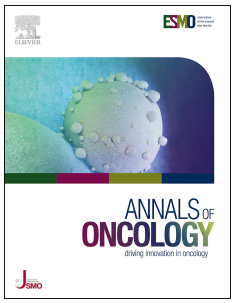

Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Key words: Anal cancer, Clinical Practice Guidelines, diagnosis, treatment, follow-up

Highlights:

- This ESMO Clinical Practice Guideline provides key recommendations for managing anal cancer
- The guidelines cover clinical and pathological diagnosis, staging and risk assessment, treatment, follow-up and survivorship
- Treatment algorithms for locoregional and advanced anal cancer are provided
- Opportunities for personalised medicine in anal cancer are discussed
- Recommendations were compiled by the authors based on available scientific data and the authors' collective expert opinions

INCIDENCE AND EPIDEMIOLOGY

Anal cancer is a rare disease that accounts for <1% and <3% of all new cancer diagnoses and gastrointestinal tumours, respectively. The most common histological subtype is squamous cell carcinoma of the anus (SCCA) with an annual incidence of 0.5-2.0 in 100 000.[1] However, the incidence of anal cancer in Europe, Australia and the United States is increasing.[1] Globally, there were approximately 40 000 new cases of anal cancer estimated in 2012, and in the United States, there has been a more than doubling increase in the reported number of new, age-adjusted cases per 100 000 people per year over last 40 years.[1]

Five-year overall survival (OS) has increased from a mean estimate of 64% [95% confidence interval (CI) 58-71] in 1980 to 75% (95% CI 70-79) in 2010 (P = 0.046).[2]

Aetiology

SCCA and its precursor lesion, anal intraepithelial neoplasia (AIN), are mostly attributable to human papillomavirus (HPV) infection, which represents the causative agent in 80%-85% of patients (especially the HPV16 and HPV18 subtypes).[3] Factors increasing the risk of HPV infection and/or modulating a host response and the persistence of this infection appear to affect the epidemiology of this tumour. Anal intercourse and a high lifetime number of sexual partners increase the risk of persistent HPV infection in men and women, eventually leading to malignancy. Other important risk factors include human immunodeficiency virus (HIV) infection, prior history of anogenital warts, lower genital tract malignancies, immune suppression in transplant recipients, a history of other HPV-related cancers, autoimmune disorders and cigarette smoking.[3-6] Cigarette smoking and HIV infection may also be important

in the modulation/persistence of HPV infection and, hence, outcomes from treatment.

DIAGNOSIS AND PATHOLOGY

Diagnosis

SCCA often presents with bleeding but diagnosis may be delayed because bleeding is attributed to haemorrhoids. SCCA may also present with any combination of a mass, non-healing ulcer, pain, bleeding, itching, discharge, faecal incontinence and fistulae. Digital anorectal examination is an essential low-cost clinical tool for detection of lesions in the anal area. The diagnosis of anal cancer is made by biopsy-proven histology. The diagnostic algorithm for anal cancer is shown in Figure 1 and the diagnostic work-up for SCCA is shown in Table 1.

Pathology

Squamous cell carcinoma histology. Histological confirmation is mandatory as histopathological entities other than squamous cell carcinomas are amongst the differentials, including adenocarcinoma, melanoma, gastrointestinal stromal tumours, poorly differentiated neuroendocrine tumours and lymphoma.

Squamous cell carcinomas can harbour various patterns and interpretation is subject to inter-observer variability. Histological sub-classifications of basaloid, transitional, spheroidal and cloacogenic cell cancers have no impact on management, and the recent World Health Organisation (WHO) classification system of anal carcinoma includes all subtypes under the same heading of squamous cell carcinoma.[7]

Anal verrucous carcinomas (VC) are similar to VC of other sites, and newer studies imply that these lesions are a separate entity not to be included with giant

condylomas, also named Buschke-Löwenstein tumours.[8] VC seems to be unrelated to HPV infections while low-risk HPV genotypes are found in giant condylomas. VC are regarded as low-grade carcinomas while giant condylomas can be regarded as benign tumours. Histologically, it can be difficult to make a distinction between the two entities but features such as koilocytosis favour condyloma. Occasionally, squamous cell carcinomas arise within giant condylomas.

AIN. Anal cancer may arise from a precursor dysplastic lesion, also known as squamous AIN. The American Joint Committee on Cancer (AJCC) recommends dividing these lesions into 'low grade' and 'high grade' squamous intraepithelial lesions (LSIL and HSIL, respectively) with AIN stage I corresponding to LSIL and AIN stages II/III corresponding to HSIL.[9]

The prevalence of AIN in the general population is low, but high-risk sexual behaviour is associated with greater rates of AIN. Further details are described in Section 1 of the Supplementary Material, available at *Annals of Oncology* online.

Anatomy and lymphatic drainage. The anal canal extends from the anorectal junction to the anal margin (see Supplementary Figure S1, available at *Annals of Oncology* online). Useful landmarks are the puborectal sling and the anal verge which roughly coincide with the inter-sphincteric groove. The columnar, or cylindric epithelium of the rectum, extends to approximately 1 cm above the dentate line where the anal transitional zone begins. Below the dentate line, the epithelium is all squamous.

Outside the anal verge lies the anal margin. The anal margin is the pigmented skin immediately surrounding the anal orifice, extending laterally to a radius of

~5 cm. Cancer in the anal margin is regarded as anal cancer, while cancer outside 5 cm from the anus is classified as skin cancer (as shown in Supplementary Table S1 and Table S2, available at *Annals of Oncology* online). Proximally, lymphatic drainage is to perirectal and paravertebral lymph nodes. Immediately above the dentate line, drainage is to internal pudendal nodes and to the internal iliac system. Infra-dentate and perianal skin drains to the inguinal, femoral and external iliac nodes.

