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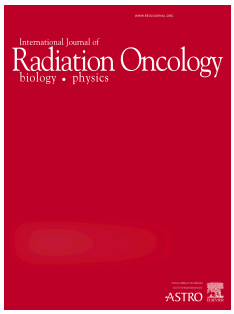

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Short title: Mitomycin-C with 5-FU or Capecitabine in the Treatment of Anal Cancer with IMRT: Evaluation of a National Cohort

Key terms: Anal Cancer; Anal Squamous Cell Carcinoma; IMRT; Chemoradiotherapy; 5-Fluouracil; Capecitabine; Mitomycin-C; Acute Toxicity.

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DISCLOSURE STATEMENT

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AUTHOR CONTRIBUTIONS

C Jones contributed to the analysis of data, in addition to authoring the first draft of the manuscript and is responsible for statistical analyses. R Adams, R Glynne-Jones, M Harrison, M Hawkins and D Sebag-Montefiore supported the collection and analysis of study data. A Downing supported the analysis of data and interpretation of their significance, in addition to contributing to revisions to the manuscript. D Gilbert and R Muirhead devised the study, coordinated the collection and processing of data and led the analysis and evaluation of audit outcomes. All authors contributed to revisions to the manuscript and all have read and approved the final version prior to submission.

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SUMMARY

We present toxicity and treatment compliance data from a national cohort of patients with anal squamous cell carcinoma managed in accordance with UK guidance using intensity-modulated radiation therapy and single-dose mitomycin-C (MMC) with either 5-FU (5-fluorouracil) or capecitabine. Similar overall rates of grade 3-4 toxicity were seen with capecitabine/MMC as with 5-FU/MMC. There were, however, differences in patterns of observed haematological and non-haematological toxicities.

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SUMMARY

We present toxicity and treatment compliance data from a national cohort of patients with anal squamous cell carcinoma managed in accordance with UK guidance using intensity-modulated radiation therapy and single-dose mitomycin-C (MMC) with either 5-FU (5-fluorouracil) or capecitabine. Similar overall rates of grade 3-4 toxicity were seen with capecitabine/MMC as with 5-FU/MMC. There were, however, differences in patterns of observed haematological and non-haematological toxicities.

ABSTRACT

Purpose: Chemoradiotherapy (CRT) with mitomycin C (MMC) and 5-fluouracil (5-FU) is established as the standard of care for the radical management of patients with anal squamous cell carcinoma (ASCC). There is emerging use of the oral fluoropyrimidine-derivative capecitabine as an alternative to 5-FU despite limited evidence for its tolerability and toxicity.

Methods & Materials: A national cohort evaluation of anal cancer management within the United Kingdom National Health Service was undertaken between February and July 2015. Toxicity rates were prospectively recorded. For this analysis we report ASCC patients managed with intensity modulated radiotherapy (IMRT) and a single dose of MMC with either 5-FU (5-FU/MMC) or capecitabine (capecitabine/MMC). All were treated with radical intent and in accordance with UK guidance.

Results: Of the 242 patients received from 40 centres across the UK, 147 met inclusion criteria; 52 of whom were treated with capecitabine/MMC, and 95 with 5-FU/MMC. There were no treatment related deaths and there was no overall difference in the proportion of patients experiencing any grade 3 or above toxicity between the capecitabine and 5-FU groups (45% vs. 55%; p=0.35). However, significantly fewer patients in the capecitabine/MMC group experienced grade 3 haematological toxicity (4% vs. 27%; p=0.001). A lower proportion of patients completed their planned chemotherapy course in the capecitabine cohort, though this did not reach statistical significance (81% vs. 90%; p=0.21). Median radiotherapy treatment duration was 38 (IQR 38-39) days for both groups. There was no difference in 1-year oncological outcomes.

Conclusion: Capecitabine/MMC resulted in similar levels of grade 3-4 toxicity overall as compared with 5-FU/MMC as CRT for ASCC, although there were differences in patterns of observed toxicities with less haematological toxicity with capecitabine. Further studies of capecitabine/MMC are required to understand the acute toxicity profile and long term oncological outcomes of this combination with IMRT in ASCC.

Carcinoma of the anus is a rare cancer, accounting for 2.5% of all digestive malignancies (1,2). It is increasing in frequency across the developed world, and is strongly associated with oncogenic subtypes of the human papilloma virus (HPV) (3,4). The vast majority of cases are anal squamous cell carcinomas (ASCC) and most present at a localised stage, either in the presence or absence of regional lymph node involvement. Treatment is directed towards achieving cure and effective local control whilst avoiding the requirement for a colostomy (5). Chemoradiotherapy (CRT) forms the international standard of care, achieving 3-year local control of between 65-74% (6).

