The Christie NHS
NHS Foundation Trust

CHRISTIE ANAL CANCER MDT

REFERRAL and MANAGEMENT OF ANAL INTRA-EPITHELIAL NEOPALSIA (AIN) GUIDELINES

This covers symptomatic and (opportunistic) screen-detected disease

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Preface

These guidelines are basically a new document and replaces sections on AIN in previous 2017 guidelines. The development of a brand new set of guidelines reflect two broad developments in the literature: (i) first, there is a perceived increasing incidence and prevalence of AIN diagnosed through both symptomatic presentation and (mainly opportunistic) screen-detection in high-risk individuals; and (ii) second, there is recent literature better defining AIN lesion risk, individual patient risk and among those at high-risk, randomised trial evidence that ablative treatment results reduce rates of malignant transformation.

Recommendations here also reflect the presence of a weekly Anal Cancer Multi-disciplinary Team (MDT) at the Christie; the existence of the 4 weekly joint anal cancer clinic and the proposed development of the two weekly joint anal cancer clinics in the future; and the recent introduction of High-Resolution Anoscopy for the detection of and surveillance of AIN (Anal Intra-epithelial Neoplasia).

These guidelines parallel the development of national guidelines for the diagnosis and management of AIN commissioned by the Association of Coloproctology of Great Britain and Ireland**. These guidelines should be considered 'dynamic' as there will be further refinements as we continuously audit and appraise our management.**

INTRODUCTION AND NEW EVIDENCE

Traditionally AIN is graded as AIN I, II and III. To aid management algorithms, the (histological) terminology of LSIL and HSIL (low- and high-grade squamous intraepithelial lesion) was introduced over a decade ago" for HPV related squamous lesions in the form of the LAST consensus (1). In broad terms, LSIL corresponded to AIN I, and Condyloma acuminatum; HSIL to AIN II and III. p16 immunohistochemistry is recommended to differentiate HSIL from mimics. Absence of p16 immunoreactivity strongly exclude a diagnosis of anal HSIL (2). H&E diagnosis of AIN II not confirmed by positive p16 immunohistochemistry is downgraded to LSIL.

The central tenet of management of AIN (analogous to CIN) is that if one can induce regression or eradicate HSIL, then malignant transformation can be prevented. However, until recently, there was no direct evidence to support this pathway to prevention of anal SCC. The publication of the ANCHOR trial (3) in 2022 changed this.

In the ANCHOR trial, 4459 persons living with HIV who were 35 years of age or older and who had biopsy-proven anal HSIL were randomly assigned (1:1 ratio) to receive either HSIL treatment (namely ablation) or active monitoring without treatment. The primary outcome measure was progression to cancer in a time-to-event analysis. With a median follow-up of 25.8 months, 9 cases were diagnosed in the treatment group (1.7 per 1,000 person-years) and 21 cases in the active monitoring group (4.0 per 1,000 person-years). The rate of progression to anal cancer was lower in the treatment group compared with that in the active monitoring group. Treatment of HSIL resulted in lower rates of progression to anal cancer than active monitoring in patients living with HIV by 57% (P = 0.03 by log-rank test). **It is therefore no longer justifiable to offer active monitoring for HSIL without accompanying HSIL eradicating treatment, at least in individuals living with HIV.** This principle might also apply to those with HSIL at high risk as defined by Clifford et al. (see next), but not living with HIV.

In 2021, Clifford and colleagues (4), as part of a collaboration between the International Agency for Research in Cancer (IARC) and the International Anal Neoplasia Society (IANS) Screening Task Force, undertook a comprehensive meta-analysis using a unifying anal cancer risk scale, to provide robust and comparable estimates of anal cancer burden across many patient groups. This is the most comprehensive summary of risk of incident anal cancer and forms the basis for defining high-risk. IANS have taken a cut of 25 per 100,000 to define high-risk and include the following:

- MSM (men who have sex with men) and living with HIV (LWH) age ≥ 35 years
- Women LWH age ≥ 45 years
- Men (not MSM) age ≥ 45 years
- MSM and transwomen not LWH age ≥ 45 years
- History of vulvar HSIL or cancer (within 1 year of diagnosis)
- Solid Organ Transplant Recipients (10 years post transplant)

The Christie Anal Cancer MDT has agreed to add 'Patients on long-term Immunosuppressants to this list, though this definition is vague and is left to clinical judgement.

