Title Page

Title: Protocol for Anal carcinoma:A retrospective review at the Department of Oncology Universitas Academic hospital Bloemfontein

Thandeka Nompumelelo Buthelezi

Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Oncology in the Faculty of Health Sciences in the University of the Free State.

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Supervisor : Prof A Sherriff

Declaration of authorship :

I Thandeka N. Buthelezi ,declare that the coursework Master's Degree mini-dissertation that I herewith submit for the Masters Degree qualification in Oncology at the University of the Free State is my independent work ,and that I have not previously submitted it for a qualification at another institution of higher education.

Abstract

Background : Anal carcinoma is an uncommon cancer worldwide.Standard therapy is chemoradiation as it is not only curative but also has the advantage of organ preservation. In our department we see mostly locally advanced carcinomas as opposed to the early stage disease investigated in international articles. The standard dose for chemoradiation is 55-59 Gy. We have given up to 70Gy in locally advanced disease.

Objectives : We aimed to assess whether the higher dose of up to 66-70 Gy, given in our department to locally advanced disease is improving survival and has a comparable side effect profile to the standard radiation dose.

Method :As will be explained later ,only patients that were from the Free State and treated in our department from 2001 to 2010 were included in the study sample. Clinical records were used to obtain data. The total number of participants were 28. Only patients that received chemoradiation or radiation only were included. The data analysed were : local demographics,local control,acute and late toxicity,colostomy free survival and progression free survival with correlation to the total radiation dose received .Numerical variables were summarised using medians and interquartile ranges. Categorical variables were summarised using frequencies and percentages.

Results : Males made up 57,1% of the participants and females 42,9%. The mean age was 45 with the youngest being 21 years old. Twelve of the participants had HIV infection. Ninety one percent of the patients had squamous cell carcinoma. All presented with locally advanced disease.Five patients defaulted post radiation.Participants that received split course radiation were 86%, 7% received continuous radiation to a total dose of 50,4 Gy,3,6% 38 Gy and 3,6% 3740cGy . The highest radiation dose received was 60 Gy. On follow-up 12 (43%) had a complete response 11(39%)had residual disease.Majority (75%) already had colostomies prior to starting treatment,three never required one.

Conclusion: The primary end point was not met as none of the patients received the dose we were aiming to assess due to exclusion criteria. Observations made with regards to demographics and side effect profile were in keeping with published literature. PFS and OS were less due to the majority of the patients having poor prognostic features and poor patient follow up. The majority of the patients were treated with radiation doses lower than 55 Gy which is the recommended minimum for locally advanced disease.

Keywords: anal carcinoma,chemotherapy,radiation,survival,toxicity,HIV

Table of contents

Chapter 1

Introduction

Anal carcinoma is a neoplasm that develops in the anal region. The anal canal extends from the anorectal junction to the anal margin which is the pigmented skin immediately surrounding the anal orifice extending laterally to a radius of approximately 5cm.It is lined with glandular,transitional and squamous mucosa. Tumours can arise from any part of the different mucosa but 75% is squamous cell carcinoma arising from the transitional zone in the anal canal.*[1].*Other types of histologies include adenocarcinoma,melanoma,neuroendocrine and rarely sarcoma and lymphoma*[1,2,3].*

Anal carcinoma is considered to be a rare type of cancer comprising 2-5% of gastrointestinal neoplasms*[1,4].*The global annual incidence rates range from 0,1-2,8 per 100 000 cases among men and 0,0-2,2 cases per 100 000 among women.
A study done in KwaZulu Natal in South Africa showed that anal carcinoma was possibly more common in that province compared to international reports*[3]*.In South Africa the National cancer registry is pathology based,this results in the under-reporting of many malignancies, therefore the true incidence of anal carcinoma in the country is unknown*[4].*The incidence of anal carcinoma has gradually been rising over the past 20-30 years and this is partly attributed to the increase in the incidence and absolute number of the most significant risk groups namely HIV(Human Immunodeficiency Virus) positive MSM (men who have sex with men) and an increase in the number of solid organ transplant recipients*[1,2,3,9,12]*.

The other risk factors associated with anal carcinoma include HPV(Human Papilloma Virus)infection,female gender,smoking,lifetime number of sexual partners,receptive anal intercourse ,genital warts and previous cervical,vulval or vaginal cancer.HPV being the main causative agent especially subtypes 16 and 18 in 80-85% of patients *[1,2,3,6,8-10,12].* Genetic mutation of the PIK3CA gene has also been implicated in the process of carcinogenesis *[10].*

Demographics in HIV infected people are different compared to the general population with regards to younger age, average of 40 years versus 62 and mostly male rather than female patients *[2,8,9].* The younger age group is in spite of being on Antiretrovirals(ARV) *[8].*An increased incidence in people on ARVs is due to increased patient survival ,as the risk of squamous cell anal carcinoma increases with duration of HIV infection *[12].*This was also supported by studies done in South Africa from KwaZulu Natal and Cape Town *[3,5]*.The oncologic outcomes in patients with HIV are comparable to HIV negative patients (5 year survival 57% vs 57% respectively) with the stage of the anal carcinoma as the only factor predictive of survival, p value of 0,05 *[8]*. They were not shown to have a shorter progression free survival.

The staging system referred to in this review is the TNM system developed by the American Joint Committee on Cancer(AJCC).See Table 1 below.The size of the primary tumour and presence of lymphadenopathy corresponds with the prognosis in anal carcinoma.*[1]*Patients with localised disease at presentation have a 80% survival rate,those with regional node metastasis have a 60% 5 year survival while those with distant metastasis have a 30,5% 5 year survival rate*[1]*.

Literature states that most patients present with T1 or T2 tumours and fewer than 20% have positive node metastasis*[3]* . Although there is scant South African based data on anal carcinoma , patients present mostly at a younger age with locally advanced disease*[4,5].* Metastasis is also uncommon at 5-8% at onset ,it spreads in a loco-regional manner within and outside of the anal canal *[6]*.Poor prognostic factors for survival include male sex,positive lymph nodes(particularly inguinal)and primary tumour more than 5 cm *[6].*

The standard of care for anal carcinoma is chemo-radiation even for early disease(T1/T2 N0 M0) due to the advantage of retaining sphincter function and avoiding a permanent colostomy, with survival outcomes similar to surgery with- APR (abdominal-perineal resection) *[3,5]*.A study done by Nigro et al in 1984 was the landmark trial that initiated the change to chemo-radiation as opposed to surgery, where they achieved a 93% complete pathological response rate with radiation and concurrent Mitomycin C(MMC) and 5 Fluorouracil(5FU). Small lesions that are </= 1cm involving the anal margin can be managed by surgery in the form of local excision if adequate margins can be obtained without compromising sphincter function*[2,6,18]*.

The current recommendations are based on results of the phase 2 and six phase 3 trials;EORTC22861,UKCCCR ACT 1,RTOG 87-04,RTOG 98-11,ACCORD-03,CRUK ACT II*[6].*Concurrent chemotherapy consists of an infusion of 5-FU 1000mg/m2 on day 1-4 and day 29- 32 plus Mitomycin C 10mg/m2 on days 1 and 29 max 20 mg per dose.

Radiation dose of 45Gy to the pelvis for early stage disease and an additional boost to the GTV(Gross Tumour Volume) of 10-14Gy in 1.8-2 Gy fractions for locally advanced disease(T3-T4 or node positive) making a total dose of 55-59Gy*[1,2].* For patients responding poorly ,higher boost doses have been used.(6)

Adenocarcinoma of the anus is treated similarly to rectum cancer.

Patients with locally advanced anal cancer have a cure rate of approximately 50-60% with standard chemoradioradiation *[6]*.In the ACCORD trial they used colostomy free survival(CFS) as the primary end point to compare induction chemotherapy (Cisplatin/ 5FU) and higher radiation boost for locally advanced anal carcinoma*[7]*. CFS rate was 77% with the standard boost of 15 Gy and 72,7% with the intensified boost of 20-25Gy

at 5 years.They were not able to find an advantage for either induction chemotherapy or high dose radiation boost in locally advanced anal canal carcinoma.

