The Christie NHS
NHS Foundation Trust

CHRISTIE ANAL CANCER MDT

FOLLOW-UP GUIDELINES

Following chemoradiotherapy for anal cancer
Following local excision for margin anal cancer
Following local excision for SISCCA of the anus
Following salvage surgery for locally relapsed anal cancer

Circulated to Anal Cancer MDT on 13th September 2023
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Preface

These guidelines are distinct from the referral guidelines for patients with anal cancer applied to the Greater Manchester Pathway Board and intended for use only within the framework of the Christie Anal Cancer Multidisciplinary Meeting (MDT). Recommended changes reflect the establishment of the weekly Anal Cancer Multi-disciplinary Team (MDT) at the Christie, since 2018; the expansion to four clinical oncologists managing anal cancer; the wider opportunities to recruit patients to anal cancer trials and research; the establishment of the 4 weekly joint anal cancer clinic in 2013 and the proposed development of the two weekly joint anal cancer clinics in the future; and for consistency with the UK national PLATO trial protocol. These guidelines should be considered 'dynamic' as there will be further refinements as we continuously audit and appraise our diagnostic work-ups, oncological outcomes and as we increasingly move towards appraising patient-reported outcomes (PROs).

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There are no major new sections.

A. FOLLOW-UP GUIDELINES AFTER CHEMORADIOTHERAPY (WITH CURATIVE INTENT)

General principles of follow-up in cancer patients

There are several indications to follow patients with cancer. The conventional model is that follow-up may be beneficial through the early detection of treatable recurrence – a "second chance at cure". There is indirect evidence that this is true for anal cancer - patients with local relapse selected for salvage surgery have a 40% post-salvage survival rate compared with none alive after 38 months in those deemed unsuitable for salvage surgery (previous publication (1) and updated Christie data).

Other indications for follow-up may include: improved psychosocial well-being and quality of life; detection and treatment of co-morbidities; opportunities for ongoing health education (e.g. smoking cessation); audit of oncological outcomes; the detection and treatment of late-effects and second primary cancers; and increasingly, for the appraisal of patient-reported outcomes (PROs).

For the purpose of this document, the main emphasis will be on the early detection and treatment of local relapse (we prefer to use the term relapse rather than residual and recurrent disease) (2).

Local relapse after initial chemo-radiation

- Despite improvements in chemo-radiotherapy regimens, approximately 18% patients with anal cancer fail locally and require consideration for salvage surgery (Christie audit data) (3).
- To facilitate early detection of local relapse, follow-up of **all** patients following initial chemo-radiotherapy should be carried out within the framework of the Anal Cancer MDT.
- The agreed centre for assessment and undertaking of salvage surgery in Greater Manchester is the Christie NHS Foundation Trust.
- Assessment for resectability and the undertaking of salvage surgery should be performed by a Anal Cancer MDT core surgeon, supported by oncoplastic surgeons and other surgical disciplines, as required (for example, urological surgery and gynaecological oncology surgery).

A stratified approach to follow-up in the first five year after treatment

- With early detection of curable local relapse disease as the main aim, our experience and research have shown that there are at least two broad levels of

risk - high- and low. This forms the basis of a stratified approach to surveillance in these patients.

- The list of *high risk* criteria is updated and shown in **Table 1**.
- For 2017, based on the PhD thesis of Dr Hema Sekhar, the local relapse rates for T3 and T4 are similar, and are grouped together. This is consistent with the ACT5 arm of the UK national PLATO trial. To be inclusive, we have included T2 tumours greater than 4 cm.
- With re-analysis of our data, the presence of fistula *per se* is not independent of tumour size for local relapse – and has been dropped.
- HIV positivity and other immunocompromised states are high-risk for the development of anal cancer. There is now a substantial body of literature, that for well treated HIV positive patients, local relapse rates after chemoradiotherapy are equivalent to those in HIV negative patients.
- To the list of high-risk for relapse, we have added N+ (AJCC 8th Edition). This is consistent with the ACT5 arm of the UK national PLATO trial.

