Standard versus reduced-dose chemoradiotherapy in anal cancer (PLATO-ACT4): short-term results of a phase 2 randomised controlled trial

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Summary

Background Localised squamous cell carcinoma of the anus is treated with radical chemoradiotherapy. Cure rates are high, but treatment can result in substantial acute and long-term morbidity. We aimed to assess whether lower dose chemoradiotherapy maintains high local control rates in patients with early-stage disease, with the secondary aim of reducing toxicity.

Methods ACT4 is a phase 2, prospective, multicentre, open-label, two-arm non-comparative, randomised, controlled trial, investigating reduced-dose intensity-modulated radiotherapy (rd-IMRT: 41·4 Gy in 23 fractions) in patients with early-stage anal cancer; T1–2 (≤4 cm) N0–NxM0. Eligible patients were at least 16 years of age, with an Eastern Cooperative Oncology Group performance status of 0–1. The primary outcome is 3-year loco-regional failure rates. Patients were randomly assigned 1:2 (with stratification by T stage, N stage, gender, HIV status, and randomising site) to standard-dose IMRT (sd-IMRT: 50·4 Gy in 28 fractions) or rd-IMRT with concurrent mitomycin and capecitabine chemotherapy. Here, we report the pre-planned, modified intention-to-treat analysis of secondary endpoints 6 months after treatment end—complete clinical response, compliance, patient-reported outcomes (EORTC QLQ-C30 and ANL27), and safety data. The trial is registered at the ISRCTN registry (ISRCTN88455282) and is ongoing but no longer recruiting.

Findings 163 patients were recruited from 28 UK tertiary centres between April 24, 2017, and Dec 1, 2020. 160 patients were included in the primary analysis (sd-IMRT n=55; dr-IMRT n=105). Data on ethnicity were not collected. The median patient age was 66 years (IQR 58–72 years); 117 (73%) were female and 43 (27%) male; and 129 (94%) of 138 evaluable samples were p16 positive. Complete clinical responses at 6 months were 87% (46 of 53) for sd-IMRT and 92% (89 of 97) for rd-IMRT. Radiotherapy interruptions of 3 days or more occurred in 14 (26%) of 55 patients in sd-IMRT and 16 (15%) of 105 patients in rd-IMRT. Chemotherapy modifications occurred in 27 (49%) of 55 patients in sd-IMRT and 39 (37%) of 105 patients in rd-IMRT. Grade 3 or worse acute toxicity was reported in 25 (46%) of 55 patients in sd-IMRT and 37 (35%) of 105 patients in rd-IMRT. The most common grade 3 or worse adverse events were radiation dermatitis (seven [13%] of 55 in sd-IMRT and ten [10%] of 105 in rd-IMRT), and diarrhoea (four [7%] of 55 in sd-IMRT and nine [9%] of 105 in rd-IMRT). Serious adverse events occurred in eight (15%) of 55 patients in sd-IMRT and ten (10%) of 105 patients in rd-IMRT. Patient-reported outcomes for most issues deteriorated at the end of treatment and resolved to baseline by 6 weeks in both groups. Poorer sexual function for men and women was observed at 6 months following sd-IMRT.

Interpretation Good 6-month complete clinical responses rates were seen in both groups. Early results suggest rd-IMRT is well tolerated with oncological outcomes maintained. 3-year locoregional failure rates are awaited.

Funding Cancer Research UK and Stand Up to Cancer.

Introduction

Anal cancer is a rare disease accounting for less than 1% of new cancer diagnoses worldwide, but its incidence is rising rapidly.[1] Approximately 1600 new cases are diagnosed annually in the UK (10 540 in the USA), with the highest incidence in people older than 75 years in the UK.[2,3] Around 90% of cases are related to previous human papillomavirus (HPV) infection, with retrospective published series describing improved outcomes in patients with p16-positive anal cancer than in those with p16-negative tumours.[4]

Three randomised phase 3 trials performed between 1988 and 1994 established radiotherapy with concurrent chemotherapy, using mitomycin and

Lancet Oncol 2025

Published Online May 4, 2025 https://doi.org/10.1016/S1470-2045(25)00213-X

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE, Embase, Cochrane Library, and Google Scholar for articles published in the English language from Jan 1, 1993, to Sept 16, 2024, reporting the results of phase 2 and 3 studies relevant to our trial. We used the terms "anal neoplasms" AND "stage I anal cancer" OR "stage II anal cancer" AND "radiotherapy "OR chemoradiotherapy" AND "clinical trials" AND "randomised clinical trials". From our search we identified six phase 3 randomised controlled trials (RCTs) which failed to improve on cure rates for early localised anal squamous cell carcinoma. Small-scale phase 2 trial evidence indicates that lower doses of radiotherapy might be appropriate, with similar cancer cure rates with a lower intensity of treatment for early localised anal cancer, and a possible reduction in late toxicity. To our knowledge, no previous RCTs have tested dose de-escalation in early-stage disease. A review of tumour control probability data undertaken by our national group (Muirhead and colleagues) in 2015 identified 13 studies with 645 patients in which dose–response rate data were evaluable. Seven of these studies contained a high proportion of data from patients with T1–2 anal squamous cell carcinoma and were used to indicate that there was scope to safely reduce radiotherapy doses in early disease. The published data were broadly consistent with a linear quadratic dose–response model. An updated literature review of manuscripts published between January, 2014, and September, 2024, identified no relevant publications that would provide further information regarding optimal radiotherapy dose for T1–2 anal cancer since 2015.

Added value of this study

ACT4 explores the de-intensification of chemotherapy and radiotherapy over a shorter period compared with standard in patients with smaller (T1–2 [≤4 cm]) and node-negative localised early anal squamous cell carcinoma. The 2:1 randomisation in this study provides a calibration group for tumour response and acute toxicity assessment using the current standard radiotherapy dose. This trial provides the highest level of evidence to date in the evaluation of de-intensification of radiotherapy for early stage anal squamous cell carcinoma, suggesting a promising 6-month complete clinical response rate, treatment compliance, and acute toxicity profile.

Implications of all the available evidence

The early 6-month findings from this trial indicate that a reduction in dose intensity of radiotherapy and chemotherapy results in complete response rates for localised anal cancer that are comparable to historical data and the concurrent calibration data for higher dose, standard of care treatment. The reduced-dose treatment appeared more tolerable, with fewer chemotherapy and radiotherapy modifications, in particular for older patients, and patient-reported outcomes indicated that sexual function recovery might improve with de-intensification. Longer follow-up for the trial's primary endpoint will provide an assessment of locoregional failure rates and late toxicity assessment, which has the potential to affect future treatment approaches globally and to provide relevant information to patients to allow them to engage in their treatment decisions.

fluorouracil, as a standard of care replacing abdominoperineal excision and permanent colostomy as initial curative treatment.[5–7] Three subsequent randomised phase 3 trials done between 1998 and 2008 did not change the standard of care through modification to concurrent chemotherapy regimens due to the following: no evidence of benefit with the addition of maintenance cisplatin and fluorouracil chemotherapy or the use of concurrent cisplatin;[8] inferior colostomy-free survival with the use of neoadjuvant and concurrent cisplatin and fluorouracil;[9] and no evidence of a benefit with neoadjuvant cisplatin and fluorouracil or with higher doses.[10]

