Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial

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Summary

Background Chemoradiation became the standard of care for anal cancer after the ACT I trial. However, only two-thirds of patients achieved local control, with 5-year survival of 50%; therefore, better treatments are needed. We investigated whether replacing mitomycin with cisplatin in chemoradiation improves response, and whether maintenance chemotherapy after chemoradiation improves survival.

Methods In this 2×2 factorial trial, we enrolled patients with histologically confirmed squamous-cell carcinoma of the anus without metastatic disease from 59 centres in the UK. Patients were randomly assigned to one of four groups, to receive either mitomycin (12 mg/m² on day 1) or cisplatin (60 mg/m² on days 1 and 29), with fluorouracil (1000 mg/m² per day on days 1–4 and 29–32) and radiotherapy (50·4 Gy in 28 daily fractions); with or without two courses of maintenance chemotherapy (fluorouracil and cisplatin at weeks 11 and 14). The random allocation was generated by computer and patients assigned by telephone. Randomisation was done by minimisation and stratified by tumour site, T and N stage, sex, age, and renal function. Neither patients nor investigators were masked to assignment. Primary endpoints were complete response at 26 weeks and acute toxic effects (for chemoradiation), and progression-free survival (for maintenance). The primary analyses were done by intention to treat. This study is registered at controlled-trials.com, number 26715889.

Findings We enrolled 940 patients: 472 were assigned to mitomycin, of whom 246 were assigned to no maintenance, 226 to maintenance; 468 were assigned to cisplatin, of whom 246 were assigned to no maintenance, 222 to maintenance. Median follow-up was 5·1 years (IQR 3·9–6·9). 391 of 432 (90·5%) patients in the mitomycin group versus 386 of 431 (89·6%) in the cisplatin group had a complete response at 26 weeks (difference –0·9%, 95% CI –4·9 to 3·1; p=0·64). Overall, toxic effects were similar in each group (334/472 [71%] for mitomycin *vs* 337/468 [72%] for cisplatin). The most common grade 3–4 toxic effects were skin (228/472 [48%] *vs* 222/468 [47%]), pain (122/472 [26%] *vs* 135/468 [29%]), haematological (124/472 [26%] *vs* 73/468 [16%]), and gastrointestinal (75/472 [16%] *vs* 85/468 [18%]). 3-year progression-free survival was 74% (95% CI 69–77; maintenance) versus 73% (95% CI 68–77; no maintenance; hazard ratio 0·95, 95% CI 0·75–1·21; p=0·70).

Interpretation The results of our trial—the largest in anal cancer to date—show that fluorouracil and mitomycin with 50·4 Gy radiotherapy in 28 daily fractions should remain standard practice in the UK.

Funding Cancer Research UK.

Introduction

The incidence of squamous-cell cancer of the anus is roughly 1·5 cases per 100 000 people per year worldwide (900 cases per year in the UK, 5000 in the USA), and is increasing, particularly in women.[1,2] Improving locoregional control without need for a colostomy is the primary aim of treatment. Chemoradiation became the standard of care for treatment of squamous-cell cancer of the anus after three phase 3 trials[3–5] showed that radiotherapy with concurrent fluorouracil and mitomycin resulted in better local control and recurrence-free or progression-free survival than did radiotherapy alone, or radiotherapy with fluorouracil. The first UK anal cancer trial (ACT I)[3,6] showed a reduction in locoregional failure—from 59% to 36%—with this combined treatment, sustained after 13 years. However, local control was achieved in only around two-thirds of patients, with a 5-year survival of roughly 50% for mitomycin and fluorouracil plus radiotherapy; 40% of deaths were caused by distant spread.[3] Although the benefits of adding mitomycin to fluorouracil and radiotherapy were established by the Radiotherapy Therapy Oncology Group 8704 trial,[5] mitomycin can cause life-threatening toxic effects and treatment-related deaths.[3,5]

ACT II was therefore designed to test whether these outcomes could be improved. The rationale for comparing

cisplatin instead of mitomycin with fluorouracil-based chemoradiation was based on seemingly higher complete response rates with cisplatin,[7–9] and acceptable acute toxic effects in phase 2 trials. Other randomised phase 3 trials[10,11] by the Radiotherapy Therapy Oncology Group (RTOG 98-11) and the Action Clinique Coordonees en Cancerologie Digestive (ACCORD-03), done while ACT II was being designed, were testing neoadjuvant cisplatin-based chemotherapy and dose-escalation of the radiotherapy boost. A maintenance chemotherapy schedule including cisplatin after chemoradiation was included to test whether intensifying treatment in this way would decrease the rate of distant disease and therefore improve survival. Our group previously piloted the feasibility of additional maintenance chemotherapy with three courses of fluorouracil, mitomycin, and cisplatin after chemo-radiation.[12] The main objectives of ACT II were to assess whether cisplatin given concurrently with fluorouracil and radiotherapy produces a higher clinical and radiological response rate than does mitomycin, with acceptable toxic effects, and whether two courses of fluorouracil and cisplatin maintenance chemotherapy after chemoradiation improves progression-free survival (ie, improve local control or prolong survival by preventing or delaying disease dissemination).

