SHOULD ABDOMINO-PERINEAL RESECTION BE CONSIDERED WHEN A DEFUNCTIONING STOMA IS REQUIRED FOR ANAL CANAL SQUAMOUS CELL CARCINOMA?

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Declaration

I, Dr Jacobus Christoffel Kloppers, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work or any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signature: ..................................

Date: 03 November 2014
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Introduction
Combined modality treatment (CMT) is the preferred treatment for anal squamous cell carcinoma, but a small subgroup needs a defunctioning colostomy with temporary intent.

Aim
The aim of this study was to evaluate the stoma closure rate of patients needing defunctioning colostomies prior to CMT for anal squamous cell carcinoma (SCC) at Groote Schuur Hospital (GSH). The key objective was to assess if abdomino-perineal resection (APR) should be offered as primary treatment modality for the subgroup of patients needing a defunctioning stoma and CMT.

Method
A retrospective chart review of all patients with histological diagnoses of anal squamous carcinoma treated at the Combined Colorectal Clinic at Groote Schuur Hospital between 1995 and 2012 were undertaken. Patients who required defunctioning colostomies prior to CMT were analysed in terms of demographics, indication for stoma, response to treatment and stoma closure rate.

Results
125 patients were treated for anal SCC. There were 58 males and 67 females with a median age of 56 years. Thirty nine patients were deemed to require a defunctioning stoma prior to CMT. Thirty of these patients were treated with curative intent (22 males and 8 females) and a defunctioning stoma. The indications for stomas were obstruction (n=14); incontinence (n=8); pain (n=4); fistula (n=3) and sepsis (n=1). In only three (10%) of the 30 patients were the stomas successfully reversed. Disease progression (n=15) was the leading reason for non-reversal of defunctioning stomas. Thirteen of the 30 patients who needed a stoma prior to CMT were clearly not resectable, while 6 were evaluated on the pre-treatment examination under anaesthesia (EUA) as resectable.

Conclusion
In this study we found that a defunctioning stoma prior to CMT was likely to be permanent. We propose that APR should be an alternative in cases where the tumour is resectable.
1. Introduction and background:

Squamous cell carcinoma (SCC) of the anal canal is rare. In the United States, for the year 2012, 780 deaths due to SCC were expected with 6230 new diagnoses.\(^1\) The condition comprises 4% of the total number of cancers of the gastrointestinal tract seen at Groote Schuur Hospital (GSH).\(^2\) Ninety percent of anal canal carcinomas are of squamous cell origin. The remainder consists of rarer subtypes including adenocarcinoma, melanoma, and neuroendocrine carcinoma of the anal canal.\(^3\) This study will include patients with squamous cell carcinoma of both the anal canal and anal margin.

Abdomino-perineal resection (APR) was the standard of care for anal canal squamous cell carcinoma before the introduction of combined modality therapy (CMT).\(^4,5\) In 1974 Nigro \textit{et al} introduced CMT as primary therapy for SCC.\(^6\) In their series a complete pathological response rate of 93% was seen in over 100 patients treated by CMT. Currently, CMT is the recommended first line therapy for invasive SCC of the anal canal. Surgical resection is now reserved as salvage therapy for patients with persistent disease, recurrent disease or for the treatment of complications associated with radiation therapy.\(^7\) The current treatment protocol at GSH combined colorectal clinic correlates with the above.\(^8\)

Some patients require a defunctioning colostomy prior to CMT to allow for safe delivery of treatment with the lowest risk of treatment interruption. The indications include the presence or risk of fistula formation, symptoms of large bowel obstruction or faecal incontinence; the latter is usually due to destruction of the anal sphincter by tumour.\(^8-11\) In a recent review at GSH, seven (23%) out of 31 patients over a four year period required a stoma prior to CMT; of these only one was closed.\(^2\) In Leeds, 35 (10%) out of 344 patients over a ten year period required stomas prior to CMT of which seven were closed.\(^9\) These findings were similar to those found in a Dutch study of 83 patients with anal cancer. In their series, seven
patients (8%) had a colostomy created before treatment with only one being permanently reversed.\textsuperscript{12}

The major benefit of CMT is preservation of the anus and thus avoiding a permanent stoma. The literature would suggest that pre-treatment colostomy in anal carcinoma should be regarded as permanent.\textsuperscript{9,10,12} If this is so, then APR would potentially shorten treatment and avoid the complications and frequent hospital visits of CMT. Common complications of CMT include diarrhoea, haematological toxicity and skin disruption. Although APR is regarded as major surgery it requires only one admission and limited follow up in most cases. APR as primary treatment for patients with SCC of the anus, who require defunctioning, has not been previously evaluated.

2. Methodology:

This study involves a retrospective folder review of patients with SCC at GSH.

Objective:

1. To evaluate the stoma closure rate of patients who required defunctioning colostomies prior to CMT for Anal SCC at GSH.
2. To assess whether APR is a suitable primary treatment modality for the subgroup of patients needing a defunctioning stoma prior to CMT.

Inclusion criteria:

All patients with histologically proven anal SCC treated at the Combined Colorectal Clinic, Groote Schuur Hospital, Cape Town from January 1998 to June 2012 will be reviewed.

Recruitment of sample:

1. Patients will be identified from an electronic database updated by the GSH Oncology Department.
2. In addition there will be a manual search of appointment diaries of the Combined Colorectal Clinic since 1998.

Data collection and storage:

Data will be collected manually from patient folders and captured on a digital Microsoft Excel 2010 spreadsheet.
Demographical information, TNM stage, potential resectability of the tumour prior to CMT, HIV status, co-morbidities, complications and length of CMT, type of stoma, indication for stoma, closure rate and evaluation at EUA will be collected.

Protection of confidentiality:

All information obtained that can be identified to specific patients will remain confidential. Patient folders will only be viewed by health professionals who are legally and ethically bound to upholding confidentiality. Additionally, all data digitally captured for the purpose of this study will be password protected. Any reports or publications resulting from the research will maintain the anonymity of the individual study participants.

3. Anticipated risks:

No direct risk to patients is anticipated in this retrospective study.

4. Anticipated benefits:

The study will have no direct benefit to patients included within the study. However, it will consolidate local understanding regarding which patients require defunctioning colostomy as well as explore reasons for non-reversal of temporary stomas. This may lead to improved informed consent and wider surgical options in first line treatment of anal carcinoma for future patients.

5. Ethical considerations:

As the data used is routine data and will be retrospectively and anonymously collected from files, no violation of privacy is expected. Consent will be obtained from the medical superintendent of Groote Schuur Hospital for access to these files and hospital databases. A waiver of need for direct consent from patients is requested, as this is a retrospective file review. No risks to the patients are anticipated and obtaining consent would be extremely difficult due to the retrospective nature of the study.

