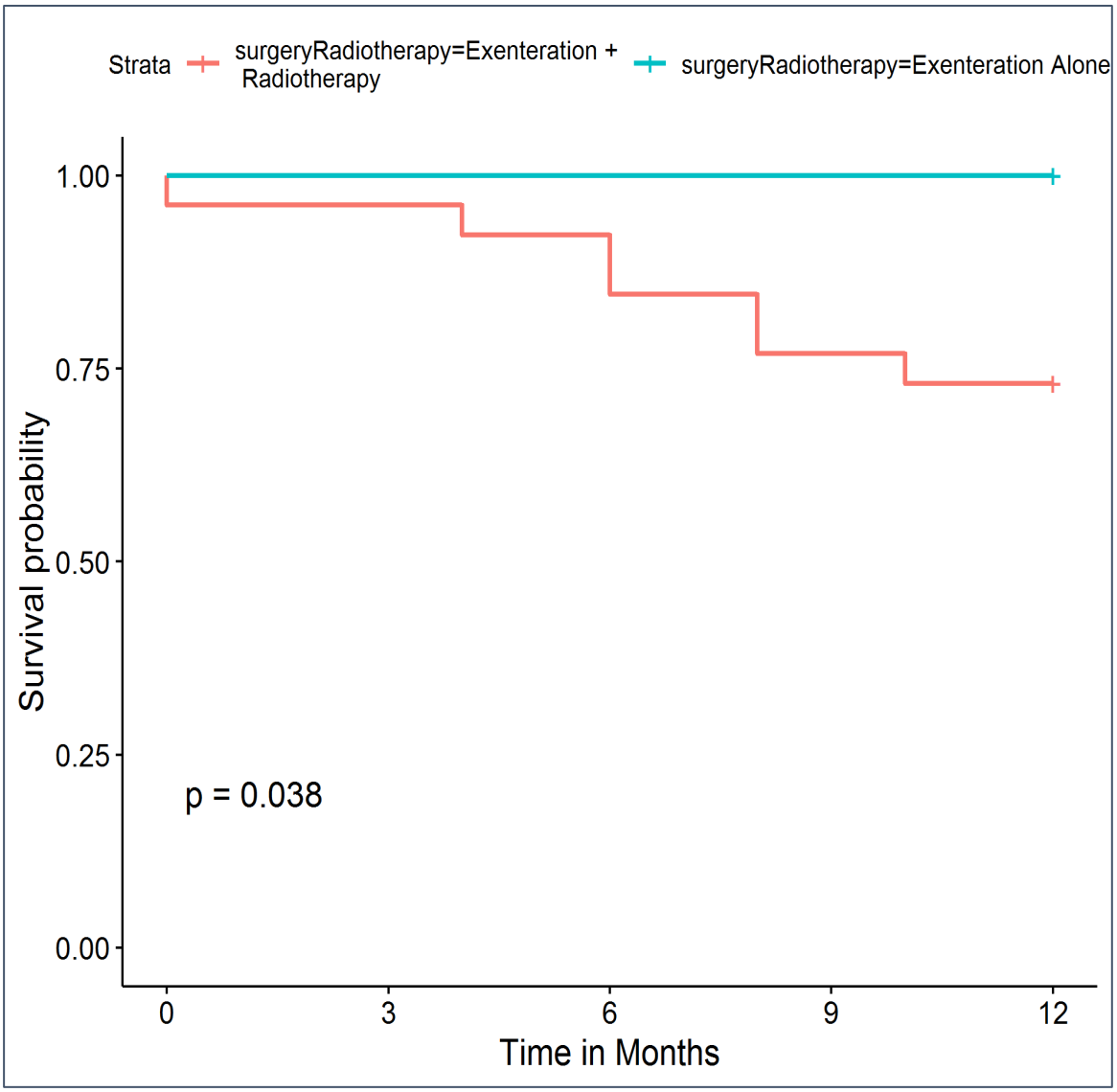


The above figure shows the survival analysis of the radiotherapy treatment arms. Of note, radiotherapy completion status of the participants did not affect survival probability (p=0.09).

7.3.1. Sensitivity Analysis; "Radiotherapy completion unknown" group

Sensitivity analysis was conducted to assess whether making certain assumptions of the group labelled "radiotherapy completion unknown", would change the survival probability of either of the groups.

Figure 9: Kaplan Meier Sensitivity Analysis Assuming Radiotherapy was Not Completed



The survival probability was noted to be negatively affected with a p=0.04 with the assumption that this group had not completed radiotherapy.

The difference in survival probability was not statistically significant (p=0.11) when the same analysis was conducted making the assumption that this group had completed radiotherapy.

7.4. Radiological findings and Metastasis

Table 3: Radiological Findings of the Two Main Treatment Arms

Indicator	**Level**	**Exenteration alone**	**Exenteration + Radiotherapy**
	N= 56	**14(25.0%)**	**42(75.5%)**
PNS along optic nerve	**Yes**	0(0.0%)	5(11.9%)
	No	5(35.7%)	12(28.6%)
	Not documented	9(64.3%)	25(59.5%)
Bone invasion	**Yes**	0(0.0%)	3(7.2%)
	No	5(35.7%)	19(45.3%)
	Not documented	9(64.3%)	20(47.6%)
Paranasal sinus extension	**Yes**	1(7.2%)	6(14.3%)
	No	5(35.7%)	22(52.4%)
	Not documented	8(57.1%)	14(33.3%)
Intracranial extension	**Yes**	0(0.0%)	3(7.1%)
	No	6(42.9%)	26(61.9%)
	Not documented	8(57.1%)	13(31.0%)

Overall 32% of the participants had evidence of radiological extension of the disease.

