

Surveillance of Anal Canal Cancers



Richard Adams, BSc, BM BS, MRCP, FRCR, MD

KEYWORDS

- Anal cancer • Follow-up • Surveillance • Radical treatment • Salvage
- Squamous cell cancer

KEY POINTS

- Patients with radically treated anal canal squamous cell cancer (SCC) require surveillance/follow-up to allow salvage surgery to take place with the aim of cure in patients with persistent or locally recurrent disease.
- Clinical evaluation is critical with documentation of abnormalities that persist; continuity of care may assist in this process.
- Acute toxicities can be severe and must be managed after treatment to prevent escalation.
- Late toxicities relating to prior tumor-related damage and radiotherapy-related long-term side effects should be managed actively with specialist referral as appropriate.

INTRODUCTION

Patients with anal SCC treated with radical intent using CRT generally have an excellent prognosis. The US Radiotherapy Oncology Group 9811 trial (completed in 2005) indicates a 5-year overall survival rate of 75%.¹ There are more than 8000 new cases of anal cancer diagnosed per year in the United States.² With a majority of these patients treated with radical intent and an expected follow-up time of 5 years with low attrition, this may equate to greater than 25,000 patients who remain on active surveillance at any one point and an even larger number alive and in remission beyond 5 years.

Surveillance is a routine part of the management of most patients treated radically for cancer but it remains important to understand the rationale and basis for this practice in each cancer subtype.

Broadly, surveillance should aim to deliver:

- Timely interventions that have an impact on an individual's chances of cure or life prolongation.

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Division of Cancer and Genetics, Velindre Cancer Centre, Cardiff University, Whitchurch, Cardiff CF14 2TL, UK

E-mail address: richard.adams@wales.nhs.uk

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- Improved quality of life, through:
 - Effective management of toxicities to prevent escalation
 - Psychological reassurance

When specifically looking at anal cancer, these factors can be mapped into the areas indicated in **Box 1**.

Although acknowledging that surveillance can offer significant psychological reassurance, this can result in marked anxieties around the time of the follow-up appointment or scan with a significant impact on an individual's quality of life.

This article explores these phenomena, the evidence, where available, and a rational approach where not.

CLINICAL GUIDELINES

International and national clinical guidelines are regularly updated and offer clinicians a benchmark by which to formulate their practice. Surveillance has infrequently been explored, however, in a rigorous fashion and thus levels of evidence are based on retrospective review and expert opinion.

The European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines^{3,4} are probably the most frequently referred to internationally for many cancers, including anal cancer. Both sets of guidelines are similarly aligned but it is acknowledged that there is limited evidence on which to base their recommendations.

There are notable differences between these guidelines, as indicated in **Table 1**.

TIMING OF SURVEILLANCE

Early evaluation is based on 3 key factors:

1. The ability to formally clinically assess the anal canal by digital rectal examination (DRE) at a time when acute toxicities are regressing. Most patients are reasonably comfortably evaluable by the 8-week mark after CRT, although earlier evaluation to ensure symptom control ahead of this time should be tailored to the individual.
2. The knowledge that after completion of CRT, SCC of the anal canal may take many months to reach a nadir, including clinical complete response.
3. Rarer relapses after 3 years surveillance.

The often slow regression of tumor after completion of CRT is based on evidence from trials, such as anal cancer trial (ACT) II, in which randomized patients had trial-based documentation of clinical complete response at 11 weeks and 26 weeks post-completion of CRT. Data from this trial indicate that 29% of patients who did not demonstrate a complete remission at 11 weeks had achieved a complete response by 26 weeks, with durable response.⁵

Box 1
Key areas relevant to surveillance after radical treatment of anal squamous cell carcinoma

- Detection and monitoring of persistent disease after completion of radical CRT
- Detection of locoregional recurrent disease after radical CRT
- Management of acute/late toxicities
- Psychological reassurance

Table 1**A comparison of international guidelines for surveillance after radical treatment of anal cancer: National Comprehensive Cancer Network and European Society for Medical Oncology**

