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CLINICS ARTICLE TITLE PAGE TEMPLATE

ARTICLE TITLE

Surveillance of Anal Canal Cancers

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The Authors have nothing to disclose.

KEY WORDS

4-8 keywords to direct and optimize search results

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 which 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 tumour related damage and radiotherapy related long term side effects should be managed actively with specialist referral as appropriate.**

SYNOPSIS

Anal squamous cell cancer (SCC) is most frequently a loco-regional disease which is amenable to curative therapy in the majority of fit patients. Complete response rates after chemoradiotherapy (CRT) are good, with upto 75% of patients with no evidence of relapse on surveillance. Relapse is most frequently loco-regional and is often amendable to salvage surgery with curative intent. Effective surveillance attempts to improve outcomes by identifying recurrent or persistent disease early, manage both acute and late toxicities and offer reassurance to patients. Here we explore the rationale and evidence for surveillance programmes after definitive CRT.

Outline :

Introduction; Clinical guidelines; Timing of surveillance; Clinical Evaluation; Imaging recommendations; Summary

Introduction:

Patients with anal squamous cell cancer treated with radical intent using chemo-radiotherapy, generally have an excellent prognosis. The US RTOG 9811 trial (completed in 2005) indicates a 5 year overall survival rate of 75% [1]. There are over 8000 new cases of anal cancer diagnosed per year in the USA [2]. With the majority of these patients being treated with radical intent and an expected follow up time of 5 years with relatively low attrition this may equate to >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 sub-type.

Broadly surveillance should aim to deliver:

- Timely interventions that will impact upon an individuals chances of cure or life prolongation
- Improved quality of life, through:
 - Effective management of toxicities to prevent their escalation
 - Psychological re-assurance

When we specifically look at anal cancer these factors can be mapped in to the areas indicated below:

Key areas relevant to surveillance after radical treatment for anal SCC:

- Detection and monitoring of persistent disease after completion of radical chemoradiotherapy (CRT)
- Detection of loco-regional recurrent disease after radical chemoradiotherapy
- Management of acute/late toxicities
- Psychological reassurance

Whilst, acknowledging that surveillance can offer significant psychological reassurance it must also be noted that this can result in marked anxieties around the time of the follow up appointment or scan with a significant impact upon the individuals quality of life.

Here we explore 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 bench mark by which to formulate their practice. However, surveillance has infrequently been explored in a rigorous fashion and thus levels of evidence are based upon retrospective review and expert opinion.

The European society of 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. Notably, both sets of guidelines are relatively similarly aligned but it is acknowledged that there is a limited evidence base upon which to base their recommendations.

There are notable differences between these guidelines as indicated in table x

Timing of surveillance:

Early evaluation is based upon two 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, though earlier evaluation to ensure symptom control ahead of this time should be tailored to the individual.
2. The knowledge that after completion of CRT squamous cell carcinoma 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 relatively slow regression of tumor after completion of CRT is based upon evidence from trials such as 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].

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

Clinical evaluation:

Clinical evaluation revolves around loco-regional assessment.

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

Digital rectal examination (DRE) and potential use of anoscopy offer an ability beyond that offered by imaging to assess local disease persistence or recurrence. Importantly, this 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 above EUA should be reserved for those with persistent abnormalities 5-6 months after CRT, stenosis, pain or scarring that prevent effective examination or new changes arising during surveillance.

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

Within the Severino data set 36 patients underwent salvage APR for persistent or recurrent invasive cancer. 80.5 % (29) had tumor identified on DRE, 13.9% (5) required examination under anaesthetic due to pain or stenosis and 5% (2) tumor was identified by imaging with no evident tumor on DRE. 3 patients had disease identified in the inguinal nodes. All patients had biopsy confirmed recurrence prior to salvage. Notably, in this data set early disease was associated with later recurrence and those with persistent disease which were more frequently of later stage had the worst prognosis. It is important to note that surgical salvage can result in durable survival. This series demonstrated a 3 year OS of 46%, which reaches nearly 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, this data reveals similar results (personal comm. Glynne Jones abstract submitted ASCO 2016).

	ESMO guidelines	NCCN guidelines
Early clinical surveillance: Timing	Initial evaluation at 8 weeks after completion of Chemo-radiotherapy. Then 3–6 monthly for those in complete remission for a period of 2 years.	Initial evaluation at 8-12 weeks after completion of Chemo-radiotherapy. Then 3-6 monthly for those in complete remission.
Late surveillance: Timing	6–12 monthly until 5 years,	3-6 monthly until 5 years
Clinical assessment at each visit to include:	<ul style="list-style-type: none"> • DRE and palpation of the inguinal lymph nodes • Anoscopy or proctoscopy (optional, 	<ul style="list-style-type: none"> • DRE and palpation of the inguinal lymph nodes • Anoscopy

	sometimes poorly tolerated and too painful following CRT)	
Imaging recommendations	Possibly: MRI on a 6 monthly basis for 3 years for locoregional assessment. CT scans for distant recurrence are not currently recommended	Chest/abdomen/pelvic imaging annually for 3 years (if T3-4 or inguinal node positive)
Persisting disease	Avoid biopsy for persisting disease at 8-12 weeks evaluation up to 6 months post CRT	Re-evaluate 4 weekly until remission upto 6 months post CRT

Table 1: A comparison of international guidelines for surveillance after radical treatment of anal cancer: NCCN and ESMO.

