ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Anal Cancer in the Era of Dose Painted Intensity Modulated Radiation Therapy: Implications for Regional Nodal Therapy

Colton Ladbury, BS, Karyn A. Goodman, MD, Tracey E. Schefter, MD, and Jeffrey R. Olsen, MD

Since the initial development of 5-fluorouracil and mitomycin as a standard of care platform for definitive anal cancer chemoradiotherapy, multiple studies have evaluated the optimal chemotherapy regimen, and radiotherapy technique. Refinements in treatment technique have taken place during an era of improved diagnostic imaging, including incorporation of FDG-PET, with implications for a possible stage migration effect. This has introduced an opportunity to develop stage-specific recommendations for primary tumor, involved nodal, and elective nodal irradiation dose. Elective nodal irradiation remains standard given the low rates of elective nodal failure with current practice, although may be subject to evolving controversy for patients with early stage disease. In this review, development of the current standard of care for anal cancer chemoradiotherapy is reviewed in the context of modern staging and dose-painted radiotherapy treatment techniques.
Semin Radiat Oncol 29:137–143

Background

Since initial implementation in the 1970s, variations of a regimen consisting of 5-fluorouracil (5-FU), mitomycin, and radiotherapy, which came to be known as the Nigro protocol, have proven to be quite effective and enduring as the standard-of-care therapy for anal canal cancer. Due to the efficacy of this regimen, a primary surgical based treatment approach has been supplanted by definitive chemoradiotherapy. Derivatives of 5-FU and mitomycin continue to be the chemotherapy agents of choice due to unsurpassed outcomes. However, in an effort to increase efficacy and decrease radiotherapy toxicity, treatment techniques have continued to evolve as new imaging and treatment modalities have developed. This article provides an overview of diagnostic and therapeutic changes in anal cancer chemoradiotherapy, in the context of the requirement for, and techniques of regional nodal irradiation.

Development of 5-FU and Mitomycin As a Standard of Care

Prior to the implementation of chemoradiotherapy, a surgical approach was considered standard treatment for anal cancer, with wide-local excisions for very limited early stage disease and abdominoperineal resection (APR) recommended for more advanced disease. In comparison to prior reports of radiation alone, surgical outcomes were relatively good, particularly in early stage disease that was amenable to wide-local excisions[1–4] (Table 1). However, there were high levels of both locoregional and distant recurrence, even in the setting of APR. This relatively high recurrence rate despite patients undergoing an extensive surgery, was hypothesized to be partially attributable to pelvic or inguinal nodal involvement that was not addressed by surgery or radiotherapy given treatment technique often directed at the primary tumor alone. It was therefore essential to develop a more regional treatment to reduce recurrence risk while maintaining acceptable toxicity.

Nigro Protocol As Current Standard of Care

The protocol consisting of 5-FU, mitomycin, and radiation was first investigated in a small case series by Nigro et al in 1971.[5] The study described the treatment of 3 patients with 30 Gy given in 2 Gy fractions over 3 weeks, 25 mg/kg 5-FU infused over 5 days starting on the first day of radiation, and 0.5 mg/kg of mitomycin infused as a bolus on the first day of radiation. Two of these patients underwent APR 6 weeks after completion of chemoradiotherapy with dissection of

Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO

Address reprint requests to Jeffrey R Olsen, MD, Department of Radiation Oncology, University of Colorado School of Medicine, 1665 Aurora Court, Room 1032, Aurora, CO. E-mail: Jeffrey.R.Olsen@ucdenver.edu

https://doi.org/10.1016/j.semradonc.2018.11.004
1053-4296/

Table 1 Outcomes of Surgical Management of Anal Carcinoma

	Treatment Received (%)				5-Year Survival (%)			Recurrence Following APR (%)		
	WLE	APR	Radiation	Other	WLE	APR	Radiation	Local	Inguinal	Distant
Hardcastle (n = 127)	6.3	65.4	15.0	13.3	75.0	48.2	31.6	27.9		24.6
Boman (n = 188)	10.1	62.8	6.4	20.7	72.2		N/A	27.1	12.7	9.3
Beahrs et al (n = 177)	14.4	54.8	8.9	21.9	83.3	60.7	18.2	19.7	N/A	N/A
Golden et al (n = 1060)	12.6	45.9	7.3	34.2	65.0	47.6	26.0	N/A	N/A	N/A

Abbreviations: APR, abdominoperineal resection; WLE, wide-local excision.

affected inguinal lymph nodes. A pathologic complete response was observed in both patients, and at 14-month follow-up, there was no evidence of recurrence in the patient who did not undergo surgery.

