A RETROSPECTIVE REVIEW: THE OUTCOMES OF PATIENTS WITH ANAL CARCINOMA RECEIVING TREATMENT AT GROOTE SCHUUR HOSPITAL

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DECLARATION

I, Dr Lisa Dalmeyer, declare that the work on this study is originally my work except where acknowledgements are indicated. This is an unsponsored study and was carried out for educational purposes only as a MMED for a postgraduate degree. I therefore declare no conflict of interest whatsoever.

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Dr. Lisa Dalmeyer

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Abstract

Objectives
The objective of this study was to compare the outcome of two cohorts of patients with anal squamous carcinoma treated with split course chemoradiation as opposed to continuous chemoradiation at Groote Schuur Hospital. Demographics including age at diagnosis, gender and HIV status were reviewed. The stage at diagnosis, the acute treatment toxicities and all surgical procedures were noted. The outcomes included complete response rate, local control rate, loco-regional failure free survival, colostomy–free survival and overall survival.

Design and Methods
The data was obtained from patient records of all patients with histologically confirmed anal squamous cell carcinoma seen and registered at the Department of Radiation Oncology at Groote Schuur Hospital. Patients included were those treated with radical intent that presented between the years of 2008 and 2012. This data was then compared with a similar study performed between 2000-2004.

Results
A total of 72 patients diagnosed with anal squamous carcinoma were seen at Groote Schuur Hospital in the 5-year period, of which 40 patients fitted the criteria for this study. The median age was 53 years, with a slight male preponderance (55%) and 27.5% tested HIV positive. A total of 68% of patients had T3 and T4 disease, with 42.5% node positive disease. The complete response rate was 60%, the local control rate was 52.5% and the loco-regional failure free survival at 5 years was 56%. The colostomy-free survival was 74% and the 5-year overall survival was 40.67%. Haematological, gastrointestinal and skin toxicities were reviewed and the most common acute side effect experienced was grade 2(32.5%) and grade 3(47.5%) skin toxicity.

Conclusion
The patient characteristics and treatment toxicities are in keeping with previous study findings. However, complete response rate and overall survival were less than expected. Although there was no statistically significant difference in overall survival between the two cohorts of patients, there was a definite trend to inferior treatment outcomes of those patients treated with continuous chemoradiation. We propose radiation dose escalation for future treatment of patients presenting with anal carcinoma at Groote Schuur Hospital.

Literature review

Anal carcinoma is a relatively rare cancer. It makes up about 1-2% of all gastro-intestinal malignancies.(1) The annual incidence is 1 per 100 000 and there appears to be a female preponderance. At Groote Schuur hospital, it makes up 4% of the total gastrointestinal malignancies diagnosed.(2) The overall 5-year survival rates of patients in the United States (US) between 2005 - 2011 were 65.7% (Surveillance, Epidemiology and End Results database). The loco-regional control rates are estimated at 81%.(3)

Human papilloma virus (HPV) infection represents a significant risk factor in the development of squamous cell carcinoma of the anus. This is mostly from HPV16 and HPV18.(4) A recent Dutch study found a high incidence of anal cancer among HIV positive patients with an incidence of 72 per 100 000 in 2011/2012.(5) The incidence is higher in HIV positive women. Smoking may play a role in the persistence of HPV infection and thus contribute to the development of malignancy. Chronic inflammation may also be a contributory factor.

Prognostic factors for survival, as found by recent multivariate analysis from the ACT I and ACT II trials, indicate that positive inguinal lymph nodes, male gender and haemoglobin levels were prognostic for local and regional failure, death from anal cancer and overall survival.(6, 7) Bartelink et al. also found skin ulceration, nodal involvement and gender to be the most important prognostic factors for both local control and survival.(8)

Patients with anal carcinoma may present with a variety of different symptoms including, rectal bleeding, an anal mass, itching, pain, non-healing ulcer, discharge, faecal incontinence or fistulae.

Histological diagnosis is vitally important. The most common pathology is squamous carcinoma, but other less common histologies such as adenocarcinoma, lymphoma or melanoma need to be excluded. Cancers of the anal margin tend to be well differentiated and tumours from the canal are often poorly differentiated.(9)

Staging investigations require magnetic resonance imaging (MRI) of the pelvis or endo-anal ultrasound. This allows for assessment of tumour size, local extent and nodal involvement. For distant metastases, computed tomography (CT) of the abdomen and chest is advised, although it is unusual for patients to present with distant metastases.

The TNM staging system uses assessment of the tumour size (T stage), the number of involved regional lymph nodes (T stage) and presence of metastases (M stage). The accepted staging classification system used is the TNM Clinical and Pathological Staging System for Anal cancer as per the American Joint Committee on Cancer/Union for International Cancer Control - AJCC/UICC classification).(10) The role of positron emission tomography with fluorodeoxyglucose (FDG-PET/CT) is beneficial in anal carcinoma as the majority are squamous cell

carcinomas and these are FDG-avid.(11) The PET-CT is able to give information regarding possible involved lymph nodes, which in turn can be used when planning radiotherapy treatment.