Screening and prevention. The existence of an identified viral aetiological agent, biological similarities to cervical cancer and the ability to detect pre-neoplastic lesions may allow the development of screening and prevention programmes. Vaccination against oncogenic HPV is now being recommended for the prevention of cervical cancer, and this may also be of importance for SCCA as infection with HPV is detected in over 90% of invasive anal cancers.[10-12] HPV vaccination programmes are expected to result in lower incidence rates of SCCA.

There are, however, many unanswered questions, including anal HPV natural history, with unknown factors determining rates of progression and regression of the presumed anal cancer precursor, HSIL. Moreover, performance of anal cytology is debatable and outcomes vary based on training and skills of the operator. Psychological and quality of life (QoL) aspects of a screening programme should also be considered. A prospective cohort study exploring the epidemiology of anal HPV infection and related abnormalities in a cohort of gay, bisexual and other men who have sex with men over 35 years of age, showed that patient perception of abnormal results may cause poor health-related QoL 2 weeks after screening.[13]

In summary, screening programmes using anal cytology and high-resolution anoscopy have been proposed for high-risk populations (GBMSM and HIV-negative

women with a history of anal intercourse or other HPV-related anogenital malignancies) based on achievements obtained in cervical cytology screening.[14, 15] However, no randomised controlled study has yet demonstrated a preventive effect of screening in these high-risk populations and thus it cannot be routinely advocated at present.

Recommendations

- Digital anorectal examination is an essential clinical tool for detection of lesions in the anal area [I, A].
- Biopsy is mandatory to confirm SCCA [I, A].
- All suspicious anal lesions should be excised or biopsied. Targeted biopsy of anal lesions suspicious for AIN is mandatory in high-risk groups to exclude invasive disease [I, B].
- Female patients with AIN should be screened for synchronous cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia [I, A].
- Consider HIV testing in patients with recurrent or multifocal AIN [V, A].

STAGING AND RISK ASSESSMENT

Clinical assessment

A comprehensive history is required to elicit symptoms, other relevant medical conditions, current medications and predisposing factors, which should all be documented. Examination should include digital rectal examination (DRE) to evaluate the anal lesion and any perirectal nodal involvement and, in women (particularly with low anteriorly placed tumours), a vaginal examination to determine the site and size of the primary tumour, vaginal/vaginal septal involvement, mucosal

involvement and exophytic or ulcerative tumour or the presence of a fistula. The presence of a large mass with near obstructing symptoms or a tumour with associated faecal incontinence may require a defunctioning stoma. In women, vaginal involvement may require a prophylactic stoma because of the risk of an anorectal-vaginal fistula. However, since most initial colostomies are not reversed, this decision should be weighed carefully. Palpation of the inguinal nodes is important, particularly superficial inguinal nodes, medial and close to the pubis. Fine needle aspiration (FNA) or biopsy of the suspicious nodes may be considered.

Colonoscopy is not required to assess pathology in the proximal bowel because synchronous colonic lesions are not reported for SCCA. HIV testing should be considered in patients with unknown HIV status (see Figure 1).

Local staging of primary anal SCC

Clinical assessment of the diameter of the tumour has been the modality upon which the TNM classification of SCCA is based (Supplementary Table S1 and Table S2, available at *Annals of Oncology* online).[16]

A more detailed assessment of the local tumour and its precise anatomic extent using high resolution T2-weighted magnetic resonance imaging (MRI) scanning techniques enables optimal assessment [III, A].[17-20]

The tumour needs to be identified in relation to clinical and anatomical landmarks for the purposes of radiotherapy (RT) planning. On MRI, the tumour is shown as a relatively high signal intensity compared with the low signal intensity of the muscle layers that form the internal and external sphincter in the anal canal and the muscularis propria of the rectal wall.[17, 21] Conventionally, the radiology report should state the relationship of the lower borders of the tumour to the anal margin,

the extent with quadrant involvement of the anal canal or rectum, the craniocaudal length of the tumour and its depth of invasion**.** Any evidence of adjacent T4 organ infiltration such as vagina, prostate, urethra or bladder wall should also be recorded.[22] In addition, it may be helpful to note the relationship of the tumour/nodes to the sacral segment levels, which would also assist in RT planning [III, B].

The MRI scanning technique uses the same sequences and parameters that have been validated for rectal cancer staging, making use of the anatomic and tumour depiction afforded by high resolution T2-weighted sequences [III, A].[22, 23]

Scans should also cover both inguinal regions, the pelvic sidewall compartments and the top of the mesorectum to the level of L5 so that the primary tumour, as well as draining nodal disease sites, can be imaged. In addition, the lower border of scans should cover the cutaneous anal margin to enable assessment of the anal margin tumours.

Lymph node assessment is notoriously difficult to predict using imaging modalities, and validation of nodal assessment criteria has not been possible due to the paucity of surgical specimens for histopathology correlation. Enlarged inguinal nodes are frequently reactive, and nodes, whether benign or malignant, will reduce in size following pelvic RT. In general, nodes are more likely to be malignant if they exhibit mixed signal intensity; they are also likely to be malignant if breach of the lymph node capsule by tumour signal intensity is observed. These features are best assessed using high resolution T2-weighted MRI [III, A].[17]

Primary tumour assessment has now been superseded by MRI; however, contrast-enhanced computed tomography (CT) scanning of the thorax, abdomen and pelvis is a requirement in all patients to assess potential metastatic disease sites at

diagnosis and follow-up [III, A].