6. Budget:

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<td>Password-protected flash drive</td>
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<td><strong>Total</strong></td>
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Source of funding: Principal investigator
7. References:


Part C
Chapter 1

Literature review

Squamous cell carcinoma (SCC) of the anus is a relatively rare condition. It comprises 4% of the total number of cancers of the gastrointestinal tract seen at Groote Schuur Hospital (GSH). Abdomino-perineal resection (APR) was the standard of care before it was replaced by combined modality therapy (CMT) which was introduced by Nigro et al in 1974. Some patients will require a defunctioning colostomy prior to CMT to allow for safe delivery of treatment with the lowest risk of treatment interruption. However the literature would suggest that a pre-treatment colostomy in anal carcinoma should be regarded as permanent.

1.1 Anatomy of the anus

The anus can be divided into the anal canal and the anal margin. The anal canal starts at the anorectal ring and extends to the anal verge. The anorectal ring is situated about 5 cm from anal verge and forms as the anorectal angle. It is about 3.5 – 5 cm in length and forms the terminal part of the entire alimentary tract. The anal margin is defined as the area 5 cm from the anal verge and is covered by epidermis.

The epithelium lining the anal canal changes within the canal. The dentate line is a landmark about 2 cm from the anal verge. The mucosa of the upper anal canal is lined by columnar epithelium. Below the dentate line, the anal canal is lined with squamous epithelium. The change is not abrupt. For a distance of 0.6 to 1.2 mm above the dentate line, there is a gradual transition where columnar, transitional, or squamous epithelium may be found. This area has been referred to as the transitional or cloacogenic zone and is important when considering neoplasms that arise from this segment. The area between the dentate line and anal margin does not contain hair, sebaceous or sweat glands. The epithelium above the dentate line is supplied by the autonomic nervous systems and the somatic nervous system below. (Figure 1)
The anal canal descends postero-inferiorly between the anococcygeal ligament and the perineal body. It is surrounded by internal and external sphincters. The internal anal sphincter is an involuntary sphincter surrounding the superior two thirds of the anal canal. The external anal sphincter is a large voluntary sphincter that forms a broad circular muscle around the inferior two thirds of the anal canal.

1.2 Incidence

SCC of the anus represents approximately 1.5% of the newly diagnosed cancers of the gastrointestinal tract and 1 to 8% of all anorectal malignancies. In general, it is more common in women than men and usually occurs in the sixth or seventh decade of life. The incidence of SCC of the anus is increasing. The incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for men and 1.5-fold for women from 1973–1979 to 1994–2000. The first published series in Africa, by Madden et al in 1981 reported 55 cases over 20 years seen at Groote Schuur Hospital, a large urban teaching hospital. A recent review at the same institution reported 31 patients over 4 years. The median age was 56 years (range 18-87). There were 15 females and 16 males. In this review anal cancer was calculated to represent 4% of all gastrointestinal tract cancers which is in contrast to the much lower rates in the developed world.
1.3 Aetiology

1.3.1 Physical Trauma or Inflammation

Chronic inflammation was thought to be a risk factor for anal cancer after case reports of patients with inflammatory bowel disease. Frisch and colleagues reviewed the hospital records of 68549 patients in the Danish Cancer Registry and found that anal cancer had not developed in any of the 651 patients with Crohn’s disease or the 509 patients with ulcerative colitis. The presence of anogenital condylomata has been shown to increase the likelihood of anal cancer. However there is no evidence of an association with haemorrhoids, fissures or fistulae.

1.3.2 Human Papillomavirus (HPV)

HPV is a common viral sexually transmitted infection, with limited clinical stigmata; only 1% of patients will develop genital warts. Frisch et al reported on 386 anal cancers and detected HPV in 90% of invasive cancers in women and in 63% of invasive cancers in men. In a similar study, Daling et al tested 262 anal cancers, and detected HPV DNA in 87.9% of tumours, though the proportion of tumours positive for HPV was no different between women and men.

1.3.3 Immunosuppression

Chronic immunosuppression medication is a risk factor for several types of squamous-cell carcinomas, including those of the anal canal. In recipients of renal allografts, persistent human papilloma virus infection has been associated with a 100-fold increase in the risk of anogenital cancer. Although an increased risk of anal cancer has not yet been demonstrated in patients who are receiving corticosteroids for autoimmune disease, these patients do appear to have a greater likelihood of persistent human papillomavirus infection.

1.3.4 Smoking

Several case-control studies have shown that a history of smoking increases the risk of anal cancer by a factor of two to five, independently of sexual practices. This relation is supported by the finding that lung cancer is twice as frequent in patients with a history of anal cancer as in the general population.
1.3.5 Sexual Practices

Using patients with colon cancer as controls, Daling et al reported the results of a population-based, case-control study of anal cancer conducted between 1978 and 1985. Women with anal cancer were more likely to have a history of genital warts or infection with herpes virus or Chlamydia trachomatis compared to those with colon cancer. Men with anal cancer were more likely to have engaged in homosexual activity, to have practiced receptive anal intercourse, and to have had a history of genital warts or gonorrhoea. These observations were made before the human immunodeficiency virus (HIV) pandemic. Subsequent studies have confirmed the relation between anal cancer and receptive anal intercourse in men.

Frisch et al compared 417 patients with anal cancer with 534 patients with adenocarcinoma of the rectum and 554 normal control subjects. Multivariate analysis demonstrated that the relative risk of anal cancer in women was highest among those with 10 or more sexual partners compared to those with a history of anal warts, genital warts, gonorrhoea, or cervical neoplasia. A history of receptive anal intercourse before the age of 30 years with multiple partners was also associated with an increased risk of anal cancer, although less than 10% of women with anal cancer reported such behaviour.

1.3.6 HIV

The association between anal cancer and HIV infection is less clear, as HIV infection often co-exists with other risk factors, especially HPV infection. Most population-based studies were done before widespread use of highly active antiretroviral therapy (HAART) and therefore results might be different in current clinical settings. Frisch et al studied the role of HIV in HPV related malignancies and they observed a higher risk for anal cancer in both men and women with acquired immunodeficiency syndrome (AIDS) (relative risk (RR), 6.8; 95% confidence interval (CI), 2.7–14.0 and RR, 37.9; 95% CI, 33.0–43.4, respectively).