Although the introduction of intensity-modulated radiotherapy (IMRT) has led to a reduction in adverse effects, patients still experience significant acute and late toxicity, in particular bowel, urinary, and sexual dysfunction.[11,12] All patients currently receive relatively high doses (compared with other cancers) of radiotherapy to the tumour (50 Gy or more), regardless of tumour stage, despite clear differences in cancer outcomes by tumour stage. This is likely to result in substantial overtreatment of early-stage disease.[1] The Personalising Radiotherapy in Anal Cancer (PLATO) trial was designed as an umbrella trial to optimise radiotherapy treatment for patients with anal cancer. For early stage disease, this was based on evidence from the seminal case report and subsequent phase 2 study by Nigro and colleagues,[13,14] showing local control rates of 84% using low-dose radiotherapy (30 Gy in 15 fractions) combined with mitomycin and fluorouracil in tumours with an average size of 3·5 cm (range 2–8 cm), as well as several sequential phase 2 studies, suggesting that doses ranging from 30 to less than 50 Gy might be effective in smaller tumours.[15–17] Additionally, our national group developed a tumour probability model to support the dose regimes evaluated within the PLATO platform.[18] These findings support the evaluation of lower dose chemoradiotherapy in early-stage disease with the aim of reducing treatment-related toxicity.[1,18]

We designed the ACT4 trial, a randomised clinical trial within PLATO, to determine whether lower dose chemoradiotherapy could maintain the high local control rate achieved using standard-dose chemoradiotherapy (using IMRT, mitomycin, and fluoropyrimidine chemotherapy) and reduce toxicity for patients with early-stage anal cancer. We report our pre-planned analysis of early endpoints, including compliance,

toxicity, patient-reported outcomes (PROs), and clinical response rates at 3 months and 6 months.

Methods

Study design and participants

ACT4 is a phase 2, multicentre, open-label, non-comparative, randomised, controlled trial in patients with early-stage squamous cell carcinoma of the anus conducted at 28 UK tertiary referral centres (appendix p 26). The trial aims to establish whether, in patients with squamous cell carcinoma of the anus, IMRT dose de-escalation in combination with concurrent mitomycin and capecitabine would result in acceptable rates of locoregional failure at 3 years and reduced acute and late toxicity compared with historical data for patients treated with standard-dose IMRT with concurrent mitomycin and capecitabine. A contemporary reference control group was incorporated to provide concurrent calibration data and to avoid selection bias during trial recruitment in this small subset of a rare disease.

Eligible patients were 16 years or older with biopsy-proven invasive primary squamous, basaloid, or cloacogenic carcinoma of the anus staged as T1 and T2 (≤4 cm), N0 or Nx anal canal, or T2 (≤4 cm) N0 or Nx anal margin (in situ or treated with previous local excision) with an anal-specific pelvic MRI scan and contrast-enhanced CT. Baseline [^{18}F]fluorodeoxyglucose PET–CT scan was strongly recommended. T2 tumours greater than 4 cm were excluded based on evidence from the RTOG 98–11 trial that these tumours might have a higher level of radiation resistance (Kachnic L, Columbia University Irving Medical Center, personal communication).[19] Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and who were either HIV-negative or HIV-positive and on antiretrovirals and had CD4 counts of more than 200 cells per mm^3 were eligible. Full eligibility criteria are available in the appendix (pp 2–3). All patients provided written informed consent. Self-reported data on patient gender were collected at baseline with the options of male and female provided. Data on ethnicity were not collected as it was not routinely considered on our case report forms at the time of trial procedure development. Patient representatives were involved at all stages of trial design and analysis. Data collection on numbers of potentially eligible patients approached was stopped on Sept 30, 2019 due to the COVID-19 pandemic (data were collected quarterly and this was the date of the last download before COVID-19) and not recommenced.

The trial was approved by Bradford Leeds Research Ethics Committee (16/YH/0157) and was registered with the ISRCTN registry (ISRCTN88455282).

Randomisation and masking

Patients were randomly assigned (1:2) to receive either standard-dose IMRT (sd-IMRT; 50·4 Gy in 28 fractions) or reduced-dose IMRT (rd-IMRT; 41·4 Gy 23 fractions) to the macroscopic tumour with lower dose radiotherapy to the elective pelvic nodal regions, in combination with concurrent mitomycin and oral capecitabine. Randomisation was performed through a 24 h automated telephone or online system based at the Leeds Institute of Clinical Trials Research (Leeds, UK). Randomisation was done by minimisation incorporating a random element, ensuring treatment groups were balanced for T stage (T1 or T2), N stage (N0 or NX), gender (male or female), HIV status (positive or negative), and randomising site. Patients and investigators were not masked to treatment allocation.

Procedures

The reduced radiotherapy dose and shorter chemotherapy schedule was agreed through expert consensus, based on consideration of available data and the dose–response modelling study.[18] UK sd-IMRT was defined as 50·4 Gy delivered in 28 fractions to gross tumour volume and 40 Gy in 28 fractions to the elective nodal volume, delivered daily (Monday to Friday). rd-IMRT was defined as 41·4 Gy delivered in 23 fractions to gross tumour volume and 34·5 Gy in 23 fractions to elective nodes. Mitomycin (12 mg/m^2, maximum 20 mg) was administered intravenously on day 1 and capecitabine (825 mg/m^2) was administered orally twice daily on days of radiotherapy (ie, ten fewer doses of capecitabine in rd-IMRT than in sd-IMRT). The use of concurrent capecitabine is derived from the EXTRA phase 2 study that led to the routine use of mitomycin and capecitabine in the UK.[20] A standard IMRT technique was mandated (appendix pp 4–6). Radiotherapy quality assurance was performed centrally by the UK National Cancer Research Institute Radiotherapy Trials Quality Assurance team both prospectively and retrospectively.

Patients were followed up in clinic at 6 weeks post-radiotherapy completion for clinical assessment including digital rectal examination, then once every 3 months to 24 months, and once every 6 months to 36 months; with MRI scans at 3 months and 6 months and CT thorax, abdomen, and pelvis scans at 12, 24, and 36 months. Response to treatment was assessed via MRI imaging (in accordance with the Tumour Regression Grading System; appendix p 133) and via physical examination at 3 months and 6 months after the end of treatment. 6 months was chosen as the optimal timing for assessment of complete response evaluation, based on current ESMO and ASTRO guidance, with the earlier 3-month assessment relevant for rare cases of progression.[21,22]

Clinician-reported acute toxicities were collected weekly over the treatment period using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All grade 2 and worse adverse reactions were collected. Grade 1 toxicity data were not recorded based on the trial using standard or reduced-dose chemoradiotherapy

regimes with well understood safety profiles and with the inclusion of PRO data to better capture lower grade symptomatic toxicity. All serious adverse reactions and related unexpected serious adverse events were collected over the treatment period only. PROs were collected on paper or electronically by the patient depending on patient preference at baseline, in the last week of treatment, and 6 weeks, 6, 12, 24, and 36 months post-end of treatment, via the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-ANL27 questionnaires.[23,24] PRO data collection was paused from April 30, 2020, to May 19, 2021, due to the COVID-19 pandemic (full details in appendix p 21).