Reports have shown that positron emission tomography (PET)/CT with [18F] fluorodeoxyglucose (FDG-PET/CT) is able to characterise inguinal lymph nodes, with two studies providing sufficient data to allow analysis of diagnostic information for PET/CT. A meta-analysis published in 2017 concluded that PET/CT seemed to add value to conventional imaging in the initial staging of patients with T2–4 disease but further high-quality research was required to validate this, mainly because the conventional imaging comparators were highly heterogenous in the studies analysed. However, there was insufficient evidence to recommend the routine use of PET/CT in the assessment of treatment response or follow-up [III,C].[24]

PET/CT can be used to help confirm suspicious features seen on MRI, particularly if such information will alter the RT plan, for example, in characterising smooth-bordered homogenous signal intensity enlarged nodes that do not fulfil criteria for malignancy on MRI. Because of the potential additional morbidity from irradiation of the inguinal regions and a high prevalence of enlarged and reactive inguinal lymphadenopathy, further characterisation of enlarged inguinal nodes by ultrasound (US)-guided FNA is helpful when confirmatory features of malignancy are not evident on either MRI or PET/CT scanning [V, C].

Occasionally, an early anal cancer has been inadvertently totally excised before histological confirmation and there is no visible anal tumour on MRI or PET-CT. These are staged as Tx tumours. Reviews of the pathological specimen and of the operative notes are imperative. Commonly these resections are R1 and patients should be considered for CRT.

Risk assessment

The presence of HPV infection measured directly or by overexpression of the surrogate marker p16 has a significant effect on patient outcomes. Individuals with HPV-negative tumours are less likely to respond to chemoradiotherapy (CRT) than those with HPV-positive tumours.[25-27] A meta-analysis has shown that patients with HPV-positive/p16-positive tumours have improved disease-free survival (DFS)/disease-specific survival/relapse-free survival (RFS), progression-free survival (PFS) and overall survival (OS) compared with patients with either HPV-negative/p16-positive or HPV-positive/p16-negative tumours.[28]

The European Organisation for Research and Treatment of Cancer (EORTC) 22861 study demonstrated that skin ulceration, nodal involvement and male sex were independent factors associated with locoregional failure (LRF) and adverse OS.[29] The Radiation Therapy Oncology Group (RTOG) 9811 analysis supported some of the factors previously reported in EORTC 22861 (clinically involved nodes and male sex) and also established tumour diameter of >5 cm as an independent variable predicting DFS and OS.[30]

HIV testing is recommended in any patient with a lifestyle that puts them at risk of contracting HIV infection. Recent evidence suggests that, compared with HIV-negative patients, HIV-positive patients treated with highly active antiretroviral therapy may have similar treatment outcomes.[31] When treating HIV-positive patients with anal cancer, coordinated follow-up with a HIV specialist should be encouraged. Histologically, a high tumour infiltrating lymphocyte (TIL) count has been found to be significantly associated with RFS in p16-positive tumours.[32] The biological understanding of HPV-positive and -negative tumours is increasing and may be of importance for the design of future clinical trials.[33]

Recommendations

- All patients with anal tumours should be referred and discussed in a multidisciplinary team meeting with a prespecified interest in anal cancer [V, C].
- Clinical examination including digital rectal examination, (and vaginal examination in women), and palpation of the inguinal lymph nodes should be performed for assessment of tumour extent [V, B].
- High resolution T2-weighted MRI is needed for optimal assessment of primary tumour and lymph nodes [III, A].
- MRI may also be helpful to note the relationship of tumour/nodes to the sacral segment levels, which would also assist in RT planning [III, B].
- Lymph nodes can be difficult to interpret on MRI. Generally, they are more likely to be malignant if they exhibit mixed signal intensity and if breach of the lymph node capsule by tumour signal intensity is observed on high resolution T2-weighted MRI [III, A].
- Contrast-enhanced CT scanning of the thorax, abdomen and pelvis is a requirement for all patients to assess potential metastatic disease sites at diagnosis and follow-up [III, A].
- Further characterisation of enlarged inguinal nodes by US-guided FNA may be helpful when confirmatory features of malignancy are not evident on either MRI or PET/CT [V, C].
- PET/CT may be considered for staging and assist in RT planning [III, C].
- HIV testing may be considered in at-risk patients [III, C].Assessment of HPV or p16 status may be considered as they have treatment response predictive value [V, C].

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Initial management of local and locoregional disease

The primary aim of treatment is to achieve cure with locoregional control, preservation of anal function and the best possible QoL. Treatment of anal cancer differs dramatically from adenocarcinomas of the lower rectum.

Combinations of mitomycin C (MMC) and 5-fluorouracil (5-FU)-based CRT have been established as the standard of care, leading to complete tumour regression in 80% to 90% of patients, with locoregional failures of ~15%; other cytotoxic agents [mainly cisplatin (CDDP)] can be considered, if clinically indicated.[34, 35] A multidisciplinary approach is mandatory, involving Radiation Oncologists, Medical Oncologists, Surgeons, Radiologists and Pathologists. The role of surgery as a salvage treatment is accepted.

CRT

Recommendations are based on results of phase II and six randomised phase III trials (EORTC 22861, UKCCCR ACT I, RTOG 87-04, RTOG 98-11, ACCORD-03, and CRUK ACT II).[29, 30, 36-40] Concomitant 5-FU and MMC with RT is generally recommended [I, A]. Other options may include 5-FU and cisplatin, and in some cases, other chemotherapy (ChT) combinations can be used.

