Clinical endpoints in trials of chemoradiation for patients with anal cancer

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This Review examines the reporting of endpoints in randomised controlled trials (RCTs) of radical chemoradiation for treatment of squamous cell carcinoma of the anus. The types, frequency, and definitions of clinical primary and secondary endpoints, and patient-reported outcome measures, reported in the methods and results sections of papers (and protocols, if available) were examined. Only six published RCTs comprising 2877 patients were identified. Primary outcome measures varied across the trials analysed: two used disease-free survival, one used progression-free survival, two used local failure, and one used colostomy-free survival. Secondary endpoints included overall survival, complete clinical response, quality of life, toxicity, and compliance. The definitions for primary and secondary endpoints were not consistent across trials, particularly for treatment failure (local, regional, and distant). We conclude that the quality of outcome reporting in RCTs of squamous cell carcinoma of the anus is inconsistent. A core set of outcomes, including clinical and patient-reported outcome measures with standardised definitions, is needed to improve the reporting of RCTs examining chemoradiation for treatment of patients with squamous cell carcinoma of the anus.

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Introduction

Phase 3 randomised controlled trials (RCTs) are considered the best study design to assess the efficacy of a particular intervention in clinical medicine on the basis of clinically meaningful and statistically significant outcomes. In addition, safety and efficacy are used to determine whether a treatment is worth using in clinical practice. Outcome measures, such as overall survival, disease-free survival, objective response or stable disease, or improvements in specific symptoms, are balanced against toxicity, loss of function, risk of second malignancy, or death. In most phase 3 cancer trials, overall survival—a clear and unequivocal event—is considered a benchmark outcome measure. Early surrogate endpoints, such as pathological complete response or clinical complete response, are often useful in clinical trials assessing the efficacy of chemoradiation for cancer because they allow a more rapidly attained assessment of treatment effects. An overview of clinical trial endpoints and design in general has been provided elsewhere;[1] in this Review, however, we focus on clinical endpoints used in trials of anal cancer.

RCTs of squamous cell carcinoma of the anus have used multiple time-to-event endpoints with different disease-related and survival events, but standardised definitions of outcome measures are not yet available because few large trials have been done. Squamous cell carcinoma of the anus is associated with a low event rate for distant metastases, unless recurrence occurs at the primary site. Hence, the use of radical chemoradiation for local control is the mainstay of treatment, which can be associated with substantial acute and late morbidity.

In assessing data from the phase 3 ACT II trial of chemoradiation for squamous cell carcinoma of the anus,[2] we discovered many pitfalls in the type of primary and secondary endpoints used and their corresponding definitions when compared with other trials. For example, the ACT II trial used three primary endpoints: complete response, recurrence-free survival, and acute toxicity. Patients who had a complete local excision (as a result of biopsy or removal of a non-suspicious nodule and usually at T1N0 stage) were ineligible. However, patients with local excision and involved margins were eligible. If the disease has been macroscopically resected and there is no evidence of residual or nodal disease on imaging, clinical complete response is an inappropriate primary endpoint, and recurrence-free survival should be used. In retrospect, therefore, some of the endpoints used in the ACT II trial were inappropriate.

Definitions also seem to be inconsistent between different phase 3 trials. For example, the definition of local failure can include or exclude disease at sites within the pelvis caused by locoregional invasion (ie, inguinal nodes) and occasionally includes new separate tumours that arise independently in the same area.

The International Rare Cancers Initiative aims to increase international collaboration in the conduct of clinical trials, and has developed a trial[3] for metastatic or relapsed squamous cell carcinoma of the anus. If successful, further multicentre international studies will be undertaken, but one of the barriers will be variably defined outcomes, which require tight standardisation as recommended by both the International Conference on Harmonisation guidelines[4] and the Consolidated Standards of Reporting Trials (CONSORT) statement.[5] Endpoint consistency has been previously discussed for squamous cell cancers of the head and neck[6] but not for squamous cell carcinoma of the anus. The need for consistent and unambiguous definitions of time-to-event endpoints for recurrence has also been highlighted for breast cancer, along with the need to retain prespecified primary and secondary outcome measures after the trial has started.[7]

In this Review, we examine standard phase 3 clinical trial endpoints with the aim of providing recommendations for their definition and use in future clinical trials of patients with anal cancer.

Methods

Search strategy and selection criteria

A computerised literature search was done to examine relevant English-language publications deposited on PubMed, MEDLINE, Cancerlit, Embase, Web of Science, and the Cochrane Library. Articles from Jan 1, 1974, to Dec 31, 2015, were eligible for inclusion. The search was supplemented by hand searching of abstracts from international meetings in the past 5 years. MeSH terms or combined free terms used included "anal cancer", "squamous cell carcinoma", "local recurrence", "survival", "concurrent irradiation", "chemotherapy", "radiotherapy", "chemoradiation", "combined modality", and "endpoints" (appendix). In addition to original research papers, we reviewed the references of included studies to find potentially eligible articles. Studies were eligible if patients with squamous cell carcinoma of the anus had been randomly allocated or treatment had been prospectively determined. Of the 2139 records identified through database searching, titles were excluded if they were deemed irrelevant (not anal cancer or adenocarcinoma, or other histology) or were duplicate publications. Of the 76 abstracts or full-text articles assessed for eligibility, only 11 publications of six randomised relevant trials were found. We read articles that seemed likely to offer original information relevant to the scope of this Review on the defined endpoints of complete clinical response, locoregional control, disease-free survival, progression-free survival, relapse-free survival, colostomy-free survival, cause-specific survival, and overall survival.