Table 4: Radiological Findings of the Exenteration Plus Radiotherapy Sub-Groups

Indicator	Level	Exenteration + Radiotherapy Completed	Exenteration + Radiotherapy not commenced	Exenteration + Radiotherapy not Completed	Exenteration + Radiotherapy (Incomplete Radiotherapy data)
	N= 42	**16(38.1%)**	**11(26.2%)**	**6(14.3%)**	**9(21.4%)**
PNS along optic nerve	**Yes**	3(18.8%)	1(9.1%)	1(16.7%)	0(0.0%)
	No	4(25.0%)	4(36.4%)	1(16.7%)	3(33.3%)
	Not documented	9(56.3%)	6(54.6%)	4(66.7%)	6(66.7%)
Bone invasion	**Yes**	2(12.5%)	0(0.0%)	0(0.0%)	1(11.1%)
	No	5(31.3%)	6(54.6%)	3(50.0%)	5(55.6%)
	Not documented	9(56.3%)	5(45.5%)	3(50.0%)	3(33.3%)
Paranasal sinus extension	**Yes**	4(25.0%)	0(0.0%)	0(0.0%)	2(22.2%)
	No	6(37.5%)	8(72.7%)	4(66.7%)	4(44.4%)
	Not documented	6(37.5%)	3(27.3%)	2(33.3%)	3(33.3%)
Intracranial extension	**Yes**	2(12.5%)	0(0.0%)	1(16.7%)	0(0.0%)
	No	9(56.3%)	8(72.7%)	3(50.0%)	6(66.7%)
	Not documented	5(31.3%)	3(27.3%)	2(33.3%)	3(33.3%)

7.5. Histology and Surgery

Table 5: Histology and Surgery of the Two Main Treatment Arms

Indicator	**Level**	**Exenteration alone**	**Exenteration + Radiotherapy**
	N= 56	**14(25.0%)**	**42(75.5%)**
Histology	**Well**	6(42.9%)	10(23.8%)
	Moderate	4(28.6%)	22(52.4%)
	Poor	0(0.0%)	4(9.5%)
	Other	1(7.1%)	0(0.0%)
	Not documented	3(21.4%)	6(14.3%)
Margin involvement	**Positive**	2(14.3%)	13(31.0%)
	Negative	5(35.7%)	15(35.7%)
	Not documented	7(50.0%)	14(33.3%)
Type of Exenteration	**Total lid sparing**	8(57.1%)	20(47.6%)
	Subtotal lid sparing	2(14.3%)	2(4.8%)
	Total non-lid sparing	4(28.6%)	15(35.7%)
	Extended non-lid sparing	0(0.0%)	4(9.5%)
Residual Tumour	**Yes**	0(0.0%)	17(40.4%)
	No	14(100%)	10(23.8%)
	Not documented	0(0.0%)	15(35.7%)

Overall the most common histological variant was moderately differentiated (46.4%) orbital SCC. Majority of the participants (35.7%) had tumour negative margins and total lid sparing exenteration being the most commonly performed surgery (50%).

Table 6: Histology and Surgery of the Exenteration Plus Radiotherapy Sub-groups

Indicator	Level	Exenteration + Radiotherapy Completed	Exenteration + Radiotherapy not commenced	Exenteration + Radiotherapy not Completed	Exenteration + Radiotherapy (Incomplete Radiotherapy data)
	N= 42	**16(38.1%)**	**11(26.2%)**	**6(14.3%)**	**9(21.4%)**
Histology	**Well**	6(37.5%)	2(18.2%)	2(33.3%)	0(0.0%)
	Moderate	7(43.8%)	7(63.6%)	3(50.0%)	5(55.6%)
	Poor	1(6.3%)	2(18.2%)	1(16.7%)	0(0.0%)
	Not documented	2(12.5%)	0(0.0%)	0(0.0%)	4(44.4%)
Margin involvement	**Positive**	8(50.0%)	2(18.2%)	2(33.3%)	1(11.1%)
	Negative	5(31.3%)	5(45.5%)	2(33.3%)	3(33.3%)
	Not documented	3(18.8%)	4(36.4%)	2(33.3%)	5(55.6%)
Type of Exenteration	**Total lid sparing**	4(25.0%)	7(63.6%)	5(83.3%)	4(44.4%)
	Total non-lid sparing	9(56.3%)	4(36.4%)	0(0.0%)	2(22.2%)
	Subtotal lid sparing	2(12.5%)	0(0.0%)	0(0.0%)	0(0.0%)
	Extended non-lid sparing	1(6.3%)	0(0.0%)	1(16.7%)	2(22.2%)
Residual Tumour	**Yes**	7(43.8%)	3(27.3%)	3(50.0%	4(44.4%)
	No	4(25.0%)	5(45.4%)	0(0.0%)	1(11.2%)
	Not documented	5(31.2%)	3(27.3%)	3(50.0%)	4(44.4%)

