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ANAL CANAL CANCER TREATMENT BY CONCURRENT CHEMORADIOTHERAPY VERSUS RADIOTHERAPY ALONE: A COMPARATIVE STUDY

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ABSTRACT

Aim: The aim of this retrospective study is analysis of results of patient treatment outcome when prescribing chemotherapy and radiotherapy as concomitant setup as compared to radiotherapy alone for patients with anal canal carcinoma and related complications of this mode of treatment.

Materials and Methods: 24 patients of anal canal cancer (squamous cell carcinoma-17 and adenocarcinoma-7)of median age 53.62 years (Range 20-80 year), tumor stage T1/T2-5 patients and stage T3/T4-19 patients with nodal positive 12, (9 inguinal, 3 pelvic) were treated . 11 patients received Pelvic RT-50 Gy/25 Fr/5 wks and concomitant CT with 5-FU and were designated as Group A, and 13 patients were treated with Radiotherapy alone and grouped as Group-B.

Results: Seven patients of concomitant chemotherapy group (63.63%) and 4 of without chemotherapy (30.76%) achieved complete response. 4 patient in concomitant CT group (36.36%) and 9 patients in without CT group (69.23%) achieved partial response. Treatment related complication developed in 13 patients (54.16%) mainly skin reaction and diarrhea of grade II.

Conclusion: The combination of radiation and chemotherapy with 5-FU as concomitant setting has produced better response and survival as well as organ preservation in anal canal carcinoma with acceptable and manageable toxicity.

INTRODUCTION: The anal canal is approximately 4 cm in length and extending from the proximal anorectal ring to distal anal verge (margin). Carcinoma of anal canal is a relatively uncommon tumor affecting 1 to 3% of all cancer of lower gastro intestinal tract [1]. The standard concomitant chemoradiation modality not only preserve sphincter functions but also able to achieve high cure rate and good prognosis [2]. Majority of anal canal carcinoma are epidermoid carcinomas [3]. Traditionally 74 to 90% carcinoma of the anal canal are cured with the combined modalities of chemo radiation reserving an abdomino- perineal resection for salvage therapy [4].

Little has changed over past three decades, resulting in minimal modifications in the treatment approach. Individual with increased risk for developing anal cancer are- human papiloma virus (HPV) infection, anogenital wart and male homosexuals [5, 6]. Most common presenting symptom are - bleeding or discharge per rectum, altered bowel habit and discomfort in perianal region. Clinical trial reporting on concurrent chemotherapy and radiotherapy showed the advantages of this association over radiotherapy alone in local control and colostomy free survival [7]. Concurrent chemotherapy and radiotherapy is the gold standard of treatment mainly for large tumors [8].

Aim: The aim of this retrospective study is analysis of results of patient treatment outcome when prescribing chemotherapy and radiotherapy as concomitant setup as compared to radiotherapy alone for patients with anal canal carcinoma and related complications of this mode of treatment.

MATERIALS AND METHODS:

Inclusion Criteria: Between January, 2006-December, 2009, 24 histopathologically proven and previously untreated, Nonmetastatic patients of anal canal carcinoma were treated at department of radiotherapy unit II, RCC, PGIMS ROHTAK. Pretreatment evaluation included history, physical examination, (KPS >60), chest radiograph, standard laboratory test, and ultrasound (US) or CT based evaluation of liver and lymph nodes. Histopathologicaly Squamous cell carcinoma patient were 17, and of Adenocarcinoma 7 in which 21 were male and 3 female patient. Mean age of patient was 53.62 years (Range 20-80 year). Primary tumor stage T1/T2 - 5 patients and Primary tumor stage T3/T4 - 19 patients. Total Nodal positive patients were 12 (9 inguinal, 3 pelvic). Details of patients characteristic are shown in **table 1**.

TABLE 1: PATIENTS CHARACTERISTICS

Total Patients	**24**	**CT+RT-11 RT-13**
Age (years)	**<65**	**18**
	66-75	**5**
	>75	**1**
Treatment	**Pelvic Irradiation**	**24**
	Pelvic Surgery	**0**
Stage	**T1/T2**	**5**
	T3/T4	**19**
Nodal Positive Total cases 12	**Inguinal**	**9**
	Pelvic	**3**
Histopathology	**Squamous cell Carcinoma**	**17**
	Adenocarcinoma	**7**
Tumor size (cm)	**<4**	**5**
	>4	**19**
Sex	**Male**	**21**
	Female	**3**