Due to the promise of this regimen, Nigro's group treated 10 more patients with the aforementioned regimen. In all the patients, the size of the lesions decreased by at least 50% following treatment, with 60% of the tumors disappearing clinically.[6] As per the previous series, nine of the patients underwent resection, with 6 specimens showing no evidence of disease on pathologic examination. The patient who did not undergo resection had no evidence of disease on biopsy. The study group was therefore expanded, and Nigro reported 2 more studies, with 28 and 45, patients respectively. These studies produced a disease-free survival (DFS) of 78.6% and 84.0%.[7,8] Proctitis, leukopenia, and neutropenia occurred, but no long-term deficits were associated with side effects. The success of the protocol was replicated by Newman and Quan, with similar outcomes and toxicity.[9] The phase II RTOG 8314 study further examined definitive chemoradiotherapy with 5-FU and mitomycin, and reported overall survival (OS) of 74% and DFS of 61% with favorable preservation of sphincter and sexual function.[10] Given demonstrated efficacy, a sphincter sparing approach was established as the standard of care.

Role of Chemotherapy

The requirement for concurrent chemotherapy was subsequently studied in 2 major randomized controlled trials, the UKCCCR Anal Cancer Trial and EORTC trial 22,921. The UKCCCR trial evaluated the benefit of 5FU and mitomycin with radiation therapy.[11] Despite no significant difference in OS, with a median follow-up of 42 months, combined radiation and chemotherapy had a 0.54 RR for local failure, and a 0.71 RR for death compared to radiation alone. Although chemoradiotherapy had higher acute morbidity, there was no difference in late effects between the arms. Follow-up at 12 years showed a 25.3% decrease in loco-regional recurrence (LRF) and a 12.5% decrease in anal cancer-related death.[12]

The EORTC trial also showed superiority of chemoradiotherapy, with DFS of 80% and 54% for chemoradiotherapy and radiation alone respectively, and an 18% improvement in locoregional control with a 26% reduction in risk of death.[13] The combined regimen was well tolerated, although an increased rate of anal ulcers was observed for the chemoradiotherapy arm. These data suggest that chemoradiotherapy leads to superior outcomes with acceptable toxicity, although there is evidence that suggests the benefits do not extend as much to patients with early stage disease. Touboul et al showed a 73.7% 10-year survival rate in patients with node-negative disease treated with radiation alone, with overall survival significantly improving when tumors were smaller than 4 cm.[14]

Specific Role of Mitomycin and 5-FU

Due to associated toxicity and in an attempt to reduce the number of chemotherapy drugs used, the importance of mitomycin was examined in RTOG 8704, which compared 5-FU, mitomycin, and radiation to 5-FU and radiation.[15] This study demonstrated that mitomycin was essential for maximizing outcomes. At 4-year follow-up, the arm that included mitomycin had significantly improved DFS and colostomy-free survival. As expected, overall toxicity was greater in the arm that included mitomycin, but given the superior results it produced, it continued to be included in the standard-of care.

In a further attempt to eliminate the need for mitomycin and increase DFS, several subsequent studies investigated using cisplatin in place of mitomycin. Initial results from Doci et al showed promise, with similar toxicity and efficacy and an improved locoregional recurrence rate.[16] However, the regimens were compared in RTOG 9811 using an induction chemotherapy technique for the cisplatin arm. At 8-year follow-up, the mitomycin arm had significantly better DFS as well as OS and an insignificant improvement in loco-regional failure.[17]