Methods

Study design and participants

ACT II was a randomised 2×2 factorial trial done in 59 radiotherapy centres in the UK between June 4, 2001, and Dec 16, 2008. Patients were eligible if they had histologically confirmed invasive squamous cell, basaloid or cloacogenic carcinoma of the anal canal and margin that was deemed fit for investigated treatment; a glomerular filtration rate of more than 50 mL/min; acceptable blood test results (haemoglobin >100 g/L, $>1\times10^{11}$ platelets per L, $>3\times10^{9}$ white blood cells per L); liver function tests within two times the normal range; and adequate cardiac function. Exclusion criteria were metastatic disease, other major malignancy likely to compromise life expectancy or completion of trial treatment, comorbidity including being HIV-positive and cardiac diseases, previous complete local excision, and previous radiotherapy to the pelvis. The study was approved by local research ethics committees, and all patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned before starting initial treatment to one of four treatment groups. Patients received fluorouracil-based chemoradiation with either concurrent mitomycin or cisplatin and with either maintenance chemotherapy or no maintenance chemotherapy. The random treatment allocation was generated by a computer program (in the trial coordinating centre). Site staff telephoned the trials centre to receive the allocation for the next patient. Patients, clinicians (including those assessing patients), and investigators analysing data were not masked to treatment allocation. Minimisation was used and stratified according to primary site (canal *vs* margin), T stage, N stage, age (<65 years *vs* ≥65 years), sex, and glomerular filtration rate (<60 mL/min *vs* ≥60 mL/min). Patients with low risk tumours (T1,N0) or those deemed inappropriate for maintenance treatment by the treating clinician were not assigned to the maintenance group.

Procedures

Radiotherapy of 50·4 Gy was delivered in 28 daily fractions over 5·5 weeks with a two-phase technique. Phase 1 delivered 30·6 Gy in 17 daily fractions to the International Commission of Radiological Units and Measurements (ICRU) intersection point, as determined following the guidelines in ICRU report 50,[13] using non-conformal rectangular parallel-opposed fields aiming to treat all pelvic nodes (except the common iliac) to a dose of 30·6 Gy. Phase 2 was conformally planned using CT images to deliver 19·8 Gy to the ICRU intersection point in 11 daily fractions over 15 days (weekends excluded) treating the primary tumour and the whole anal canal with a 3 cm margin around all macroscopic tumours defining the field size (for further details see protocol, available from the UCL Clinical Trials Centre website). The quality assurance of this trial will be reported elsewhere.

For the **UCL Clinical Trials Centre** see http://www.ctc.ucl.ac.uk

Patients received fluorouracil 1000 mg/m² per day on days 1–4 (week 1) and 29–32 (week 5) by continuous 24 h intravenous infusion with radiotherapy, and either 12 mg/m² of mitomycin as an intravenous bolus on day 1 only (maximum single dose 20 mg) or 60 mg/m² of cisplatin by intravenous infusion on days 1 and 29 (up to a maximum surface area of 2·0 m², therefore maximum single dose was 120 mg). Dose reductions were allowed for patients with a glomerular filtration rate of 50–59 mL/min, and for the second course of chemotherapy because of toxic effects. Maintenance chemotherapy

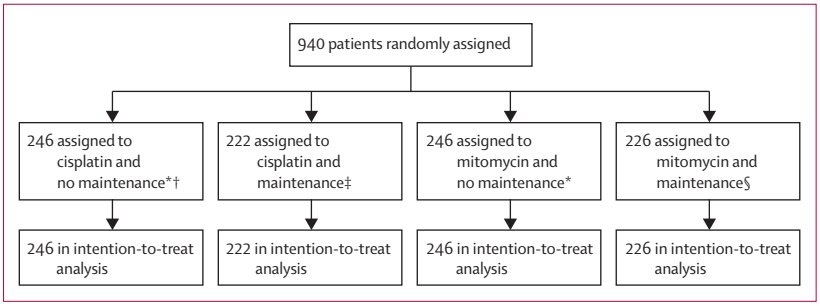

Figure 1: **Trial profile**
Four patients assigned to cisplatin received mitomycin: two treated off trial, one administrative error, one had an inadequate glomerular filtration rate; two patients assigned to mitomycin received cisplatin during week 5 of chemoradiation: one treated off trial, one because of toxic effects (see appendix for details of compliance). *23 patients assigned to the cisplatin group and 23 assigned to the mitomycin group were not eligible for maintenance randomisation and were excluded from the analysis of progression-free survival for the maintenance endpoint. †One patient ineligible (adenocarcinoma). ‡One patient ineligible (liver metastasis). §One patient ineligible (high volume of pelvic nodal disease).

consisted of two additional courses of fluorouracil (1000 mg/m² per day on days 71–74 [week 11] and 92–95 [week 14]) and cisplatin (60 mg/m² on days 71 and 92).

