Review Article

Sphincter Preservation in Anal Cancer: A Brief Review

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ABSTRACT

Management of anal cancer is a challenge. The goal of treatment is to eradicate tumor without sacrificing the anal sphincters. The idea of organ preservation emerged following the discovery of a high complete response rate from preoperative combined chemoradiation (CRT) prior to abdominoperineal resection. CRT is widely accepted as the standard therapy for treating anal squamous cell cancer. The combination of external beam radiotherapy with interstitial brachytherapy increases the dose to the tumor volume and decreases dose to normal tissues. The current goal is to avoid colostomy, and surgery has become a salvage or secondary therapy. In this article, we review the non-surgical management of anal cancer with special emphasis on CRT, role of intensity modulated radiation therapy and brachytherapy.

Key Words: Anal cancer, brachytherapy, chemoradiation, intensity modulated radiation therapy, interstitial, radiotherapy

Received: 09.01.2013, Accepted: 26.03.2013
How to cite this article: Khosla D, Kumar R, Kapoor R, Sharma SC. Sphincter preservation in anal cancer: A brief review. Saudi J Gastroenterol 2013;19:101-7.

The management of anal cancer has undergone an interesting transformation over the last three decades. Prior to this period, the standard definitive treatment for carcinoma of the anal canal was abdominoperineal resection (APR) with the formation of a permanent end colostomy. The 5-year survival following an APR ranges from 40% to 70% with an associated mortality of approximately 3%.[1-3] Multimodality treatment to preserve sphincter function whenever possible is the preferred management for squamous cell cancers of the anal region. Combined modality treatment (CMT) for anal cancer was first described in 1974 by Nigro *et al*.[4] Since then, interest in CMT has increased. Given the high rate of complete pathologic response associated with the Nigro regimen, an approach of initial chemoradiation (CRT) followed by APR, only if residual tumor remained at the time of post-radiation biopsy, was proposed.[5]

Delivery of radiotherapy in anal cancer is complex because of the varying size and shape of the target volume, and the close proximity to dose-sensitive critical structures. Intensity modulated radiation therapy (IMRT) has the potential to minimize acute and late adverse events, by reducing the dose to genitals, perineum, small bowel and bladder in comparison to conventional parallel-opposed anterior-posterior/posterior-anterior (AP/PA) fields. Brachytherapy has been used since decades to treat anal cancer, either as the only modality of therapy for small tumors or to boost the residual of large tumors after CRT.[6-8] Thus, the treatment of anal cancer has shifted from surgical to a nonsurgical paradigm over the past 30 years.

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.111949

COMBINED MODALITY TREATMENT

Radiation therapy had been employed for anal cancer as early as the 1920s. The use of chemotherapy in combination with radiotherapy was first evaluated in the early 1970s by a group at Wayne State University. Nigro, *et al*.,[4] administered 5-fluorouracil (5-FU) (1,000 mg/m^2 continuously on days 1-4 and 29-32) and mitomycin C (MMC) (10-15 mg/m^2 on day1) in combination with external beam radiation therapy of 30 Gy. The three patients treated with this regimen had no evidence of residual disease at the time of surgery, thus leading to the concept of sphincter preservation in anal cancer.

The effectiveness of CRT as a radical treatment has been demonstrated since in numerous nonrandomized

studies and confirmed in randomized trials. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR)[9] and the European Organization for Research on Treatment of Cancer[10] both showed significant improvement in control of the primary cancer and in colostomy-free survival (CFS) in patients who received radiation combined with chemotherapy. Although the overall survival (OS) rates of those who received radiation and chemotherapy were slightly better than those of the patients treated with radiation therapy alone, the advantage did not reach statistical significance in either trial. Both studies clearly indicate superior locoregional control (LRC) and a decrease in colostomy rates with the addition of 5-FU and MMC to radiation therapy. Recently, the UKCCCR updated their results with a median follow-up of 13 years.[11] This analysis confirmed the superiority of CMT over radiotherapy alone in terms of significant reduction of the risk of locoregional recurrence ($P < 0.001$), improvement of recurrence-free survival (RFS) ($P < 0.001$) and CFS ($P = 0.004$). Twelve years after starting treatment, for every 100 patients given CMT, there are 25.3 fewer patients with a locoregional recurrence, 12.0 more who are alive and relapse free, 5.6 more who are alive and 12.5 fewer deaths from anal cancer, compared with 100 patients given radiotherapy alone. However, OS was not significantly different which may be explained by an increased number of second cancers (especially lung cancers) observed during the 10 years following treatment in patients treated with CMT. There was no significant difference between the two arms in terms of late complication rate.