Anal carcinoma regresses slowly and could take up to 26 weeks post chemoradiation to achieve a complete response or stable disease as shown in the ACT II trial(19).This trial also demonstrated that grade 3 and 4 toxicities were similar when using concurrent MMC/5FU and Cispaltin/5FU with radiation.The common grade 3 and 4 toxicities were skin 48% versus 47%,pain 26% versus 29%,haematological 26 versus 16% and gastrointestinal 16 versus 18% for MMC/5FU versus Ciplatin/5FU respectively.

In our department of Oncology at Universitas Annex Academic Hospital our protocol for definitive chemo-radiation is concurrent chemotherapy Cisplatin/5FU or MMC/5FU (D1-4,29-32)depending on the patients general condition and HIV status.Radiation dose is 59.4Gy but for advanced local disease we give up to 66Gy to the primary tumour.For palliative radiation we use a split course of 2400cGy over 2 weeks in 2 Gy fractions,rest 4 weeks then another 2400 cGy with a boost of 8-14 Gy.

We will be looking at demographics, local control,progression free survival and side effect profile,acute and late toxicity but with emphasis on late toxicity, and correlating this with total radiation dose received.

Table 1.1 Staging system

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm
T4	Tumor of any size invades adjacent organ(s), such as the vagina, urethra, bladder

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Anatomic Stage/Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-T2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3-T4	N1	M0
Stage IV	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Chapter 2.

Methods

2.1 Setting

The study was carried out at the Universitas Annex Academic Hospital Oncology Department. As this was a retrospective descriptive study, for data we used patient records in our filing system.Administrative staff collected all files with the ICD 10 code C21 treated between 2001-2010 with chemo-radiation or only radiation.This was to ensure at least a 5 year follow-up of the study participants.The researcher then selected files using the inclusion and exclusion criteria.

Inclusion criteria:

-Patients with confirmed histological diagnosis of anal canal/peri-anal carcinoma

-Age above 18 years

-Received chemoradiation or radiation only

Exclusion criteria :

-Patients from Lesotho and Northern Cape as we do not follow them up

-Patients who received only chemotherapy

-Stage IV disease at diagnosis

2.2 Sample

The sample consisted of patients with a histological diagnosis of anal/peri-anal carcinoma treated with chemo-radiation or radiation in our department between the years 2001 and 2010.Because we were looking at survival as a primary end point,patients that were not followed up in our department were excluded,namely patients from Lesotho (N=25) and the Northern Cape (N=27) which constitute a significant number of the patient population. See Table *2.1* .Other exclusion criteria included patients who received only chemotherapy and patients who presented with metastatic disease (stage IV) and are below 18 years.The total number of patients that presented to the Department of Oncology that were from the Free State during this period(2001-2010) were 52,of which 13 defaulted before starting treatment,2 had wide local excision,4 were metastatic , 4 had plasmablastic lymphoma and treated with chemotherapy,1 had neuroendocrine small cell carcinoma and received chemotherapy

only.Meeting the requirements for inclusion was a sample size of 28 (N.28). The total number of patients with anus cancer treated in the department in 2016 were 23 and in 2017 were 21,this shows a dramatic increase compared to the earlier years with an average of 8-12 cases per year.

2.3 Study Design

This was a Descriptive study . A data form was used to capture information from each patient file.The files are identified by a RT number which is used in our department for filing purposes.This number is unique and specific to a particular patient,this will help to ensure that a patients information is not repeated.Values with prognostic significance that we evaluated include: the albumin,heamoglobin level ,CD4 count as well as the performance status.The normal heamoglobin(Hb) reference range for males is 14.0-17,5 g/dl and for females 12,3-15,3 g/dl. Aneamia is directly associated with an increased risk of death in patients with various malignancies*[13]*.A low Hb level is common in cancer and it affects the choice of treatment as well as outcome.Anaemia may exacerbate tumour hypoxia leading to radio resistance.The normal albumin reference range is 35-55g/L.Albumin is a reliable indicator of an individuals nutritional status.It is also an independent prognostic indicator in various cancers*[14].*A low pretreatment serum albumin is associated with poor survival *[15]* . The normal CD4 count range is 460 - 1600 cell per cubic millimetre of blood.In anal carcinoma a low CD4 count (<200) is associated with increased morbidity and toxicity *[16]*. The Eastern Cooperative Oncology Group (ECOG) performance status is used to assess the functional status of cancer patients with regards to status of symptoms and functions namely ambulatory status and need for care.Graded from 0 to 4 with 0 being normal activity and 4 being preterminal. Age is prognostic for overall survival *[17]*

2.4 Statistical Analysis

Data analysis was done by Department of Biostatistics at the University of Free State.Numerical variables were summarised using medians and interquartile ranges. Categorical variables were summarised using frequencies and percentages.

2.5 Ethical considerations

Permission was obtained from the Oncology Head of Department at Universitas Hospital. Approval was granted by the Department of Health in the Free State as well as the Health Sciences Research Ethics Committee at the University of the Free State.

Table 2.1

	Northern Cape (N=27)	Lesotho (N=25)
Stage	IIA - 0 IIB - 6 IIIB - 7 IIIC - 12 IV - 2	IIA - 1 IIB - 5 IIIB - 6 IIIC - 9 IV - 4
Radiation Doses	24 Gy - 2* 48 Gy - 6 50 Gy - 2 54 Gy - 5 56 Gy - 1 60 Gy - 2 66 Gy - 2 70 Gy - 3	37,4cGy - 2 48 Gy - 2 50 Gy - 1 54 Gy - 6 56 Gy - 2 60 Gy - 2 66 Gy - 2 70 Gy - 2
Defaulted before starting treatment	4	5

**Both these patients defaulted before completing the treatment course*

Chapter 3

Results

There was a total number of 28(N=28) study participants of which 12(42,8%) were female and 16(57,1%) male.The mean age was 45 with the youngest being 21 and eldest 85 years old.The age distribution was skew therefore the median was used as summary statistic with the interquartile range.

Most of the patients had a good performance status,ECOG 1 39% , ECOG 2 57% and ECOG 3 4%, hence most patients received concurrent chemotherapy with the radiation. The median albumin was 30 and Heamoglobin 11,see *Table 3.1.*

Table 3.1

	N	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
Albumin (g/L)	27*	30	21	38	9	40
Heamoglobin (g/dL)	28	11	9,6	13,4	7,4	16
Age(years)	28	45	37	58,5	21	85

**one patients albumin was not recorded in the clinical notes*

Histological typing

The dominant histology was squamous cell carcinoma which was in 20 patients (71%),followed by adenocarcinoma in 6 patients(21%) ,lastly unspecified carcinoma and lymphoma accounted for 4% each.

Twelve(43%) of the patients were HIV positive ,most (91%) from that group had squamous cell carcinoma except one patient who had plasmablastic lymphoma,see *Table 3.2* .All of these patients presented with locally advanced disease,see *Table 3.3*.The majority of the *HIV negative* patients also presented with locally advanced disease.The dominant histology in this group was also squamous cell carcinoma (9 patients), 4 had Adenocarcinoma and one unspecified carcinoma.The two patients that declined testing for HIV presented with locally advanced disease,IIIA and IIIC both Adenocarcinoma.

Only 2 patients (16%) were on ART at the time of treatment initiation,most likely due to the government guidelines on ART initiation and the stigma surrounding HIV at that time period.The National South African guidelines for ART initiation at that time(2005-2010) was a CD4 count below 200 cells/mm3.The median CD4 count was

359 cells/mm3, minimum 55 and maximum 867 cells/mm3.Two patients declined to test for HIV and 14 were negative.

Table 3.2 : Pathology

	Frequency	Percentage (%)
Adenocarcinoma	6	21
Carcinoma not specified	1	4
Squamous cell carcinoma	20	71
Lymphoma	1	4

Table 3.3 : Stage Groups

Stage	HIV pos (N-12)	HIV neg (N-14)	HIV unknown (N-2)
IIA	0	1	0
IIB	0	0	0
IIIA	1	2	1
IIIB	4	4	0
IIIC	7	7	1

One patient from the HIV positive-not-on-ART group received neo-adjuvant chemotherapy,one cycle of Cisplatin/5FU .Three patients that were HIV negative received neo-adjuvant FUMI and one received 5FU/Leucovorin.

