Research Article

Analysis of outcomes achieved with squamous cell carcinomas of the anus in a single university hospital over the last two decades: clinical response rate, relapse and survival of 190 patients.¹

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Running head: Anal cancers.

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Synopsis: Anal cancers have been treated with radical primary chemoradiotherapy in the last two decades in our institution. Complete response occurred in 92.6% of patients but 23% had subsequent recurrence. Salvage abdominoperineal resection was performed in 41% of patients with locoregional failure (either residual or recurrent disease). Five-years cancer-specific survival was 69%.

Authors contributions

Gianpiero Gravante, Mohamed Elshaer, James Andrew Stephenson, Joseph H Mullineux, Mohamed Akil Dilawar Gani, David Sharpe: acquisition of data, analysis and interpretation of data; drafting the article and final approval of the version to be published.

Subramaniam Vasanthan, Ahmed Osman, Justin Yeung, Michael Norwood, Kirsten Boyle, Andrew Miller, David Hemingway: conception and design, interpretation of data; revising the article critically for important intellectual content; and final approval of the version to be published.

Abstract

Background and Objectives: We reviewed our series of anal squamous cell carcinomas (ASCC) treated over the last two decades. **Methods:** ASCC patients undergoing treatment at the Leicester Royal Infirmary between 1998 and 2016 were selected. Age, gender, pathological tumor characteristics, treatment adopted, the overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS) at five-year follow-up were recorded and calculated. **Results:** A total of 190 ASCC were reviewed, of these 64.2% (n=122) received primary radical chemoradiotherapy. Complete response rate was 92.6% (n=113) and four patients with residual disease underwent a salvage APER. Twenty-eight patients experienced recurrent disease (23.0%) either systemic (n=8), local (n=14) or both (n=6); six had a salvage APER. Complete follow-up data are available for 63.1% patients (77/122). Overall, the locoregional failure rate of primary chemoradiotherapy (residual + recurrent disease) was present in 29 patients (29/122; 23.8%). OS was 41.6% CSS was 69.2% and DFS 60.0% at five years follow-up. **Conclusions:** In our series of ASCC primary chemoradiotherapy had achieved significant initial complete response rates, however long term-follow ups still present systemic and local recurrences. APR is able to treat 30% of the

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pelvic recurrences (6/20), the others are either associated with systemic disease or locally inoperable masses.

Keywords: Anal squamous cell carcinoma, chemoradiotherapy, recurrences, survival.

Introduction:

Anal cancer (AC) represents 2.4% of all gastrointestinal tumours and affects 1 in 100,000 males and 3 in 100,000 females each year [1-3]. Anal squamous cell carcinoma (ASCC) is the most frequent tumour (85%), in addition to adenocarcinomas (10%), neuroendocrine tumours, malignant melanomas, lymphomas and mesenchymal tumours [3, 4]. More than half of the newly diagnosed patients are aged 65 or more, with a lifetime risk is 1 in 795. ASCC incidence has increased in the last decade because of its association with the human immunodeficiency virus type 1 and human papillomavirus type 16; almost 91% of anal cancer cases in females and 75% in males are found to be HPV positive [5].

Standard treatment of ASCC supported by level 1 evidence consists of primary radical chemoradiotherapy including 5-Fluorouracil and Mitomycin C and radiation doses of 50 to 60 Gray, which results in complete response in 75-86% of patients [6, 7]. Nevertheless, approximately 27% of patients will experience persistent disease or local recurrence after definitive treatment with chemoradiotherapy and need salvage abdominoperineal resection of the anorectum (APER) [6, 8]. Response to chemoradiotherapy may be immediate or take several months; the median time to complete response is 3 months [3] although some tumours may take up to 12 months. Therefore, long term follow-up is recommended for ASCC patients to monitor response to therapy over time and detect recurrence [9]. The reported five-year overall survival for ASCC is 64% [10, 11].