WITH OR WITHOUT MMC

Given the concern over adverse events related to chemotherapy, there was interest in evaluating a combination regimen without MMC as this drug was felt to add significant toxicity. The Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group established in a randomized trial that the combination of MMC with 5-FU and radiation is more effective than 5-FU alone with radiation.[12] Results showed significantly better local control for the arm that included MMC, with post-treatment biopsies positive in 15% of patients in the 5-FU/radiation arm versus 7.7% in the arm that included MMC. CFS (71% vs. 59%, $P = 0.014$) and disease-free survival (DFS) (73% vs. 51%, $P = 0.0003$) were also superior in the MMC group despite a greater incidence of treatment-related toxicity.

Cisplatin versus mitomycin and role of induction or maintenance chemotherapy

A new direction in the elimination of MMC from the treatment regimen was the effort to substitute some other active agent for it. However, cisplatin has been shown to have activity in numerous other squamous cell cancers, so its use in anal cancer was evaluated. The Cancer and Leukemia Group B evaluated the regimen of induction chemotherapy with 5-FU (1000 mg/m^2 days 1-4 and 29-32) and cisplatin (100 mg/m^2 on days 1 and 29) followed by CRT with 5-FU and MMC for patients with locally advanced anal cancer.[13] Complete response (CR) was found in 82% of cases, CFS in 50% of patients, and OS was 68%. Because of these impressive data in poorer prognosis patients, RTOG 98-11 trial evaluated the use of a cisplatin-based regimen in patients with anal cancer.[14] It randomly assigned 682 patients to receive neoadjuvant 5-FU/cisplatin followed by CRT or to receive standard concomitant FU and MMC, providing an opportunity to examine the role of neoadjuvant chemotherapy in the management of anal cancer. In this trial, no benefit was seen for the neoadjuvant approach, despite the obvious attraction and rationale for using cisplatin in this setting. In fact, trends favored the 5-FU/MMC CRT arm. The results of RTOG 98-11 with more mature follow-up were recently published.[15] On the basis of the long-term updated analysis, CRT with 5-FU and MMC has statistically better DFS and OS than cisplatin based regimen (5-year DFS: 67.8% vs. 57.8%, $P = 0.008$; 5-year OS: 78.3% vs. 70.7%, $P = 0.026$). There was a trend toward statistical significance for CFS ($P = 0.05$), locoregional failure ($P = 0.087$), and colostomy failure ($P = 0.074$). The second UK anal cancer trial (ACT II) as reported at the American Society of Clinical Oncology 2009 meeting, addressed the issues in the RTOG study design and directly evaluated the role of MMC versus cisplatin in the CMT and two cycles of maintenance chemotherapy after CRT in anal cancer.[16] A total of 940 patients (T1-4) were randomized to receive 5-FU plus cisplatin with radiation or 5-FU plus MMC with radiation. Both the MMC and cisplatin arms were randomized further to receive adjuvant cisplatin plus 5-FU for two cycles (maintenance) or to observation for 4 weeks after CRT. ACT II is the largest trial conducted in anal cancer. High CR (95%) and RFS (75% at 3 years) rates were achieved with this CRT. This excellent outcome may have been influenced by the absence of a gap in the radiotherapy schedule. There was no difference in CR rates between MMC and cisplatin or in RFS rates with or without maintenance chemotherapy. No difference was noted in locoregional recurrence between the MMC arm (11%) versus the cisplatin arm (13%). Non-hematologic toxicities were seen to the same extent in both arms while hematologic toxicities were significantly higher in the MMC arm. Thus, 5-FU and MMC with radiotherapy remains the standard of care.