Radiation doses and schedules

The majority(85 %) of the patients received split course radiation and 82 % completed it.Treatment was stopped for 2 patients due to a poor general condition,one of them was the eldest study participant at 85 years old.Four patients received continuous chemoradiation ,two to a total dose of 5040cGy with concurrent chemotherapy (FUMI and weekly 5FU)given at 180 cGy x 28 daily , one patient received 3800cGy given at 200cGy x 19 with no chemotherapy and one patient received 3740 cGy given at 340cGy x 11 four times a week with no chemotherapy.The latter dose was given due to a poor

general condition ,she was also HIV positive and not on ART with a CD4 count of 55.The other two patients that received continuous chemoradiation were HIV negative.

Different schedules used:

2400cGy in 12 fractions of 200 cGy
3740 cGy in 11 fractions of 340 cGy four times a week
3800cGy in 19 fractions of 200 cGy
4800cGy given in 12 fractions of 200 cGy rest 4 weeks then 200 cGy x 12 fractions
5000 cGy given 12 fractions of 200 cGy rest 4 weeks then 200 cGy x 13
5040cGy given in 28 fractions of 180 cGy
5200cGy given in 12 fractions of 200 cGy rest 4 weeks then 200 cGy x 14
5400cGy given in 12 fractions of 200 cGy rest 4 weeks then 200 cGy x 15
5800cGy given in 14 fractions of 200 cGy rest 4 weeks then 200 cGy x 15
6000cGy given in 12 fractions of 200 cGy rest 4 weeks then 200 cGy x12 and boost x6

The average duration of treatment was 56 days (split course) . All patients were treated using 2D.Options for chemotherapy were MMC/5FU(81%),Cisplatin/5FU(15%) and weekly 5FU(4%).In total 11 % received neo-adjuvant chemotherapy,MMC/5FU.Of the 28 study participants,25 received concurrent chemotherapy of which 81% was MMC/5FU, 15% Cisplatin/5FU and 4% weekly 5FU.

Five patients died post completing radiation. Time to death was an average of 17 months from diagnosis. The longest being 48 months from diagnosis to death.Five patients were lost to follow up just after completing treatment and their outcome is unknown.

HIV positive on ART

The two patients that were on ART presented with stage IIIB and IIIC disease,received 48Gy and 60 Gy,concurrent Cisplatin/5FU and FUMI respectively.The patient that was treated with 48 Gy had an acute radiation dermatitis during treatment .He also never required a colostomy. They both subsequently developed fibrosis and pain on follow up.Both patients had residual disease at 6 and 5 months respectively and were lost to follow up at that point without receiving salvage therapy.See *Table 3.4*

HIV positive not on ART

The other 10 patients that were not on ART also had locally advanced disease,*see Table 3.5.* The one patient with stage IIIA disease had Plasmablastic lymphoma and received continuous treatment of 38 Gy with no chemotherapy but demised 3 months post radiation.All the patients with stage IIIB disease had SCC histology and all were treated with different fractionations: 48 Gy,54 Gy and 58 Gy .They received concurrent Cisplatin/5FU.During radiation these patients had radiation dermatitis but tolerated

radiation fairly well. One patient had residual disease at 3 months post radiation.The other two had recurrence at 8 months and at 9 years post radiation respectively.They all received palliative Cisplatin/5FU.The study participant that survived the longest was from this group with progression only after 9 years post radiation,she had received 58Gy.They all had colostomies before starting treatment .The long term side effects in this group included fibrosis and pain.

Patients that were HIV positive and not on ART that were stage IIIC were 6 in total.One patient received a continuous dose of 3740 cGy with no chemotherapy due to the poor performance status and a CD4 count of 55,she was last seen on the day she was discharged after completing radiation. Five patients were treated with split course radiation to a total dose of 54 Gy,one with concurrent Cisplatin/5FU and four with concurrent FUMI.They all had colostomies before starting radiation.The one patient that received concurrent Cisplatin/5FU had residual disease at 3 months and at 4 months post radiation received palliative Cisplatin/5FU.He was last seen 1 year 3 months post radiation.

The four patients that received concurrent FUMI: one required a blood transfusion during chemoradiation,two had radiation dermatitis.One patient had local recurrence 3 years 5 months post radiation and demised without receiving salvage treatment.The one patient who received 1 cycle of neo-adjuvant Cisplatin/5FU had residual disease at 3 months post chemoradiation .He received palliative Cisplatin/5FU at 9 months and was last seen 1 year post radiation.One patient from this group progressed at 10 months post chemoradiation and received Cisplatin/5FU palliatively , he was last seen 2 years post radiation.The one patient that did not progress was last seen 2 years 3 months post radiation. See *Table 3.5*

Table 3.4 HIV Positive on ART (N-2)

	Stage IIIB (N-1)	Stage IIIC (N-1)
Histology	SCC	SCC
Neo-adjuvant chemotherapy	nil	nil
Concurrent chemotherapy	Cisplatin/5FU	FUMI
Radiation dose (Gy)	48 Gy	60 Gy
Colostomy before radiation	nil	yes
Colostomy post radiation	nil	nil
Complete response	nil	nil
Time to progression	unknown	unknown
Salvage treatment	nil	nil
Last seen post radiation	6 months	5 months

Table 3.5 HIV positive not on ART

	Stage IIIA (N-1)	Stage IIIB (N-3)	Stage IIIC (N-6)
Histology	Plasmablastic lymphoma	Squamous cell carcinoma(3)	Squamous cell carcinoma(6)
Neo-adjuvant chemotherapy	nil	nil	Cisplatin/5FU (1)
Concurrent Chemotherapy	nil	Cisplatin/5FU (3)	nil (1) Cisplatin/5FU (2) FUMI (3)
Radiation dose (Gy)	38 Gy(1)	48 Gy (1) 54 Gy (1) 58 Gy (1)	37,4Gy (1) 54 Gy (5)
Colostomy before radiation	Yes (1)	Yes (2) No (1)	Yes (6)
Colostomy post radiation	nil	nil	nil
Residual disease at 3 months	unknown	Yes (1)	unknown (1) Yes (2)
Complete Response	unknown	Yes (2)	Yes (3)
Time to progression	Demised 3 months post radiation	8 months -local+lung(1) 9 yrs -local(1)	unknown (1) 3 yrs 5 months-local (1) 10 months-local+nodes(1) no progression (1)
Salvage treatment	none	Cisplatin/5FU (3)	Cisplatin/5FU (3) none (3)
Last seen post radiation	Demised 3 months post radiation	16 months(1) 20 months (1) 9 years 8 months (1)	Last day of radiation (1) 1 yr 3 months (1) Demised 3yrs 5 months (1) 1yr (1) 2 yrs (1) 2 yrs 3 months (1)

yr(s)- year(s)

HIV negative

There were 14 patients that were HIV negative, 1 patient had stage IIA disease which was an Adenocarcinoma.This patient received 52 Gy with concurrent FUMI,he only required a colostomy 2 years 6 months post radiation when he had local progression.He refused an APR.

There were 2 patients with Stage IIIA disease,both had squamous cell carcinoma(SCC).They received 52 and 50 Gy with concurrent FUMI. The patient that received 52 Gy had a complete local response at 3 months but presented with lung

metastasis at 5 months,he was treated with Cisplatin/5FU (2 cycles) and demised 1 year post radiation.The patient that received 50 Gy progressed with local recurrence at 5 months then had a colostomy and palliative FUMI,last seen 1 year post completion of radiation.

All four patients with Stage IIIB disease had SCC and were treated with 54 Gy and concurrent FUMI.Three had colostomies before starting treatment and one never had one.The patient that never had a colostomy had residual disease at 3 months and subsequently demised 6 months post radiation without receiving salvage treatment.The other 3 patients had a complete response at 3 months , they were last seen at 13 ,4 and 6 months post radiation.