Table 1. High-risk of local relapse

2017 Manchester criteria for 'high-risk'	**2023 Manchester criteria for 'high-risk'**
T3 and 4 tumours (T ≥ 5 cm)	Bulky mrT2, mrT3 and mrT4 tumours (mrT ≥ 4 cm)
Patients intolerable of chemotherapy	Patients intolerable of chemotherapy
Patients with perianal adenocarcinoma	Patients with perianal adenocarcinoma
N2* and N3* disease	Any N+ disease†
Incomplete radiotherapy	Incomplete radiotherapy
Others as determined by MDT	Others as determined by MDT – e.g. fistulation

*AJCC TNM 7th Edition. † AJCC TNM 8th Edition.

- The remaining patient group are at risk of local relapse and are referred to as *low risk*.

Time zero to 26 weeks (the first 6 months)

- The follow-up for all patients with anal cancer following chemoradiotherapy is the same for low- AND high-risk patients.
- The setting for this follow-up is in the clinical oncology clinic. All patients are reviewed at 6 to 8 weeks following chemoradiotherapy

- At 3 months, there is the first round of imaging – MR and PET-CT
- At 6 months, there is the second round of imaging – MR only
- MR scans will be reported using the tumour regression grade (TRG) system as detailed by Kochhar et al. (4). Patients with TRG grades 3 to 5 require clinical correlation and return to the MDT.
- The above protocol has been included within the UK national PLATO trial follow-up protocol (5).

Time 26 weeks to 5 years

Patients are stratified into two risk-groups. The term local relapse is preferred to the terms residual or recurrence disease. However, the Anal Cancer MDT recognises that there are early (within first 12 months) and late local relapses.

The guidelines are summarised as **Tables 2 and 3**, and as the updated coloured flow diagram (Appendix 1) used in the clinics.

High-risk patients

- For patients at high-risk of local relapse (criteria above), additional MR scans are performed at 12, 18, 24, 30 and 36 months.

Low-risk patients

- The mainstay of surveillance is regular clinical assessment, ideally by the same experienced clinician.
- There are no MR scan after 6 months until the 36 month MR scan (The Christie Anal Cancer MDT recognises that currently the 36 month scan is not always performed. This needs to be audited).

All patients

- For all patients (high- and low-risk), there is ‘an exit’ 36 month MR scan. This is consistent with the UK national PLATO follow-up protocol (5) to determine the primary endpoint of that trial, namely 3-year loco-regional failure.
- For all patients (high- and low-risk), surveillance CT scans of the thorax, abdomen, and pelvis should be requested at 12, 24 and 36 months to assess for distant metastases.
- Beyond 3 years, patients should be considered for clinical follow-up until 5 years after chemoradiotherapy.

- Currently, high-resolution anoscopy is not routinely included in surveillance in patients with anal cancer after CRT.

Table 2 Baseline & FU:

High-risk treated by chemo-radiotherapy

Proposed Christie protocol to coincide with PLATO. FU in clinical oncology clinics

		Year 1					Years 2 to 5 (in months)									
	B'line	6 wks	3 mo	6 mo	9 mo	12 mo	15	18	21	24	30	36	42	48	54	60
Clinical exam	✓	✓	✓	✓	✓	✓	✓*	✓*	✓*	✓*	✓*	✓*		✓*		✓*
Pelvic MR	✓		✓	✓		✓		✓		✓		✓				
PET-CT	✓		✓													
CT T/A/P	✓					✓				✓		✓				

*Clinical visit also includes assessment of late effects

Table 3 Baseline & FU:

Low-risk treated by chemo-radiotherapy

Proposed Christie protocol to coincide with PLATO. FU in clinical oncology clinics

		Year 1					Years 2 to 5 (in months)									
	B'line	6 wks	3 mo	6 mo	9 mo	12 mo	15	18	21	24	30	36	42	48	54	60
Clinical exam	✓	✓	✓	✓	✓	✓		✓*		✓*	✓*	✓*		✓*		✓*
Pelvic MR	✓		✓	✓								✓				
PET-CT	✓		✓													
CT T/A/P	✓					✓				✓		✓				

