Toxicity and survival of anal cancer patients treated with intensity-modulated radiation therapy

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ABSTRACT

INTRODUCTION The definitive treatment of anal cancer with chemoradiotherapy spares abdominoperineal resection for salvage treatment but carries a high burden of toxicity. Intensity-modulated radiation therapy has been implemented to reduce toxicity, reduce treatment breaks and improve survival. However, large and long-term studies are lacking. We aimed to investigate the toxicities and long-term survival of anal cancer patients treated with intensity-modulated radiation therapy at James Cook University Hospital, Middlesbrough.

MATERIALS AND METHODS We conducted a retrospective analysis of all patients with squamous cell anal cancer treated at James Cook University Hospital between July 2010 and April 2017. All patients were uniformly treated with intensity-modulated radiation therapy-based chemoradiation with curative intent. A subset of these patients was followed-up prospectively by an oncologist for acute and late toxicity. We calculated Kaplan–Meier estimates of survival statistics and compared our results with those of previous trials which used conventional radiotherapy.

RESULTS We studied 132 patients, including a toxicity subset of 64, for a median follow-up time of 43 months (range 3–84 months). Eleven patients (8.3%) underwent salvage abdominoperineal resection. Grade 3+ acute non-haematological, gastrointestinal, genitourinary and dermatological toxicity were found in 56.2%, 12.3%, 0% and 50.7% of the toxicity subset ($n = 64$). Median treatment duration was 37 days. Overall and colostomy-free survival at five years were 68.3% and 85.3%, respectively. Tumour size ($P = 0.006$) and age ($P = 0.002$) predicted shorter overall survival.

CONCLUSIONS Intensity-modulated radiation therapy probably reduces acute gastrointestinal and genitourinary toxicity compared with conventional radiotherapy, while resulting in similar overall and colostomy-free survival. We suggest that further dose escalation may improve survival in patients with T3/T4 tumours.

KEYWORDS

Anal cancer – Intensity-modulated radiation therapy – Chemoradiation – Abdominoperineal resection – Survival – Toxicity

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Introduction

Anal cancer is a rare squamous-cell carcinoma, with approximately 27,000 cases recorded worldwide in 2008.¹ A 2017 epidemiological study shows that the incidence is on the rise in both sexes, with associated risk factors including human papillomavirus (HPV), HIV and risky sexual behaviours.² The majority of anal cancers are caused by HPV-16.^{1,3,4} It is also estimated to be nine times higher in HIV-positive men who have sex with men than HIV-negative who have sex with men.⁵

Since the work of Norman Nigro at Wayne State University Hospital,^{6–8} chemoradiotherapy has been established as the primary treatment, with abdominoperineal resection reserved as salvage treatment.⁹

Several randomised controlled trials have since confirmed the supremacy of the original regimen over others.^{10–14} Chemoradiotherapy offers a good prospect of cure with reduced morbidity and improved sphincter preservation. In most patients, chemoradiotherapy precludes the need for permanent colostomy. However, this treatment is not free from serious adverse effects, which include acute dermatological, gastrointestinal, haematological and cardiovascular toxicities. Large studies have demonstrated high levels of toxicity related to chemoradiotherapy.^{11,12,15} In the ACT II study, which examined cisplatin compared with mitomycin chemoradiotherapy, 62% of patients in the mitomycin group experienced an acute grade 3 or 4 non-haematological toxicity.¹¹

Intensity-modulated radiation therapy (IMRT) has been introduced to mitigate some of these untoward effects by reducing the radiation exposure of organs at risk. Its efficacy in the treatment of anal cancer has only been demonstrated in a number of small prospective and retrospective studies,^{16–22} and long-term survival data are limited.

Our study was conducted in a tertiary referral centre – the sole provider of treatment for anal cancer to a population of 1.5 million in the North-East of England.²³ Since July 2010, all anal cancer patients at James Cook University Hospital, Middlesbrough, have been treated exclusively with IMRT. We aimed to study the toxicity experienced by patients treated for anal cancer at our hospital, their long-term survival and the frequency of salvage abdominoperineal resection to determine the relative benefits of IMRT compared with conventional radiotherapy.

