Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trial†

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Background: Squamous cell carcinoma of the anus (SCCA) is highly sensitive to chemoradiation (CRT) which achieves good loco-regional control and preserves anal function. However, some patients require permanent stoma formation either as a result of surgery on relapse, poor anal function or treatment-related symptoms. Our aim was to determine patient, tumour and treatment-related colostomy rates following CRT and maintenance chemotherapy in the ACT II trial.

Patients and methods: The ACT II trial recruited 940 patients comparing 5FU-based CRT using cisplatin (CisP) or mitomycin C (MMC) with or without additional maintenance chemotherapy. We investigated the association between colostomy-free survival (CFS) and progression-free survival (PFS) with age, gender, T-stage, N-stage, treatment and baseline haemoglobin.

Results: The median follow-up was 5.1 years (n = 884 evaluable/940); tumour site canal (84%), margin (14%); stage T1/T2 (52%), T3/T4 (46%); N+ (32%), NO (62%). Twenty out of 118 (17%) colostomies fashioned before CRT were reversed within 8 months. One hundred and twelve patients had a post-treatment colostomy due to persistent disease (98) or morbidity (14). Fifty-two per cent (61/118) of all pre-treatment colostomies were never reversed. The 5-year CFS rates were 68% MMC/Maint, 70% CisP/Maint, 68% MMC/No-maint and 65% CisP/No-maint. CRT with CisP did not improve CFS when compared with MMC (hazard ratio: 1.04, 95% confidence interval: 0.82–1.31, P = 0.74). The 5-year CFS rates were higher for T1/T2 (79%) than T3/T4 (54%) tumours and higher for node-negative (72%) than node-positive (60%) patients. Significant predictors of CFS were gender, T-stage and haemoglobin, while treatment factors had no impact on outcome. Similar associations were found between PFS and tumour/treatment-related factors.

Conclusions: The majority (52%) of pre-treatment colostomies were never reversed. Neither CRT with 5FU/CisP nor maintenance chemotherapy impacted on CFS. The low risk of colostomy for late effects (1.7%) is likely to be associated with the modest total radiotherapy dose. The predictive factors for CFS were T-stage, gender and baseline haemoglobin.

Clinical trial registration number: ISRCTN 26715889.

Key words: squamous cell carcinoma, anal cancer, chemoradiation, loco-regional control, colostomy-free survival, risk factors

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introduction

The incidence of squamous cell cancer of the anus (SCCA) is ~1.5 per 100 000 annually (900 UK, 5000 USA) [1, 2]. SCCA is highly sensitive to chemoradiation (CRT), which represents the current standard of care [3–5]. The aims are to achieve loco-regional control and preserve anal function avoiding a colostomy and maintain good quality of life (QoL).

Despite CRT’s effectiveness, 10%–40% of patients fail to respond to treatment or relapse (risk depending on initial stage) [1–6] with an associated loco-regional recurrence-free survival of ~60%–80% at 3–5 years [3–5, 7–9]. Salvage surgery for localized pelvic recurrence invariably requires a radical anorectal excision (ARE) and permanent colostomy formation. Alternatively, a defunctioning stoma may be required for palliation of symptoms from locally recurrent disease or for late complications of radiotherapy.

A temporary defunctioning stoma/colostomy before radiotherapy is sometimes needed to alleviate presenting symptoms from anal cancer (pain, frequency of defaecation or faecal incontinence), or to palliate rectovaginal or rectovesical fistulae in anterior tumours [10]. The fistula and poor function may persist, particularly in patients where the sphincter complex is extensively involved [11–14]. A temporary colostomy following CRT may be needed to alleviate pain caused by a non-healing ulcer, despite a good response to treatment.

Phase III trials suggest radical CRT results in colostomy rates of 15%–36% [3–6, 15], and CFS at 5 years of 70%–75% [3–5, 7–9]. Since survival has not improved in the randomized trials despite better local control, QoL and cause-specific colostomy rates are relevant end points.