Interestingly, they failed to show a higher risk among patients with CD4 counts less than 200/mm$^3$ compared to CD4 counts greater than 200/mm$^3$. The authors concluded that while HPV-related malignancies are common, this may not be related to HIV-related immunosuppression but rather to unknown cofactors. Additionally, if HIV was directly associated with anal cancer, one would expect the incidence to decrease in the era after the introduction of HAART. This has been observed for other HIV-related malignancies, including non-Hodgkin's lymphoma and Kaposi's sarcoma, but not for anal cancer. A population-based study demonstrated that the incidence of anal cancer increased when comparing pre-HIV years (incidence, 0.6 per 100,000) with both HIV years (incidence, 0.8 per 100,000) and years after introduction of HAART (incidence, 1.0 per 100,000).
Table 1: Risk factors for Anal Cancer

**Strong evidence**
- Human papillomavirus infection (anogenital warts)
- History of receptive anal intercourse
- History of sexually transmitted disease
- History of cervical, vulvar, or vaginal cancer
- Immunosuppression after solid-organ transplantation

**Moderately strong evidence**
- Human immunodeficiency virus infection
- Long-term use of corticosteroids
- Cigarette smoking

1.4 Screening

Given the known high-risk groups for anal cancer, several studies have addressed screening in these populations. Similar to the cervical Papanicolaou (Pap) smears, anal swabs for cytology are a possible screening method for anal squamous intraepithelial lesion (SIL) and anal cancer. Sensitivity of anal cytology is in the range of 50%–80%, with sensitivity being higher in the HIV-positive population. Studies of the potential cost-effectiveness of screening have found that screening HIV-positive and HIV-negative homosexual and bisexual men every 2–3 years would be cost-effective and have life-expectancy benefit. Other groups in which there is a potential role for screening are women with a history of cervical dysplasia or cancer, and transplant recipients.

1.5 Presentation

The presentation of SCC of the anal canal is very similar to common benign anal conditions such as haemorrhoids and fissures, and is relatively non-specific. Delays and misdiagnoses are common and the presence of benign conditions further obscures the diagnosis. Rectal bleeding is the most common initial symptom of anal cancer, occurring in about 45% of patients. Anorectal pain or the sensation of a mass is present in 30%, while 20% of patients have no tumour-related symptoms. Additional common symptoms include pruritus and anal discharge. Tenesmus and faecal incontinence can suggest tumour invasion into the anal sphincters. Weight loss, change in stool calibre, constipation, inguinal lymphadenopathy and rectovaginal fistulae are indicators of advanced disease.
1.6 Diagnosis and special investigations

All suspicious lesions in the anal canal should be biopsied. The examination should document the appearance, size, location, mobility and extent of the lesion. If patient discomfort precludes adequate examination, an examination under anaesthesia (EUA) should be performed. As per local protocol, baseline investigations include full blood count (FBC), urea and electrolyte analysis (U&E), HIV, liver function tests (LFT) and a chest X-ray. The size of the primary lesion is determined by direct examination. Computed tomography (CT) scan of the abdomen and pelvis is used to evaluate the liver, the extent of local invasion and involvement of adjacent organs as well as pelvic and inguinal lymphadenopathy. All clinically suspicious inguinal lymph nodes should be assessed by fine needle aspiration (FNA) or open biopsy. Positron emission tomography-CT (PET-CT) scan does not replace a diagnostic CT and the routine use of a PET-CT scan for staging or treatment planning has not been validated. Bone scan, CT chest, magnetic resonance imaging (MRI) of the pelvis and abdomen can be added if there is a specific indication or diagnostic doubt. For women, a gynaecologic examination should be done, including screening for cervical cancer.

1.7 Staging

Unlike other gastrointestinal malignancies, the staging of anal carcinoma remains unchanged following the revisions of the American Joint Committee on Cancer Staging (AJCC) version 7.0 system. (Table 2)
Table 2: AJCC staging system for anal canal carcinoma.

**Primary tumour (T-stage)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T-stage</th>
<th>N-stage</th>
<th>M-stage</th>
</tr>
</thead>
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<td>M0</td>
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<td>M0</td>
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<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
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<td>N1</td>
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<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
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<td><strong>Stage IIIB</strong></td>
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<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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1.8 Treatment

1.8.1 Surgery

Before the introduction of CMT in 1974, APR was routinely performed for tumours arising in the anal canal. This radical procedure required removal of the anorectum with creation of a permanent colostomy. In early series, the overall probability of five year survival following APR for anal canal cancer was 40 to 70 %, with a perioperative mortality rate of 3%. APR fell out of favour as the initial therapy as increasing evidence demonstrated that SCC of the anal margin had a favourable prognosis and rarely required radical surgery. Wide local excision (WLE) with primary closure could be performed for anal margin SCC. Although local recurrence rates were as high as 50%, a second local excision or inguinal lymphadenectomy was able to salvage the majority of patients. The five-year survival for patients with cancers less the 2 cm in greatest dimension was over 80%. Nigro et al published a landmark report in 1974 describing 3 patients treated with neo-adjuvant chemoradiotherapy. They noticed two patients had complete pathological response on surgical specimens and one patient had a complete clinical response but refused surgery. Subsequent reports of patients by Nigro showed an overall 5-year survival of 80% (34% of tumours > 4cm), with a 93% clinical tumour response and an 89% pathological response. Thereafter routine APR was abandoned, and surgery was used only for salvage if residual tumour was found on biopsy 6 to 8 weeks after initial therapy.

1.8.2 Chemoradiotherapy

The Nigro protocol consisted of 5 flurouracil (5-FU) (1000mg/m² per day by continuous infusion days 1 through 4 and 29 through 32), mitomycin (10 to 15mg/m² on day 1 only), and intermediate dose radiotherapy (30 Gy). The finding that the first three patients had complete pathologic or clinical responses led to the development of strategies that were directed at preservation of the anal sphincter. In a follow up series, patients with anal canal cancer were initially treated with chemoradiotherapy (same regimen) and proceeded to an APR only if there was residual tumour on a post radiation biopsy. The majority of patients treated with chemoradiotherapy were cured (five-year survival 67%) without an APR (five-year colostomy-free survival 59%).

These findings were subsequently confirmed by several other studies using a variety of regimens. Taken together, the use of combined chemoradiotherapy resulted in local failure rates of 14 to 37 percent, five year overall survival rates of 72 to 89 percent, and five-year colostomy-free survival rates of 70 to 86 percent.
use of concurrent radiotherapy (RT) with infusional 5-FU and mitomycin has become established as the standard of care for patients with SCC of the anal canal.

The necessity of including chemotherapy in the non-operative treatment regime for anal cancer has been addressed in at least two randomized trials.

The Anal Cancer Trial Working Party of the United Kingdom Coordination committee on Cancer Research (UKCCCR) randomly assigned 585 patients with T1 to T4 SCC of the anal canal or margin to receive either RT alone (45 Grey (Gy) external beam in 20 or 25 fraction over four to five weeks plus a 15 Gy external beam or 25 Gy brachytherapy boost), or RT plus concurrent infusional 5-FU (1000mg/m² for four days or 750 mg/m² for five days during the first and final weeks of RT) and mitomycin (12 mg/m² on day 1 only).