Treatment is directed at locoregional cure of disease with an acceptable functional outcome for the patient. Sphincter preservation is the goal. Historically surgery, namely abdominoperineal resection (APR), was acknowledged as the mainstay of treatment.(12) Treatment modalities were then reviewed when multiple studies (mostly phase II and case-series studies) showed that chemoradiation had proven efficacy in the radical treatment of patients with anal carcinoma.(13) Nigro et al. in the 1980's first reported high rates of pathologic complete response with chemoradiation and demonstrated that chemoradiation could preserve sphincters as opposed to surgery, which would generally require removal of the sphincters. This study included 19 patients that received preoperative chemoradiotherpy (5-FU 100mg/m^2/24hours as a continuous infusion for 4 days on day 1 and 20-31 and Mitomycin C 15mg/m^2 IV bolus on day 1 with radiotherapy 3000rads to rectum and local nodal areas day 1 to 21).There was no gross tumour found in 15 patients and the other 4 had at least a 50% decrease in size. Those with residual tumour and microscopically present went on to have APR surgery. The authors felt that chemoradiation is effective enough to avoid APR if there is no evidence of residual disease.(13) Local excision can still be considered for small (<2cm diameter) lesions of the anal margin. However the excision margins must be adequate (>5mm) and sphincter function must be maintained.(14)

Subsequent research lead to the development of the current standard of care which is radiotherapy given concurrently with the cytotoxic agents 5-Fluorouracil (5-FU) and mitomycin C. In the UKCCCR trial chemotherapy with 5-FU (1000 mg/m^2 for 4 days or 750 mg/m^2 for 5 days) by continuous infusion during the first and final weeks of radiotherapy and mitomycin (12 mg/m^2) on day 1 of the first course was given. Bartelink et al. used 750 mg/m^2 daily 5-FU as a continuous infusion on days 1 to 5 and 29 to 33, and a single dose of mitomycin 15 mg/m^2 on day 1. (6, 8, 13) This became the basis of treatment after the ACT I trial showed a reduction in loco-regional failure from 61% to 39%. This trial compared 585 patients with epidermoid anal cancer treated with either radiotherapy alone or combined modality treatment (radiotherapy with 5-FU and mitomycin C). The patients were treated using split course radiotherapy. The median follow–up time was 42 months and in this time there was a 46% reduction in the risk of local failure in the patients receiving combined modality treatment (Local failure rate RR = 0.54, CI = 0.42-0.69, $p<0.0001$). There was no overall survival benefit.(6)

Further trials supported this, including Bartelink et al., which was a randomized trial (total of 110 patients) which compared the outcome of patients given radiotherapy alone (total of 45Gy in 1.8Gy fractions with a 6 week rest followed by a 15-20Gy boost), with patients given radiotherapy with concurrent 5-FU and mitomycin C (5-FU 750 mg/m^2 as a continuous infusion on days 1 to 5 and 29 to 33, and a single dose of mitomycin 15 mg/m^2 on day 1). This study showed that patients receiving radiation alone had a complete remission rate of 54% as opposed to patients receiving combined modality treatment who had a complete

remission rate of 80%. The loco-regional control rate increased by 18% at 5 years and the colostomy-free rate increased by 32% in the combined treatment arm (locoregional control interval P=0.02 and colostomy-free interval P=0.002) (8).

Flam et al. compared 2 groups of patients treated with either radiotherapy and 5-FU or radiotherapy, 5-FU and the addition of mitomycin C(5-FU 1000mg/m^2/day for 4 days and MMC 10mg/m^2 per dose for 2 doses). Radiotherapy doses of 40-50.4Gy were given in "split course" with a 4-6 week break. They found that despite higher toxicities, the use of mitomycin C showed a significant improvement in colostomy free-survival (71% vs. 59% P=0.014) and disease-free survival (73% vs. 51% P=0.0003).(15)

The use of mitomycin was questioned due to its significant toxicity, including renal, pulmonary and bone marrow toxicity. However, the joint trial from the Radiation Therapy Oncology group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) by Flam et al as described, supported the use of mitomycin C in the definitive treatment for anal cancer.(15)

The replacement of mitomycin C with cisplatin has been researched. Two studies have investigated this. The ACT II trial was a 2x2 trial, and compared patients treated with cisplatin, 5FU and radiotherapy (50.4Gy in 28 fractions) to those treated with mitomycin C, 5FU and radiotherapy, with or without maintenance chemotherapy.(7) The results showed similar toxicities in both arms, although the mitomycin arm did have more grade 3 and 4 haematological toxicity. The complete response rate was 90.5% in the mitomycin group versus 89.6% in the cisplatin arm (95%CI -4.9 – 3.1; P=0.64). At a median follow up time of 5.1 years the two groups had similar overall survival and progression-free survival.(7) The 3-year progression free survival was 74% in the maintenance group versus 73% in the non-maintenance group (95% CI 0.75-1.21; P=070). There was no benefit found for maintenance treatment. The 3-year colostomy free survival was 73% in the mitomycin and maintenance group; 75% in the cisplatin and maintenance group; 75% in the mitomycin and non-maintenance group and 72% in the cisplatin and non-maintenance group.

