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## Short Report

## The Effect of the UK Coordinating Centre for Cancer Research Anal Cancer Trial (ACT1) on Population-based Treatment and Survival for Squamous Cell Cancer of the Anus

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## Abstract

Between 1987 and 1994, three randomised phase III trials showed that chemoradiotherapy with mitomycin C and 5-fluorouracil was superior to radiotherapy alone (ACT1, European Organization for Research and Treatment of Cancer) or radiotherapy with 5-fluorouracil (Radiation Therapy Oncology Group 87-04, Eastern Cooperative Oncology Group 1289) for squamous cell carcinoma of the anus. We explored the population-based changes in England before, during and after the UK-based ACT1 trial. Information was extracted from the National Cancer Data Repository on patients diagnosed with squamous cell anal cancer in England between 1981 and 2010 ( $n = 11\,743$ ). Robust treatment information was available for the Yorkshire region ( $n = 1065$ ). Changes in treatment patterns and 3 year survival were investigated in 7 year cohorts before, during and after the ACT1 trial. In Yorkshire, the proportion of patients receiving surgery alone fell from 61.6% before, 29.8% during and 12.5% after ACT1; the proportion of patients receiving primary chemoradiotherapy rose from 6.5% before, 17.7% during and 58.8% after ACT1 and continued to rise to 70.3% in the subsequent period. Three year survival improved during the study period from 59.5% (95% confidence interval 56.6–62.2) before ACT1 to 73.6% (95% confidence interval 71.9–75.2) after the trial. Survival in Yorkshire was comparable with that in England. The treatment for squamous cell carcinoma of the anus changed dramatically during the study period. The predominant use of surgery before ACT1, a transition phase during the trial and a dramatic increase in the use of chemoradiotherapy after ACT1 provide strong evidence of the effect of the trial on population-based practice. Survival continued to increase during this period.

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Key words: ACT1 trial; anal cancer; chemoradiotherapy; surgery; survival; treatment

## Introduction

Cancer of the anus is a rare disease whose incidence is steadily rising [1]. Around 1000 cases are now diagnosed in the UK each year, with the majority of cases squamous cell carcinoma (SCC). In 1980, radical surgery was the standard treatment for SCC of the anus. Single centres then started to report high rates of durable complete response to

radiotherapy alone or with the combination of chemotherapy and radiotherapy, with surgery reserved as a salvage therapy [2,3].

In the UK, the UK Coordinating Centre for Cancer Research anal working party designed the first anal cancer trial (ACT1) [4]. Rather than compare radical surgery against non-surgical treatment, a two-arm trial was designed that compared radiotherapy alone versus concurrent chemotherapy using mitomycin C (MMC) and 5-fluorouracil (5-FU). In both arms, a 5 week course of radiotherapy was used with a subsequent radiotherapy boost in responding patients. Early salvage surgery was recommended for patients

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not responding to the initial course of treatment. The trial randomised 577 patients between 1987 and 1994.

At the same time the European Organisation for Research and Treatment of Cancer (EORTC) trial used the same design and recruited 110 patients [5]. In the USA, the Radiation Therapy Oncology Group (RTOG) trial compared 5-FU and radiotherapy with MMC 5-FU and radiotherapy in 310 patients [6]. The consistent finding across the three trials was that MMC 5-FU and radiotherapy led to the highest rate of locoregional control, thus reducing the need for radical surgery and colostomy.

Here we explored the effect of the ACT1 trial on routine population-based clinical practice. We hypothesised that surgery was the standard of care before the trial and that the outcome of the ACT1 trial together with the other two international trials would lead to a change in routine clinical practice after the results of the trial were presented/published.

## Materials and Methods

All patients diagnosed with a first primary cancer of the anus and/or anal canal (International Classification of Diseases Version 10 code C21 [7]) in England between 1981 and 2010 were identified from the cancer registry component of the National Cancer Data Repository (NCDR). Cases were limited to those with squamous cell, basaloid and cloacogenic cancers based on their ICD-O morphology codes [8].

Robust treatment information is not available from all of the cancer registries that contribute data to the NCDR. In order to look at treatment patterns over time, cases of anal cancer (criteria as above) registered in the Yorkshire region of England (where data quality is high) were identified from the cancer registry database. All available treatment data for patients diagnosed between 1981 and 2010 were obtained and cases were split into the following groups: surgery alone; chemoradiotherapy (with or without subsequent salvage surgery); radiotherapy (with or without subsequent salvage surgery); other treatment (all other combinations of treatment); no treatment (none recorded by the cancer registry).