Neither cisplatin-based neoadjuvant chemotherapy [7, 8] nor maintenance chemotherapy following CRT [15], nor an increased dose of radiotherapy boost (ACCORD-03 trial) [9] has shown an advantage in terms of CFS. A combined analysis of both MMC and cisplatin arms in the RTOG 98-11 trial [16] showed that tumour diameter (irrespective of nodal status) was the only independent predictor of time to colostomy and 5-year colostomy rate.

The aim of the present paper is to use the ACT II trial data (i) to identify patient, pre-treatment and treatment factors associated with the risk of colostomy, (ii) to estimate the cumulative incidence of colostomy according to the categories proposed earlier [17] and (iii) to check the validity of colostomy as a relevant end point for future anal cancer trials.

methods

trial design

ACT II was a randomized 2 × 2 factorial trial of 940 patients conducted in 59 UK centres (2001–2008) [16]. Progression-free survival (PFS) was a primary end point and colostomy rate a secondary end point. Results on the primary end points have been reported previously [16] together with full details on inclusion–exclusion criteria and treatment schedules. Radiotherapy to 50.4 Gy was delivered in 28 daily fractions over 5.5 weeks using a two-phase technique in combination with either concurrent 5FU/MMC or 5FU/cisplatin. Patients randomized to receive maintenance were administered two additional courses of 5FU/CisP following CRT.

assessments

Tumour stage and nodal status were assessed according to UICC criteria [18]. Residual/recurrent disease required biopsy confirmation before surgical salvage or further therapy. After assessment at week 26, patients were reassessed every 2 months in the first year, once every 3 months in the second year, half-yearly until the fifth year and yearly thereafter.

Clinicians often do not consider reversing pre-treatment colostomies until 6 months from the start of treatment. Hence, colostomy reversal data were collected from 8 months after the start of treatment (the first follow-up).

classification of colostomies. We classified colostomies into three groups: (i) ‘pre-treatment colostomies’ created before CRT due to anal cancer-related reasons, (ii) ‘treatment-related colostomies’ carried out during CRT or following the completion of CRT to allay late effects of treatment in the absence of any histological evidence of cancer and (iii) ‘tumour-related colostomies’ carried out for persistent disease or recurrence at the time of surgery or for a defunctioning stoma or to alleviate symptoms of recur rent tumour.

statistical considerations

All analyses included 884 assessable patients, 56 patients with inadequate follow-up data were excluded. CFS events included: all post-treatment colostomies carried out either as surgical salvage for persistent/recurrent disease or to alleviate late effects of radiation; pre-treatment colostomies not reversed after completion of treatment (event on day 1); patients who underwent ARE after relapse who had missing/uncertain colostomy data (n = 5) and death from any cause.

PFS events included progressive disease, local recurrence, metastases or death from any cause, but not new tumours. All survival end points were measured from date of randomization. Patients without CFS/PFS events were either censored on last date seen alive or date of new tumour diagnosis. The Kaplan–Meier plots and Cox regression analyses were carried out using STATA 12. All P-values were two-sided.

Univariable and multivariable Cox proportional hazards models were used to estimate crude and adjusted hazard ratios (HR) and their 95% confidence intervals (95% CI) for the potential risk factors for colostomy formation (CFS analysis) or disease progression (PFS analysis). A stepwise backward selection method was employed (P-value cut-off ≤0.05) to identify significant prognostic factors. The factors included were: treatment (CisP or MMC, Maint or No-maint) age, gender, nodal status (involved versus uninvolved), tumour size T3 versus T1/T2 (>5 versus ≤5 cm), tumour spread to neighbouring organs (yes versus no) and baseline haemoglobin. The multivariable analysis did not include tumour spread as it correlates to tumour size. Multivariable analyses were repeated using the Fine and Gray [19] competing risks regression method which considers colostomy-free death as a competing risk factor.