Chemoradiotherapy was associated with significant reductions in local failure and mortality secondary to cancer. However there was more acute morbidity, including six deaths, in the combined modality therapy group, but late morbidity was similar. Overall survival was similar between the two groups, which was attributed to an early increase in non-anal cancer deaths in the first five years, which disappeared by year 10. Only 11 patients in the chemoradiotherapy group suffered a loco-regional relapse as a first event after 5 years.

In a second trial, The European Organization for the Research and Treatment of Cancer (EORTC) randomly assigned 110 patients with locally advanced (T3-4 or N1-3) anal cancer to receive RT (45 Gy with a 15 or 30 Gy boost) with or without concurrent infusional 5-FU (750mg/m² per day on days 1 through 5 and 29 through 33) plus mitomycin (15 mg/m² day 1 only).

Chemoradiotherapy was associated with a significantly higher pathologic complete remission rate (80 versus 54 %), an 18% higher five-year loco-regional control rate, a 32% higher colostomy-free rate, and higher event-free and progression-free survival. Overall survival was not significantly different and, in contrast to the UKCCCR trail, the incidence of acute and late side effects and treatment-related mortality did not differ between the groups.
Table 3 Multimodality Treatment of Anal Canal Cancers

<table>
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<tr>
<th>Series</th>
<th>Radiation dose (GY)</th>
<th>Complete tumour regression (%)</th>
<th>3-5 year survival (%)</th>
<th>Overall APR/colostomy rate (%)</th>
<th>APR/colostomy for complications (%)</th>
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<td>Allal et al 1993</td>
<td>48-68</td>
<td>66</td>
<td>75</td>
<td>19</td>
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<tr>
<td>Tanum 1992</td>
<td>50</td>
<td>84</td>
<td>72</td>
<td>6</td>
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<tr>
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<td>50</td>
<td>93</td>
<td>77</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Beck and Karuf 1994</td>
<td>30-45</td>
<td>97</td>
<td>89</td>
<td>10</td>
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<tr>
<td>Smith et al 1994</td>
<td>30</td>
<td>98</td>
<td>91</td>
<td>21</td>
<td>0</td>
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<tr>
<td>Bassier et al 1994</td>
<td>30-60</td>
<td>77</td>
<td>81</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Martenson et al (ECOG E7283) 1995</td>
<td>41</td>
<td>73</td>
<td>58</td>
<td>15</td>
<td>0</td>
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<tr>
<td>Bartelink et al 1997 (EORTC)</td>
<td>45-65</td>
<td>80</td>
<td>56</td>
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<td>Amott et al (UKCCCR) 1996</td>
<td>45</td>
<td>39</td>
<td>65</td>
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<tr>
<td>Flam et al (ECOG/RTOG) 1996</td>
<td>45-50.4</td>
<td>82</td>
<td>76</td>
<td>9</td>
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<tr>
<td>Martenson et al (ECOG E4292) 1996</td>
<td>59.4</td>
<td>68</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gabriele et al 1997</td>
<td>50</td>
<td>100</td>
<td>78</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
The need for mitomycin has been questioned since it does not sensitisise tumour cells to the effects of RT, has only modest anti-tumour activity against SCCs and is associated with renal, pulmonary and bone marrow toxicity.\textsuperscript{79,80} The need for mitomycin in curative treatment of anal cancer was addressed in a joint trial from the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) in which 310 patients with anal cancer of any tumour or nodal stage were randomly assigned to combined modality therapy with or without mitomycin.\textsuperscript{76} Patients who received mitomycin had significantly better four-year colostomy-free survival (71 versus 59\%) and disease-free survival (73 versus 51\%), but pathologic complete response rates and overall survival were similar. Grade 4 toxicity (23 versus 7\%) and fatal neutropenic sepsis (4 versus 1 patient) were significantly more common in the mitomycin group. The authors concluded that, despite greater toxicity, the use of mitomycin in a definitive complete response regime for anal cancer was justified.

Cisplatin is more active in the treatment of SCC of other organs than mitomycin. Early uncontrolled studies suggested encouraging colostomy-free and overall survival rates with the substitution of cisplatin for mitomycin in the treatment of anal cancer.\textsuperscript{50-52,81} This has been addressed in two large controlled studies with conflicting results.\textsuperscript{82,83} The substitution of cisplatin for mitomycin in the treatment of anal cancer was not supported by the results of the US Intergroup trial (RTOG 98-11).\textsuperscript{82} On the other hand, the therapeutic equivalence of cisplatin and mitomycin when used in combination with infusional 5-FU concurrent with RT was suggested in the ACT II randomised trial of 940 non-HIV infected patients with anal SCC.\textsuperscript{83} Taken together, this data suggests that 5-FU plus mitomycin remains the standard of care, but 5-FU and cisplatin could also be considered a reasonable approach. There appears to be no role for induction chemotherapy or a continuation of chemotherapy after chemoradiotherapy.

Patients are typically treated with external beam RT using fields that initially encompass the pelvis from the S1-S2 level, inguinal lymph nodes (even if palpably negative), and anus. After a dose of 30 to 36 Gy is reached, the treatment fields are reduced to the low pelvis encompassing the anal tumour and the total dose to the primary tumour is 45 to 50 Gy in daily 2 Gy fractions. If there is palpable or radiographic evidence of inguinal node metastases, a RT boost to the groin is added.\textsuperscript{84}
1.8.3 Persistent or Recurrent Disease

The effects of chemoradiation on anal cancer persist for weeks after completion of treatment. Response is best assessed at least 6–8 weeks after completion. There is currently no consensus as to whether response should be assessed by physical examination alone or in combination with a biopsy. It is also not clear whether biopsy should play a role in the management of those individuals with a complete clinical response.\(^ {19}\)

There is little data available about predictors of local failure. In a retrospective study Renehan and colleagues evaluated the outcomes of 254 patients with anal cancer treated with either radiotherapy alone \((n = 127)\) or combined chemoradiation \((n = 127)\) between 1988 and 2000 at a hospital in the United Kingdom, and found that local failure occurred in 99 (39%) patients and the median time to failure was 20.4 months.\(^ {85}\) Five-year local failure rates were significantly different between those patients receiving radiation alone (52.5%) and those patients receiving combined chemoradiation (35.3%). For patients receiving radiation alone, age, total radiation dose <50 Gy and higher T stage predicted local failure. However, for patients receiving combined chemoradiation, no single factor was predictive of local failure.