The proportion of patients within each treatment group was calculated for each calendar year and in 7 year cohorts corresponding to the periods before, during and after the ACT1 trial. Three year relative survival (which takes into account the background mortality of the population) in the Yorkshire and national cohorts was calculated for the same 7 year periods using the 'strel' command in STATA version 13.1 (for cases diagnosed up to 2008 to allow sufficient follow-up time).

## Results

Between 1981 and 2010, 11 743 individuals were diagnosed with SCC of the anal canal in England. During the same period in the Yorkshire region, 1065 cases of anal cancer were diagnosed.

### Treatment in the Yorkshire Region

Table 1 and Figure 1 show the changes in treatment for anal cancer over the study period. In the period preceding the ACT1 trial (1981–1987), 61.6% of patients underwent surgery alone. During the ACT1 trial (1988–1994), this figure decreased to 29.8% and reduced further, to 12.5%, in the period after the trial (1995–2001). By contrast, the proportion of patients receiving chemoradiotherapy as their primary treatment rose from 6.5% before ACT1, 17.7% during and 58.8% after the trial. Thereafter chemoradiotherapy remained the dominant treatment; 70.3% received this as primary treatment between 2002 and 2010, with 10.4% having surgery only during the same period. The proportion of patients receiving radiotherapy as their primary treatment increased during the ACT1 period (from 16.7% to 29.8%) and then decreased to 11.7% in the period after the trial.

### Survival in England and the Yorkshire Region

Three year relative survival improved from 59.5% (95% confidence interval 56.6–62.2) in the period 1981–1987 to 73.6% (95% confidence interval 71.9–75.2) in the period 2002–2008 (Figure 2a). In the Yorkshire region, 3 year relative survival was comparable with that in England at 50.4% (95% confidence interval 40.6–59.4) in the period 1981–1987, increasing to 72.8% (95% confidence interval 67.2–77.5) in the period 2002–2008 (Figure 2b).

## Discussion

Treatment for SCC of the anus in England changed dramatically during the study period. There is strong evidence that the ACT1 trial led directly to a major change in population-based practice, together with the supporting evidence from the EORTC and RTOG trials. This view is supported by the dominant use of surgery before ACT1, a transition phase during the trial and a dramatic increase in the use of chemoradiotherapy after. To justify this conclusion, a brief review of the evolution of chemoradiotherapy for anal cancer is necessary to show that is unlikely that other factors would have significantly influenced this observed change in practice.

A seminal case report was published in 1974 by Nigro *et al.* [9] describing the success of chemoradiotherapy in four patients with anal cancer. Nigro *et al.*'s group subsequently published a series of 45 patients treated by low dose chemoradiotherapy in 1985 and showed that 84% patients had locoregional control after chemoradiotherapy [2]. Similar findings were reported from single institutions treating 30–121 patients with radiotherapy or chemoradiotherapy [3,10–12]. It is unlikely that these small series would have resulted in a major change in population-based clinical practice in the UK.

The accrued evidence from the three phase III trials (ACT1, EORTC and RTOG) representing a total of 1005 patients determined MMC 5-FU as the standard of care. The

**Table 1**

Anal cancer treatment by period of diagnosis in the Yorkshire region of England

	Pre-ACT1 (1981–1987)	During ACT1 (1988–1994)	Post-ACT1 (1995–2001)	(2002–2010)
Chemoradiotherapy	9 (6.5%)	35 (17.7%)	141 (58.8%)	344 (70.3%)
Surgery alone	85 (61.6%)	59 (29.8%)	30 (12.5%)	51 (10.4%)
Radiotherapy	23 (16.7%)	59 (29.8%)	28 (11.7%)	29 (5.9%)
Other treatment*	15 (10.9%)	31 (15.7%)	17 (7.1%)	29 (5.9%)
No treatment	6 (4.3%)	14 (7.1%)	24 (10.0%)	36 (7.4%)
Total	138 (100%)	198 (100%)	240 (100%)	489 (100%)

\* Other treatment refers to other combinations of treatment, i.e. surgery and radiotherapy, chemotherapy only, surgery and chemotherapy.