The RTOG 98-11 trial findings were not as supportive of cisplatin replacement. This trial also compared patients receiving either mitomycin C, 5FU and radiotherapy versus cisplatin, 5FU and radiotherapy (the dose of radiotherapy was at least 45Gy in 25 fractions to the primary cancer and involved nodes. The nodal sites at risk received 30.6 to 36Gy in 17 to 20 fractions. Patients with T3-4N+ disease received an additional dose of 10 to 14Gy in 2Gy fractions) to the primary tumor/involved nodes (total dose 55- 59Gy in 30 - 32 fractions over 5.5 to 6.5 weeks). The mitomycin arm showed an improvement in colostomy failure as well as meaningful impact on disease-free survival and overall survival. The 5-year disease-free survival was 67.8% versus 57.8% (p=0.006) and the 5-year overall survival was 78.3% versus 70.7% (p=0.026). The colostomy-free survival was 71.9% versus 65% (p=0.05).(16)

Although mitomycin and 5FU remain the standard of care, cisplatin and 5FU can be considered a reasonable alternative when there is a concern about myelotoxicity such as in HIV positive patients.(13)

The optimal doses of radiation in patients with anal carcinoma are unclear. Retrospective reviews suggest that dose is a prognostic for local control and survival.(17) Constantinou et al found that patients treated for anal carcinoma with doses ≥54Gy were associated with a significant overall survival benefit with 84 vs. 47% (p=0.02) at 5 years when compared to lower doses. This was applicable to disease-free survival (74% vs. 56% p=0.09) as well as local control (77% vs. 61% p=0.04).(17) Radiotherapy was given, with concurrent 5FU and mitomycin C.

Higher doses of radiotherapy have been considered. An RTOG trial reviewed patients receiving a total dose of 59.6Gy as a "split course" (delay of 2 weeks after 36Gy) with concurrent 5-FU and mitomycin C, compared with patients treated with 45 – 50.4Gy also with concurrent chemotherapy(18) The outcome was that the higher dose of radiotherapy given in split course did not appear to improve local control. However, they hypothesized that if given continuously, there may be an increase in local control but at the expense of toxicities. (18)The French ACCORD trial also reviewed the issue of a higher radiation dose (radiation given as split course with 45Gy to the pelvis with either standard dose of 15Gy boost or boost according to response - 25Gy for minor partial response and 20Gy for complete response). It also questioned the need for induction chemotherapy with Cisplatin, 5-FU and mitomycin C. The colostomy-free survival was the main end-point. They did not find an advantage for either induction chemotherapy or high dose radiotherapy in locally advanced anal cancer (5-year colostomy-free survival was 76.5% versus 75% P=0.37) (19)

European and National Comprehensive Cancer Network (NCCN) guidelines recommend a minimum continuous dose of at least 45Gy to all patients. Radiation doses of 45-50Gy are recommended for T1-2 and N0 tumours.(20) Higher doses may be required for more advanced tumours. Previously a treatment gap was used, which was thought to allow time for tumour shrinkage and recovery from acute toxicities. However, this school of thought has changed and uninterrupted treatment, avoiding a treatment gap, is now considered the standard of care as it is radiobiologically more effective. Studies that have reviewed the impact of a treatment gap have shown that shortening the gap contributes to optimizing locoregional control, whereas treatment time longer than 5 weeks correlates with poorer locoregional control.(21-23)

Radiotherapy for anal carcinoma remains challenging. The complexity of the target volume as well as the close relation of numerous organs at risk makes planning difficult. Treatment has evolved from 2D based radiotherapy technique, where bony anatomic landmarks were used to plan radiotherapy, to 3D conformal radiotherapy to highly conformal techniques. The newer more conformal treatment approaches such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) allow for sparing of organs at risk and less toxicities, and are thus recommended for treatment of anal carcinoma.(24)

The radiation field must include the primary tumour and all involved lymph nodes. For early stage disease (T1, T2, N0) one could consider treating only the primary tumour. However for T3 and T4 tumours all potentially involved nodes should be included even in the absence of disease.(22) A Radiation Therapy Oncology Group (RTOG) consensus panel agreed that nodal groups at risk need to be included in the elective clinical target volumes (CTV). For anal cancer this would include a CTVA, CTVB and CTVC. The CTVA refers to the internal iliac, pre-sacral and peri-rectal nodal areas. The CTVB includes the external iliac nodes and the CTVC the inguinal node region.(25) The Australasian Gastrointestinal Trials Group (AGITG) published guidelines for intensity-modulated radiotherapy (IMRT) in anal cancer. This atlas provides practical planning guidelines with respect to tumour definition; nodal groups at risk and organs at risk, as well as addressing fractionation and other IMRT related aspects of treatment.(26)

The acute side effects during chemoradiation relate to the gastrointestinal, skin, genitourinary and haematological systems. The acute gastrointestinal side effects include diarrhea, nausea and mucositis; the skin may develop ulceration, moist desquamation and skin breakdown; and haematologically myelosuppresion may occur. The genitourinary system is also affected and patients may experience dysuria, urgency and frequency.(19, 27)The late effects of radiotherapy may range from anal fistulae (e.g. rectovaginal fistula) or stricture, anal incontinence, rectal bleeding to skin fibrosis and telangiectasia. Female patients may develop vaginal stenosis and ovarian failure; male patients may experience impotence and sterility. There is also potential of patients developing femoral head fractures.(24)