Relatively few patients with stage I disease were included in the CRT trials and so application of overall data to T1 tumours is limited. However, for small tumours (T1), some investigators have used external beam RT alone followed by a small volume boost. In contrast, early investigators[34, 41] reported that CRT with the addition of MMC to 5-FU demonstrated excellent local control in small tumours (<4 cm). Sequential phase II studies with CRT have shown the efficacy of relatively

low total RT doses (30–50 Gy) in combination with 5-FU and MMC.[42] In general, CRT is recommended, however the optimal RT dose is not known. The ongoing PLATO (PersonaLising Anal cancer radioTherapy dOse, ISRCTN88455282) trial is a single protocol 'umbrella platform' comprising the ACT3, 4 and 5 trials, where the ACT4 trial is investigating different RT doses for stage I–IIA anal cancer.[43]

Early randomised controlled European studies have demonstrated that synchronous CRT with 5-FU and MMC as the primary modality is superior to RT alone.[29, 40] The RTOG phase III study compared 5-FU with 5-FU and MMC, both in combination with RT. This study confirmed the superiority of the combination of MMC and 5-FU.[30] The 6-8 weeks treatment gap used in early trials has since been abandoned.

The second generation of randomised studies investigated the role of cisplatin to replace MMC in combination with 5-FU and RT.[37-39] In these studies, cisplatin and 5-FU were also used before or after CRT as neoadjuvant or maintenance treatment, respectively. The results of these studies found that cisplatin in combination with infused 5-FU and RT did not improve either complete response rates or DFS compared with MMC. Induction ChT or maintenance ChT did not improve outcomes.[37-39] RT was given with total doses of 45-60 Gy depending on treatment protocols (including boost) and disease stage. The optimal RT dose for curative CRT is not clear; however, for patients with locally advanced anal cancer, the RT dose should be >50.4 Gy.[38]

Treatment with 5-FU has been usually given as 1000 mg/m^2 on days 1-4 and 29-32 of RT; alternatively, a 5-day infusion at 800 mg/m^2 has been used by some centres, while MMC has been given either as 12 mg/m^2 (maximum dose 20 mg) on day 1,[38] or 10 mg/m^2 (maximum dose 20 mg) on days 1 and 29.[39] In recent years,

based on logistical reasons and availability of data from relatively small case series, 5-FU can be replaced with capecitabine 825 mg/m^2 twice daily, 5 days per week for all days of RT [III, B].[44] A proposed treatment algorithm for the management of localised Stage I-III anal cancer is shown in Figure 2.

RT technique and treatment fields

The total doses, including the boost doses used, vary between countries from 50.4 Gy used in the ACT II trial, 55-59 Gy for T3-4 or node-positive disease used in the RTOG 98-11 trial, and up to 60 Gy used in a large series from the Nordic countries.[38, 39, 45] Tumour control probability models suggest that lower doses may be sufficient for small tumours, while higher doses – in the range of 50-55 Gy or higher – may be required for more advanced tumours such as T3-4 or N1.[46, 47]

It is not possible to make a definitive recommendation (based on inter-trial comparisons of differing dose fractionations with or without a treatment gap) on the type (external beam or brachytherapy) or dose for a boost after 50 Gy. The optimal RT doses for different target volumes and disease stages are not known and should be determined in randomised clinical trials. In the ongoing integrated PLATO trial, patients with T2N1-3 or T3-4 tumours in the ACT5 trial are randomised to receive total tumour doses of 53.2 Gy, 58.8 Gy or 61.6 Gy in 28 fractions.[43]

Treatment fields should encompass the primary tumour, anal canal, nodal regions and inguinal nodes initially,[48] with field reduction recommended to treat the primary tumour and any sites of likely nodal involvement within the high-dose volume. Alternatively, patients may be treated with simultaneous integrated boost (SIB). Delivery of RT in anal cancer is complex because of the varying size and shape of the target volume and the proximity to dose-sensitive critical structures

such as the small bowel, rectum, bladder, femoral heads, perineum and external genitalia. These structures often received high doses of RT with conventional parallel opposed techniques. Whilst earlier randomised trials have mainly relied on two dimensional (2D)-based RT planning, later trials have used conformal (CT-guided or 3D) RT-based treatments, which allowed oncologists to identify normal as well as target soft tissue structures on axial CT images, and led to improved treatment accuracy and delivery. The most common grade 3/4 acute toxicities were skin, haematological and gastrointestinal.[38, 39]

More conformal treatment strategies such as intensity-modulated RT (IMRT) spare at-risk organs, reduce toxicity and may allow full or even escalated doses to be achieved within a shorter overall treatment time with limited unplanned treatment interruptions.[49] Hence, IMRT or volumetric modulated arc therapy (VMAT) are currently recommended for the treatment of anal cancer, setting strict RT dose constraints to normal organs [III, B]. Also, IMRT and VMAT allow for treatment with SIB.[50]

Several ‘proof-of-principle’ studies of IMRT in anal canal carcinoma have reported significant reductions in the RT doses delivered to the bowel, bladder and genitalia/perineal skin. Prospective phase II multicentre studies (including RTOG 0529) have shown that IMRT is deliverable in a multicentre setting,[49, 51] with a reduction in toxicity compared with the best arm of the RTOG 9811 trial. Guidance for IMRT with simultaneous boost has been developed and is being used in ongoing clinical trials.[52]

Australasian contouring and planning guidelines provide a high-resolution atlas for contouring gross disease and organs at risk,[48] which complements the earlier RTOG elective anorectal atlas[53] and the RTOG pelvic normal tissue

contouring guidelines.[54] The descriptions of the elective target volumes or compartments are useful and reproducible and have been supplemented with recent contouring guidance.[52]

The inguinal nodes should be included in the RT fields in most cases, even in the absence of clearly demonstrable involvement. The incidence of inguinal nodal involvement increases with increasing primary tumour size and is at least 20% in patients with T3 disease. The risk is higher for primary tumours located below the dentate line or near the anal orifice, or in patients with N1 disease.