Materials and methods

Study design

We retrospectively collected data on the demographics, TNM staging, survival and disease recurrence of patients with anal cancer. Data had been recorded in hospital databases by clinicians during episodes of routine care. From July 2010, a prospective patient subset was created under a designated consultant oncologist to monitor treatment-related toxicity closely. The patients in this toxicity subset were selected only because they had been treated by the oncologist collecting toxicity data and not because of any disease or patient-related factors. Patients in the prospective toxicity subset were followed up routinely. This involved three-monthly follow-up for the first two years following treatment and six-monthly follow-up thereafter until five years after treatment.

Study participants

All patients diagnosed with an anal malignancy between July 2010 and April 2017 who were subsequently referred to our hospital for further investigations and treatment were added to the hospital's cancer registry. Following histological clarification, only patients with a diagnosis of squamous cell carcinoma were retained for further analysis.

Treatment

Prior to July 2010, patients were treated with conventional radiotherapy as per the ACT II protocol.¹¹ After the installation of a TomoTherapy® machine in the oncology department in 2010, an IMRT protocol was developed. Volumetric modulated arc therapy became available in October 2012 and both forms of IMRT were used subsequently. All patients included in this study received IMRT-based chemoradiation with curative intent. For T1/2 tumours a standard regimen of 50.4 Gy and 42 Gy in 28 fractions were prescribed for the main tumour and nodal volume, respectively. For T3/4 tumours, 54 Gy to the main tumour volume and 45 Gy to the nodal volume in 30 fractions for uninvolved nodes were prescribed, and 50.4 Gy in 30 fractions to involved lymph nodes if 3 cm or less, or 54 Gy in 30 fractions if greater than 3 cm.

Data collection

Patient data were collected from WebICE, the hospital's electronic database. For the patients who formed the prospectively collected toxicity subset, the severity of toxicities was assigned a grade according to the Common Terminology Criteria for Adverse Events (version 4.0).²⁴ Vital status, including mortality of participants, was recorded from WebICE. Overall survival and colostomy-free survival were defined from the date of diagnosis, while disease-free survival and metastasis-free survival were defined from the initiation of chemoradiotherapy. Only post-treatment colostomies were counted as events in the colostomy-free survival statistic.

Statistical analysis

The statistical programming language and environment R-studio was used for all analyses. We calculated the Kaplan–Meier estimate for survival curves. Differences between groups were assessed by building a Cox regression model and using the log-rank method to test for significance. The time to metastases, non-parametric survival curve were calculated using interval-censored data. Prognostic data were derived by extrapolating both univariate and multivariate Cox proportional hazards regression models. The proportional hazards assumption held true for each variable tested. Multivariate analysis included tumour size, nodal status, tissue differentiation grading, age at diagnosis and sex.

Results

A total of 147 patients presented to this unit with an anal malignancy during the period July 2010 to April 2017. Of these patients, 132 had histologically-proven squamous cell carcinoma. Ten patients were diagnosed with adenocarcinoma, two with malignant melanoma, two with neuroendocrine carcinoma and one with adenosquamous carcinoma. Only patients with squamous cell carcinoma were further analysed.

Of those diagnosed with squamous cell carcinoma, 70.5% were female ($n = 93$) and 29.5% were male ($n = 39$). The median age at diagnosis was 67 years (range 33–98 years). The results of histopathological and radiological investigations are summarised in Table 1.

Disease progression

After a median follow-up of 43 months (range 3–84 months), the incidence of locoregional failure was 9.8% ($n = 13$). Of those patients who developed locoregional failure, 11 had salvage abdominoperineal resection (8.3%), with a clear resection margin achieved in 8 patients. Two of these patients subsequently died (out-of-hospital deaths of unknown aetiology). Neither patient had been recently admitted to hospital and neither was known to have metastases. Distant metastases were found in 19 patients (14%), 3 of whom presented at diagnosis. Five patients were given de-functioning stomas for symptom relief. Their primary reasons for de-functioning stoma were impending obstruction ($n = 2$), tenesmus ($n = 2$) and incontinence ($n = 1$).

Table 1 Summary of tumour grades and radiological TNM staging for 132 patients with squamous cell carcinoma.