The aim of our study was to review our activity over the last 20 years with the management of ASCC in a large university hospital and report the long term clinical and oncological outcomes achieved.

Materials and Methods

A retrospective study was performed on a consecutive series of patients affected by ASCC at the Leicester Royal Infirmary (LRI) between October 1998 and September 2016. Excluded were rectal cancers (including anal adenocarcinomas extending to the anal canal) and non-squamous cell anal cancers (i.e. melanomas).

The colorectal unit has a prospectively maintained database which was interrogated; data collected included basic demographics, local response to chemoradiotherapy, date of surgery, reason for surgery (partial response or recurrence following complete initial response). Histological and radiological reports were obtained from hospital electronic databases. Survival data were calculated from patients' follow-up.

LRI Protocol for the management of anal cancers:

1) Diagnosis and staging

Patients underwent assessment including a medical history, physical examination with digital rectal examination. Suspected anal cancers required a definite histological diagnosis to avoid inappropriate treatment of benign disease or malignancies of other histological types, usually obtained at examination under anaesthesia (EUA). Since 2009 all patients being considered for radical treatment also underwent a contrast enhanced computed tomography (CT) of the chest, abdomen and pelvis, and an anal protocol pelvic magnetic resonance (MRI) to complete the staging. Pelvic MRI is the main radiological modality for local staging

unless contraindicated (i.e. presence of metallic objects), in which case only CT is used. Furthermore, a PET CT scan is considered in patients who are being assessed for resection of locally advanced (T4) or metastatic (M1) anal cancer when identified on CT or MRI.

2) Treatment

Since 1998 the treatment differed for anal canal and anal margin tumours (Fig.1). Primary treatment for anal canal tumours consisted in radical chemoradiotherapy, administered to all patients without metastatic disease or with potentially resectable metastases. In patients without inguinal nodal disease the radiation field included the inguinal nodes if the local cancer staging was T3 or T4. If there was proven metastatic disease in the inguinal nodes the patient was considered for a radical block dissection of those nodes, usually performed in conjunction with a plastic surgeon, and the primary lesion treated with chemoradiation without irradiating the inguinal lymph nodes. Patients that already had a pelvic radiation from previous malignancies (i.e. rectum, prostate) were submitted to an APER as initial treatment; patients unfit to receive primary chemoradiotherapy were referred for radiotherapy only or palliative treatments. Differently, anal margin tumours have been treated with local excision if the diameter is smaller than 5 cm (T1 and T2) and the surgical resection margins were predicted not involved, or chemoradiotherapy if greater than 5cm (T3 or T4) or the excision could have produced involved margins. Adjuvant chemoradiotherapy or chemotherapy was eventually added following local excisions or APERs, respectively, in those patients with anal tumours and unexpected involved surgical margins at the histological examination.

Until 2013 radical chemoradiotherapy followed the regime used in the Anal Cancer Trial I (ACT I) protocol [12]. Radiotherapy consisted of two phases, phase I of 45 Gy in 25 fractions administered with 6MV/10MV photons (dependent on the patient's size), and if

indicated phase II of 15Gy in 6 fractions administered with electrons 4-6 weeks after the end of phase I. Concurrent chemotherapy consisted in Mitomycin (MMC) administered on day 1, 5 Fluorouracil (5-FU) on day 1-4 and day 21-25. From 2013 radical chemoradiotherapy followed the regime used in the Anal Cancer Trial II (ACT II) protocol [13]. Radiotherapy consisted of two phases, 30.6Gy in 17 fractions and 19.8 Gy in 11 fractions administered with 6MV/10MV photons dependent on the patient's size. The radiation field normally included the groin nodes therefore an en-block nodal dissection was reserved only for patients with residual or recurrent nodal disease following chemoradiotherapy. Chemotherapy consisted in Mitomycin (MMC) administered on day 1, 5 Fluorouracil (5-FU) on day 1-4 and day 21-25.