The RTOG 0529 phase 2 trial evaluated the use of dose-painted intensity modulated radiation therapy (DP-IMRT) with 5-FU and mitomycin C compared with conventional radiotherapy. The primary aim of this study was to reduce grade 2 acute gastrointestinal and genitourinary adverse events by at least 15%. Although the end point was not met, the DP-IMRT was associated with significant sparing of acute grade 2 haematologic ($P=0.032$) and grade 3 skin ($P<0.0001$) and gastrointestinal toxicity ($P=0.0082$).(28) The study did however report promising treatment related outcomes with a two-year local control rate of 95%, overall survival of 94% and a colostomy-free survival of 90%.(24)

Response to treatment is evaluated by digital rectal examination approximately six weeks after completion of chemoradiation to assess if regression of tumour is present. Clinical examination of the inguinal regions with or without imaging such as CT/MRI helps to establish response. Response to treatment can be slow and it is important to allow sufficient time for tumour regression before offering salvage surgery. Following the evaluation at six weeks patients should be reviewed at 3 months and then again at 5 months post treatment. As long as there is evidence of tumour regression at each assessment salvage surgery is not indicated. However if there is persistent disease at five months after treatment a biopsy should be done to confirm this and then salvage surgery with an abdomino-perineal resection is indicated. In the ACT II trial patients were assessed for response up to 26 weeks after completion of treatment.(7)After complete response if recurrence is suspected, this must be confirmed with a biopsy. If complete remission is

achieved, follow-up is 3-6 monthly for 2 years and then 6-12 monthly until 5 years.(14) Visits include clinical examination with proctoscopy if indicated. Very few patients relapse after 3 years (<1%) as per the ACT II trial.(7) If relapse does occur, it is more likely to be loco-regional than distant metastases and salvage surgery is then an option for these patients. An abdomino-perineal resection (APR) is a surgical option for persistent or recurrent disease, in the hope of obtaining clear surgical margins.(14) This should be discussed in a multidisciplinary setting with the surgeons.

Patients who develop distant metastases can be treated with palliative chemotherapy. Treatment is usually cisplatin-based chemotherapy (cisplatin 100mg/m^2 on day 2), given with fluorouracil as an infusion at 1000mg/m^2/d over 5 days. If cisplatin-based chemotherapy fails, no other regimens have proven to be effective.(20)
It is vitally important to adopt a multidisciplinary approach to treatment of these patients, thus including input from the radiation oncologist, surgeons and radiologists. It is best that treatment and follow up takes place at specialized centers.

The understanding and treatment for anal cancer has evolved over the last few decades. Chemoradiation is the standard of care, however there are many aspects of treatment that still need to be clarified. One area that needs further investigation is dose escalation, especially for larger tumours. Further research is also required for the treatment of patients with anal cancer and HIV infection. In metastatic disease, further treatment options after first line cisplatin and 5FU-based chemotherapy are needed.

The aim of this research study is to compare the outcome of two cohorts of patients with anal squamous carcinoma treated at Groote Schuur Hospital. The first cohort was treated with split course chemoradiation, which was an earlier management approach, the second with continuous chemoradiation, which is now the accepted standard of care. We expect that the patients treated with continuous radiotherapy over a shorter treatment time should have a superior therapeutic outcome, as has been documented in the literature.

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Article

Introduction:

Anal squamous carcinoma represents a small percentage of gastro-intestinal malignancies. It is estimated at about 1-2% worldwide.(1) At Groote Schuur hospital, anal carcinoma constitutes 4% of all gastro-intestinal cancers.(2) Human papilloma virus (HPV) infection is a known risk factor for the development of this disease, especially the HPV 16 and 18 strains.(3) The treatment for anal carcinoma has evolved over the last few decades. Initially surgery was the mainstay of treatment, until 1983 when Nigro et al. found promising results for treatment of patients with chemoradiation.(4) Further phase II and III trials supported these findings and today chemoradiation with 5-fluoroucacil and mitomycin C is regarded as the standard of care. This treatment, very importantly, allows for organ preservation. European and NCCN (National Comprehensive Cancer Network) guidelines recommend a minimum continuous dose of at least 45Gy to all patients. Radiation doses of 45-50Gy are recommended for T1-2 and N0 tumours.(5) Higher doses may be required for more advanced tumours. Loco-regional control rates are found to be as high as 81% with the 5-year overall survival estimated at 66% in central Europe, and slightly lower in Eastern Europe at 44%.(6, 7)

The objective of this study was to compare the outcome of two cohorts of patients with anal squamous carcinoma treated with split course chemoradiation as opposed to continuous chemoradiation at Groote Schuur Hospital. Demographics including age at diagnosis, gender and human immunodeficiency virus (HIV) status were reviewed. The stage at diagnosis, the acute treatment toxicities and all surgical procedures were noted. The outcomes included complete response rate, local control rate, loco-regional failure free survival, colostomy–free survival and overall survival. Since split course chemoradiation has a longer overall treatment time and may allow for repopulation, we expected the patients treated with continuous chemoradiation to have a better outcome.

Methods:

Study design:

This was a retrospective review. Ethics approval was granted for the study by the University of Cape Town faculty of Health Sciences Human Research Ethics Committee (ref. 785/2014). The data was obtained from patient records of all patients with histologically confirmed anal squamous cell carcinoma seen and registered at the Department of Radiation Oncology at Groote Schuur Hospital. Patients included were those treated with radical intent that presented between the years of 2008 and 2012.

