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## TABLE OF CONTENTS

### *Original Studies*



### *Case Reports*



### *Conference Highlights /Scientific Contribution*

# Disease Profile And Treatment Results Of Anal Canal SCC: Experience From AIIMS, New Delhi

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## Abstract

### *Introduction*

Anal Canal squamous cell carcinoma (SCC) accounts for nearly 2% of all cancers of the alimentary tract. Over the past few years, the management of anal canal cancer has changed from primary surgery to primary chemo-radiotherapy (CRT).

### *Methods*

A total of 83 patients' (pts) records (62 males, 21 females) were retrospectively reviewed. Length of disease was <5 cm in 44 pts and confined to primary in 46 pts. Ten pts have anti-cancer therapy outside. We delivered radiotherapy (RT) alone to 16 pts, chemotherapy (CT) alone to 4 pts, CRT in 51 pts and pre-operative (pre-op) RT in 2 pts. RT dose was up to 30 Gray (Gy) =16; 30-50 Gy=12 and >50 Gy=41 pts. Results: RT compliance was optimal in 64/69, grade (Gr) ≤ 2 toxicity in 56/69 and Gr ≥ 2 in 13/69 pts. Thirteen pts (18.84%) were hospitalized during RT. No response (NR) was found in 4/83, <50% in 18/83, >50-<100% in 39/83 and complete response (CR) in 22/83 pts. Recurrence at primary site was seen in 7 and loco-regional in 2 pts. Salvage therapy was done in all 9 pts (surgery=8 and CT=1). Status at last follow up, alive without disease = 22/83 and with disease = 61/83 pts.

### *Conclusion*

This retrospective analysis revealed that the advanced disease was in 47%, the optimal anti-cancer therapy could be delivered to 63.9%. Despite heterogeneity of patient population and management, the overall disease-free survival (DFS) with sphincter-preservation was achieved in 26.5% pts.

### *Keywords*

*Anal canal, squamous cell carcinoma, chemo-radiotherapy, sphincter preservation, disease free survival*

## Introduction

Anal canal cancer accounts for nearly 2% cancer of all gastrointestinal and 10% of anorectal malignancies.[1] Annual incidence rate for invasive anal carcinoma is 0.5-1/100,000 among women and 0.3-0.8/100,000 among men[2] However on the basis of cases diagnosed between 2002 to 2006 from 17 Surveillance, Epidemiology and End Results (SEER) geographic areas, the age adjusted incidence rate was found at 1.6 per 100,000 men and women per year.

The incidence has doubled in the last two and half decade and is likely to increase further[3] In India, at a particular given time, anal canal cancer constitutes 0.7% among males and 0.4% in females considering all age groups. However in geriatrics age group, the incidence is higher (males 0.9%, females 1.1%).[4]

Risk factors for developing anal SCC in both men and women include anogenital human papilloma virus (HPV) infection, anal receptive intercourse, multiple sexual partners, history of sexually transmitted disease (STD), human immunodeficiency virus (HIV) infection and history of anal condyloma. Women with anal SCC are likely to have a prior history of cervical intraepithelial neoplasia (CIN) or cervical carcinoma. Other causes of immunosuppression, including steroid therapy

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and renal transplantation, are also associated with an increased risk of all types of anogenital carcinoma.[5]

Anal squamous intraepithelial lesions, or ASIL, arise in the transition zone of the anus, an area extending from the squamous mucosa of the anus through the dentate line to the squamo-columnar junction with the rectal columnar mucosa. In this area of transition, there is an active changeover of columnar epithelium to squamous epithelium through the process of squamous metaplasia. This process is accelerated by trauma, healing, and repair such as might be expected to occur with receptive anal intercourse.[5]

The transition zone is also peculiarly susceptible to HIV infection with benign, low-risk genital types leading to condyloma, and the intermediate/high-risk genital types associated with ASIL and SCC. Anal condylomas are most often associated with HPV types 6/11, while HPV type 16 is the most common HPV-type in ASIL and SCC.[5]

The use of anal-rectal cytology is becoming more common for evaluating HPV-related disease of the anal canal, especially in at-risk populations, as the incidence of anal SCC in men who have sex with men is currently estimated to be 35 per 100,000.[6]

For invasive cancers, early detection of anal carcinoma is essential because tumor size is an important prognostic factor.[6] Tumors less than 2 cm are curable with local therapy in 70 to 90 percent of cases. The cure rate drops to 50 percent or less for tumors with nodal involvement or tumors greater than 5 cm.[5]

The management of anal canal cancer was surgery until the period of 1980s. The preliminary report of their study published by Nigro et al (1974) changed the mode of management from surgery to chemo-radiotherapy (CRT).[7] However, surgery has still role to play in residual or recurrent disease.