3) Follow-up

After 6 weeks from the end of the treatment patients that received chemoradiotherapy underwent a clinical assessment during an outpatient visit and a second EUA with inspection of the perineum, digital anal examination and groin examination with biopsy of any eventual residual disease. Biopsies were conducted until recurrent disease was proven histologically or the ulceration completely healed. From 2013 a radiological follow-up at 6 weeks from the end of the treatment (either chemoradiotherapy or surgery) was also introduced to assess the eventual presence of local or metastatic disease, from 2014 this was extended also at 6 and 12 months. The radiological follow-up was performed with a CT of the chest, abdomen and pelvis and a pelvic MRI. A second MDT discussion followed: if no residual disease was present then the clinical follow-up consisted in outpatient visits at the LRI every 3 months for the first two years, then every 6 months for the 3rd and 4th year, then one last visit at 5 years. If perianal residual disease was confirmed histologically then a salvage APER was

considered for patients without metastatic disease or with metastatic disease deemed resectable, associated with an en-bloc groin lymph nodes dissection if these were involved. If residual disease was present in the lymph nodes alone than only the groin dissection was performed. If recurrent disease manifested clinically at follow-up after an initial complete response to chemoradiotherapy then the same radiological staging (CT of the chest, abdomen and pelvis and a pelvic MRI) and surgical approach were used.

The primary outcome of this study was the response rates following primary radical chemoradiotherapy. Locoregional failure was defined as biopsy-confirmed tumour recurrence or persistent residual disease in the pelvic or inguinal regions [6]. The secondary outcome was the overall survival (OS), cancer specific survival (CSS) and disease free survival (DFS) following initial complete response, residual disease and recurrent disease for those patients that underwent primary radical chemoradiotherapy and achieved 5 years follow-up as identified via the surveillance program. OS was defined as patients who were alive as documented by the last clinic, date of the latest blood results conducted for any reasons and available in the hospital database, endoscopy or radiology visit. CSS was defined following exclusion of patients that died for causes not related to the ASCC and calculated as patients alive (either with or without ASCC) / patients alive (either with or without ASCC) + patients that died because of the ASCC. DFS was defined following exclusion of patients that died for causes not related to the ASCC and calculated as patients alive without ASCC / patients alive (either with or without ASCC) + patients that died because of the ASCC. Locoregional failure was defined as biopsy-confirmed tumour recurrence or persistent residual disease in the pelvic or inguinal regions [6].

Statistical Analysis

All data were inserted into an Excel database (Microsoft, Redmond, Washington – United States) and analyzed with the Statistical Package for the Social Sciences Windows version 20.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics used were the mean $\pm$ standard deviation for continuous parametric variables, the median and range for continuous non-parametric variables and frequencies for categorical variables. Normality assumptions were demonstrated with histograms and the Kolmogorov/Smirnov test.

All calculations of OS and DFS at five year follow-up were performed using time-to-event analysis (Kaplan-Meier) and curves presented. A *P* value less than 0.05 was considered statistically significant.

Results

A total of 190 patients affected by anal cancers were treated in our institution during the study period. Of these, 135 (71.1%) were cancers involving the anal canal, 40 (21.1%) the anal margin and for 15 patients (7.9%) this information was not available in the histological report. Thirteen patients (6.8%) received palliative treatments only (6 from the anal canal, 7 of unknown location), 26 patients (13.7%) radiotherapy only (11 from the anal canal, 8 from the anal margin and 7 unknown) and one patient chemotherapy only (0.5% - unknown location) because of their general comorbidities that prevented more aggressive therapies. Twenty-eight patients (14.7%) received an operation as their initial treatment: 26 anal margin cancers had a wide local excision and two anal canal cancers had an APER because of a previous irradiation of the pelvis (one for a rectal cancer and one for a prostate cancer).