Patients were staged according to the Union International Contre Le Cancer staging system.[14] All patients had abdominopelvic CT scan and chest radiography (or whole body CT); MRI and PET were not essential. Patients were assessed for tumour response by digital examination using the Response Evaluation Criteria in Solid Tumors (RECIST)[15] at 11, 18, and 26 weeks from the start of treatment. Routine biopsies were not recommended because of the risk of radionecrosis but the 26-week assessment included imaging (abdominopelvic CT and radiography and whole body CT) as at baseline. Residual or recurrent disease was confirmed by biopsy sample before further treatment when the results of other

	Mitomycin, no maintenance n=246*	Cisplatin, no maintenance n=246*	Mitomycin, maintenance n=226	Cisplatin, maintenance n=222
Median age (IQR; years)	60 (52–65)	57 (51–65)	57 (50–65)	58 (50–66)
Age <65 years	184 (75%)	184 (75%)	166 (73%)	165 (74%)
Age ≥65 years	62 (25%)	62 (25%)	60 (27%)	57 (26%)
Sex				
Female	153 (62%)	153 (62%)	141 (62%)	140 (63%)
Male	93 (38%)	93 (38%)	85 (38%)	82 (37%)
Site of primary tumour				
Canal	202 (82%)	208 (85%)	187 (83%)	190 (86%)
Margin	38 (15%)	33 (13%)	35 (15%)	26 (12%)
Not reported	6 (2%)	5 (2%)	4 (2%)	6 (3%)
T stage				
T1	25 (10%)	24 (10%)	21 (9%)	21 (9%)
T2	99 (40%)	109 (44%)	87 (39%)	100 (45%)
T3	80 (33%)	71 (29%)	79 (35%)	65 (29%)
T4	33 (13%)	34 (14%)	33 (15%)	35 (16%)
TX	9 (4%)	6 (2%)	6 (3%)	1 (<1%)
Not reported	0	2 (<1%)	0	0
Nodal status				
Negative	156 (63%)	155 (63%)	141 (62%)	135 (61%)
Positive	77 (31%)	78 (32%)	73 (32%)	77 (35%)
NX	13 (5%)	10 (4%)	11 (5%)	10 (5%)
Not reported	0	3 (1%)	1 (<1%)	0
Glomerular filtration rate				
<60 (mL/min)	13 (5%)	12 (5%)	12 (5%)	8 (4%)
≥60 (mL/min)	233 (95%)	234 (95%)	214 (95%)	214 (96%)
Differentiation				
Well	29 (12%)	38 (15%)	25 (11%)	29 (13%)
Moderate	100 (41%)	102 (41%)	104 (46%)	89 (40%)
Poor	75 (30%)	73 (30%)	60 (27%)	69 (31%)
Unknown	42 (17%)	32 (13%)	37 (16%)	35 (16%)
Not reported	0	1 (<1%)	0	0
Tumour type				
Basaloid	28 (11%)	25 (10%)	29 (13%)	26 (12%)
Cloacogenic	5 (2%)	5 (2%)	3 (1%)	1 (<1%)
Squamous	201 (82%)	201 (82%)	182 (81%)	185 (83%)
Unknown	12 (5%)	14 (6%)	12 (5%)	10 (5%)
Not reported	0	1 (<1%)	0	0
Pretreatment colostomy				
No	213 (87%)	210 (85%)	191 (85%)	192 (86%)
Yes	31 (13%)	36 (15%)	35 (15%)	29 (13%)
Not reported	2 (<1%)	0	0	1 (<1%)

*23 patients in the mitomycin group and 23 in the cisplatin group were not randomly assigned to maintenance or no maintenance groups.

Table 1: **Baseline characteristics**

assessments were ambiguous. Toxic effects were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Adverse events were assessed weekly during weeks 1–8 of concurrent chemoradiotherapy. Haematological toxic effects were assessed at week 11 for all patients, and for those receiving maintenance treatment, haematological toxic effects were checked before the first and second cycles of maintenance treatment and non-haematological toxic effects were checked weekly until 30 days after the last dose of study drug.

After the assessment at week 26, patients were reassessed once every 2 months in the first year, once every 3 months in the second year, once every 6 months until the fifth year, and yearly thereafter. Abdominopelvic CT was done at 12 and 24 months after the start of treatment and afterwards only when clinically indicated or if the patient had signs or symptoms of recurrence.

For the comparison of mitomycin with cisplatin the primary endpoints were complete response (complete disappearance of clinically or radiologically overt disease) at 26 weeks from start of chemoradiation, and grade 3 or 4 acute toxic effects for 4 weeks after chemoradiation (haematological, gastrointestinal, and genitourinary). For the comparison of maintenance with no maintenance treatment the primary endpoint was progression-free survival.

Secondary endpoints included colostomy-free survival (including pretreatment colostomies not reversed within 8 months after starting treatment, or any colostomies after treatment); in-field recurrence rate; cause-specific survival; and overall survival (death from any cause). We also analysed progression-free survival by treatment during chemoradiation; by disease stage (T1 or T2 and T3 or T4); and by node status (node positive and node negative disease).

Statistical analysis

We calculated a target sample size of 950 patients based on detecting an improvement in 3-year progression-free survival from 75·0% to 82·5% (for the maintenance comparison). This sample size would enable us to detect an increase in the number of patients with complete response from 90% to 95% for cisplatin versus mitomycin. Both comparisons had 80% power and two-sided 5% statistical significance. We used 99% CIs in the subgroup analyses to account for having multiple comparisons. The sample size was increased in March, 2007, from 600 to 950 patients, on the recommendation of the independent data monitoring committee because fewer progression-free survival events occurred than expected.

