THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 12

RESEARCH ARTICLE

Innovative Approaches to Non-Metastatic Anal Cancer: Bridging Today and Tomorrow

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OPEN ACCESS

PUBLISHED
30 December 2024

CITATION
Ferreira, AR., et al., 2024. Innovative Approaches to Non-Metastatic Anal Cancer: Bridging Today and Tomorrow. Medical Research Archives, [online] 12(12). https://doi.org/10.18103/mra.v12i12.6190

DOI
https://doi.org/10.18103/mra.v12i12.6190

ISSN
2375-1924

ABSTRACT

Anal cancer, although rare, has seen an increasing incidence and mortality, primarily due to high-risk sexual behaviors, HIV, and low HPV vaccination coverage. This review examines current treatment strategies for non-metastatic squamous cell carcinoma of the anus, with a focus on chemoradiation therapy (CRT) and emerging therapies. The historical and scientific basis for chemoradiation therapy using 5-fluorouracil and mitomycin C (MMC) is discussed as the standard treatment, although alternatives such as cisplatin and capecitabine show promise, particularly in settings where MMC is unavailable or when access to infusion pumps is restricted. Negative data regarding treatment intensification, induction or maintenance chemotherapy, and combinations with targeted therapies that have not demonstrated significant benefits are also reviewed. Ongoing research on immune checkpoint inhibitors presents new opportunities to improve patient outcomes. Surgical interventions may be recommended for very early disease but are usually reserved for cases of recurrence or failure after CRT. Despite challenges related to immunization efforts and high-risk behaviors, advancements in CRT and the development of novel therapies offer hope for improved outcomes with reduced toxicity.

Keywords: anal cancer, squamous cell carcinoma of the anus, chemoradiation, locoregional.

Introduction

Anal cancer is a relatively uncommon malignancy, with an estimated 55,000 new cases each year.[1] Over the past few decades, its incidence and mortality rates have steadily increased by approximately 2.7% annually.[2] This rise is largely associated to high-risk sexual behaviors, a resurgence of HIV infections, and inadequate HPV vaccination coverage.[3] However, recent data show a decline in incidence among younger populations, likely reflecting the success of HPV vaccination efforts, given that over 90% of squamous cell carcinoma of the anus (SCCA) cases are associated with persistent HPV infection.[4]

Once SCCA is diagnosed, thorough staging is essential to determine the most effective treatment. High-resolution pelvic MRI is the preferred imaging technique for local tumor evaluation, as it provides clear differentiation between the tumor and surrounding muscle layers and structures.[5] While there is no consensus on the use of FDG-PET scans, they can be valuable in assessing suspected metastatic disease in locally advanced anal cancer and in planning radiotherapy, particularly for identifying regional lymph node involvement.[6]

Most patients are diagnosed with disease localized to the primary site (47%) or lymph nodes (33%), without distant metastases.[7] Localized and locoregional SCCA is typically curable in most patients through definitive chemoradiation therapy (CRT), which avoids the morbidity associated with abdominal-perineal resection (APR).[8]

Accurate staging in anal cancer is crucial, as disease burden correlates with survival outcomes and influences treatment strategies. In the RTOG 98-11 study, tumor size and lymph node involvement were significantly linked to survival. Patients with T3-4N+ disease exhibited the poorest survival rates and higher locoregional failure rates compared to those with T2-3N0 disease. Interestingly, lower T stages with nodal involvement had outcomes similar to or better than higher T stages without nodal involvement.[9] Recent advancements in managing locoregional anal cancer emphasize tailored treatment approaches based on disease burden while minimizing both acute and long-term treatment-related toxicities.[10]

In this review, we will explore the key studies that have shaped the current definitive treatment strategies for localized and locoregional SCCA, highlighting both successful and unsuccessful alternatives aimed at improving patient outcomes, along with future perspectives in this field.

Management of local and locoregional SCCA

The treatment of anal canal tumors has evolved significantly over the past few decades, incorporating procedures that have led to improved oncological outcomes and a significant reduction in the morbidity traditionally associated with therapies.[11]

In the past, non-advanced anal canal tumors were typically treated with local or radical excision through APR. However, this approach resulted in a high rate of local recurrence, a 5-year overall survival rate of 40 to 70%,[12,13] non-negligible perioperative mortality (2.5%),[14] and a significant impact on quality of life due to the morbidity associated with colostomy.