Patient demographics including age at diagnosis, gender and HIV status were recorded. Staging investigations included chest X-ray and CT abdomen and pelvis. MRI of the pelvis was not done due to limited access of this imaging for routine staging. Baseline bloods were also done for every patient, which included HIV test, full blood count, renal, and liver function tests. Patients with suspicious inguinal nodes had fine needle aspiration cytology of these nodes. Stage of disease was documented (Tumour stage, nodal stage and metastatic stage) according to the

American Joint Committee on Cancer/Union for International Cancer Control – (AJCC/UICC) classification. The chemo-radiotherapy regimen used, surgical procedures performed, and the response to treatment at follow up visits were all documented. The acute toxicities of treatment were included. Acute toxicities were noted from documented visits during treatment. These included skin, gastrointestinal and haematological toxicities. The toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) guidelines.

Treatment:
All patients were assessed by a multidisciplinary team. Patients with faecal incontinence or with tumours causing obstruction had a defunctioning colostomy prior to chemoradiation. Patients received chemoradiotherapy with mitomycin C and 5-Fluorouracil (5-FU). Mitomycin C was given at 12mg/m2 intravenously on day 1 with the first fraction of radiotherapy. 5-FU was given as a 24-hour intravenous infusion at 1000mg/m2 during the first four and last four fractions. The patients received a total dose of 50.00Gy in 2.00Gy fractions. The nodal groups at risk received 36.00Gy followed by 14.00Gy given as a boost to the tumour plus involved nodes. Radiotherapy planning included both 2-dimensional (2D) and 3-dimensional (3D) planning. Patients were followed up 6 weeks post completion of chemoradiation, and then again at 3 and 5 months post treatment. Thereafter 3-monthly for the first 2 years, then 6 monthly for 3 years and then annually. Each visit consisted of a clinical examination in order to assess response. Patients with persistent tumour at five months after completion of chemoradiation had a repeat biopsy to confirm persistent disease and were then offered abdominoperineal resection. Progressive disease or recurrence had to be histologically proven with a biopsy.

The patients in the previous study done at Groote Schuur hospital between 2000-2004 received chemoradiation in the form of split course treatment. The patients received a total dose of 42-44Gy in 20 fractions with the same concurrent chemotherapy. This was followed by a 6-week rest period and then a boost of 15.00Gy was given in 2.50Gy fractions. The patients were treated using 2D planning with an anterior and posterior field technique. The practice changed at Groote Schuur hospital to continuous radiotherapy omitting the six week break in 2008.

End points and statistical analysis:
Colostomy-free survival (CFS) was calculated from commencement of treatment to colostomy or death or last follow up.

Overall survival (OS) was measured from the date of treatment commencement to death from any cause. The log rank test was used to compare the loco-regional failure free survival and the overall survival of the two treatment groups.

The statistical analysis was done with Matlab R2015a statistical program. This included the Kaplan Meier survival analyses.

Results:

Patient characteristics:

Between 2008 and 2012 a total of 72 patients were diagnosed with anal squamous cell carcinoma at Groote Schuur hospital. Only 40 of these patients were included in this study as they were treated with curative intent with radical chemoradiation. The other patients were treated palliatively as they either had stage IV disease or had a poor performance status.

The median age was 53 years with a slight male predominance of 55% (table 1). All 40 patients were tested for human immunodeficiency virus (HIV). A total of 11 patients tested HIV positive. A total of 68% of patients had T3 and T4 disease, with 42.5% node positive disease. The majority of patients presented with stage II (52.5%) and IIIB (40%) disease as shown in figure 1.

Table 1.
Patient characteristics

Characteristic	Number of patients (%)
Age	
Median (range)	53 years (28-73)
Gender	
Females	18 (45)
Males	22 (55)
HIV status	
HIV positive	11 (27.5)
HIV negative	29 (72.5)
Colostomy prior to CRT	7 (17.5)
Median tumour size (range)	6.7cm(5-10)