results

A total of 884 of the 940 patients recruited to ACT II trial were evaluable and their baseline characteristics were balanced (supplementary Table S1, available at Annals of Oncology online). The median age was 57 years; 52% had primary tumour ≤5 cm in diameter (T1/T2), 31% >5 cm (T3); 14% with tumour spread to neighbouring organs (T4); 32% had positive lymph nodes; and 84% with tumour in the anal canal, 14% anal margin. The mean haemoglobin at baseline was 13.6 g/dl (range: 8.2–18). The median follow-up, censoring deaths, was 5.1 years (6 days to 10.5 years).
timing and reason for colostomy

At the time of randomization, 118 out of 884 (13%) patients had a colostomy (Figure 1) and were included in the pre-treatment colostomy group. Twenty of these (17%) were reversed within 8 months. The remaining 98 colostomies remained in situ after all treatments were completed, 70 out of 98 patients were CR at 6 months and none had relapsed by the first follow-up at 8 months. Thirty-eight per cent (37/98) of these colostomies were reversed later during follow-up. At 6 years, 61 out of 118 patients (52%) had pre-treatment colostomies in situ of these (87% were T3/4). At baseline, 23 out of 61 (38%) were T3 and 30 out of 61 (49%) T4, indicating that patients with more advanced tumours were more likely to have permanent stomas.

Following CRT, 112 patients required a colostomy as a result of surgical salvage for persistent/recurrent disease (n = 98) or symptoms of late morbidity (n = 14) (Figure 1). In addition, 3 out of 20 pre-treatment colostomies reversed after all treatment needed a subsequent colostomy for disease and 1 out of 20 for late treatment effects. In all, 101 out of 884 (11%) patients had ‘tumour-related’ and 15 (1.7%) ‘treatment-related’ colostomies.

Cumulative incidences of colostomy for each of the three categories are shown in Figure 2. The curve for pre-treatment colostomies is shown as the inverse of the cumulative incidence of pre-treatment colostomy reversals. There were 57 reversals of pre-treatment colostomies during follow-up (Figure 1). Two-thirds (61/98) of the pre-treatment colostomies not reversed by 12 months were permanent. All tumour-related colostomies (n = 101) had occurred within 6 years of treatment completion. The combined cumulative incidence of pre- and post-treatment colostomies at 5 years was 20% (176/884).

![Figure 1. ACT II trial colostomy schema. *Fifty-six patients did not have follow-up data. Reasons were death before 6 months (n = 23), too ill to attend follow-up (n = 27), withdrawal from the trial (n = 2), ineligibility (n = 2), lost to follow-up (n = 1), data missing (n = 1). **At 8 months since the start of treatment (first follow-up). *Due to disease (n = 3), late treatment effects (n = 1).](https://academic.oup.com/annonc/article-abstract/25/8/1616/273321)

![Figure 2. Cumulative incidence of different types of colostomies.](https://academic.oup.com/annonc/article-abstract/25/8/1616/273321)
colostomy-free survival

There were 286 CFS events including 72 deaths. Sixty-one per cent (44/72) were anal cancer deaths. Five-year CFS rates for the four groups were similar (68% MMC/Maint, 70% CisP/Maint, 68% MMC/No-maint and 65% CisP/No-maint, Figure 3). The overlapping curves indicate the absence of any interaction between the treatment groups. The 5-year CFS rates were 79% for T1/T2 (≤5 cm), 54% for T3/T4 patients (Figure 3), 72% for node-negative and 60% for node-positive.