This scenario changed significantly following the groundbreaking work of Nigro and colleagues in the 1970s. They established definitive CRT as the standard treatment, reserving surgical management as a backup plan for those who did not respond to the initial therapy. Nigro et al. shifted the paradigm by integrating 5-Fluorouracil (5-FU) and Mitomycin (MMC) into radiotherapy (RT) before performing the APR, which should take place six weeks after the completion of chemoradiotherapy (CRT). Two out of the three patients referred for surgery showed complete pathological response. However, the third patient declined the procedure and maintained a sustained clinical complete response at the time of the original publication.[15] These findings were later confirmed in a series of 45 patients with localized disease treated with RT in combination with 5-FU

(1000 mg/m² on Days 1-4 and Days 29-32) and MMC (15 mg/m² on Day 1), which demonstrated a complete response rate of 84%.[16]

Based on these findings and subsequent studies, despite the absence of randomized trials comparing surgery and CRT in this context, the use of definitive CRT with 5-FU plus MMC has become the standard treatment for SCCA. This holds true even for initial T1N0 disease, resulting in complete tumor regression in 80%-90% of cases and locoregional recurrence rates of 15%.[17,18]

This regimen has continued to be regarded as standard procedure for treatment over the past four decades, despite various attempts to examine alternative protocols which also aimed at improving survival outcomes and tolerability.[19]

CHEMORADIOTHERAPY VERSUS RADIOTHERAPY ALONE

Randomized studies demonstrate the benefit of CRT compared to RT regarding response rate (RR) and disease-free survival (DFS).

The United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC) compared concurrent RT with 5-FU and MMC versus RT alone.[20-22]

The UKCCCR study (ACT I) randomized 585 patients with SCCA or anal margin T1-T4 to RT (45 Gy) or RT combined with 5-FU 1000 mg/m² D1-4 (or 750 mg/m² D1-D5) during the first and last weeks of RT along with MMC 12 mg/m² D1.[20] Clinical response assessment was conducted 6 weeks post-RT. Patients with poor responses were referred for surgical treatment, while responders received a boost to the primary tumor site. The study demonstrated lower rates of locoregional recurrence favoring the CRT arm (36% vs 59%; relative risk 0.54, 95% CI 0.42-0.69, $p < 0.0001$), but no difference in overall survival (OS), possibly attributed to early increased deaths from non-anal canal cancer in the CRT group during the initial follow-up years.[20] A 13-year follow-up update showed the continued benefit of CRT in locoregional control, reduced risk of anal canal cancer death (HR 0.67; 95% CI 0.51–0.88; $p = 0.004$), and higher colostomy-free survival (CFS) in 5 years (47% vs 37%; $p = 0.004$) compared to RT treatment alone.[21]

Similar data were observed in the EORTC publication. In this study, patients with SCCA T3-T4N0-3 or T1-2N1-3 were randomized to RT (45 Gy with a boost of 15-20 Gy, if initial response) or the same RT regimen combined with 5-FU (750 mg/m² D1-D5 and D29-33) and MMC (15 mg/m² D1 only). The rates of locoregional control (LRC) in 5 years were higher in the CRT group (68% vs 50%; $p = 0.02$), as were with CFS of 5 years (72% vs 40%; $p = 0.02$) and complete response rate (CCR) (80% vs 54%). As with the ACT I study, no differences were found in OS.[22]

WHAT IS THE OPTIMAL CRT REGIMEN IN NON-ADVANCED DISEASED?

Once the role of CRT in the definitive treatment of anal canal tumors was established, efforts were made to determine whether alternatives to the concurrent RT regimen with 5-FU and MMC could optimize oncological outcomes and potentially reduce early and/or late treatment toxicities. Table 1 summarizes studies on the treatment of localized/locally advanced disease.

The RTOG 87-04 study, despite demonstrating higher toxicity, confirmed the role of adding MMC to CRT with 5-FU in the curative treatment of localized SCCA.[23] A total of 310 patients with any tumor (T) or nodal (N) stages, M0, were randomized to standard CRT with 5-FU (1000 mg/m² D1-4 and D29-32) and MMC (10 mg/m² D1 and D29) or CRT with 5-FU only. After 4-6 weeks post-treatment, a biopsy of the primary tumor was recommended. If residual disease was present, patients received rescue CRT based on 5-FU and cisplatin (CDDP).[23] The 4-year DFS was significantly worse with the omission of MMC (51% vs 73%; $p = 0.0003$), as was the 4-year CFS (59% vs 71%; $p = 0.014$). Colostomy rates were also significantly higher with 5-FU alone (23% vs 9%; $p = 0.002$). There was no statistical difference

in biopsy negativity after treatment (92% in the 5-FU/MMC group vs 86% in the 5-FU group; p = 0.135) or OS (p = 0.31). Notably, the addition of MMC significantly increased grade 4 acute toxicity (23% vs 7%).[23]