The role of the surgeon for locoregional anal canal cancer

The anal cancer surgeon is an important member of the anal cancer multidisciplinary team (MDT).[55] Although 80% of patients with anal cancer are initially treated by CRT, the anal cancer surgeon should provide input into the management of most patients from the outset. There are four key areas for input as part of initial management.

Approximately 10%-20% of patients with anal cancer will require a pre-treatment colostomy. The two main indications are anorectal pain and faecal incontinence or anticipated faecal incontinence during CRT. In contrast to upper rectal cancers, large bowel obstruction is rare for an anal cancer. Although closure or reversal of colostomy is documented in the literature, it should be considered the exception and only indicated if the anorectum is functionally intact. More commonly, faecal incontinence or anal stenosis persist because of the high RT dose to the anal sphincters, and thus, patients should be advised of the high likelihood that their pre-treatment colostomy will be permanent. For the surgical technique, loop colostomy is discouraged because of the high rates of parastomal hernias and prolapses. The technique of choice is an end colostomy, carried out either by open surgery or

laparoscopically. CRT can be started 2 weeks after this surgery.

Up to a quarter of patients may have a perianal fistula at the time of anal cancer diagnosis. The fistula may be long-standing as an ano-cryptal fistula unrelated to the malignancy or it may be a malignant fistula. Such fistulae are at high-risk for local sepsis during CRT, which may necessitate a treatment gap of >5 days. This is a very unfavourable yet avoidable scenario. The MDT at first diagnosis should specifically document if a fistula is present (clinically or radiologically) and the anal cancer surgeon should insert a seton to secure drainage without delay. The seton might need to remain *in situ* (with 6-monthly changes) for up to 18 months to allow the RT changes to completely settle before definitive fistulotomy. Patients should be fully informed of this potential pathway.

Whilst radical abdomino-perineal excision (APE) has been replaced by CRT as primary treatment for most anal cancers,[56] there are a number of uncommon scenarios where there are relative indications for APE as the primary treatment. These include the following: (1) where there has been previous pelvic RT and curative RT cannot be given; (2) a histology of anal adenocarcinoma or adenosquamous carcinoma where complete response to RT is less likely than for SCCA; (3) the setting of SCCA in a transplant patient on immunosuppressants where there may be doubt that the patient will complete CRT uninterrupted; and (4) an exceptional patient who refuses CRT.

Local excision of early-stage cancers in the anal canal is contraindicated. This is associated with an unacceptably high proportion of margin-positive resections, and if followed by CRT, is associated with considerable morbidity to the anal sphincter.[57] Piecemeal resections (anywhere in the anorectum) are strongly discouraged as it renders assessment of resection margins in the specimen impossible. The only

exception is local excision, usually as a biopsy, of very early cancers in the form of superficial invasive squamous cell carcinoma (SISCCA).

A specific mention of VC is warranted. These typically arise in the anal margin, are generally RT-resistant and are usually treated by local excision. However, VC may be locally infiltrating into the anal sphincters and may necessitate a radical APE. Similarly, giant condyloma mainly arise from the anal margin but may be locally infiltrating necessitating a radical APE.

Management of anal margin cancer

Up to 5% of all anal cancers are suitable for local excision as definitive treatment. The majority of these are early anal margin cancers (cT1N0M0). The anal margin is defined as the pigmented skin immediately surrounding the anal orifice, extending laterally to a radius of approximately 5 cm. The aim of this operation is to achieve a histological clearance of >1 mm without damage to the anal sphincter muscle (consensus from the PLATO trialists).[43] This commonly requires a macroscopic surgical clearance of 0.5 to 1.0 cm. Preoperative assessment by MRI may be informative for nodal staging, for example, but MRI assessment of external sphincter muscle involvement from a tumour is suboptimal. Direct closure of these wounds has a high risk of wound dehiscence and consideration should be given to a combined procedure with plastic surgery reconstruction.

Approximately 20%, but up to 40% in some series, have a histologically positive margin after local excision. Re-excision has been practiced in this setting, as this is common practice for skin cancers. However, for perianal SCC, this should be discouraged as it is associated with high morbidity, low histological yield and long-

term high local recurrence rates. Anal margin SCC is a HPV-related cancer and exquisitely RT-sensitive,[46] and should be considered for low-dose RT with concurrent ChT. PLATO (ACT3) is a non-randomised, phase II, multicentre, open-label trial, primarily in patients with T1N0 anal margin tumours that will assess the overall treatment strategy of local excision with selective low-dose CRT for patients with ≤1 mm margins.[43]

Previous guidelines have recommended that CRT is used, either as the primary treatment or as adjuvant therapy after local excision, irrespective of the resection margin status, where the histology is poorly differentiated.[35] The present authors are unaware of evidence to support or dispute this, and thus considered that no recommendation should be made in relation to tumour differentiation.