Events included in progression-free survival were progressive disease, local recurrence (with or without metastatic disease), metastases, or death from any cause, but new tumours were not included. Colostomy-free survival events were all post-treatment colostomies,

	Mitomycin group (n=432)	Cisplatin group (n=431)
Complete response	391 (90·5%)	386 (89·6%)
Partial response	14 (3·2%)	24 (5·6%)
Stable disease	5 (1·2%)	6 (1·4%)
Progressive disease	22 (5·1%)	15 (3·5%)

Table 2: **Primary tumour response at 26 weeks**

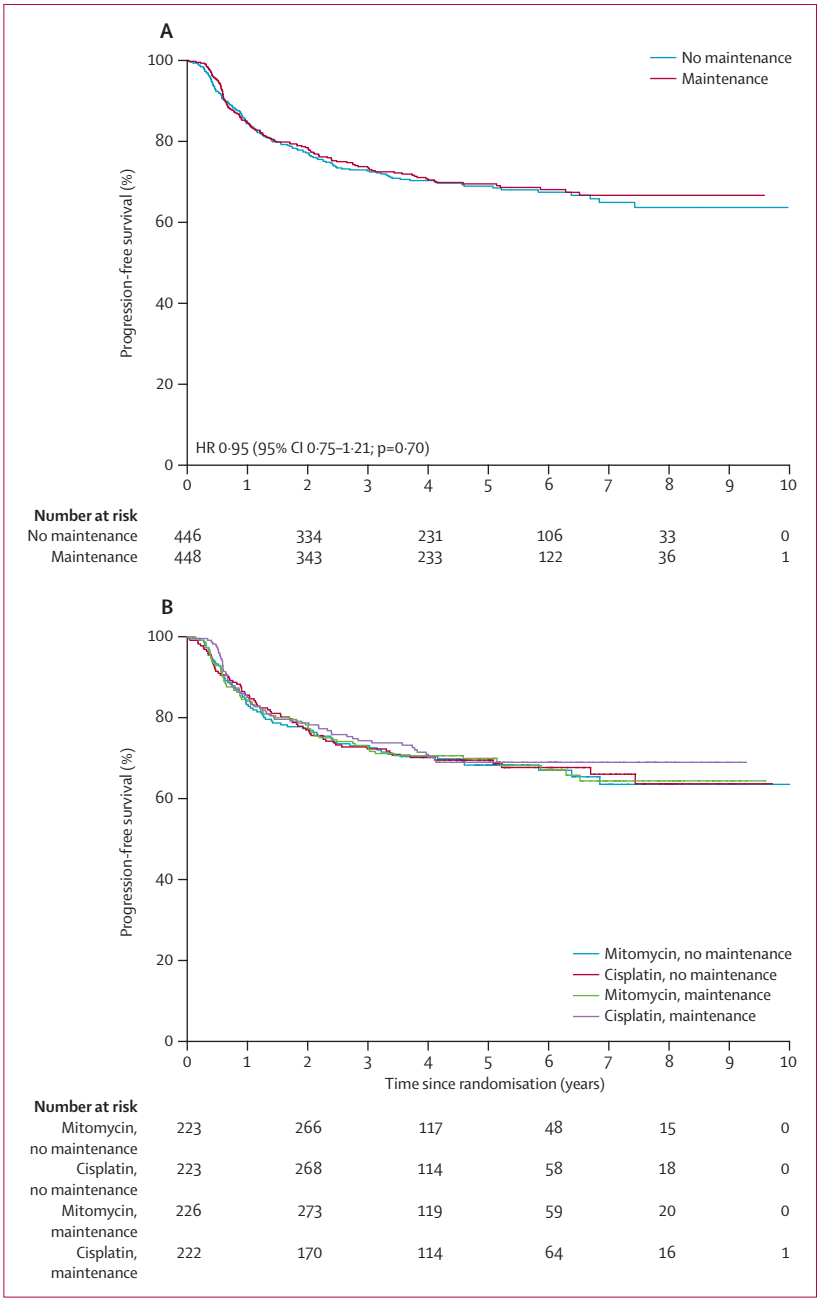

Figure 2: **Progression-free survival**
Comparing the maintenance versus no maintenance groups (A), and all four groups (B). The four curves in B overlap, providing no evidence for an interaction between chemoradiotherapy regimen and maintenance (p=0·94).

pretreatment colostomies not reversed within 8 months from the start of treatment, and death from any cause. The maximum toxic effect grade was used for each patient and each event type.

All survival endpoints were measured from the date of randomisation, and patients who did not have the event of interest were censored at the date of last follow-up. Data about deaths were also obtained from the Office for National Statistics. We used Kaplan-Meier analysis and Cox regression to analyse the endpoints. We tested the proportional hazards assumption with Schoenfeld residuals. All analyses were intention-to-treat unless otherwise specified (done with STATA version 12) and all p-values are two-sided.

See Online for appendix

This study is registered at controlled-trials.com, number 26715889.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RJ, RG-J, and DS-M had final responsibility for the decision to submit for publication. The corresponding author had full access to all the data.