Despite conflicting studies, CDDP can be considered a safe and effective alternative to MMC, particularly in regions where MMC availability is limited.[9,24-26]

The phase III RTOG 98-11 study evaluated the role of CDDP as a substitute for MMC and the use of induction chemotherapy (CT). Patients with T2-4, N0-3 were randomized into two arms: standard treatment with CRT using 5-FU (1000 mg/m² days 1-4 and 29-32) and MMC (10 mg/m² days 1 and 29) or induction CT with 5-FU plus CDDP for two cycles, followed by concomitant RT with the same CT regimen.[9] The use of MMC was associated with lower colostomy rates at three years (10% vs 16%; p = 0.02), with no differences in 3-year DFS or 3-year OS.[25] However, long-term follow-up showed better DFS at five years (67.8% vs 57.8%; p = 0.006), OS (78.3% vs 70.7%; p = 0.026), and a slight difference in CFS of 5 years (71.9% vs 65%; p = 0.05) for patients treated with MMC. Differences in locoregional failure rates (20% vs 26%; p = 0.087) and colostomy rates (12% vs. 17%; p = 0.074) did not reach statistical significance.[9]

Table 1. Clinical trials in locally advanced disease.

Study	Phase	Population (n)	Treatment Arms	Locoregional outcomes	DFS	OS
ACT I[20]	III	T1-T4 NxM0 (585)	Arm 1: RT Arm 2: 5FU/MMC/RT	Decreased LF with CRT: 36% x 59%; p < 0.0001		Decreased 3-year anal cancer mortality (28% x 39%); p = 0.02 No difference in 3-y OS; p = 0.25
EORTC 22861[22]	III	T3-T4;N1-N3 (110)	Arm1: RT Arm2: 5FU/MMC/RT	Improved 5-y LRC with CRT: 50% x 68%; p = 0.02 Improved 5-y CFS with CRT: 40% x 72%; p = 0.02	Improved 5-year PFS with CRT p=0.05	No difference in 5-y OS; p = 0.17
RTOG 87-04[23]	III	Any T or N stage (310)	Arm 1: 5FU/RT Arm 2: 5FU/MMC/RT	Improved 4-y CFS with MMC MMC: 59% x 71%; p = 0.014	Improved 4-y DFS with MMC: 51% x 73%; p = 0.0003	No difference in 4-y OS; p = 0.31
RTOG 98-11 [9,25]	III	T2-4, N0-3 (682)	Arm 1: 5FU/MMC/RT Arm 2: induction 5FU/CDDP x 2 5FU/CDDP + RT (starting on day 57)	No difference in 5y-LF; p = 0.087 5-y CFS: 71.9% (arm 1) x 65% (arm 2); p = 0.05	Improved 5-y DFS in arm 1: 67.8% x 57.8%; p = 0.006	Improved 5-y OS in arm 1: 78.3% x 70.7%; p = 0.026
ACT II[26]	III	T1-T4, any N stage (940)	Arm 1: 5FU/MMC/RT Arm 2: 5FU/CDDP/RT Second randomization (+/-maintenance 5FU/CDDP x 2)	No difference in 26-weeks cCR; p = 0.64	No difference in 3-y DFS	No difference in 3-y OS

ACCORD 03[39]	III	T ≥ 4 cm; N1-3M0 (307)	Arm A: ICT (5FU/CDDP) + 5FU/CDDP/RT SD Arm B: ICT (5FU/CDDP) + 5FU/CDDP/RT HD Arm C: 5FU/CDDP/RT SD Arm D: 5FU/CDDP/RT HD	No difference in 5-y CFS, 5-y LRC for arm A+B vs C+D or arm A+C vs B+D comparisons		
VITAL[45]	II	T2-T4, any N,M0 (58)	5FU/MMC/Panitumumab/RT	3-y CFS 68.1% 3-y LRC 64.8% cCR 81.0%	3-y DFS 61.1%	3-y OS 78.4%

Abbreviations: LRC, Locoregional control; CRT, Chemoradiotherapy; RT, Radiotherapy; LF, Local Failure; CFS, Colostomy free survival; cCR, Complete clinical response; DFS, Disease free survival; OS, Overall Survival; PFS, Progression free survival; MMC, Mitomycin; 5FU, 5-fluorouracil; CDDP, Cisplatin; ICT, Induction chemotherapy; SD, Standard dose boost; HD, High dose boost