Christie Anal Cancer MDT structure relevant to management of AIN

- There is a weekly dedicated Anal Cancer MDT at the Christie NHS Foundation Trust.
- This MDT was successfully peer-reviewed annually until the COVID-19 pandemic.
- The MDT includes a team of four clinical oncologists, two colorectal surgeons, dedicated GI radiologists, consultant radiographer and pathologists, supported by a dedicated MDT coordinator and Advanced Nurse Specialists.
- All patients with a new diagnosis of anal cancer from the Greater Manchester Cancer Pathway Board (plus Macclesfield and Leighton hospitals) should be reviewed through this MDT process for consideration of initial treatment.
- The Anal Cancer MDT is a source for identification and recruitment of patients into trials.
- Anal margin tumours (within 5 cm of the anal canal), without overlapping involvement of the anal cancer, are relatively uncommon. The presentations and pathways for this patient undergoing 'curative' local excision varies. The histology and clinical case should be reviewed through the Anal Cancer MDT.
- Not all patients with AIN need to be discussed at the anal cancer MDT.
- Patients with complex AIN – for example, multizonal disease or disabling disease refractory to initial therapies – are discussed at the anal cancer MDT. The decision to discuss is at the judgement of the responsible consultant.
- There is currently no dedicated anal cancer data manager.
- There is currently no nominated gynaecological input into the anal cancer MDT or joint anal cancer clinic. This should be considered a future objective.
- The current lead clinician for the Anal Cancer MDT is Professor Andrew Renehan

GENERAL

- Many of the principles listed in the recommendations here echo the parallel guidelines being development through the Association of Coloproctology of Great Britain and Ireland (ACPGBI) commissioned AIN Guideline Development Group (co-lead: Professor Andrew Renehan).

REFERRALS

- The following histological classifications are encouraged – HSIL and LSIL (LAST nomenclature) to replace the terms AIN I, II and III.
- All patients with a new diagnosis of HSIL from the Greater Manchester Cancer Pathway Board (plus Macclesfield and Leighton hospitals) should be referred for review through this MDT process for consideration of initial diagnosis and management.
- Patients with LSIL do not require referral. If the histological diagnosis is in doubt, the case can be reviewed by the Christie Pathology Department
- Not all patients with HSIL will be discussed at MDT level. For pragmatic reasons, MDT discussion will be limited to complex HSIL cases as judged at a consultant core member of the Anal Cancer MDT.
- Many patients will be referred with symptoms.
- Other patients will be asymptomatic having been diagnosis by opportunistic screening. Currently, there is no national anal cancer screening programme.
- Some high-risk individuals will be referred for screening. Currently, there is no national anal cancer screening programme. Screening will be on an ad hoc basis.
- Female patients with anal HSIL should be screened for synchronous CIN, VIN and VAIN.
- Superficially invasive squamous-cell carcinoma of the anus (SISCCA) is 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 (Darragh et al., 2012). This diagnosis needs be considered through a specialist Anal Cancer MDT.
- Older terminology such as perianal Bowen's disease AND Carcinoma-in-situ both of which are synonymous with HSIL have been abandoned.

QUANTIFYING THE BURDEN OF DISEASE

- Currently, there is no internationally recognised system for anal intraepithelial neoplasia to quantify the burden of disease.
- Classification in the anal canal, perianus or both seems a reasonable descriptive process.
- Stratification by burden of disease might be relevant for comparing results and also for differential surveillance programmes. In the ANCHOR trial, patients with greater than 50% canal or margin involvement had an increased risk of malignant transformation.
- The use of 5% acetic acid and/or Lugol iodine is used in many centres and was used in every case in the ANCHOR study and has a role in enhancing detection and extent of disease, particularly in the setting of hoc screening.
- Clinical photography is recommended to quantify disease burden and is encouraged as baseline, after treatment and during surveillance.
- MR imaging and/or PET-CT is generally not required where the diagnosis is HSIL only. These are required where the diagnosis is invasive anal SCC and MRI in particular may be considered in cases of diagnostic doubt – for example, in bulking AIN disease.