	European Society for Medical Oncology Guidelines	National Comprehensive Cancer Network Guidelines
Early clinical surveillance: timing	Initial evaluation at 8 wk after completion of CRT. Then 3–6 monthly for those in complete remission for a period of 2 y.	Initial evaluation at 8–12 wk after completion of CRT. Then 3–6 monthly for those in complete remission.
Late surveillance: timing	6–12 Monthly until 5 y	3–6 Monthly until 5 y
Clinical assessment at each visit to include	• DRE and palpation of the inguinal lymph nodes • Anoscopy or proctoscopy (optional, sometimes poorly tolerated and too painful after CRT)	• DRE and palpation of the inguinal lymph nodes • Anoscopy
Imaging recommendations	Possibly: MRI on a 6-mo basis for 3 y for locoregional assessment CT scans for distant recurrence are not currently recommended	Chest/abdomen/pelvic imaging annually for 3 y (if T3-T4 or inguinal node positive)
Persisting disease	Avoid biopsy for persisting disease at 8–12 wk evaluation up to 6 mo post-CRT	Re-evaluate 4 weekly until remission up to 6 mo post-CRT

Retrospective review of the phase III trials of radical CRT in anal cancer indicate that a majority of relapses and thus the most efficient time for more frequent surveillance are within the first 3 years of completion of CRT. The ACT II trial with long-term follow-up demonstrated less than 1% of relapses occurring beyond 3 years (Fig. 1).⁵ Other trials suggest this may be closer to 5%; thus, there seems to be some rationale to continue surveillance out to 5 years.

CLINICAL EVALUATION

Clinical evaluation revolves around locoregional assessment.

Although many patients with earlier-stage disease have a return to a normal-feeling anal canal mucosa, those with more advanced initial disease, especially T3-T4 disease, often have residual changes and scarring even in the absence of residual tumor. Those patients with residual changes require consistent follow-up with good documentation of the changes identified. Any new thickening, growth, or ulceration should be evaluated. Examination under anesthetic (EUA) and potential targeted biopsy should be considered by a surgeon with experience in this disease.

DRE and potential use of anoscopy offer an ability beyond that offered by imaging to assess local disease persistence or recurrence. These can also give critical information relating to functional difficulties causing significant effects on quality of life, which may then be amenable to targeted intervention. Regional relapse can, at least in part, be assessed with inguinal nodal examination. As discussed previously, EUA should be reserved for those with persistent abnormalities 5 to 6 months after CRT, stenosis, pain, or scarring that prevents effective examination or new changes arising during surveillance.

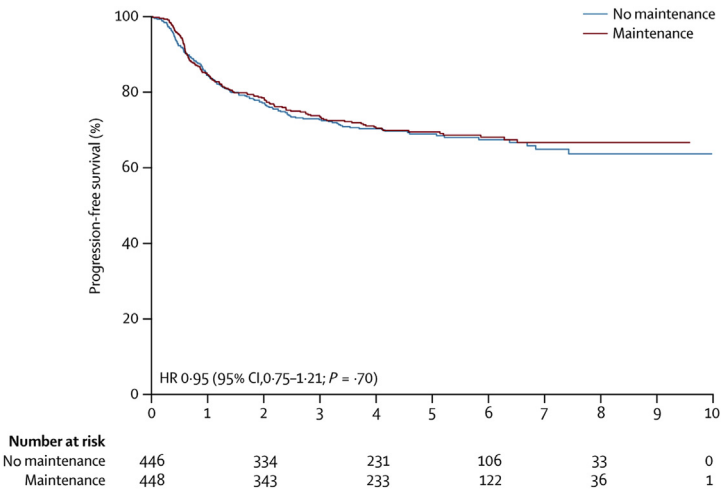


Fig. 1. Kaplan-Meier curves showing progression free survival in the ACT II trial of radical CRT for anal cancer. HR, hazard ratio. (From James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus [ACT II]: a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013;14(6):519; with permission.)

It is widely acknowledged that locally persistent or recurrent disease can be salvaged surgically with curative intent with abdominoperineal excision with flap reconstruction and permanent stoma formation. Recent data seem to suggest that those patients with later relapse locally may have a better prognosis than those persisting or recurring early.⁶

Within the Severino and colleagues⁶ data set, 36 patients underwent salvage abdomino-perineal resection for persistent or recurrent invasive cancer: 80.5% (29) had tumor identified on DRE, 13.9% (5) required EUA due to pain or stenosis, and in 5% (2), tumor was identified by imaging with no evident tumor on DRE. Three patients had disease identified in the inguinal nodes. All patients had biopsy-confirmed recurrence prior to salvage. In this data set, early disease was associated with later recurrence and those with persistent disease, which was more frequently of later stage, had the worst prognosis. Surgical salvage can result in durable survival. This series demonstrated a 3-year overall survival of 46%, which reaches approximately 90% in the late recurring disease group. A similar analysis has been performed on the patients from the ACT II trials in which 103 patients underwent surgical salvage; these data reveal similar results (Glynne Jones, personal communication, abstract submitted American Society of Clinical Oncology, 2016).