	Patients	
	(n)	(%)
Grade:		
1	27	20.5
2	52	39.4
3	43	32.6
Unidentified	10	7.6
Tumour size:		
Tis	2	1.5
T1	24	18.2
T2	41	31.1
T3	30	22.7
T4	35	26.5
Nodal disease stage:		
N0	71	53.8
N1	26	19.7
N2	25	18.9
N3	5	3.8
Nx	5	3.8
Mets staging:		
M0	129	97.7
M1	3	2.3

All five had stomas performed prior to the initiation of chemoradiotherapy. One further patient was given a de-functioning stoma for symptom relief following the failure of chemoradiotherapy, as she was not fit for salvage abdominoperineal resection.

Survival

Table 2 summarises the overall survival, colostomy and disease-free survival for this study and compares them to the results of major phase three trials using conventional three-dimensional radiotherapy. Figure 1 shows the Kaplan–Meier survival curves for overall survival, colostomy-free survival and disease-free survival, respectively. Figure 2 shows the time-to-metastasis survival curve for the 19 patients who developed distant metastases. Patients were more likely to present with metastases in the first 12 months after diagnosis than afterwards ($P = 0.01$).

Toxicity

The three-year overall and colostomy-free survival of the toxicity subset were similar to those of the overall patient cohort (overall survival 78%; 95% confidence interval, CI, 68–89%), colostomy-free survival 81% (95% CI 72–92%, $n = 64$). The median number of days between treatment start and end was 37, while the median number of days on which radiotherapy was received was 30. Acute toxicity (gastrointestinal, genitourinary or dermatological) of stage 3 or greater was experienced by 34 patients (55%), of which nine (14%) were grade 4 reactions. Three patients did not receive the prescribed dose of radiation: two had severe acute toxicities, while one did not attend. Twenty-three patients (36%) had a treatment break of one day or more. Median duration of treatment was 37 days. Overall,

Table 2 Comparison of James Cook University Hospital outcomes with landmark three-dimensional radiotherapy trials.

Trial	Radiotherapy regimen	Overall survival (%)		Colostomy-free survival (%)		Disease-free survival (%)		Grade 3+ acute toxicity (%)			
		3 years	5 years	3 years	5 years	3 years	5 years	GI	GU	Derm.	Acute NH
JCUH	50.4 in 28 fx and 54 Gy in 30 fx	76 (68–84) ^a	68 (59–79) ^a	85 (78–93) ^a	85 (78–93) ^a	68 (60–78) ^a	59 (49–70) ^a	12	0	51	56.2
ACT I ^b	45 Gy in 20–25 fx	65	53	NA	NA	39	41	14	3	50	67 ^c
RTOG 98-11	45–50.4 Gy in 1.8 Gy per fx ± 5–8 Gy boost	NA	78	90	90	67	60	36	3	49	74
ACT II ^{d,e}	50.4 Gy in 28 fx	NA	79	NA	68	NA	69	16	1	48	62

Derm., dermatological; fx, fractions; GI, gastrointestinal; GU, genitourinary; NH, non-haematological; JCUH, James Cook University Hospital; RTOG, Radiation Therapy Oncology Group.

^aBrackets: 95% confidence interval.

^bClassified severity of acute toxicity as 'mild, moderate or severe'.¹³

^c'Severe'.

^dACT II followed up acute toxicity until 4 weeks post-chemoradiotherapy and counted death as an event in colostomy-free survival.

^eMitomycin group.

11% of patients in the toxicity group experienced a grade 3 or 4 chronic toxicity (Table 3).

Radiation dose-related outcomes

Kaplan-Meier estimates of the survival curves for patients who received IMRT radiotherapy with a total dose to the main tumour volume of either 50.4 Gy or 54 Gy are shown in Figure 3. Patients who did not receive the prescribed dose were excluded from this analysis. The five-year survival estimates for patients who received either 50.4 Gy or 54 Gy were 84% (95% CI 72–98%) and 64% (95% CI 46–88%), respectively. The difference between the two groups was not statistically significant ($P = 0.061$, hazard ratio, HR, 1.32; 95% CI 0.98–1.78). Total grade 3+ acute toxicity (gastrointestinal, genitourinary and dermatological) was 54% in the 50.4 Gy group and 52% in the 54 Gy group.

