# Toxicity, Tolerability & Compliance of Concurrent Capecitabine versus the Standard 5-Fluorouracil in the Radical Management of Anal Cancer with Single-Dose Mitomycin-C and Intensity Modulated Radiation Therapy: a Prospective National Cohort Evaluation

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## SUMMARY

This prospective national multi-centre dataset suggests that Capecitabine is a tolerable alternative to 5-Fluorouracil in the radical management of anal cancer with IMRT and a single dose of Mitomycin C.

## 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 carcinoma of the anus. Many units use the oral fluoropyrimidine derivative Capecitabine as an alternative treatment option to 5-FU despite limited evidence for its tolerability and toxicity.

*Methods & Materials:* A prospective national evaluation of anal cancer management within the United Kingdom National Health Service was undertaken between February and July 2015. Patients managed with radical intent using intensity modulated radiotherapy (IMRT) in accordance with UK guidance and a single dose of MMC with either 5-FU or Capecitabine were selected for analysis.

*Results:* Of the 242 patients received from 40 centres across the UK, 148 met inclusion criteria; 53 of whom were treated with MMC and Capecitabine, and 95 with MMC and 5-FU. There were no treatment related deaths and there was no overall difference in the proportion of patients experiencing any toxic event between the Capecitabine and 5-FU groups (45% vs. 55%; p=0.35). Significantly fewer patients in the Capecitabine group experienced haematological toxicity (4% vs. 27%; p=0.001), though this cohort experienced higher rates of diarrhoea (17% vs. 7%; p=0.60) and anal pain (19% vs. 9%; p=0.10). There was no difference in the proportion of patients completing their radiotherapy course, or in rates of treatment interruption. However, proportionately fewer patients managed with Capecitabine than treated with 5-FU completed their planned chemotherapy course (79% vs. 90%; p=0.14).

*Conclusion:* In this prospective multicentre cohort of patients undergoing chemoradiotherapy with IMRT for anal cancer, Capecitabine was a tolerable alternative to 5-FU when used with a single dose of MMC and led to lower rates of haematological toxicity, albeit with a trend towards higher gastrointestinal toxicity.

## INTRODUCTION

Carcinoma of the anus is a rare cancer, accounting for 2.5 per cent of all digestive malignancies (1, 2). It is nevertheless increasing in frequency across the developed world, due at least in part to an association 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). A minority of patients with the earliest of anal margin tumours will proceed to surgical excision. For the majority, definitive chemoradiotherapy (CRT) forms the international standard of care and is reported to achieve 3-year local control of between 65-74% (6).

Concurrent CRT with Mitomycin-C (MMC) and 5-Fluouracil (5-FU) is well established as a superior treatment option in anal cancer when compared with radiotherapy (RT) alone or in combination with 5-FU (7-9). Despite a number of attempts to improve outcomes through either substituting MMC or through the introduction of neoadjuvant or adjuvant chemotherapy regimens, concurrent CRT with MMC and 5-FU retains the highest-level of evidence for use in the treatment of anal carcinoma (10-13). There is however no 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)**.

The oral tumour-activated fluoropyrimidine derivative Capecitabine provides a convenient alternative option to 5-FU which does not require central venous access and continuous drug infusion. In colorectal cancer Capecitabine has achieved comparable efficacy to 5-FU within phase III trials in both the adjuvant setting and as part of concurrent chemoradiotherapy regimes (14-17).Within both contexts, though different to 5-FU, the toxicity profile of Capecitabine appears non-inferior.

In light of this, the potential use of Capecitabine in place of 5-FU in the management of anal cancer is of growing relevance. NCCN, ESMO-ESSO-ESTRO, French Intergroup and relevant UK intensity-modulated radiation therapy (IMRT) guidelines support Capecitabine as an alternative option to 5-FU in radical CRT (18-21). There is however a paucity of evidence for the tolerability and toxicity of Capecitabine when used in a doublet with MMC within this context (22,23). Notably, there is no relevant phase III data and the largest of the small number of relevant existing reports are retrospective, with significant heterogeneity in treatment parameters both within and across studies (24-28). This includes the use of both 3D-RT and IMRT, divergent radiotherapy doses and target volumes, and significant variation in MMC dosing.