The preferred treatment for persistent disease following combined modality therapy is APR. This surgery is radical and associated complications appear to be greater in patients undergoing APR after combined modality therapy.\(^ {86}\) Nilsson and colleagues retrospectively evaluated the outcomes of 35 Swedish patients (21 with persistent disease and 14 with recurrent disease) undergoing salvage APR following loco-regional failure after combined modality therapy for anal squamous carcinoma.\(^ {87}\) Thirteen patients developed perineal wound infection necessitating re-operation, and 23 patients had delayed wound healing (defined as healing time >3 months). In addition 15 patients, 12 of whom had undergone salvage APR for persistent disease, experienced secondary failure. The median survival duration after secondary failure was 19 (range, 1–78) months. In the UKCCCR trial, there were 29 patients who underwent salvage APR; 40% eventually relapsed.\(^ {56}\)

Salvage chemoradiation therapy for persistent disease has also been evaluated.\(^ {84}\) In the Intergroup study evaluating the role of mitomycin, those patients with persistent disease received salvage 5-FU, cisplatin, and 9 Gy EBRT. Of 29 patients treated in this manner, 10 continued to have persistent disease. Nine of these patients went on to salvage APR and six eventually recurred.
1.8.4 Inguinal nodal disease

Metastatic spread to the inguinal nodes can occur in 15-60% of anal cancer patients at some time during the course of the disease. The risk is associated with the size and location of the primary lesion. Suspicious inguinal lymph nodes found at initial presentation should be assessed with FNA or open biopsy. Pelvic irradiation fields for SCC of the anus include the inguinal nodal basins whether metastatic disease is evident or not. For synchronous nodal disease, radiation therapy to the nodal basins or CMT with inclusion of the nodal basins in the treatment field provides good results with initial disease control rates of 65% and 90%, respectively. For persistent inguinal disease, therapeutic lymph node dissection can be offered. Similarly for patients with recurrent or metachronous inguinal disease, lymph node dissection can provide good long-term results, with 5-year survivals over 50% reported. Additional chemotherapy and radiation therapy can be offered as an alternative if the nodal basin has not reached treatment tolerance. Inguinal lymph node dissections in a radiated field are associated with significant wound morbidity due to seroma and infection. In highly irradiated fields, closure with rotational musculocutaneous flaps may decrease morbidity.

1.8.5 Treatment of distant metastatic disease

Approximately 10% of patients with SCC of the anus will have distant metastatic disease at presentation, the usual sites being liver and lung. For patients with inguinal lymphadenopathy or a tumour greater than 5 cm, distant metastases may develop in up to 25% of cases at some point in the course of the disease. The development of distant metastatic disease portends a uniformly poor prognosis. Currently available treatment in this setting is palliative. Salvage chemotherapy using cisplatin-based regimens, often in combination with 5-FU, offer some efficacy. However, complete responses are rare, and duration of response is often short. Radiation therapy for symptomatic metastases can be effective for palliation.
1.9 Defunctioning stomas

Some patients will require a defunctioning colostomy prior to CMT to allow for safe delivery of treatment with the lowest risk of treatment interruption. The indications for pre-treatment colostomies are large bowel obstruction, faecal incontinence usually due to destruction of the anal sphincter by tumour, presence or risk of fistula formation, which usually occurs when macroscopic tumour invades the vagina, and pain. (Table 4)

Table 4: Indications for pre-treatment defunctioning stomas

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cooper et al 2010 $^3$</th>
<th>Sunesen et al 2011 $^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 of 344 patients</td>
<td>20 of 235 patients</td>
</tr>
<tr>
<td>Vaginal fistula</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Obstruction</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Incontinence</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Abscess</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diverting stomas are offered with temporary intent, with reversal planned after completion of organ preserving treatment with CMT. Four different authors noticed in their respective series that this was not necessarily the case.

De Bree and colleagues from the Netherlands reported on 83 patients over a 20 year period. Seven (8%) patients needed defunctioning colostomies prior to CMT. Four (57%) of the 7 patients retained their initially temporary colostomy because of either progressive disease ($n=1$), recurrent disease ($n=2$) or a persistent anal ulcer ($n=1$). One patient with a prophylactic colostomy underwent APR for residual disease. The remaining 2 patients were relieved from their colostomy 3 and 4 months after the initiation of RT, but 1 of them later underwent a diverting colostomy for a late radiation ulcer.
Cooper et al evaluated 344 cases of anal cancer between 1997 and 2007. Thirty five patients treated with radical intent needed a defunctioning stoma prior to CMT. Seven (20%) patients had the stoma reversed subsequently. The reasons for non-reversal were progressive disease ($n = 9$), persistent fistula ($n = 3$), predicted poor function ($n = 4$), cavity formation ($n = 1$), fibrosis ($n = 3$), death from another cause ($n = 2$), patient choice ($n = 3$) and salvage surgery ($n = 2$).

Sunesen et al from Denmark reviewed 235 patients diagnosed with anal canal SCC between 1995 and 2003, of which 20 needed pretreatment stomas. One year after the completion of radiotherapy the only patient with reversal of a pre-treatment colostomy had a second colostomy as a result of faecal incontinence.

A cohort from Groote Schuur Hospital of 31 patients between 2000 and 2004 was published by Robertson et al. Seven patients required stomas prior to chemoradiation. Only one patient had an attempt at closure but subsequently developed faecal incontinence and required re-placement of the colostomy.

From above it can be postulated that if a patient requires a defunctioning colostomy for anal cancer prior to CMT for any indication the patient is likely to have a permanent stoma. The rationale of combined modality treatment as originally described by Nigro et al is organ preservation and in other words, avoidance of permanent stoma. It is thus not clear whether this protocol is most beneficial for this small specific subgroup of patients. It may be that this subgroup of patients actually represents advance disease and that the need for a defunctioning colostomy implies a poor prognostic outcome. Nevertheless, the impression remains that colostomies created before initiation of radiotherapy or chemoradiotherapy for anal cancer are not reversed. Patients should be informed that a pre-treatment colostomy is probably permanent. With this knowledge, the surgeon should plan the operation to achieve a stoma that will best serve the patient long term. A transverse colostomy, with its tendency to prolapse, should be avoided and some authors prefer an ileostomy for which spill-over in the distal limb is uncommon. Ileostomy is not universally accepted and most would still do a loop sigmoid stoma. An end stoma with closure of the distal limb could also be considered as the danger of a closed loop obstruction is very rare. The possibility of more radical surgery in the form of an APR might be suggested. This would mean that patients would avoid the side effects of chemoradiotherapy.
1.10 Complications of chemoradiation