*Clinical visit also includes assessment of late effects

High suspicion for local relapse and assessment for salvage surgery

- A high suspicion for local relapse should be identified through surveillance and brought to the Anal Cancer MDT.
- The Anal Cancer MDT will make the decision to examine under anaesthesia (EUA). The role of the EUA is threefold: (i) obtain histological diagnosis of relapsed carcinoma; (ii) assess resectability, the type of operation, and the multi-disciplinary surgical team required for that operation; and (iii) assess the fitness of the patient for a major salvage surgery operation. Many patients with anal cancer have co-morbidities and may require substantial anaesthetic work-up.
- Consideration of the resectability of the local relapse should start at the MDT prior to the EUA.
- The EUA should be performed by an Anal Cancer MDT core surgeon.

- In men with suspicion of relapsed disease, combined EAU with a urological surgeon to assess prostatic involvement should be considered.
- In women with suspicion of relapsed disease, combined EAU with a gynaecological surgeon to assess vaginal involvement should be considered
- Return of a case to the MDT after EUA for further discussion is the exception. There is window of opportunity to undertake salvage anal cancer surgery. Multiple MDT discussions might be associated with loss of the opportunity.

After 5 years

Traditional practice has been to discharge patients with anal cancer after five years. It is increasingly recognised in long-term cancer survivors that there are late effects of treatment and increased risk of second primary cancers of the same tissue origin or from adjacent tissues. Thus, follow-up passed 5 years is encouraged. At the Christie, in the long-term, it is envisaged that these patients will fall within a late-effects pelvic clinic suited for protocol-driven follow-up and clinical research.

Multidisciplinary team

- The structure of the Anal Cancer MDT is covered in the Referral Guidelines

Prospective Audit

- A database of patients with anal cancer treated in the North West of England and Network region has been established since 1998.
- In 2014, the database included over 1000 patients.
- The Christie anal cancer database is operated under audit data governance.
- Currently, there is no anal cancer data manager to update these data.

B. FOLLOW-UP GUIDELINES AFTER LOCAL EXCISION FOR MARGIN ANAL CANCERS

We broadly follow the 2017 ACPGBI guidelines (6), which state the following key points:

- Local excision alone may adequately treat small tumours at the anal margin and can achieve good local control. The tumour should be excised with a margin of normal perianal skin and deeper tissue.
- Small wounds may be left open or closed directly whereas larger defects may require some form of advancement or rotational flap to cover. This should ideally be performed by an anal cancer MDT surgeon, following agreement within the MDT to attempt a complete excision.

- Local excision tumours can be considered for follow-up similar to the (now closed) ACT3 of the UK national PLATO trial (5). Tumours with positive resection margin (≤ 1m) on histology should be considered for low-dose chemoradiotherapy.
- Re-operation is generally discouraged for positive resection margins as it is associated with considerable morbidity.
- The follow-up protocol is summarised in **Table 4**. The key unknown is inguinal lymph node metastases. Hence, we recommend MR scans six monthly in the first two years.
- For all these patients, there is 'an exit' 36 month MR scan. This is consistent with the UK national PLATO follow-up protocol (5) to determine the primary endpoint of that trial, namely 3-year loco-regional failure.
- As for other anal cancer, surveillance CT scans of the thorax, abdomen, and pelvis should be requested at 12, 24 and 36 months to assess for distant metastases.
- The setting for this follow-up is in the joint anal cancer clinic.

Table 4 Baseline & FU:
margin ASCC treated by local excision (< 4 cm N0)

Proposed Christie protocol to coincide with PLATO. FU in joint anal cancer clinic

		Year 1					Years 2 to 5 (in months)							
	Baseline	6 wks	3 mo	6 mo	9 mo	12 mo	18	24	30	36	42	48	54	60
Clinical exam	✓	✓*	✓†	✓	✓	✓	✓	✓	✓	✓		✓		✓
Pelvic MR	✓			✓‡		✓‡	✓‡	✓‡		✓‡				
PET-CT	✓													
CT T/A/P	✓					✓		✓		✓				

*If the primary local excision has been performed elsewhere, this visit is likely to coincide with the first visit to the Anal Cancer Clinic
†Optional – for example, there might be a need to assess flap healing
‡ By contrast with CRT patients, the risk here is sub-clinical inguinal lymph nodes

C. FOLLOW-UP GUIDELINES AFTER LOCAL EXCISION FOR SISCCA OF THE ANUS

- In 2012, consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology encouraged the use of the term 'superficially invasive squamous-cell carcinoma of the anus' (SISCCA), defined by three criteria: an invasive squamous carcinoma that (i) has an invasive depth of ≤3 mm from the basement membrane of the point of origin, and (ii) has a horizontal spread of ≤7 mm in maximal extent, and (iii) has been completely excised (7).