Within the UK, the implementation of nationwide guidance has supported the standardisation of IMRT delivery in the treatment of anal cancer (29). We outline here prospectively collated acute toxicity and tolerability data comparing Capecitabine to 5-FU when used in doublet chemotherapy with a single dose of MMC in the radical management of patients with anal cancer;

as collected in a 2015 nationwide multi-centre evaluation and previously presented at the American Society for Radiation Oncology 2017 Annual Meeting (30).

## MATERIALS & METHODS

### Setting & approach

A prospective national audit of patients with a diagnosis of anal cancer managed within the United Kingdom (UK) National Health Service (NHS) was undertaken with the support and approval of the United Kingdom Royal College of Radiologists (RCR), as has been extensively described in our previous publication (30). In summary, 240 patients who commenced treatment with radical intent within 40 participating centres between 9th February 2015 and 27th July 2015 were included. This represented 71% of a total of 56 centres delivering radiotherapy within the UK, with two centres referring patients elsewhere.

Collected data included patient and tumour demographics, staging investigations, details of chemotherapy and radiotherapy treatment, survival status and weekly recordings of acute toxicity during chemoradiotherapy measured against Common Toxicity Criteria (v4.03, 2010). The Radiotherapy Oncology Group (RTOG) grading system was used to record skin toxicity.

### Data processing & analysis

Instances of grade three toxicity were documented by each centre at the time of weekly grading. An additional review of collated data was undertaken by two authors (RM and DG) and if not already noted within weekly grading, grade three toxicity was assigned in instances in which an admission or interruption to either chemotherapy or radiotherapy had occurred. In total, grade three toxicity was retrospectively assigned in one (0.6%) patient who received MMC and 5-FU, and none of those who received MMC and Capecitabine. 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). Where not directly provided, neutrophil count was estimated as 50 per cent of the absolute white cell count. In line with guidance from the Royal College of Radiologists, 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 was used for each patient and each event type.

Participants were included in this analysis if they had undergone treatment delivered in accordance with UK IMRT guidance using MMC and either Capecitabine or 5-FU. Data analyses were undertaken using Microsoft Office Excel 2013 (Microsoft Corporation, CA, USA) and Graphpad (Graphpad Software, Inc., CA, USA). Patient, treatment and toxicity characteristics were compared using Fisher's exact test, Chi-square or the Mann-Whitney U test. Bonferroni correction was applied to account for multiple significance testing. All analyses are intention-to-treat unless otherwise specified. Two-tailed significance testing was used at a significance level of $p<0.05$.

This evaluation was coordinated through the RCR as part of a national clinical audit in which governance approvals for participation were acquired locally by each participating centre.

## RESULTS

### Included participants

Of the 240 cases received in the audit, 157 were managed with IMRT in accordance with UK guidance. Eight patients were excluded from this analysis; four of whom did not receive chemotherapy and four who received a drug combination consisting of cisplatin alone (n=1) or with either etoposide (n=2) or 5FU (n=2) **Supp. Fig. 1** provides an overview of the process for participant selection. Of the 148 cases included, 53 (35.8%) were treated with MMC and Capecitabine, and 95 (64.2%) with MMC and 5FU. Of the high volume centres submitting ten or more patients, four solely used MMC and 5FU, and two solely used MMC and Capecitabine.

Data relating to treatment time, completion and the overall number of interruptions were available for all 53 patients who received MMC and Capecitabine, and for all 95 patients who received MMC and 5-FU. Of the 53 in the MMC and Capecitabine group, non-haematological and haematological toxicity data were respectively available for 47 (88.7%) and 48 (90.6%) patients. In comparison, of the 95 patients receiving MMC and 5-FU, non-haematological and haematological toxicity data were available for 71 (74.7%) and 66 (69.5%) patients respectively. Disease free survival at one year is known for 42 (79.2%) patients managed with MMC and Capecitabine, and 55 (57.9%) of those who received MMC and 5-FU.

### Patient & tumour characteristics

A summary of included patient demographics is provided in **Table 1.** The median age of patients within the 5-FU group was 63 years (IQR 29-81), compared with 61 years (IQR 31-88) for the Capecitabine group. Other assessed baseline patient

characteristics were comparable between the groups, including smoking status, HIV positivity and the presence of a pre-treatment colostomy.