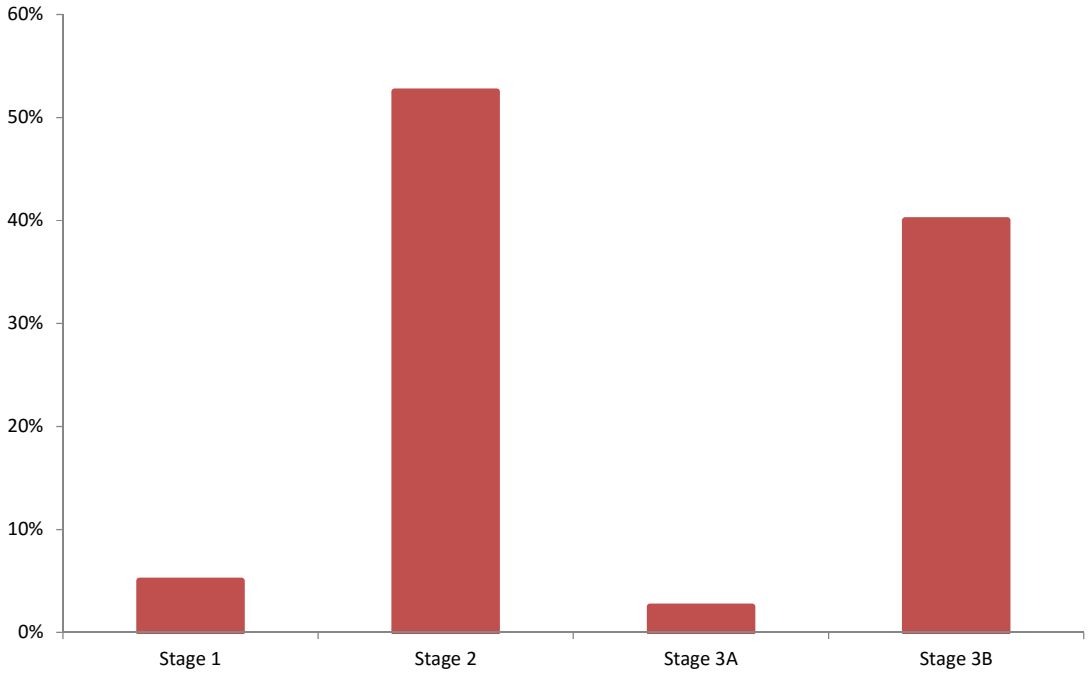

Figure 1. Stage distribution

Treatment outcomes:
There was a complete response rate of 60% at 6 months post completion of radiotherapy. The local control rate was calculated at 52.5% and the loco-regional failure free survival at 5 years was 56% (figure 2). The colostomy-free survival was 74% and the 5-year overall survival was 40.67% (figure 3).

All 40 patients in this cohort completed chemoradiation. The mean treatment time was calculated at 42 days (6 weeks).

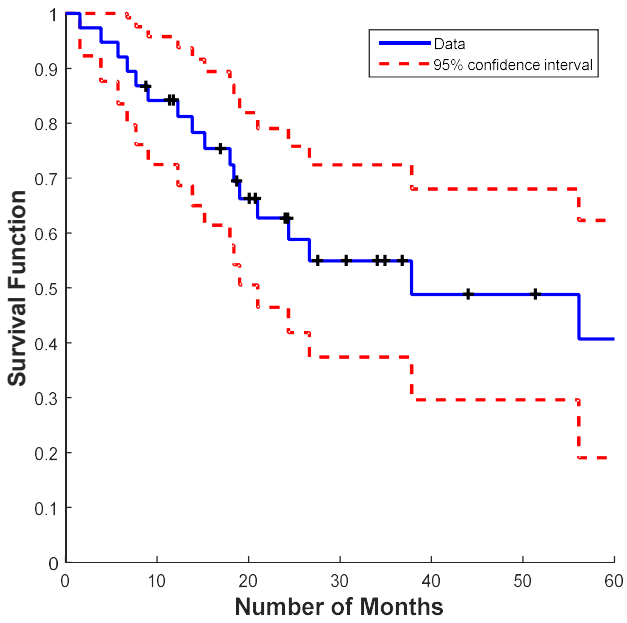

Figure 2. Loco-regional failure free survival

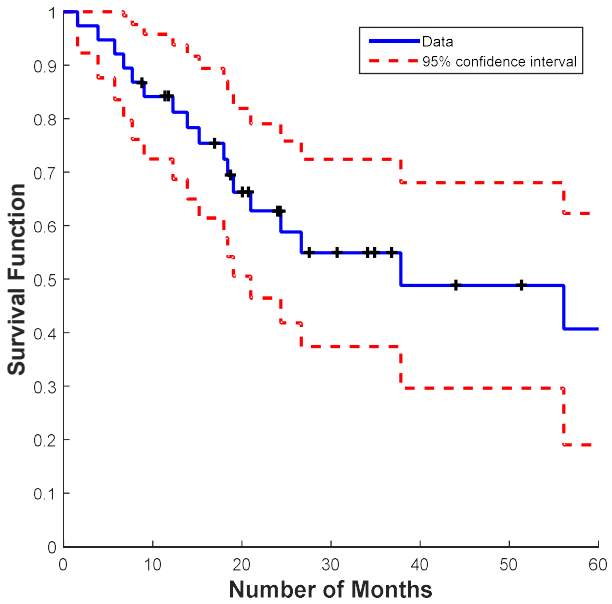

Figure 3. 5-year overall survival

Toxicity:
Haematological, gastro-intestinal and skin toxicities are known acute effects of treatment. Radiation dermatitis was the most common in this cohort. A total of 32.5% (13 patients) experienced grade 2 skin toxicity and 27.5% (19 patients) had grade 3 toxicity. All toxicities are shown in table 2. Gastro-intestinal grade 1 toxicity was present in 27.5% (11 individuals) of patients and grade 3 toxicity in 6 patients (15.8%). Haematological toxicity was less common at only 26%, the most common being grade 2 toxicity at 20%. Toxicities and their effect on overall survival were assessed. There was no statistically significant effect of skin and haematological toxicities on survival. However, the patients experiencing GIT toxicity appeared to have a superior overall survival when compared to the patients having had none. This was statistically significant with a P value of 0.05.

Table 2.
Toxicities

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Haematological	1 (2.5)	8 (20)	0	1 (2.5)
Gastro-intestinal	11 (27.5)	3 (7.5)	6 (15)	0
Skin	0	13 (32.5)	19 (47.5)	0

We compared the outcomes of the two groups of patients treated at Groote Schuur Hospital. The results are shown in table 3 and figure 3.