7.6. Radiotherapy

Table 7: Radiotherapy doses and duration of therapy

Indicator		**Exenteration + Radiotherapy completed**	**Exenteration + Radiotherapy not completed**	**p.value**
Total number of Grays prescribed	**Median** (IQR)	55 (43.8-60.0)	50 (43.8-60.0)	0.350
Number of Grays per session prescribed	**Median** (IQR)	2 (2.0-2.0)	2 (1.8-2.0)	0.146
Total Grays received	**Median** (IQR)	60 (47.5-60.0)	33.7 (16.3-47.5)	0.042
Grays per session received	**Median** (IQR)	2 (2.0-2.0)	2 (1.8-2.0)	0.716
Duration of therapy in weeks	**Median** (IQR)	4.4 (4.4-6.6)	5.4 (4.5-6.6)	0.833

Mean (SD) number of grays prescribed for those who were prescribed radiotherapy but did not commence was 47.3 SD=9.7.

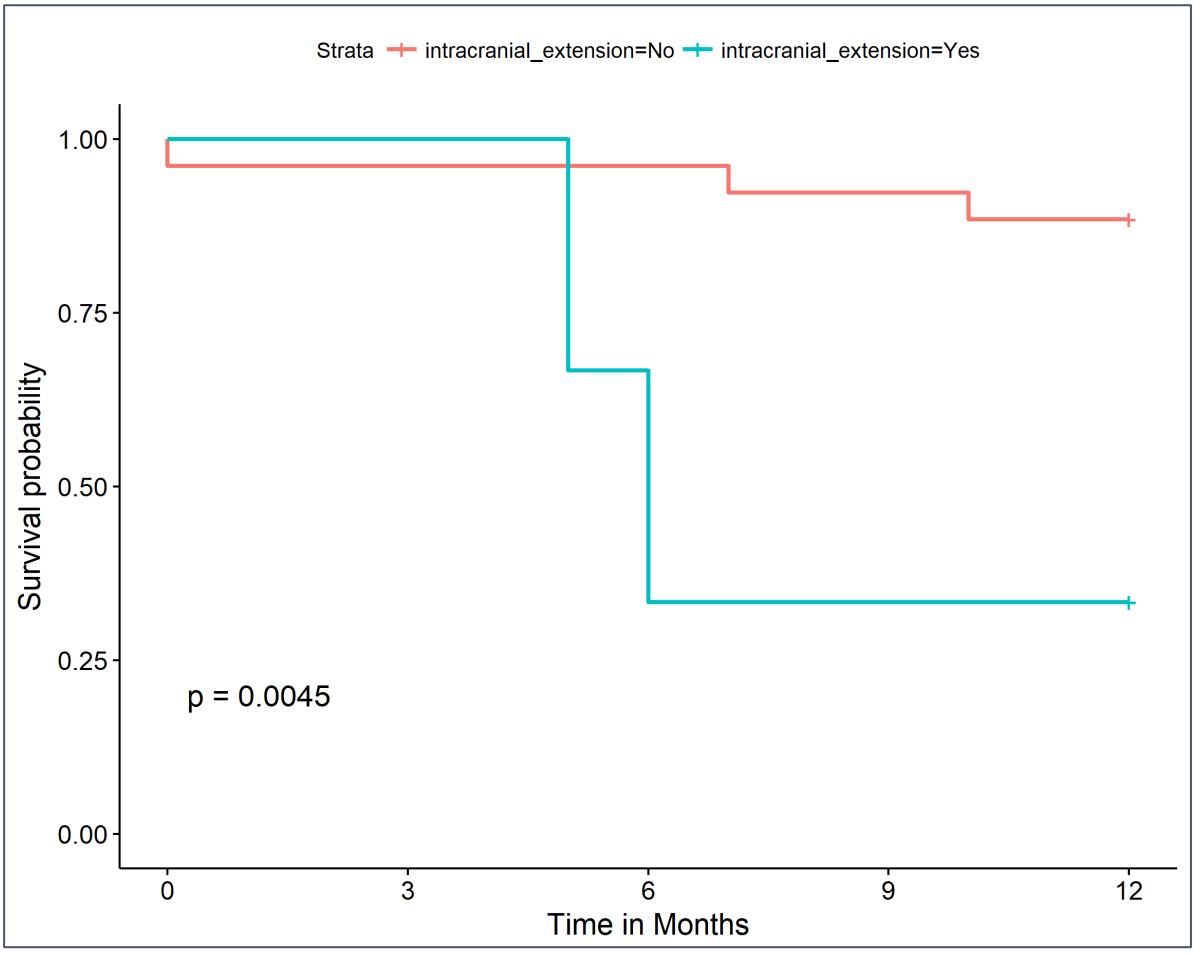
7.7. Correlates of Survival

Table 8: Univariate analysis

Covariate	level	Hazard Ratio	CI	p.value
Sex	Female (n=4(44.4%))	Ref		
	Male (n=5(55.7%))	1.190	0.32-4.44	0.79
HIV	Negative (n=1(11.1%))	Ref		
	Positive (n=5(55.6%))	0.690	0.08-5.88	0.73
CD4 Count	≤250 cells/mm^3 (n=3)	Ref		
	≥250 cells/mm^3 (n=2)	0.51	0.05-5.66	0.59
ART use	No (n=1(11.1%))	Ref		
	Yes (n=3(33.3%))	0.510	0.05-4.93	0.56
Spread Along Optic Nerve	No (n=3(33.3%))	Ref		
	Yes (n=2(22.2%))	3.090	0.51-18.65	0.22
Bone invasion	No (n=2(22.2%)	Ref		
	Yes (n=7(77.8%)	0.000	0-Inf	1.00
Paranasal Extension	No (n=3(33.3%)	Ref		
	Yes (n=0(0%)	0.000	0-Inf	1.00
Intracranial Extension	No (n=3(33.3%)	Ref		
	Yes (n=2(22.2%)	11.310	1.8-71.02	0.01
Histological grading	Well (n=3(22.2%)	Ref		
	Poor (n=2(22.2%)	4.410	0.77-17.85	0.14
	Moderate (n=4(44.4%)	1.810	0.34-6.32	0.73
Margin Positive	Negative (n=2(22.2%)	Ref		
	Positive (n=3(33.3%)	2.040	0.34-12.21	0.44
Residual Tumour	No (n=3(33.3%)	Ref		
	Yes	2.040	0.46-9.12	0.35

Intracranial tumour extension was the only factor found to be statistically significant, with a p=0.01. All other variables analysed were not found to affect the probability of survival.

Figure 10: Kaplan Meier Survival Probability of Intracranial Tumour Extension



As described in the univariate analysis, participants with intracranial tumour extension had a lower survival probability as is depicted in this Kaplan Meier graph (p=0.01).

7.8. Repeat Surgery

Table 9: Participants who Underwent Repeat Surgery

Indicator	**Level**	**Exenteration alone**	**Exenteration + Radiotherapy**
	N= 56	**14**	**42**
Repeat Surgery	Yes	0	3 (7.1%)
Outcome	Alive		3 (100%)

Overall 5.4% of the participants underwent repeat surgery.

All were in the exenteration plus radiotherapy arm, and were alive at the end of the study period.

8. DISCUSSION

Orbital squamous cell carcinoma is a vision threatening and potentially life threatening condition and therefore survival rates are important aspects of the disease process to address.

Our study population was largely young patients living with HIV. This is consistent with other studies done in our setting, where younger patients presented with orbital squamous cell carcinoma(5,14,40). Bearing in mind our study setting was a referral centre, our population came from across the country. The HIV prevalence in our study was therefore also in keeping with our National average HIV prevalence of 5.9% with a range between 0.4%- 26% during the study period(54).

There was a male preponderance in the exenteration alone arm. This may be explained by the fact that men are generally more likely to be employed in outdoor occupations, however they are also more likely to access medical treatment earlier than females(20,55). Males have also been found to respond poorer to antiretroviral therapy compared to females hence leading them to seek medical care sooner(56).