As shown in **Table 2**, all 95 patients managed with 5-FU had ASCC, the majority of which were moderately (n=37, 39%) or poorly (n=37, 39%) differentiated. In the Capecitabine group, one malignancy was an adenocarcinoma and the remainder were ASCCs. There was no significant variation in tumour differentiation. Although the number of patients undergoing diagnostic PET/CT was significantly higher in the Capecitabine group (55% vs. 34%; p=0.02), this did not translate into higher stages within this group.

Treatment toxicity

**Table 3** summarises rates of grade three and four toxicity within the two groups. There was no overall difference in the proportion of patients experiencing any toxic effect between the Capecitabine and the 5-FU group (45% vs. 55%; p=0.35), and there were no treatment-related deaths in either cohort. Significantly fewer patients in the Capecitabine group experienced haematological toxicity (4% vs. 27%; p=0.001), reflecting lower rates of neutropenia (2% vs. 20%; p=0.004) and thrombocytopenia (0% vs. 14%; p=0.01), though this latter comparison did not reach significance when corrected for multiple significance testing. A single case of febrile neutropenia was recorded within the Capecitabine group.

No difference was seen in non-haematological toxicity rates, with a proportionate incidence of 42% in both cohorts. However, a greater proportion of patients within the Capecitabine and 5-FU groups respectively experienced diarrhoea (17% vs. 7%; p=0.60) and anal pain (19% vs. 9%; p=0.10).

Treatment tolerance

Median 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 4**, a similar proportion of patients within each studied cohort received the full dose of radiotherapy planned for their treatment, though 11.3% of those receiving Capecitabine and 14.7% of patients managed with 5-FU experienced an unplanned treatment interruption (p=0.63).

A greater proportion of patients completed their planned course of MMC and 5-FU than MMC and Capecitabine, though this did not reach significance (90% vs. 79%; p=0.14). In both treatment groups the predominant reason for adjustment or discontinuation of chemotherapy was toxicity. 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 chest pain in two patients for each and due to infection in a further instance. In contrast, of the 10 patients for whom 5-FU was discontinued or dose adjusted, four experienced bone marrow toxicity, one developed significant mucositis and a further patient was diagnosed with acute kidney injury. Reassuringly, there were no treatment-related deaths in either cohort.

One-year disease free survival

Cancer related outcomes were available for 97 patients (42 treated with Mitomycin and Capecitabine and 55 who received Mitomycin-5FU). The single case of anal adenocarcinoma within the Capecitabine group was excluded from survival analysis. Disease-free survival rates at 1 year (defined as the absence of local recurrence and/or metastatic disease) were not different between the two groups; 32/42 (76.2%) in the Capecitabine group and 43/55 (78.2%) in the patients receiving 5-FU remained disease free (p=0.8124).

**DISCUSSION**

We have demonstrated no difference in overall treatment time or the incidence of toxicity at grade three or above in severity following the use of Capecitabine in place of 5-FU when used in a doublet with single-dose MMC. Toxicity profiles did nevertheless differ, with significantly fewer patients in the Capecitabine cohort experiencing haematological toxicity, underpinned by lower rates of neutropenia and thrombocytopenia. In contrast, a trend towards a greater incidence of gastrointestinal toxicity was seen in the Capecitabine group, in which a 10 per cent greater incidence of grade 3/4 diarrhoea was seen. This did not however reach significance and rates of nausea, vomiting and stomatitis were comparable between treatment groups, as was the incidence of skin toxicity. Treatment with Capecitabine was not associated with any change in the proportion of patients completing their planned radiotherapy regimen, though ten per cent fewer patients completed their intended course of Capecitabine than received their planned dose of 5-FU.

These findings are generally supportive of the use of Capecitabine in place of 5-FU in the management of anal cancer with IMRT. However, the toxicity and tolerability profile elucidated from this prospectively-collated national multi-centre dataset carries a number of important distinctions from that suggested within the existing literature, much of which is limited to retrospective analyses (as summarised in **Table 1**). Retrospective studies may under-report toxicity, particularly with respect to more subjective non-haematological components. Interpretation from the majority of series to date is also hindered by their use

of traditional conformal RT rather than the currently applied modality of IMRT, in addition to heterogenous radiotherapy doses and volumes, and variation in the administration of backbone chemotherapeutic agents.