The ACT II trial further examined replacing mitomycin with cisplatin in a 2 × 2 design that also assessed the role of maintenance cisplatin.[18] Use of cisplatin, or addition of maintenance therapy did not yield a significant improvement in terms of survival and had a similar toxicity profile (improved grade 3/4 hematologic toxicity but no difference in neutropenic sepsis). Given additional resources required for cisplatin administration compared to mitomycin, inclusion of mitomycin remained standard of care and continued

to be a component of the standard chemotherapy regimen. In the last decade results have been published from studies that investigated substituting capecitabine for 5-FU. The rationale behind the change is largely one of convenience, as capecitabine is a prodrug of 5-FU that can be administered orally rather than intravenously.[19] Clinical response has been shown to be equivalent between the 2 regimens, with no significant difference in LRC and OS, with lower hematologic toxicity suggested for capecitabine.[20] A subsequent study by Goodman et al showed a significant absolute reduction of grade 3+ hematologic toxicity by 32% and associated treatment interruptions by 26%.[21] As such, capecitabine is considered a suitable alternative to 5-FU in the chemotherapy regimen for anal canal cancer and could yield improved outcomes.

Evolution of Radiation Therapy Technique

The historical pelvic field for anal cancer was delivered with an AP-PA technique with a superior border at the L5/S1 and a cone down after 30.6 Gy bringing the superior border to the bottom of the SI joints, lateral borders 1.5-2 cm outside the pelvic brim that included inguinal lymph nodes, and an inferior border 3 cm below the tumor or anal verge.[22]

Das et al reported that of the patients who developed loco-regional recurrence with this technique, 75% of recurrences were at the anus or rectum, 21% were in the presacral or iliac area, and 4% were in the inguinal area. All of the patients with presacral or iliac recurrences were treated with superior borders at the bottom of the SI joints, which suggested a benefit of more completely covering the pelvis to decrease the risk of loco-regional recurrence. A subsequent report by Wright et al further supported the primary tumor being at the greatest risk of failure, while highlighting the requirement for inclusion of all pelvic nodal groups in the radiotherapy field given the pattern of regional failure observed.[23] Peiffert et al investigated the use of dose intensification of the boost, with 45 Gy initial treatment and a 15-20 Gy boost to involved areas.[24,25] Initially, there was a 96% complete response rate and at 3-year follow-up, DFS was 67%.

These data suggested a benefit to radiation dose escalation to the primary tumor higher than that given by Nigro et al and Doci et al. Investigation into optimal radiation dose found 55 Gy to improve OS and local control rates compared to doses below 52 Gy.[26] That conclusion was supported by Huang et al who showed that patients who receive at least 54 Gy within 60 days have an LRF rate of 11% vs 58% in those who received lower doses or more prolonged courses.[27] Dose escalation was not associated with increased toxicity and there was no noticeable difference in preservation of sphincter function. Further investigation into the utility of higher doses was undertaken with a split-course regimen, with a total dose of 59.6 Gy given with a 2-week rest period in the middle in an attempt to mitigate the increased acute toxicity associated with the higher radiation dose. This regimen did not offer any improvement in local control compared to dosages of 50.4 Gy, suggesting if higher doses were to have any positive impact on outcomes, they need to be tested when given as a continuous course, with acceptance of greater acute toxicity.[28]

Based on 30 years of pooled data from Myerson et al, conventional chemoradiotherapy given in a dose escalated, continuous, manner was associated with 28.3% and 24.7% of patients experiencing grade 3 or greater acute and chronic complications, respectively.[29] Specifically, 11.3%, 7.2%, and 2.6% of patients experienced hematologic toxicity, soft-tissue toxicity, and lymphedema or lymphangitis, respectively. Although favorable treatment efficacy was established, efforts shifted toward mitigation of the known toxicity risk.