The ACCORD 03 randomized study compared in a 2 × 2 factorial manner moderate-dose with high-dose RT, and induction chemotherapy with 5-FU/cisplatin before CRT or

not.[17] Patients included were randomly assigned to one of the four treatment arms: Induction chemotherapy followed by "conventional" treatment (arm1); induction chemotherapy, CRT and radiotherapy dose intensification (arm2); "conventional" treatment alone (arm3) and radiotherapy dose intensification (arm4). The primary outcome measure of this trial was the 5-year CFS. Considering the 2×2 factorial analysis, the 5-year CFS was76.5% versus 75.0% ($P = 0.37$) in groups 1 and 2 versus 3 and 4, respectively (induction chemotherapy effect), and 73.7% versus 77.8% in groups 1 and 3 versus 2 and 4, respectively (radiotherapy-dose intensification effect; $P = 0.067$), respectively. Neither induction chemotherapy nor the additional boost of radiation resulted in any improvement in outcome measures. Thus, the lack of a clinical benefit for induction or maintenance chemotherapy does not support the implementation of these strategies in clinical practice outside the setting of a clinical trial.

The optimal dose of external beam radiotherapy for the treatment of the anal canal cancer is the subject of considerable debate. The National Comprehensive Cancer Network (NCCN) guidelines recommend a minimum radiotherapy dose of 45 Gy to primary cancer. The recommended initial dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes, with the superior field border at L5-S1 and the inferior border to include the anus with a minimum margin of 3 cm distal to the lowermost extension of the primary tumor. Field reduction off superior border at 30.6 Gy and additional field reduction off node-negative inguinal nodes after 36 Gy is recommended. For patients treated with an AP-PA rather than multifield technique, an anterior electron boost (matched to the PA exit field) should be used to bring the lateral inguinal region to the minimum dose of 36 Gy. Patients with T3, T4, node-positive disease or patients with T2 residual disease after 45 Gy, should receive an additional boost of 9-14 Gy.

MANAGEMENT OF INGUINAL NODES

Lymph node metastases represent a significant independent prognostic factor for local recurrence and survival. The probability of nodal spread is relative to the tumor size. Mesorectal and iliac lymph nodes are routinely targeted within the radiation field, whereas the inclusion of inguinal regions still remains controversial because of the potential adverse side effects. However, the 5-year survival rates for patients with regional node metastases are upto 20% lower than in node negative patients.[18] The control rate after CRT alone or local excision followed by CRT or radiation is generally 80% or better in patients with lymph node metastases not fixed to skin or deep structures.[19,20] Currently inguinal lymph node dissection is reserved for residual or recurrent disease after radiation-based treatment. The question of omitting prophylactic inguinal irradiation in selected patients with early stage tumor is still under debate. However, elective irradiation of clinically normal inguinal node areas reduces the risk of late nodal failure in the volume irradiated to less than 5%.[12] When clinically normal lymph nodes are irradiated electively, doses of about 36 Gy in 18 fractions in 3.5 weeks in combination with chemotherapy appear adequate,[12] and doses as low as 24 Gy in 12 fractions in 2.5 weeks have been used successfully.[20] In future, prophylactic inguinal irradiation may become more selective with an increasing reliance on sentinel node biopsy. Nodal metastases should be treated to the same dose as the primary cancer.

Cercle des Oncologues Radiotherapeutes du Sud (CORS-03) [Society of Southern France Radio-oncologists] study (multicentric retrospective study) explored the benefit of prophylactic inguinal irradiation in anal cancer. The 5-year cumulative rate of inguinal recurrence was 16% in the non-prophylactic inguinal irradiation group versus 2% in the prophylactic inguinal irradiation group, respectively ($P = 0.006$). When prophylactic inguinal irradiation was omitted in patients with T3-T4 tumor, one third of them developed inguinal recurrence within 5 years. Therefore, the authors concluded that prophylactic inguinal irradiation is safe and highly efficient to prevent inguinal recurrence and should be recommended for all T3-4 tumors. For patients with early-stage tumors, prophylactic inguinal irradiation should also be discussed, because the risk of 5-year inguinal recurrence is more than 10% in such cases.[21]