Keeping all the recent advancement in the management of anal canal cancer in mind, we have done a retrospective analysis of the cases being registered in the department of Radiation Oncology from April 1995 to August 2007. This analysis is in continuation of earlier published report from this institute in 2005.[8]

## Methods

The present analysis was done on the anal canal carcinoma patients registered from April 1995 to August 2007 in the Department of Radiation Oncology, at one of the major Regional Cancer Centre (RCC) of India. Of all the histologically proven carcinoma, only 83 pts with squamous cell carcinoma (SCC) type were found suitable to be reviewed. The age was between 24-80 years (yrs) with median age of 55 yrs. There were 62 males (74.7%) and 21 females (25.3%). Karnofsky Performance Scale (KPS) was between 50 and 100, median was 70 (Table 1). All investigation reports including

| | Number(n) | % of Total |
|---|---|---|
| **Age** | | |
| **Range** | 24-80 yrs | |
| **Median** | 55 yrs | |
| **Sex** | 83 | 100 |
| **Males (M)** | 62 | 74.7 |
| **Females (F)** | 21 | 25.3 |
| **KPS** | | |
| **50** | 2 | 2.4 |
| **60** | 10 | 12.1 |
| **70** | 14 | 16.9 |
| **80** | 19 | 22.9 |
| **90** | 2 | 2.4 |
| **100** | 1 | 1.2 |
| **Not documented** | 35 | 42.1 |

**Table 1 : Patients Characteristics**

| Length (cm) | Number(n) | % of Total |
|---|---|---|
| <5 | 44 | 53 |
| 5-10 | 34 | 41 |
| >10 | 5 | 6 |
| **Spread** | | |
| Perianal | 46 | 55.4 |
| Lymph nodes | 6 | 7.2 |
| Perianal + Lymph nodes | 31 | 37.4 |
| **Clinical Stage** | | |
| Primary | 46 | 55.4 |
| Primary + Metastasis | 37 | 44.6 |

**Table 2: Disease Characteristics**

biopsy, haemogram, liver function test (LFT), renal function test/kidney function test (RFT/KFT), chest roentgenogram, contrast enhanced computerized tomography (CECT), abdomen and pelvis scans along with clinical finding notes were reviewed. Disease at presentation showed the length was <5 cm in 44 (53.0%), between 5-10 cm in 34 (41.0%) and >10 cm in 5 pts (6.0%). Disease was confined to the primary site in 46 (55.4%), and loco-regional spread was present in 37 pts (44.6%). Regional/pelvic nodes = 6 pts (7.2%), both peri-anal region and nodes = 31 pts (37.4%). (Table 2)

Ten patients (12.1%) have either single or multimodality anti-cancer therapy outside before being registered at our institute for further evaluation and management, if required. Out of 10 pts, 6 pts have undergone radical surgery, 2 pts have CT and 2 pts have received combined modality of treatment i.e. CRT. The remaining 73 pts (87.9%) were assessed thoroughly and treatment decisions were taken based on patient's general condition i.e. KPS, extent of the disease and tolerability of the treatment. Regarding RT treatment, a total of 69 pts (83.1%) were found suitable. We delivered RT alone to 16 pts with palliative intent, combined CRT in 51 pts and pre-op RT in only 2 pts. RT dose up to 30 Gy was given in 16 pts for palliation; 30-50 Gy in 12 pts and >50 Gy in 41 pts as curative intent. CT was given to 55 pts (66.3%), CT alone=4, CRT=51 in the department of Medical Oncology as per protocol (1 cycle=4, 2 cycles=36, >2 cycles=15 pts). Four patients were in the CRT protocol but after taking 1 cycle of CT, further treatment was deferred due to intolerance and patients were put on palliative management. The patients received mainly cisplatin (CDDP) 50 mg/m2 d1, d2 and 5-Fluorouracil (5-FU) 750 mg/m2 d2-d5 in 1st and 5th week of RT. Radical surgery i.e. abdomino-perineal resection (APR) was done only in 2 pts (2.4%) in the department of Surgical Oncology after receiving preoperative RT. (Table 3)

| | Number(n) | % of Total |
|---|---|---|
| **Outside** | 10 | 12.1 |
| Surgery | 6 | 7.2 |
| Chemotherapy (CT) | 2 | 2.4 |
| Combined | 2 | 2.4 |
| **At our institute** | 73 | 87.9 |
| **Radiotherapy (RT)** | 69 | 83.1 |
| ≤ 20 Gy | 16 | 19.3 |
| 30-50 Gy | 12 | 14.5 |
| >50 Gy | 41 | 49.3 |
| **Chemotherapy (CT)** | 55 | 66.3 |
| ≤ 2 cycles | 40 | 48.2 |
| >2 cycles | 15 | 18.1 |
| **Surgery (APR)** | 2 | 2.4 |