univariable and multivariable analyses

Cox proportional hazards method. Statistically significant predictors of CFS in univariable analysis were site of primary (borderline significance), haemoglobin (analysed as a continuous variable), tumour size (>5 versus ≤5 cm), tumour spread and nodal status (Table 1). However, primary site and nodal status were not significant when adjusted for the other factors in the multivariable analysis. Gender, although not significant in univariable model, was a significant predictor when adjusted for other factors. Tumour spread was significant in the univariable model (HR: 2.40, 95% CI: 1.82–3.17, P < 0.001; Table 1). There was a 56% increase in the risk of colostomy for males compared with females (adjusted HR: 1.56, 95% CI: 1.16–2.11, P = 0.004). The lower the haemoglobin levels at baseline, the higher the risk of having a colostomy (adjusted HR: 0.82, 95% CI: 0.74–0.90, P < 0.001). Patients with tumours of >5 cm (T3) had approximately twofold higher risk of colostomy than those with tumours < 5 cm (HR 1.86, 95% CI: 1.38–2.50, P < 0.001). Stepwise backward elimination resulted in a final model with gender, tumour size and haemoglobin as independent predictors of CFS (supplementary Table S2, available at Annals of Oncology online). Age, treatment and primary site did not impact CFS.

We carried out subgroup analysis of patients within the different T stage groups (supplementary Table S3, available at Annals of Oncology online). T1 and T2 patients were similar in their risk of colostomy (crude HR: 1.23, 95% CI: 0.73–2.07, P = 0.43), whereas T3 + T4 patients had a significantly higher risk of colostomy compared with T1 + T2 patients (HR 2.46, 95% CI: 1.93–3.14, P < 0.001). Repeating the comparison between T stage groups for NO patients only did not change the overall results (supplementary Table S3, available at Annals of Oncology online), indicating that the increased risk in colostomy was due to the increasing tumour size and not nodal spread.

The significant prognostic factors for PFS were gender, tumour size and baseline haemoglobin (see adjusted HRs, supplementary Table S4, available at Annals of Oncology online). The predictive factors were the same for both CFS and PFS (gender, tumour size and haemoglobin, supplementary Table S5, available at Annals of Oncology online), suggesting that CFS is an important end point in anal cancer trials.

To compare the independent predictors of CFS from ACT II directly with other published studies, we carried out multivariable analysis using the Fine and Gray competing risks regression method [20] considering colostomy-free death as a competing event. Although gender was not an independent predictor in this model, the increased risk for lower baseline haemoglobin and higher tumour size were similar in the final models obtained by the two regression methods (supplementary Table S2, available at Annals of Oncology online).
The ACT II study demonstrated CFS and colostomy rates are not improved by CisP/5-FU CRT compared with standard 5FU/MMC CRT, or by using maintenance chemotherapy [15]. We investigated potential tumour- and treatment-related factors prognostic for colostomy. We grouped patients requiring colostomy into pre-treatment, tumour-related and treatment-related colostomies. We show that tumour size, baseline haemoglobin and gender are independent predictors of CFS.

Gender was a significant factor in the multivariable model, with a 56% increase in the risk of colostomy for males compared with females (adjusted HR: 1.56, 95% CI: 1.16–2.11, P = 0.004). This finding probably reflects the different fluoropyrimidine kinetics in women and leading to higher efficacy, despite the confounding factors of lower haemoglobin in premenstrual patients and pre-existing obstetric anal injuries.

The increased risk of colostomy for larger tumours compared with smaller tumours in ACT II (adjusted HR: 2.06, supplementary Table S2, available at *Annals of Oncology* online) is less than that reported by Sunesen et al. [20] (adjusted HR: 3.8) probably because of the different cut-offs used in the two studies (>5 versus ≤5 cm contrasting with ≥6 versus < 4 cm in Sunesen’s study).

Our results show that approximately twice as many patients with T3 or T4 progressed and received colostomy (n = 178) when compared with T1/T2 patients (n = 104).