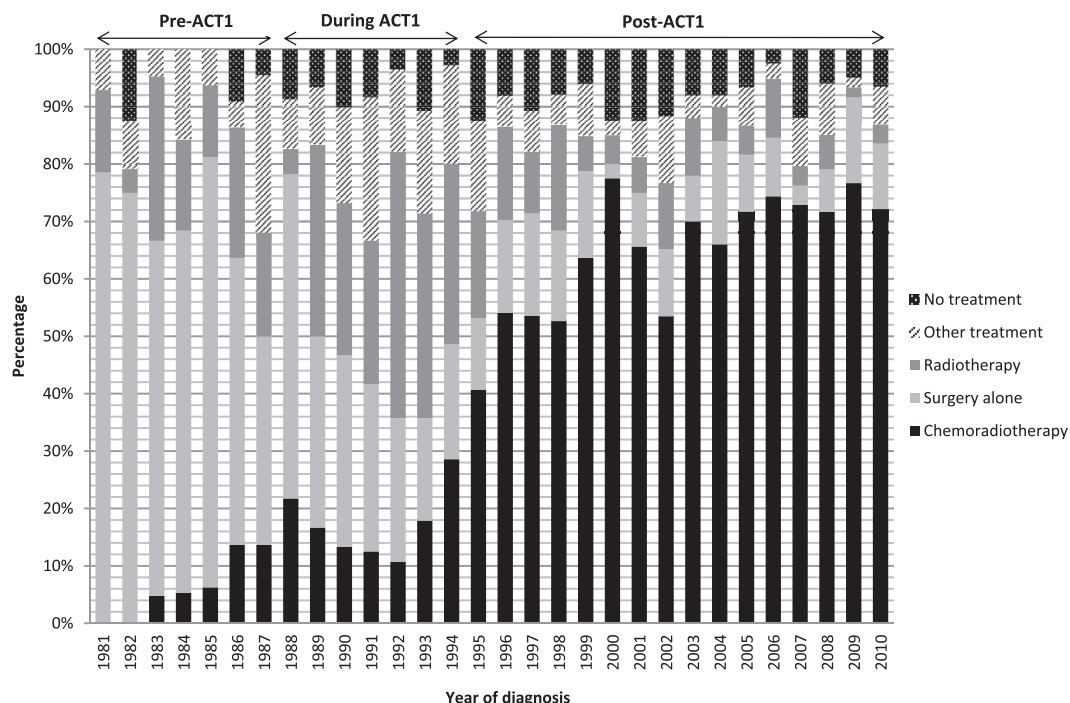
chief investigator of ACT1 indicated the success of non-surgical treatments in the primary management of the disease in 1991, 3 years before the completion of the trial [13].