IMAGING RECOMMENDATIONS

There is little evidence in terms of optimized surveillance radiologic imaging. This is manifest in the differing recommendations from ESMO and NCCN (see [Table 1](#)).

To the authors’ knowledge, no good data exist that early identification of distant metastatic disease is of any benefit to the patient. Individual case reports identify positive outcomes from isolated metastectomies or stereotactic radiotherapy for oligometastatic disease but are rare and inevitably these reports suffer from positive reporting bias. There are no data to indicate that early intervention in the palliative setting with

chemotherapy improves outcome, although with the evolving interest in immunotherapies, such as the immune checkpoint inhibitors and tumor vaccines, it is rational that a low burden of disease may respond more effectively and durably.

A recent international survey involving 149 clinicians who specialize in anal cancer indicates that 87% routinely arrange surveillance imaging in the first 2 years; 18% of these were with CT/PET (all within the United States) and 21% with MRI, predominantly in Europe.⁷ The variation seen in response to this questionnaire in itself underlines the uncertainty in this area but also indicates the allegiance to more regional guidelines.

MRI of the pelvis in line with pretreatment staging seems to be evolving as a relevant investigation to assess for locoregional relapse that may offer an earlier ability to salvage, although its strength in identifying anal canal recurrence remains limited compared with clinical evaluation.

The ESMO and NCCN guidelines for surveillance after radical CRT for cervix cancer are more relaxed in terms of their recommendations. In terms of recommending imaging only, if symptomatically indicated, ESMO cervix cancer surveillance guidelines state, "No definitive agreement exists on the best post-treatment surveillance...CT or PET/CT scan should be performed as clinically indicated."⁸ NCCN cervix cancer surveillance guidelines state, "Imaging chest radiography, CT, PET-CT, MRI as indicated based upon symptoms or examination findings suspicious for recurrence but not recommended for routine surveillance, a single PET-CT performed at 3–6 months after CRT for locally advanced cervical cancer can be used to assess early or asymptomatic persistence or recurrence."⁹

SUMMARY

The surveillance of patients who have been treated radically with CRT for anal canal SCC is based on limited evidence. The guidelines that exist, however, are broadly based on sound principles. The major focus is on optimizing the opportunities for surgical salvage of persistent or locoregionally recurrent disease, with the aim of cure.

There is increasing interest in using the surveillance period to optimize quality of life; addressing significant late toxicities (addressed in allied chapter).

To date there is little to recommend a hunt for distant metastatic disease during this surveillance period and limited evidence to indicate a group of patients who are fit and do not warrant continued review over 5 years.

REFERENCES

1. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299(16):1914–21.
2. Available at: <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>. Accessed April 1, 2016.
3. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3):iii10–20.
4. Available at: http://www.nccn.org/professionals/physician_gls/PDF/anal.pdf. Accessed April 1, 2016.
5. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013;14(6):516–24.

6. Severino N, Chadi S, Rosen L, et al. Survival following salvage abdominoperineal resection for persistent and recurrent squamous cell carcinoma of the anus; do these disease categories affect survival Survival following salvage abdominoperineal resection for persistent and recurrent squamous cell carcinoma of the anus: do these disease categories affect survival? *Colorectal Dis* 2016. <http://dx.doi.org/10.1111/codi.1328>.
7. Eng C, Adams R, Kachnic L, et al, on behalf of the International Rare Cancer Initiative (IRCI) Working Group. Post-treatment surveillance in locally advanced squamous cell carcinoma (SCCA) of the anal canal: a global subspecialist survey. *J Clin Oncol* 2016;34(Suppl 4S):573 [abstract].
8. Colombo N, Carinelli S, Colombo A, et al, on behalf of the ESMO Guidelines Working Group Cervical cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Supplement 7):vii27–32.
9. Available at: http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed August 13, 2016.