There were 7 patients with Stage IIIC disease,3 had SCC, 3 Adenocarcinoma and 1 unspecified poorly differentiated carcinoma.All but one received concurrent FUMI ,3 required blood transfusions for anaemia during chemoradiation. Three patients received 48 Gy: 1 had local recurrence 1year 9 months post radiation for which he had an APR then 1 cycle of FUMI and demised 2 years post radiation,the 2nd one was last seen on completion of radiation and the last one had residual disease at 3 months and was started on Cisplatin/5FU 4 months post radiation she was last seen 1 year 2 months post radiation.The two patients that received 54 Gy ,one defaulted 2 months post radiation and had residual disease at that time.The 2nd patient required a colostomy 1 month post radiation for incontinence , seen 1 year post completion of radiation.One patient received 5040 cGy,he had residual disease at 3 months and a month later had liver metastasis and was started on Cisplatin/5FU,last seen 8 months post radiation. The patient that received 60 Gy had received 2 cycles of neo-adjuvant FUMI and no concurrent chemotherapy,last seen on completion of radiation. See *Table3.6*

HIV Unknown

There were 2 patients that declined HIV testing both had Adenocarcinoma,one had stage IIIC disease and received 24 Gy with concurrent FUMI,he didn't receive the 2nd split course due to a poor clinical condition and found to have liver metastasis during radiation.He was last seen on day of discharge without ever having a colostomy.The other patient had Stage IIIA disease and received 5040cGy with weekly 5FU.This patient had a colostomy before starting treatment and was lost to follow up 1 month post radiation,he was assessed as having a complete local response at that time. See *Table 3.7*

Toxicities

The most common late complication with all the radiation doses was skin fibrosis(78%) ,anal stenosis(46%) and pain(67%). See *Table 3.8.* The patients that

received 2400 cGy ,3740 cGy and 3800 cGy could not be assessed for late toxicities due to defaulting follow-up post treatment.

One patient required a treatment break of 2 days due to radiation dermatitis,she was HIV negative and getting a split course with a total dose of 48 Gy. Due to poor clinical note keeping ,the toxicities for most patients are not documented

Table 3.6 HIV negative (N-14)

	Stage IIA (N-1)	Stage IIIA(N-2)	Stage IIIB(N-4)	Stage IIIC(N-7)
Histology	Adenocarcinoma	SCC (2)	SCC (4)	Unspecified (1) SCC (3) Adenocarcinoma(3)
Neo-adjuvant chemotherapy	5FU/LV x 1	nil	FUMI x 1 (1)	FUMI (2)
Concurrent Chemotherapy	FUMI	FUMI (2)	FUMI (4)	FUMI (6) nil (1)
Radiation Dose	5200 cGy	5000 cGy (1) 5200 cGy (1)	5400 cGy (4)	4800 cGy (3) 5400 cGy (2) 5040 cGy (1) 6000 cGy (1)
Colostomy before radiation	nil	yes (1)	yes (3)	yes (5)
Colostomy post radiation	2yrs 6 months	5 months post radiation (1)	nil	yes (1)- 1 month post radiation
Complete response	nil	yes (2)	yes (3)	yes (1)
Residual disease at 3 months	yes	nil	yes (1)	unknown (2) yes (4)
Time to progression	N/A	5 months -local 5 months - lung mets	6 months(1) - local nil(2)	1 yr 9 months(1)
Salvage treatment	FUMI x 6 (refused surgery)	FUMI x 3 Cisplat/5FU x 2	nil(4)	FUMI (1) Cisplatin/5FU (1) APR then FUMI (1)
Last seen post radiation	3 yrs 6 months	1 yr (1) Demised 1 yr post radiation(1)	Demised 6 months post radiation(1) 13 months (1) 4 months 6 months	1 yr (1) 1 yr 2 months (1) 2 months (1) Last day of radiation-(2) 8 months(1) Demised 2 yrs(1)

Table 3.7 HIV Unknown (N-2)

	Stage IIIA (N-1)	Stage IIIC (N-1)
Histology	Adenocarcinoma	Adenocarcinoma
Neo-adjuvant chemotherapy	nil	nil
Concurrent chemotherapy	Weekly 5FU	FUMI
Radiation dose (Gy)	50.4 cGy	24 Gy
Colostomy before radiation	yes	yes
Colostomy post radiation	nil	nil
Residual disease at 3 months	nil	unknown
Complete response	1 month	unknown
Time to progression	unknown	unknown
Salvage treatment	nil	nil
Last seen post radiation	1 month	on completion of radiation

Clinical Outcome

Complete Clinical Response

Of the total study participant,12 (42,8%) had a complete local response(no residual disease at 3 months or less) of which 2 were on biopsy and the rest on clinical examination. Five were HIV positive and not on ART with stage IIIB(2) and IIIC(3) disease.Subsequently they progressed, 3 with local recurrence at 10 months, 3 years 5 months and 9 years.One progressed locally as well as with lung metastasis at 8 months post radiation.One was lost to follow-up at 2 years 3 months without having progressed. One of the patients with CR was HIV unknown and was lost to follow up 1 month post radiation having already achieved a CR.The two patients that were on ART never had a complete response.

The other 6 patients that had a complete response were HIV negative with stage IIIA(2),stage IIIB (3) and stage IIIC(1) disease. The two with stage IIIA disease both progressed at 5 months,one locally and one with lung metastasis.The patients with stage IIIB disease were lost to follow up at 4, 6 and 13 months post radiation. The one patient with stage IIIC disease progressed with local disease at 1 year 9 months post radiation and had an APR then 1 cycle of FUMI,he demised 2 years post radiation.

Colostomy free survival

One of the outcomes we looked at was colostomy free survival, 21 (75%) of the patients already had colostomies before starting radiation.Four patients required colostomies after completing radiation;one at 1 month for incontinence, 2 at 5 months and 2 years 6 months for local recurrence. Three patients never had colostomies,one required one but refused.

Palliation was done with chemotherapy for 8 patients with Cisplatin/5FU and for 2 patients with FUMI . Only one patient had surgery and no one was reirradiated.

During this time era(2001-2010) the median time from diagnosis to starting treatment was 1 month and 6 days. From diagnosis to completing treatment was 3 months and 5 days.

Table 3.8 :Late Toxicities

	4800 cGy (N-5)	5000 cGy (N-1)	5040 cGy (N-2)	5200 cGy (N-2)	5400 cGy (N-11)	5800 cGy (N-1)	6000 cGy (N-2)
Skin Fibrosis	2	1	2	1	9	1	1
Anal incontinence	NR	NR	NR	NR	1	NR	NR
Urinary incontinence	NR	NR	NR	NR	NR	NR	NR
Vaginal stenosis	NR	NR	NR	NR	2	NR	NR
Atrophy	NR	NR	NR	NR	NR	NR	NR
Anal stenosis	NR	NR	2	1	3	1	NR
Urinary frequency	NR	NR	NR	NR	NR	NR	NR
Dyspareunia	NR	NR	NR	NR	NR	NR	NR
Telangiectasia	NR	NR	NR	NR	1	NR	NR
Radiation proctitis	NR	NR	NR	NR	NR	NR	NR
Pain	3	NR	NR	NR	6	1	1
Vaginal dryness	NR	NR	NR	NR	NR	NR	NR

NR- Not Reported

Note: 5 patients were last seen at completion of treatment and are not included in this table as their late toxicities were unknown.

Chapter 4

Discussion

There were more male than female patients which is in keeping with the reported incidence of anal carcinoma being higher in males. As a significant number of the patients were HIV positive this correlated with the younger mean age of 40 years which is in keeping with findings in literature *(2,8,9)*.The majority (83 %) of this patient population presented with locally advanced disease. A study done in South Africa at Groote Schuur Hospital also found that the majority of their patients present with advanced disease,67% compared to 30% in United States of America.*(5)*

The primary end-point was to assess if the high radiation dose we give in our department improves survival and its impact on long term toxicity .Unfortunately none of the study participants received this dose ,so the primary end point could not be met. This could be due to the inclusion and exclusion criteria since patients from outside of the Free State could not be included.

The second end-point was local control and correlating this with total radiation dose. A total of 12(42,8%) patients achieved a complete local response,6 were HIV negative,5 HIV positive and not on ART and one who declined HIV testing.The cure rate in locally advanced anal carcinoma is 50-60 % ,our departments cure rate was below this at 39% *(6)*. The majority of this patient population presented with poor prognostic features which resulted in a poor locoregional control and a lower cure rate.These features that were proven in the EORTC 22861 trial include clinically palpable nodes ,male sex ,low heamoglobin and albumin. There were 75% patients with clinically palpable nodes and the average heamoglobin was below normal at 11g/dL.