Several hypotheses may explain the detrimental effect of induction CT, including the greater radiosensitizing effect of MMC, the prolonged time to initiation of CRT in the experimental treatment arm, and potential radioresistance induced by platinum before CRT. An important limitation of this study is that both interventions (induction CT and the use of CDDP) occurred in the standard treatment arm, making it difficult to analyze the effects of induction CT and CDDP-based CRT.[9]

The factorial 2x2 study ACT II randomized 940 patients with non-advanced SCCA to compare CRT with 5-FU (1000 mg/m² D1-4 and D29-32) plus CDDP (60 mg/m² D1 and D29) against CRT with 5-FU (1000 mg/m² D1-4 and D29-32) plus MMC (12 mg/m² D1).[26] After completing CRT, patients were further randomized to receive 2 cycles of maintenance CT with 5-FU plus CDDP or observation only. In this study, CRT with 5-FU/CDDP did not yield better outcomes than CRT with 5-FU/MMC. There were no significant differences in cCR at 26 weeks (90.5% vs 89.6%; p = 0.64) or in DFS between patients receiving MMC or CDDP during CRT (p = 0.63) or in progression-free survival (PFS) of 3 years with maintenance CT (p = 0.70). No differences were noted in CFS or OS, regardless of the maintenance or CRT regimen. Similar rates of acute grade 3 or 4 adverse effects were observed between MMC and CDDP (71% vs 72%), though there was a higher incidence of hematological events in patients treated with MMC (26% vs 16%; p < 0.001).[26]

Hence, when considered collectively, this information indicates that: there is no place for maintenance CT in non-advanced SCCA; CRT with 5-FU plus MMC remains the standard treatment; and the combination of 5-FU plus CDDP can be considered an alternative when MMC is unavailable or in patients with low tolerance to this drug. Both combinations of CRT are included in the guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO).[17,18]

Available data on the use of other chemotherapeutic agents in the treatment of SCCA are limited.

Capecitabine (Cap) has been increasingly used as a substitute for 5-FU in gastrointestinal tumors, including gastric and colorectal cancers, revealing its safety and comparable efficacy.[27-29] In localized/locally advanced SCCA, there is no phase III data supporting the use of Cap as a replacement for 5-FU; however, available retrospective and phase II studies show comparable rates of complete response and locoregional control to the standard treatment.[30-33] (Table 2)

Table 2. Role of capecitabine as part of CRT treatment in patients with non-advanced anal canal tumors.

Study	(n)	Protocol	Locoregional control (LRC)	Complete response	Grade 3-4 Toxicities
Oliveira et al[30] phase II	43	Cap 825 mg/m2 bid during RT + MMC 15 mg/m2 D1	86% (FU 6 mo)	86% (FU 6 mo)	23.2% (G3 dermatitis) 11.6% (G3 lymphopenia)
EXTRA[31] phase II	31	Cap 825 mg/m2 bid during RT + MMC 12 mg/m2 D1	90% (FU 6 mo)	90% (FU 6 mo)	38.7% (G3 dermatitis) 9.6% (G3 Neutropenia)
Peixoto et al[32] retrospective study	300	Cap/MMC + RT vs 5FU/MMC + RT	2-y DFS: 79.7% (Cap/MMC + RT) x 78.8% (5FU/MMC + RT)	-	-
Meulendijks et al[33] retrospective study	105	Cap/MMC + RT vs 5FU/MMC + RT	3-y LRC: 79% x 76% (Cap vs 5FU; p = 0.690)	89.6% x 89.1% (Cap vs 5FU), 3 weeks after treatment	31% x 13% (G3 dermatitis, Cap vs 5FU)

Abbreviations: Cap, Capecitabine; MMC, Mitomycin; 5FU, 5-fluorouracil; CRT, Chemoradiotherapy; DFS, Disease Free Survival; FU, Follow-up; Mo, Months

A recent prospective cohort evaluated the efficacy and safety of CRT with Cap 825 mg/m² BID during RT plus CDDP 60 mg/m² on days 1 and 29 in patients with T2-4, N0-3. After six months, complete and partial response rates were observed at 55% and 22.5%, respectively, but with a high incidence of grade 3-4 toxicity (27.5%), primarily radiodermatitis.[34] Thus, this combination represents an alternative for the definitive treatment of non-advanced anal canal tumors, especially in underdeveloped countries with restricted access to MMC and infusion pumps, but requires careful monitoring for adverse events.