Primary chemoradiotherapy group

The remaining patients (n=122, 64.2%) received primary radical chemoradiotherapy as initial treatment of their ASCC. These corresponded to 116 anal canal cancers and 6 anal

margin cancers. There were thirty-five males (28.7%) and 87 females (71.3%), mean age was 63 years $\pm$ 12. One patient (0.5%) experienced a perforation caused by colitis while receiving the chemoradiotherapy, underwent an emergency subtotal colectomy but died of multiorgan failure on the 10th postoperative day. Nine patients had residual disease at the end of the treatment (complete response rate = 113/122, 92.6%): four patients underwent a salvage APER and the remaining received palliative therapies because the residual disease was considered inoperable.

At the time of the data analysis, twenty-eight patients out of 122 experienced recurrent disease (23.0%): fourteen patients had pelvic recurrences only, eight systemic recurrences (involving lung, liver, and paraortic lymph nodes) and six both. Of the fourteen patients with pelvic recurrences six had a salvage APER while eight underwent palliative therapies because the disease was considered inoperable. Therefore, twelve APERs (12/122; 9.8%) were performed in our group, four for residual disease at the end of the chemoradiotherapy and eight for recurrent disease. Three patients with recurrent disease underwent an additional procedure: one patient had an associated groin dissection, one a liver resection and one a total abdominal hysterectomy and bilateral salpingo-oophorectomy due to the extensive amount of local invasion.

Overall, the locoregional failure rate of primary chemoradiotherapy, defined as residual + recurrent disease at the end of the treatment, was present in 29 patients (29/122; 23.8%): nine patients with residual disease, fourteen patients with pelvic recurrences only and six patients with both pelvic and systemic recurrences. Pelvic recurrences manifested after 23 months from the initial treatment (range 7-88 months).

Overall and disease-free survivals

Out of 122 patients that received primary radical chemoradiotherapy 45 patients (45/122; 36.9) are alive but have not yet reached the 5 years follow-up, therefore complete follow-up data are available for the remaining 77 patients (77/122; 63.1%).

Forty-five patients are alive (OS: 45/77; 58.4%, CI95% 47.4%-69.4%) and 32 (32/77; 41.6%, CI95% 30.5%-52.6%) dead at five-year follow-up. Mean OS is 46.4 months (95% CI 42.1-50.8 months; Fig. 2). Of the 45 patients alive at five years, 39 were disease-free (39/45; 86.7%) and six had recurrent or residual disease (6/45; 13.3%): five patients had pelvic disease, one systemic (lungs, splenic and distant lymph nodes). Among dead patients 12 (12/32; 37.5%) were disease-free at the time of death whilst 20 (20/32; 62.5%) had recurrent or residual disease (10 pelvic, five systemic, five both). Systemic disease involved the lungs in six patients, liver in 5 patients, and the paraortic lymph nodes in one patient.

In total fifty-one patients were disease-free (51/77; 66.2%, CI95% 55.6%-76.8%) and 26 had residual or recurrent disease (26/77; 33.8%, CI95% 23.2%-44.4%) at five-year follow-up: 15 patients had pelvic disease; six patients had systemic disease, and five patients both. After exclusion of patients that died for causes not related to the ASCC (n=12), CSS was 69.2% (45/65; CI95% 57.9%-80.4%) while DFS was 60.0% (39/65; CI95% 48.0%-71.9%) at five-year follow-up. Mean DFS was 47.6 months (95% CI 43.1-52.1 months; Fig.3). The earliest systemic recurrence manifested at 6 months of follow-up, the earliest pelvic recurrence at 7 months of follow-up. Of note, among patients that died for causes unrelated to ASCC there were 5 new primary cancers: one meningioma, one oesophageal, one lung, one pancreatic and one gastric carcinoma.

Discussion

Definitive chemoradiotherapy (CRT) is recommended for all patients with ASCC [12, 14], and a recent large study examining the adherence to this recommendation revealed that

61.5% of patients with stage I AC received CRT. The remaining patients either received radiotherapy (4.8%) or surgery only (33.7%) - elderly males with small or low grade tumours were more common to undergo surgical excision alone [15]. In our study, the majority of our patients received combined definitive CRT (64.2%) while 13.7% of patients received radiotherapy only because of their comorbidities, and 14.7% of patients underwent either wide local excision or primary APER due to previous pelvic radiotherapy.

