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Treatment of squamous cell carcinoma of the anus, unresolved areas and future perspectives for research

Perspectives of research needs in anal cancer

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Abstract

Anal cancer is a relatively rare, mostly HPV-related cancer. The curative treatment consists of concurrent chemoradiation delivered with modern radiotherapy techniques. The prognosis for most patients with early localized disease is very favourable; however patients with locally advanced disease and/or HPV negative tumours are at higher risk of locoregional and distant treatment failure. Tailored approaches are presently being investigated to determine the most suitable regimen in terms of radiotherapy dose prescription, target volume selection, normal tissue avoidance and combination therapy. Metastatic anal cancer is treated with chemotherapy aiming at prolonged survival. The role of immune therapy in the clinical setting is being investigated. There is little knowledge on the biology of anal cancer, and an urgent need for more clinical and translational research dedicated to this disease. In this manuscript, the evidence-base for the current treatment is briefly reviewed, and perspectives on future research needs are high-lighted.

Keywords: Anal Cancer, Radiotherapy, Chemotherapy, Human Papilloma Virus, Immune Checkpoint Inhibition

Introduction

Squamous cell carcinoma of the anus (SCCA), or anal cancer, is a rare disease, however with an increasing incidence in several countries in Europe, Australia, and the US.[1] Given the rarity of the disease, there has been relatively few randomized controlled trials, and a paucity of translational research to provide knowledge of the biology of SCCA, however the situation is presently improving. In brief, the recommended treatment for early stage SCCA is chemoradiotherapy (CRT) with concurrent mitomycin C (MMC) and 5-fluoropyrimidine (5-FU) based chemotherapy,[2,3] with precision radiotherapy techniques such as intensity-modulated radiotherapy (IMRT).[4] The prognosis of SCCA is in general favourable,[5] however patients with locally advanced stage or adverse biological features are at risk of treatment failure and/or metastatic spread. Salvage surgery should be considered for patients with local treatment failure. Chemotherapy is recommended for metastatic disease.[3]

During recent years, clinical and research collaborations have targeted this disease, promoting research and trials. Examples include the International Rare Cancer Initiative (IRCI) Relapsed/metastatic anal cancer group, the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Group (GITCG) (Rectum, Anal canal Task Force), and the Nordic Anal Cancer Group (NOAC). The IRCI anal cancer group initiated the first multi-centre randomized controlled trial on advanced anal cancer, the InterAACT trial, which was successful in patient recruitment across the collaborative groups in Europe (EORTC, UK, Nordic Group), the US (NCI endorsed), and Australia, leading to a new standard of care for metastatic SCCA.[6]

The European Society for Medical Oncology (ESMO) has developed Clinical Practice Guidelines for the diagnosis and treatment of anal cancer[2] and updated guidelines have recently been published.[3] The National Comprehensive Cancer Network (NCCN) also provides guidelines for treatment of SCCA.[7] These evidence-based guidelines provide useful guidance for clinicians treating this relatively rare cancer. Also, trials within CRT and chemotherapy are ongoing, and the established anal cancer groups and networks work to promote and enable future research resulting in a larger

knowledge base for SCCA. However, there are several important unresolved areas with respect to biology and optimal treatment of SCCA that need to be addressed by further research. The aim of this manuscript is to give a very brief overview of the evidence-base for SCCA treatment, and to highlight some of the important challenges and perspectives for future research on anal cancer.

Incidence, etiology

SCCA is a rare cancer, with an incidence of 0.5–2 new cases in 100 000 per year.[1] The incidence is increasing in Europe, the US and Australia.[1,8-10] Most SCCA are related to high-risk genotype human papilloma virus (HPV) infection.[11] Other risk factors include immunosuppression, in particular human immunodeficiency virus (HIV) infection and organ transplant recipients, or previous HPV-related cancer.[12,13] Further research into the mechanism and biology of HPV-related cancer and also of HPV-negative cancer may guide future targeted treatment options for HPV positive and possibly HPV negative SCCA (Table 1).