A proposed treatment algorithm for the management of localised T1N0M0 anal margin cancer is shown in Figure 2.

Postoperative CRT

Postoperative CRT should be considered, and discussed in an MDT meeting, for all patients who have had local excision of a cancer in the anal canal, patients who had local excision of an anal margin cancer with a histological margin ≤1 mm, patients who have undergone excision where piecemeal histological assessment and completeness of excision cannot be guaranteed, and in those considered at risk of pelvic node involvement [IV, B]. Other indications include rare cases where radical surgery has been carried out as the primary treatment but the resection margin is involved.

Re-excision for a histological positive or close (≤1 mm) margin is not

recommended.

Management of elderly patients, toxicity and supportive care

The rationale for treatment recommendations for the elderly and additional considerations regarding toxicity and supportive care during RT as well as brachytherapy are described in Section 2 of the Supplementary Material, available at *Annals of Oncology* online.

Response evaluation

Anal cancers tend to regress slowly after completion of CRT. DRE has been the mainstay of determining complete response after treatment, defined as the absence of tumour and/or ulceration. Examination may be more informative when carried out under general anaesthesia if pain persists or response is difficult to quantify. Clinical examination of the inguinal regions in addition to radiographic evaluation (with pelvic MRI and CT scans) is also necessary. Oedema, residual fibrosis or scar tissue can be difficult to distinguish from persistent active disease. However, biopsies of persistent, clinically suspicious lesions 8-12 weeks after CRT completion are not routinely recommended. Treatment-related effects may confound the pathological interpretation of post-treatment biopsies.

The majority of tumours that persist/ recur typically do so within the first 24 months following completion of CRT.[17] Lack of clinical response at 3 months does not necessarily indicate that surgery is required for non-response since reassessment at 6 months often shows late but clinically significant regression. Using data from the ACT II trial, the optimum timepoint to assess clinical tumour response after CRT was judged to be 26 weeks [II, B].[58]

To date, few FDG-PET/CT studies have assessed treatment response, and

the timing of assessment is controversial. If disease progression occurs, salvage surgery is recommended. Residual or 'recurrent' tumour should be confirmed histologically before considering proceeding to radical surgery. The mainstay of salvage is an extra-levator abdomino-perineal (APR) excision.[59]

Management of local recurrence/regrowth

Assessment of recurrence/regrowth for salvage surgery. In patients with histologically confirmed locally recurrent anal cancer, imaging assessment in conjunction with a specialist MDT assessment is important to optimise surgical cure. Involvement of the anal sphincter complex requires exenterative [beyond total mesorectal excision (TME)] surgery, and imaging assessment should include a thorough assessment of the pelvic compartments to enable surgical planning (beyond TME) [III, A].[60-62]

More detailed information on the recommendations for salvage surgery are described in Section 3 of the Supplementary Material, available at *Annals of Oncology* online.

Recommendations

Primary treatment

- All patients with anal tumours should be referred and discussed in a multi-disciplinary team meeting with a pre-specified interest in anal cancer [V, C].
- RT with concomitant 5-FU and MMC is recommended as standard of care for patients with localized SCCA [I, A].
- CRT for locally advanced anal cancer should be given with an RT dose of >50 Gy; the optimal dose for different tumour stages is not known [III, B].
- Capecitabine can be possibly used as an alternative to 5-FU in combination

with MMC and RT [III, B].

- Neoadjuvant or adjuvant ChT is generally not recommended [I, D].
- Elderly patients who can tolerate treatment should be treated with curative CRT. Patients who cannot tolerate CRT may benefit from RT for local control [V, C].
- The optimal RT dose for primary anal cancer is not known, but doses of at least >45–50 Gy are recommended for T1–2N0 tumours, and doses of 50.4 Gy or higher for T3–4 or N1 tumours [III, B].
- Contouring guidelines are helpful for defining treatment volumes [V, C].
- IMRT, VMAT or 3D conformal RT are the recommended RT techniques, with RT dose constraints to normal tissue [III, B].
- Pre-CRT colostomy should be considered in patients with locally advanced anal cancers with (or anticipated) anorectal pain or faecal incontinence and rectovaginal fistula. Patients should be advised of the likelihood that their colostomy will be permanent [III, C].
- There are uncommon scenarios where radical abdomino-perineal excision may be considered instead of CRT as the primary treatment e.g. previous pelvic RT [IV, C].

Response assessment

- The optimum timepoint to assess tumour response after CRT is 26 weeks [II, B].
- Clinical assessment must be undertaken pre- and post-treatment [II, B].
- A side-by-side comparison of the baseline and post-treatment MRI scans enables an accurate assessment of response [IV, A].
- There is insufficient evidence to recommend the routine use of PET/CT in the

assessment of treatment response or follow-up [III, C].

Toxicity

- Patients should be assessed for skin and haematological toxicity during CRT treatment [III, B].
- Patients should be informed of expected late effects, including changes in anorectal and sexual function, menopause and risk of infertility [IV, C].

Locally recurrent or residual disease

- Patients with locally residual or recurrent disease after CRT should be considered for salvage surgery [III, B].
- Residual or recurrent tumours may be considered for histological confirmation [II, B].
- For patients with locally recurrent disease, MRI imaging in conjunction with specialist MDT assessment is important to optimise surgical cure [III, A].
- Involvement of the anal sphincter complex requires exenterative surgery, and imaging assessment should include a thorough assessment of the pelvic compartments to enable surgical planning (beyond TME) [III, A].
- The mainstay of salvage surgery is an APR excision, but more radical exenterative operations can be considered to achieve an R0 resection [III, C].
- APR for relapsed anal cancer is a different operation from that used for rectal cancer. Perineal plastic reconstruction with musculo-cutaneous flaps should be considered in almost all cases [IV, C].
- Patients should be warned that long-term morbidity after salvage surgery is high [IV, C].
- Many organisations in Europe advocate that this specialised multidisciplinary surgery is centralised [IV, B].