CMT has both acute and chronic side effects. Acute effects include diarrhoea, mucositis, skin erythema and desquamation, and myelosuppression (thrombocytopenia and neutropenia). Late complications, some of which necessitate surgery with or without colostomy, include anal ulcers, strictures, fistulae and necrosis.\textsuperscript{19} Reported late event rates following chemoradiation therapy for anal cancer are in the range of 3\%-16\%.\textsuperscript{86} The inclusion of inguinal radiation fields is associated with epidermolysis, leg oedema and vascular damage.\textsuperscript{89}

In a recent Groote Schuur review, 7\% of patients did not complete their treatment due to toxicity, and 38\% required treatment interruptions. A further 7\% needed permanent stomas for late toxicity.\textsuperscript{1}

Based on the 2 phase III trials, RTOG 98-11 and ACCORD 03, and earlier studies with planned treatment delays, it is clear that any treatment delays in the initiation of, or during chemoradiation therapy are deleterious for patient outcomes. Should treatment related toxicities be a concern, rather than withholding all chemoradiation therapy, chemotherapy may be deferred temporarily if needed, but radiation therapy should not be withheld for prolonged periods unless medically necessary.\textsuperscript{90-93}

The use of mitomycin has been associated with a higher risk of acute hematologic toxicity, typically manifesting as neutropenia. In the RTOG trial, there were four deaths in the mitomycin arm, all due to neutropenic sepsis, compared with one death in the 5-FU alone arm.\textsuperscript{64}

Gastrointestinal side-effects are frequently observed during radiotherapy of malignancies in the abdomen and pelvis. Radiation-induced diarrhoea requires regular symptomatic medications.\textsuperscript{94} Sacral insufficiency fractures after pelvic radiation occur more commonly than previously described. Independent risk factors associated with fracture were osteoporosis, female gender and age greater than 60 years.\textsuperscript{95} Fertility is often impaired after chemotherapy and radiotherapy. Cytotoxic therapy influences spermatogenesis at least temporarily and in some cases permanently.\textsuperscript{96}

Secondary cancers are a known complication of radiotherapy, but there is no clear evidence associated with the Nigro protocol. In a large cohort of 2658 patients of prostate cancer patients the incidence of a secondary malignancy after radiotherapy was not significantly different from that after radical prostatectomy, when adjusted for patient age and smoking history.\textsuperscript{97}
1.11 Fate of a long term defunctioning stoma

Diversion proctocolitis is an iatrogenic disorder caused by surgical diversion of the faecal stream away from the colorectal mucosa. A chronic lymphoplasmocytic inflammatory infiltrate and the hallmark feature, lymphoid follicular hyperplasia, characterize the histopathological changes. Diversion colitis can be asymptomatic or present with blood and mucous discharge and abdominal pain.98

1.12 Complications of APR

Complications from APR are similar to those of any major abdominal procedure, including sepsis, myocardial infarction, pulmonary embolus, and wound problems. There are some specific problems related to APR, although usually described with the operation when it is done for rectal cancer. These include impaired sexual function. There is at least a 50% incidence of significant impotence in men after resection of the rectum for cancer.99

Perineal wound complications are common following APR. In the largest review of perineal wound complications by Christian et al, the overall rate of perineal complications following APR was 35 percent, with 14 percent being major wound complications and 24 percent minor wound complications. Pre-operative radiation appeared to increase the risk of major wound complication for patients with anal cancer.100

A specific problem that can occur intra-operatively during the performance of the rectal dissection is massive venous bleeding from the presacral space. Urethral injury can also occur, but again uncommon when the operation is being done for anal pathology.99

Complications which occur after formation of a stoma include ischemia, retraction, hernia, stenosis, prolapse and fistula.

The operative mortality after an APR should be less than 2%. As with all forms of major abdominal surgery, improved anaesthesia and the use of invasive perioperative monitoring have resulted in a the reduction in mortality from 42% reported by Miles in 1908.99
Chapter 2

Aim

The aim of this study was to evaluate the stoma closure rate of patients needing defunctioning colostomies prior to CMT for anal SCC at GSH. The key objective was to assess if abdomino-perineal resection (APR) should be offered as primary treatment modality for the subgroup of patients needing a defunctioning stoma and CMT.
Chapter 3

Methods

All patients who presented to the Combined Colorectal Clinic at Groote Schuur Hospital with a histologically proven diagnosis of anal squamous cell carcinoma over a 17 year period from 01 April 1995 to 30 June 2012, were included in this study. Prior to April 1995 patients were treated using a different protocol and were excluded. The charts of the patients were retrospectively reviewed.

The Combined Colorectal Clinic is a weekly multidisciplinary team meeting and all management decisions regarding colorectal, including anal, cancers are undertaken there. The team consists of specialist colorectal surgeons, radiation oncologists, diagnostic radiologists, social workers and stoma therapists. The Combined Colorectal Clinic's weekly patient lists and appointment books for the given period were the basis for identifying patients with SCC of the anus. Names were extracted from an electronic database and manually checked in appointment books.

Approvals from the Department of Surgery Research Committee and the Faculty of Health Sciences Human Research Ethics Committee (HREC 429/2012) were obtained prior to accessing data. (Appendix p. 55)

The patient charts were obtained from medical records and a numeric code assigned in order to maintain confidentiality. Both GSH folders for the surgical notes and the separate oncology folders were studied. The National Health Laboratory Services’ DISALAB online results facility was used to verify blood and histology results.

Demographic data including age at presentation, race and gender were recorded to characterize the cohort. Risk factors for anal SCC namely; smoking, HIV status with CD4 count and HPV status were documented. Unfortunately testing for HPV was not routinely done in all patients. Although sexual orientation and sexual practice are important considerations in anal cancer, this information was not part of the original data collection, and was therefore not included in the current study.

Tumour characteristics were documented and subdivided into well, mild or poorly differentiated squamous carcinoma. Staging was documented in the standard TNM format of the American Joint Committee on Cancer Staging system. The maximum diameter of the tumour was also documented. Both anal canal and anal margin cancers were included in the data collection.
The treatment plan was documented as palliative or radical (curative) intent. Data collection included patients treated with palliative intent. Patients with anal margin carcinoma had a wide local excision if it was deemed as resectable with preservation of the sphincter. The histology, specifically the resection margin was documented.