Concurrent CRT with mitomycin-C (MMC) and 5-fluouracil (5-FU) is well established as superior to radiotherapy (RT) alone or RT in combination with 5-FU in ASCC (7-9). Efforts to improve outcomes, including the substitution of MMC with cisplatin and the introduction of neoadjuvant or adjuvant chemotherapy regimens, have not changed this standard of care (10-13). There is however no international consensus on the optimal dosing of MMC, with two doses administered to patients in both RTOG 8704 and RTOG 9811, in contrast to a single dose used in the ACT I, ACT II and EORTC trials **(**summarised in **Supp. Table 1)**.

Capecitabine is a tumour-activated fluoropyrimidine derivative, administered orally as a twice daily tablet. It provides a convenient alternative to 5-FU, which requires continuous infusion and central venous access. In colorectal cancer, capecitabine is non-inferior with respect to efficacy and has a comparable toxicity profile to 5-FU both in the adjuvant setting and as part of concurrent CRT (14-17). With respect to anal cancer, NCCN, ESMO-ESSO-ESTRO, French Intergroup and recent UK intensity-modulated radiation therapy (IMRT) guidelines support the use of capecitabine as an alternative option to 5-FU in radical CRT (18-21). However, current evidence for capecitabine in ASCC is derived from single centre studies and a number of relatively small phase II trials (22-24). Treatment parameters also vary widely across these studies, with significant variation in the use of 3D-RT or IMRT, in radiotherapy dose and in target volume (25-28).

Within the United Kingdom (UK), national guidance provided a framework for the standardisation of IMRT delivery in the treatment of anal cancer (29). A nationwide audit was undertaken to assess the implementation of IMRT for ASCC within the

UK National Health Service, including prospective collection of toxicity and outcomes (30). We present here comparative toxicity and early outcomes data for patients treated with standardised IMRT and either capecitabine/MMC or 5-FU/MMC.

Setting

With the support of the Royal College of Radiologists (RCR), we sought to detail the current management of patients diagnosed with anal cancer with respect to national guidance. All 56 centres involved in the delivery of RT within the UK were approached and asked to include every patient with confirmed anal cancer managed over a six-month period extending from 9th February to 27th July 2015. Data were obtained from 40 (71%) centres.

Population and treatment

UK IMRT guidance (20) was designed in 2013, converting the two phase technique and fractionation used in the UK ACT2 trial (12) into a single phase IMRT technique with a simultaneous integrated boost. For T1/2 node negative tumours, the primary receives a dose of 50.4Gy and elective nodal regions 40Gy over 28 fractions. For T3/4 or node positive tumours, the primary receives 53.2Gy and involved nodes 50.4Gy with elective regions again receiving 40Gy over 28 fractions. The guidance includes details on target volume definitions (20) and allows either concurrent 5FU or capecitabine (with a single dose of MMC (12mg/m^2 day 1) for CRT. Optimal and mandatory constraints are provided for PTV, bladder, small bowel, femoral heads, and genitalia. There are no constraints used to minimise bone marrow toxicity. To facilitate a comparison between chemotherapy regimens (i.e. standardising the radiotherapy component of treatment) only patients treated in accordance with the UK IMRT consensus document were included. Patients had to have received at least one dose of MMC and either infusional 5-FU (1000 mg/m^2 per day on days 1-4 and 29-32) or daily capecitabine (825 mg m^2) concurrently with IMRT. Patients who did not receive chemotherapy or who received an alternative treatment regimen were not included. Tissue types other than ASCC were excluded.

Data collection

Data were collected using an online data collection tool that was first piloted in five centres. Each centre was asked to provide information relating to patient and tumour demographics, staging investigations and details of chemotherapy and radiotherapy treatment, including whether this was completed as planned. A structured toxicity reporting form was completed weekly during each patient's treatment, with an optional report made six weeks after completion of CRT, and subsequently uploaded. Clinicians were asked to provide a weekly assessment during and shortly after treatment of the presence or absence of grade 1

or above treatment-related toxicity. This was measured against Common Toxicity Criteria for Adverse Events v4.03, 2010 (CTCAE). The Radiotherapy Oncology Group (RTOG) grading system was used to record skin toxicity.

A subsequent survey was sent to all participating centres for completion between 1st September 2016 to 30th November 2016. Details regarding response assessment at 6 months and 1 year, disease status and the presence or absence of a colostomy (and reasons thereof) were collected.