See Online for appendix

Findings

Only six phase 3 RCTs and updates on squamous cell carcinoma of the anus have been published in the past 25 years.[2,8–15] We examined primary and secondary endpoints used (table 1) and noted how composite disease-related endpoints are variably defined (table 2). Possible time-to-event outcomes for patients with squamous cell carcinoma of the anus following chemoradiation are shown in the figure, and definitions of time-to-event endpoints used are shown in table 3.

Overall survival and cause-specific survival

Overall survival is a clearly defined endpoint that is not modified by investigator definitions of failure, compliance of patients with long-term follow-up, clinical or radiographical assessments, or physician bias. However, mortality is relatively low in anal cancer and there can be competing risks for death in elderly populations.[16] To assess whether a treatment improves survival, either a large number of patients or long-term follow-up would be needed to test a realistic effect size. The availability of subsequent effective surgical salvage treatments, and the effect of successive treatment lines with novel chemotherapy or biological systemic therapy, can also potentially introduce bias because they can prolong survival. Additionally, the risk of non-cancer-related deaths from medical intervention increases with time.

In the ACT I trial,[9] 77% (182 of 236) of deaths were due to anal cancer, and this proportion was 73% (155 of 211) in

	Primary endpoint	Secondary endpoints
ACT I[9,13]	Local treatment failure (composite of local failure and the need for colostomy to prevent toxicity)	Overall survival
EORTC 22921[10]	Local failure	Event-free survival
RTOG 8704[8]	Disease-free survival	Overall survival, colostomy-free survival, time to colostomy, locoregional control, incidence of negative biopsy after induction, incidence of positive salvage biopsy, and incidence of toxicity
RTOG 9811[11,14,15]	Disease-free survival	Overall survival, cumulative incidence of colostomy, cumulative incidence of local regional failure and distant metastases, and toxicity hazard ratios for overexpression of the tumour marker p53, human papillomavirus (HPV) status, and the enzyme marker HAP1
ACCORD 03[12]	Colostomy-free survival	Overall survival, cancer-specific survival, and local control
ACT II[2]	Two separate endpoints for 2 × 2 factorial design: recurrence-free survival, complete response (complete disappearance of clinically and radiologically overt disease), and acute toxicity (grade 3 or 4) up to 4 weeks after chemotherapy for comparison of mitomycin with cisplatin	Overall survival, cancer-specific survival, colostomy-free survival, and incidence of in-field recurrence

Table 1: **Primary and secondary endpoints used in six randomised controlled trials of anal cancer**

	Composite endpoint	Locoregional disease*	Pelvic disease†	Distant metastases	Death	Secondary malignancy	Colostomy‡
ACT I[9,13]	Local treatment failure	✓	✓	✓	✓	..	✓
ACT II[2]	Progression-free survival§	✓	✓	✓	✓	..	✓
EORTC 22921[10]	Event-free survival	✓	..	..	✓	✓	..
ACCORD 03[12]	Event-free survival	✓	..	✓	✓	..	..
RTOG 8704[8]	Disease-free survival	✓	..	✓	✓	..	..
RTOG 9811[11,14,15]	Disease-free survival	✓	..	✓	✓	..	..

*Locoregional disease includes original site and associated lymph nodes. †Pelvic disease includes other pelvic organs and lymph nodes within the pelvis. ‡Colostomy for treatment morbidity in absence of disease. §Definition for regression-free survival given in protocol used but subsequently renamed progression-free survival.

Table 2: **Definition of composite disease-related endpoints used in six anal cancer trials**

ACT II.[2] Surgical reports suggest that abdominoperineal resection for non-metastatic recurrent or persistent anal cancer can salvage some recurrences, resulting in a 5-year overall survival of around 60%.[17,18] These factors can substantially dilute the observed effect of treatment on survival and could explain why, despite large differences in local control, initial treatment did not affect overall survival outcomes in RCTs comparing radiotherapy alone with chemoradiotherapy.[9,10,13] However, substantial differences were observed in ACT I with the use of cause-specific survival as a secondary endpoint (ie, only deaths related to anal cancer). The disadvantage of this endpoint, however, is the potential for misclassifying causes of death and varying practices in how treatment-related death is included or excluded as an event.

Other composite time-to-event endpoints

Other cancer-related time-to-event endpoints include a disease-related event (such as progression or recurrence) and survival, depending on whether or not all patients have detectable disease at the time of randomisation. Major differences exist in radiotherapy treatment schedules (planning volumes and doses), not only between but also within individual RCTs, partly because of a reliance on early response, either histopathological[8] or clinical,[11,12] to decide the appropriate total radiation dose after the first phase of treatment. Varying compliance with the planned treatment programme, through protocol-defined dose reductions of chemotherapy because of toxicity, might also affect outcomes.