For patients treated with chemoradiation, the radiation dose was either 42.00 Gy in 20 fractions (1995 to May 2003) or 44.20 Gy in 20 fractions (after June 2003), four fractions weekly using 60-Cobalt. Anterior and posterior fields to the pelvis were based on bony landmarks as well as tumour extent. The superior border of the radiation field was placed at the lower border of the sacroiliac joint or the upper border of the acetabulum. The inferior border was placed 2 cm below the anal verge or 2 cm below visible tumour if the tumour protruded from the anal canal. For patients with no inguinal node involvement the lateral border was 1 cm lateral to the widest brim of the pelvic sidewalls. In patients with involved inguinal nodes the lateral border was placed 2 cm lateral to the palpable nodes. Patients without stomas were treated prone. The chemotherapy regimen was mitomycin C 12 mg/m² on day 1 and 5FU 1 000 mg/m² as a continuous infusion on days 1 - 4, i.e. with the first four fractions, and 5FU 1 000 mg/m² with the last four fractions of irradiation.\textsuperscript{1, 38}

All patients were reviewed 6 weeks after completing treatment. If the size of the primary tumour had decreased by more than 50% a further dose of 15.00 Gy in 6 fractions was given to the perineum. Patients with less than 50% response were evaluated for surgery. The response to treatment for patients receiving chemoradiation was assessed clinically at the completion of treatment.\textsuperscript{1, 38} Side effects of radiotherapy and whether a treatment break was needed for severe skin toxicity were noted. The histology of those requiring salvage APR was reviewed to assess residual disease and resection margins.

In the patients who required a stoma prior to chemoradiotherapy, the indication for the stoma, the type of stoma, the closure rate and reason for non-closure were recorded. To evaluate the resectability of these patients pre-radiotherapy the operation notes of the examination under anaesthesia and the comments of the operating surgeon were noted. The staging CT pelvis and abdomen was also studied in order to gain insight in possible surgical options.
Data and variables were collected and analysed on a Microsoft Excel 2010 spreadsheet. The data sheet was password protected to ensure confidentiality. All captured data was kept anonymous.

This study contains mostly descriptive statistics therefore no bio statistical package was used. Numbers, percentages, tables and flow charts were used to describe subgroups.
4.1 Patient demographics

One hundred and forty one patients treated for cancer of the anus during the 17-year period from 01 April 1995 to 30 June 2012 were identified. Sixteen patients were excluded. The reasons for exclusion included either a different histological diagnosis, incomplete histological diagnoses (n=5), or medical records unobtainable (n=11). One hundred twenty five patients were analysed. The demographic characteristics are summarized in tables 5 and 6. There were 58 (46.4%) males and 67 (53.6%) females with a mean age of 56 (±13) years.

The HIV status was reported in 88 patients, and only 10 (11.4%) were positive for HIV. The majority of patients were smokers (n=78), while 21 were non-smokers, and the smoking status was not recorded in 26 patients.

Table 5: Demographics and risk factors of 125 patients with anal squamous cell carcinoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>(46)</td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>(54)</td>
</tr>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Mean</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested</td>
<td>88</td>
<td>(70)</td>
</tr>
<tr>
<td>Negative</td>
<td>78</td>
<td>(89)</td>
</tr>
<tr>
<td>Positive</td>
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<td>Unknown</td>
<td>37</td>
<td>(30)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78</td>
<td>(62)</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>(17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26</td>
<td>(21)</td>
</tr>
</tbody>
</table>
4.2 Tumour characteristics

The mean tumour size was 5.5 cm (range 0 - 12 cm). Seventy two patients (58%) had a tumour greater than 5 cm. The HPV status was not part of routine testing. However 7 patients were reported to have HPV on their histology, and four of these were HIV positive. Fourteen tumours were well differentiated squamous cell carcinoma; 42 were moderately differentiated and 22 poorly differentiated. In 47 patients the degree of differentiation as not recorded. (Figure 3)
4.3 Treatment

One hundred and seven of the 125 patients received treatment with curative intent. (Figure 4) Eighteen patients were offered palliation, either with a palliative stoma or radiotherapy. The main indications for palliation were advanced or systemic disease and patients medically unfit for CMT. (Table 6)

![Figure 4: Treatment intent](image)

<table>
<thead>
<tr>
<th>Table 6: Indication for palliative stomas (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
</tr>
<tr>
<td>Incontinence</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Fistula</td>
</tr>
<tr>
<td>Pain</td>
</tr>
</tbody>
</table>
The patients with anal margin cancer were evaluated if the lesion could be treated with wide local excision (WLE) without compromising the anal sphincters. Eleven such patients were treated as anal margin cancer with a WLE. Three of these needed a second WLE after surgical margins were noted to be involved after the first surgery. None of these patients required a stoma. Six patients were treated with an APR without CMT with good outcomes. (Figure 5) The indications are tabulated in table 7.

Figure 5: Curative treatment in anal SCC
Table 7: Indications and outcome of primary APR in anal SCC

<table>
<thead>
<tr>
<th>Indication</th>
<th>Histological Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Evaluated as rectal pre-op</td>
<td>Involved</td>
</tr>
<tr>
<td>2 Too frail for CMT</td>
<td>Clear</td>
</tr>
<tr>
<td>3 Destruction of sphincters</td>
<td>Clear</td>
</tr>
<tr>
<td>4 Previous radiotherapy</td>
<td>Clear</td>
</tr>
<tr>
<td>5 Previous radiotherapy</td>
<td>Clear</td>
</tr>
<tr>
<td>6 Too frail for CMT</td>
<td>Close</td>
</tr>
</tbody>
</table>

Ninety patients were treated with CMT based on the Nigro protocol. The most common complication was skin toxicity in 37 patients, in which 14 needed interruption of their treatment. Twenty-four patients received a pelvic boost dose after evaluation of response on 6 weeks. (Figure 6)

Figure 6: Skin toxicity of radiotherapy
Salvage APR was offered to 12 patients. The indication and outcomes are summarized in Table 8 and Figure 7.

Table 8: Indications for Salvage APR after CMT

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent disease</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>3</td>
</tr>
<tr>
<td>Non-functioning anus</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 7: Surgical outcomes of Salvage APR for Anal SCC
Thirty patients required defunctioning colostomies prior to CMT with the most common indications being obstruction and incontinence. (Table 9) Only 4 (13%) of these stomas were eventually reversed. One patient had the stoma restored for incontinence post reversal. Three patients from this subgroup needed a salvage APR. (Figure 8)

Table 9: Indications for pre-treatment defunctioning stoma

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>14</td>
</tr>
<tr>
<td>Incontinence</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Fistula</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 8: Outcome of pre-treatment defunctioning stomas
The reason for non-reversal in 58% of these patients was disease progression. Three were lost to follow up and it is presumed that they still had their stomas. (Table 10) Therefore, of the cohort of 30 patients requiring pre-treatment stomas, only one was successfully reversed.

