Research Article

Outcomes of Salvage Surgery for Anal Squamous Cell Carcinoma: Results from a Tertiary Centre

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Abstract

Introduction: Squamous cell carcinoma of the anus (SCCA) is a rare cancer with a lifetime incidence of 0.2%, however the incidence is increasing. First line treatment is chemoradiotherapy (CRT), however approximately 20% of patients will have 'recurrent' or 'persistent' disease. These patients then undergo 'salvage surgery' consisting of an abdominoperineal excision and reconstruction, which is associated with serious morbidity. Five-year survival rates range from 23-69%. The aim of this study is to examine the post operative and oncological outcomes from our tertiary care regional anal neoplasia centre.

Methods: Retrospective case series including all consecutive patients undergoing salvage surgery for SCCA from 2017 to 2023 were included. Demographical data, pre-operative parameters including TNM staging, resection margin status (R0 vs R1), post operative complications particularly wound complications were collected. Patient survival and time to recurrence were measured over this 6-year period and information regarding surveillance following completion of CRT and salvage surgery gathered.

Results: Twenty-five patients were included. Our overall survival and disease-free survival rates were 51% and 57% over a six-year period. No patients died within 30 days of their operation. Seven patients (28%) died during follow-up period with median survival of these patients was 12.7 months (IQR: 8.3 - 18.2). Eight patients (32%) developed recurrent disease. Median time to recurrence was 5.3 months (IQR: 3.3 - 12.5). R1 resection showed a trend towards higher chance of recurrence and lower survival rate compared to R0 resections but was not statistically significant. Of note, two patients with R1 resections had re-recurrence picked up on early CT and MRI at 2 and 3 months respectively. Two thirds of patient with recurrent SCCA had T3/T4 tumours. Only three patients were screened for HIV.

Conclusions: Our survival and recurrence rates are in keeping with reported literature. There are limited data regarding the follow up and imaging of the post salvage surgery for SCCA. We propose close follow up of SCCA following CRT with consideration of High Resolution Anoscopy and early imaging in R1 resections may aid decision making for systemic cancer treatment.

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Introduction

Anal cancer is a rare malignancy, and has a lifetime incidence of 0.2% [1], accounting for less than 2.5% of all gastrointestinal malignancies [2]. However the incidence of anal cancers specifically squamous cell carcinoma

of the anus (SCCA) is rising by 2.7% annually [1,3]. HPV (human papilloma virus) infections are a major factor in anal cancer oncogenesis, with 80-85% of anal cancer cases associated with HPV [4,5]. Other risk factors associated with anal cancer include immunosuppression and HIV, smoking, and anal intercourse [6].

Nigro et al. showed that SCCA responded to initial treatment with chemoradiotherapy (CRT) [7]. The ACT II trial showed 90% of patients had a complete response at 26 weeks with 5-fluorouracil and mitomycin combined with radiotherapy [8,9]. Other regimens have been explored to try and reduce toxicity and side effects, including cisplatin and intensity modulated radiation therapy [10].

After completion of CRT follow up consists of digital rectal examination at 8-12 weeks, with biopsy verification if any clinical signs of persistent disease. Current guidelines suggest clinical examination every three to six months for up to two years, and after this every six to twelve months until five years is reached. In terms of imaging MRI scans every six months for the first three years has been recommended however the use of CT scans has been debated, as recurrence usually occurs locally [11,12]. Patients with possible persistent disease can be followed up closely with further examinations to allow them to reach the 26-week timepoint as per the ACT II trial. In these patients' observation and examination is recommended at 3 monthly intervals. PET/CT imaging can help to differentiate between inflammation and persistent disease [13].