Data processing

All submitted toxicity reports were reviewed by two senior oncologists (XX and XX). In one patient treated with MMC/5-FU, toxicity was retrospectively upgraded to grade 3 due to a resultant interruption in CRT. No retrospective changes to toxicity grading for those who received capecitabine/MMC were made. Manual clarification of disease stage using criteria from the 7th Edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* was undertaken if discordance was noted between lymph node involvement and recorded disease stage (31). In line with guidance from the RCR, an extension to the *a priori* planned treatment time of greater than two days was counted as an interruption to radiotherapy treatment (32). The maximum toxic effect grade is reported here for each assessed toxicity parameter.

For clinical outcomes, centres were specifically asked whether patients were alive, had a stoma in situ, had recurrent disease or had had salvage surgery at 6 months and 1 year from completion of CRT. Patients were deemed 'relapse-free' at assessed time-points in the absence of local recurrence, surgery and/or metastatic disease. Complete response was defined as the absence of residual disease or surgery. Colostomy-free survival included all those without a stoma. Patients with a stoma included those placed prior to CRT and not reversed, those who underwent salvage surgery and those requiring a stoma for CRT morbidity.

Data analysis

Data analyses were undertaken using Microsoft Office Excel 2013 (Microsoft Corporation, CA, USA), IBM SPSS Statistics 24 (IBM Corporation, NY, USA) and Stata Version 15 (StataCorp, TX, USA). Patient, treatment and toxicity characteristics were compared using Fisher's exact test or the Mann-Whitney U test. To account for any differences in baseline patient and tumour factors, a propensity score matching approach was explored. Inverse-probability of treatment weighting (IPTW) was used to balance the two treatment groups according to age, sex, the presence of a pre-treatment colostomy, primary tumour site and T-

stage.(33) This resulted in a balanced sample of 119 patients and presence of grade 3 or 4 toxicity was compared across the treatment groups. Treatment effect could not be estimated for the toxicity subgroups with a small number of events or no events in one of the treatment groups. Bonferroni correction was applied to account for multiple significance testing. Two-tailed significance testing was used at a significance level of $p<0.05$, unless otherwise stated.

Governance approval

This evaluation was coordinated through the RCR as part of a national clinical audit programme in which governance approvals for participation were acquired locally by each participating centre. In accordance with UK practice for healthcare audits, approval for data collection was obtained by each NHS institution's research and governance board.

Patient & tumour characteristics

Of the 242 cases submitted, 180 were treated with IMRT. One-hundred-and-fifty-seven of these were treated in accordance with the UK consensus document. Ten patients were excluded from this analysis; one of whom had a confirmed anal adenocarcinoma, four of whom did not receive chemotherapy and five who received a drug combination consisting of cisplatin alone (n=1) or in combination with etoposide (n=2) or 5FU (n=2). **Fig. 1** provides an overview of the process for participant selection. Of the 147 cases included, 52 (35.4%) were treated with capecitabine/MMC, and 95 (64.6%) with 5-FU/MMC. Of the high volume centres submitting ten or more patients, four solely used 5-FU/MMC, and two solely used capecitabine/MMC. The rationale behind the decision to select capecitabine or 5FU for individual patients within the smaller volume centres is unknown.

Summaries of included patient and disease demographics are provided in **Tables 1 and 2.** Baseline patient characteristics (age, smoking history, HIV status and presence of pre-treatment colostomy) were comparable between the groups. Although the number of patients undergoing diagnostic PET/CT was significantly higher in the capecitabine group (56% vs. 34%; p=0.01), this did not translate into higher stages within this group.

Patients and treatment details

Data relating to overall radiotherapy treatment time, completion of radiotherapy and the overall number of interruptions to radiotherapy were available for all patients. Of the 52 in the capecitabine/MMC group, non-haematological and haematological toxicity data were respectively available for 47 (90.4%) and 48 (92.3%) patients. In comparison, of the 95 patients receiving 5-FU/MMC, non-haematological and haematological toxicity data were available for 71 (74.7%) and 66 (69.5%) patients respectively. For those patients for whom we have reported haematological toxicity, weekly data for full blood count (FBC) were available for at least five weeks for 45 (93.8%) of the capecitabine group and 51 (77.3%) of the 5-FU group. In the capecitabine group, FBC data were available for four weeks in two further patients and for three weeks in a final patient. In the 5-FU group, FBC data were available for four weeks in five (7.6%) patients and three weeks in five (7.6%) patients. For three patients data were available for two weeks (at an interval of greater than two weeks between readings) and for one patient data were available for the second week of treatment only.