Results

We enrolled 940 patients (figure 1). Baseline characteristics were balanced (table 1). Overall, median age was 58 years (IQR 51–65); 486 patients (52%) had a primary tumour of 5 cm or less in diameter (T1 or T2) versus 430 (46%) who had one of more than 5 cm (T3 or T4). 305 (32%) had positive lymph nodes, and 787 (84%) had a tumour in the anal canal, 132 (14%) in the anal margin, and 21 (2%) were unknown. Median follow-up, censoring deaths, was 5·1 years (IQR 3·9–6·9). 46 patients had T1,N0 tumours or were deemed inappropriate for maintenance treatment by the treating clinician, and therefore were not assigned to the maintenance group. These patients were excluded from the analysis of progression-free survival for the maintenance endpoint.

Compliance to radiotherapy was good with few patients failing to complete the planned dose of 50·4 Gy in either group (37 of 472 [8%] in the mitomycin group and 44 of 468 [9%] in the cisplatin group). 370 of 472 patients (78%) in the mitomycin group versus 352 of 468 (75%) in the cisplatin group completed radiotherapy as planned (ie, with no treatment gap or dose reduction; appendix). The median total radiotherapy dose was 50·4 Gy (IQR 50·4–50·4) for both mitomycin and cisplatin groups. 926 of 940 patients (99%) completed phase 1 of radiotherapy as per protocol. Median overall treatment time was 38 days (IQR 38–39) in both the mitomycin and cisplatin groups. Only 126 patients (13%) had interruptions to treatment for a maximum of 7 days: 59 in the mitomycin group and 67 in the cisplatin group. Only 18 patients—nine in the mitomycin group and nine cisplatin group—had interruptions to treatment for 8 days or more.

862 of 940 (92%) patients received the full first course of fluorouracil with mitomycin or cisplatin without delays or dose reductions (433 of 472 in the mitomycin group, 429 of 468 in the cisplatin group, appendix). 15 patients in the mitomycin group and 18 in the cisplatin group had chemotherapy in week 1 only. 703 of 940 patients (75%) completed the entire chemotherapy regimen during chemoradiation without delays or dose reductions (365 of 472 in the mitomycin group, 338 of 468 in the cisplatin group). Of the 237 who did not, 222 (94%) had either dose delays, reductions, or both in line with protocol recommendations or to prevent toxic effects. Only two (<1%) were not given any chemotherapy during chemoradiation (one died and did not have radiotherapy, and one withdrew from the study, both in the cisplatin group; not excluded from the intention-to-treat analysis); and data were missing for six patients in the cisplatin group and seven in the mitomycin group. The main reasons for non-completion were toxic effects (66 patients in the mitomycin group and 78 in the cisplatin group).

357 of 448 (80%) patients assigned to receive maintenance chemotherapy started treatment. 286 (64%) completed the first course of treatment according to schedule, and 196 (44%) completed both courses without any delay or dose reduction (105 of 226 [46%] in the mitomycin group and 91 of 222 [41%] assigned to cisplatin; appendix). 119 patients had dose modification because of toxic effects. 91 patients assigned to maintenance did not receive it, 41 of the 91 (45%) choosing not to receive any maintenance chemotherapy (appendix).

77 of 940 patients (8%) were not assessed for response at 26 weeks (appendix) and therefore were excluded from response analysis (18 in the mitomycin, no maintenance group; 21 in the cisplatin, no maintenance group, 22 in

	Mitomycin, no maintenance (N=246)	Cisplatin, no maintenance (N=246)	Mitomycin, maintenance (N=226)	Cisplatin, maintenance (N=222)
Anal cancer*	34 (14%)	41 (17%)	38 (17%)	34 (15%)
Treatment-related deaths				
During or up to 4 weeks after chemoradiation†	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
5–8 weeks after chemoradiation‡	1 (<1%)	0	2 (1%)	0
During or after maintenance	0	0	1 (<1%)§	0
Other cancer	3 (1%)	7 (3%)	3 (1%)	7 (3%)
Non-cancer	9 (4%)	8 (3%)	4 (2%)	3 (1%)
Not known	2 (1%)	0	4 (2%)	6 (3%)

Data are n (%). Of the 46 patients assigned to mitomycin or cisplatin, but not randomly assigned to a maintenance group, ten died: seven from anal cancer, one related to surgery, one from another cancer, and one not related to cancer. *Includes three post-surgery deaths. †One case of neutropenic sepsis in the mitomycin, no maintenance group; one acute myocardial infarction in the cisplatin, no maintenance group; one case of pancolitis in the mitomycin, maintenance group; and one bowel perforation in the cisplatin, maintenance group. ‡The precipitating event was non-neutropenic sepsis in all three patients. Although all were taking mitomycin, it is unlikely that any of these deaths are attributable to mitomycin only. §A cerebrovascular event 6 days after second course of maintenance treatment.