**Table 3 : Treatment Characteristics**

## Results

CRT was well tolerated in most of the patients. The patients have weekly follow ups in Radiation Oncology Department during treatment. RT compliance was optimal in 64/69 pts (92.8%). Toxicities were assessed according to Radiation Therapy Oncology Group (RTOG) criteria. The main RT related toxicity was gastrointestinal (GI), grade (Gr) ≤ II in 56/69 pts (81.2%) and Gr > II in 13/69 pts (18.84%). Thirteen patients having more than Gr II toxicity were hospitalized during the course of RT for the management while other patients were symptomatically managed on outpatient department (OPD) basis. Toxicity related to CT was mainly mucositis, Gr≤ II in 50/55 pts (90.9%) and Gr >II in 5/55 pts (9.1%) which were managed accordingly.

Response was assessed after completion of the treatment and subsequent follow up. The schedule was monthly follow up on the first year, two monthly on the second year, three monthly on the third year, six monthly up to five years and annually afterwards. Both clinical and radiological methods were used to measure the response. For radiological assessment of response, Radiological Response Criteria in Solid Tumors (RECIST) criteria were followed. CECT abdomen and pelvis was done 1 month after completion of treatment and 6 monthly thereafter. Other investigations were done as per requirement depending on the patient's signs and symptoms.

| Response | Number(n) | % of Total |
|---|---|---|
| No response (NR) | 4 | 4.8 |
| <50% | 18 | 21.7 |
| >50-<100% | 39 | 47.0 |
| 100% | 22 | 26.5 |
| **Recurrence** | 9 | 10.8 |
| Primary | 7 | 8.4 |
| Primary+Lymph nodes | 2 | 2.4 |
| **Salvage Treatment** | 9 | 10.8 |
| Surgery | 8 | 9.6 |
| Chemotherapy (CT) | 1 | 1.2 |
| **Second Primary** | 2 | 2.4 |

**Table 4 : Treatment outcome of present study**

At the time of evaluation of this data, NR was found in 4/83 pts (4.8%), patients who had taken only 1 cycle of CT at our institute and intolerant to treatment, were put on palliative treatment; <50% response in 18/83 pts (21.7%); patients who have taken palliative CT at our institute (n=16) and CT outside (n=2) are >50-<100% in 39/83 pts (47.0%) and CR was found in 22/83 pts (26.5%). (Table 4)

Recurrence was seen in 9/83 pts (10.8%); at the primary site=7 pts and at the primary and lymph nodes=2 pts. Salvage therapy was done in all 9 pts (surgery=8 and CT= 1). Second primary developed in only 2/83 pts (2.4%). In one patient, peri-ampullary carcinoma was found during evaluation and in another female patient carcinoma of labia majora was diagnosed. (Table 4)

The total follow up period was 0-134 months (median 12 months). Overall survival (OS) was up to 12 months in 50/83 (60.2%), 12-24 months in 17/83 (20.5%), 24-36 months in 5/83 (6.0%), 36-48 months in 4/83 (4.8%), 48-60 months 0/83 (0.0%) and more than 60 months in 7/83 pts (8.5%). Patients' status at last follow-up: alive without disease 22/83 pts (26.5%) i.e. disease free survival (DFS) and colostomy free survival (CFS), and with disease 61/83 pts (73.5%). Of the 22 pts without disease, 19 pts (86.4%) have received CRT, thus defining the feasibility as well as better mode of treatment in the management of anal canal carcinoma. (Table 4)

## Discussion

Anal canal cancer is primarily a loco-regional disease. The metastasis found in advance disease is in the range of 10 - 17% in various studies. Three decades earlier, surgery was the primary treatment but the outcome was not so encouraging irrespective of added morbidity. [9]

Anal canal cancer is found to be sensitive to CRT as per revolutionary study done and published by Nigro et al (1983).[10] Subsequently, various regimens and treatment protocols have been tried with varying outcomes of organ preservation.[11, 12]

In early stage I disease, local excision was sufficient but it provides only 60% of the survival benefit.[13] RT alone can provide up to 100% response rate but many centers prefer CRT. In the intermediate stage II and III, the pre-op CRT was given and 78.6% pts were alive with no sign of tumor in the Wayne State University study.[10]