Prognostication

The assessment of the prognostic factors in our study revealed that in both univariate and multivariate analysis, age at diagnosis ($P = 0.02$, HR 1.04; 95% CI 1.01–1.07) and tumour size ($P = 0.006$, HR 1.42; 95% CI 1.02–1.98) predict shorter survival among patients with anal cancer (Figure 4; Tis not included). However, nodal disease ($P = 0.67$) and tissue differentiation grading ($P = 0.41$) did not significantly influence the survival of these patients in either univariate or multivariate analysis. Male sex was not significantly associated with worse survival on univariate analysis.

Table 3 Comparison of patients experiencing grade 3+ chronic toxicity at James Cook University Hospital with patients in the Radiation Therapy Oncology Group 98-11 trial.

Trial	Overall ^a (%)	Gastrointestinal (%)	Genitourinary (%)	Dermatological (%)
JCUH	9.4	4.7	3.1	3.1
RTOG 98-11	6.9	3.2	NA	1.6

JCUH, James Cook University Hospital ; NA, not available; RTOG, Radiation Therapy Oncology Group.

^aEach patient counted once.

($P = 0.13$) but was on multivariate analysis ($P = 0.04$, HR 2.19; 95% CI 1.02,4.68).

Discussion

A 15-year follow-up of the ACT I trial found a higher rate of non-anal cancer-related deaths in the group receiving chemoradiotherapy compared with those receiving radiotherapy alone. Although chemoradiotherapy showed superior locoregional control over radiotherapy, absolute risk of mortality was not significantly different at 5, 10 and 12 years after beginning treatment.¹⁵ The Intergroup Radiation Therapy Oncology Group (RTOG) 98-11 trial compared chemoradiotherapy with mitomycin and fluorouracil to chemoradiotherapy with cisplatin and fluorouracil.¹² In a long-term update of the RTOG 98-11 trial, 200/325 patients (61.5%) in the mitomycin arm of the study and 163/324 (50.3%) in the cisplatin arm required treatment breaks due to acute toxicity related to chemotherapy.²⁵ The ACT II trial also reported high rates of adverse events related to chemoradiotherapy toxicity. Overall, 62% of patients in the mitomycin group experienced a grade 3 or 4 non-haematological toxicity.¹¹

In addition to the immediate adverse effects experienced by the patient, treatment breaks may reduce the efficacy of the treatment, presumably due to accelerated tumour repopulation.²⁶ A number of studies have also demonstrated a benefit from reduced length of treatment.^{27–29} Taken together, the results of these trials demonstrate that patients receiving chemoradiotherapy are exposed to a large burden of toxicity, which may reduce overall survival and may have the potential to increase the rate of colostomies required for high stool frequency and poor sphincter control.

Dosimetric studies predict a reduction in the radiation exposure to bowel, bladder, genitalia and perianal skin,^{30–32} and this benefit has been borne out in several retrospective and prospective studies.^{16–22} In the RTOG 05-29 trial, IMRT led to shorter overall treatment times relative (median 43 days, range 32–59 days), compared with the RTOG 98-11 trial's radiation/fluorouracil/mitomycin arm (median 49 days, range 4–100 days; $P < 0.0001$).^{20,33} In our study, 12 patients in the toxicity subset (18.8%) required a treatment break of at least one day, while the median treatment time was 37 days, which is less than that in the RTOG 98-11 trial (49 days) and the ACT II trial (38 days). ACT I did not give a median treatment duration. ACT I and ACT II had treatment delays of at least one day in 19 and 15.7% of their patients, so it is important to point out that we could further reduce our treatment time by reducing the number of delays. Treatment delays may be caused by factors other than acute toxicity, such as patient concordance and illness not related to acute toxicity from radiotherapy.