Imaging recommendations:

There is little evidence in terms of optimized surveillance radiological imaging. This is manifest in the very differing recommendations from ESMO and NCCN as per table 1.

To our 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 oligo-metastatic disease but are rare and inevitably these reports suffer from positive reporting bias. There is no data to indicate that early intervention in the palliative setting with chemotherapy improves outcome, though with the evolving interest in immunotherapies such as the immune check point 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 US) and 21% with MRI predominantly in Europe [7]. This in itself underlines the uncertainty in this area but also indicates the allegiance to more regional guidelines.

MRI of the pelvis in line with pre treatment staging appears to be evolving as a relevant investigation to assess for loco-regional relapse that may offer an earlier ability to salvage, though its strength in identifying anal canal recurrence remains relatively limited when compared to clinical evaluation.

It is interesting to note that the ESMO and NCCN guidelines for surveillance following radical chemoradiotherapy for cervix cancer are more relaxed in terms of their recommendations. Notably in terms of recommending imaging only if symptomatically indicated:

ESMO cervix cancer surveillance guidelines state [8]:

“No definitive agreement exists on the best post-treatment surveillance..... CT or PET/CT scan should be performed as clinically indicated.”

NCCN cervix cancer surveillance guidelines state [9]:

“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 ca can be used to assess early or asymptomatic persistence or recurrence.”

Summary:

The surveillance of patients who have been treated radically with CRT for anal canal squamous cell carcinoma is based upon limited evidence. However, the guidelines that exist are broadly based upon sound principles. The major focus is on optimizing the opportunities for surgical salvage of persistent or loco-regionally recurrent disease, with the aim of cure.

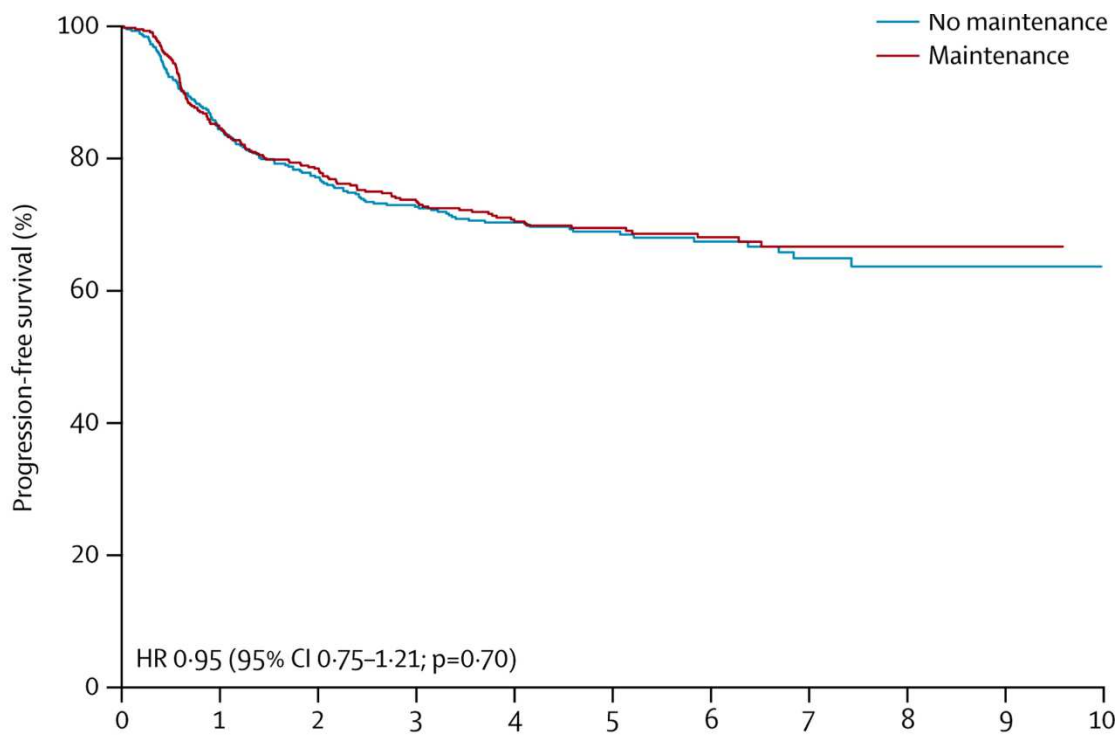
There is increasing interest in using the surveillance period to optimize quality of life; addressing significant late toxicities (addressed in allied chapter).

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.

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Number at risk

No maintenance	446	334	231	106	33	0
Maintenance	448	343	233	122	36	1

Figure1: K-M curves showing progression free survival in the ACT II trial of radical chemoradiotherapy for anal cancer. From: James et al Lancet Oncol 2013 (with permission)