Current Standard of Care for Anal Irradiation and Elective Nodal Irradiation

Intensity-modulated radiation therapy (IMRT), a modality that was able to produce more conformal radiation delivery came into use at the beginning of the 21st century and has since become the preferred radiation technique for treating anal cancer. IMRT can provide similar coverage of planned target volumes when compared with conventional techniques, with a greater ability to spare organs at risk.[30] The clinical utility of IMRT at reducing toxicity was evaluated by Kachnic et al in the phase II RTOG 0529 study, which established IMRT with a simultaneous integrated boost as a current standard of care for definitive chemoradiotherapy for anal cancer.[31] This study sought to compare toxicities associated with IMRT compared to the control arm used in RTOG 9811. Although there was no change in rates of grade 2+ gastrointestinal and genitourinary toxicity compared to RTOG 9811, IMRT led to improvements in grade 2+ hematologic, grade 3+ gastrointestinal, and grade 3+ dermatologic toxicities. Although target delineation was recommended according to published RTOG consensus guidelines, the study highlighted challenges in target delineation and treatment planning, given that 81% of patients required replanning based on initial central review.[32]

Long-term follow-up (median of 7.9 years) of RTOG 0529 showed no significant difference in DFS, LRF, and OS in RTOG 0529 compared to RTOG 9811.[33] However, it maintained improvements in acute toxicity and similar rates of late toxicity. On a more specific analysis of data from RTOG 0529 by Olsen et al, GI toxicities trended toward statistical significance based on increasing small bowel dose and anterior pelvic contents dose, and are therefore important contributors to planning constraints, which further attests to the impact of the improvements associated with IMRT.[34]

As a result, current NCCN guidelines for the radiation planning and treatment of anal cancer are based on RTOG-0529.[35] The initial radiation volumes should have a superior border of at least L5-S1, an inferior border of the anus and tumor with at least a 2.5 cm margin, and lateral borders including lateral

inguinal nodes, with an attempt to spare the femoral heads as much as possible. PET/CT should be considered to aid in treatment planning by helping to identify subclinical areas of disease. In attempts to mitigate toxicity, women should be considered for vaginal dilators for mitigation of vaginal stenosis, and all patients should be counseled about the risk of infertility, including banking of reproductive material. More detailed contouring guidelines are specified in the RTOG Consensus Atlas for anorectal cancer.[32]

Effect of Stage Migration

Advances in imaging, namely the development of FDG-PET/CT, has led to better detection of regional and metastatic disease for newly diagnosed patients with anal cancer. In a review of twelve studies, PET/CT scans were far more sensitive to detecting primary anal cancer compared to CT (99% vs 60%, respectively).[36] Further, compared to conventional imaging PET upstaged 15% and down-staged 15% of nodal disease. The utility of PET/CT also extends to post-treatment imaging, with improved outcomes noted for patients who achieve a complete metabolic response.[37] This has implications for both monitoring as well as consideration for additional therapy.

Improvements in disease staging mandate consideration of stage migration or the "Will Rogers" phenomenon when comparing treatment results across different eras. The "Will Rogers" phenomenon is a paradoxical improvement in stage-specific prognosis without outcomes themselves changing, which can be attributed to changing criteria for stage classification.[38] Patients now have the potential to be assigned a higher stage than they would have prior to the introduction of such imaging advancements, when they would be staged on clinical assessment, and staging criteria that had not incorporated diagnostic advances. These patients, with effectively higher staged disease, appear to have improved outcomes as their equivalent outcomes are assigned to higher stages. Stage migration has likely been present in anal cancer, with lymph node positive disease appearing to increase from a rate of 15.3% in 1980 to 37.1% in 2012 in a review of 62 studies containing over 10,000 patients.[39] As a result, a higher proportion of patients with anal cancer are upstaged due to improved detection of node positive disease despite the true incidence of node-positive disease not actually increasing.

This also has the consequence of increasing false-positive rates, which may lead to over-treatment. In one series, PET/CT was responsible for changing the TNM stage of 41% of patients. In another study PET/CT and CT detected nodal disease in 19.5% of pelvic nodes while CT detected only 9.8%.[40] Additionally, CT had false positives in 12.2% of cases. PET/CT identified suspicious nodes in the groins of 20% of patients who were normal on CT and in 23% with normal appearance on physical examination. Furthermore, 17% of groins that appeared normal on physical exam and CT were positive on PET/CT. Overall, 25% of patients who had no groin involvement on CT were upstaged by PET/CT. Thus, although the introduction of PET has a risk of contributing to stage migration in long-term outcomes comparisons, its use may significantly impact the initial evaluation and planning of patients.