Of the 12 patients that had a CR :7 subsequently progressed with local disease and distant metastasis.The shortest progression free survival (PFS)was 4 months (N-2),both patients were HIV negative with stage IIIA disease and had received concurrent FUMI with a total radiation dose of 50 Gy and 52 Gy.The former progressed with local recurrence while the latter with lung metastasis.The longest PFS was 9 years,this patient was HIV positive and not on ART (CD4 count 317).The patient had stage IIIB disease and was treated with 58 Gy and concurrent FUMI.New local disease developed.

Five of the 12 patients were lost to follow-up without recorded clinical progression,the longest followed up of these patients was 2 years 3 months.

Five patients were lost to follow-up 3 months or less post radiation there no comment can be made about the longterm outcome.But one already had a complete local response when they were last seen one month post radiation.

Residual disease was found in 11(39%) patients on follow-up all of whom received split course radiation except for one that received continuous radiation to a total dose of 5040 cGy.

All the patients (3)that received 2400 cGy,3740 cGy and 3800 cGy were lost to follow up just after completing radiation.This reflects the poor general condition they were in to receive the lower radiation dose

Colostomy-free survival was achieved in 3 (11%)patients,they never required one. One patient required a colostomy but opted not to have it.Twenty one patients (75%) already had colostomies prior to initiating treatment.The reasons for colostomies before starting radiation were obstruction(N-4),incontinence (N-4),rectovaginal fistula (N-1) and the rest the reason is not stated .One patient required a colostomy for faecal incontinence at 1 month post radiation with no local recurrence.Two patients had colostomies due to local recurrence at 5 months and 2 years 6 months post radiation.

Only one patient required a break in treatment due to a radiation dermatitis. Three patients required a blood transfusion due to aneamia during chemoradiation .Two were HIV negative receiving concurrent FUMI with total radiation doses of 48 Gy and 54 Gy.The 3rd patient was HIV positive and not on ART with a CD4 count of 330 cell/mm3 receiving 54 Gy with concurrent FUMI. This possibly reflects on poor note keeping than the actual very low incidence of acute toxicities in patients receiving chemoradiation.

Concurrent chemotherapy was used for almost all the patients (89%),4 of these patients received Cisplatin/5FU,they were HIV positive with three not on ART and one on ART.One HIV negative received weekly 5FU and the rest received FUMI (both HIV negative and positive).

All the patients that were followed up did have late toxicities,the most common being skin fibrosis(61%) ,anal stenosis(25%), vaginal stenosis (7%) and pain(39%). This was seen in both split and continuous course and similar in both HIV negative and positive patients.

Limitations

A significant number of patients with locally advanced disease come from Lesotho and the Northern Cape see T*able 2.1*,these patients could not be included in the study due to the exclusion criteria.We wanted to assess the overall survival and late toxicity which would not have been possible in this group as we do not follow them up.

This study was retrospective using patient records as the only source of patient information .Record keeping on patient follow-up visits was very limited which posed a huge challenge on how much information was available especially on acute and late toxicity symptom recording.This raises a question of possible under reporting of progression of disease and late toxicity signs and symptoms.

Poor patient follow-up post radiation resulted in only a limited number of participants being assessed for late toxicity and survival, this greatly compromised the outcome of the results.

Chapter 5

Conclusions

Our findings with regards to demographics are in keeping with international findings especially in HIV positive patients.In South Africa ,when compared to other countries ,patients present with locally advanced disease which is what we also observed *(2,5)*. Squamous cell carcinoma is the most frequently diagnosed histology in anal carcinoma .The most prevalent chronic side effects were pain ,anal stenosis and fibrosis regardless of the radiation dose received .There was decreased overall survival and local control rate due to the majority of the patients having poor prognostic features and poor follow-up post treatment.HIV positive and HIV negative patients were treated the same in terms of radiation dose but in terms of chemotherapy,Cisplatin/5FU was used in some of the HIV positive patients. The radiation doses used were below the recommended 55-59 Gy for locally advanced disease ,only 3 patients were treated with doses in this range.Continuous treatment ,without a planned gap is considered to be radiobiologically more effective than split course radiation. If a treatment gap/split course is planned then doses higher than 45-50 Gy should be used*[6]*.

The majority of our patients had colostomies prior to referral to oncology for reasons that are not clearly stated. This could be due to poor note keeping or surgical intervention that was not warranted ,as one of the advantages of chemoradiation in anal carcinoma is sphincter preservation.

The total number of patients that presented to the Department of Oncology from 2001-2010 were 104. Due to the inclusion and exclusion criteria ,less than a third were part of this study.This resulted in an underpowered study.

Recommendations

The Department of Oncology at Universitas Academic Hospital had a diverse approach to anal carcinoma management during the researched period with no clear standardised approach in keeping with international guidelines. A wide range of radiation doses were used and patients with poor performance status and low albumin received concurrent chemotherapy.

The approach has since changed with standardised department guidelines in place. This topic should be revisited in a more recent time period.

The advantage of chemoradiation for anal carcinoma is sphincter preservation. Seventy five percent of the study participants already had colostomies prior to referral to oncology. Whether this was indicated or not is unclear.

We recommend that colleagues in the referring system be educated about the indications for a colostomy and the preferred management outcome in anal carcinoma.

Negative research highlights limitations and areas of improvement within the department that need to be addressed if not already addressed.

Recommendations for the Department:

1. The importance of clear and comprehensive note keeping was highlighted in this study.
2. Having standardised management guidelines in keeping with international standards.
3. Discussing management plans in a multidisciplinary setting so that all parties involved are in agreement with the recommended approach.
4. Encouraging patient follow-up .
5. Ideally patients from Lesotho and the Northern Cape should follow-up at our institution in Bloemfontein but due to the very limited resources and staff this is not feasible at the present moment. This can be explored again in future should circumstances change.

The use of conformal radiation such as IMRT would improve both acute and long term side effects ,this is described in literature . IMRT is available at our institution although currently limited to certain cancers/anatomical sites because of large number of patients and shortage of resources .

Recommended Follow-up Checklist :

TNM Stage …..

Colostomy before ….. or after radiation ……

Palliative …… or Radical …..

Radiation dose given ……

Number of months since completion of radiation …….

Residual local disease at 3 months post radiation : yes/no

If yes : biopsy and restage

Pain - grade

Toxicity :

incontinence - anal ……. urinary ……

fibrosis - yes ……. no …….

stenosis- vaginal ……. anal ……

vaginal dryness- yes…… or no ……..

List of Tables

Abbreviations

ART - Anti-Retro Viral Therapy

APR - Anterior perineum resection

CFS - Colostomy Free Survival

CR - Complete Response

2D - Two dimensional

ECOG - Eastern Cooperative Oncology Group

FUMI - Mitomycin C and Flourouracil

5FU - 5 Flourouracil

GTV - Gross Tumour Volume

Hb - Heamoglobin

HPV - Human Papilloma Virus

HIV - Human Immunodeficiency Virus

KZN - KwaZulu Natal

MSM - Men who have Sex with Men

MMC - Mitomycin C

N - Number

OS - Overall survival

PFS - Progression Free Survival

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Appendices

A.