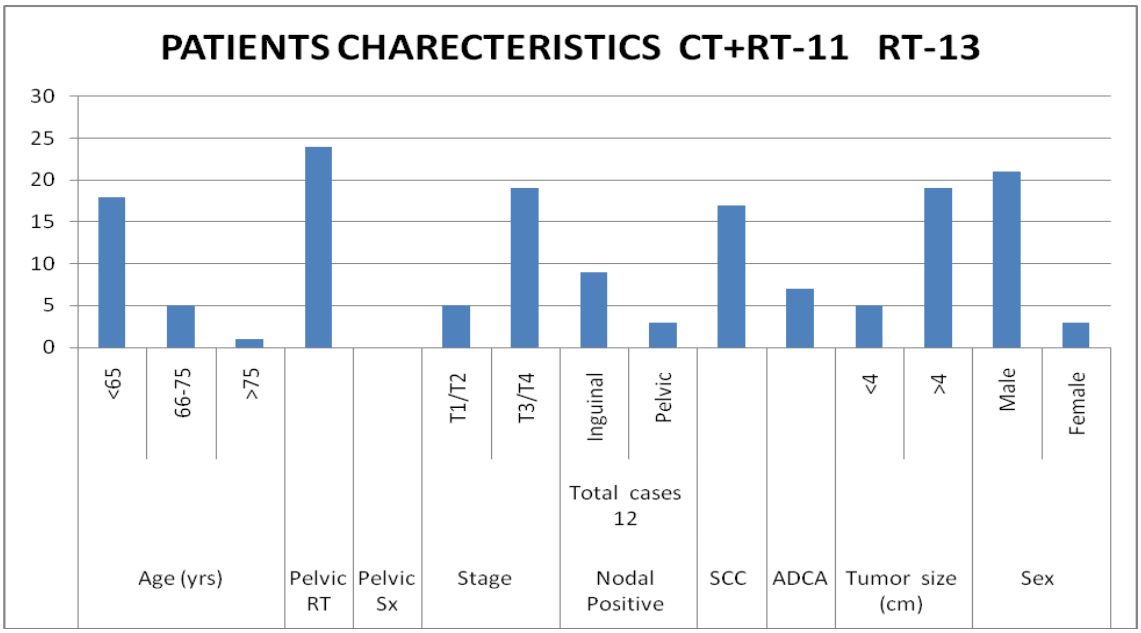

FIG. 1: PATIENTS CHARACTERISTICS

Treatment Design: 11 patients received Pelvic EBRT-50 Gy/25 Fr/5 weeks, 5Fr in a week and concomitant CT with 5-FU 750 mg^2 IV D1-4 in first and last week of RT and were designated as Group-A, and 13 patients were treated with Radiotherapy alone and grouped as Group-B. Radiotherapy was delivered by photon beam by Cobalt-60, TH 780E machine. Radiotherapy volumes and prescribed dose for chemo therapy was different for different group of patients. Age and general condition of the patient was main factor in determining the treatment plans whether patient would undergo chemotherapy or not.

Patients were irradiated by AP-PA parallel opposed field to pelvis,

- Superior margin located at L5-S1 interspace,
- Bottom field 2 cm below the lowest margin of tumor,
- Lateral margin 1-2cm away from widest point of pelvic brim.

The inguinal nodes were only covered by anterior field. A boost of 15-20Gy was delivered to responding patients using direct perineal field or reduced four field.

RESULTS:

Statistical analysis: Patients were compared in the two treatment groups with Fisher's exact test. Median duration of follow up was- 21 months, Mean age- 53.62 years, Sex ratio (men: women) - 7:1. Seven patients of concomitant chemotherapy group (63.63%) and 4 of without chemotherapy (30.76%) achieved complete response. Four patient in concomitant CT group (36.36%) and nine patients in without CT group (69.23%) achieved partial response. The overall 3 year survival rate (OSR) with concomitant Chemotherapy and Radiotherapy was 56% and without chemotherapy was 44%. For concomitant CT with Radiotherapy group relapse free survival (RFS) was 61% and without chemotherapy group 39%. 75% of patients (n-18) were of age group less than 65 years, 25% of patients (n-6) were of above 65 years.

TABLE 2: RESPONSE

Parameter	CCRT Group A	RT Alone Group B	P Value
Complete Response	63.63 % (7)	30.76 % (4)	<0.0001
Partial Response	36.36 % (4)	69.23 % (9)	<0.0001
3 yr. OSR	56 %	44 %	0.5661
3 yr. RFS	61%	39 %	0.5661

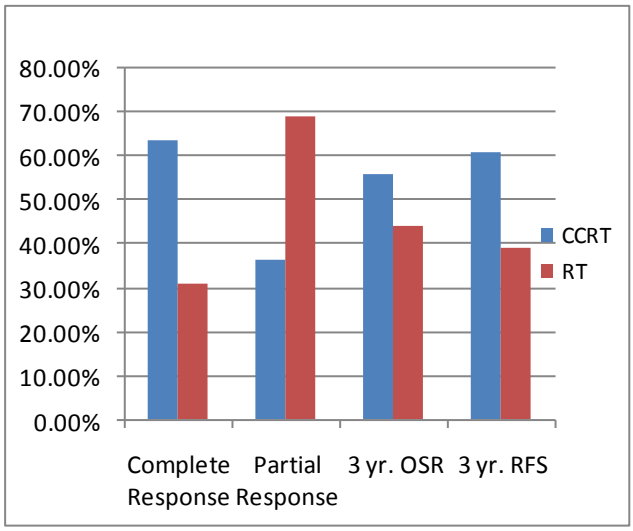

FIG 3: RESPONSE

Toxicity: Treatment related complication developed in 13 patients (54.16%) in which grade III Skin reaction developed in four patients, diarrhoea in four patients (Grade II-3, Grade III-1) and another five patient developed pain abdomen bleeding per rectum and perineal fibrosis.