Vaccination against HPV is associated with a substantially reduced risk of cervical cancer.[14] However, it is anticipated that HPV vaccination will also be efficient in preventing SCCA, therefore the incidence of SCCA is expected to decrease in the future. The role of HPV vaccination in patients already diagnosed with SCCA, and the possible role of a vaccine in the treatment of SCCA is not yet clear.

Diagnosis and staging

When patients present with symptoms, the tumour is often detected by digital rectal examination and clinical assessment including palpation of the inguinal nodes. Anoscopy and/or proctoscopy is performed to evaluate the tumour extension and to enable a biopsy for histological confirmation of

squamous cell carcinoma. Assessment of p16 or HPV status of the tumour has prognostic information. A HIV test should be considered in patients with unknown HIV status. Locoregional staging is performed by magnetic resonance imaging (MRI) and/or positron emission tomography (PET)/ computed tomography (CT), and staging for distant disease by CT and/or PET/CT.[15-17] However, the role of modalities such as diffusion weighted MRI is not yet clear. Ultrasound-guided fine needle aspiration of suspicious inguinal nodes may be considered when MRI or PET/CT is not conclusive. More research is needed to define the best staging procedure, especially for lymph node staging. Uniformly accepted criteria for discrimination between malignant and benign lymph nodes are lacking, particularly when merging information from MRI and PET/CT (Table 1). Also, the optimal imaging for response evaluation, and predictive effects of MRI and/or PET/CT should be further investigated.

Chemoradiotherapy

Chemoradiotherapy (CRT) has been established as the standard of care, after the report by Nigro et al [18] and subsequent randomized controlled trials.[19-25] Three early trials established that CRT with MMC and 5-FU was superior to RT alone [19,22,25] or CRT with 5-FU (Table 2).[20] Three later randomized trials found no benefit of substituting MMC with cisplatin,[23,24] and no benefit for induction chemotherapy,[21,24] higher radiation boost dose,[21] or maintenance chemotherapy.[23] A Nordic patient series supported treatment with CRT as better than RT.[26] Addition of EGFR inhibitor increased toxicity with no signal of benefit.[27-29] Several phase II studies and patient series support that 5-FU can be safely replaced by capecitabine.[30-32]

Precision CRT has been improved by the use of anatomy-based contouring guidelines for accurate target volume selection and delineation,[33-35] which can be further updated based on detailed patterns of inguinal lymph node metastases.[36] Further refinement of precision CRT has been obtained with the use of intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), or

image-guided radiotherapy (IGRT), which can deliver high doses to tumour while sparing organs at risk and thereby reducing toxicity.[4,32,37-42] Boost to the tumour and/or involved lymph nodes can be delivered with a sequential or simultaneous integrated approach.[39]

After CRT, assessment of response is performed, and in some cases a complete response may occur as late as 6 months after commencing CRT.[43] For response evaluation, in addition to clinical examination, MRI and/or PET/CT are frequently used, although the literature on this subject is still limited. In both MRI[44] and PET/CT,[17] resolution of malignant features after CRT is associated with locoregional treatment control, whereas the ability to predict local failure needs to be improved. Biopsy has no routine role, but is useful for suspicion of treatment failure. In patients with residual tumour, or who later develop recurrence, salvage surgery results in 3- and 5-year survival rates of 55% and 40%.[45,46] The optimal follow-up protocol after CRT remains poorly defined.

Thus, the preferred treatment for stage I-III anal cancer is CRT with concomitant MMC and either 5-FU or capecitabine, delivered with IMRT or VMAT. Patients with treatment failure such as residual disease or locoregional recurrence should be considered for salvage surgery. Future research should determine the optimal radiation dose during CRT for anal cancer according to stage (Table 1). Although a previous randomized trial did not show benefit for higher radiation doses,[21] there is variability with different radiation doses used in Europe, and publications suggest that lower doses to early stage SCCA and higher doses for more advanced stage SCCA can be used,[47,48] however high level clinical trial evidence for this benefit is still required. Improved prognosis is reported with modern CRT.[5,10,49] The ongoing Cancer Research UK funded PLATO trial (ISRCTN88455282)[50] consists of 3 separate trials, the ACT 3, 4 and 5, recruiting patients with different stages of non-metastatic anal cancer, and investigates the optimal treatment intensity, with different radiation doses, to personalize radiation dose depending on risk stratification based on clinical staging and context. The clinical questions to be answered with PLATO are: a) ACT3: Do small, resected anal margin cancers require additional CRT? A recent literature review reported high recurrence rates and need for