Anal margin cancers

- Early anal margin cancers (cT1N0M0) can be treated definitively by local

excision. The aim of this operation is to achieve a histological clearance of >1 mm without damage to the anal sphincter muscle [IV, C].

- CRT is recommended for anal margin cancers (T1N0M0) if the margin is ≤1 mm [III, B].

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Approximately 10%-20% of patients suffer distant relapse and approximately 10% present with *de novo* metastatic disease.[29, 36] Twenty percent of patients develop local failures following CRT, and salvage surgery is only feasible for a proportion of such patients.[29, 36, 63] The common sites of metastatic spread are the para-aortic nodes and the liver, whereas the lungs, bones, peritoneum and skin are involved less frequently. The prognosis of all metastatic patients is poor with a 5-year relative survival rate of 30%. Information on best supportive care is described in Section 4 of the Supplementary Material, available at *Annals of Oncology* online.

ChT options

Otherwise fit patients with symptomatic metastatic or recurrent disease not amenable to surgery should be considered for ChT. Despite a lack of high-quality prospective evidence, several small case series have shown efficacy in favour of combination therapy with cisplatin and 5-FU.[35, 64-66]

Activity has also been reported for carboplatin, doxorubicin, taxanes and irinotecan ± cetuximab, or combinations of these agents.[67-70] These options will be influenced by the disease-free interval and the patient's preferences and performance status. Responses are rarely complete and usually short in duration.

Recently, Kim et al reported encouraging activity in a single-arm phase II trial of triplet ChT with modified docetaxel, cisplatin and 5-FU (DCF).[70]

The International Rare Cancers Initiative (IRCI), which is a consortium of international investigators from the UK, United States, Europe and Australia, reported findings from a multicentre international trial testing the role of carboplatin/paclitaxel versus the common standard of 5-FU/cisplatin. InterAACT is the largest and only multicentre randomised controlled phase II study, recruiting 91 patients between 2013 and 2017. Patients were randomly assigned to carboplatin/paclitaxel (N = 45) and cisplatin/5-FU (N = 46). Median follow-up was 28.6 months. Objective response rate (ORR) was 57% (95% CI 39.4-73.7) for cisplatin/5-FU versus 59% (95% CI 42.1-74.4) for carboplatin/paclitaxel. Median OS was 12.3 months for cisplatin/5-FU (95% CI 9.2-17.7) versus 20 months (95% CI 12.7- not reached) for carboplatin/paclitaxel [hazard ratio (HR) 2.00; 95% CI 1.15-3.47, *P* = 0.014].[71] Based on these findings, carboplatin/paclitaxel should be regarded as the standard of care in patients with ChT-naive advanced anal cancer and should be the cytotoxic platform for future phase III trials [I, B].

A proposed treatment algorithm for the management of advanced anal cancer is shown in Figure 3.

Immunotherapy landscape in anal cancer

Immunotherapy has been deemed an important biological consideration in anal cancer in view of its causal association with HPV infection. Beside the oncogenic properties of HPV viruses, HPV proteins, E6 and E7, are known to promote recruitment of TILs, which triggers activation of an anti-cancer immune response.

Twenty-four patients with advanced anal cancer and programmed death-ligand 1 (PD-L1)-positive tumours (cut-off ≥1% membrane staining of both neoplastic cells and mononuclear inflammatory cells) were evaluated in the multi-tumour type KEYNOTE-028 study.[72] This study showed encouraging findings with pembrolizumab in a cohort of patients with refractory anal cancer and no other available standard systemic therapy options. The ORR and stable disease (SD) rates were 17% and 42%, respectively. Median duration of response was not reached while median PFS and OS were 3.0 months and 9.3 months, respectively; 1-year survival was 47.6%.

Similar efficacy outcomes were reported in NCI9673, a phase II study investigating the safety and activity of nivolumab in patients who had received ≥1 prior systemic therapy for advanced disease.[73] Of the 37 heavily pre-treated patients with advanced anal cancer, 24% achieved a response (partial response in 19%, complete response in 5%) while SD was achieved in a further 47% of cases. Median PFS and OS were 4.1 months and 11.5 months, respectively. Further testing of programmed cell death protein 1 (PD-1)/PD-L1 inhibitors and other immunotherapy-based approaches are currently underway. Microsatellite instability (MSI)/mismatch repair (MMR) testing is not required for the use of PD-1/PD-L1 inhibitors in metastatic anal cancer.

Based on the significant promise shown by such approaches thus far, the authors recommend that clinical trials evaluating the role of immunotherapy in patients with advanced anal cancer should be considered, where possible (Figure 3).

Recommendations

- Carboplatin in combination with paclitaxel should be considered a new

standard of care in patients with ChT-naive advanced anal cancer [I, B].

- Cisplatin in combination with 5-FU, carboplatin, doxorubicin, taxanes and irinotecan ± cetuximab, or combinations of these agents, can be considered as alternatives in patients with advanced anal cancer [III, B].
- PD-1/PD-L1 inhibitors are not currently approved but may be considered in patients who have progressed on first-line therapy in clinical trials where possible [II, B].