Increased incidence of haematological complications was observed with concurrent chemotherapy (*P*<0.001). Difference in the rates of cutaneous and digestive, complications was noted between both the treatments.

TABLE 3: TOXICITY

Toxicity	CCRT	RT
Diarrhoea(Grade –II and III)	4 (36.36%)	2 (15.38%)
Skin reaction(Grade -III)	4 (36.36%)	1 (7.69%)
Bleeding PR	1 (9.09%)	0
Perineal fibrosis	1 (9.09%)	0

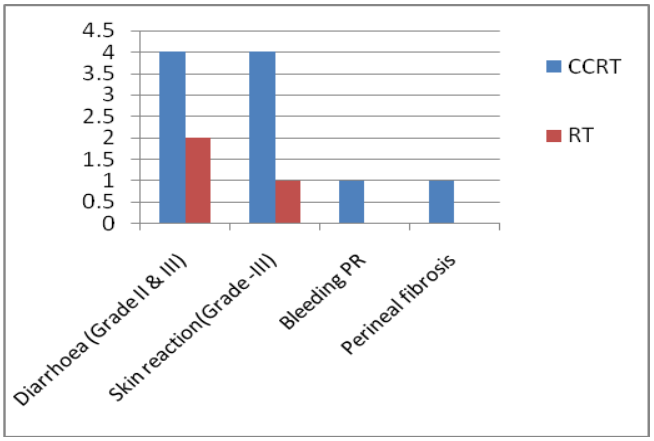

FIG 4: TOXICITY

DISCUSSIONS: In this series, eleven patients were given the combined treatment. The combined modality of treatment was mainly given to patients with large size of tumor and younger age group. Early local complication rate seemed to increase with concomitant chemotherapy; especially the haematological toxicity increased. Patients experienced mostly minor but disturbing complications such as diarrhoea, rectal haemorrhage and perineal fibrosis. Complications required medical treatment in eight patients. European Organization for Research and Treatment of Cancer (EORTC) explored the role of chemo radiation and its potential benefit in Loco Regional Control (LRC) and colostomy free survival [9]. A total 110 patients randomized to radiation 45Gy or continuous infusion of 5-FU 750mg/m^2 on days 1 to 5 and 29 to 33/Mitomycin C (15mg/m^2 on day 1). Results are shown in **table 4**.

TABLE 4:

UKCCR	RADIATION	CHEMORADIATION
	N= 285	N= 292
COMPLETE RESPONSE	30%(76)	39%(100)
PARTIAL RESPONSE (>50%)	62%(157)	53%(138)
THREE YEAR LOCAL FAILURE	61%(164)	39%(101)
THREE YEAR OVERALL SURVIVAL	58%	65%
EORTC	**N=52**	**N=51**
COMPLETE RESPONSE	54%	80%
THREE YEAR OVERALL SURVIVAL	65%	72%
RCC, ROHTAK	**N=13**	**N=11**
COMPLETE RESPONSE	30.76 %	63.63 %
PARTIAL RESPONSE (>50%)	69.23 %	36.36 %
THREE YEAR OVERALL SURVIVAL	44%	56%

United Kingdom Coordinating Committee on Cancer Research (UKCCR) randomized 585 patients to radiation alone 45Gy vs. continuous infusion 5-FU 1000mg/m^2 on days 1 to 4 or 750mg/m^2 on days 1to 5 during first and last week of radiation with Mitomycin C 12mg/m^2 on day 1 were given [10]. Results are shown in table 4 after a median follow up of 48 months. Most important point is difference of chemotherapy i.e., single agent 5-FU. In another retrospective study Flam et al [11] showed an increased complications rate after concomitant chemotherapy and radiotherapy. In conclusion, our recommendation is not to treat older patient with co-morbidity with concomitant chemotherapy and radiotherapy due to increased late complications rate.

CONCLUSION: The combination of Radiation and Chemotherapy with 5-FU as concomitant setting has produced better response and survival as well as organ preservation in anal canal carcinoma with acceptable and manageable toxicity. Concurrent chemotherapy and radiotherapy has been considered the gold standard of treatment of anal canal carcinoma**.**

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