further studies.[51,52] b) ACT4: Should patients with early stage SCCA receive lower radiation doses, relying on the fact that dose modelling suggests that lower doses may be sufficient?[47,48] In addition to the PLATO ACT4 trial, the EA2182 DECREASE trial in the US (NCT04166318) also investigates this clinical question. c) ACT5: Should patients with locally advanced disease be treated with dose-escalated RT given the substantially higher risk for locoregional treatment failure? It has been suggested that higher radiation doses can improve treatment control.[47,48] Dose escalation using IMRT may result in less treatment failures with acceptable toxicity. It has also been suggested that selective high-dose boost to regions with high SUV on PET may be feasible in clinical trials, which should be investigated.[53]

Further research should investigate novel radiation treatment options. Proton therapy may improve CRT delivery while sparing organs at risk and thereby potentially reducing late toxicity. Its role will be investigated in clinical trials, such as the Swedish SWANCA trial (NCT04462042) and the Danish trial of proton re-irradiation for anal cancer recurrences (DACG ReRad-III).

Another method to optimise treatment outcome with radiation comprises the integration of novel systemic therapy, such as addition of a PD-1 inhibitor to CRT. There is a biologic rationale for investigating the effect of PD-1 inhibition in combination with CRT, and trials are ongoing.[54,55] The EA2165 trial (NCT03233711) randomizes patients after CRT to nivolumab or observation. The CORINTH trial (NCT04046133) investigates pembrolizumab during CRT and for 6 months. The RADIANCE trial (NCT04230759) randomizes patients to standard CRT alone or in combination with durvalumab starting before CRT and administered for 1 year.[56] Translational research is important as we need to understand the immune response and effects. Areas of future research are schematically depicted in Figure 1.

Treatment may be optimised by increased understanding of tumour and microenvironment biology. A biological model describes prognosis according to HPV status and the presence of TIL.[57] The prognostic effect of tumour-infiltrating lymphocytes (TIL) in p16 positive tumours suggests a role

for the immune response.[58] Strong immune marker expression has been shown to be associated with HPV16 and predict for improved local control and disease-free survival.[59] Patients with HPV or p16 negative tumours have worse outcomes in terms of locoregional treatment failure and survival.[60-62] Future research should aim at improved treatment outcomes for patients with HPV negative tumours. A next generation of biology driven clinical trials is needed.

Other patient factors such as age and comorbidities may impact treatment options. It has been suggested to treat frail elderly anal cancer patients with low-dose CRT,[63] but further research is needed to determine the optimal treatment. Patients with HIV co-infection appear to have a worse outcome, although data is limited and often based on data of patients treated in an era prior to effective antiretroviral therapy. Until recently, many trials excluded the HIV positive population; more recently these patients have been included using separate stratification to allow comparison with the HIV negative cohort, and patient series have reported on comparable outcomes.[64-66]

Metastatic SCAA

The randomized InterAACT trial determined carboplatin/paclitaxel as first line standard of care treatment for metastatic SCAA.[6] In a single-arm phase II study, modified docetaxel, cisplatin and 5-FU (mDCF) has shown efficacy in terms of progression-free survival rates.[67] Prior to these studies, cisplatin/5-FU was recommended because of documentation from patient series, and some other chemotherapy regimens have been used, as described in reviews.[68,69]

PD-1 inhibition has shown promising activity in patients who have progressed on chemotherapy, for the PD-1 inhibitors nivolumab,[70] pembrolizumab,[71] and retifanlimab.[72] Patients with high tumour mutational burden in solid tumours seem to have a relevant tumour response to PD-1 inhibition.[73]

Several current trials investigate the use of immune check point inhibitors in combination with chemotherapy for advanced SCCA (Table 1). An ongoing US trial randomizes treatment-naïve patients to carboplatin/paclitaxel alone or with nivolumab (EA2176; NCT04444921). The international multi-centre POD1UM-303/InterAACT2 trial (NCT04472429) for patients with advanced or metastatic SCCA eligible for first-line therapy randomises patients to carboplatin/paclitaxel combined with either retifanlimab or placebo. The SCARCE trial in France (NCT03519295) randomizes patients to mDCF alone or in combination with atezolizumab.[74] In treatment refractory patients with metastatic anal cancer, patients are randomized to nivolumab with or without ipilimumab (NCI9673; NCT02314169).