In a recent retrospective single-centre analysis of patients managed with doublet chemotherapy incorporating two doses of MMC alongside IMRT, Goodman et al compared 63 patients treated with infusional 5-FU to 44 who received Capecitabine (28). In keeping with data presented within this manuscript, the authors identified reduced rates of haematological toxicity with Capecitabine when compared to 5-FU. However, the relative incidence of both neutropenia (52% vs. 20%) and thrombocytopenia (19% vs. 9%) in both the 5-FU and Capecitabine cohorts was considerably higher than that described here (20% vs. 2% for neutropenia and 14% vs. 0% for thrombocytopenia). This is likely to relate to the use of larger RT field sizes in the Goodman study, in addition to a second dose of MMC. Importantly, within the Goodman cohort haematological toxicity resulted both 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 we have described here (only 5.7% of those managed with Capecitabine and 8.4% of the 5-FU cohort required a break due to toxicity).

However, gastrointestinal toxicity at grade three or above is seen in just 0% of the 5-FU cohort and 2% of the Capecitabine cohort described by Goodman et al. In contrast, we identified a 10% greater incidence of diarrhoea at grade three or above in patients managed with Capecitabine (17% vs. 7%). The contrasting relative excess of diarrhoea with 5-FU in the Goodman cohort may result from increased use of granulocyte colony stimulating factor (GCSF) - a side-effect of which is diarrhoea - for the relative excess of haematological toxicity seen in this group. It is in addition possible that the lower overall rates of grade three gastrointestinal toxicity seen in the Goodman series when compared to the results provided here reflects underestimation as a consequence of its retrospective approach.

Interestingly, an earlier assessment of Capecitabine dosage was undertaken by Deenen *et al* in a phase I analysis of CRT with IMRT in 18 patients (33). The reported maximum tolerated dose of Capecitabine taken on days in which radiotherapy was delivered within this study was 825 mg $m^{-2}$ B.I.D. These patients were incorporated in a subsequent single-centre retrospective series of 66 patients managed using IMRT with concurrent MMC and Capecitabine (23). Grade 4 toxicity was seen in five cases (9%), two of which were dermatological, two haematological and one was gastrointestinal; likely a consequence of all patients receiving a significantly higher dose than UK Guidance suggests (12 patients - 64.8Gy, 6 patients - 59.4Gy). Rates of grade three toxicity for haematological and other non-gastrointestinal parameters were otherwise consistent with our results. Only three per cent of patients were reported to have experienced grade-three gastrointestinal toxicity. This appears low when compared to the 17 per cent of patients in the cohort reported here for whom diarrhoea alone reached grade three in severity. In a comparator

cohort of 63 patients managed with either 3D-RT or IMRT and infusional 5-FU with MMC described within the same study, rates of gastrointestinal (2% vs. 3%), haematological (6% vs. 6%) and genitourinary (4% vs. 2%) toxicity were comparable, though significantly fewer patients experienced grade 3-4 dermatological toxicity (13% vs. 31%).

In a multicentre though, again, retrospective series, Thind *et al* report similar rates of gastrointestinal toxicity, with only three per cent of patients experiencing diarrhoea (26). Rates of skin toxicity were however far higher, with 63% experiencing a grade 3 toxicity compared with 27.6% reported by Meulenijks and 26% reported in our study. Despite this, only one patient required dose reduction of Capecitabine as a consequence of skin toxicity and the wide range in radiotherapy doses used is likely to have been a significant contributory factor to high rates of dermatitis. The proportion of patients completing planned chemotherapy was similar in both reports to that described within the series reported here.

Higher-level evidence has been provided by two small phase II studies, though patients managed with IMRT were in the minority and as such the toxicities reported may not be representative of CRT delivered with current radiotherapy techniques. In the EXTRA trial, Glynne-Jones *et al* report on the use of concurrent Capecitabine with MMC in 31 patients treated using conventional parallel-opposed pelvic fields in which the pelvis and groin were initially treated to 30.6 Gy with further shrinking fields applied to encompass the primary tumour and involved nodes to a total of 50.4 Gy (27). At 39%, skin toxicity was seen in a greater proportion of patients than reported here, as was haematological toxicity; 9.7% experienced neutropenia and 3.2% thrombocytopenia, compared with 2% and 0%, respectively. Gastrointestinal toxicities included both vomiting and diarrhoea, in 9.7% and 3.2% of patients. Only 68% of patients completed Capecitabine as initially planned, which the authors attribute to the median age of their cohort. Reassuringly, at 61 years this is identical to the series described here in which a comparably greater proportion of 79% of patients completed their planned course of Capecitabine without interruption or dose modification.