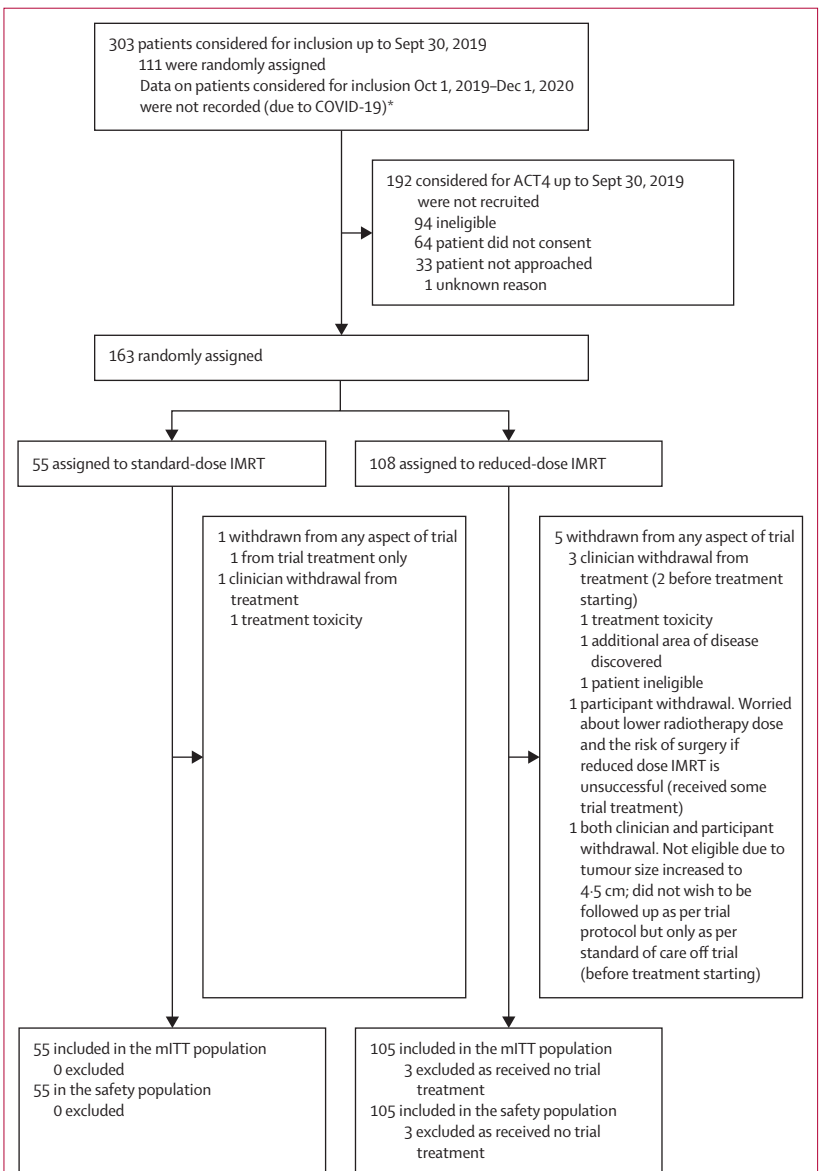

Figure 1: **Trial profile**
IMRT=intensity-modulated radiotherapy. mITT=modified intention-to-treat. *Data were collected quarterly and Sept 30, 2019 was the date of the last download before COVID-19.

All patients were eligible for HPV and p16 analysis. Full details are reported in the appendix (p 22). Formalin-fixed and paraffin-embedded samples were reviewed to confirm the presence of invasive anal squamous cell carcinoma, stained for p16, and slides were categorised as p16 positive or negative; p16 was considered positive if there was block staining (strong and diffuse nuclear and cytoplasmic expression in a continuous segment of cells).[25] Sequence-based HPV genotyping was performed using an updated version of previously published methods[26] and HPV status was allocated using two complimentary methods (details in appendix p 22).[27,28]

Outcomes

The primary endpoint of the study is 3-year locoregional failure rates, defined as failure (histologically or radiologically confirmed) at the primary site (local), or surrounding nodal sites (regional; ie, any failure within the pelvis up to the level of the sacral promontory). Secondary endpoints are clinician-reported acute toxicity during treatment (CTCAE version 5), treatment compliance, clinical response rates at 3 months and 6 months, disease-free survival, colostomy-free survival, progression-free survival, overall survival, and PROs as assessed by EORTC QLQ-C30 and QLQ-ANL27 from baseline up to 3 years. Patterns of treatment failure and occurrence of salvage surgery were also collected.

In this pre-planned analysis, we report our short-term endpoints. We report patient characteristics, p16 and HPV status, acute toxicities, radiotherapy compliance (defined as interruptions or modifications to radiotherapy, including total dose received and treatment duration), chemotherapy compliance (defined as any modifications to the schedule of chemotherapy [ie, any dose delays, omissions, and reductions and the reasons for these]), adverse events, and PROs up to 6 months from the start of treatment, alongside clinical response rates at 3 and 6 months. Complete clinical response was defined as a tumour regression grade score of 1 or 2, or if clinical assessment only was used to define response this included those participants categorised as having a complete response. Local response of the primary tumour was evaluated as per standard of care clinical practice with pelvic MRI and clinical evaluation with digital rectal examination. If MRI scans demonstrated a tumour regression grade 1 or 2 and clinical exam suggested partial response, the MRI result was used, given the greater capacity to differentiate between fibrosis and tumour signal.[29] Patient responses were investigator-assessed.

Statistical analysis

The study sample size was 162 participants (sd-IMRT n=54; rd-IMRT n=108), powered to exclude locoregional failure-free rates of 80% or below with a targeted rate of 90%, using an exact A'Hern single-stage

design[8,30] and including a calibration group. A minimum target efficacy rate of 90% was set based on a summation of data including: Das and colleagues' single centre cohort study with locoregional failure rates of 10% for Tx–T1N0 and 15% for T2N0–1;[31] Gunderson and colleagues' 98–11 trial with 17% locoregional failure rate in T2N0 tumours (T1N0 were excluded);[32] Wright and colleagues' single institution outcomes with 18% locoregional failure rate for T1–T2N0 and T1–2N(any);[33] and unpublished data from the ACT2 trial with 10% locoregional failure for T1–2N0 at 3-years post-randomisation.[8] The sd-IMRT group was included to provide a calibration group for interpretation and to prevent selection bias. With 80% power and 5% one-sided significance, 123 patients were required. The sample size was inflated by 20% for the pre-planned p16-positive subgroup analysis; expecting 90% of patients to present with this genotype, 90% of samples suitable for analysis, and allowing for a 10% dropout rate, a total sample size of 162 was planned. All analyses were prespecified in a statistical analysis plan (appendix) before being undertaken, unless otherwise stated. Analysis of the short-term endpoints took place when the participants had been followed up for 6 months after the end of treatment. There was no formal statistical comparison between the trial groups, as per design.