The most-recent edition of the AJCC staging manual takes steps to address stage migration with updated nodal staging. In the newest edition, external iliac lymph nodes are included in the staging criteria. Additionally, N2 and N3 categories are removed, with more-extensively-detected nodal disease included as a N1 classification. Perianal skin cancers additionally are staged similar to cancers of the anal canal. A comparison of the criteria and nodal staging modified from the seventh and eighth editions of the AJCC staging manual can be found in Table 2.[41,42]

Impact of Improved Staging Sensitivity on Requirement for Elective Nodal Irradiation

Improvements in detection of regional nodal disease also have implications regarding the requirement for elective nodal irradiation (ENI). In theory, radiation fields may be able to be reduced or eliminated if FDG-PET/CT imaging is negative, knowing that a possible risk of subclinical disease may remain. Given the very low risk of nodal failure when ENI is included, elimination of ENI in the context of definitive treatment requires careful study.

Such a concept has been evaluated retrospectively in T2N0 anal cancer. Zilli et al evaluated outcomes of patients undergoing definitive chemoradiotherapy or radiation alone, with analysis of outcomes based on inclusion of elective inguinal nodal radiotherapy (INRT).[43] None of the patients who received INRT developed inguinal recurrence, while 4.7% of patients who did not receive INRT developed inguinal recurrence. The relatively low risk of inguinal recurrence is within a range of risk where some patients may find omitting ENI to be a justifiable choice. There was no significant

Table 2 Guidelines for Nodal Staging Adapted From AJCC Manuals

AJCC 7th Edition
Regional lymph nodes include: perirectal, lateral sacral, internal iliac (hypogastric), inguinal
N0—no lymph nodes
N1—perirectal lymph nodes
N2—unilateral internal iliac or (unilateral) inguinal lymph nodes or both
N3—perirectal AND inguinal lymph nodes; and/or bilateral internal iliac; and/or (bilateral) inguinal lymph nodes
AJCC 8th Edition
Regional lymph nodes include: mesorectal, inguinal (superficial, deep), superior rectal (hemorrhoidal), external iliac, internal iliac (hypogastric)
N0—no regional lymph node metastases
N1a—inguinal, mesorectal, or internal iliac lymph nodes
N1b—external iliac nodes
N1c—external iliac nodes + N1a

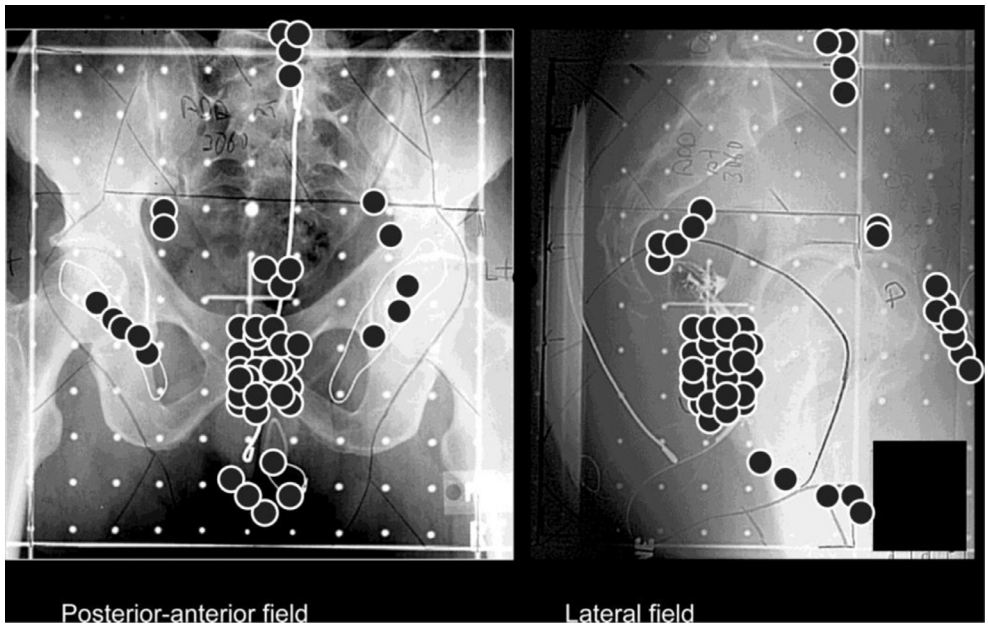

Figure 1 Representative simulation films depicting fields for conventionally delivered radiation with locations of failure superimposed. Reprinted from Wright et al.[23] (With permission from Elsevier)