Several series have noted a failure to reverse pre-treatment colostomy despite long-term disease control. The indications which lead to pre-treatment colostomies (e.g. pain, incontinence or fistula) often persist despite disease control, especially in the case of circumferential tumours which often result in extensive fibrosis and tight anal strictures [3, 21]. Although initially, the stoma could be considered tumour-related, the definition is inaccurate for patients who achieve long-term control. The ACCORD-03 trial excluded patients with permanent pre-treatment colostomies from their analyses but grouped those

| Table 1. Univariable and multivariable analysis on patients with colostomy data |
|---------------------------------------------------|-----------|-----------------|-----------|-----------------|
| Factors                                           | Crude HR* | CFS events/patients | Adjusted HRb |
|                                                   | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (years) (continuous)                          | 1.00 (0.99, 1.01) | 0.73 | 286/884 | 1.01 (1.00, 1.03) | 0.08 |
| Gender                                           |          |          |          |          |          |
| Female                                           | 1        |          | 170/561 |          | 1        |
| Male                                             | 1.18 (0.94, 1.50) | 0.06 | 116/323 | 1.56 (1.16, 2.11) | 0.56 |
| Site of primary                                  |          |          |          |          |          |
| Canal                                            | 1        |          | 249/743 |          | 1        |
| Margin                                           | 0.70 (0.48, 1.02) |          | 31/122 | 0.90 (0.59, 1.38) |          |
| Haemoglobin, g/dl (continuous)                   | 0.79 (0.73 to 0.85) | <0.001 | 284/878 | 0.82 (0.74, 0.90) | <0.001 |
| Tumour size (>5 versus ≤5 cm)                    |          | <0.001   |          | <0.001   |
| T1 + T2                                          | 1        |          | 104/464 |          | 1        |
| T3                                               | 2.19 (1.68 to 2.86) |          | 113/274 | 1.86 (1.38, 2.50) |          |
| Spread versus no spread*                          |          | <0.001   |          |          |
| T1 + T2 + T3                                     | 1        |          | 217/738 |          |          |
| T4                                               | 2.40 (1.82 to 3.17) |          | 65/124 |          |          |
| N0 versus N+                                     |          | <0.001   |          | 0.44     |
| N0                                               | 1        |          | 160/556 |          | 1        |
| N+                                               | 1.55 (1.22, 1.98) |          | 112/283 | 1.13 (0.83, 1.53) |         |
| Treatment                                        |          | 0.54     |          | 0.53     |
| MMC/No maint                                     | 1        |          | 74/232  |          | 1        |
| CisP/No maint                                    | 1.16 (0.85, 1.59) |          | 83/230  | 1.12 (0.77, 1.63) |          |
| MMC/Maint                                        | 1.01 (0.72, 1.40) |          | 67/212  | 1.02 (0.69, 1.51) |          |
| CisP/Maint                                        | 0.92 (0.65, 1.28) |          | 62/210  | 0.83 (0.55, 1.25) |          |
| MMC versus CisP                                   |          | 0.74     |          |          |
| MMC                                              | 1        |          | 141/444 |          |          |
| CisP                                             | 1.04 (0.82, 1.31) |          | 145/440 |          |          |
| No maint versus Maint                            |          | 0.24     |          |          |
| No maint                                         | 1        |          | 146/420 |          |          |
| Maint                                            | 0.87 (0.69, 1.10) |          | 129/422 |          |          |

*aBased on 884 assessable patients.  
bAdjusted for age, gender, site of primary, tumour size, nodal status and treatment. Analysis was based on 684/884 assessable patients and 200 CFS events.  
cT3 versus T1 + T2 for tumour size and T4 versus T1 + T2 + T3 for tumour spread as per UICC staging [18].  
NB. Tumour spread not entered together with tumour size due to collinearity.
with reversed pre-treatment colostomies together with those who never needed a colostomy [9]. We recommend that patients with pre-treatment colostomies should be grouped separately even if they are subsequently reversed. Future studies should investigate the rationale for fashioning pre-treatment colostomy. A pre-treatment colostomy should be used as a stratification factor in trials where CFS is considered as either a primary or secondary end point.

In ACT II, the cumulative incidence at 5 years was 13% for post-treatment colostomies and 20% for pre- and post-treatment colostomies combined. The latter is lower than the 26% reported by Sunsen et al. [20] who defined pre-treatment colostomies as tumour-related including temporary stomas. Such temporary stomas can occur in up to 15%–20% [3, 16, 22]. It may not be appropriate to include these pre-treatment colostomies as tumour-related.