In the later of these phase II studies, Oliveira *et al* report on 43 patients managed with Capecitabine and MMC, though only 10 (23%) of these received IMRT with 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* state that outcomes for patients managed with Capecitabine and MMC were comparable to those treated with 5-FU and MMC, though supporting data is not provided (34). 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%) (35). 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 (36-41).

Limitations

There was no prospective matching of the comparator groups outlined in this cohort and the management of acute toxicity was as per centre protocol. Given that toxicity data were not submitted for all patients, it is in addition possible that these results are prone to responder bias. Despite these limitations, the cohort presented here is the largest to have been managed with IMRT 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 the use of prospective data collection. Whilst disease-free survival rates at 1 year appear comparable from the data presented here, neither this nor prior analyses are adequately powered to conclude on the relative efficacy of Capecitabine versus 5-FU. Finally, we have presented only toxicity at grades 3 and 4 in severity, though it is at this level that toxicity is most likely to influence choice of treatment agent.

## CONCLUSION

In this prospective national multi-centre series we have provided evidence for the use of Capecitabine as a tolerable alternative to 5-FU in the radical management of anal cancer with IMRT and single-dose MMC. We additionally provide further evidence for a comparatively better haematological toxicity profile from Capecitabine used in this context, though these data demonstrate a non-significant trend towards increased gastrointestinal toxicity. The Cancer Research UK funded PLATO trial (PersonaLising *Anal cancer* RadioTherapy dOse, ISRCTN88455282) is investigating the role of dose escalation in patients with locally advanced anal cancer in the ACT5 trial (42). This will provide prospective evidence for comparative toxicity using standard and two radiotherapy dose escalation arms where 5-FU and Capecitabine are allowed/used

## 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. 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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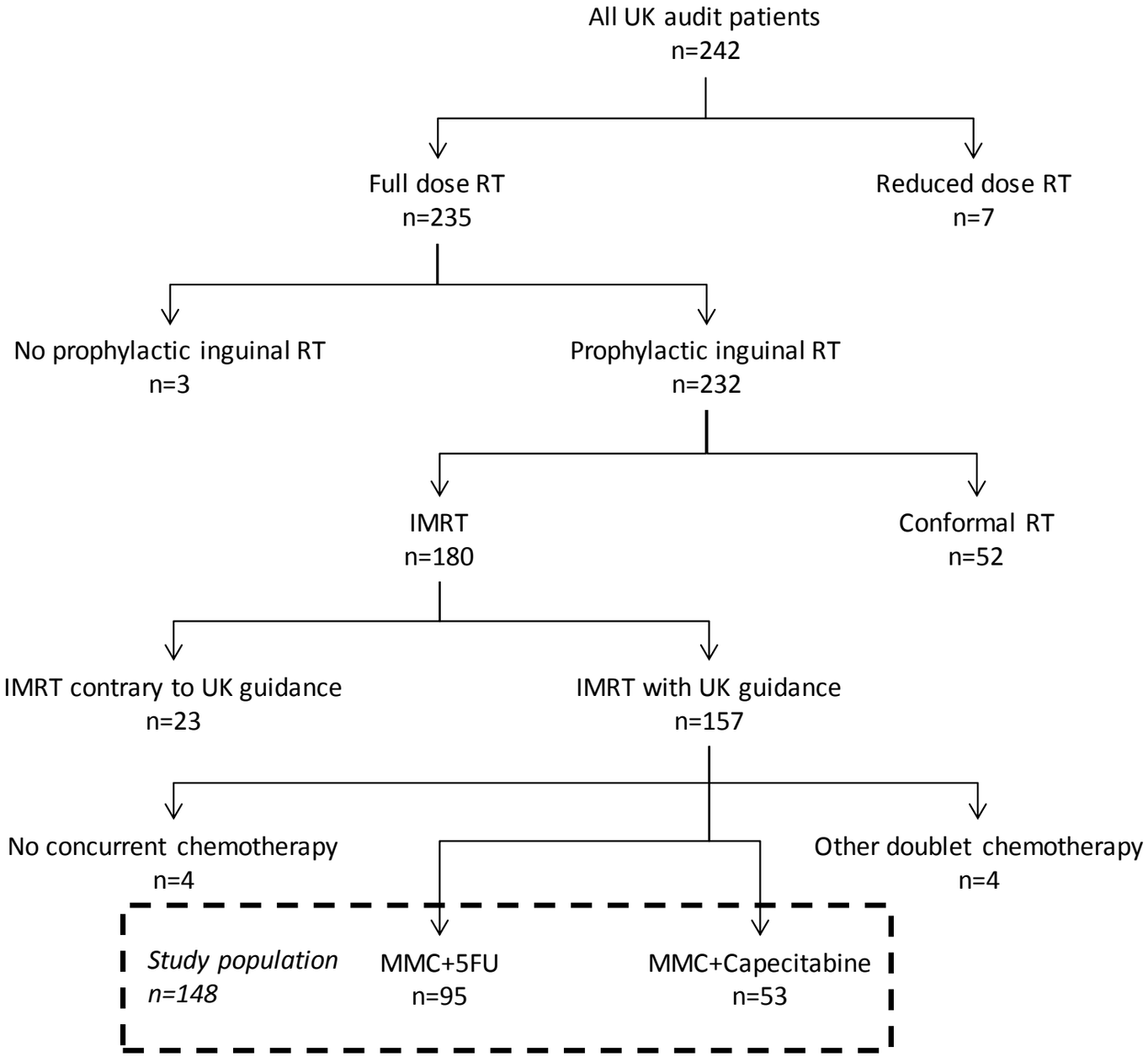
**FIGURES**