All summaries, except for the safety data, were based on the modified intention-to-treat population (mITT), in which participants were included according to the group to which they were randomly assigned if they received at least one dose of trial treatment. Data were presented on the safety population according to treatment received. The safety analysis set included all participants who received at least one dose of chemoradiotherapy. Serious adverse events of interest were defined as angina or myocardial infarction and pulmonary embolism. Treatment compliance was presented by summary statistics for radiotherapy and chemotherapy. Participants were considered to have adhered to the radiotherapy schedule if they completed their scheduled course of radiotherapy with no greater than 3 treatment days of delays due to toxicity. Participants were considered to have adhered to their chemotherapy treatment if there were no modifications to the schedule of chemotherapy (ie, any dose delays, omissions, and reductions and the reasons for these). Clinician-reported acute toxicities are summarised, including by type and maximum CTCAE grade. Number and proportion of participants with any grade 3 or worse acute toxicity are reported along with 95% CIs. For PROs, EORTC-QLQ guidelines were used for analyses and management of missing data and deriving missing values in scaled items by imputation.[34] Higher symptom scores reflect a greater level of symptoms, whereas higher functional scores reflect a better level of functioning. Changes in mean scores were classified as per Osoba and colleagues[35] as a small change of 5 to 10 points (unlikely to be clinically relevant), moderate change of 10 to 20 points, or a large change greater than 20 points. The proportion of participants achieving a complete clinical response at 3 months and 6 months is presented with 95% CIs. A pre-planned exploratory analysis of complete clinical response by p16 status is also presented.

	Standard-dose IMRT (n=55)	Reduced-dose IMRT (n=105)	All patients (n=160)
T stage			
T1	12 (22%)	20 (19%)	32 (20%)
T2	43 (78%)	85 (81%)	128 (80%)
N stage			
N0	55 (100%)	104 (99%)	159 (99%)
Nx	0	1 (1%)	1 (1%)
Method of determining TNM stage			
MRI and CT only	18 (33%)	39 (37%)	57 (36%)
MRI, CT, and PET	37 (67%)	64 (61%)	101 (63%)
Missing	0	2 (2%)	2 (1%)
Gender			
Male	14 (26%)	29 (28%)	43 (27%)
Female	41 (75%)	76 (72%)	117 (73%)
Age (years)			
Mean (SD)	61·6 (11·4)	65·2 (9·8)	64·0 (10·5)
Median (range; IQR)	64·0 (38·0–87·0; 53·0–70·0)	68·0 (35·0–84·0; 59·0–73·0)	66·0 (35·0–87·0; 58·0–71·5)
<70 years	41 (75%)	65 (62%)	106 (66%)
≥70 years	14 (26%)	40 (38%)	54 (34%)
HIV status			
Positive	1 (2%)	4 (4%)	5 (3%)
Negative	54 (98%)	101 (96%)	155 (97%)
ECOG performance status			
0	48 (87%)	90 (86%)	138 (86%)
1	7 (13%)	15 (14%)	22 (14%)
Tumour histology			
Squamous (including basaloid or cloacogenic)	55 (100%)	105 (100%)	160 (100%)
Tumour site			
Anal margin	11 (20%)	24 (23%)	35 (22%)
Anal canal	44 (80%)	81 (78%)	125 (78%)
Maximum tumour size (cm)			
Mean (SD)	2·6 (0·9)	2·5 (0·8)	2·5 (0·8)
Median (range; IQR)	2·7 (0·3–4·0; 2·1–3·3)	2·4 (0·5–4·2*; 2·0–3·0)	2·5 (0·0–4·2; 2·0–3·0)
AJCC anatomic stage or prognostic group (valid from January, 2018)			
Stage I	10 (18%)	19 (18%)	29 (18%)
Stage IIA	45 (82%)	86 (82%)	131 (82%)
Tumour treated by previous excision (anal margin tumours only)			
Yes	5/11 (46%)	9/24 (38%)	14/35 (40%)
No	6/11 (55%)	15/24 (63%)	21/35 (60%)
Total	11/11 (100%)	24/24 (100%)	35/35 (100%)
Smoking status			
Yes	12 (22%)	20 (19%)	32 (20%)
No (ex-smoker)	21 (38%)	35 (33%)	56 (35%)
No (never smoked)	22 (40%)	50 (48%)	72 (45%)

(Table 1 continues on next page)

	Standard-dose IMRT (n=55)	Reduced-dose IMRT (n=105)	All patients (n=160)
(Continued from previous page)			
p16 status			
Positive	45 (82%)	84 (80%)	129 (81%)
Negative	5 (9%)	4 (4%)	9 (6%)
Baseline sample not received	4 (7%)	9 (9%)	13 (8%)
Missing	0	1 (1%)	1 (1%)
Not assessable	1 (2%)	7 (7%)	8 (5%)
Total	55 (100%)	105 (100%)	160 (100%)

Data are n (%) unless otherwise stated. AJCC=American Joint Committee on Cancer. ECOG=Eastern Cooperative Oncology Group. IMRT=intensity-modulated radiotherapy. *Maximum tumour size of 4·2 cm was notified by site following randomisation. The protocol specifies eligibility as T2 ≤4 cm, however as T2 staging is 2–5 cm the participant was randomly assigned in error.

Table 1: **Baseline characteristics**

We also did an exploratory post-hoc analysis of compliance, toxicity, and complete clinical response in an older age group of patients (≥70 years).[36] Older age was defined as 70 years and older; WHO's definition of an older population is 65 years and older, but the definition used more recently in cancer clinical trials has been 70 years and older.[37] As the recruited participants in this study had ECOG performance status 0–1 and were generally fitter than the general population, this higher cutoff was considered appropriate.[36,37]

The analysis was performed using SAS version 9.4.

Role of the funding source

The funders of the study had no role in data collection, data analysis, data interpretation, or writing of the report. Cancer Research UK reviewed and approved the study design.

Results

163 patients were recruited from 28 centres across the UK between April 24, 2017, and Dec 1, 2020. Data from 160 patients were used in the mITT analysis (55 patients given sd-IMRT and 105 given rd-IMRT; figure 1); three patients were withdrawn before commencing treatment as they became ineligible (one at screening; and two patients were found to have larger tumours or node involvement at the time of the planning scan). Radiotherapy quality assurance processes were carried out for contouring and planning on 38 patients (sd-IMRT 14 of 55 patients; rd-IMRT 24 of 105 patients). In 26 (68%) of 38 patients, contouring was approved on first attempt and 37 (97%) of 38 in planning (appendix pp 6–7).

Important prognostic factors are equally distributed in the different trial groups. 128 (80%) of 160 patients had T2 tumours, with a median tumour size of 2·5 cm (IQR 2·0–3·0; table 1). 14 (40%) of 35 anal margin tumours had undergone a previous excision. 117 (73%) of 160 patients were female and 43 (27%) were male. The median age was 66 years (range 35–87; IQR 58–72), with 54 (34%) of 160 patients aged 70 years or older. No patients had a stoma before starting treatment. The proportion of patients with HIV was low (five [3%] of 160). All recruited participants consented to sample collection. 147 baseline tumour samples in total were collected for p16 and HPV analysis and, of those, 138 (94%) cases were suitable for evaluation for p16 immunohistochemistry. 129 (93%) of 138 evaluable samples were p16 positive and nine (7%) of 138 were p16 negative. 109 (74%) of 147 samples were evaluable for HPV status. 93 (85%) of 109 evaluable samples were classified as high-risk HPV positive (HPV16 in 92 samples; HPV18 in one sample). Three (3%) of 109 were classified as potential high-risk HPV (unclear subtype) and 12 (11%) of 109 samples were classified as HPV negative (appendix pp 22–23). 94 (87%) of 108 patients were dual positive for p16 and high-risk HPV, five (5%) of 108 patients dual negative, and only eight (7%) of 108 patients were p16 positive with no detectable high-risk HPV.