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

23-Apr-2018

Dear **Dr Thandeka Buthelezi**

Ethics Clearance: **Protocol for anal carcinoma : A retrospective review at the Department of Oncology Universitas Academic Hospital Bloemfontein**

Principal Investigator: **Dr Thandeka Buthelezi**

Department: **Oncology (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2017/1535**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

B.

health
Department of Health
FREE STATE PROVINCE

27 March 2018

Dr T Buthelezi
Dept. of Oncology
Faculty of Health Science
University of the Free State

Dear Dr T Buthelezi

Subject: Protocol for Anal Carcinoma: A retrospective review at the Department of Oncology at Universitas Hospital Bloemfontein Free State

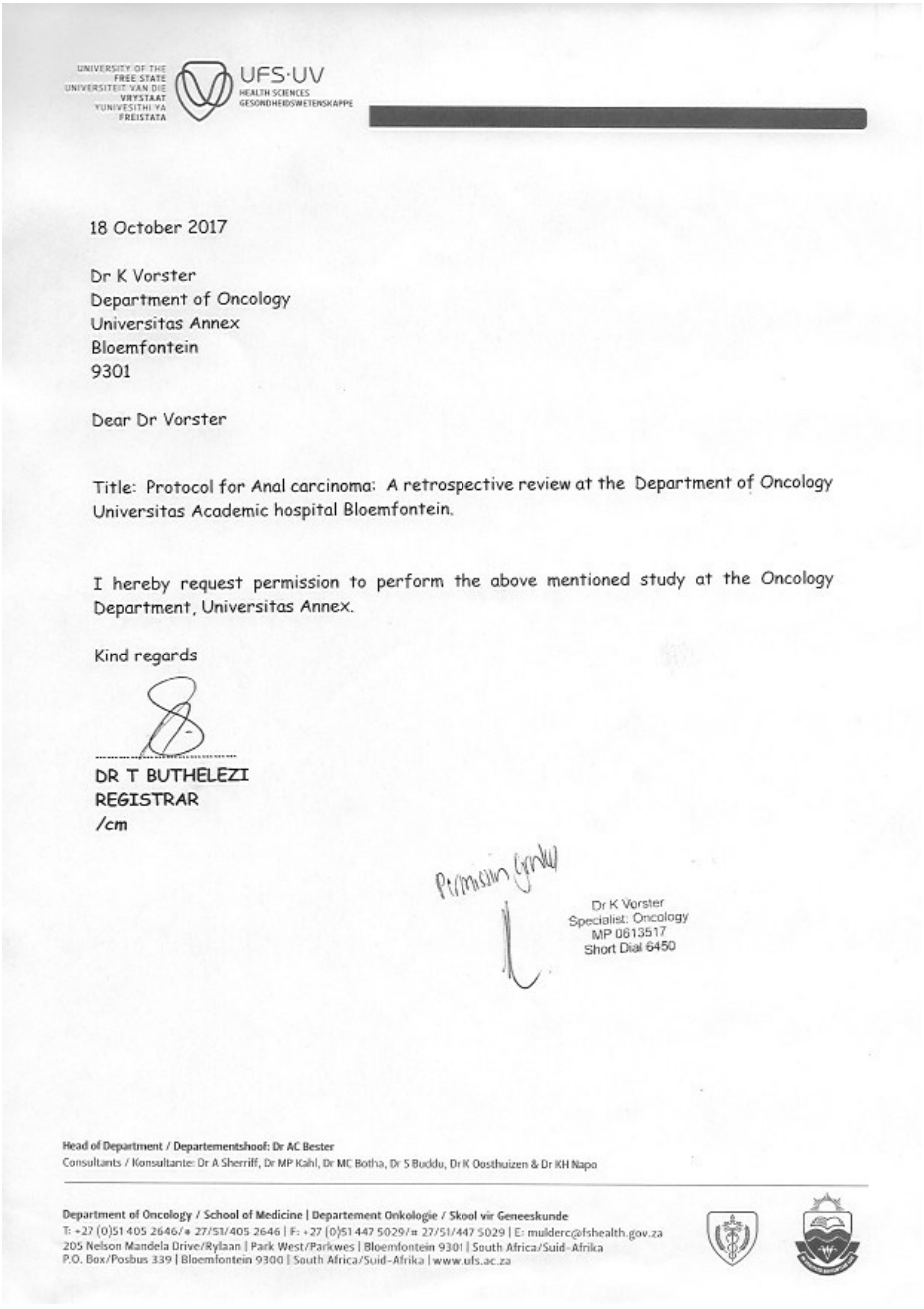
- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- This letter replaces that letter dated **01 March 2018** and should be considered the only approval letter.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 29/03/18

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za
www.fs.gov.za

C.



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[redacted]

18 October 2017

Dr K Vorster
Department of Oncology
Universitas Annex
Bloemfontein
9301

Dear Dr Vorster

Title: Protocol for Anal carcinoma: A retrospective review at the Department of Oncology Universitas Academic hospital Bloemfontein.

I hereby request permission to perform the above mentioned study at the Oncology Department, Universitas Annex.

Kind regards

.....
DR T BUTHELEZI
REGISTRAR
/cm

Permission granted

Dr K Vorster
Specialist: Oncology
MP 0613517
Short Dial 6450

Head of Department / Departementshoof: Dr AC Bester
Consultants / Konsultante: Dr A Sherriff, Dr MP Kahl, Dr MC Botha, Dr S Buddu, Dr K Oosthuizen & Dr KH Napo

Department of Oncology / School of Medicine | Departement Onkologie / Skool vir Geneeskunde
T: +27 (0)51 405 2646/+ 27/51/405 2646 | F: +27 (0)51 447 5029/+ 27/51/447 5029 | E: mulderc@ufshealth.gov.za
205 Nelson Mandela Drive/Rylaan | Park West/Parkwes | Bloemfontein 9301 | South Africa/Suid-Afrika
P.O. Box/Posbus 339 | Bloemfontein 9300 | South Africa/Suid-Afrika | www.ufs.ac.za

D.

Annexure A : patient data sheet

RT Number : _____ Year of diagnosis: _____

Demographics :

Sex : male ☐
female ☐

Age : I___I

Functional and nutritional status :

- ECOG status before treatment ☐
- Albumin level : ☐ g/L
- Presenting Heamoglobin level ☐ g/dL

Histopathological diagnosis and stage :

Squamous cell carcinoma ☐ Adenocarcinoma ☐ Neuroendocrine differentiation ☐

Melanoma ☐ Lymphoma ☐ Other _____

grade: well ☐ moderately ☐ poorly ☐ differentiated

stage : T ☐ N ☐ M ☐

HIV Status :

positive ☐ negative ☐ unknown ☐

If positive : on ART yes ☐ no ☐ CD4 count : ☐

Dates

Histological diagnosis _____
New patient _____
Initiation of treatment _____
Completion of treatment _____

Chemo- radiation

Palliative radiation :

Split course : yes ☐ no ☐

Concurrent chemotherapy yes ☐ no ☐

Radical chemoradiation :

Concurrent chemotherapy: yes ☐ no ☐

Cisplatin and 5FU (D1-4,D29-32) ☐ MMC and 5FU(D1-4,29-32) ☐ Cisplatin only ☐

Neo-adjuvant chemotherapy: yes ☐ no ☐

If yes, how many cycles : ___

- Total radiation dose _____

modality of radiation :2D ☐ 3D conformal ☐ IMRT ☐

Completed treatment course : yes ☐ no ☐

If yes,duration of treatment : _____ weeks
If not,reason for not completing treatment:

Acute toxicity- Radiation dermatitis ☐ Neutropenia ☐ Infection ☐

Patient decision ☐ Death ☐ Poor general condition ☐

Treatment breaks : yes ☐ no ☐

If yes,duration of break :_____ weeks
Reason for treatment break:

Radiation dermatitis ☐ Neutropenia ☐ Septiceamia ☐

Outcome

Lost to follow up : ☐

Complete local response at : ___ months
Residual disease :

on clinical exam ☐ on biopsy ☐

Late toxicity :

Skin fibrosis ☐	Atrophy ☐	Telangiectasia ☐
Anal incontinence ☐	Anal stenosis ☐	Radiation proctitis ☐
Urinary incontinence ☐	Urinary frequency ☐	Pain ☐
Vaginal stenosis ☐	Dyspareunia ☐	Vaginal dryness ☐

Colostomy :

before starting treatment ☐ during treatment ☐

after completing treatment ☐

If after completing treatment : _____ years

Progression of disease:

☐ loco-regional disease

☐ metastatic disease

☐ death

Time to progression after completion of treatment: _____ years

Salvage therapy :

☐ re-irradiation

☐ palliative chemotherapy

☐ surgery

E.

Protocol for Anal carcinoma:A retrospective review at the Department of Oncology Universitas Academic hospital Bloemfontein

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F .