Other areas of future research include the importance of HPV/p16 positivity/negativity, and the prognostic or predictive role of PD-1 expression for treatment with PD-1 inhibitors. Other possible markers for outcome should be investigated. An increased biologic understanding from translational research is important for stratification in clinical trials and to guide future trial designs.

Limited metastatic disease

There is a paucity of data regarding treatment of limited metastatic disease. However, case series have reported that patients with para-aortic lymph node metastases that can be comprised within radiotherapy treatment volumes are amenable for extended-field CRT.[75,76] Patients were mostly treated with IMRT and concomitant MMC- or cisplatin-based chemotherapy regimens. The authors described extended radiation fields to the para-aortic region, with elective treatment volumes to uninvolved pelvic and para-aortic nodes, and boost to the primary tumour and involved lymph nodes. Care was taken to minimize dose to organs at risk, however toxicity was observed, and distant metastases were the predominant pattern of relapse. Extended-field CRT was suggested as a potentially curative treatment option.[75,76] This view was supported in a recent patterns of recurrence analysis.[77] Institutional series have reported on favourable outcomes of liver resection of selected

patients with anal cancer metastases. Case series have demonstrated that surgery[78,79] or multi-modality treatment with chemotherapy and surgery or ablation can result in good outcomes.[80-82] Improved survival after hepatic metastasectomy was observed in a registry-based study, suggesting this as a treatment option for highly selected patients.[83] The potential role for stereotactic radiotherapy is not clear, nor the role of induction and/or adjuvant chemotherapy. Multi-disciplinary treatment of patients with limited metastatic disease is an area where further research is warranted, to establish treatment guidance.

Biology

SCCA is most frequently related to HPV infection, and this is generally assessed by analysing the tumour tissue for either HPV or p16.[84] Most (80-90%) of SCCA are HPV or p16 positive, and these often have PIK3CA mutations. Among HPV/p16 positive tumours, it has been shown that high rates of TIL confers better prognosis.[57,58]

In the 10-20% of cases that are HPV/p16 negative, tumours often have p53 mutations, correlating with a worse prognosis.[57,60,61] Lampejo and colleagues published a systematic review on prognostic biomarkers for anal cancer, and found expression of *TP53* to have prognostic significance.[85] In a review by Bernardi et al, this was discussed, and furthermore, the EGFR and PI3K/AKT pathways seem to be promising targets, as does the tumor-host interaction and immune-mediated mechanisms.[84]

Most SCCA express EGFR, while KRAS mutations are uncommon,[86,87] suggesting this may be another target. High expression of squamous cell carcinoma antigen was associated with reduced survival. There is a rationale to combine CRT and immune therapy, as described in a review by Martin et al.[54] In addition to the biologic rationale, radiotherapy may promote immunostimulatory effects, and a stratified approach based on HPV status and TIL expression was proposed.

There are no blood biomarkers in routine clinical use. Squamous cell carcinoma antigen has been proposed as a possible biomarker.[88] Leukocytosis and neutrophilia are prognostic factors for survival,[89,90] and similar to other tumour types, the neutrophil to lymphocyte ratio has been investigated in both primary and metastastic disease.[91,92] Other markers such as the systemic index of inflammation and baseline eosinophil level have been investigated in terms of prognostication.[93,94]