Table 10: Reasons for non-reversal of stomas

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Progression</td>
<td>15</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>3</td>
</tr>
<tr>
<td>Anal stenosis</td>
<td>3</td>
</tr>
<tr>
<td>Incontinence</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Still to be considered</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 11: Pre-treatment evaluation of stoma subgroup

| Not resectable (clinical or radiological) | 13  |
| Patient not fit for major surgery       | 2   |
| Inadequate data retrospectively         | 9   |
| **Resectable**                          | **6** |
Organ preservation is an important endpoint and the rationale behind CMT for anal SCC. In our series 38% of the patients, including anal margin SCC, needed a permanent stoma. (Figure 9)

Figure 9: Permanent stoma in Anal SCC
CMT is currently the standard of care for patients with anal canal SCC with favourable outcomes reported. The good of CMT is cure of the cancer, with natural orifice preservation and avoidance of a permanent stoma. This is achievable in the majority of patients with anal canal SCC who are treated with curative intent. In our study 39 (36%) of the 107 patients treated with curative intent had a permanent stoma at the end of their treatment. Six patients (6%) had primary APR’s, nine (8%) had salvage APR’s and 24 (22%) patients who required pre-treatment defunctioning stoma, the stoma was never reversed. This number is even more significant as this group included patients with anal margin SCC.

In this series 30 (32%) patients with anal canal SCC treated with curative intent needed a temporary defunctioning colostomy to prevent treatment interruption of the CMT. This is significantly higher than reported in other series (8 to10%) incidence of a defunctioning colostomy). In the literature between 0% and 20% of the pre-CMT treatment stomas were eventually reversed. The conclusion of both Cooper et al and Sunesen et al was that pre-treatment stomas must be made with permanent intent. They suggested that these patients should be consented and informed that the stoma is likely to be permanent. This is not currently standard practice at GSH and our patients are treated with a laparoscopic assisted loop sigmoid colostomy with temporary intent.

The most common reason for non-reversal in our series was disease progression in 58% of patients. This figure correlates with that reported in the literature. Obstruction was the leading indication for defunctioning colostomy, which would suggest a more advanced T stage.

Before the introduction of CMT, APR was the preferred treatment for anal cancer. Madden et al reported a case series including 55 patients from our institution during the APR era and they suggested that even large carcinomas of the anal margin could be resected with a fair prognosis. However the early intra-pelvic spread of carcinoma of the anal canal prevented APR from achieving a high cure rate. In the current series, five of the six patients who received an APR as primary treatment for anal SCC achieved clear surgical margins without significant perioperative morbidity.

Lefevre et al reported on 95 patients who had an APR for anal SCC, including eight patients who had APR as primary modality due to a contra-indication to radiotherapy. Five of the eight needed a vertical rectus abdominis myocutaneus flap.
CMT for anal SCC is not universally well tolerated. Radiotherapy caused skin toxicity in 41% of our patients, and 15% of the patients required treatment interruption because of this. Added to this is the systemic side effect profile of chemotherapy, with related mortality. GSH services a large geographical area. Patients are often from poor socioeconomic backgrounds without transport who have to travel long distances to the city to receive regular CMT. This could be avoided with a single admission for surgery.

If a defunctioning stoma is required for SCC of the anal canal, the use of an APR should be considered as an alternative approach. As a result patients would avoid the side effects of CMT. In the long term both groups of patients would have a permanent colostomy. The majority of these patients would not be amenable to primary surgery or will require very radical surgery. The alternative of neo-adjuvant radiotherapy would be counterproductive, as a diverting stoma with CMT would have the same functional outcome. In 6 patients who received a pre-treatment stoma the primary was deemed resectable before the initiation of the CMT. This subgroup should be considered for an APR.

The limitations of this study include its retrospective nature, relative small sample size and the short follow-up. Unfortunately, when one studies a small subgroup within a rare disease it is difficult to obtain a large cohort of patients. As APR is not the current preferred treatment for anal SCC, not all patients were evaluated or adequately documented if they were deemed resectable. The presence of potential pathological nodes is one variable that would potentially change the outcome and the absence of this from the data is a limitation. Nine of the thirty patients needing defunctioning colostomies had inadequate information to clearly label them resectable. This could potentially add to the 6 mentioned above.
Conclusion

This study supports the observations of other authors, that a defunctioning stoma prior to CMT has a very high likelihood of being permanent. Patients should be informed and consented in this regard. Primary APR for anal squamous cell carcinoma had good results in previous older studies, and this was confirmed in this study for the patients treated with this modality. For these reasons, APR should be considered as primary treatment in a subgroup of patients requiring de-functioning stoma, as long as the disease is resectable. Prospective evaluation of this hypothesis with long term follow up is necessary.
References


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<td>AJCC</td>
<td>American Joint Committee on Cancer Staging</td>
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<td>APR</td>
<td>Abdomino-perineal resection</td>
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<td>CMT</td>
<td>Combined modality treatment</td>
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<tr>
<td>CT</td>
<td>Computer tomography</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EUA</td>
<td>Examination under anaesthesia</td>
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<tr>
<td>FBC</td>
<td>Full blood count</td>
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<tr>
<td>FNA</td>
<td>Fine needle aspirate</td>
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<td>GSH</td>
<td>Groote Schuur Hospital</td>
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<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>Human papillomavirus</td>
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<td>LFT</td>
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<td>Positron emission tomography</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
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<tr>
<td>SIL</td>
<td>Squamous intraepithelial lesion</td>
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<tr>
<td>TNM</td>
<td>Tumour, Lymph nodes, Metastasis</td>
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<tr>
<td>U&amp;E</td>
<td>Urea &amp; Electrolytes</td>
</tr>
<tr>
<td>WLE</td>
<td>Wide local excision</td>
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<tr>
<td>5-FU</td>
<td>Fluorouracil</td>
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7th August 2012

Dr C Kloppers
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Kloppers,

RE: PROJECT 2012/076

PROJECT TITLE: Should APR be considered when a defunctioning stoma is required for anal cancer

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE
22 August 2012

HREC REF: 429/2012

Dr C Kloppers
c/o Prof P Goldberg
General Surgery
F-17
NGSH

Dear Dr Kloppers

PROJECT TITLE: SHOULD APR BE CONSIDERED WHEN A DEFUNCTIONING STOMA IS REQUIRED FOR ANAL CANCER?

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above mentioned study.

Approval is granted for one year till the 28 August 2013.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form, if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
1 October 2012

Dr C Kloppers
Division of General Surgery
J.45, Old Main Building
Groote Schuur Hospital
Observatory
7925

Dear Dr Kloppers

RESEARCH: Should APR be considered when a defunctioning stoma is required for anal cancer?

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) No patient folders may be removed from the premises or be inaccessible.
e) Please introduce yourself to the person in charge of an area before commencing.

I would like to wish you every success with the project.

Your sincerely

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