Table 2 summarises treatment compliance. Patients were defined as adhering to protocol if they completed radiotherapy with no more than 3 days delay due to toxicity. Radiotherapy interruptions of 3 days or more occurred in 14 (26%) of 55 patients in sd-IMRT and 16 (15%) of 105 patients in rd-IMRT. One patient had a radiotherapy delay of more than 3 days in the rd-IMRT group due to gastrointestinal toxicity. One patient assigned to rd-IMRT was withdrawn from capecitabine during week 1 due to toxicity and completed standard-dose radiotherapy in 5·5 weeks. Overall, radiotherapy interruptions due to toxicity were observed in five (9%) of 55 patients in the sd-IMRT group and four (4%) of 105 patients in the rd-IMRT group. Radiotherapy interruptions for toxicity occurred between week 2 and the final week of treatment (median: week 3). Where the type of toxicity was specified (for three patients in sd-IMRT and one in rd-IMRT), they were reported as gastrointestinal (detail on type of toxicity leading to interruptions was not mandated throughout the whole duration of the trial). Overall modification of chemotherapy (omission, reduction, delay, or extra dose taken) occurred in 27 (49%) of 55 participants in sd-IMRT and 39 (37%) of 105 in rd-IMRT, with toxicity cited as the reason for modification in 20 (36%) of 55 in sd-IMRT and 26 (25%) of 105 in rd-IMRT. For capecitabine omissions, most patients missed less than or equal to 1 week (10 of 55 in sd-IMRT; 14 of 105 in rd-IMRT) of capecitabine and 29% (SD 28; sd-IMRT) and 22% (SD 19; rd-IMRT) of the expected total dose was omitted. Mitomycin compliance was very high given that UK practice is to administer a day 1 dose of mitomycin alone (further details for all chemotherapy modifications are in the appendix pp 8–12).

In sd-IMRT, six (11%) of 55 patients had no adverse events reported, and 25 (46%) of 55 had at least one grade 3 or worse event (table 3). In rd-IMRT, 18 (17%)

	Standard-dose IMRT (n=55)	Reduced-dose IMRT (n=105)	All patients (n=160)
Total radiotherapy dose received (Gy)			
Median (range; IQR)	50·4 (28·8–50·4; 50·4–50·4)	41·4 (23·4–50·4*; 41·4–41·4)	..
Treatment duration (days)			
Median (range; IQR)	38·0 (30·0†–40·0; 38·0–38·0)	31·0 (17·0‡–38·0*; 31·0–31·0)	..
Radiotherapy interrupted per participant (all events)			
Yes (all)	14 (26%; 95% CI 15–39)	16 (15%; 95% CI 9–24)	30 (19%)
Yes, due to toxicity	4 (7%)	4 (4%)	8 (5%)
Yes, due to other§	9 (16%)	12 (11%)	21 (13%)
Yes, due to toxicity and other	1 (2%)	0	1 (1%)
No	41 (75%)	89 (85%)	130 (81%)
Radiotherapy extended >3 days			
Yes	0	2 (2%)*	2 (1%)
No	55 (100%)	103 (98%)	158 (99%)
Total	55 (100%)	105 (100%)	160 (100%)
Radiotherapy interrupted per participant by age (any reason)			
Age <70 years			
Yes	9 (22%; 95% CI 11–38)	10 (15%; 95% CI 8–27)	19 (18%)
No	32 (78%)	55 (85%)	87 (82%)
Total	41 (100%)	65 (100%)	106 (100%)
Age ≥70 years			
Yes	5 (36%; 95% CI 13–65)	6 (15%; 95% CI 6–30)	11 (20%)
No	9 (64%)	34 (85%)	43 (80%)
Total	14 (100%)	40 (100%)	54 (100%)
Chemotherapy as per protocol?			
Yes	28 (51%; 95% CI 37–65)	66 (63%; 95% CI 53–72)	94 (59%)
No	27 (49%)	39 (37%)	66 (41%)
Total	55 (100%)	105 (100%)	160 (100%)
Mitomycin as per protocol?¶			
Yes	55 (100%)	104 (99%)	159 (99%)
No	0	1 (1%)	1 (1%)
Total	55 (100%)	105 (100%)	160 (100%)
Overall capecitabine modifications per participant‖			
At least one modification due to toxicity	20 (36%)	26 (25%)	46 (29%)
Modifications: none due to toxicity	7 (13%)	13 (12%)	20 (13%)
No chemotherapy modifications	28 (51%)	66 (63%)	94 (59%)
Total	55 (100%)	105 (100%)	160 (100%)
Capecitabine modification by age per participant			
Age <70 years			
At least one modification due to toxicity	15 (37%)	14 (22%)	29 (27%)
Modifications: none due to toxicity	3 (7%)	7 (11%)	10 (9%)
No chemotherapy modifications	23 (56%)	44 (68%)	67 (63%)
Total	41 (100%)	65 (100%)	106 (100%)
Age ≥70 years			
At least one modification due to toxicity	5 (36%)	12 (30%)	17 (32%)
Modifications: none due to toxicity	4 (29%)	6 (15%)	10 (19%)
No chemotherapy modifications	5 (36%)	22 (55%)	27 (50%)
Total	14 (100%)	40 (100%)	54 (100%)

Data are n (%) unless otherwise stated. Age groups ≥70 years and <70 years were included post-hoc. IMRT=intensity-modulated radiotherapy. *N=1 received standard-dose radiotherapy after being unable to continue on capecitabine in week 1. †N=1 chemoradiotherapy was delayed due to toxicity. ‡N=1 withdrawn. §Other reasons for interruption were predominantly logistical and include bank holidays and machine maintenance/breakdown. ¶n=1 modification was a delay due to low platelets. Although these data were not requested on the case report form, an additional participant received a dose reduction of mitomycin in week 1 (not per protocol) with older age given as the reason. ‖Participants categorised into mutually exclusive groups. Full details of modifications in supplementary materials.