Table 3: **Causes of death**

	Mitomycin group (N=472)			Cisplatin group (N=468)		
	Grade 3	Grade 4	Grade 3 or 4*	Grade 3	Grade 4	Grade 3 or 4*
Non-haematological†	249 (53%)	45 (10%)	294 (62%)	271 (58%)	45 (10%)	316 (68%)
Gastrointestinal	91 (19%)	3 (1%)	75 (16%)	125 (27%)	5 (1%)	85 (18%)
Nausea	10 (2%)	0	10 (2%)	25 (5%)	0	25 (5%)
Vomiting	9 (2%)	0	9 (2%)	20 (4%)	1 (<1%)	21 (4%)
Diarrhoea	43 (9%)	1 (<1%)	44 (9%)	42 (9%)	3 (1%)	45 (10%)
Stomatitis	14 (3%)	0	14 (3%)	19 (4%)	1 (<1%)	20 (4%)
Other gastrointestinal	15 (3%)	2 (<1%)	16 (3%)	19 (4%)	0	19 (4%)
Genitourinary	5 (1%)	1 (<1%)	6 (1%)	7 (1%)	1 (<1%)	8 (2%)
Skin	193 (41%)	35 (7%)	228 (48%)	201 (43%)	21 (4%)	222 (47%)
Pain	114 (24%)	8 (2%)	122 (26%)	120 (26%)	15 (3%)	135 (29%)
Cardiac	7 (1%)	7 (1%)	7 (1%)	2 (<1%)	4 (<1%)	6 (1%)
Vascular	1 (<1%)	2 (<1%)	7 (1%)	2 (<1%)	1 (<1%)	3 (<1%)
Other non-haematological	35 (7%)	4 (<1%)	34 (7%)	50 (11%)	8 (2%)	50 (11%)
Haematological†	107 (23%)	17 (4%)	124 (26%)‡	60 (13%)	13 (3%)	73 (16%)‡
White blood cells	103 (22%)	13 (3%)	112 (24%)§	48 (10%)	8 (2%)	55 (12%)§
Platelets	19 (4%)	2 (<1%)	21 (4%)	2 (<1%)	3 (1%)	5 (1%)
Haemoglobin	1 (<1%)	1 (<1%)	2 (<1%)	1 (5%)	2 (<1%)	7 (1%)
Febrile neutropenia	3% (14)	1 (<1%)	15 (3%)	12 (3%)	2 (<1%)	14 (3%)
Other haematological	5 (2%)	3 (<1%)	7 (3%)	0	0	0
Any toxic effect†	297 (63%)	60 (13%)	334 (71%)	297 (63%)	56 (12%)	337 (72%)

Eight of 940 patients died as a consequence of treatment.*Only the highest grade is counted and patients with more than one toxic effect of a particular grade were counted only once. †Patients with more than one toxic effect counted only once. ‡p=0·0001. §p<0·0001.

Table 4: **Grade 3–4 adverse events during chemoradiation**

the mitomycin, maintenance group; and 16 in the cisplatin, maintenance group). 386 (89·6%) in the cisplatin group and 391 (90·5%) in the mitomycin group had a complete response at 26 weeks; absolute difference –0·9% (95 CI –4·9 to 3·1; p=0·64; table 2).

We assessed progression-free survival in 223 patients in the cisplatin, no maintenance group; 222 in the cisplatin, maintenance group; 223 in the mitomycin, no maintenance group; and 226 in the mitomycin, maintenance group. We recorded 292 progression-free survival events. 3-year progression-free survival was 74% (95% CI 69–77) in the maintenance group and 73% (68–77) in the no maintenance group (HR 0·95, 95% CI 0·75–1·21; p=0·70; figure 2). Progression-free survival did not differ significantly between patients who took mitomycin and cisplatin during chemoradiation (HR 0·95, 95% CI 0·75–1·19; p=0·63; appendix). 3-year progression-free survival of patients without maintenance treatment was 73% (95% CI 67–78) in the mitomycin group versus 72% (66–78) in the cisplatin group; for those who were given maintenance treatment, it was 73% (66–78) versus 74% (68–80).

3-year progression-free survival of patients with stage T1 or T2 disease was 80% (95% CI 74–84) for patients taking maintenance treatment, 84% (78–88) for those not taking maintenance treatment, 80% (74–84) for those taking mitomycin, and 83% (78–87) for those taking cisplatin. The respective progression-free survivals for T3 or T4 disease were 67% (60–73), 62% (55–68), 65% (59–71), and 62% (55–69). Overall progression-free survival was 68% (62–73) for node-positive patients and 76% (72–79) for node-negative patients; with similar rates for the treatment groups (67% [59–74] with mitomycin *vs* 69% [61–76] with cisplatin for node-positive disease; 76% [70–80] *vs* 76% [71–81] for node-negative disease). The overlapping curves in figure 2B suggest no interaction between the two treatment strategies (p=0·94).

211 patients died, 155 from anal cancer (including treatment-related deaths; table 3). Overall survival did not differ substantially between groups (appendix). The HR for cisplatin versus mitomycin was 1·05 (95% CI 0·80–1·38; p=0·70); and for maintenance versus no maintenance the HR was 1·07 (0·81–1·41; p=0·65). 3-year anal cancer survival rates were also much the same for each treatment group (appendix).