- Currently, reported series are small but it may be that many of these can be managed by watch and wait (8). This decision needs be considered through the Anal Cancer MDT.
- For consistency, the imaging surveillance protocol in these patients is identical to that for local excision of margin anal cancer (see **Table 5**).
- The setting for this follow-up is in the joint anal cancer clinic.
- Older terminology such as perianal Bowen's disease and Carcinoma in-situ have been abandoned.

Table 5 Baseline & W&W: canal & margin SISCCA (superficial invasive squamous cell carcinoma of the anus)

- invasive depth of 3 mm from the basement membrane of the point of origin, AND
- horizontal spread of 7 mm in maximal extent, AND
- completely excised

Proposed Christie protocol to coincide with PLATO. FU in joint anal cancer clinic

		Year 1				Years 2 to 5 (in months)							
	Baseline	3 mo	6 mo	9 mo	12 mo	18	24	30	36	42	48	54	60
Path review	✓												
Clinical exam	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
Pelvic MR	✓		✓		✓	✓	✓		✓				
PET-CT	✓												
CT T/A/P	✓				✓		✓		✓				

D. Follow-up guidelines after salvage surgery for locally relapsed anal cancer

- After undergoing, these individuals are at high-risk of both further local disease failure and/or distant metastases.
- For these patients, the follow-up guidelines are similar to those for high-risk patients after chemoradiotherapy, with the clear exception that a 3 month 'response' MR scan is not required.
- **Table 6** summarised the work-up and surveillance for patients undergoing salvage surgery for locally relapsed anal cancer.
- The setting for this follow-up is in the joint anal cancer clinic.
- Surgery in this setting is associated with high morbidity and regular clinical follow-up is required. More frequent clinical visits that those in Table 6 might be required.

Table 6 Re-staging & FU:
post-salvage surgery for local relapse of anal cancer

Proposed Christie protocol to coincide with other updated protocols.
FU in joint anal cancer clinic

		Year 1					Years 2 to 5 (in months)							
	Re-staging	6 wks	3 mo	6 mo	9 mo	12 mo	18	24	30	36	42	48	54	60
EUA*	✓†													
Clinical exam		✓	✓‡	✓	✓	✓	✓	✓¶	✓¶	✓¶		✓¶		✓¶
Pelvic MR	✓			✓		✓	✓	✓	✓	✓				
PET-CT	✓													
CT T/A/P						✓		✓		✓				

*EUA: examination under anaesthesia to: (i) obtain histology; (ii) assess resectability & type of operation: and (iii) initiate/ optimise anaesthetic work-up
† The EUA generally marks the beginning of the 31 day 'clock' to definitive salvage surgery
‡ Optional – for example, there might be a need to assess flap healing
¶ Clinical visit also includes assessment of late effects

E. FOLLOW-UP GUIDELINES IN PATIENTS WITH ANAL INTRA-EPITHELIAL NEOPLASIA (AIN)

This is a specific patient sub-group. Follow-up guidelines for these patients are currently being developed, and will be a stand-alone document.

January 2024

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And ratified by the core members of the anal cancer MDT group: Professor Mark Saunders, Dr Noo Alam, Dr Victoria Lavin, Dr Peter Mbanu (Clinical Oncology); Mr Hamish Clouston (Colorectal Surgery); Dr Rohit Kochhar, Dr Joseph Mercer, Dr Hugh Burnett, Dr Damian Mullan (Radiology); Dr Bipasha Chakrabarty, Dr Rola Salama (Pathology); Sarah Mitchell; David Wilson, Rachel Connolly, Lisa Wardlow (Cancer Nurse Specialists); Lucy Buckley; Imogen Hemy (Radiotherapy radiographers).