Table 2: **Treatment compliance**

	Standard-dose IMRT (n=55)	Reduced-dose IMRT (n=105)	All patients (n=160)
Worst CTCAE grade per participant*			
None reported	6 (11%)	18 (17%)	24 (15%)
2	24 (44%)	50 (48%)	74 (46%)
3	22 (40%)	35 (33%)	57 (36%)
4	3 (6%)	2 (2%)	5 (3%)
Total	55 (100%)	105 (100%)	160 (100%)
Grade 3 or worse toxicity			
Yes	25 (46%; 95% CI 32–60)	37 (35%; 95% CI 26–45)	62 (39%)
No	30 (55%)	68 (65%)	98 (61%)
Total	55 (100%)	105 (100%)	160 (100%)
Has the participant reported an SAR/SAEoI†/RUSAE‡?			
Yes	8 (15%; 95% CI 7–27)	10 (10%; 95% CI 5–17)	18 (11%)
No	47 (86%)	95 (91%)	142 (89%)
Total	55 (100%)	105 (100%)	160 (100%)
Number of SARs/SAEoIs/RUSAEs per participant for those who have experienced one or more event			
Mean (SD)	1·1 (0·4)	1·1 (0·3)	1·1 (0·3)
Median (range; IQR)	1·0 (1·0–2·0; 1·0–1·0)	1·0 (1·0–2·0; 1·0–1·0)	1·0 (1·0–2·0; 1·0–1·0)
Number of SARs/SAEoIs overall	9	11	20
Grade 3 or worse toxicity (by age)			
Age <70 years			
Yes	18 (44%; 95% CI 28–60)	25 (39%; 95% CI 27–51)	43 (41%)
No	23 (56%)	40 (62%)	63 (59%)
Total	41 (100%)	65 (100%)	106 (100%)
Age ≥70 years			
Yes	7 (50%; 95% CI 23–77)	12 (30%; 95% CI 17–47)	19 (35%)
No	7 (50%)	28 (70%)	35 (65%)
Total	14 (100%)	40 (100%)	54 (100%)

Data are n (%) unless otherwise stated. Age groups ≥70 years and <70 years were included post-hoc. CTCAE=Common Terminology Criteria for Adverse Events. IMRT=intensity-modulated radiotherapy. SAEoI=serious adverse events of interest. SAR=serious adverse reaction. RUSAE=related unexpected serious adverse events. *Grade 1 toxicity was not recorded. †Two SAEoIs of angina or myocardial infarction reported: one in the standard-dose group and one in the reduced-dose group. ‡No RUSAEs were reported.

Table 3: **Toxicity and safety**

of 105 patients had no adverse events reported and 37 (35%) of 105 reported at least one grade 3 or worse toxicity. The most common grade 3 or worse adverse events were radiation dermatitis (seven [13%] of 55 patients in sd-IMRT and ten [10%] of 105 in rd-IMRT), diarrhoea (four [7%] of 55 patients in sd-IMRT and nine [9%] of 105 in rd-IMRT), and neutropenia (two [4%] of 55 patients in sd-IMRT and six [6%] of 105 in rd-IMRT; appendix p 13). In a post-hoc analysis, older patients (≥70 years old), seven (50%) of 14 in sd-IMRT and 12 (30%) of 40 in rd-IMRT experienced overall grade 3 or worse toxicity. Corresponding figures for younger patients (<70 years old) were 18 (44%) of 41 in sd-IMRT and 25 (39%) of 65 in rd-IMRT. Serious adverse reactions and serious adverse events of interest were experienced by eight (15%) of 55 patients in sd-IMRT and ten (10%) of 105 patients in rd-IMRT. Serious adverse events of interest were reported equally in both groups (one in each group; angina or myocardial infarction; appendix p 14). There were no treatment-related deaths. One participant died of an unrelated cause in the rd-IMRT group.

The data on complete clinical response rates are shown in table 4. The 6-month complete clinical response rates were 46 (84%) of 55 in sd-IMRT and 89 (85%) of 105 in rd-IMRT (where missing response status is included in the denominator as per the statistical analysis plan) and 46 (87%) of 53 and 89 (92%) of 97 respectively, excluding missing data. 111 (86%) of 129 p16-positive patients and all p16-negative patients (eight of nine; one patient with missing data) had a confirmed complete clinical response at 6 months (appendix p 23).

PRO compliance was good, with 102 (87%) of 117 patients completing patient-reported outcome questionnaires at 6 months (33 [83%] of 40 in sd-IMRT and 69 [90%] of 77 in rd-IMRT). Key quality of life (QOL), symptom, and function issues are presented in figure 2. All PRO scores and compliance data are reported in the appendix (pp 16–21). The two groups appeared to have similar QOL at baseline. There was a near-universal worsening in all areas of QOL, EORTC QLQ-C30 function scores, and anal cancer-specific issues from baseline to the end of treatment assessment for all patients, but with improvement in most areas at 6 months. In particular, there was a marked decline (>20 points; as per Osoba and colleagues[33]) at the end of treatment for global QOL, role, and social functioning in both groups, associated with a large deterioration in scores (>20 points) for fatigue, pain (general and anorectal-specific pain), bowel function, toilet dependency, needing to clean yourself more often, planning activities due to symptoms, diarrhoea, loss of appetite, and urinary frequency.

By 6 weeks post-treatment, general pain (EORTC QLQ-C30) and anorectal-specific pain (EORTC QLQ-ANL27 pain or discomfort) had returned to baseline levels in both groups. Anorectal-specific pain then improved to better than baseline levels for both groups by 6 months (appendix pp 18–19). For general QOL, social and role function, fatigue, overall bowel function, planning activities, cleaning more often, and diarrhoea, these issues improved at 6 weeks but did not return to baseline levels (or near baseline) until 6 months. For both groups, at 6 months a moderate deterioration (10–20 points) in toilet dependency (the need to be close to a toilet) was reported from baseline scores. Overall, 65 (84%) of 77 female patients completing PROs at the 6-month timepoint (18 [69%] of 26 in sd-IMRT and 47 [92%] of 51 in rd-IMRT) reported on their vaginal or sexual function (penetrative sex or use of vaginal dilators; appendix p 20). Both groups reported a deterioration in sexual function at the end of treatment. Female patients' sexual function scores reported improvements to near

baseline at the 6-week and 6-month timepoints in the reduced-dose group but did not report an improvement up to 6 months in sd-IMRT. 24 (96%) of 25 male patients reported on 6-month sexual function (seven [100%] of seven in sd-IMRT; 17 [94%] of 18 in rd-IMRT). Male patients' sexual function scores at 6 months returned to near-baseline for patients in rd-IMRT, but lower sexual function scores continued to be reported by patients in sd-IMRT (appendix pp 19–20).

In a post-hoc analysis by age, there were more radiotherapy interruptions for patients in the sd-IMRT group for patients 70 years or older (five [36%] of 14) than patients younger than 70 years (nine [22%] of 41), but the number of interruptions in patients in both age groups were similar in the rd-IMRT group (six [15%] of 40 and ten [15%] of 65). The number of chemotherapy modifications reported due to toxicity in patients younger than 70 years was 15 (37%) of 41 in sd-IMRT and 14 (22%) of 65 in rd-IMRT, and in patients 70 years or older was five (36%) of 14 in sd-IMRT and 12 (30%) of 40 in rd-IMRT. Despite differences in radiotherapy and chemotherapy compliance between age groups (<70 years and ≥70 years), there was no clear impact of these differences on complete clinical response rates (appendix p 15).