ROLE OF HIGH-RESOLUTION ANOSCOPY

- Targeted biopsies are generally encouraged. Using HRA to examine the anal canal mucosa is the preferred method to identify ‘targets’ of HSIL.
- The Christie has recently started using HRA.
- The exact indications for its use will evolve but currently HRA is likely to have a role in (ad hoc) anal cancer screening and surveillance after treatment.
- The is currently no plan to routinely use HRA in follow-up after chemoradiotherapy for invasive anal cancer.

MANAGEMENT OF HSIL

- There are several options for medical management of HSIL. The list includes topical therapies 5FU and immunomodulator creams (such as imiquimod). The exact indications for the use of medical therapies versus surgical options are not clear. Similarly, the relative indications and risk-benefits between medical therapies are understudied.
- There are several options for surgical management of HSIL. The list includes ablative therapies: infrared coagulation, electrocautery, carbon dioxide laser, argon

beam plasma coagulation and photodynamic therapy, alongside surgical excision. The exact indications for the use of medical therapies versus surgical options are not clear.

- HPV vaccination may be considered in patients under 40 years. One route of access to HPV vaccination is through the genito-urinary clinic.

Multizonal lesions including anal /perianal HSIL concurrently with other genital HSIL

The term 'multizonal' rather than 'multifocal' is preferred and endorsed by organisations such as the British Society for Colposcopy. There are five zone – cervix, vagina, vulva, perianal and perineum, and anal canal. Currently, penis is not considered a zone.

- The treatment of multizonal lesions with HSIL in more than one anogenital zone is challenging and requires a multidisciplinary approach.
- A planned staged (or phased) approach to treatment may be required.
- Consider HIV testing in patients with recurrent, multifocal, or multizonal HSIL.
- Many cases require complex surgical planning including the assistance of the oncoplastic surgeon.
- Many cases require discussions with gynaecologists with a dedicated interest in VIN and VAIN.

ASSESSMENT OF TREATMENT RESPONSE

- Currently, treatment assessment is a combination of symptom monitoring and clinical examination.
- Increasingly, HRA will be used to define treatment response. This requires better definition.
- Complete treatment of HSIL 'fields' is likely to take 3 to 4 'sittings'. This will have implications for resources.

FOLLOW-UP AND SURVEILLANCE

- The 2017 ACPGBI guidelines stated that "surveillance of patients with [anal] HSIL is predominantly aimed at the identification of early invasive carcinoma that can be treated by local excision or localized CRT with reduced treatment-related morbidity.
- After treatment of HSIL, patients should be followed up at six monthly intervals for at least 5 years, ideally with periodic photographic documentation of the anal canal

and perianal region. There should be a low threshold to repeat biopsies or to excise any changing or bleeding lesion.

- There is likely to be a low risk group with HSIL for whom intensive long-term surveillance is not required. This has yet to be defined but the current DNA methylation study in the Netherlands (MARINE) may help characterise.
- Non-targeted (blind) 'mapping' biopsies (as advocated in historic textbooks) are strongly discouraged. This procedure is painful for patients and does not treat anal HSIL.

PROSPECTIVE AUDIT

- The Christie anal cancer database is operated under audit data governance.
- There is currently no collection of data on patients with AIN.
- Currently, there is no anal cancer data manager to update these data.

January 2024

Professor Andrew Renehan, Clinical Lead for the Anal Cancer MDT

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).