**Figure 1:** Study profile indicating participant selection from total audit population. All patients managed with 5FU & MMC had been diagnosed with anal squamous cell carcinoma (ASCC). On patient in the Capecitabine & MMC group was diagnosed with anal adenocarcinoma, with the remainder diagnosed as ASCC.



## TABLES

**Table 1:** Baseline characteristics for patients with anal cancer treated with radical intent using intensity modulated radiotherapy and concurrent chemoradiotherapy using MMC and either capecitabine or 5-FU.

| | **MMC & Capecitabine n=53** | **MMC & 5-FU n=95** | |
|---|---|---|---|
| | No. (%) | No. (%) | p-value |
| Sex | | | |
| Male | 19 (35.8) | 25 (26.3) | 0.26 |
| Female | 34 (64.2) | 70 (73.7) | |
| Age (years) | | | |
| <65 | 31 (58.0) | 56 (59.0) | 1.0 |
| ≥65 | 22 (42.0) | 39 (41.0) | |
| Smoking status | | | |
| Current smoker | 12 (22.6) | 24 (25.3) | 0.84 |
| Ex-smoker | 11 (20.8) | 17 (17.9) | |
| Never smoked | 24 (45.3) | 33 (34.7) | |
| Not known | 6 (11.3) | 21 (22.1) | |
| HIV status | | | |
| Positive | 3 (5.7) | 2 (2.1) | 0.34 |
| Negative | 28 (52.8) | 36 (37.9) | |
| Not tested | 22 (41.5) | 57 (60.0) | |
| Pre-treatment colostomy | | | |
| Yes | 6 (11.3) | 16 (16.8) | 0.47 |
| No | 47 (88.7) | 79 (83.2) | |

**Table 2:** Baseline disease characteristics for patients with anal cancer treated with radical intent using intensity modulated radiotherapy and concurrent chemoradiotherapy using MMC and either capecitabine or 5-FU.

| | **MMC & Capecitabine n=53** | **MMC & 5-FU n=95** | |
|---|---|---|---|
| | No. (%) | No. (%) | p-value |
| Tumour classification | | | |
| Squamous | 52 (98) | 95 (100) | 0.36 |
| Adenocarcimoma | 1 (2) | 0 (0) | |
| Tumour differentiation | | | |
| Well | 4 (8) | 5 (5) | 0.15 |
| Moderately | 25 (47) | 37 (39) | |
| Poorly | 11 (21) | 37 (39) | |
| Unknown | 13 (25) | 16 (17) | |
| Staging PET/CT | | | |
| Yes | 29 (55) | 32 (34) | *0.02* |
| No | 24 (45) | 63 (66) | |
| Primary tumour site | | | |
| Anal canal | 41 (77) | 75 (79) | 0.47 |
| Anal verge | 3 (6) | 9 (9) | |
| Distal rectum | 5 (9) | 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 (13) | 8 (8) | 0.59 |
| T2 | 24 (45) | 40 (42) | |
| T3 | 11 (21) | 27 (28) | |
| T4 | 11 (21) | 18 (19) | |
| Tx | 0 (0) | 2 (2) | |
| N-stage | | | |
| Negative | 23 (43) | 49 (52) | 0.39 |
| Positive | 30 (57) | 46 (48) | |
| M-stage | | | |
| M0 | 52 (98) | 89 (94) | 0.38 |
| M1 | 1 (2) | 3 (3) | |
| Mx | 0 (0) | 3 (3) | |