	Standard-dose IMRT (n=55)	Reduced-dose IMRT (n=105)	All patients (n=160)
Tumour regression grade (3 months)			
Grade 1 (no evidence)	25 (46%)	53 (51%)	78 (49%)
Grade 2 (fibrosis only)	24 (44%)	35 (33%)	59 (37%)
Grade 3 (partial)	2 (4%)	7 (7%)	9 (6%)
Grade 4 (minimal response)	0	1 (1%)	1 (1%)
Grade 5 (no response or progression)	1 (2%)	1 (1%)	2 (1%)
Missing*	3 (6%)	8 (8%)	11 (7%)
Total tumour regression grade 1 and 2 excluding missing data	49/52 (94%)	88/97 (91%)	137 (92%)
Tumour regression grade (6 months)			
Grade 1 (no evidence)	26 (47%)	49 (47%)	75 (47%)
Grade 2 (fibrosis only)	19 (35%)	36 (34%)	55 (34%)
Grade 3 (partial)	4 (7%)	5 (5%)	9 (6%)
Grade 4 (minimal response)	0	1 (1%)	1 (1%)
Grade 5 (no response or progression)	1 (2%)	1 (1%)	2 (1%)
Missing*	5 (9%)	13 (12%)	18 (11%)
Total tumour regression grade 1 and 2 excluding missing data	45/50 (90%)	85/92 (92%)	130 (92%)
Combined MRI with clinical responses (3 months)			
Complete	50 (91%; 95% CI 80–97)	91 (87%; 95% CI 79–87)	141 (88%)
Intermediate	2 (4%)	8 (8%)	10 (6%)
No response	1 (2%)	2 (2%)	3 (2%)
Death	0	1 (1%)	1 (1%)
Previous progression	1 (2%)	0	1 (1%)
Previous withdrawal	0	1 (1%)	1 (1%)
Missing†	1 (2%)	2 (2%)	3 (2%)
Total	55 (100%)	105 (100%)	160 (100%)
Total complete clinical response excluding missing data	50/54 (93%)	91/101 (90%)	141 (92%)
Combined MRI with clinical responses (6 months)			
Complete	46 (84%; 95% CI 71·2–92·2)	89 (85%; 95% CI 76·4–91·0)	135 (84·4%)
Intermediate response	4 (7%)	5 (5%)	9 (6%)
No response	1 (2%)	2 (2%)	3 (2%)
Death	0	1 (1%)	0
Previous progression	2 (4%)	1 (1%)	2 (1%)
Previous withdrawal	0	1 (1%)	0
Missing†	2 (4%)	5 (5%)	2 (1%)
Not assessed	0	1 (1%)	1 (1%)
Total	55 (100%)	105 (100%)	160 (100%)
Total complete clinical response excluding missing or not assessed	46/53 (87%)	89/97 (92%)	135 (91%)

Data are n (%) or n/N (%) unless otherwise stated. IMRT=intensity-modulated radiotherapy. *Not assessable: no primary tumour post-excision, missing imaging, or death. †Missing: imaging and clinical examination.

Table 4: **Response rates at 3 and 6 months**

Discussion

We present a pre-planned analysis of the early endpoints from ACT4. To our knowledge, ACT4 is the first randomised, non-comparative trial globally of reduced-dose chemoradiotherapy in early-stage anal cancer to complete recruitment and report short-term endpoints.[38] The trial addresses an unmet need in the treatment of early-stage anal cancer where the optimal curative dose of chemoradiotherapy is unknown. Our early data suggest that reducing overall treatment time by 1 week, reducing radiotherapy dose, and reducing concurrent capecitabine exposure results in high 6-month clinical complete responses. Our 6-month complete response outcomes are aligned with our contemporary sd-IMRT reference group, as well as historical data from similar cohorts (disease-free and local control rates between 82% and 95% reported;[15,17] summarised in appendix pp 24–25), and our tumour control probability modelling study (noting that the tumour control probability model was based upon an locoregional failure rate endpoint).[14,18] The primary outcome, 3-year locoregional failure rates, will be reported in an oral abstract in May, 2025. Longer-term toxicity and colostomy rates, alongside the primary outcome, are awaited before considering a change in practice.

Most tumours were associated with the presence of high-risk HPV subtypes, which often had positive immunohistochemistry for p16. It is not possible to formally assess the correlation between p16 status and complete response rates at 6 months given the small numbers. However, there is a need for an improved biological understanding of mechanisms of treatment resistance.

Compliance with radiotherapy and chemotherapy was higher in the reduced-dose group, and overall acute toxicities were lower with reduced-dose treatment, with particular benefits seen in the older population (aged ≥70 years). Historical data on toxicity and compliance

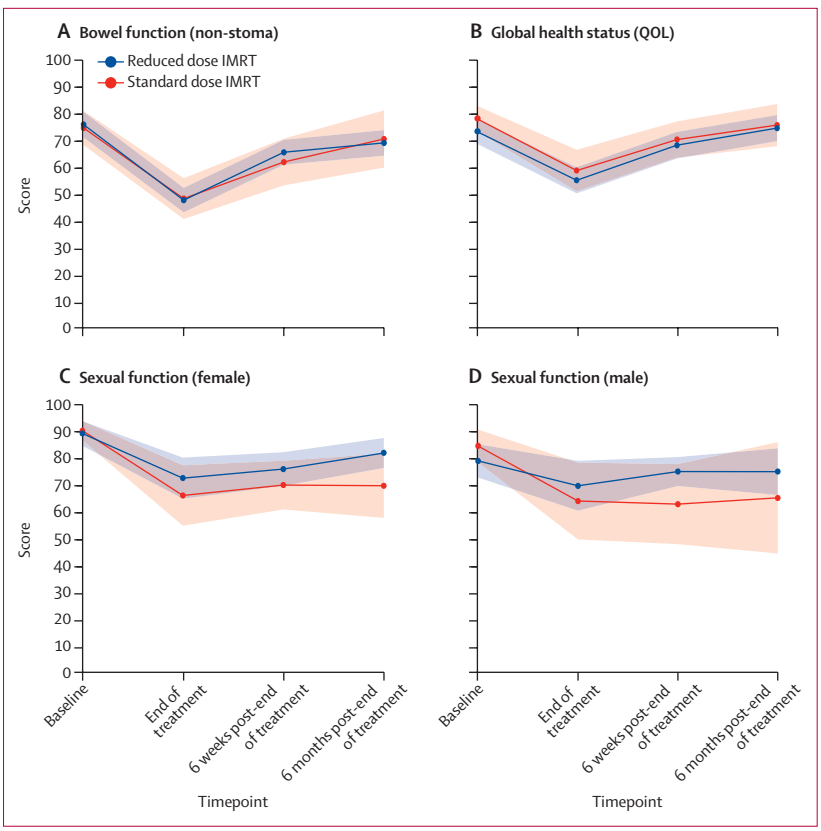

Figure 2: **Patient-reported outcomes**
A score of 0 indicates no function (A, C, D) or low QOL (B) and 100 indicates high function (A, C, D) or high QOL (B). End of treatment was the final week of treatment. IMRT=intensity-modulated radiotherapy. QOL=quality of life.

from studies evaluating lower dose chemoradiotherapy are poorly reported. However, the introduction of IMRT has led to a marked reduction in acute toxicity. In comparison with the ACT2 trial,[8] in which 71% of patients reported grade 3 or worse toxicity using conformal radiotherapy techniques, 46% of patients in the standard-dose group and 35% in the reduced-dose group had grade 3 or worse toxicity in the current study. The compliance with radiotherapy and chemotherapy in the reduced-dose group was higher in all patients, but particularly in patients aged 70 years or older. In both groups, considerable modifications to chemotherapy were observed (49% of patient had modifications in the standard-dose group and 37% in the reduced-dose group) with this difference most apparent for older patients in the standard group. In the EXTRA phase 2 trial of concurrent mitomycin and capecitabine, similar proportions of modifications were observed, with 68% of participants receiving chemotherapy as per protocol.[20] As compliance with radiotherapy and chemotherapy is known to have a detrimental impact on cancer outcomes, it is important to minimise unplanned interruptions.