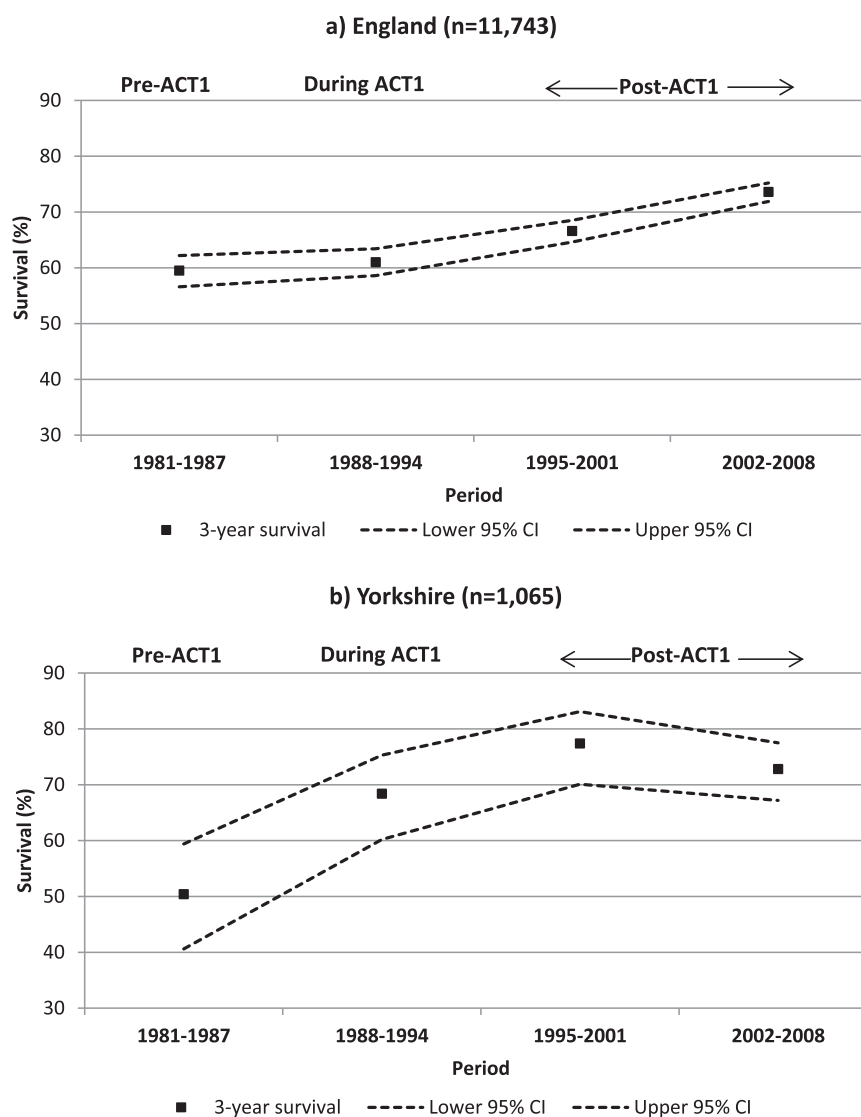
This dramatic change in management of a rare disease from surgery to non-surgical treatment is relatively unusual in solid tumour oncology. These findings emphasise a key benefit of a phase III trial. The rapid uptake of chemoradiotherapy was also probably related to the strong advocacy by leading surgeons with experience of both surgical and chemoradiotherapy outcomes. In this example, the observed treatments used and the results not only apply to the selected clinical trial population, but were extended to change population-based practice.

We also show that population-based survival improved in England throughout the study period, with the most significant increase occurring from 1996. We cannot determine a direct causal relationship, as other factors, such

as the increasing prevalence of human papilloma virus-driven malignancy, may be relevant. However, the change from surgery to chemoradiotherapy probably contributed to the observed improvement in survival rates. Chemoradiotherapy additionally treated all pelvic and inguinal nodes in addition to the primary tumour. The absolute improvement in relative survival throughout the study period was about 25% for both the English and Yorkshire data.

Few studies have investigated the effect of different treatment regimens on patient outcomes at a population level. In the USA, a study of 38 882 patients with anal cancer found that those undergoing recommended treatment (primary chemoradiotherapy with or without surgery) had an 18% lower risk of death within 5 years than those who underwent non-guideline treatment [14]. Large single-centre series have shown similar results. For example, a study of 308 patients in the Stockholm region of Sweden

**Fig 1.** Changes in anal cancer treatment over time in the Yorkshire region of England.



**Fig 2.** Three year relative survival of anal cancer by period of diagnosis.

found that patients treated with neoadjuvant platinum-based chemotherapy had significantly better complete response rates and increased overall 5 year survival than patients treated with radiotherapy with or without bleomycin [15]. In the UK, a series of 254 treated at a regional cancer centre showed that chemoradiotherapy was associated with a significant improvement in local control in comparison with radiotherapy alone and this effect persisted 6 years after the initial treatment [16].

The main limitation of this study was the lack of robust treatment data for the whole country. Although data quality has improved in recent years with the introduction of the National Cancer Intelligence Network and other initiatives, historically it has varied from region to region, with some collecting virtually no treatment information. The data from Yorkshire represent around 10% of the patient population, with two radiotherapy centres and nine referring National Health Service Trusts. There is no reason to suggest that treatment or referral patterns in Yorkshire would differ from other regions in England. Linkage to other datasets,

such as Hospital Episode Statistics, can overcome some of the limitations of cancer registration data but, again, historically coding was not as reliable as it is for recent years.

## Conclusion

Population-based treatment for SCC anus changed dramatically during the study period. The predominant use of surgery before ACT1, a transition phase during the trial and a dramatic increase in the use of chemoradiotherapy after ACT1 provides strong evidence of the effect of the ACT1 trial on population-based practice. A significant improvement in survival was also observed.

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