There is a group of patients who have recurrent or persistent disease despite CRT. Approximately 20% of patients will have locoregional failure after CRT [14,15] for whom salvage surgery, if feasible, is the next step [12]. Salvage surgery consists of an abdominal-perineal excision of rectum (APER) which can extend to a pelvic exenteration if there is involvement of other organs / compartments. The operation confers significant morbidity, particularly with wound healing. Often a wide incision is needed in the perineal area and primary closure can be challenging due to previous radiotherapy which often necessitates a reconstructive flap. Reported overall five year survival rates of APER for SCCA range from 23% to 69% [16-19].

The aim of salvage surgery is curative in the majority of cases, and patient selection is important. There is consensus in literature that a negative resection margin is key for a good oncological outcome. A R1 resection shows microscopic tumour at the resection margin whereas an R0 resection shows clear margins with no tumour involvement. Yet there are resections whereby the margin is clear, but tumour is less than one millimetre from the resection margin. These are often given an R1 status but the recurrence rates from these resections are unclear. Furthermore, there is a lack of consensus on follow up protocol after salvage surgery.

Although disease recurrence in this group of patients has a poor outcome, there can be options for further surgery or palliative systemic treatments.

Objectives

1. Our primary outcome is to determine our overall survival and disease-free survival rates compared with the literature in salvage surgery for anal SCC.

2. Our secondary outcome is to assess our follow up protocol for patients post-operatively after salvage surgery and frequency of follow up and use of further imaging.

Methods

This is a retrospective study of all patients undergoing salvage surgery for SCCA from February 2017 to December 2023 at the Royal Liverpool University Hospital, which is a tertiary centre for the management of anal cancer in the Northwest of England. All patients underwent standardised CRT or primary radiotherapy. Those who were diagnosed with persistent or recurrent disease were advised to go onto have salvage surgery following multi-disciplinary team discussion.

Salvage surgery consisted of APER with perineal closure +/- flap reconstruction. Electronic patient records were used for data collection. Patient's demographic data were gathered including age, sex, BMI, ASA, HIV status and whether they were immunocompromised. Pre-operative TNM staging was recorded, and further details included time to operation, perineal closure method, post-operative wound healing and post-operative complications using Clavien-Dindo classification. Post-operatively the R status and tumour size were recorded. Patient survival and time to recurrence was calculated over the 6-year follow up period.

Statistical analysis was done using GraphPad Prism. Kaplan Meier curves were generated to show overall survival (OS) and disease-free survival (DFS). A p-value of less than 0.05 was considered statistically significant. Fisher's test was also used to see if there was any correlation between post operative complications and survival/ recurrence.

Results

Twenty-five patients were included. Sixteen were female (65%) and nine patients were male (35%). The median age was 59 years (IQR: 72-53), median BMI was 26.5 kg/m^2 (IQR: 30.83 - 23.4) and median ASA was 2 (IQR: 1-3). Four patients were diagnosed as diabetic (16%). Ten patients were non-smokers (40%), thirteen patients were ex-smokers (52%), and two patients were smokers (8%). In our patient selection, three patients were immunocompromised with two patients diagnosed as HIV positive, and one who is immunocompromised due to medication for a renal transplant.

Table 1: Demographical data.

	Number of patients (n=25)
Male	16
Female	9
Age (median)	59
BMI (median)	26.6
ASA (median)	2
Smoking status	
Smoker	2
Ex-smoker	13
Non-smoker	10
Diabetes	4
Immunocompromised	
HIV positive	2
Renal Transplant	1

All patients underwent CRT except for two individuals who only had radiotherapy as they were considered high risk for chemotherapy. Of the 25 patients included, ten had persistent disease, and fifteen developed recurrent disease. The median wait to surgery was 25.5 days (IQR: 19-33). Table one shows the TNM staging of the patient cohort. There were no deaths within 30 days of the operation. Eight patients (32%) were diagnosed with a recurrence disease post-operatively and seven patients died (28%). Of the population studied overall, 5 yr survival was 51% and disease-free survival was 57% (Figure 1). The median time to recurrence was 5.3 months (IQR: 3.3 - 12.5). Kaplan Meier survival curves were generated for persistent disease versus recurrent disease. There was no statistical difference between these groups in terms of survival with a p value of 0.42.