In UKCCCR trial, all stages of tumor were randomly allocated in RT and CRT arm. Loco-regional failure was 28% in CRT arm and 52% in RT arm alone. But treatment-related deaths were more in CRT arm compared to RT alone (2% vs. 0.7%).[14] Comparing with the UKCCCR trial, EORTC trial had a better loco-regional control and overall survival which was statistically significant.[15] Initially, 5-FU and Mitomycin C (MMC) were used in combination with better response (RTOG-ECOG Trial).[15] Over the past decade, there has been a growing interest in combining 5-FU with CDDP rather than MMC because of a) high efficacy of CDDP and 5-FU combination in SCC on other sub-site of alimentary tract b) high response rate even in metastatic anal cancer c) more favorable toxicity profile of CDDP compared to MMC and d) more intense radio-sensitization by CDDP.[16] In recent phase III trial, MMC+5-U along with RT does not show any benefit over CDDP+5 FU with RT arm.[17]

Despite the growing consensus among oncologists for the management with CRT, surgery has the adjuvant role to play. Surgery is reserved for salvage in failure of CRT (residual/ recurrent disease) intolerance to CRT/RT (e.g.

| Studies | Number of Patients (pts) | Overall Survival (OS) | Disease free Survival (DFS) | Colostomy free Survival (CFS) |
|---|---|---|---|---|
| Deo SV et al, 2005[8] | 40 | 80% | 77.5% | 72.5% |
| Ferrigno R et al, 2005[9] | 43 | 68% | - | 52% |
| Hung A et al, 2005 | 92 | 85% | 77% | 8% |
| Kichenadasse G et al, 2007 | 34 | - | 53% | 71.5% |
| Ceresoli G L et al, 1998 | 35 | - | 83% | 70% |
| Present Study | 83 | 100% | 26.5 | 26.5% |

**Table 5 : Treatment outcomes in various studies**

IBD), incontinence due to irreversible sphincter damage, ano-vaginal fistula (<5%), complication of CRT refractory to medical treatment. The advantage of salvage surgery (APR) is long term local control (LC) and OS in 1/3 to 1/2 of patients who are fit for surgery. Three years survival after salvage surgery is 10% to 50%. [11, 12, 13, 18]

In advanced stage, palliative CT has a response of up to 50% and RT has a role in local palliation for specific metastatic sites. However some heterogeneity exists among anal cancer patients in their outcomes which may be due to patient factors, clinical factors, treatment-related factors, and biologic factors as depicted in our study in comparison with other studies (including a previous study published from our institute in 2005). [8, 19] (Table 5), (Figure 1).

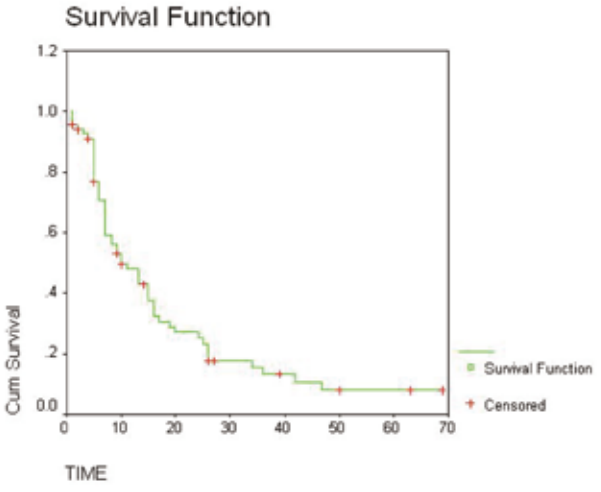


**Figure 1.** Figure showing the Kaplan Meier Curve of survival. It can take into account some types of censored data, particularly right-censoring, which occurs if a patient withdraws from a study, i.e. is lost from the sample before the final outcome is observed. On the plot, small vertical tick-marks indicate losses, where a patient's survival time has been right-censored.

Various trials are ongoing (FRENCH trial [FFCD 9804], UKCCCR ACT II, and EORTC 22011) which could provide in the future the doses, schedules, combinations of drugs with RT, so that a better consensus can be developed in the management of anal cancer patients.

## Conclusion

Retrospective analysis revealed that the advanced disease (>5 cm length, perianal/node extension) was documented in 39/83 pts (47%). Optimal anti-cancer therapy could be delivered to 53/83 pts (63.9%) in spite of the advanced condition of many patients during presentation. Defining the feasibility of CRT, overall DFS with Sphincter-preservation was achieved in 26.5% pts. (Table 5), (Figure 1). The above-mentioned response is less compared with other studies including the previous study done on the same institute in 2005[8] but this is mainly due to heterogeneity in the extent of the disease, age, general condition of the patients, KPS, tolerability of the treatment and other disease factors. The defined extent of the disease (i.e. TNM stage, Histological grade, Tumor volume etc.) age-adjusted, good KPS, more number of homogeneous patient populations and treatment modality with long term follow-up are all required for a more consistent result and which will further be refined by the results of ongoing trials mentioned above.

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