However, in the exenteration plus radiotherapy arm, there were slightly more females than males and this is likely due to the fact that women have multiple delays due in part to household and child-care responsibilities hence, have more difficulty attending health facilities(26). Therefore by the time they present, they probably have more advanced disease requiring adjuvant radiotherapy.

It therefore appears that males generally have higher risk of developing OSSN due to their outdoor occupations and immunosuppression. Although they are able to access health facilities earlier than females, they still present with orbital disease due in part to poorer response to antiretroviral therapy.

We also found that majority of the participants had similar risk factors for developing OSSN that have been well described in other studies, including HIV infection and outdoors occupation(5,57–59).

Several series have described the higher tumour grading in people living with HIV(34,51). In our study majority of the participants in the exenteration plus radiotherapy group were noted to have more severe disease both on radiological and histological features. Furthermore, all the participants with tumor left insitu were also in this group. This can be expected to lead to lower survival rates and tumour recurrence, hence they were more likely to be prescribed radiotherapy.

In our study the overall 1 year survival rate was 83.9%. In the intention-to-treat analysis, all the deaths occurred in the exenteration plus radiotherapy arm with a 1 year survival rate of 78%. These findings

are comparable to other studies that have assessed survival rates. In one study assessing 10 year follow up of patients who underwent, orbital exenteration, the survival rates were 72% at 1 year, 48% at 3 years, and 37% at 5 years(60). In yet another study assessing orbital involvement of locally advanced squamous cell carcinoma, the 3 year survival rate was 59%(61). These studies imply that over time, the survival rates of patients decline and therefore it would be important for us to conduct a 3 year and 5 year survival assessment of this cohort. This will further provide us with a better understanding of the survival rates especially in the exenteration alone arm where no deaths were experienced.

The survival rates in the exenteration plus radiotherapy arm may not be surprising as we also found that this group had participants with more severe disease including extension of tumour and higher histological grading hence, may be the reason why the initial deaths occurred only in this group. Furthermore, intracranial extension of the tumour, was noted to be the only factor that negatively affected survival probability of the participants. The participants with intracranial extension, were all in the exenteration plus radiotherapy arm. This is a clinically significant finding, as it is well known that patients who have tumour spread especially to the brain are likely to fair off worse than their counterparts without brain involvement of disease. We found similar findings in other studies that indicate poorer prognosis for patients with intracranial tumour extension, with a 5 year survival rate between 3.4% and 42.9% depending on extent of intracranial involvement(62).