In total thirteen patients (52%) had an R1 resection, and twelve patients (48%) had an R0 resection. Survival curves were plotted for both groups (Figure 2). There is a trend for R1 resections to have a lower survival rate however, significance was not reached (p= 0.09). Patients with R1 resections also tended to have lower disease free survival rate compared to R0 resections however again significance wasn't reached (p=0.06).

Figure 3 shows survival curves for patients with different pre-operative nodal status. This showed no difference in survival (p=0.25) or disease free survival (p=0.89) between patients with different nodal status.

Post-operative complications were classified by the Clavien Dindo system. Ten patients had Grade 1 complications (40%), twelve patients had Grade 2 complications (48%), and two patients had Grade 3 complications (8%) both of which required return to theatre. In terms of wound morbidity ten patients suffered complications. Six patients had a superficial dehiscence, two had a deep dehiscence and three had an infection of the flap with one patient having a concurrent abdominal wound infection. The majority of these were handled conservatively, however two patients required a vacuum assisted closure (VAC) therapy, and one patient needed a return to theatre. There was no correlation between post-operative complications and survival (p=0.38) or recurrence (p=0.39).

Post operative follow-up was variable. At twelve months 16% had no follow-up appointments, 28% of patients had one follow-up, 28% had two follow up appointments, and 24% had three reviews. Post operative imaging protocol was variable, with eight patients having CT scans in the first twelve months and six patients had MRI scans in the first year. One patient had a PET scan, and another had an EUA post-operatively. Interestingly, only three patients in the cohort were tested for HIV status.
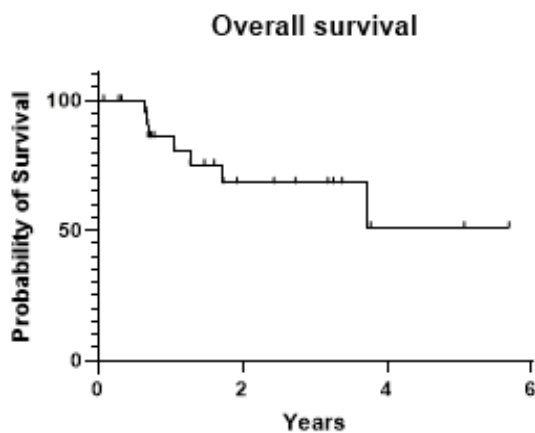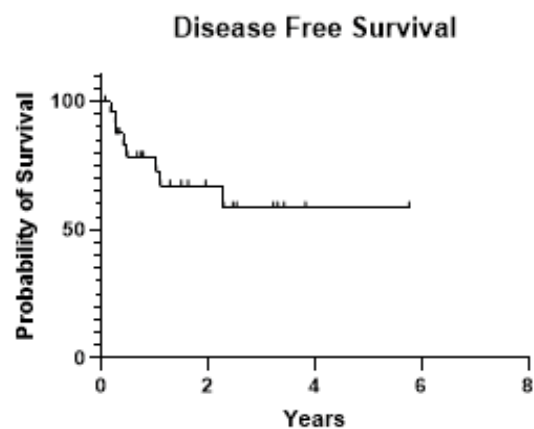