Treatment toxicity

Overall there was no evidence of a significant difference in rates of grade 3-4 toxicity between the capecitabine/MMC and 5-FU/MMC treated cohorts (45% vs. 55%; p=0.35). There were no treatment related deaths in either group. Rates of grade 1-4 toxicity (haematological, gastrointestinal, skin and anal pain) are presented in **Table 3**. **Table 4** details statistical comparisons of grade 3/4 toxicity, including following an inverse-probability of treatment weighting (IPTW) analysis.

Treatment Compliance

Median radiotherapy treatment duration did not differ between treatment cohorts at 38 (IQR 38-39) days for patients receiving 5-FU and 38 (IQR 38-39) days for those receiving capecitabine. As summarised within **Table 5**, a similar proportion of patients within each studied cohort received the full dose of planned radiotherapy.

A greater proportion of patients completed their planned course of 5-FU/MMC than capecitabine/MMC, though this did not reach significance (90% vs. 81%; p=0.21). In the 11 patients for whom capecitabine was dose adjusted, ten of the changes were due to toxicity. For four patients this related to gastrointestinal sequelae whilst treatment was discontinued due to thrombocytopenia and cardiac chest pain in two patients for each and due to infection in a further instance. In contrast, of the ten patients for whom 5-FU was discontinued or dose adjusted, four experienced bone marrow toxicity, one developed significant stomatitis and a further patient was diagnosed with acute kidney injury.

Oncological outcomes

Disease and treatment specific outcomes were submitted in the subsequent survey for 100 of the original 147 patients (42 (80.8%) treated with capecitabine/MMC and 58 (61.1%) patients who received 5-FU/MMC). At six months, three patients treated with capecitabine/MMC had residual disease and a further two had already undergone salvage surgery, giving a six-month complete response rate of 37/42 (88.1%). In the 5-FU/MMC group, four patients had residual disease at six months and a further one patient had undergone salvage surgery, hence 53/58 (91.4%) had a six-month complete response (p=0.74).

One year relapse-free rates were not significantly different between groups; 32/42 (76.2%) in the capecitabine/MMC group and 46/58 (79.3%) in patients receiving 5-FU/MMC (p=0.80). Two patients treated with capecitabine/MMC and four patients in the 5FU/MMC group had died, all from metastatic anal cancer.

In the capecitabine/MMC group, three of 42 patients required pre-treatment colostomies and at one-year follow-up five had undergone salvage surgery, two had died and one required a stoma post-treatment to manage faecal incontinence. In the 5-FU/MMC group, two of 58 patients required pre-treatment colostomies for symptoms relating to their disease and at one-year follow-up, two had undergone salvage surgery, four had died and one had required a post-treatment stoma for CRT morbidity. One year colostomy-free survival rates were therefore 31 of 40 patients alive at one year in the capecitabine/MMC group (77.5%) and 49 of 54 (90.7%) patients in the 5-FU/MMC group (p=0.09).

There is a paucity of literature relating to the toxicity of capecitabine when used as a component of CRT for anal cancer. We present here toxicity and tolerability data from a national cohort of patients with ASCC managed in accordance with UK guidance using IMRT and single-dose MMC with either 5-FU or capecitabine. There were no treatment-related deaths and there was no significant difference between the cohorts in median treatment duration, rates of complete response at 6 months or those remaining disease free at 1 year. Rates of interruption of RT were comparable. Of those managed with 5-FU/MMC, 10% failed to complete planned chemotherapy compared with 20% of those treated with capecitabine/MMC, though this difference was not significant. In both groups this was for the most part a consequence of toxicity. The capecitabine/MMC combination was associated with reduced haematological toxicity but a non-significant trend for more grade 3-4 diarrhoea when compared with 5-FU/MMC.

5-FU/MMC forms the standard of care for concurrent CRT in ASCC, supported by six randomised phase III trials, the largest of which (ACT2) randomised 472 patients to the 5-FU/MMC arm (12). By comparison, there are no randomised data informing the substitution with capecitabine but the data presented here add to, and are consistent with, those from previously published series and a phase II evaluation (summarised in **Supp. Table 2**).