Regarding radiotherapy, patients who completed radiotherapy, were likely to have better survival probability compared to those who did not complete radiotherapy. This was related to the dose of radiotherapy received, whereby those who did not complete their radiotherapy regimen had only received half the total dose. This is an important finding as we have previously highlighted the numerous delays and challenges patients face while accessing health care in our setting(26). These include machine breakdown for a prolonged periods, clinical status of the patient, non-compliance to treatment as well as financial constraints. In a study conducted in Kenya, only 21% of patients had medical insurance at first presentation(20), hence the high cost of treatment for a patient paying out of pocket is a major hindrance in receiving treatment.

Recurrence of tumours has been described to be as high as 44% in some studies(9,10,14). In our study, repeat surgery was used as a proxy of disease recurrence, whereby we had a few participants who underwent repeat surgery, however they were all alive at the end of the study period. This may likely be attributed to better tumour histological grading, no intracranial extension of tumour or even completion of prescribed radiotherapy treatment and hence better survival probability.

These findings have a major impact in the lives of these patients, as we must remember that the population of patients being addressed, are young patients at the prime of the careers and most likely the breadwinners in their homes. Therefore the system issues need to be addressed in order to avoid the negative impact of the disease that may ensue.

Finally, we must also keep in mind that HIV is still a fairly stigmatized disease in our setting and these young individuals are then faced with the facial disfigurement of orbital SCC, coupled later with the result of orbital exenteration. Although we did not study the psycho-social component of orbital SCC, the treatment and its effects on patients, these patients may require continuous psychotherapy for a period of time while they undergo the healing process and later reconstructive surgeries(48). The psychosocial effects of having a fungating mass on the face, the extensive surgical procedure and its attendant facial disfigurement should be established in further studies.

9. **STUDY LIMITATIONS**

There were participants who either did not commence or complete the prescribed radiotherapy, presumably due to financial constraints, machine breakdown and other factors which were not being assessed in this study.

We could only conduct a 1 year follow up period. This is due to several disruptions in radiotherapy treatment at KNH prior to January 2013. Therefore we were unable to collect data earlier than this time period.

There were medical files with missing or incomplete records.

10. **CONCLUSIONS**

There was no difference in survival rates between patients who underwent exenteration alone versus those who underwent exenteration and received adjuvant radiotherapy.

Baseline characteristics like sex, HIV status, CD4 level, ART use, occupation, radiological findings, histopathology, exenteration method, and surgical findings – residual tumor or not, did not significantly influence survival.

Intracranial extension of tumour was the only factor found to influence survival rates in participants by reducing the participant's probability of survival.

There were few participants who underwent repeat surgery, but this factor did not negatively influence their probability of survival.

11. **RECOMMENDATIONS**

1. From our study, radiotherapy does not seem to improve survival of patients and therefore, its utility needs to be further investigated.
2. A longer follow up cohort study to assess mortality in the exenteration only arm should be conducted, to further support the findings of this study
3. A quality of life study comparing the two interventions to assess patient uptake and perceptions and psychosocial effects should be conducted.

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13. **APPENDICES**

Appendix 1: Study Tool

Serial No _____ Data Collection date _____

Demographics

1. Sex: Male (0) □
   Female (1) □
2. Date of Birth: _____
3. Age in years: _____
4. Occupation: Indoors (0) □
   Outdoors (1) □

Co-morbidities

1. HIV status: Positive (0) □
   Negative (1) □
   Not documented (2) □
   **If Negative or Not documented, skip to No.5*
2. What was the absolute CD4 count at/around the time of exenteration in cells/ml? _____
   **If Not done or Not documented, skip to No.3*
3. Was the patient on highly active antiretroviral therapy (HAART) at the time of exenteration?
   Yes (0) □
   No (1) □
   **If No or Not documented, skip to No.5*

4. Duration of HAART use in years prior to exenteration:_____

PARTICULAR		RESPONSE
1.	Date of noticing ocular lesion	
2.	Date of presentation at KNH	
3.	Date of clinical diagnosis	
4.	Was imaging of the head and orbit done?	Yes (0) □ No (1) □ **If No, skip to No.11* □
5.	Was the imaging available/ documented?	Yes (0) □ No (1) □ **If No, skip to No.11* □
6.	Date of initial imaging	
7.	Date(s) of repeat imaging	
8.	Was perineural spread along the optic nerve noted on imaging?	Yes (0) □ No (1) □ Not documented (2) □
9.	Was bone erosion noted on imaging?	Yes (0) □ No (1) □ Not documented (2) □
10.	Was paranasal sinus extension noted on imaging?	Yes (0) □ No (1) □ Not documented (2) □