118 of 884 (13%) assessable patients had colostomies at randomisation (appendix). 20 of these colostomies (17%) were reversed within 8 months from the start of treatment. 112 patients had a post-treatment colostomy because of anal cancer (n=98) or morbidity (n=14). 3-year colostomy-free survival was 73% (95% CI 67–79) in the mitomycin, maintenance group, 75% (68–80) in the cisplatin, maintenance group, 75% (68–80) in the mitomycin, no maintenance group, and 72% (66–77) in the cisplatin, no maintenance group (appendix). 3-year colostomy-free survival was 84% (81–88) for patients

	Mitomycin group (N=226)			Cisplatin group (N=222)		
	Grade 3	Grade 4	Grade 3–4*	Grade 3	Grade 4	Grade 3–4*
Non-haematological†	28 (12%)	4 (2%)	32 (14%)	30 (14%)	3 (1%)	33 (15%)
Gastrointestinal	17 (8%)	1 (<1%)	15 (7%)	18 (8%)	1 (<1%)	14 (6%)
Nausea	0	0	0	0	0	0
Vomiting	3 (1%)	0	3 (1%)	2 (1%)	0	2 (1%)
Diarrhoea	8 (4%)	0	8 (4%)	7 (3%)	0	7 (3%)
Stomatitis	4 (2%)	0	4 (2%)	5 (2%)	1 (<1%)	6 (3%)
Other gastrointestinal	2 (<1%)	1 (<1%)	3 (1%)	4 (2%)	0	3 (1%)
Genitourinary	1 (<1%)	0	1 (<1%)	0	0	0
Skin	3 (1%)	0	3 (1%)	5 (2%)	2 (1%)	7 (3%)
Pain	4 (2%)	0	4 (2%)	8 (4%)	0	8 (4%)
Cardiac	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Vascular	1 (<1%)	4 (2%)	5 (2%)	2 (<1%)	0	2 (<1%)
Other non-haematological	12 (5%)	0	12 (5%)	9 (4%)	0	9 (4%)
Haematological†	7 (3%)	2 (1%)	9 (4%)	4 (2%)	3 (1%)	7 (3%)
White blood cells	6 (3%)	0	6 (3%)	4 (2%)	0	4 (2%)
Platelets	0	1 (<1%)	1 (<1%)	0	2 (1%)	2 (1%)
Haemoglobin	0	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Febrile neutropenia	1 (<1%)	0	1 (<1%)	0	0	0
Any toxic effect†	33 (15%)	6 (3%)	39 (17%)	33 (15%)	6 (3%)	39 (18%)

*The highest grade alone counted and patients with more than one toxicity of a particular grade counted only once.
†Patients with more than one toxic effect counted only once.

Table 5: **Reported grade 3–4 adverse events during maintenance treatment**

with T1 or T2 disease and 61% (56–66) for patients with T3 or T4 disease.

Toxic effects during chemoradiation were as expected for this population and were much the same in the mitomycin and cisplatin treatment groups (table 4). The proportion of patients who had a maximum grade 1–2 adverse event was 133 of 472 (28%) in the mitomycin group versus 126 of 468 (27%) in the cisplatin group and the proportion of patients who had grade 3–4 adverse events was 334 of 472 (71%) versus 337 of 468 (72%; table 4), although more patients had grade 3 haematological toxic effects in the mitomycin group than in the cisplatin group (26% *vs* 16%; p<0·001). Grade 3 or 4 toxic effects were generally uncommon, and occurred in similar proportions in patients who had previously taken mitomycin (39/226; 17%) and those who had previously taken cisplatin (39/222; 18%; table 5). Treatment-related mortality was less than 1% (n=8, four died during or up to 4 weeks after chemoradiation, three died 5–8 weeks after chemoradiation, and one died shortly after maintenance; table 3). Subgroup analyses according to baseline characteristics did not show significant differences in progression-free survival for any comparison (appendix), or overall survival (data not shown).

Discussion

Our results show no evidence of any improvement in the complete response rate or 3-year progression-free survival, and similar acute grade 3–4 toxic effects, when fluorouracil plus cisplatin chemoradiation is compared with fluorouracil plus mitomycin chemoradiation. Our 2×2 randomisation enables us to examine complete response to chemoradiation with either concurrent mitomycin or cisplatin in a straightforward and simple manner, and also to test the benefit of adding further maintenance chemotherapy after initial chemoradiation to assess whether it enhances the chemoradiation response, or improves progression-free survival. Also, our trial is the first anal cancer trial to include continuous radiotherapy (panel).

A key strength of ACT II is that it was done nationally in academic, regional, small centres and captured 20–25% of patients presenting with anal cancer in the UK. The results can therefore be extrapolated to many real world situations. Preliminary results from our trial have already been used to guide practice.[17] Also, maintenance chemotherapy with fluorouracil and cisplatin—which had been used in some places—could now be stopped, and future patients can avoid unnecessary treatment (as well as reducing financial costs).

Although grade 3–4 haematological toxic effects were less common with fluorouracil plus cisplatin (26% *vs* 16%) patients, these were almost entirely related to white blood cells but were not sufficient to increase neutropenic sepsis. This marginal benefit is likely to be outweighed by the extra resources needed to administer cisplatin—two courses of either all day or overnight intravenous treatment with hydration, compared with only a single dose of mitomycin delivered over 10 min. Cisplatin could be used when mitomycin is contraindicated; however, this situation is rare.

Maintenance chemotherapy using two cycles of fluorouracil plus cisplatin did not improve progression-free survival compared with no maintenance chemotherapy. Exploratory subset analyses (appendix) show no evidence of any benefit for maintenance chemotherapy in any subgroups including patients with a high rate of relapse (T3 or T4 and N+ disease). These findings accord with the RTOG-98 and ACCORD-03 trials,[10,11,16] which used neoadjuvant cisplatin-based chemotherapy before chemoradiation.