References

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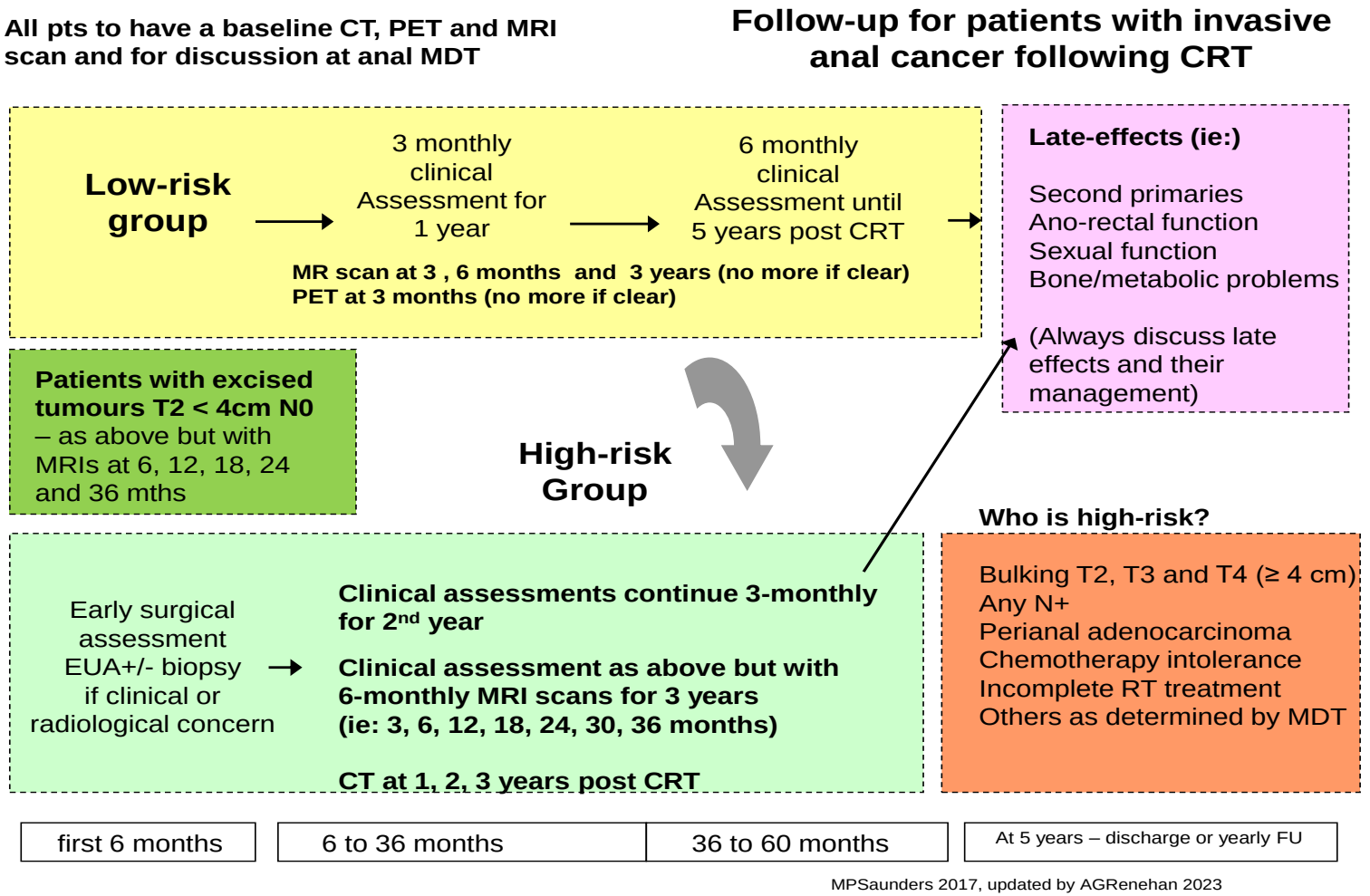
5. Geh I, Gollins S, Renehan A, Scholefield J, Goh V, Prezzi D, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) - Anal Cancer. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2017;19 Suppl 1:82-97.

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



MPSaunders 2017, updated by AGRenehan 2023