Complete response rate following primary chemoradiotherapy is one of the main clinical outcomes measured in anal cancer trials [10] and depends on the regimen adopted and on the timeframe selected for the assessment between the end of the treatment and the clinical evaluation [11]. Assessment of the response after CRT is usually performed at 6-12 weeks from the end of the treatment. In the ACCORD-03 trial the complete response rate was 79% at 8 weeks [16]. In a randomised controlled trial comparing 5-FU vs. 5-FU/MMC Flam and colleagues reported complete response rates of 86% and 92.2% at 4-6 weeks respectively [17]. In the UK ACT II trial the complete response rate was 90.5% with 5-FU/MMC/RT vs. 89.6% with 5-FU/cisplatin/RT at 26 weeks [13]. Interestingly, 72% of patients with no clinical response at 11 weeks showed a complete clinical response at 26 weeks [11], suggesting that an early assessment could expose the patients to the risk of unnecessary surgery [11]. . In our series the post-chemoradiotherapy assessment was conducted at six weeks from the end of the treatment using imaging and EUA and complete response rates were observed in 92.6% of patients.

Patients with ASCC may experience local disease recurrence which is the main pattern of relapse post CRT [10]. A study by Kapacee et al. on 148 patients showed a local recurrence rate of 15%. The authors found that tumour size > 5cm and involvement of over two-thirds of anal canal circumference to be predictors of local recurrence [6]. In the study of Flam and colleagues the local recurrence rate was 16 % at four years [17], while the UK ACT

II trial presented a local relapse rate of 11% with MMC and 13% with Cisplatin [13]. In contrast, two different RCTs reported higher local recurrence rates (RTOG 98-11 and ACCORD-03). In RTOG 98-11 trial, local recurrence rate was 25% and 33% with 5-FU/MMC vs. 5-FU/cisplatin respectively [18], while in the ACCORD-03 trial, the overall local recurrence rate was 19% at five years [16]. In our series, the local recurrence rate was 16.4% (20/122), which is comparable to the main RCTs reported in the literature.

OS was reported by Flam and colleagues to be 71% in 5-FU group and 78.1% in 5-FU/MMC group [17]. In the UK ACT II trial the three-year OS was 85% and 84% in both arms of trial [13]. Our five-year OS was 58.4% and DFS was 60%, however the CSS 69.2%.

One main limitation has to be acknowledged in our study which directly derives from the long timeframe considered. Our follow-up protocol changed over the years with a major landmark in 2009 when CT and MRI were systematically introduced for each patient. Prior to that date the protocol also involved the use of other radiological modalities such as chest x-rays or ultrasound and was not systematic. In view of this limitation TNM staging could not be recorded for a consistent proportion of patients as not reported. Consequently, an analysis of prognostic factors (including TNM staging) for patients undergoing primary radical chemoradiotherapy was not performed in our study.

Conclusions:

ASCC have been treated for the last two decades in our institution and in our series primary chemoradiotherapy had achieved significant initial complete response rates however long term-follow ups are plagued by systemic and local recurrences. In fact 23% of patients experienced a subsequent recurrence. and APR was able to treat only 30% of the pelvic ones

(6/20), the others were either associated with systemic disease or locally inoperable masses. With these premises our 5-years cancer-specific survival rate was 69.2%.

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Legend

Fig. 1: Protocol developed by our unit for the treatment of anal squamous cell carcinoma (ASCC). RTx: Radiotherapy. CTx: Chemotherapy.

Figure 2: Kaplan-Meyer curve showing the 5-year overall survival of ASCC patients treated with chemoradiotherapy.

Figure 3: Kaplan-Meyer curve showing the 5-year disease-free survival of ASCC patients treated with chemoradiotherapy

Figure 1

Figure 2

Figure 3

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