While some small studies indicate a potential benefit of induction CT,[36,37] others suggest a likely detrimental effect of this strategy.[9,25,38,39] After a median follow-up of 50 months, results from the French phase III randomized study ACCORD 03 showed no benefit of induction CT with 5-FU plus CDDP on 5-year CFS (76.5% induction vs 75% non-induction; p = 0.37) or OS.[39] Therefore, collectively, these findings indicate that both induction and maintenance therapies do not improve oncological outcomes compared to standard CRT alone and are not recommended.[40]

A treatment intensification strategy combining triple therapy (5-FU plus MMC plus CDDP) with RT was found to be excessively toxic (89% grade 3-5 toxicities) in a multicenter phase II study and should not be recommended.[41]

Initially promising approaches that later failed include the use of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR). EGFR is known to be expressed in up to 80-90% of SCCA, and K-RAS mutations predictive of resistance rarely occur in this pathology.[42] Two phase II non-randomized studies, E3205 and AMC045, incorporated Cetuximab into a CRT regimen based on 5-FU plus CDDP in immunocompetent patients and those with HIV, respectively.[43,44] In both studies, patients with stage I-III SCCA received CDDP, 5-FU, and Cetuximab in combination with RT. In the E3205 study, patients also received induction with two cycles of 5-FU and

CDDP prior to CRT,[43] a strategy halted after the results of RTOG 98-11.[9] Similar locoregional recurrence rates were observed at three years (21% in E3205 and 20% in AMC045), with significant grade 4 toxicity due to the addition of Cetuximab (32% in E3205 and 26% in AMC045, respectively).[43,44]

Similar findings were observed in the phase II VITAL study. CRT with 5-FU plus MMC and panitumumab resulted in grade 3-4 adverse event rates in 94.8% of patients and a three-year DFS rate below expectations (61.1%).[45]

Therefore, in light of the lack of clear benefit in locoregional control and the significant side effect profile, the addition of EGFR inhibitors to standard CRT should not be recommended for the definitive treatment of non-advanced SCCA at this time.

ROLE OF SURGERY IN LOCALIZED DISEASE

With the incorporation of CRT into the treatment of SCCA tumors, surgical management of this condition has become limited to a few indications in early disease. When indicated, it has shifted from APR to local excision or ablation. APR is now reserved for salvage therapy if tumor persistence occurs or recurs after definitive initial treatment.[46]

Due to screening policies for anal canal tumors in high-risk populations and other scenarios, there has been an increase in the incidence of these early lesions, leading to more frequent recommendations for local excisions.[47]

Despite the lack of randomized data, local excisions may be indicated, particularly in two situations: well-differentiated T1N0 epidermoid carcinomas of the anal margin; and selected cases of T2N0 tumors without involvement of the anal sphincter.[18] Both conditions can be treated with wide local excision as long as safety margins of 1 cm are maintained. Local excision of T1 tumors has been associated with favorable outcomes and low complication rates. In a retrospective series of 57 T1N0M0 patients, there were no differences in 5-year DFS between individuals treated with local excision (91%) and those treated with CRT (83%) (p = 0.57).[48] Another retrospective cohort compared 5-year OS in 2,243 T1N0M0 patients treated with local excision or standard CRT, confirming the equivalence of these two strategies in this subgroup of patients (85.3% for local excision vs 86.8% for CRT; p = 0.93).[47]

Secondly, superficially invasive tumors eligible for complete excision, with invasion of the basement membrane ≤ 3 mm and maximum horizontal extension ≤ 7 mm, without lymphovascular invasion and negative margins, can also be treated with local excision. In cases of inadequate margins or R1 resection, a new local excision should be considered, provided that the R0 resection can be achieved.

It is recommended that all cases of patients undergoing initial local resection be discussed by an appropriate multidisciplinary team,[49] especially in high-volume centers, to facilitate decisions regarding further surgical intervention, local RT, or definitive CRT.[50] It is important to note that recurrence rates after local treatment are not infrequent. Therefore, close clinical follow-up with anoscopy is necessary after initial treatment to detect local recurrences.[46]

Future perspectives on localized disease

Despite advancements in treatment, there are several knowledge gaps in the management of non-advanced SCCA, such as the development of biomarker-driven therapies and the need to define the optimal CRT/RT regimen to reduce treatment-related toxicities. The PLATO study (Personalizing Anal Cancer Radiotherapy Dose) (International Standard Randomized Controlled Trial [ISRCT] number ISRCTN88455282) includes three studies (ACT3, ACT4, and ACT5) and is evaluating the optimization of CRT/RT for non-advanced SCCA based on recurrence risk .[51]