To our knowledge, ACT4 is the first randomised controlled trial globally to evaluate PROs using a dedicated anal cancer questionnaire, the validated EORTC QLQ-ANL27.[23] PROs were similar during treatment and follow-up in both groups; however, better sexual function scores were observed for men and women at 6 months in the reduced-dose group, despite the dose constraints for organs at risk being standard for both groups. As the vagina and penile bulb are directly adjacent to the primary tumour, only a lower radiotherapy dose delivered to the primary tumour would impact on the function of these organs. Two recent systematic reviews have highlighted high rates of male and female sexual dysfunction following treatment for anal cancer. A review of 19 studies, published in 2023, found sexual dysfunction was reported in up to 85% of women.[39] In men, a 2021 review including 14 studies reported erectile dysfunction rates between 66% and 100%.[40] The authors commented on the need for de-escalation studies to improve function as well as the poor PRO response rates in women. Our compliance rates for PROs, including self-reported female sexual function, were high using the EORTC QLQ-ANL27; possibly the result of female patients being able to respond to the questions in relation to vaginal dilators usage as well as penetrative sex. Ensuring highly relevant PRO content not only improves the quality of our results but also improves our understanding of the impact of our treatment on patient experience.

In addition to ACT4, the randomised phase 2 ECOG-ACRIN DECREASE study (NCT04166318) is evaluating the role of dose de-escalation in early-stage anal cancer. The trial evaluates two schedules in patients with T1N0 (36 Gy in 20 fractions) and T2 (<4 cm)N0 (41·4 Gy in 23 fractions) with concurrent mitomycin and fluorouracil or capecitabine compared with standard-dose chemoradiotherapy (50 Gy in 28 fractions). Maintained 2-year disease control and improved patient-reported bowel function are co-primary endpoints. The trial has recently completed recruitment (a target of 252 patients) and a future individual patient data meta-analysis between ACT4 and DECREASE is planned (Dorth J, University Hospitals Seidman Cancer Center, and Meyer J, Fox Chase Cancer Center, personal communication).

This trial does have some limitations. ACT4 is not a randomised comparative trial; the control group is incorporated to provide essential concurrent calibration data to enable interpretation of the results in the reduced-dose group and to avoid selection bias. Therefore, a formal comparison between treatment groups is not possible. This design was considered an acceptable choice for a phase 2 trial, where early-stage anal cancer is a relatively small subset of a rare disease. An appropriately powered equivalence study for the primary endpoint was not considered feasible given the rarity of the subgroup. COVID-19 impacted very little on recruitment; only on data collection for ineligibility and

for a few PRO datapoints (figure 1; appendix p 16). Although participants with well-controlled HIV were eligible, our numbers were lower (3%) than estimates of incident cases reported in high-income countries in older series (8–15%). This might reflect that most patients with HIV with early-stage disease will be diagnosed through anoscopy screening programmes and so meet the entry criteria for the ACT3 trial (which is investigating T1N0 anal margin tumours offered selective adjuvant chemoradiotherapy depending on margin post excision) rather than ACT4, or that incidence of anal cancer is lower with improvements in antiretroviral therapy. Both groups used the same organ at risk dose constraints, which might limit the longer-term radiotherapy-related toxicity differences observed.

We included an exploratory analysis of older patients because data on treatment of older patients in cancer clinical trials are scarce. Not only is anal cancer incidence higher in older age groups, but older patients have potentially more to benefit from a reduced-dose regimen, and therefore it was considered important to evaluate the tolerability and early efficacy in this patient cohort specifically. For our exploratory analysis, age was used as a surrogate of frailty given a formal prospective frailty assessment was not incorporated and only patients with ECOG performance status 0–1 were included. Proportionally, more older patients aged 70 years or older were recruited into the rd-IMRT group than into the sd-IMRT group. Interestingly, this imbalance has not affected the complete clinical response rates, and we have observed lower acute toxicity and better sexual function scores in the rd-IMRT group. A detailed sensitivity analysis of PRO data is planned in the primary outcome publication to address this finding. An additional retrospective analysis of frailty using PRO scoring and impact on compliance and tolerability is also planned.

In conclusion, early results from the ACT4 trial indicate there is a high complete clinical response rate at 6 months with reduced-dose chemoradiotherapy in early anal cancer. Although the two groups were not statistically compared, ACT4 suggests benefits in reduced acute toxicity and improved patient-reported sexual function for men and women with reduced-dose IMRT. Longer term follow-up and primary endpoint data on 3-year locoregional failure rates are required to fully determine whether these early findings translate into high locoregional failure free-rates and numerically reduced longer-term toxicity using reduced-dose chemo-radiotherapy. However, given the improvements in compliance and tolerability of the de-escalated regimen in older patients, with preserved early cancer outcomes, this reduced-dose regimen could be considered a new treatment option for frailer patients not fit for standard-dose chemoradiotherapy.

Contributors

All authors had full access to trial data and had final responsibility for the decision to submit for publication. DS-M, RA, MHar, SRB, AG, MHaw, DG, RM, AGR, SRa, and VG made substantial contributions to study conception and design. JW, JC, AS, SRB, SRu, RA, MHar, MHaw, DS-M, AG, DCG, SDR, MAW, DB, HMW, SK, SRa, AJS, NC, NLA, RG-J, SF, AGR, LB, VG, and RM contributed to data interpretation or analysis (or both). All authors contributed to data collection, had access to all the data reported in the study, and accept responsibility for the decision to submit the manuscript for publication. JC, JW, SRu, and AS provided acquisition of data. JC and JW accessed and verified the raw data. The corresponding author, RA, MHar, DS-M, DCG, and JW had full access to all data and vouch for the integrity of the data and adherence to the study protocol.

Declaration of interests

AG was funded by a Cancer Research UK clinical trials fellowship (CRUK/28301). MHaw is supported by the National Institute for Health and Care Research (NIHR) University College London Hospitals Biomedical Research Centre (BRC). DB, SDR, and HMW are supported in part by the NIHR Leeds BRC (NIHR203331). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. All other authors declare no competing interests.

Data sharing

Data sharing requests will be considered by the trial management group on written request to plato@leeds.ac.uk. De-identified participant data or other pre-specified data will be available, subject to a written proposal and an agreed data sharing agreement.

Acknowledgments

ACT4 was supported by a grant from Cancer Research UK (A19121: CRUK/15/007) to DS-M, DB, AG, HMW, JW, MAW, RG-J, SDR, AS, DG, VG, and SRB, and Standup to Cancer (A24480) to DS-M and JW. Cancer Research UK reviewed, approved, and funded the study design.

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