Figure 1a

Figure 1b

Figure 1: Figure 1a shows the overall survival for the patient group (51%), and figure 1b shows disease free survival for entire patient group (57%).
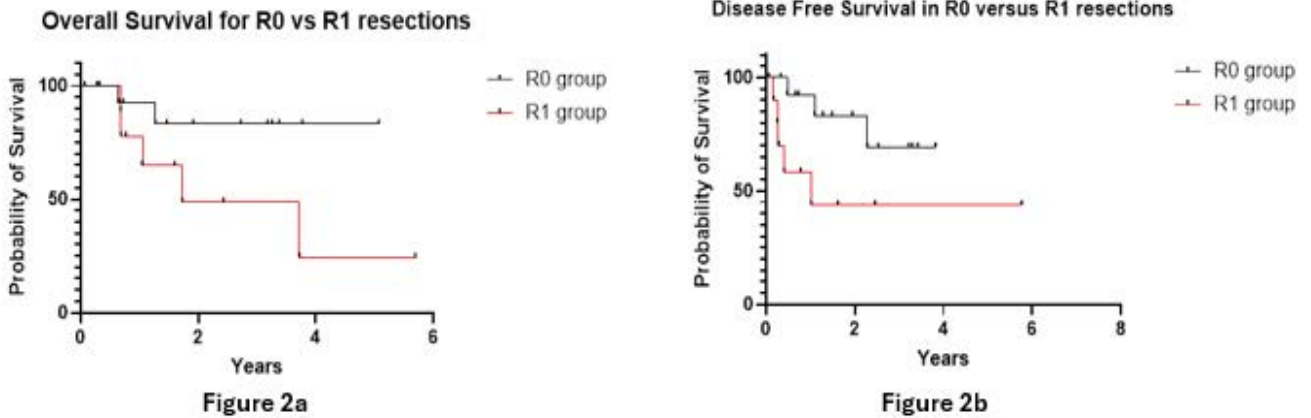
Figure 2a

Figure 2b

Figure 2: Overall survival for R0 vs R1 resections in Figure 2a (p=0.09) and disease free survival for R0 vs R1 resections in figure 2b (p=0.06.
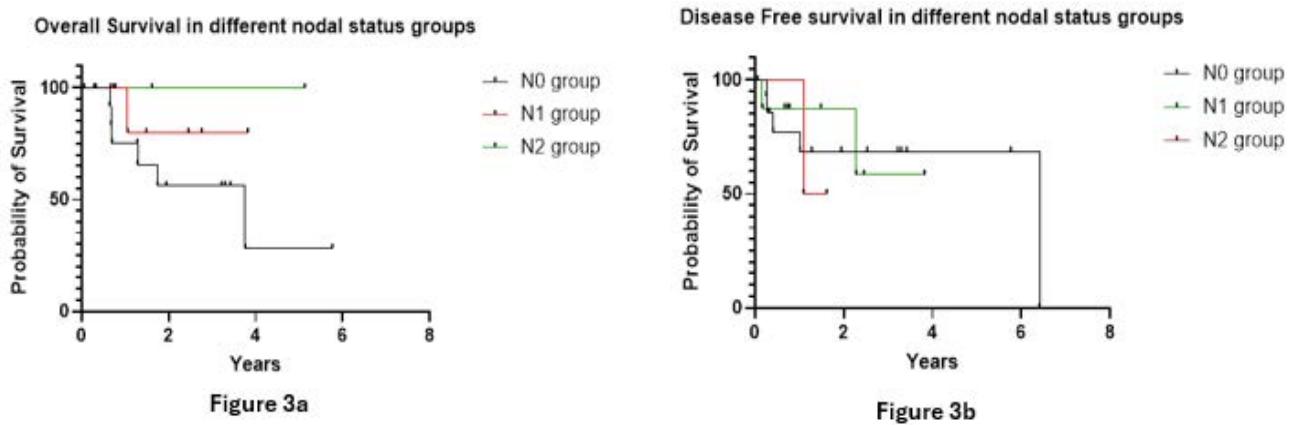

Figure 3a

Figure 3b

Figure 3: Figure 3a shows the overall survival curves between different pre-operative nodal status groups (p=2.6), Figure 3b shows disease free survival between the different nodal status groups (p=0.89)

Table 2: Pathological data for persistent and recurrent patient groups.