Preclinical data indicate that anti-PD-1/PD-L1 therapies act synergistically when combined with RT in the management of non-advanced disease.[52] This is a major area of interest and encompasses

efforts in localized disease treatment, with studies involving several immune checkpoint inhibitors (ICI) both in the concurrent setting with CRT and as adjuvant therapy for high-risk recurrence tumors. Another promising strategy, already in development for other tumors, is the evaluation of ctDNA in monitoring HPV+ patients compared to standard follow-up for early recurrence detection. Table 3 includes some ongoing clinical studies in non-advanced SCCA.

Table 3: Ongoing studies in local/locally advanced disease.

Study NCT Identifier	Phase	Population	Treatment Arms	Primary endpoint	Status
CORINTH NCT04046133	Ib/II	Stage IIIA or IIIB (T3-4Nx M0)	Pembrolizumab + CRT	Safety/Tolerability	Unknown
INTERACT-ION NCT04719988	II	TxN1 or T4N0	Ezabenlimab + mDCF + RT	cCR at 10 mo	Active, not recruiting
EA2165 NCT03233711	III	High Risk Stage II-IIIB	5FU/MMC+RT or Cap/MMC+RT or 5FU/Cisplatin+RT Randomization Arm A: Nivolumab 480 mg IV every 4 weeks Arm B: Observation	DFS	Active, not recruiting
AMC110 NCT04929028	II	T3-T4N0M0 or T2-4N1M0	Low-risk stratum: De-intensified CRT (20 or 23 fractions) High-risk stratum: Nivolumab every 4 weeks x 6 cycles after CRT	Incidence of adverse events	Recruiting
RADIANCE NCT04230759	II	Stage IIB-IIIC	5FU/MMC+RT vs 5FU/MMC/Durvalumab+RT	DFS	Active, not recruiting
NCT05060471	II	Stage I-III	Neoadjuvant toripalimab, Docetaxel and Cisplatin followed by Toripalimab + RT	cCR at 3 Mo	Enrolling by invitation
DECREASE NCT04166318	II	T1-2NM0 anal canal or anal margin ≤ 4 cm	Standard-dose CRT (28 fractions) vs De-intensified CRT	DCR in the de-intensified CRT arm	Recruiting
TIRANUS NCT05661188	II	Stage I-IIIB, except Stage I anal margin	Tiragolumab + Atezolizumab + CRT followed by maintenance of Tiragolumab + Atezolizumab x 6 cycles	cCR and cCR rate at week 26	Recruiting
NOAC9 NCT05572801	NA	SCCA eligible for definitive therapy	No Intervention - Arm A: HPV (+) SOC FU Experimental - Arm B: HPV (+) ctDNA guided imaging in FU No Intervention - Arm O: HPV (-) observational arm	DFS	Recruiting

Abbreviations: CRT, Chemoradiotherapy; mDCF, modified docetaxel, cisplatin, 5-fluorouracil; RT, Radiotherapy; cCR, Clinical complete response; Mo, Months; 5FU, 5-fluorouracil; MMC, Mitomycin; Cap, Capecitabine; DFS, Disease Free Survival; DCR, Disease Control Rate; NA, Not Applicable; SCCA, Squamous cell carcinoma of the anus; SOC, Standard of care; FU, follow-up
NCT: Available at:https://clinicaltrials.gov/ Accessed September 26, 2024

Conclusion

As many individuals remain inadequately immunized against HPV and continue to engage in risk factors such as smoking and high-risk sexual behaviors, advances in anal cancer treatment are essential. Definitive CRT with 5-FU or Cap plus CDDP or MMC remains the gold standard. So far, efforts to intensify treatment or combinations with anti-EGFR therapy have not demonstrated significant benefits. Surgery should be considered only for small, well-differentiated early lesions without involvement of the anal sphincter. Moving forward, risk stratification should inform new treatment guidelines, allowing for the de-escalation of drug regimens and radiation doses for less advanced tumors, thereby sparing patients unnecessary toxicities, while integrating ICIs in conjunction with or sequentially to CRT for higher-risk cases.

All authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and agree to its submission to the Journal.

Declarations of interest:

none.

Financial support:

none to declare.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Warnings:

The opinions expressed in the report presented are those of the authors and do not necessarily represent the official position of the institution to which they belong.

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