Event-free survival

Event-free survival is not an immediately meaningful term for clinicians, unless the event or various events of interest are well defined and not excessively complex. The RTOG-9811 trial[11] and the JCOG0903 phase 1–2 trials[19] define event-free survival as the time from the date of registration to the date of death from any cause; the first evidence of disease progression (assessed as non-complete response at the second evaluation after complete response); incidence of colostomy; or the first evidence of second primary cancer, whichever occurs first.

Disease-free survival

Disease-free survival serves as both a surrogate endpoint and an endpoint in itself.[20] It is defined as the time from randomisation to the first event of recurrent disease or death (occasionally persistent or progressive disease and second primary tumours are counted as events). The RTOG-9811 trial[14] used disease-free survival as its primary endpoint, which included second malignancies. Unless prespecified, the date of disease recurrence is subject to measurement error and other forms of bias because of differences in the precision and timing of clinical follow-up, and radiological and histological assessments between arms. Standardised follow-up protocols might therefore be required.

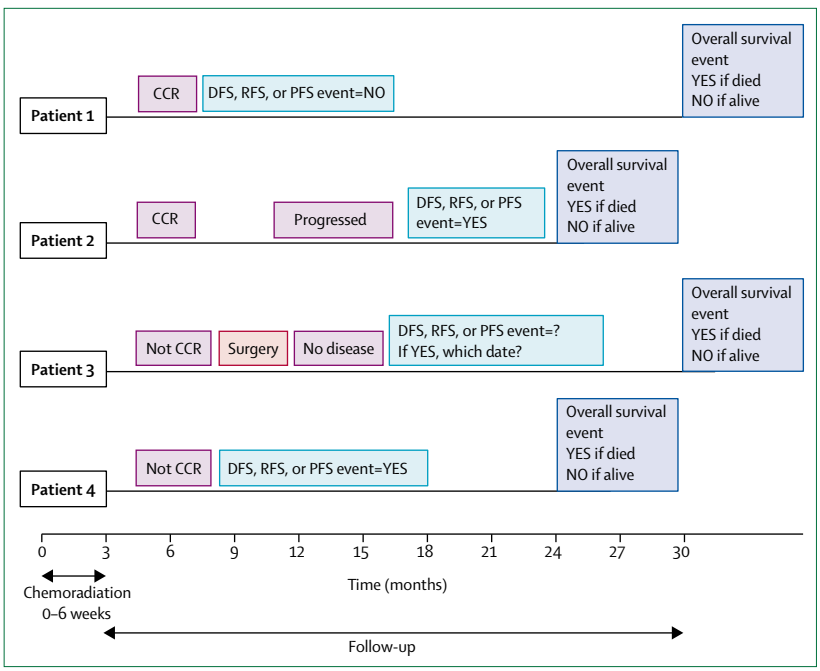

***Figure*: Possible time-to-event outcomes for patients with squamous cell carcinoma of the anus following chemoradiation**

CCR=clinical complete response. DFS=disease-free survival. RFS=recurrence-free survival. PFS=progression-free survival.

Disease-free survival often counts the following as an event: non-complete response (usually 4–11 weeks after chemoradiation); radiological local, nodal, pelvic, or distant disease following a complete response after chemoradiation; or death from any cause. However, it is paradoxical to consider disease-free survival as a meaningful endpoint for patients who have slow or no response to treatment, but are salvaged by surgery and have no clinical disease thereafter.

At randomisation, all patients have clinically or radiologically measurable disease. Following chemoradiation, 80–90% of patients become disease-free, but up to 10% will have persistent disease.[2] This outcome is not the same as an endpoint such as disease-free survival, which is usually used following surgery at a timepoint when there is definitely no detectable tumour. The use of disease-free survival is appropriate when the analysis can be done only on patients who are disease-free at a fixed timepoint (eg, 6 months after treatment) but important early information within these 6 months is lost. There is both an early and late pattern to locoregional relapse or failure. Moreover, some patients never become disease-free. Treatment is considered to be unsuccessful in such patients, and we can assume that their event occurs at the time of randomisation. By contrast, there is an actual timepoint for disease-free survival for other patients, which is usually 3–9 months after the completion of treatment. At this point not only can we conclude that residual active cancer is still

	ACT I[9,13]	EORTC 22921[10]	RTOG8704[8]	RTOG 9811[11,14,15]	ACCORD 03[12]	ACT II[2]
Disease-related time-to-event endpoints						
Local recurrence	..	LRF	..	..	..	..
Local recurrence, distant metastases, secondary maligancy, or death	..	..	DFS	DFS	..	..
Local recurrence, distant metastases, or death	..	..	..	..	..	PFS
Local recurrence, secondary malignancy, or death	..	EFS	..	..	..	..
Local recurrence, distant metastases, incidence of colostomy, or death	..	..	..	..	EFS	..
Local recurrence or incidence of colostomy due to recurrence or complications	LRF	..	..	..	..	..
Survival endpoints						
All deaths	OS	..	..	..	..	OS
Deaths due to anal cancer or related to treatment	CSS	..	..	..	..	CSS
Colostomy-related time-to-event endpoints						
Colostomy (due to any cause) or death	CFS	..	..	CIS	CFS	CR (CFS)

LRF=locoregional failure. DFS=disease-free survival. PFS=progression-free survival. EFS=event-free survival. OS=overall survival. CSS=cause-specific survival. CFS=colostomy-free survival. CIS=cumulative incidence of colostomy. CR=colostomy rate.