INTENSITY MODULATED RADIATION THERAPY

Undoubtedly, combined CRT approaches are quite toxic owing to the inclusion of multiple normal tissues, including the small bowel, rectum, bladder, genitalia and pelvic bone marrow. This toxicity can cause gaps or delay in treatment completion, further compromising therapeutic ratio and treatment response, and can result in acute and long-term impairments in quality of life. IMRT may provide a means to deliver curative doses of radiotherapy without a gap in these patients and may also facilitate dose escalation of the tumor, with improved sparing of surrounding normal tissues, thereby reducing the risk of normal tissue toxicity. Dosimetric studies have demonstrated that IMRT for anal cancer can decrease the dose to normal structures while maintaining dose to target volume.[22-25] Various retrospective clinical studies support the safety of IMRT in conjunction with concurrent chemotherapy.[26-28] Furthermore, the RTOG 0529 multi-institutional prospective study of IMRT for anal cancer reported low rates of gastrointestinal, genitourinary,

and dermatologic toxicity, with excellent 2-year rates of OS and CFS. Although the primary end point of reducing grade 2+ combined acute gastrointestinal and genitourinary adverse events of 5-FU and MMC CRT for anal cancer by at least 15% compared with the conventional radiation/5FU/MMC arm from RTOG 98-11 was not met, dose-painted IMRT (DP-IMRT) was associated with significant sparing of acute grade 2+ hematologic and grade 3+ dermatologic and gastrointestinal toxicity. Although DP-IMRT proved feasible, the high pretreatment planning revision rate emphasizes the importance of real-time radiation quality assurance for IMRT trials.[29]

The overall duration of treatment may be prolonged by planned or unplanned interruptions in radiation. With IMRT, it is possible to reduce total treatment time by abandoning gap: Median treatment time was 49 and 43 days in the RTOG 98-11 trial and the 0529 trial, respectively.[29] Certain studies have reported that prolonged overall treatment time and treatment interruptions or gaps were associated with a poorer prognosis.[30-32] In a retrospective series by Bazan, *et al.*,[28] the patients who did not have a treatment break had superior 3-year OS, LRC and progression-free survival (PFS) than those who had breaks (90% vs. 45%, $P = 0.03$; 95% vs. 67%, $P = 0.02$; 89% vs. 63%, $P = 0.04$, respectively). The median total treatment duration was significantly higher in the conventional radiotherapy group versus the IMRT group (57 vs. 40 days, $P < 0.0001$). In contrast, some of the studies showed no association between the length of treatment interruption and poor local control or diminished survival.[33,34] An update of RTOG 92-08 phase II trial showed that 5-year estimates of DFS and CFS in patients treated on the mandatory treatment break arm were lower than reported on RTOG 87-04 while DFS and CFS in the no mandatory treatment break cohort of RTOG 92-08 were comparable to other reported series. It further concluded that treatment breaks should be kept to a minimum.[35]

A draft contouring atlas and planning guidelines for anal cancer IMRT has been developed by the Australasian Gastrointestinal Trials Group[36] which complements the existing RTOG[37] elective nodal ano-rectal atlas and provide additional anatomic, clinical, and technical instructions to guide radiation oncologists in the planning and delivery of IMRT for anal cancer.

BRACHYTHERAPY

Brachytherapy is often used as a boost after external radiotherapy of cancer in the anal canal.[38,39] Brachytherapy is the most conformal treatment available to boost a small volume and limits the volume of irradiated normal tissue, thereby decreasing late toxicity, which cannot be accomplished by other techniques. Compared with external beam therapy, it has the potential to deliver a high dose to a more restricted tissue volume with sparing of surrounding normal tissues. A frequent treatment approach is external beam for first 45 Gy followed by an additional 15-20 Gy with a perineal boost or brachytherapy. In earlier times, radium needles were used for implanting in more accessible tumors which has been replaced by iridium-192 (^{192}Ir). The use of interstitial brachytherapy for treating anal carcinoma following CRT is a controversial issue, especially in the United States. Interstitial implantation is used more often in some European institutions. Both high dose rate (HDR) and pulsed dose rate brachytherapy have been tested in clinical practice.[40-42] The presence of lymph nodes in the rectal wall may not contraindicate interstitial boost as long as they are located in the distal 8 cm and respond well to CRT.[38]

Ideally, implants should be restricted to lesions that require implantation of no more than half the circumference of the anal canal, 5 mm in thickness, and 5cm in craniocaudal length for preservation of sphincter function.[38] Single, double-plane, or volume implants may be necessary, depending on the extent of the tumor. The catheters are inserted through the perianal area in the central plane 0.5 cm away from the anal or rectal mucosa with 1 finger in the rectum to verify appropriate placement. Peripheral planes are placed at 1-1.5 cm spacing. Parallelism between needles can be secured with a template. The anal canal is kept distended with an obturator or anal dilator, which reduces the dose to the opposite side of the canal to < 15% of the minimum tumor dose at the implanted area.