11.	Was intracranial sinus extension noted on imaging?	Yes (0) □ No (1) □ Not documented (2) □
12.	Was extension into the contralateral orbit noted on imaging?	Yes (0) □ No (1) □ Not documented (2) □
13.	Was an incisional biopsy done?	Yes (0) □ No (1) □ Not documented (2) □ **If No or Not documented, proceed to No.14*
14.	Date of incisional biopsy	
15.	What was the histological grading (differentiation) of the incisional biopsy?	Well (0) □ Moderate (1) □ Poor (2) □ Undifferentiated (3) □ Other (4) □ Cannot be assessed (5) □ **If Other, please specify*
16.	Date of exenteration	
17.	What type of exenteration was performed?	Subtotal lid sparing (0) □ Subtotal non-lid sparing (1) □ Total lid sparing (2) □ Total non-lid sparing (3) □ Extended lid sparing (4) □ Extended non-lid sparing (5) □

18.	Was gross remnant tumour left in situ during the exenteration?	Yes (0) □ No (1) □ Not documented (2) □
19.	Was bone destruction noted during the exenteration?	Yes (0) □ No (1) □ Not documented (2) □
20.	Date when the exenteration histology results were released	
21.	What was the histological grading (differentiation) of the exenteration specimen?	Well (0) □ Moderate (1) □ Poor (2) □ Undifferentiated (3) □ Other (4) □ Cannot be assessed (5) □ **If Other, please specify*
22.	On histology, were the margins noted to be positive for tumour?	Yes (0) □ No (1) □ Not documented (2) □
23.	On histology, was ocular invasion noted?	Yes (0) □ No (1) □ Not documented (2) □
24.	On histology, was perineural invasion noted?	Yes (0) □ No (1) □ Not documented (2) □
25.	Was repeat surgery performed?	Yes (0) □ No (1) □

		**If No, skip to No. 29*
26.	Date(s) of repeat surgery	
27.	Was radiotherapy prescribed?	Yes (0) □ No (1) □ **If No, skip to No.37*
28.	What was the indication for radiotherapy?	Curative (0) □ Palliative (1) □ Not documented (2) □
29.	Total number of Grays prescribed?	
30.	Number of Grays per session prescribed?	
31.	Was radiotherapy commenced?	Yes (0) □ No (1) □ Not documented (2) □ **If No or Not documented, skip to No. 35*
32.	Date of commencement of radiotherapy?	
33.	Date of completion of radiotherapy?	
34.	Was the total dose of prescribed radiotherapy completed?	Yes (0) □ No (1) □ Not documented (2) □
35.	Total number of Grays received	
36.	Number of Grays per session received?	
37.	Vital status of patient 12 months after exenteration	Alive (0) □ Deceased (1) □

		Lost to Follow Up (2) □
38.	Date of death	

Appendix 2: Consent Form

Participant

English

My name is Dr. Anne Kamere, a resident at the University of Nairobi, currently pursuing a master's degree in Ophthalmology. I am conducting a study as a partial fulfilment of my degree.

I am doing a study on survival rates of patients who receive treatment for orbital squamous cell carcinoma. With your permission, I would like to collect data from your medical records, using a questionnaire. Participation is on a voluntary basis and there will be NO repercussions if you choose not to participate in the study. The information you provide in this questionnaire will be used for research purposes only. Once the study is complete, the data will be archived in order to make it available with other researchers in line with current data sharing practices. This data will be anonymized and will not be used in a manner to allow identification of the individual responses.

Please feel free to ask any questions that you may have. Do you agree to participate?

I acknowledge that this consent form has been fully explained to me in a language that I understand and had the opportunity to ask questions which have been answered to my satisfaction. I agree voluntarily to participate in this study and understand that I have the right to withdraw at any time without penalty.

Participant's name (optional): _____

Date: …….. Study No.:……

Kiswahili

Jina langu ni Dr Anne Kamere, mkazi katika Chuo Kikuu cha Nairobi, kwa sasa nafuatilia shahada ya bwana katika Ophthalmologia. Ninafanya utafiti kama kutimiza sehemu ya shahada yangu.

Ninafanya utafiti juu ya viwango vya maisha ya wagonjwa ambao, wameshapata matibabu kwa ajili ya saratani ya macho katika Hospitali ya Taifa ya Kenyatta. Kwa idhini yako, ningependa kukusanya data kutoka kwa rekodi yako ya matibabu, kwa kutumia hojaji. Kushiriki ni kwa hiari na hakutakuwa na matokeo yoyote ikiwa unachagua kutoshiriki katika utafiti huu. Taarifa ambayo hutoka katika

swala hili yatatumika kwa madhumuni ya utafiti tu. Mara tu utafiti ukamilika, data itahifadhiwa ili iweze kupatikana na watafiti wengine kulingana na mazoea ya sasa ya ushirikiano wa data.

Data hii haitatambulika na haitatumiwa kwa namna ya kuruhusu utambuzi wa majibu ya mtu binafsi.

Asante sana kwa kukubali kushiriki katika utafiti huu.

Tafadhali jisikie huru kuuliza maswali yoyote ambayo unaweza kuwa nayo.

Je, unakubali kushiriki?

Nakubali kwamba fomu hii ya ridhaa imenipeleleza kikamilifu kwa lugha ambayo ninaelewa na nilikuwa na fursa ya kuuliza maswali ambayo yamejibiwa kwa kuridhika kwangu. Nakubali kushiriki katika utafiti huu na kuelewa kwamba nina haki ya kujiondoa wakati wowote bila adhabu.