difference in loco-regional control between patients who were and were not treated with INRT, and the group that did not receive INRT also trended toward decreased rates of Grade 3/4 acute and late toxicities. It should be emphasized that the study was limited to patients with cT2N0 disease, and studies with higher staged tumors do not have as positive of results. In a review of patients up to stage IIIB treated with INRT vs no INRT, Ferrigno et al reported increased inguinal failure for patients who did not receive elective INRT.[44] Ortholan et al showed inguinal recurrence rates of 2% and 16% in elective INRT and non-INRT-treated patients, respectively. In patients who did not receive elective INRT, inguinal recurrence was 12% in T1-T2 tumors and was 30% in T3-T4 tumors.[45]

Further studies are required to determine the optimal treatment for early stage disease, as only 10%-15% of anal canal tumors studied in major clinical trials were T1, and there is therefore a paucity of high level evidence regarding necessity for inclusion of chemotherapy or ENI for early-stage disease.[46]

Future Directions

Treatment of anal cancer will continue to aim to reduce toxicity and over-treatment while maintaining or improving outcomes. IMRT is the radiotherapy modality of choice, but the optimal dose, fractionation, and requirement for ENI will continue to be the subject of study. The upcoming DECREASE trial (deintensified chemo radiation for early-stage anal squamous cell carcinoma) is a single arm, phase II study seeking to address one of those questions by de-escalating the dosage delivered to T1-2N0 tumors to 36 Gy, with primary endpoints being 2-year disease control and health-related quality of life. Proton therapy is also being investigated as a modality that may be able to reduce toxicity.[47]

With the advances in imaging such as PET/CT, there is a greater opportunity for accurate staging evaluation, planning, and treatment of disease. Improvements in systemic treatment, including evaluation of immunotherapy, may also impact optimal radiation delivery. Specifically, the role of immune therapy will be better characterized based on results from the upcoming EA2165 study, evaluating the role of nivolumab after combined modality therapy in high-risk anal cancer.[48] Other immunotherapies targeting BRAF, EGFR, and PDL1 are also being evaluated in early-phase trials.[49-51] In the same vein, approximately 80% of anal cancers are positive for HPV-16 or HPV-18 and are associated with a relatively better prognosis compared to HPV negative tumors. The known association between HPV and anal cancer provides a rationale for subsequent development of vaccine therapy and immunotherapy approaches.[52,53]

Although marked advancements have been made since the initial development of the Nigro regimen, further studies are required to characterize the appropriate local therapy, the requirement for ENI, and role of novel systemic/immunotherapies in the context of improved staging. Such risk-adapted treatment will be imperative to balance the need for disease control with quality of life outcomes (Fig. 1).

References

1. Hardcastle JD, Bussey HJ. Results of surgical treatment of squamous cell carcinoma of the anal canal and anal margin seen at St. Mark's Hospital 1928-66. Proc R Soc Med 6:629-630, 1968