To our knowledge, the data presented here represent the largest outcome study of patients treated with IMRT for anal cancer. We report low rates of salvage abdominoperineal resection (8.3%) and overall, colostomy-free and disease-free survival rates of 68%, 85% and 59% at five years,

respectively, which is comparable or slightly lower than large phase 3 trials that used three-dimensional conformal radiotherapy (Table 2). We found that increasing age at diagnosis was associated with worse survival ($P = 0.02$), although the effect was subtle (HR 1.035). This is in keeping with a large epidemiological study ($n = 19,199$) which found lower five-year survival in patients 65 years or older compared with those between 18 and 65 years in multivariate Cox regression analysis.³⁴ Interestingly, this study also found that those living in lower-income areas also had lower five-year survival even when controlling for age and disease stage at presentation (HR 1.09). Given that ours is a single institution catering to a relatively low socioeconomic demographic, it is likely that our survival outcomes will be lower than the national average. As of 2015, average household incomes in the Tees Valley were 15% below the national average.³⁵

We have demonstrated benefit from IMRT compared with chemotherapy and conventional radiotherapy as delivered in the RTOG 98-11 and ACT II trials. We delivered a larger radiation dose to T3 and T4 tumours (54 Gy in 30 fractions) while seeing an apparent reduction in acute toxicities. Overall, grade 3 and 4 acute gastrointestinal, genitourinary or dermatological toxicities were experienced by 53% of our patients. Our patients experienced fewer grade 3 and grade 4 gastrointestinal and genitourinary toxicities than those of RTOG 98-11 and ACT II (Table 2). However, we report a similar rate of grade 3 and 4 dermatological toxicity, possibly because radiation therapy unavoidably passes through skin. Unpublished observations from the oncologist who followed up the toxicity group of this study suggest that the area of affected skin is reduced in IMRT compared with conformal radiotherapy, but the severity of the toxicity is comparable or worse. Some institutions have demonstrated a reduction in dermatological toxicity with IMRT compared with conventional three-dimensional radiotherapy,^{36,37} while others have demonstrated no difference.³⁸ In the RTOG 05-29 trial, IMRT resulted in fewer dermatological toxicities relative to RTOG 98-11 (23% vs 49%; $P < 0.0001$).³⁷ Our rates of chronic toxicity were comparable to those of RTOG 98-11 despite IMRT (Table 3).

The larger dose prescribed for T3 and T4 tumours did not prevent these patients from continuing to have a worse prognosis relative to those with T1 and T2 tumours ($P = 0.006$; Figure 4). However, the difference in overall survival between those patients in the toxicity group who received 50.4 Gy and those who received 54 Gy only bordered on significant ($P = 0.061$; Figure 3). Comparison of the total grade 3+ acute toxicities (gastrointestinal, genitourinary and dermatological) experienced by patients who received 50.4 Gy compared with 54 Gy shows similar rates in both groups (54% vs 52%, respectively). Furthermore, our rates of acute toxicities are lower than those of previous studies (Table 2), despite the larger radiation dose in our patients. Janssen *et al* delivered 59 Gy to all tumours regardless of stage and demonstrated exceptional outcomes in terms of acute toxicities (24% overall) with good tumour control (two-year local control, colostomy-free survival, distant metastases-free survival and overall survival

rates were 92%, 92%, 92%, and 88%, respectively).⁵⁹ Given this result, there are grounds for considering an increase in the radiotherapy dose for T3 and T4 tumours. Further dose escalation for locally advanced tumours is currently being investigated by the PLATO Anal Cancer Trial 5.⁴⁰

We acknowledge that, as a single-institution study, there are limitations to the applicability of our results. However, given that our institution delivers care to a large and varied demographic spread over both urban and rural areas, these limitations are not likely to negate the importance of our conclusions. The retrospective nature of the survival data means that events which are not recorded in hospital records are absent from our data. As the raw data of the ACT I, ACT II and RTOG 98-11 trials are not available to us, we are not able to make a statistical comparison between the survival and toxicity results from our study and theirs. Furthermore, it is less than ideal that we were not able to prospectively follow-up all patients for toxicity. Instead, we have closely followed up a subset of the total patient group. Conversely, both the overall patient cohort and toxicity subset are large ($n = 132$ and $n = 64$, respectively), follow-up was long (median 43 months) and we have obtained a rich dataset due to the meticulous records in electronic hospital databases.

Conclusions

IMRT is likely to reduce the incidence of acute grade 3+ gastrointestinal and genitourinary toxicities compared with trials using conventional radiotherapy, while maintaining similar overall, colostomy and disease-free survival. Most patients are treated successfully with salvage abdominoperineal resection for locoregional failure.

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