Jina la mshiriki (hiari): _____

Tarehe : …….. Study No.:……

Ukiwa na swali lolote kuhusu utafiti huu, waweza nipigia simu ama kuandika barua kwenye komitee ya ethics kupitia njia hizi;

Dr. Anne Kamere University of Nairobi Ophthalmology department Nambari ya simu: 0722756154	Kenyatta National Hospital/University of Nairobi Ethics and research committee College of health sciences P.O Box19676 Code 00202 Nairobi Nambari ya simu (254) 020 2726300-9 Ext 44355 Barua pepe: uonknh-erc@uonbi.ac.ke

Next of Kin

English

My name is Dr. Anne Kamere, a resident at the University of Nairobi, currently pursuing a master's degree in Ophthalmology. I am conducting a study as a partial fulfilment of my degree.

I am doing a study on survival rates of patients who receive treatment for orbital squamous cell carcinoma. With your permission, I would like to collect data from the medical records of …… using a questionnaire. Participation is on a voluntary basis and there will be NO repercussions if you choose not to participate in the study. The information you provide in this questionnaire will be used for research purposes only. Once the study is complete, the data will be archived in order to make it available with other researchers in line with current data sharing practices. This data will be anonymized and will not be used in a manner to allow identification of the individual responses.

Please feel free to ask any questions that you may have. Do you agree to participate?

I acknowledge that this consent form has been fully explained to me in a language that I understand and had the opportunity to ask questions which have been answered to my satisfaction. I agree for you to use the data of the participant in this study and understand that I have the right to withdraw at any time without penalty.

Informant name (optional): _____

Date: …….. Study No.:……

Kiswahili

Jina langu ni Dr. Anne Kamere, mkaazi katika Chuo Kikuu cha Nairobi, kwa sasa nafuatilia shahada ya bwana katika Ophthalmologia. Ninafanya utafiti kama utimizaji wa sehemu ya shahada yangu.

Ninafanya utafiti juu ya viwango vya maisha ya wagonjwa ambao, wameshapata matibabu kwa ajili ya saratani ya macho katika Hospitali ya Taifa ya Kenyatta. Kwa idhini yako ningependa kukusanya data kutoka kwa rekodi ya matibabu ya..... kwa kutumia hojaji. Kushiriki ni kwa hiari na hakutakuwa na matokeo yoyote ikiwa unachagua kutoshiriki katika utafiti huu. Taarifa ambayo hutoka katika swala hili yatatumika kwa madhumuni ya utafiti tu. Mara tu utafiti ukamilika, data

itahifadhiwa ili iweze kupatikana na watafiti wengine kulingana na mazoea ya sasa ya ushirikiano wa data.

Data hii haitatambulika na haitatumiwa kwa namna ya kuruhusu utambuzi wa majibu ya mtu binafsi.

Tafadhali Jisikie huru kuuliza maswali yoyote ili muweze kuwa. Je, unakubali kushiriki?

Nakubali kwamba fomu hii ya ridhaa imenipeleleza kikamilifu kwa lugha ambayo ninaelewa na nilikuwa na fursa ya kuuliza maswali ambayo yamejibiwa kwa kuridhika kwangu. Nimewakubalisha kutumia data ya mshiriki katika utafiti huu na kuelewa kwamba nina haki ya kujiondoa wakati wowote bila adhabu.

Wahojiwa jina (hiari): _____

Tarehe : …….. Study No.:……

Ukiwa na swali lolote kuhusu utafiti huu, waweza nipigia simu ama kuandika barua kwenye komitee ya ethics kupitia njia hizi;

Dr. Anne Kamere University of Nairobi Ophthalmology department Nambari ya simu: 0722756154	Kenyatta National Hospital/University of Nairobi Ethics and research committee College of health sciences P.O Box19676 Code 00202 Nairobi Nambari ya simu (254) 020 2726300-9 Ext 44355 Barua pepe: uonknh-erc@uonbi.ac.ke

Appendix 3: Transcript of Phone Inquiry

Hello, how are you? I would like to speak to …… My name is Dr. Kamere and I am based at the Eye Department in Kenyatta National Hospital. I would like to follow up on the progress ……. following the treatment received in this hospital. I would like to enquire on whether they alive and well.

Thank you.

Habari yako? Ningetaka kuzungumza na …… Kwa majina naitwa Dr. Kamere na mimi ninahudumu katika wadi ya Macho katika hospitali kuu ya Kenyatta. Ningetaka kuwasiliana nawe kuhusu …….. mwenye aliyepata matibabu katika hospitali hii ya Kenyatta. Naomba kuuliza kama bado wangali hai kwa hali nzuri.

Asante.

Appendix 4: Letter of Introduction to Next of Kin

Dear Sir/Madam,

My name is Dr. Kamere and I am based at the Eye Department in Kenyatta National Hospital. I would like to follow up on the progress of your family member following the treatment he/she received in this hospital and would like to discuss it with you. Please send me a text message or flash me on the following number 0722756154 and I will call you back.

Thank you,

Dr. Anne Njeri Kamere.