A recent single-centre analysis of patients with anal cancer managed with IMRT also reported reduced rates of grade ≥3 haematological toxicity with capecitabine when compared to 5-FU (28). However, the relative incidence of both grade ≥3 neutropenia/leukopenia (52% vs. 20%) and thrombocytopenia (19% vs. 9%) in both the 5-FU and capecitabine cohorts was considerably higher than that described in our series (20% vs. 2% for neutropenia/leucopenia and 14% vs. 0% for thrombocytopenia). Potential reasons for this might include the use of an additional dose of MMC, larger doses to the prophylactic pelvic field or the higher superior border of the radiotherapy fields. UK guidance suggests the superior border of the prophylactic clinical target volume (CTV) be placed 20mm above the inferior aspect of the sacroiliac joint; with a further 5mm CTV to planned target volume (PTV) margin. In contrast the above series used the RTOG atlas, which suggests the superior border of the CTV lies at the bifurcation of the common iliac vessels (approximate bony landmark: sacral promontory) and a larger CTV to PTV margin of 7-10mm (34). The haematological toxicity resulted in a significantly greater proportion of patients in the 5-FU cohort requiring a treatment break (41% vs. 14%), and in a relatively higher overall requirement for

treatment suspension than our series (only 5.7% of those managed with capecitabine and 8.4% of the 5-FU cohort required a break due to toxicity). Gastrointestinal toxicity was generally low with only one patient (2%) in the capecitabine/MMC group and none of the 5-FU/MMC treated patients experiencing grade 3 diarrhoea. Grade 2 diarrhoea was actually greater in the 5-FU/MMC group (17% vs 5%). In contrast, we identified a 10% greater incidence of diarrhoea at grade three or above in patients managed with capecitabine (17% vs. 7%).

Rates of grade 3 gastrointestinal toxicity were also comparatively low in two prior series. A single-centre analysis of 66 patients treated with IMRT reported 3% grade 3 gastrointestinal toxicity (25). Similarly, *Thind et al* describe a 3% frequency of diarrhoea and 7.6% stomatitis in a multi-centre series of 66 patients managed with 3D-conformal RT (76%) or IMRT (24%) (26). Rates of skin toxicity within the *Thind* cohort were high at 63%. This compared with 27.6% reported by *Meulendijks* and 26% reported in our study. The wide range in radiotherapy doses used is likely to have been a significant contributory factor to high rates of dermatitis and only one patient required a dose reduction of capecitabine. Within the cohort described by *Meulindijks,* grade 4 toxicity was present in five cases (9%); two of which were dermatological, two haematological and one was gastrointestinal. This is likely a consequence of patients receiving a significantly higher dose than UK Guidance recommends (12 patients - 64.8Gy, 6 patients - 59.4Gy). The proportion of patients completing planned chemotherapy was similar in both reports to that described within the series reported here. Higher overall rates of grade 3 gastrointestinal toxicity within our cohort may also reflect prospective collection of toxicity data in our series.

Two prior phase II studies investigated capecitabine/MMC in CRT for ASCC. The EXTRA trial treated 31 patients with a combination of conventional parallel-opposed and 3D conformal pelvic fields (27). Skin (39%) and haematological (9.7% neutropenia and 3.2% thrombocytopenia) toxicity was greater than reported here. Only 68% of patients completed capecitabine as planned whereas, in our series, a greater proportion of 79% of patients completed their planned course of capecitabine. Oliveira *et al* report on 43 patients managed with capecitabine and MMC, though only 10 (23%) of these received IMRT (the remainder receiving 3D-RT (24)). Capecitabine treatment was interrupted in 55.8% of the patients within this cohort and discontinued for one in view of grade 4 toxicities. Skin and haematological toxicity were seen in a comparable proportion of patients, whereas gastrointestinal toxicities were less common than we have reported.

In a report focussed on the use of simultaneous integrated boost-IMRT in anal cancer, Tomasoa *et al* report comparable outcomes with capecitabine to 5-FU, though supporting data is not provided (35). In a further Canadian multi-centre analysis published only in abstract form, a significantly lower proportion of patients reported adverse effects with capecitabine than 5-FU (51% vs. 26%), with a lower incidence of stomatitis (6% vs. 40%) and hand-foot syndrome (1% vs. 8%) (36). These patients were however managed with a range of radiotherapy doses and it is not clear what proportion received cisplatin rather than MMC as a backbone. A number of additional studies have reported on the use of capecitabine as a component of a chemotherapy doublet in anal cancer with either cisplatin, MMC or another chemotherapeutic backbone, though these do not report on the specific toxicity profiles of MMC and capecitabine (37-42).