Table 3.

	Group 1(%)	Group 2 (%)
Complete response	80	60
5 year loco-regional failure free survival	60.7	56
5 year overall survival	65.6	40.6

Group 1: patients treated from 2000-2004, split course chemoradiation
Group 2: patients treated from 2008-2012, continuous chemoradiation

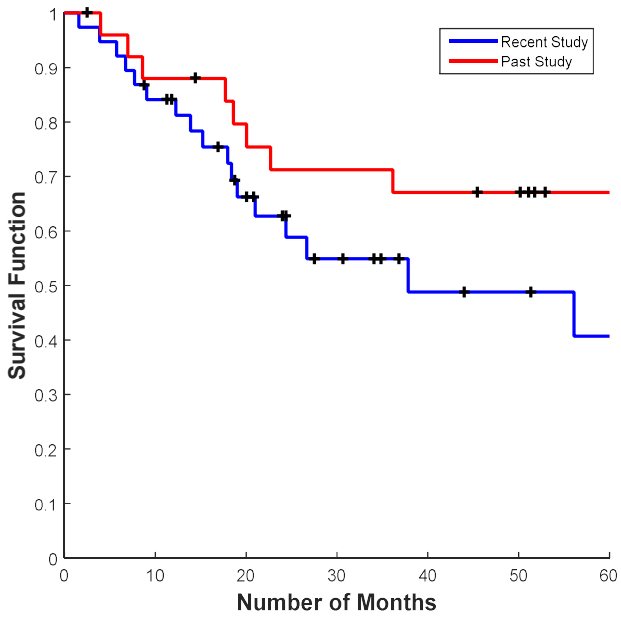

Figure 4. Comparison of overall survival

Discussion:

The results of this retrospective review, in terms of patient characteristics, confirmed our previous findings in that the median age at presentation of our patients was slightly lower when compared to that from Europe and North America. We again noted that there were more male patients in our cohort whereas other centers report a female predominance for this disease.(2, 8-11) There was a significant increase in the total number of patients with anal squamous carcinoma referred to Groote Schuur hospital. A total of 72 patients were seen between 2008-2012, whereas only 31 patients were seen between 2000-2004. Our cohort showed a significant increase in the number of HIV positive patients when compared to the previous study done at our institution, 27.5% versus 3.8%. The increase is attributed to overall increase of HIV prevalence and its burden on the health system. Kachnic et al investigated the role of dose-painted intensity-modulated radiation in anal cancer, and they reported 21% HIV positive patients in this study.(12) HPV is a known risk factor in anal carcinoma, however its presence was not tested for in our study.

The vast majority of patients presented with stage II (52.5%) and stage IIIB (40%) with 63.2% of patients having T3 tumours and 42.5% with positive nodal disease. This appears to have increased by 10% when compared to the previous study, where 53.8% of patients had T3 disease. Similar results were found in a recent study in Kwazulu-Natal. This was an analysis of an on-going local database. They too report the majority of patients presenting in stage II and III (67%).(9) However, when comparing with literature from Europe and North America it seems that our patients present with more advanced tumours. The ACT II trial reports T3 tumours ranging from 29%-35% depending on the treatment arm.(10) We are seeing almost double that at our institution.

The complete response rate was calculated at 60% and local control rate was 52.5%. Constantinou et al reported local control of disease at 70% at 5 and 8 years post treatment.(13) This was also a retrospective review of patients with anal carcinoma treated with concurrent radiotherapy and cisplatin with 5FU.
The ACT II trial was a 2x2 factorial trial investigating the use of maintenance chemotherapy as well as replacing mitomycin C with cisplatin. This study reported complete response rates for the mitomycin C group at 90.5% and the cisplatin group at 89.6%.(10) Both these studies showed improved local control rates when compared with our patients.

The loco-regional failure free survival, colostomy-free survival and 5-year overall survival were also all lower than expected. The loco-regional failure free survival was 56%, the colostomy-free survival was 74% and the overall survival was 40.67%. The French ACCORD trial was a 2x2 factorial study that reviewed the use of induction chemotherapy and higher radiation dose. The colostomy-free survival in the relevant study arm (concomitant chemoradiation with a standard boost) was 77.1%, which is comparable with this study.(8) The ACT II trial also had results comparable with ours, a 3-year colostomy free survival of 84% for patients with T1 and T2 disease, and 61% for patients with T3 or 4 disease.(10) Overall survival was not an objective in the ACT II trial. The RTOG 98-11 trial compared 5FU, mitomycin C and radiotherapy versus 5FU, cisplatin and radiotherapy. The outcome showed a significant impact on disease-free survival and overall survival for concurrent 5FU and mitomycin C. The 5-year overall was 78.3%.(14) The UKCCCR trial that compared radiotherapy alone versus combined modality treatment (chemoradiotherapy with 5FU and mitomycin C) reported a 3-year overall survival of 65% in the combined modality treatment group.(11)

The influence of disease stage at presentation may determine treatment outcomes. When comparing our patients with stage I and II disease versus patients with stage III disease with regard to loco-regional control, there was a trend for patients with earlier stage disease at presentation having better outcome. However, this was not statistically significant ($P = 0.14$). Similarly, with overall survival, there was a trend towards the patients with stage III disease having a poorer survival outcome. This, again, was not statistically significant ($P=0.07$).