Content

Page number

Title

Protocol for Anal carcinoma:A retrospective review at the Department of Oncology Universitas Academic hospital Bloemfontein

Researcher

Dr T N Buthelezi
Registrar in the Department of Oncology
University of the Free State,Bloemfontein,South Africa

M.MED Study supervisor

Dr A Sherriff
Head of Department at Oncology
University of the Free State,Bloemfontein,South Africa

Contact details

Dr Thandeka Buthelezi 0837306204
thandz@ymail.com

Dr Alicia Sheriff
sherriffa@ufs.ac.za 0828221092

Department of Radiation Oncology Universitas Academic Hospital 0514052646

Summary in lay terms

Anal cancer is considered to be rare worldwide and patients usually present with early stage disease. In South Africa we see mostly advanced disease therefore the international studies and guidelines do not adequately cater for the extensive disease we see. The Department of Oncology at Universitas Academic Hospital uses radiation doses that are higher than those recommended in the international guidelines due to our patient population. We want to evaluate if the departments current protocol for chemotherapy and radiation in advanced anal carcinoma is justified.

Introduction

Anal carcinoma is a neoplasm that develops in the anal region. The anal canal extends from the anorectal junction to the anal margin which is the pigmented skin immediately surrounding the anal orifice extending laterally to a radius of approximately 5cm.It is lined with glandular,transitional and squamous mucosa. Tumours can arise from any part of the different mucosa but 75% is squamous cell carcinoma arising from the transitional zone in the anal canal.[1, 2].Other types of histologies include adenocarcinoma,melanoma,neuroendocrine and rarely sarcoma and lymphoma[1,3,4].
Anal carcinoma is considered to be a rare type of cancer comprising 2-5% of gastrointestinal neoplasms[1, 5].
A study done in KwaZulu Natal in South Africa showed that anal carcinoma was possibly more common in that province compared to international reports[5].In South Africa the National cancer registry is pathology based,this results in the under-reporting of many malignancies therefore the true incidence of anal carcinoma in the country is unknown[3,6].The incidence of anal carcinoma has gradually been rising over the past 20-30 years and this is partly attributed to the increase in the incidence and absolute number of the most significant risk group namely HIV(Human Immunodeficiency Virus) positive MSM (men who have sex with men) and an increase in the number of solid organ transplant recipients[1,3,4,11,14]. The other risk factors associated with anal carcinoma include ; HPV(Human Papilloma Virus)infection,female gender,smoking,lifetime number of sexual partners,receptive anal intercourse ,genital warts and previous cervical,vulval or vaginal cancer.HPV being the main causative agent especially subtypes 16 and 18 in 80-85% of patients [1,3,4,8,10-12,14]. Genetic mutation of the PIK3CA gene has also been implicated in the process of carcinogenesis [10].

Demographics in HIV infected people are different compared to the general population with regards to younger age, average of 40 years versus 62 and mostly male rather than female patients [3,10,11]. The younger age group is in spite of being on Antiretrovirals(ARV) [10].An increased incidence of people on ARVs is due to increased patient survival as the risk of squamous cell anal carcinoma increases with duration of HIV infection [14].This was also supported by studies done in South Africa,KZN and Cape Town [5,7].The oncologic outcomes in patients with HIV are comparable to HIV negative patients (5 year survival 57% vs 57% respectively) with stage of the anal carcinoma as the only factor predictive of survival, p value of 0,05 [10].

Literature states that most patients present with T1 or T2 tumours and fewer than 20% have positive node metastasis[4] . Although there is scant South African based data on anal carcinoma , patients present mostly at a younger age with locally advanced disease[5,7]. Metastasis is also uncommon at 5-8% at onset ,it spreads in a loco-regional manner within and outside of the anal canal [8].Poor prognostic factors for survival include male sex,positive lymph nodes(particularly inguinal)and primary tumour >5 cm [8].

The standard of care for anal carcinoma is chemo-radiation even for early disease(T1/T2 N0 M0) due

to its advantage of retaining sphincter function with survival outcomes similar to surgery withAPR (abdominal-perineal resection) and avoiding a permanent colostomy[4,7].A study done by Nigro et al in 1984 was the landmark trial that initiated the change to chemo-radiation as opposed to surgery where they achieved a 93% complete pathological response rate with radiation and concurrent Mitomycin C and 5 Flourouracil. Small lesions that are </= 2 cm involving the anal margin can be managed by surgery in the form of local excision if adequate margins can be obtained without compromising sphincter function[8].

The current recommendations are based on results of the phase 2 and six phase 3 trials;EORTC22861,UKCCCR ACT 1,RTOG 87-04,RTOG 98-11,ACCORD-03,CRUK ACT II[8].Concurrent chemotherapy consists of an infusion of 5-FU 1000mg/m2 on day 1-4 and day 29-32 plus Mitomycin C 10mg/m2 on days 1 and 29 max 20 mg per dose.
Radiation dose of 45Gy for early stage disease and an additional boost of 10-14Gy in 2Gy fractions for locally advanced disease(T3-T4 or node positive) making a total dose of 55-59Gy[2].

Patients with locally advanced anal cancer have a cure rate of approximately 50-60% with standard chemoradioradiation [8]. Higher boost doses are required for poor responders,usually its 15-25Gy but there is no recommended appropriate dose for a boost after 50Gy[4,8].In the ACCORD trial they used colostomy free survival(CFS) as the primary end point to compare induction chemotherapy (Cisplatin/5FU) and higher radiation boost for locally advanced anal carcinoma[9]. CFS rate was 77% with the standard boost of 15Gy and 72,7% with the intensified boost of 20-25Gy at 5 years.They were not able to find an advantage for either induction chemotherapy or high dose radiation boost in locally advanced anal canal carcinoma.

In our department of Oncology at Universitas hospital our protocol for definitive chemo-radiation is concurrent chemotherapy Cisplatin/5FU or MMC/5FU (D1-4,29-32)depending on the patient condition.Radiation dose is 59.4Gy but for advanced local disease we give up to 66Gy to the primary tumour.For palliative radiation we use a split course of 6000cGy total dose with a 4 weeks rest period after 3000cGy.This is given with or without concurrent chemotherapy .

We will be looking at local demographic, local control,progression free survival and side effect profile,acute and late toxicity but with emphasis on late toxicity, and correlating this with total radiation dose received.

Research question

Review the effectiveness of our departmental chemo-radiation protocol for anal carcinoma in comparison to international data in view of our patient population and the advanced disease we see. Is our higher dose for anal carcinoma radiation effective/justified?

Aim

We aim to evaluate local demographic,local control,progression free survival, colostomy free survival and side effect profile and correlating this with total radiation dose received.
The study will be conducted on data from patients diagnosed and initiated treatment for anal carcinoma at our department from 2001 to 2010.This will allow us to have at least a 5 year follow up to analyse.

Methodology

Study design

This will be a descriptive study.

Sample/study participants

The sample will consist of patients treated for anal carcinoma at our department between 2001 and 2010,this is to ensure that included patients had at least 5 years of follow-up. The data will be obtained through records in our filing system. The files all have ICD10 codes,the code for cancer of the anus is C21. The administration staff obtained a list of all the files with this code,patients from Lesotho and Northern Cape were excluded from the list which resulted in a total of 83 files. A total of 83 files will be included in the sample size.Limitation to the sample size is poor follow up.

Inclusion criteria : Patients with confirmed histological diagnosis of anal canal/ perianal carcinoma
Age above 18 years
Received chemo-radiation or radiation only

Exclusion criteria : patients from the Northern Cape and Lesotho as we do not follow them up
patients who only received chemotherapy.
stage IV disease

Measurement

The administration staff will collect the files in the study sample .The researcher will then evaluate the files at the departments administration department where files are kept.A data form will be used to capture information from each file.The files are identified by an RT number which is unique and specific to a particular patient,this will also help ensure that a patients information is not repeated.Values with prognostic significance that we will be looking at include the albumin,heamoglobin level ,CD4 count as well as the performance status.The normal heamoglobin(Hb) reference range for males is 14.0-17,5 g/dl and for women 12,3-15,3 g/dl. Aneamia is directly associated with an increased risk of death in patients with various malignancies.[15].A low

Hb level is common in cancer and it affects the choice of treatment as well as outcome.Anaemia may exacerbate tumour hypoxia leading to radio resistance.The normal albumin reference range is 35-55g/L.Albumin is a reliable indicator of an individuals nutritional status.It is also an independent prognostic indicator in various cancers.[16]A low pretreatment serum albumin is associated with poor survival [17] . The normal CD4 count range is 460 - 1600 cell per cubic millimetre of blood.In anal carcinoma a low CD count (<200) is associated with increased morbidity and toxicity [18]. The Eastern Cooperative Oncology Group (ECOG) performance status is used to assess the functional status of cancer patients with regards to status of symptoms and functions namely ambulatory status and need for care.Graded from 0 to 4 with 0 being normal activity and 4 being completely bedridden. Age is prognostic for overall survival [19]

Methodological and measurement errors

To overcome variation and ensure consistency with no bias, there is only one researcher, Dr Buthelezi,who will be responsible for collecting patient information and filling in the data sheet. Patients will only be included once because of the identification system mentioned previously which is the RT number on the patients' file. The same form will be used for all the records and the inclusion and exclusion criteria will be adhered to.To ensure data integrity ,data will be typed in Excel then rechecked every 3rd entry.
A pilot study will be conducted pending the ethics committee approval,it will consist of the first two files in the sample.Results from the pilot study will be included in the final research results.