Limitations

The nature of a national cohort evaluation such as this captures real world data but brings several limitations. Although a relatively large cohort by the standards seen in ASCC, the numbers of patients within each cohort limits more sophisticated analysis (e.g propensity scoring) to account for potential bias from treatment selection that may have occurred based on patient characteristics. Nevertheless, the baseline demographic, staging and tumour demographics are comparable, which strengthens the validity of the results presented here. In considering responder bias, to our knowledge there is no systematic difference in those centres who chose to respond to the audit compared with those who did not.

With respect to specific categories of data, there were lower proportions of haematological toxicity returned for the 5-FU/MMC cohort than the capecitabine/MMC group. The continuous nature of the capecitabine makes weekly blood tests routine whereas this is not necessarily the case with 5-FU, which might in part have underestimated the reporting of haematological toxicity in the 5-FU/MMC group. It must be noted that despite possible underestimation of haematological toxicity in the 5FU cohort, there was a statistically significantly more haematological toxicity in this group. Therefore any additional haematological toxicity would serve to increase this statistical difference. The other factor that could affect the haematological toxicity is the use of constraints on the bone marrow. This is not used in the UK and as such no patients would have had bone marrow sparing. The use of IMRT has been demonstrated to increase dose to bone marrow and as such consideration of bone marrow constraints should be given for future (43,44).

The proportion of patients for whom oncological outcomes data were available is relatively low. The follow-up survey requesting outcome data from participating centres achieved a 68% response rate. Neither this nor prior analyses are adequately powered to conclude on the relative efficacy of capecitabine versus 5-FU. In addition, one-year DFS is unlikely to be adequate for outcomes reporting in anal cancer which requires at least two or three-year data. We also cannot in this analysis determine whether comparable survival outcomes to 5-FU are achieved by capecitabine when the overall received dose is reduced due to toxicity. There is therefore a need for further evidence of long-term outcomes in anal cancer with capecitabine.

Finally, in the absence of adequately powered analyses, non-significant p-values reported here must be interpreted as demonstrating no evidence of a difference between groups, rather than conclusive evidence of a lack of a difference between groups.

Despite these limitations, the multi-centre cohort presented here is the largest to have been managed with standardised IMRT treatment and single-dose MMC that has been reported to-date, and has considerable strengths as a consequence both of its national scope, the defined time period over which data were collated and from prospective collection of toxicity data. The Cancer Research UK funded PLATO trials (PersonaLising *Anal cancer* RadioTherapy dOse, ISRCTN88455282) are investigating the role of different radiotherapy doses in patients with ASCC and allow either 5-FU/MMC or capecitabine/MMC (45). In the ACT5 trial evaluating dose escalation, centres choose to use capecitabine or 5-FU as per centre policy. This will provide further information regarding toxicity, compliance and cancer outcomes with tightly controlled quality assurance.

CONCLUSION

Data from this national multi-centre cohort using a standardised IMRT technique show similar levels of grade 3-4 toxicity overall between either 5-FU or capecitabine in combination with MMC as CRT for ASCC. There were, however, differences in patterns of observed haematological and non-haematological toxicities. Whilst the toxicity of CRT with MMC/5-FU is well characterised, further studies of MMC/capecitabine are required to understand the acute toxicity profile with IMRT. Early oncological outcomes appear comparable but again, prospective studies with longer term follow up are required.

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FIGURES

Figure 1: Study profile indicating participant selection from the total audit population.

TABLES

Table 1: Baseline characteristics for patients treated with radical intent using intensity modulated radiotherapy and concurrent chemoradiotherapy using mitomycin-C (MMC) and either capecitabine or 5-fluorouracil (5-FU).

	MMC & capecitabine n=52	**MMC & 5-FU n=95**	
	No. (%)	No. (%)	p-value
Sex			
Male	18 (34.6)	25 (26.3)	0.34
Female	34 (65.4)	70 (73.7)	
Age (years)			
<65	30 (57.7)	56 (59.0)	1.0
≥65	22 (42.3)	39 (41.0)	
Smoking status			
Current smoker	12 (23.1)	24 (25.3)	0.78
Ex-smoker	11 (21.2)	17 (17.9)	
Never smoked	23 (44.2)	33 (34.7)	
Not known	6 (11.5)	21 (22.1)	
HIV status			
Positive	3 (5.8)	2 (2.1)	0.65
Negative	28 (53.8)	36 (37.9)	
Not tested	21 (40.4)	57 (60.0)	
Pre-treatment colostomy			
Yes	5 (9.6)	16 (16.8)	0.33
No	47 (90.4)	79 (83.2)	

Statistical analyses were undertaken using Fisher's-Exact Test.