The combined cumulative incidences for pre- and post colostomies were 18% and 22% for the CisP and MMC groups, respectively (P = 0.13). The MMC rate is higher than reported by the RTOG9811 [7, 16] (19% CisP and 10% MMC) possibly because permanent colostomies were included in our analysis and we included fewer patients with small tumours (73% ≤5 cm RTOG9811 versus 52% ACT II). The cumulative incidence for CisP and MMC groups disregarding the pre-treatment colostomies in ACT II was 9% and 10%, respectively. Unlike the RTOG 98–11 trial [8], we did not find an increased cumulative colostomy rate for CisP when compared with MMC. We attribute this to the continuous CRT schedule with no planned treatment breaks used in ACT II.

In ACT I, only 40 out of 577 patients had a colostomy formed to ameliorate late effects [3], and in ACT II, this figure fell to 15 out of 940, reflecting the fact that estimated doses to the anorectal sphincter in ACT II are low [23]. The consistency of dose received in ACT II—98% of patients received 51.4 Gy to the anal sphincter with an IQR for duration of treatment 38–39 days—indicates that the data presented are robust and unique. Poor sphincter control may be associated with doses of ≥53 Gy received by the lateral aspect of the anal sphincter [24].

In conclusion, we have identified patient, pre-treatment and treatment factors associated with the risk of colostomy to allow better stratification in subsequent trials and to capture colostomy data more informatively. The ACT II schedule led to high CFS because of good local control. Infrequent late morbidity probably reflects the low total dose (50.4 Gy). The establishment of recognized pre-treatment variables (gender, tumour size and haemoglobin) may help to identify patients with a high risk of failure who could be given alternative therapeutic strategies (e.g. surgical salvage), and facilitate the development of novel therapeutic strategies for such patients.

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The authors have declared no conflicts of interest.

references
ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥ 4 baseline): final results in stage III–IV low-risk Hodgkin lymphoma (IPS 0–2) of the LYS A H34 randomized trial†


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Background: Treatment with escalated BEACOPP achieved a superior time to treatment failure over ABVD in patients with disseminated Hodgkin lymphoma. However, recent clinical trials have failed to confirm BEACOPP overall survival (OS) superiority over ABVD. In addition, the gain in low-risk patients is still a matter of debate.

Patients and methods: We randomly compared ABVD (8 cycles) with BEACOPP (escalated 4 cycles ≥ baseline 4 cycles) in low-risk patients with an International Prognostic Score (IPS) of 0–2. The primary end point was event-free survival (EFS). This parallel group, open-label phase 3 trial was registered under #RECF0219 at French National Cancer Institute.

Results: One hundred and fifty patients were randomized in this trial (ABVD 80, BEACOPP 70): 28 years was the median age, 50% were male and IPS was 0–1 for 64%. Complete remission rate was 85% for ABVD and 90% for BEACOPP. Progression or relapses were more frequent in the ABVD patients than in the BEACOPP patients (17 versus 5 patients). With a median follow-up period of 5 years, seven patients died: six in the ABVD arm and one in the BEACOPP arm (HL 3 and 0, 2nd cancer 2 and 1, accident 1 and 0). The EFS at 5 years was estimated at 62% for ABVD versus 77%, for BEACOPP (hazards ratio (HR) = 0.6, P = 0.07). The progression-free survival (PFS) at 5 years was 75% versus 93% (HR = 0.3, P = 0.007). The OS at 5 years was 92% versus 99% (HR = 0.18, P = 0.06).

Conclusion: Fewer progressions/relapses were observed with BEACOPP, demonstrating the high efficacy of the more intensive regimen, even in low-risk patients. However, additional considerations, balancing treatment-related toxicity and late morbidity due to salvage may help with decision-making with regard to treatment with ABVD or BEACOPP.

Key words: Hodgkin lymphoma, intensive chemotherapy, phase 3 trial, prognostic factors, secondary malignancy

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