	Persistent (n=10)	Recurrent (n=15)
T0	1	0
T1	1	1
T2	5	2
T3	1	3
T4	2	7
Tx	0	2
N0	6	9
N1	4	4
N2	0	2
M0	9	10
M1	0	2
Mx	1	3
Median tumour size (mm)	37 (range 21-145)	34 (range 19-80)

R0 resection	5 out of 10	9 out of 15
R1 resection	5 out of 10	6 out of 15
Number of patients with locoregional failure post op	2	7
Number of patients died	2	5
Median time to recurrence	7.6 months (n=2)	5.31 months (n=6)

Discussion

Our overall survival and disease-free survival rates of 51% and 57% are in keeping with oncological outcomes reported in the literature. This falls within a similar range of outcomes reported from one the largest systematic reviews done on survival and recurrence after salvage APR (20). There was also no mortality within 30 days of the operation, in keeping with existing evidence. Although our data did show a trend for a lower survival rate with an R1 resection, it was not statistically significant. R1 resections are considered to be a major predictor in poor prognosis after salvage surgery [21,22]. It is likely that our sample size is too small

to be able to show this trend. Our data set showed a trend between recurrence and an R1 resection however it did not reach significance likely due to the small sample size. It is unsurprising that R1 resections are linked to recurrence, however it does emphasise the importance of negative resection margins in salvage surgery.

This study highlights the importance of close follow-up following completion of CRT as two thirds of patients in our cohort with recurrences had T3/T4 tumours and can be considered as advanced disease. This makes the case for using High Resolution Anoscopy (HRA) for following up patients after completion of CRT. The National Comprehensive Cancer Network (NCCN) guidelines recommend that post treatment surveillance with HRA and inguinal lymph node exam every 3-4 months for the first 2 years may help diagnose SCCA recurrences at an early stage. HRA and anal cytology has already been evaluated in the screening for AIN and anal SCC in high risk groups [23,24]. Adding these methodologies into practice for surveillance post salvage surgery could allow us to catch early recurrence of disease and allow early consideration of systemic cancer therapeutics. Furthermore, developing convolutional neural networks using AI for lesion recognition in HRA should be explored [25].

There is evidence to suggest that pathological nodal status can be an indicator of a poor outcome [26,27]. We therefore examined whether clinical nodal staging had any effect on survival or recurrence. There was no correlation between pre-operative nodal status and survival/ recurrence in our data. Our patient group is small though and this may be worth examining this in a larger patient series. Other factors that have been reported to be predictors of local recurrence after salvage surgery include higher T stage [28] and lower radiation dose [29].

It has been suggested that persistent disease could be more aggressive than recurrent disease as it is radio-resistant and therefore has a poorer prognosis. Akbari et al found that post-operatively patient's diagnosed with persistent disease had a 5 year survival of 31% compared to 51% for recurrent disease [26], however this result has not been replicated by other studies. We found no difference in survival between persistent and recurrent disease.

Interestingly two patients had R1 resections but with small margins. One had a 1mm margin to the diathermy edge and the other had 0.2mm margin from the circumferential resection margin. Both patients are still alive at five and three years' post-operatively. Interestingly Bignell et al reported a range of 0.9-20mm in their resection margins, and found no statistical difference between the median resection margin in those that developed recurrence and those that didn't [2]. Gaining a negative resection margin is key to reduce risk of recurrence, but there is uncertainty as to how close these resection margins can be.

Our study has shown the variability in follow up and imaging. Of note we did have two patients with very early recurrences picked up on MRI and CT at two and three months post-operatively. Both patients had R1 resections, and so it is unsurprising that they developed recurrences. However, it raises the question of whether early imaging post-operatively can be beneficial in R1 resections and aid decision making for further systemic treatments (e.g. palliative chemotherapy).

There are limitations in this study. It has a small sample size, is retrospective in nature, which limits the conclusions that can be drawn from it. However, our findings add to the limited data set available in literature highlighting the importance of close follow up after CRT with special consideration for HRA, re-visiting the definition of an involved resection margin comprehensively and need for surveillance protocols for patients following salvage surgery.

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