Table 3: **Definitions of time-to-event endpoints used in six anal cancer trials**

present and surgical salvage is required, but also that chemoradiation has failed. A positive biopsy could define the endpoint conclusively, but a premature positive biopsy might indicate an active tumour that is likely to disappear if observed for an extended period.

Recurrence-free survival

Recurrence-free survival includes any recurrence (local, regional, or distant) and also death due to any cause (both from the cancer and other causes). In the original ACT II protocol, the primary endpoint was named recurrence-free survival, defined as above. After the trial results were published,[2] however, this endpoint was renamed progression-free survival (while retaining the events included as originally defined) because, at the time of publication, it was considered misleading and progression-free survival best suited the events included in the original endpoint definition.

Progression-free survival

For progression-free survival, events are captured in a non-continuous framework, so the timing and intervals between the clinical and radiological assessments are crucial to its precision. Progression-free survival in metastatic disease is not defined by the stable persistence of the tumour, but by the enlargement of lesions or the appearance of new lesions. By contrast, in squamous cell carcinoma of the anus following chemoradiation, no observed change to the original primary tumour is eventually considered as progression. Progression-free survival can therefore be ambiguous and can be criticised as a primary endpoint because of the potential liability and subjectivity, which depends on the frequency and timing of radiographical surveillance. A new term is therefore required for patients treated with radical chemoradiation for head and neck squamous cell carcinoma, oesophageal cancer, cervical cancer, and squamous cell carcinoma of the anus. This new term should accurately capture both the first clinical detection of disease progression (preferably defined by biopsy; ie, local, regional, or distant), as well as persistence of the primary tumour, and recurrence or death from any cause, with censoring of the very few patients who are lost to follow-up or did not experience the event on the date they were last seen before their death. In addition, subsequent lines of treatment or salvage surgery can affect overall survival. Information about subsequent treatment after documented progression is therefore essential.[21] A detailed discussion of progression-free survival and its limitations[22] is beyond the scope of this Review.

Local failure-free survival

In the ACT I trial,[9,13] the primary endpoint was the occurrence of local failure, which was assessed 6 weeks after the initial treatment and defined as a composite of locoregional failure, the need for surgery for treatment-related morbidity, or failure to close a pre-treatment colostomy 6 months after the end of treatment. Local tumour failure was defined as evidence of persistent local disease, local regrowth, or local recurrence in the primary tumour after protocol therapy. Patients who never attained local control after chemoradiotherapy were classified as treatment failures at the first assessment 6 weeks after treatment. This composite endpoint assumed all patients with persistent or recurrent disease would undergo a colostomy, which turned out not to be the case as 31% (82 of 265) of patients with local failure either had too advanced disease, were too frail, or were otherwise unsuitable for surgery. 8% (20 of 265) of patients required colostomies for treatment morbidity, and in 5% (14 of 265) of patients there was an unexplained failure to close a pre-treatment colostomy. By including all these events, the trial described a population that was both tumour-free and colostomy-free, which was a useful

comparison of chemoradiotherapy with surgery as primary therapy for this population of patients. However, for future trials, separate data for disease and colostomy status are required.

Local failure-free survival seems to be the most logical endpoint as it includes all relevant events, irrespective of surgical salvage, and does not have the problems associated with disease-free survival (not all patients are disease-free at baseline) or progression-free survival (which includes persistent stable disease as an event). Yet, in the RTOG-8704 study,[8] patients who had a colostomy, abdominoperineal resection, or exenteration for any reason were considered treatment failures on the day of surgery even if subsequent long-term local control was achieved. Even if salvage surgery remains possible after locoregional failure, the survival gain can be offset by permanent functional impairment and a decreased quality of life, although many patients will accept this compromise in exchange for gains in survival.

Locoregional failure-free survival

Regional failure is defined by the Radiation Therapy Oncology Group (RTOG) as the persistence, regrowth, or recurrence of regional nodal disease. Locoregional failure can therefore be defined as a clinically proven (preferably by biopsy) local failure or disease recurrence in pelvic lymph nodes included in the original external beam treatment volume, irrespective of any distant failures. Patients with persistent disease, who never become disease-free, are classified as treatment failures on the day of randomisation; if the disease disappears and then recurs, they are classified as treatment failures on the date when convincing clinical evidence of recurrent disease is obtained (when available), through biopsy or imaging. Salvage surgery on the primary site (unless histopathology shows no residual tumour) and death as a result of index cancer without a documented site of recurrence or unknown cause are considered locoregional failures.