Table 2: Baseline disease characteristics for patients treated with radical intent using intensity modulated radiotherapy and concurrent chemoradiotherapy using mitomycin-C (MMC) and either capecitabine or 5-fluorouracil (5-FU).

	MMC & capecitabine n=52	**MMC & 5-FU n=95**	
	No. (%)	No. (%)	p-value
Tumour differentiation			
Well	4 (8)	5 (5)	0.14
Moderately	24 (46)	37 (39)	
Poorly	11 (21)	37 (39)	
Unknown	13 (25)	16 (17)	
Staging PET/CT			
Yes	29 (56)	32 (34)	*0.01*
No	23 (44)	63 (66)	
Primary tumour site			
Anal canal	40 (77)	75 (79)	0.53
Anal verge	3 (6)	9 (9)	
Distal rectum	5 (10)	5 (5)	
Peri-anal skin	4 (8)	3 (3)	
No primary identified	0 (0)	2 (2)	
Unknown/Other	0 (0)	1 (1)	
T-stage			
T1	7 (14)	8 (8)	0.58
T2	24 (46)	40 (42)	
T3	10 (19)	27 (28)	
T4	11 (21)	18 (19)	
Tx	0 (0)	2 (2)	
N-stage			
Negative	22 (42)	49 (52)	0.31
Positive	30 (58)	46 (48)	
M-stage			
M0	51 (98)	89 (94)	0.69
M1	1 (2)	3 (3)	
Mx	0 (0)	3 (3)	

Statistical analyses were undertaken using Fisher's-Exact Test.

Table 3: Comparison of grades 1-4 toxicity during chemoradiotherapy in the group treated with capecitabine/mitomycin-C (MMC) and the group treated with 5-fluorouracil (5-FU)/MMC.

		n	**G1-4** n (%)	**G1** n (%)	**G2** n (%)	**G3** n (%)	**G4** n (%)	***p***
Non-haematological toxicity[#]								
Gastrointestinal								
Nausea	Cape/MMC	47	21 (44.7)	15 (31.9)	5 (10.6)	1 (2.1)	0 (0.0)	0.61
	5FU/MMC	71	41 (57.8)	29 (40.9)	9 (12.7)	3 (4.2)	0 (0.0)	
Vomiting	Cape/MMC	47	6 (12.8)	5 (10.6)	0 (0.0)	1 (2.1)	0 (0.0)	0.82
	5FU/MMC	71	12 (16.9)	9 (12.7)	1 (1.4)	2 (2.8)	0 (0.0)	
Diarrhoea	Cape/MMC	47	33 (70.2)	15 (31.9)	10 (21.3)	8 (17.0)	0 (0.0)	0.04
	5FU/MMC	71	58 (81.7)	41 (57.8)	12 (16.9)	5 (7.0)	0 (0.0)	
Stomatitis	Cape/MMC	47	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	*0.001*
	5FU/MMC	71	17 (23.9)	9 (12.7)	5 (7.0)	3 (4.2)	0 (0.0)	
Non-gastrointestinal								
Skin	Cape/MMC	47	46 (97.9)	6 (12.8)	28 (59.6)	12 (25.5)	0 (0.0)	0.84
	5FU/MMC	71	68 (95.8)	5 (7.0)	43 (60.6)	19 (26.8)	1 (1.4)	
Anal pain	Cape/MMC	47	40 (85.1)	15 (31.9)	16 (34.0)	9 (19.2)	0 (0.0)	0.27
	5FU/MMC	71	60 (84.5)	20 (28.2)	34 (47.9)	6 (8.5)	0 (0.0)	
Haematological toxicity[$]								
Haemoglobin	Cape/MMC	48	34 (70.8)	28 (58.3)	5 (10.4)	1 (2.1)	0 (0)	0.16
	5FU/MMC	66	35 (53.0)	31 (47.0)	3 (4.5)	1 (1.5)	0 (0)	
WCC	Cape/MMC	48	25 (52.1)	20 (41.7)	4 (8.3)	1 (2.1)	0 (0)	0.04
	5FU/MMC	66	37 (56.1)	12 (18.2)	12 (18.2)	11 (16.7)	2 (3.0)	
Platelets	Cape/MMC	48	28 (58.3)	25 (52.1)	3 (6.3)	0 (0.0)	0 (0.0)	0.02
	5FU/MMC	66	46 (69.7)	27 (40.9)	10 (15.2)	8 (12.1)	1 (1.5)	

Key: Cape/MMC: capecitabine & mitomycin-C; 5FU/MMC: 5-fluorouracil & mitomycin-C; G1: grade 1; G2: grade 2; G3: grade 3; G4: grade 4; WCC: white cell count.
All analyses undertaken using Fisher's exact test.
$ At an alpha value of 0.05 a Bonferroni adjusted p-value of less than 0.02 was considered significant to account for multiple significance testing.
# At an alpha value of 0.05 a Bonferroni adjusted p-value of less than 0.008 was considered significant to account for multiple significance testing.