Analysis of data

Data analysis will be done by Department of Biostatistics at the University of Free State.Numerical variables will be summarised using means,standard deviation or median and interquartile range. Categorical variables will be summarised using frequencies and percentages.

Implementation of findings

The findings will be used to adjust ,if necessary,the departments protocols for anal carcinoma chemo-radiation.

Time schedule

Submission to Ethics Committee : December 2017
Data collection : April 2018 to June 2018
Data analysis : July 2018 to October 2018
Writing up of research project : November 2018 to April 2019

Budget

Stationary :

Ink for the printer	- R300
Paper for printing of data sheet	- R100
Miscellaneous	- R100
Total	R500

The costs of the research will be funded by the researcher.

Ethical Aspects

This study is subject to the approval of the Health Sciences Research Ethics Committee and the Department of Health of the Free State.
Permission to perform the study will be obtained from :
Department of Oncology - Dr K Vorster
Confidentiality will be ensured as the file identification system (RT number) is limited to the Oncology department.

G.

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References for this Review were identified through searches of PubMed with the search terms "young onset", "early onset", "presenile", and "dementia" from 1990 until April, 2010. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review

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- For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless inappropriate. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work in the format outlined below (see *Lancet* 2014; **384**: 2176–77, for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

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Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

PRISMA guidelines
http://www.prisma-statement.org/

Formatting guidelines
http://www.thelancet.com/for-authors/forms#meta-analysis

Data sharing

From July 1, 2018, all submitted reports of clinical trials must contain a data sharing statement, to be included at the end of the manuscript. Data sharing statements must indicate:

- Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others ("undecided" is not an acceptable answer);
- What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set);
- Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form);
- When these data will be available (beginning and end date, or "with publication", as applicable);
- Where the data will be made available (including complete URLs or email addresses if relevant);
- By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions).

See table for examples. Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. For reports of research other than clinical trials, data sharing statements are encouraged but not required. Mendeley Data is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

Meta-analysis

- In general, these should follow the PRISMA guidelines. Please refer to *The Lancet*'s formatting guidelines for systematic reviews and meta-analyses.
- Manuscripts should be structured around five sections: Summary, Introduction, Methods, Results, and Discussion
- Aim for a maximum length of about 3000 words and 75 references
- Meta-analyses should also contain a semistructured summary as described previously for Articles

Blue section (Comment, Correspondence, etc)

Editorial

- Editorials are the voice of *The Lancet Oncology*, and are written in-house by the journal's editorial-writing team and signed "The Lancet Oncology"

Comment

- This section contains commentaries that accompany papers

- References selected for publication should be chosen for their importance, ease of access, and for the "further reading" opportunities they provide; citations to papers published in non-peer-reviewed supplements are discouraged. In addition to references, authors should consider supplying a short list of useful websites where readers can find further information on the subject
- A 150-word unstructured summary should be included. Use of up to 5–6 illustrations is encouraged to aid the reader
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages. An example is shown below:

Search strategy and selection criteria
References for this Review were identified through searches of PubMed with the search terms "young onset", "early onset", "presenile", and "dementia" from 1990 until April, 2010. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review

- Systematic reviews should be prepared according to the PRISMA guidelines

Formatting guidelines for randomised trials
http://www.thelancet.com/for-authors/forms#rct

Formatting guidelines for revised manuscripts
Guidelines on format for text and figures can be found at
http://www.thelancet.com/for-authors/forms#artwork

Personal View
- These should be 2000–4000 words in length, with a maximum of 75 references
- These opinion pieces may reflect an individual perception, involvement, or contribution to oncology, and should be prepared in a similar way to a Review. Unsolicited contributions are welcome, although please contact the Editor before submission to ensure that the proposed topic is within the remit of the journal

Policy Review
- Manuscripts considered for this section are narrative reviews (not original research) and should follow the same guidelines as a Review
- These papers should cover developments in oncology related to policy, treatment guideline development, health systems, or economics. Other related topics will be considered. Please contact the Editor before submitting to ensure the proposed topic is suitable

Clinical Picture
- The ideal Clinical Picture provides visual information that will be useful to other clinicians. Clinical Pictures should be interesting, educational, and respectful of the patient. The Lancet Oncology is less interested in pictures that simply illustrate an extreme example of a medical condition, a unique response, or first use of a new intervention
- Each Clinical Picture must be accompanied by text that puts the image in context. This text should include a brief patient history, and should explain what the Clinical Picture shows and why it is of interest to the general reader. Maximum text length is 300 words, with no references
- All Clinical Picture submissions must be accompanied with a challenging clinical question related to the case along with four possible answers. This quiz will be peer-reviewed and will be used on the journal's website to encourage users to read the underlying article
- Authors must obtain signed, informed patient consent. Do not use "blackout" bars or similar devices to anonymise patients: if you have taken consent appropriately, masking is not necessary

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- Topics for *The Lancet Oncology* Commissions are selected by our editors, who work with academic partners to identify the most pressing issues in science, medicine, and global health with the aim of producing recommendations to change public policy or improve practice. Projects usually last 2–3 years, and author groups will represent a broad range of international expertise. All *The Lancet Oncology* Commissions are academic publications and are subject to the same rigorous peer review process as all other research papers published in our journals. *The Lancet Oncology* does not provide direct financial support to Commissioners for the research or writing of the reports. Funding is sought directly by authors, with oversight from our editors.

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- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated along with email and telephone details

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- Type a single space at the end of each sentence
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- Do not worry about type of font or point size
- We use a comma before the final "and" or "or" in a list of items
- Type decimal points midline (ie, 23·4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables

(eg, commentaries) may be peer-reviewed; decisions are made on a case-by-case basis
- On submission to *The Lancet Oncology*, your report will first be read by one or more of the journal's staff of physicians and scientists. This is an important feature of our selection process that many papers are turned away on the basis of in-house assessment alone. That decision will be communicated quickly
- Research papers and most other types of paper that receive positive in-house reviews are followed by peer review by at least three reviewers. You will receive notification of which editor is handling the peer review of your paper

Decision
- Submissions that survive in-house assessment and peer review might be referred back to authors for revision. This is an invitation to present the best possible paper for further scrutiny by the journal; it is not an acceptance
- Authors should give priority to such revisions; the journal will reciprocate by making a final decision quickly
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References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example:
  "...as reported by Saito and colleagues.[15]"
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen
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- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or "long" hyphen):

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Index Medicus
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Text

- Main heading for the web extra material should be in 12 point Times New Roman font BOLD
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point BOLD

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- Main table heading should be in 10 point Times New Roman font BOLD
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- SI units are required
- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- p values should be given to two significant figures, unless p<0·0001

Drug names

- Recommended international non-proprietary name (rINN) is required

Drug names
For more on neuroscience-based nomenclature see **http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366(17)30098-6.pdf**

- We encourage use of neuroscience-based nomenclature for psychotropic drugs

References

- Vancouver style—eg,

—Smith A, Jones B, Clements S. Clinical transplantation of tissue-engineered airway. *Lancet* 2008; **372:** 1201–09.

—Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: Elsevier, 2008: 230–47.

- Numbered in order of mention in Webappendix and numbered separately from references in the full paper

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