Locoregional failure and metastatic disease should be analysed separately as the site of first failure. Since different doses are mandated for the involved nodes and the primary tumour compared with elective nodes, it is probably important to separate or distinguish between local primary failure and locoregional failure within the treatment fields as separate endpoints, as well as locoregional failure outside the treatment fields. The 3-year rate of pelvic locoregional disease-related events—based on time-to-event analyses with censoring—should be the defining factor in distinguishing between local primary failure and locoregional failure.

Second malignancies

Second malignancies are common in anal cancer. In ACT II, 20 patients died of secondary cancers: six who received chemoradiation with mitomycin, and 14 who received cisplatin either as chemoradiation or as maintenance therapy.[2] According to some investigators, the development of squamous cell carcinoma of the anus in the anorectum after a disease-free interval of 3–5 years constitutes a new primary tumour, therefore any so-called local failure after 3–5 years could be miscategorised and confound the analysis. Other studies, such as RTOG-9811,[11] consider a second malignancy to contribute to disease-free survival. Such decision making should be made clear in the protocol, and separated from the key analyses.

Colostomy-free survival

For patients, being both disease-free and colostomy-free is important. However, only four of the six trials reported colostomy-free survival as either a primary or secondary endpoint. Both the ACT I trial[9,13] and the European Organization for Research on Treatment of Cancer (EORTC) 22921 trial[10] showed significant improvements in colostomy-free survival in patients who received chemoradiation compared with radiotherapy alone. Colostomy-free survival was the primary outcome measure of the ACCORD-03 trial,[12] and was a secondary endpoint in both the ACT II[2] and RTOG-9811[9] trials.

All trials included colostomy formation as part of salvage surgery after local disease relapse, which does not account for the need for colostomy in the absence of disease occurring either after treatment to manage excessive faecal discharge or incontinence, or before treatment to avoid morbidity. Results of these trials do not show whether subsequent reversal is achieved or not. These non-disease-associated colostomy events were included in the colostomy-free survival analysis in both the ACT I and ACT II trials. Although colostomy-free survival captures both disease-associated and treatment-associated outcomes, it discriminates poorly between the two.[23] This is because the intervention will vary from unit to unit and can be subject to inherent selection bias. This bias usually occurs because colostomy before treatment is not part of the randomisation process, some patients refuse to have a stoma for various reasons, and there are well-recognised geographical and cultural differences in acceptance of a colostomy.

Non-time-to-event endpoints

Tumour response

Tumour response is the most commonly used indicator of antitumour activity, and can provide an objective assessment since cancers rarely shrink spontaneously.[24] Overall tumour response has limitations as a surrogate endpoint for long-term clinical outcomes, but clinical complete response is a valid endpoint if the response can be sustained for long periods.

In squamous cell carcinoma of the anus, sustained clinical complete response after definitive chemoradiation is considered a useful early clinical endpoint, because this response implies destruction of the cancer

and possible avoidance of a permanent stoma. There is a balance between waiting for a response (a minimum of 4 weeks) and the need for early salvage surgery before the tumour grows and becomes unresectable.[25] Response to chemoradiation has been assessed histopathologically, clinically, and radiologically, and has a more well-defined role than that of endoanal ultrasound and MRI.[26]

After chemoradiation, the interval to wait for best response might be partially dependent on the tumour (ie, its size, stage, or nodal status) or the modality of treatment (radiotherapy or chemoradiation). Standardised serial clinical and imaging assessments are therefore required for follow-up, and the timing of clinical complete response as an event should be defined (eg, 26 weeks from the start of treatment).[25] Although standard Response Evaluation Criteria in Solid Tumors (RECIST)[27] are applied, the RECIST system was not designed for primary tumour assessment since it stipulates assessment at 6–8 weeks and excludes tumours smaller than 1 cm.

Adverse events

CONSORT guidance offers specific and comprehensive guidelines regarding the reporting of adverse events in RCTs, but adherence to these guidelines seems to be poor in oncology.[28] Additionally, the maximum adverse event grade might be less relevant than a progressive worsening of the adverse event over time.

Acute toxicity

Acute toxicity might be a suitable primary endpoint when overall survival is unlikely to be improved by a novel intervention (eg, intensity-modulated radiotherapy *vs* standard radiotherapy).[29] Different studies with varying types and intensities of chemotherapy, with a range of radiotherapy doses and schedules, would be likely to lead to different toxicity profiles. Acute toxicity and compliance have very broad definitions, which include different symptoms, conditions, and protocol-mandated dose reductions. Defining toxicity is also important because the severity of acute effects has been associated with eventual improved outcomes.[30]

Specific adverse events could be flagged as being more important for a particular drug, with the causality and duration of the event estimated. The number of patients experiencing these adverse events could be recorded and distinguished by severity levels according to the treatment group.