2. Boman BM, Moertel CG, O'Connell MJ, et al: Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer 1:114-125, 1984
3. Beahrs OH, Wilson SM. Carcinoma of the anus. Ann Surg 4:422-428, 1976
4. Golden GT, Horsley JS. Surgical management of epidermoid carcinoma of the anus. Am J Surg 3:275-280, 1976
5. Nigro ND, Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: A preliminary report. Dis Colon Rectum 3:354-356, 1974
6. Buroker TR, Nigro N, Bradley G, et al: Combined therapy for cancer of the anal canal: A follow-up report. Dis Colon Rectum 8:677-678, 1977
7. Leichman L, Nigro N, Vaitkevicius VK, et al: Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy. Am J Med 2:211-215, 1985
8. Nigro ND, Seydel HG, Considine B, et al: Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 10:1826-1829, 1983
9. Newman HK, Quan SH. Multi-modality therapy for epidermoid carcinoma of the anus. Cancer 1:12-19, 1976
10. Sischy B, Doggett RL, Krall JM, et al: Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: Interim report on Radiation Therapy Oncology Group study no. 8314. J Natl Cancer Inst 11:850-856, 1989
11. Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet 9034:1049-1054, 1996. London England
12. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al: Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR anal cancer trial (ACT I). Br J Cancer 7:1123-1128, 2010
13. Bartelink H, Roelofsen F, Eschwege F, et al: Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol Off J Am Soc Clin Oncol 5:2040-2049, 1997
14. Touboul E, Schlienger M, Buffat L, et al: Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. Cancer 6:1569-1579, 1994
15. Flam M, John M, Pajak TF, et al: Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: Results of a phase III randomized intergroup study. J Clin Oncol Off J Am Soc Clin Oncol 9:2527-2539, 1996
16. Doci R, Zucali R, La Monica G, et al: Primary chemoradiation therapy with fluorouracil and cisplatin for cancer of the anus: Results in 35 consecutive patients. J Clin Oncol Off J Am Soc Clin Oncol 12:3121-3125, 1996
17. Gunderson LL, Moughan J, Ajani JA, et al: Anal carcinoma: Impact of TN category of disease on survival, disease relapse, and colostomy failure in US gastrointestinal intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys 4:638-645, 2013
18. James R, Wan S, Glynne-Jones R, et al: A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II). J Clin Oncol 18S. LBA4009-LBA4009
19. Chintala L, Vaka S, Baranda J, et al: Capecitabine versus 5-fluorouracil in colorectal cancer: Where are we now? Oncol Rev 2:129-140, 2011
20. Meulendijks D, Dewit L, Tomasoa NB, et al: Chemoradiotherapy with capecitabine for locally advanced anal carcinoma: An alternative treatment option. Br J Cancer 9:1726-1733, 2014
21. Goodman KA, Julie D, Cercek A, et al: Capecitabine with mitomycin reduces acute hematologic toxicity and treatment delays in patients undergoing definitive chemoradiation using intensity modulated radiation therapy for anal cancer. Int J Radiat Oncol Biol Phys 5:1087-1095, 2017
22. Das P, Bhatia S, Eng C, et al: Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol Biol Phys 3:794-800, 2007
23. Wright JL, Patil SM, Temple LKF, et al: Squamous cell carcinoma of the anal canal: Patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. Int J Radiat Oncol Biol Phys 78:1064-1072, 2010
24. Peiffert D, Seitz JF, Rougier P, et al: Preliminary results of a phase II study of high-dose radiation therapy and neoadjuvant plus concomitant 5-fluorouracil with CDDP chemotherapy for patients with anal canal cancer: A French cooperative study. Ann Oncol Off J Eur Soc Med Oncol 6:575-581, 1997
25. Peiffert D, Giovannini M, Ducreux M, et al: High-dose radiation therapy and neoadjuvant plus concomitant chemotherapy with 5-fluorouracil and cisplatin in patients with locally advanced squamous-cell anal canal cancer: Final results of a phase II study. Ann Oncol Off J Eur Soc Med Oncol 3:397-404, 2001
26. Fung C.Y., Willett C.G., Efird J.T., et al: Chemoradiotherapy for anal carcinoma: What is the optimal radiation dose? Radiat Oncol Investig 3:152-156,
27. Huang K, Haas-Kogan D, Weinberg V, et al: Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. World J Gastroenterol 6:895-900, 2007
28. John M, Pajak T, Flam M, et al: Dose escalation in chemoradiation for anal cancer: Preliminary results of RTOG 92-08. Cancer J Sci Am 4:205-211, 1996
29. Myerson RJ, Outlaw ED, Chang A, et al: Radiotherapy for epidermoid carcinoma of the anus: Thirty years' experience. Int J Radiat Oncol Biol Phys 2:428-435, 2009
30. Chen YJ, Liu A, Tsai PT, et al: Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: Dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol Biol Phys 1:274-281, 2005
31. Kachnic LA, Winter K, Myerson RJ, et al: RTOG 0529: A phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 1:27-33, 2013
32. Myerson RJ, Garofalo MC, Naqa IE, et al: Elective clinical target volumes for conformal therapy in anorectal cancer: An RTOG consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 3:824-830, 2009
33. Kachnic LA, Winter K, Myerson RJ, et al: NRG oncology/RTOG 0529: Long-term outcomes of dose-painted intensity modulated radiation therapy, 5-fluorouracil, and mitomycin-C in anal canal cancer. Int J Radiat Oncol Biol Phys 2:S64-S65, 2017
34. Olsen JR, Moughan J, Myerson R, et al: Predictors of radiation therapy-related gastrointestinal toxicity from anal cancer dose-painted intensity modulated radiation therapy: Secondary analysis of NRG oncology RTOG 0529. Int J Radiat Oncol Biol Phys 2:400-408, 2017
35. National Comprehensive Cancer Network. Anal Carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/anal_blocks.pdf; 2017
36. Jones M, Hruby G, Solomon M, et al: The role of FDG-PET in the initial staging and response assessment of anal cancer: A systematic review and meta-analysis. Ann Surg Oncol 11:3574-3581, 2015
37. Cardenas ML, Spencer CR, Markovina S, et al: Quantitative FDG-PET/CT predicts local recurrence and survival for squamous cell carcinoma of the anus. Adv Radiat Oncol 3:281-287, 2017
38. Sormani MP. The Will Rogers phenomenon: The effect of different diagnostic criteria. J Neurol Sci 2009: S46-S49
39. Sekhar H, Zwahlen M, Trelle S, et al: Nodal stage migration and prognosis in anal cancer: A systematic review, meta-regression, and simulation study. Lancet Oncol 10:1348-1359, 2017
40. Cotter SE, Grigsby PW, Siegel BA, et al: FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys 3:720-725, 2006
41. Edge S, Byrd DR, Compton CC, et al: AJCC Cancer Staging Manual. ed 7 Springer; 2011