Our findings are based on a 2×2 factorial trial design in which no evidence exists of an interaction between the chemoradiation and maintenance chemotherapy comparisons. Fluorouracil and mitomycin chemoradiation should remain the standard of care for anal cancer because of similar efficacy and toxic effects, fewer cycles of chemotherapy, fewer non-chemotherapy drugs, less time in the chemotherapy suite, less expense, and no risk of neuropathy compared with cisplatin, and the addition of maintenance chemotherapy in routine clinical practice is not justified.

The high complete response rate (90%), similar 3-year progression-free survival in the mitomycin and cisplatin groups, an overall 3-year colostomy-free survival of 74%, and the very few (14 of 844 patients) colostomies done for

late treatment effects compares favourably with the results of other phase 3 trials.[10,11,16] 75% of patients had local control with organ preservation and avoided colostomy.

We ascribe these outcomes to an efficient radiobiological schedule. The two main achievements of our trial were the ability to maintain high compliance with 50·4 Gy and the ability to give concurrent chemotherapy over a short overall treatment time by avoiding a planned gap in treatment.[18,19] The median overall treatment time in the RTOG 8704 trial was 49 days and in the RTOG 9811 trial it was 42 days.[5,11,20] A shorter overall treatment time is clinically important because a longer overall duration of radiation treatment adversely affects local control in anal cancer.[21,22] In the ECOG E4292 phase 2 study using cisplatin-based chemoradiotherapy,[23] the clinical complete response rates were higher in patients who did not get a planned radiotherapy treatment break compared with those who did (12/13 *vs* 13/19; 92% *vs* 68%).

Results for T1 and T2 cancers were excellent, with a 3-year progression-free survival of 81%. By contrast, patients with T3 or T4 cancers and nodal metastases fared badly (3-year progression-free survival was 63%). The pattern and timing of locoregional failure will be reported elsewhere. Possible strategies for improvement include the use of a non-cross-resistant induction chemotherapy (eg, a taxane,[24] as used in head and neck cancer), the integration of biological agents (eg, an EGFR inhibitor[25]), or dose-escalation above 50·4 Gy enabled by intensity-modulated radiotherapy, which should be tested in appropriately designed clinical trials.

Our study has several limitations. At the time the study was done, baseline staging pelvic MRI and FDG PET CT were not routinely used. We did not collect quality-of-life data (patient-reported outcomes) to investigate the pattern and severity of late radiotherapy-related toxic effects. Because of the intensiveness of the chemoradiation, maintenance treatment was difficult to deliver at full doses because of cumulative toxicity and low compliance, although most dose reductions were according to protocol. Additionally, 41 maintenance patients chose not to start treatment and investigators might not have encouraged full compliance—especially at the start of the trial—since the effectiveness of maintenance treatments is unproven. Our per-protocol analysis—excluding patients who were assigned to maintenance but never started treatment—also showed no difference in progression-free survival (data not shown).

A pilot study done before ACT II showed that triplet maintenance was associated with low compliance and high toxic effects.[12] Compliance in our study using doublet chemotherapy was also low. Finally, the radiotherapy technique we used was technically crude by present standards. Prospective trials using modern radiotherapy techniques are needed to assess the severity of acute and late toxic effects.

Panel: Research in context

Systematic review

We searched PubMed, Medline, and Cancerlit and abstracts of ASCO/ASTRO/ESTRO meetings with the terms "anal cancer", "squamous cell carcinoma", complete clinical response", "local recurrence", "survival", "concurrent", " chemotherapy", "cisplatin", "mitomycin C ", "radiotherapy", "chemoradiation", "radiochemotherapy", and "combined modality". We had no language or date restrictions. We did the search on Jan 22, 2013. We found two other phase 3 trials in progress testing additional neoadjuvant cisplatin-based chemotherapy (ACCORD 03 and RTOG 9811),[10,11,16] but found no studies testing additional maintenance chemotherapy.

Interpretation

In our trial, fluorouracil and cisplatin had the same effect on complete response rate, progression-free survival, and colostomy-free survival compared with fluorouracil and mitomycin. Nor did we see any improvement in progression-free survival when additional maintenance chemotherapy was used. These results compare favourably with two contemporary trials (RTOG 9811 and ACCORD 03), which had different designs. The low dose of elective nodal irradiation and a continuous radiotherapy schedule might have contributed to the good long-term outcomes.

In conclusion, large phase 3 trials of primary anal cancer are feasible, even though this disease is uncommon (we recruited roughly 25% of the UK incident cases). Neither of the two strategies investigated—chemoradiation with cisplatin, and further maintenance chemotherapy using fluorouracil and cisplatin—is more effective than standard care with mitomycin for achieving complete response, progression-free survival, or overall survival. Our results show that fluorouracil and mitomycin and 50·4 Gy radiotherapy in 28 daily fractions should be standard practice in the UK.

Contributors

All authors were members of the Trial Management Group, which oversaw the trial design and conduct. RDJ and RG-J designed the study, wrote the report, and interpreted data. HMM and DC designed the study, collected and interpreted data, and wrote the report. ASM, MPS, TM, AM, SE, ML, SF, CW, and SG enrolled patients and collected data. RB collected data. LK analysed and interpreted data, and wrote the report, DS-M designed the study, interpreted data, and wrote the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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