Toxicity assessments can to some extent be subjective between patient groups, measured with different assessment tools (eg, WHO, the US National Cancer Institute [NCI], or the Cancer Trials Centre [CTC] tools), and provide very different levels of compliance depending on the recommended scale of the dose reductions for toxicity. Therefore, another possible explanation for the heterogeneity shown for toxicity in these studies is that they are, indeed, reflecting different results. Furthermore, varying assessment periods (4–8 weeks following completion of treatment) are used.

In the ACT I trial,[9] the toxicity scale used was simply "mild, moderate, and severe" and graded subjectively by the investigator.[9] Meaningful comparison of this scale with other more modern assessments is difficult. The EORTC trial used the WHO acute morbidity scoring system, but the RTOG-8704[8] and the RTOG-9811[14] trials assessed chemotherapy toxicity according to the NCI common toxicity criteria (version 1 for RTOG-8704 and version 2 for RTOG-9811), and radiotherapy toxicity was graded according to RTOG toxicity criteria for radiation effects,[8,11] whereas ACT II used the NCI common toxicity criteria.[2]

The use of patient-reported outcome measures is recommended[31] because many important symptoms are subjective and often poorly categorised or under-categorised by clinicians.[32] The number and manner of patient-reported outcome and quality-of-life measures to be collected should be documented in the patient information sheet so that patients both understand what might be expected of them and are not worried about being questioned too often.

Toxic deaths

Specific definitions of treatment-related or cancer-related mortality in an elderly patient population with multiple comorbidities are problematic. Our experience is that the approach for defining death events as treatment-related is subjective. It might be better to report the cause of death as being due to anal cancer, being treatment-related (including acute deaths such as neutropenic sepsis or myocardial infarction), or being non-cancer-related. Deaths within 90 days of commencing therapy could be documented separately.

Late effects

No common language and no standardised and well-defined system exist for both recording and reporting acute and late radiation morbidity. Nor is there an accepted timeframe. Late morbidity is usually defined as morbidity persistent or existing after 6 or 12 months, but in some studies only morbidity present after 5 years is considered a late effect. Patients are not good at reporting symptoms;[33] although questionnaires can increase responses, these questions are designed to identify premorbid conditions as opposed to radiotherapy-associated effects. The RTOG late effects instrument[34] is not sufficiently specific or extensive to be able to capture these effects. Hence, appropriate patient-reported outcome measures are in development to help to do so.

Tolerability

Secondary tolerability endpoints could include the dose intensity achieved (mg per m² per week; ie, the total dose per body surface area divided by the duration of drug treatment [the number of weeks between the start and end

of chemotherapy]), the relative dose intensity (expressed as a percentage; ie, the ratio of the dose intensity achieved compared with the planned dose intensity), or the relative treatment duration (the ratio of the duration of treatment observed in the trial to the planned duration of treatment). The reasons for reductions, delays, and omissions should be documented to determine whether they were due to toxicity or another cause.

Compliance

Compliance refers to the degree or extent of conformity to trial recommendations with respect to the timing, dose, and frequency of the intended treatment. Compliance should be distinguished from continuation of the treatment for the prescribed duration.[35]

Reporting of compliance is essential for the interpretation of results and to determine the effect of treatment in a real-world setting. Without data for compliance, reproducibility of trial results might not be possible. However, definitions of compliance vary. For example, in the RTOG-9811 trial the definition of radiotherapy compliance was per protocol and an acceptable minimal variation in radiation dose, thereby categorising patients receiving less than the total dose as compliers. Yet the ACT II trial defined compliance as patients receiving the full dose only. Clear descriptions of the median radiation dose received and overall treatment time with interquartile ranges are required. A simple composite classification of the adequacy of radical chemoradiation with the three grades based on the actual drug doses received, the dose intensity, and duration in days of any planned or unintended break in treatment could suffice.

Compliance with concurrent chemotherapy is also problematic as the chemotherapy dose will be compromised to ensure the maximum radiotherapy dose if toxicity occurs. The second course of chemotherapy is crucial to maintain efficacy.[36] A conservative trial design that allows 50% dose reductions for subsequent chemotherapy courses if specific toxicities occur (grade 3 or worse) will have a lower dose intensity than less permissive protocols. In these cases, it might be useful to report both total dose and dose intensity curves.[37]

Patient-reported outcomes

Only two trials, ACT I[9] and ACCORD-03,[12,38,39] captured data for quality of life because of the absence of available validated questionnaires specific to squamous cell carcinoma of the anus at the time of trial design. According to the generic Rotterdam Symptom Checklist[40] and Hospital Anxiety and Depression Scales,[41] chemoradiotherapy appeared to improve quality of life compared with radiotherapy alone, but this outcome was probably due to better disease control.[38] The ACCORD-03 trial[39] used the EORTC core quality-of-life questionnaire (QLQ-C30 version 3.0) and the anal sphincter conservative treatment (AS-CT) questionnaire for short-term assessment of quality of life for patients with anal cancer both during and shortly after treatment. There are known adverse effects of pelvic radiotherapy on continence and quality of life.[42] A mixed methods approach[43] in the reporting of patient-reported outcomes for patients with squamous cell carcinoma of the anus identifies gaps in the currently available questionnaires, and indicates that the EORTC-QLQ questionnaire is the most comprehensive in terms of the number of domains. We therefore recommend the inclusion of long-term reports on both continence and quality of life, with patient-reported outcome measures, in future trials of anal cancer.