**Table 3:** Comparison of grade three and four toxicity during chemoradiotherapy seen in the group treated with Capecitabine and the group treated with 5-FU.

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

Key

G3 – Grade 3. G4 – Grade 4.

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

$ At an alpha value of 0.05 a Bonferroni adjusted p-value of less than 0.0045 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 mulitiple significance testing.

All p-values have been corrected for multiple significance testing using the Bonferroni method.

**Table 4:** Comparison of treatment interruptions following chemoradiotherapy for anal cancer with MMC and either Capecitabine or 5-FU.

| | | | **MMC & Capecitabine n=53** | **MMC & 5-FU n=95** | |
|---|---|---|---|---|---|
| | | | No. (%) | No. (%) | p-value |
| Median treatment duration | | | 38 days | 38 days | 1.0 |
| Radiotherapy | Received planned dose* | | 52 (98.1) | 89 (93.7) | 0.22 |
| | Treatment interruptions: | ≥1 Interruption | 6 (11.3) | 14 (14.7) | 0.63 |
| | | 1-3 Interruptions | 5 (9.4) | 11 (11.6) | 0.70 |
| | | 4-6 Interruptions | 0 (0.0) | 2 (2.1) | |
| | | >6 Interruptions | 1 (1.9) | 1 (1.1) | |
| | Reason for treatment interruption: | Toxicity | 3 (5.7) | 8 (8.4) | 0.29 |
| | | Unrelated to toxicity | 2 (3.8) | 6 (6.3) | |
| | | Not known | 1 (1.9) | 0 (0.0) | |
| Chemotherapy | Completed as planned | | 42 (79.2) | 85 (90.0) | 0.14 |
| | Reason for not completing treatment as planned: | Toxicity | 10 (18.9) | 9 (9.5) | 0.36 |
| | | 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 holidays.

**SUPPLEMENTARY DATA**

**Supplementary Table 1:** A summary of existing series outlining Capecitabine toxicity when used in combination with Mitomycin-C as part of radical chemoradiotherapy for anal cancer managed with curative intent