Measurement of circulating tumour DNA in different solid tumours has shown value as a marker of minimal residual disease and strong correlation to prognosis. In HPV-related squamous cell carcinomas, HPV is integrated into the tumour DNA, and is therefore a relevant marker for tumour DNA. Circulating tumour HPV DNA has a prognostic impact after CRT [95] and also seems to correlate with outcome in metastatic anal cancer treated with chemotherapy.[96] High levels of circulating free DNA before CRT were associated with risk factors and treatment failure,[97] and distinct patterns of plasma HPV elimination during CRT has been demonstrated to have prognostic impact.[98] Ongoing research will elucidate the optimal time-point for plasma HPV measurement during and after primary treatment, and the possible role as a selection tool for intensified therapy in more advanced disease. The planned NOAC9 trial will investigate the role of circulating tumour HPV DNA in follow-up.

Well known features of squamous cell carcinomas are accelerated repopulation and hypoxia, which should be further investigated in pre-clinical and clinical studies also in SCCA. In addition, there is a lack of preclinical models in SCCA.[84]

There is an urgent need for further research to increase the understanding of biology and thereby to improve treatment stratification and guide future clinical trials. The role of circulating tumour markers should be investigated.

Quality of life and late effects

Late effects of CRT for SCCA are common and may lead to impaired health-related quality of life (QOL),[99-102] such as affected anorectal[103] and sexual functions,[104] together with other QOL aspects.[101] Core outcomes for clinical trials of CRT for anal cancer (CORMAC) have been defined, including toxicity (anal incontinence, faecal urgency, pelvic fistula, stoma, skin loss) and life impact (physical function, sexual function, health-related QOL).[105] The EORTC QOL Group has developed an anal cancer specific questionnaire, EORTC QLQ-ANL27,[106] which has recently completed phase IV validation. Traditionally, late toxicity in clinical trials has mainly been presented as physician-reported measures, however studies have shown poor concordance between physician- and patient-reported outcomes.[107] Therefore it is encouraged to use the EORTC QLQ-ANL27 [106] and to assess outcomes defined by CORMAC [105] in future clinical trials. More research is needed to better understand why some patients develop severe late toxicity and others do not. Patient-reported outcome measures (PROMs) combined with detailed normal tissue complication probability (NTCP) analyses are needed with the perspective of optimal sparing of organs at risk, such as the bowel and bladder, and to reduce the risk of sexual dysfunction and pelvic insufficiency fractures.[108] Further studies are also needed with respect to the evidence-based management of different late toxicity profiles. The psychosocial impact of this disease, both at time of diagnosis and treatment, and longer term, remains understudied.

Discussion and Conclusion

Evidence-based treatment and clinical trials aimed at improving therapy can be challenging for rare cancers such as anal cancer, because of the difficulty in setting up large randomized trials. Trial design can be challenging and therefore different strategies may be considered.[109] In addition to this, there is generally a paucity of translational research performed, and thereby the biological understanding of these cancers is less understood. There is an unmet need with respect to the combination of clinical trials with translational research.

Clinicians and researchers organised an International Multidisciplinary Anal Cancer Conference (IMACC) Webinar in 2020. This IMACC webinar raised several important questions that should be considered for future anal cancer research collaborations, of which several have been discussed above. In addition, it was suggested to collect data in a prospective international database, also for studying outcomes of specific subgroups such as HIV positive patients. Other measures that should be discussed are global harmonization of clinical trial designs and outcomes, to facilitate that data from different trials can be pooled for joint analyses. In addition, research on biological features, translational studies, and clinical trials in other squamous cell cancers could guide future relevant directions for research for SCCA. The experience from the IMACC webinar was very encouraging. The first IMACC symposium is planned to be held in Århus, Denmark, November 2021.

Modern technology can offer new opportunities of data assembly. An example is the model of distributed learning, which recently was demonstrated to be feasible across three institutions for anal cancer.[110] This project is being further developed, and aims for a larger dataset and incorporating more variables.

In conclusion, multi-centre and multi-disciplinary international collaborations are strongly encouraged. In addition, all clinical trials should aim at including biobanking and translational studies to further increase biological understanding, for better treatment stratification and possibly future biology-driven clinical trials, as well as QOL and other patient-reported outcomes.

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Figure 1. Proposed future research areas for anal cancer.