Table 4: Comparison of grade three and four toxicity during chemoradiotherapy seen in the group treated with capecitabine/mitomycin-C (MMC) and the group treated with 5-fluorouracil (5-FU)/MMC.

	MMC & capecitabine n=47 (non-haematological) n=48 (haematological) No. (%)	**MMC & 5-FU** n=71 (non-haematological) n=66 (haematological) No. (%)	p-value	IPTW p-value^
Any G3/G4 toxic effect*	21 (45)	39 (55)	0.35	0.19
Non-haematological*$	20 (43)	30 (42)	1.00	0.72
Gastrointestinal	8 (17)	9 (13)	0.60	0.72
Nausea	1 (2)	3 (4)	1.00	0.39
Vomiting	1 (2)	2 (3)	1.00	0.7
Diarrhoea	8 (17)	5 (7)	0.60	0.12
Stomatitis	0 (0)	3 (4)	0.16	-
Other	0 (0)	1 (1)	1.00	-
Skin	12 (26)	20 (28)	0.83	0.71
Anal pain	9 (19)	6 (9)	0.10	0.1
Cardiac	2 (4)	1 (1)	0.56	-
Other	2 (4)	4 (6)	1.00	0.2
Haematological*#	2 (4)	18 (27)	*0.001*	*<0.001*
WCC	1 (2)	13 (20)	*0.004*	*<0.001*
Platelets	0 (0)	9 (14)	0.01	-
Haemoglobin	1 (2)	1 (2)	1.00	0.82
Febrile neutropenia	1 (2)	0 (0)	0.42	-

Key

G3 – Grade 3. G4 – Grade 4. WCC: white cell count.

* Patients who experienced more than one toxic effect are counted once at the highest grade recorded.

^ p-Values are shown both for statistical analyses undertaken using Fisher's Exact test and following inverse-probability of treatment weighting (IPTW). Treatment groups were balanced according to the following baseline characteristics: age, sex, the presence of a pre-treatment colostomy, primary tumour site and T-stage. It was not possible to obtain estimates for the toxicity subgroups with a small number of, or no, events in one of the treatment groups.

$ At an alpha value of 0.05 a Bonferroni adjusted p-value of less than 0.0046 was considered significant to account for multiple significance testing.

At an alpha value of 0.05 a Bonferroni adjusted p-value of less than 0.01 was considered significant to account for multiple significance testing.

Mitomycin-C with 5-FU or Capecitabine in the Treatment of Anal Cancer with IMRT: Evaluation of a National Cohort

Table 5: Comparison of treatment interruptions following chemoradiotherapy with mitomycin-C (MMC) and either capecitabine or 5-fluorouracil (5-FU).

			MMC & capecitabine n=52	**MMC & 5-FU n=95**	
			No. (%)	No. (%)	p-value
Median treatment duration			38 days	38 days	1.0
Radiotherapy	Received planned dose*		51 (98.1)	89 (93.7)	0.42
	Treatment interruptions:	≥1 Interruption	6 (11.5)	14 (14.7)	0.80
		1-3 Interruptions	5 (9.6)	11 (11.6)	0.94
		4-6 Interruptions	0 (0.0)	2 (2.1)	
		>6 Interruptions	1 (1.9)	1 (1.1)	
	Reason for treatment interruption:	Toxicity	3 (5.8)	8 (8.4)	1.0
		Unrelated to toxicity	2 (3.9)	6 (6.3)	
		Not known	1 (1.9)	0 (0.0)	
Chemotherapy	Completed as planned		42 (80.8)	85 (90.0)	0.21
	Reason for not completing treatment as planned:	Toxicity	10 (19.2)	9 (9.5)	1.0
		Patient choice	1 (1.9)	0 (0.0)	
		Not known	0 (0.0)	1 (1.1)	
Treatment-related deaths			0 (0)	0 (0)	1.0

Key

* Regardless of interruptions. $ Includes requirement for revised radiotherapy planning during treatment, machine failure and public holiday. Statistical analyses were undertaken using the Mann-Whitney U and Fisher's Exact tests.