PERSONALISED MEDICINE

Despite recent developments in our understanding of the molecular biology of anal cancer, there remains considerable heterogeneity in terms of outcomes, particularly for advanced disease stages. One of the major obstacles in establishing clinically relevant biomarkers is the lack of sufficient data from clinical trials owing to small numbers of patients. However, more clinically meaningful information is emerging from recent studies utilising highly sensitive molecular characterisation techniques and comprehensive genome sequencing panels, and this may influence clinical decision-making for patients with anal cancer in the future.[74]

The association between anal cancer and HPV has long been established; the cell cycle regulator p16 is overexpressed in high-risk HPV-related cervical cancers, which may represent a simple surrogate biomarker for identifying squamous cell carcinomas harbouring HPV DNA. Patients with moderate/strong p16 staining may achieve a better response to CRT and have a lower risk of relapse than patients with absent or weak staining. However more research is needed before a recommendation can be made.[25, 27, 33] Furthermore, assessment of TILs is thought to add to the prognostic information of HPV status in anal cancer following CRT and provides evidence of the perceived clinical importance of the immune response,

although more research is needed.[32] More detailed information on personalised medicine is described in Section 5 of the Supplementary Material, available at *Annals of Oncology* online.

FOLLOW-UP LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Locoregional disease

Follow-up should be considered in all patients within a protocol-driven programme by the anal cancer MDT.

Patients in complete remission should be evaluated every 3–6 months for a period of 2 years, and every 6–12 months until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes [II, B]. Anoscopy or proctoscopy is an additional option but is sometimes poorly tolerated and too painful following CRT. Suspicious lesions should be assessed by MRI and/or PET and be biopsied if possible. Data from the ACT II study suggest very few (<1%) relapses occur after 3 years so extended imaging surveillance after this time is not recommended [II, C]. Once tumour regression is confirmed at 3 and 6 months, annual CT scans for surveillance at 12, 24 and 36 months are recommended to identify disease relapse or metastatic disease.

Long term implications and survivorship

Data on long-term QoL and functional outcomes are relatively sparse but show that disease and treatment can affect anorectal and sexual function. In addition, continence and ‘urgency’ appear impaired in many patients.[75, 76 77] Acute and late adverse events during IMRT correlate with RT doses to the small bowel and anterior pelvic contents.[78] Pelvic RT usually results in menopause and loss of fertility in

women and may also affect male fertility. Information regarding treatment-related side-effects should be provided clearly, particularly on anorectal and sexual functioning.

Several aspects of long-term function and QoL have been identified as among the core outcomes to investigate after treatment for anal cancer.[79] Efforts should therefore be made to document QoL and late effects [V, C]. An anal cancer-specific QoL questionnaire has recently been developed and is currently being validated.[80]

The challenge is to fine-tune the balance between treatment intensity (RT dose and volume) and long-term side effects given the high cure rate of anal cancer at the locoregional stage.

Recommendations

- Follow-up should be considered in all patients within a protocol-driven programme by the anal cancer MDT [III, B].
- The primary aim of follow-up is to detect disease which is amenable to salvage therapy; a secondary aim is to manage symptoms related to the cancer and its treatment [III, C].
- Patients in complete remission should be evaluated every 3–6 months for a period of 2 years, and every 6–12 months until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes [II, B].
- Very few (<1%) relapses occur after 3 years so extended imaging surveillance after this time is not recommended [II, C].
- Patients with locally advanced anal cancer may benefit from intensive MRI surveillance in the first 12 months [III, C].
- Efforts should be made to document QoL and late effects [V, C].

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for Clinical Practice Guidelines development, available at http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S3, available at *Annals of Oncology* online.[81] Statements without grading were considered as justified standard clinical practice by the experts.

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Table 1. Diagnostic work-up of SCCA

CT, computed tomography; DRE, digital rectal examination; FNA, fine needle aspiration; HIV, human immunodeficiency virus; HPV, human papillomavirus; MRI, magnetic resonance imaging; PET, positron emission tomography; SCCA, squamous cell carcinoma of the anus.

Figure 1. Diagnostic algorithm for anal cancer

CT, computed tomography; HIV, human immunodeficiency virus; HPV, human papillomavirus; MRI, magnetic resonance imaging; PET, positron emission tomography; SCCA, squamous cell carcinoma of the anus.

Figure 2. Treatment algorithm for localised anal cancer

5-FU, 5-fluorouracil; CRT, chemoradiotherapy; M, metastasis; N, node; MMC, mitomycin C; RT, radiotherapy; T, tumour.

[a] Optimum timepoint to assess clinical tumour response after CRT is 26 weeks [II, B].

[b] In cases where surgery cannot be carried out.

Figure 3. Treatment algorithm for advanced anal cancer

5-FU, 5-fluorouracil; BSC, best supportive care; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 1. Diagnostic work-up of SCCA

Mandatory	**Recommended**	**Optional**
Biopsy	HIV test	Endo-anal ultrasound
DRE	PET/CT	Ultrasound-guided FNA of inguinal nodes
Complete medical history	P16/HPV assessment	Examination under anaesthesia
Full clinical examination		
High Resolution Pelvic MRI		
CT of thorax, abdomen and pelvis		
Anoscopy/proctoscopy		
Gynaecological examination		

CT, computed tomography; DRE, digital rectal examination; FNA, fine needle aspiration; HIV, human immunodeficiency virus; HPV, human papillomavirus; MRI, magnetic resonance imaging; PET, positron emission tomography; SCCA, squamous cell carcinoma of the anus.