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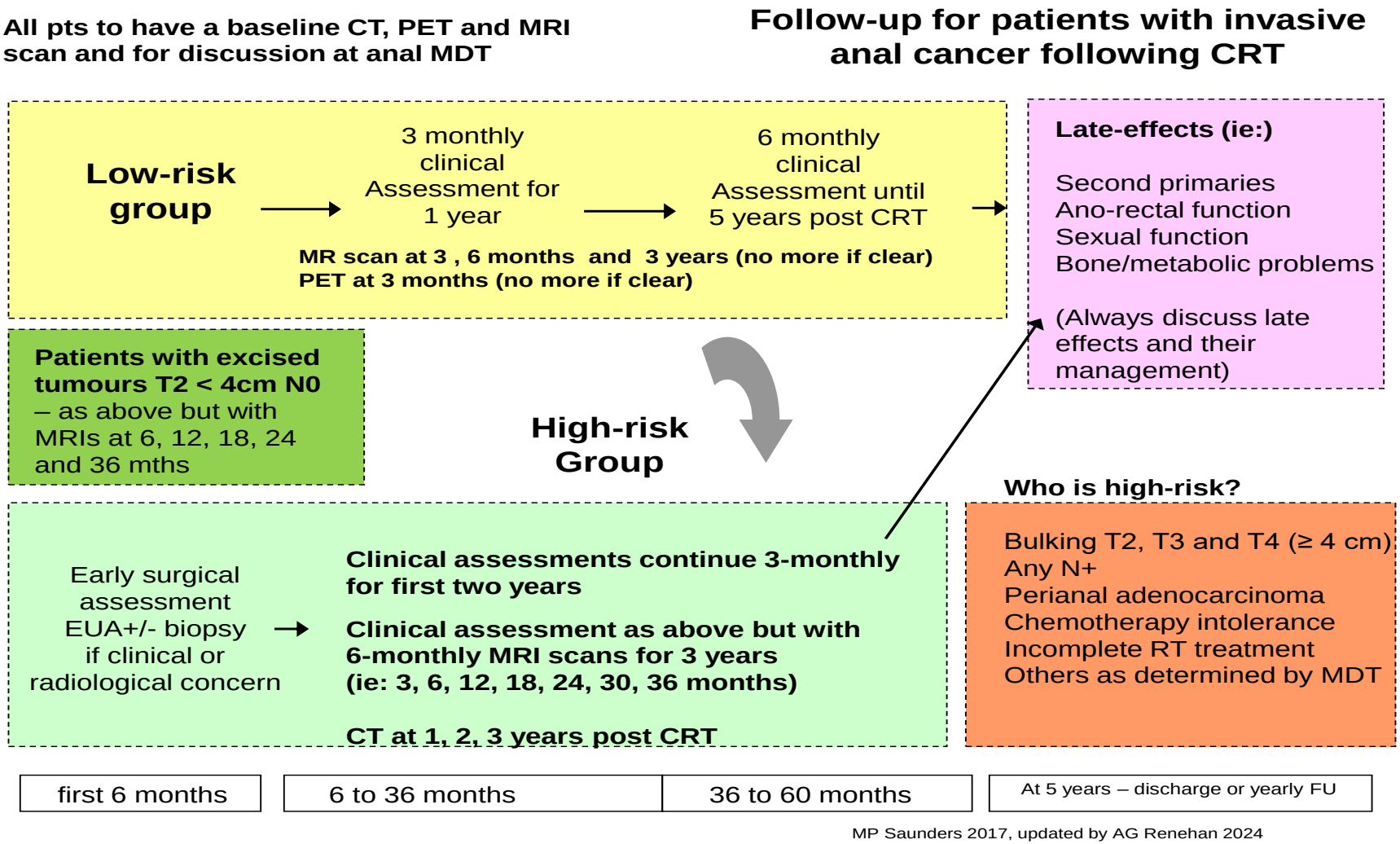
Appendix 1 Update coloured flow diagram of follow-up for patients with anal cancer following chemoradiotherapy



MP Saunders 2017, updated by AG Renehan 2024