Computer dosimetry is based on two orthogonal films of the implant, and the duration of the irradiation calculated according to the rules of the Paris system adapted to curve planar implants. Another method for planning is computerized 3 dimensional image based treatment planning, which allows volumetric optimization based on doses to clinical target volume and critical organs. The integration of 3D planning helps to optimize dose delivered to the target volume while reduces dose to the critical organs and thus decreasing late toxicity.

Papillon, *et al.*,[7] from France, reported on 221 patients with epidermoid carcinoma of the anal canal treated with a combination of external irradiation and 5-FU and MMC, followed by a ^{192}Ir implant 2 months later. The patients underwent a 2-month rest to recover from side effects and also to permit regression of the tumor. A minimum dose of 15-20 Gy was delivered in 15-28 hours. The 5-year survival rate was 65% and an anal preservation rate of 61% was achieved, thus, preserving the anus and retaining normal sphincter function in more than 90% of surviving patients.

Severe complications were uncommon, with a total of 7 cases needing colostomy. The main toxicity was tissue necrosis, which appeared in more than 20% of cases. Berger *et al*.,[43] retrospectively analyzed 69 patients treated with external radiotherapy (40 Gy/20 fractions) and interstitial brachytherapy (20 Gy) after a mean interval of 6 weeks for a localized epidermoid carcinoma of the anal canal. Forty-five patients received 5-FU-and/or MMC-based chemotherapy regimen. CR was 81%. Actuarial local control rate was 65% and 59% at 2 and 5 years, respectively (median follow-up: Eight years). At 2, 5 and 10 years, actuarial colostomy rate was 26%, 33% and 33% respectively, and CFS rates 61%, 47% and 37%.

The boost dose delivered after 44-46 Gy external beam radiation therapy to the target volume is in most cases 15-20 Gy (LDR-PDR) at a 0.3-0.6 Gy dose rate. There are currently limited data on the use of HDR brachytherapy in anal cancer and lack of consensus on optimal fractionation schedule.[42,44,45] However, because of the fragility of the anal canal mucosa, it seems preferable to deliver fractions 3 Gy or less, spaced at least 6 hours apart. Interstitial brachytherapy must be used cautiously as it may result in anal necrosis and sphincter atony.

RESPONSE ASSESSMENT AND FOLLOW-UP

A clinical assessment of response by physical examination is typically performed at 6-8 weeks following the completion of therapy. Clinical response to treatment is broadly classified as CR, persistent disease, or progressive disease. There is considerable controversy regarding the optimal time to assess response to treatment as squamous cell carcinomas regress slowly and continue to decrease in size for upto 26 weeks following therapy.[20,46] ACT II study investigated the association between observation of CR at 3 different time-points and PFS, OS, to determine the optimal time to assess this early end point. It showed that assessment at 26 weeks is the most discriminating endpoint with the most significant effect on the outcome, and is therefore the optimum time point for assessment. The majority (60%) of patients not in CR at 11 weeks achieved CR at 26 weeks.[46] The authors also emphasized that response assessment at 26 weeks benefits late responders to therapy; earlier response assessment at 11-18 weeks is still necessary to identify patients with progressive disease. For patients with a clinical CR, re-evaluation every 3-6 months with digital rectal examination, anoscopy, and inguinal node palpation is recommended for 5 years and then yearly after 5 years. Patients with persistent disease should be watched for an additional 4 weeks to see if there is further regression. If there is no regression on serial examination or if progression occurs, biopsy is recommended and APR should be considered as a salvage procedure.

CONCLUSION

Definitive chemoradiotherapy with concurrent FU and MMC remains the standard of care in patients with anal cancer. The paradigm developed by Nigro more than 30 years ago remains the standard of care. Radical surgery should be reserved for local recurrence or persistent disease after irradiation. High dose irradiation with brachytherapy in residual disease after CRT or external radiotherapy appears to give a high rate of long-term local control. Recent studies suggest that IMRT significantly reduces the dose to critical structures while maintaining excellent target coverage in anal cancer radiotherapy.

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Source of Support: None, **Conflict of Interest:** None declared.