In the comparison of the two treatment groups, we noted the complete response for group 1 was 80%, which is higher than the current data.(2) The patients in group 1 had a higher 5 year overall survival. This was however not statistically significant (P = 0.244). Although not significant, the recent data does suggest that our patients receiving continuous chemoradiation have a worse outcome. The reasons for the inferior outcome were explored.

The number of HIV positive patients in group 2 was higher. HIV status and its effect on overall survival was assessed using Kaplan Meier statistics for group 2. We expected the HIV negative group to have a better survival than the positive group. However, there was no statistically significant outcome found between the two groups (P value = 0.86). This was re-iterated by the results in Kwazulu-Natal. This study reviewed patients with anal carcinoma and analyzed demographics, pathology, treatment and outcome.(9)

The previous study at our institution using split course radiotherapy had a 5-year overall survival of 65.6%.(2) The 5-year overall survival of 40.6% of group 2 is lower (although not statistically significant). It is also lower than international standards. However, when compared to data from Kwazulu-Natal, our results are actually superior. The calculated 5-year overall survival was 33.4%. Although this study included both squamous cell carcinoma and adenocarcinoma the majority (85%) were squamous carcinomas.(9)

The median tumour size for the T3 and T4 patients in this study was 6.5cm (range 5-10cm) (100% of patients with T≥5cm) with 75% having ulceration. For nodal involvement 40% of patients had N2 or N3 disease. In group 1, although the exact tumour size was not recorded for all patients, only 58% of patients had a tumour size of > 5 cm and 50% were ulcerated. There were nine (34%) patients with N2 or N3 disease. The importance of tumour size in predicting outcome was showed by Ajani et al. This article aimed at establishing prognostic variables for patients with anal carcinoma, among them tumour diameter, nodal status and gender. The analysis revealed that tumour diameter, regardless of nodal status, is the only independent variable that predicted DFS and OS.(15-17). The higher percentage of patients with tumours > 5 cm and more advanced nodal disease in group 2 could have contributed to the worse outcome.

Overall treatment time must also be considered in treatment related outcomes. Graf et al reviewed the impact of overall treatment time on local control of anal cancer. Their findings proved the 5-year overall survival was significantly improved in patients treated with an OTT (overall treatment time) of less than 41 days (58% for OTT >41 days vs. 79% for OTT <41days, P=0.04). The median treatment time for group 2 was 6 weeks (42 days) whereas the median treatment time for group 1 was 13.4 weeks. Therefore the inferior outcome of group 2 is not due to prolonged treatment time.(17)

The most common toxicity was radiation dermatitis with grade 2(32.5%) and grade 3(47.5%) dermatitis being the most significant. Grade 1 gastro-intestinal (27.5%)toxicity and grade 2 haematological toxicity (20%) were also of note. The

presence of toxicities was also evaluated in terms of their effect on survival as calculated with Kaplan Meier analyses. There was no statistically significant effect on overall survival with respect to skin and the haematological toxicities. However, there was a survival benefit in the group of patients that did experience gastrointestinal toxicities (P value = 0.05). This result was attributed to the large number of patients censored in the toxicities group, as well as the small sample size. This result is therefore interpreted with caution. The previous study also reported the majority of patients experiencing radiation dermatitis at 27%.(2) The other toxicities were negligible. The literature corresponds with the current findings. The ACT II trial showed grade 3 skin toxicity of 41% in the mitomycin arm and 43% in the cisplatin arm.(10) The ACCORD trial did not comment on dermatitis.(8)

We have to consider the effect of total dose on outcome of the current findings. The previous split course radiotherapy regimen at our institution allowed for a total dose of 57-59.00Gy. This did however include a treatment gap prior to the 15.00Gy boost. The treatment for group 2 was a total dose of 50.00Gy (36.00Gy to nodal sites at risk and 14.00Gy boost to tumour). A recent study by Muirhead et al in the United Kingdom, suggests dose-individualization for anal cancer radiotherapy. This was a systematic review with the aim to fit a tumour-control probability (TCP) model for anal cancer in patients treated with intensity modulated radiotherapy (IMRT). A TCP curve was demonstrated that suggests in late stage tumours dose should be escalated from 50.00Gy to 54.00Gy as this improves local control from 50% to 80%. In early stage tumours dose reduction from 50.00Gy to 45.00Gy decreases the local control minimally from 98% to 95%.(18)

In conclusion we have shown that patients in our unit treated with continuous chemoradiation tended to have a worse outcome than those treated with split course chemoradiation. Although the total radiation dose was higher in the split course group the overall treatment time was longer. It is unlikely that the inferior outcome is due to treatment but rather to tumour factors, such as larger size and more advanced nodal disease. The limitations of this study are the fact that this is a retrospective review with a small number of patients. However, the inferior results of group 2 compared with group 1 and other centers cannot be ignored. Our proposed plan for future treatment of our patients is aimed at dose escalation in order to improve local control and survival. We plan to increase the total dose of continuous radiotherapy, however the exact dose will need further investigation. Increasing the radiation dose will result in an increase in toxicity. This will therefore require advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), which allow for more conformal radiation to the tumour with better sparing of normal tissue. A review of this regimen and its outcomes is planned for the future.

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