Kwa

Kwa majina naitwa Dr. Kamere na mimi ninahudumu katika wadi ya Macho katika hospitali kuu ya Kenyatta. Ningetaka kuwasiliana nawe kuhusu memba wa familia yenu mwenye aliyepata matibabu katika hospitali hii ya Kenyatta. Naomba tafadhali uwasiliane nami katika njia ya sms au kunitumia "please call me" kwa hii nambari 07227156154 kisha nitakupigia simu.

Asante,

Dr. Anne Njeri Kamere.

Appendix 5: Work Plan

	2018								2019		
	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar
Proposal presentation											
Ethics approval											
Data collection											
Data analysis											
Report writing											
Presentation of the results											

Appendix 6: Budget

MMed Thesis Budget **TITLE: Survival rates of patients with orbital squamous cell carcinoma in Kenyatta National Hospital** **Principal Investigator: Dr. Anne Njeri Kamere**			
Item	Quantity	Unit Cost	Total Cost
Proposal/Ethical approval and ministry of Education approval			
Proposal writing & printing	6 copies	Ksh 10 per page	4000
Binding Proposal	6 copies	100	600
Ethics	1	2000	2000
Airtime		Ksh. 3 per minute	2000
		Subtotal	**8600**
Data Collection			
Typing and Printing of Questionnaires		60 per copy	300
Photocopy of questionnaires		18 per copy	10000
Stationary –pens, erasers, etc.			1000
Flash Disc 16GB HP	1	4500	4500
Box files for filing questionnaires	5	450 each	2250
		Subtotal	**18050**
Contracted services			

Statistician	1		15000
		Subtotal	**15000**
Printing costs and binding of Final book			
Finished book printing (80 pages approximately)	8 copies- 80 pages	Ksh 10 per page	6400
	8 copies- coloured 20 pages	Ksh 30 per page	4800
Binding Finished book	2 copies- marking	100 per book	200
	8 final copy (black cover)	300	2400
		Subtotal	**13800**
TOTAL BUDGET			**55450**

Appendix 7: Letter of approval from the Ethics and Research Committee

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL APPROVED 20 SEP 2018 P.O. BOX 20723-00202 NAIROBI

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/340

20th September 2018

Dr. Anne Njeri Kamere
Reg. No.H58/86844/2016
Dept. of Ophthalmology
School of Medicine
College of Health Sciences
University of Nairobi

ASSISTANT DIRECTOR:HEALTH INFORMATION SERVICES KENYATTA NATIONAL HOSPITAL 10 DEC 2018 P. O. Box 20723 - 00202 NAIROBI

etc

Dear Dr. Kamere

RESEARCH PROPOSAL – SURVIVAL RATE OF PATIENTS WITH ORBITAL SQUAMOUS CELL CARCINOMA IN KENYATTA NATIONAL HOSPITAL – A RETROSPECTIVE COHORT STUDY (P387/06/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 20th September 2018 – 19th September 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chairperson, Dept. of Ophthalmology, UoN
Supervisors: Dr. Millicent Kariuki, Dr. Stephen Gichuhi

Appendix 8: KNH Ophthalmology Department Study Registration Certificate

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
DR. ANNE NJERI KAMERE

2. Email address: dr.ankamere@gmail.com Tel No. 0722 756 154

3. Contact person (if different from PI).....

4. Email address: ..... Tel No. .....

5. Study Title
Survival Rates of Patients with Orbital Squamous Cell Carcinoma in Kenyatta National Hospital; A Retrospective Cohort Study

6. Department where the study will be conducted KNH Eye Clinic
(Please attach copy of Abstract)

7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
Name: J R J. WACHIRA Signature ..... Date 29/10/18

8. Endorsed by KNH Head of Department where study will be conducted.
Name: DR P.T. NYAGA Signature ..... Date 31/10/18

9. KNH UoN Ethics Research Committee approved study number P357/06/2018
(Please attach copy of ERC approval)

10. I DR. ANNE NJERI KAMERE commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
Signature ..... Date 25/10/18

11. Study Registration number (Dept/Number/Year) Opthalmology /12 /2018
(To be completed by Research and Programs Department)

12. Research and Program Stamp KENYATTA NATIONAL HOSPITAL 18 DEC 2018

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014

Appendix 9: KNH Cancer Treatment Centre Study Registration Certificate

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
DR. ANNE NJERI KAMERE
2. Email address: dr.ankamere@gmail.com Tel No. 0722756194
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
Survival Rates of Patients with Orbital Squamous Cell Carcinoma in Kenyatta National Hospital; A Retrospective Cohort Study
6. Department where the study will be conducted KNH Cancer Treatment Centre
(Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
Name: ..... Signature ..... Date .....
8. Endorsed by KNH Head of Department where study will be conducted.
Name: Dr C Nyongesa Signature ..... Date 10/12/18
9. KNH UoN Ethics Research Committee approved study number _____
(Please attach copy of ERC approval)
10. I DR. ANNE NJERI KAMERE commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
Signature..... Date 10/12/18
11. Study Registration number (Dept/Number/Year) Cancer Treatment Centre /[illegible] /2018
(To be completed by Research and Programs Department)
12. Research and Program Stamp _____

KENYATTA NATIONAL HOSPITAL * P.O. Box 20723 - 00202 Nairobi * Cancer Treatment Centre
10 DEC 2018

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014