| **Study details** | | **Current series** | **Goodman** | **Oliveira** | **Meulinijks**[#] | **Thind** | **Glynne-Jones** |
|---|---|---|---|---|---|---|---|
| Year | | 2017 | 2017 | 2016 | 2014 | 2014 | 2008 |
| Type | | Prospective cohort | Retrospective | Phase II | Retrospective | Retrospective | Phase II |
| No. | | 53 | 44 | 43 | 66 | 66 | 31 |
| **Treatment** | | | | | | | |
| CT | Capecitabine dose** | | 825 mg/m$^2$ BID | 825 mg/m$^2$ BID | 825mg/m$^2$ BID (n=59)<br>500-650mg/m$^2$ BID (n=7) | 825mg/m$^2$ BID | 825mg/m$^2$ BID |
| | MMC dose | | 10mg/m$^2$ D1 & D29 | 15mg/m$^2$ D1 | 10mg/m$^2$ D1 | 12mg/m$^2$ D1 | 12mg/m$^2$ D1 |
| RT | Type | IMRT | IMRT | 3D RT (77%)<br>IMRT (23%) | IMRT | 3D RT (76%)<br>IMRT (24%) | 3D RT |
| | Planned dose | | 50Gy/25#<br>+ 6Gy/3# boost if tumour ≥2cm | 50.4-54Gy/28-30# | 45Gy/25# | 50.4Gy/28# | 50.4Gy/28# |
| **Patient demographics** | | | | | | | |
| Median age, *years* (range) | | 61 (29-81)* | 60 (42-84) | 57.4 (NR) | 59.3 (41-86) | 60 (44-82) | 61 (45-86) |
| M (%) | | 36 | 29 | 28 | 38 | 38 | 45 |
| HIV (%) | +ve : -ve : U | 6:53:42 | 8:92:0 | 9:91;0 | 7:47:47 | 1:99:0 | NR |
| Smoker (%) | Have ever : Never : U | 4:45:1 | NR | NR | NR | 26:74 | NR |
| PS (%) | 0:1:2:3 (%) | NR | NR | 49:51:0:0 | NR | 64:29:5:3 | NR |
| Colostomy pre-treatment (%) | | 11:89 | 2.0 | 4.7 | NR | NR | NR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Treatment tolerability** | | | | | | | |
| Average treatment time | | 38 (IQR 38-39) days | 37 (range 32-44) days | NR | NR | 5.5 (range 2.5-6) weeks | NR |
| RT | Requiring treatment break | 11.3% | 14.0% | 25.6% | NR | 0% | 12.9% |
| | Median treatment break | NR | NR | 12.2+/-10.3 days | NR | N/A | NR |
| | Reduced total dose received | 1.9% | 2.3% | 0.0% | NR | 2.0% | 6.5% |
| CT | Treated as planned | 79.2% | 70.0%*** | 46.2% | 86% | 80.0% | 68.0% |
| | Capecitabine dose reduction | 20.8% | 16.0% | 2.3% | NR | 20.0% | 6.5%[$$] |
| **Treatment toxicity** | | | | | | | |
| Non-haematological grade 3/4 toxicity | | | | | | | |
| GI | Nausea | 2% | NR | NR | | NR | 0% |
| | Vomiting | 2% | NR | 2.3% | | NR | 9.7% |
| | Diarrhoea | 17% | 2.0% | 4.6% | 3% (all GI) | 3.0% | 3.2% |
| | Stomatitis | 0% | 0.0% | NR | | 7.6% | 0% |
| | Dehydration | 0% | NR | 2.3% | | NR | NR |
| Skin | | 26% | 2.0% | 23.2% | 31% | 63.0% | 38.7% |
| Pain | | 19% | NR | NR | NR | NR | 0% |
| Cardiac | | 2% | NR | NR | NR | NR | 0% |
| Lethargy | | 0% | NR | NR | NR | NR | 0% |
| GU | | 0% | NR | NR | 2% | NR | 0% |
| Haematological grade 3/4 toxicity (%) | | | | | | | |
| Neutropenia | | 2.0% | 20.0% | 2.3% | | NR | 9.7% |
| Thrombocytopenia | | 0.0% | 9.0% | 2.3% | 6% (all haematological) | NR | 3.2% |
| Anaemia | | 2.0% | 7.0% | NR | | NR | 0.0% |
| Febrile neutropenia | | 2.0% | NR | NR | | NR | NR |

Key

3D RT: 3D conformal radiotherapy; #: Number of fractions; CT: chemotherapy; D: Day(s); GI: gastrointestinal; GU: genitourinary; Gy: Grays; IMRT: Intensity Modulated Radiotherapy; MMC: Mitomycin-C; NR: not recorded; PS: performance status; RT: radiotherapy; U: unknown.

* IQR shown in place of range

** Administered on days of radiotherapy unless otherwise stated.

*** 16% of patients required a reduction in the second dose of MMC and a further 27% did not receive a second dose of MMC.

# Includes a phase I dose escalation cohort published by Deenan *et al* at three Capecitabine dose levels: 500 mg/m$^2$ (n=3), 650 mg/m$^2$ (n=4) and 825mg/m$^2$ (n=11).

$ Mean +/- SD. $$ Mean (IQR)

$$ A reduced dose of Capecitabine was administered in two further patients due to prescribing/administration error

**Supplementary Table 2**: Mitomycin-C dosing in existing phase three studies.

| Trial | Day 1 | Day 29 | Total |
|---|---|---|---|
| **ACT I** | MMC 12mg/m2 | None | MMC 12mg/m2 |
| **EORTC** | MMC 12mg/m2 | None | MMC 12mg/m2 |
| **RTOG 8704** | MMC 10mg/m2 | MMC 10mg/m2 | MMC 20mg/m2 |
| **RTOG 9811** | MMC 10mg/m2 | MMC 10mg/m2 | MMC 20mg/m2 |
| **ACT II** | MMC 12mg/m2 (max dose 20mg) | None | MMC 12mg/m2 |