Discussion

An important limitation of our analysis is that it is based on only six randomised trials with different entry criteria and different treatments. The advantages and disadvantages of each endpoint used are summarised in table 4. As the efficacy of chemoradiotherapy improves in squamous cell carcinoma of the anus, and higher doses of radiotherapy are integrated with more sophisticated irradiation techniques than those used at present, such as intensity-modulated radiotherapy, we could observe similar findings to those observed in head and neck cancer, where locoregional control and overall survival is decoupled because distant events after treatment are more common in squamous cell carcinoma of the anus than at present.

A systematic review[44] of 125 RCTs found that almost half the papers did not even have clear definitions of the survival endpoint. Much effort has been expended on adjuvant endpoints following surgery and for metastatic disease, but less focus has been placed on endpoints following radical treatment of locoregional pelvic disease with chemoradiation. Neither the EORTC radiotherapy group[45] nor the proposed EORTC-ROG phase 3 trial protocol[46] has specifically addressed the need for such endpoints.

The choice of the most appropriate and unambiguous outcome measures is a vital component of trials as outlined in the CONSORT statement.[5] However, the utility of cross-trial comparisons and meta-analyses remains limited.[47] Positive results can also sometimes represent a chance finding, or factors within an underpowered trial can lead to a heterogeneous patient population, confounding results.[48]

At baseline, all patients have disease before receiving chemoradiation, and most achieve a complete response, whereas others might have an initial response but never become disease-free and either remain in this state or have no detectable disease following salvage surgery. Current outcomes such as disease-free survival and progression-free survival can be difficult to apply in this situation, since they are most appropriate when patients have undetectable or measurable disease at the point of origin and are therefore all at risk of recurrence or progression. Moreover, the tumour might initially respond, but the nadir will not be defined; the actual date

	Utility	Advantages	Disadvantages
Overall survival	Gold standard	Easy to define, precise, widely accepted, and universally available through registries	Less robust than other endpoints cited below as a measure of patient benefit from treatment if used in an older population (>70 years) because it is more likely to be confounded by deaths due to causes other than cancer, and because more than 50% of patients can be salvaged by surgery in case of treatment failure
Cause-specific survival	Focuses on the effect of cancer on survival; competing events treated as censoring events; death from causes unrelated to carcinoma are considered lost to follow-up from the date of death; analysis minimises effect of age, comorbidity, and other risk factors on survival	Easy to define, widely accepted, useful in a cancer that affects elderly patients, and is effective when surgical salvage is required	Reliable information about the cause of death is not always available; death certificates are often inaccurately recorded
Disease-free survival	Often used after surgery when no detectable disease is present at randomisation; difficult to use in chemoradiation trials since a proportion of patients never become disease-free	Earlier endpoint than overall survival; requires fewer numbers and shorter follow-up	Not validated as a surrogate endpoint for survival in anal cancer; definitions vary between trials; outcome can depend on frequency of imaging
Relapse-free or recurrence-free survival	Used as primary endpoint when no detectable disease is present at enrolment; difficult to use in chemoradiation trials since many patients never become disease-free	Earlier endpoint than overall survival; requires fewer numbers and shorter follow-up	Subject to assessment bias; outcome can depend on frequency of imaging
Progression-free survival	Often used in metastatic setting when all patients have the disease at randomisation	Objective and quantitative, not affected by salvage surgery with abdominoperineal excision of the rectum or subsequent treatment	Stable disease not necessarily of clinical benefit; subject to assessment bias
Colostomy-free survival	Used as primary endpoint in trials: as a measure of treatment failure, as a surrogate for disease status, and as an indicator of anal function	Outcome is easy to define	Initial colostomy can be reversed but is often irreversible; colostomy can be done for both recurrence and late effects
Complete clinical response	Often used as a surrogate endpoint, especially in phase 2 and phase 3 trials	Assessed early (6 months); smaller studies possible	Needs to be sustained and not a direct measure of clinical benefit; time dependent and prone to immortal time bias

Table 4: **Advantages and disadvantages of clinical endpoints used in six randomised controlled trials of anal cancer**

of progression is also unlikely to be accurately defined and is instead overestimated by the timing of the next scan or doctor visit.

Current trials of squamous cell cancers of the head and neck, such as RTOG 0522,[49] use progression-free survival and its components (locoregional failure and distant metastasis), which are often reported instead of protocol-specified disease-free survival to facilitate comparisons with published meta-analyses. If the tumour is present 3–9 months following completion of treatment, we usually conclude that the patient has residual active cancer and chemoradiation has failed. Progression is defined as either radiological enlargement of the tumour or a steady persistence of disease observed at this arbitrary timepoint. The line between disease and no disease is not necessarily clear and distinct, but it represents a dynamic process. Moreover, secondary endpoints are often defined and assessed less rigorously than primary endpoints.[50] The need to develop optimal primary and secondary endpoints for clinical trials will become increasingly important as clinical trials become more complex. Improvements in trial design need to be accompanied by improvements in available endpoints, and patients and investigators will need to work together to achieve this goal.[51]

Conclusion

The objectivity, reliability, and validity of endpoints in clinical trials is variable. Time-to-event endpoints other than overall survival share little uniformity across RCTs of squamous cell carcinoma of the anus. Different trials use different procedures to determine whether a patient is having an event, which leads to reduced consistency across trials. Rigorous definitions and consistent terminology are mandatory for future studies. The validity and feasibility of these endpoints for future international trials has already been discussed in International Rare Cancers Initiative meetings, and we hope to work towards a consensus document by the end of 2017.