42. Amin MB, Edge S, Greene F. et al eds: AJCC Cancer Staging Manual. ed 8 Springer International Publishing; 2017
43. Zilli T, Betz M, Bieri S, et al: Elective inguinal node irradiation in early-stage T2N0 anal cancer: Prognostic impact on locoregional control. Int J Radiat Oncol Biol Phys 1:60-66, 2013
44. Ferrigno R, Nakamura RA, Novaes PERDS, et al: Radiochemotherapy in the conservative treatment of anal canal carcinoma: Retrospective analysis of results and radiation dose effectiveness. Int J Radiat Oncol Biol Phys 4:1136-1142, 2005
45. Ortholan C, Resbeut M, Hannoun-Levi J, et al: Anal canal cancer: Management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys 5:1988-1995, 2012
46. Glynne-Jones R, Nilsson PJ, Aschele C, et al: Anal cancer: ESMO−ESSO−ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol 3:330-339, 2014
47. Kharofa J. Proton therapy in reducing toxicity in anal cancer. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03018418; 2017
48. Rajdev L: Nivolumab after combined modality therapy in treating patients with high risk stage II-IIIB anal cancer ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03233711; 2017
49. Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/KEYNOTE-158): ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT02628067; 2015
50. Walker J: Avelumab with valproic acid in virus-associated cancer ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03357757; 2017
51. Moreau M. Radiochemotherapy with panitumumab in the localised epidermoid carcinoma of the anus. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT01581840; 2012
52. Steinau M, Unger ER, Hernandez BY, et al: Human papillomavirus prevalence in invasive anal cancers in the United States before vaccine introduction. J Low Genit Tract Dis 4:397-403, 2013
53. Mai S, Welzel G, Ottstadt M, et al: Prognostic relevance of HPV infection and p16 overexpression in squamous cell anal cancer. Int J Radiat Oncol Biol Phys 4:819-827, 2015