We recommend consistency in the reporting of acute and late toxicity and compliance, and support the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project[52] for consensus-based recommendations. In rare cancers, unanimously agreed definitions are essential because large, long-term studies are rare and difficult to perform. Journals in particular should agree to accept only standard definitions for survival endpoints. Hence, investigators, statisticians, reviewers, and editors should all take responsibility for the precision of clinical trial endpoints.

Although there are no perfect endpoints, the ideal objective for gauging success in future phase 3 trials of squamous cell carcinoma of the anus should be anal dysfunction-free survival. This measure is still, to some extent, susceptible to the limitations and pitfalls that have been described above, but we believe it is likely to be the most meaningful outcome for patients with anal cancer. An internationally agreed definition should form the primary endpoint. We recommend the following secondary endpoints: overall survival and cause-specific survival, as well as deaths not due to anal cancer. The late

effects of radiotherapy captured by patient-reported outcome measures with long-term follow-up are essential. We also recommend the use of colostomy-free survival and recurrence-free survival, which include any recurrence (local, regional, or distant) and also death due to any cause. Long-term follow-up for overall survival is still required in case unexpected adverse effects of treatment are not captured by an earlier endpoint. Yet, with the increasing development of effective immunological treatments for metastatic disease, recurrence-free survival might be less relevant in the future and therefore should be uncoupled from the priority of overall survival. Since most recurrences occur within the first 3 years, a minimum of 3 years of monitoring and follow-up is mandatory for the required number of events to be captured.

Future RCTs in squamous cell carcinoma of the anus should document the median or mean radiation dose received, compliance to chemotherapy during each week of treatment (as a percentage of the intended dose), the total dose of radiation achieved, the overall treatment time, and the precise site of recurrence in relation to radiotherapy treatment fields.

Finally, we recommend that methodological research should address the validation of surrogate endpoints, such as local control or complete clinical response, at 6 months.

Contributors

RG-J and HM contributed to the original design of this Review and gathered data. All authors contributed to the analysis, data interpretation, and writing. All authors critically reviewed several iterations of the manuscript and gave final approval.

Declaration of interests

RG-J reports grants from Roche and Merck Serono, and personal fees from Roche, Merck Serono, Sanofi, Amgen, Eli Lilly, Servier, and Eisai, outside the submitted work. All other authors declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Glynne-Jones R, Adams R, Lopes A, Meadows H. Clinical endpoints in trials of chemoradiation for patients with anal cancer. *Lancet Oncol* 2017; **18:** e218–27.

Online Table 1. Complete list of search terms applied

Area	Terms
Anal Cancer	Anus neoplasm (MeSH term) Anal neoplasm Anal cancer Anus cancer Anal carcinoma Anus carcinoma (no hits) Anal canal cancer Anal canal carcinoma Anal tumour Anus tumour (no hits) Anal intraepithelial neoplasia Anal canal intraepithelial neoplasia Anal squamous intraepithelial lesions Anal squamous cell carcinoma Anal cloacogenic carcinoma (no hits) Cloacogenic carcinoma of the anal canal
Treatments **Radiochemotherapy** **Stoma**	Chemoradiotherapy Radiochemotherapy Chemoradiation Chemotherapy Radiotherapy Combined modality therapy Antineoplastic chemotherapy Antineoplastic agents Colostomy Surgical stoma (Exp Stoma and stoma bag)
Health-related quality of life	Quality of Life QOL Health related quality of life HRQOL Subjective health status Patient reported outcome Patient based outcome Patient reported outcome measure PROM Self report Side effect Toxicity Adverse effect Adverse event Safety Complication Dysfunction Disturbance Disorder Impairment Complaint Symptom

Online Table 2: Showing important compliance to RT parameters

Mean Dose of RT received	Median	Range	
% of patients receiving 90-110% of total dose recommended	Median	Range	
Number of days RT omitted	Median	Range	Reasons
Number of days RT dose reduced	Median	Range	Reasons
Overall treatment time (OTT) in days	Median	Range	Reasons

Online Table 3: Showing important compliance to chemotherapy parameters

Mean Dose of chemotherapy received	Median	Range	
% of patients receiving 90-110% of total dose recommended	Median	Range	
Number of days chemotherapy omitted	Median	Range	Reasons
Number of days chemotherapy dose reduced	Median	Range	Reasons
If delay in administration - Overall treatment time (OTT) in days	Median	Range	Reasons