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ANAL CANAL SQUAMOUS CELL CARCINOMA TREATED WTH INTENSITY MODULATED RADIATION THERAPY BASED CONCURRENT CHEMORADIATION–RETROSPECTIVE ANALYSIS OF CLINICAL OUTCOME AND TOXICITIES

Oncology

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ABSTRACT

Purpose: This retrospective analysis is aimed to report the single institution experience from an Asian country utilizing Intensity Modulated Radiotherapy (IMRT) based Chemo radiation in Anal Canal Squamous Cell Carcinoma (ASCC) with an emphasis on efficacy, toxicity and disease and treatment-related variables associated with outcomes. **Materials And Methods:** Study was conducted in the department of Radiation Oncology at Regional Cancer Center, Thiruvananthapuram. All Patients with biopsy proven ASCC diagnosed between January 2014 and December 2018 and receiving curative intent IMRT were identified and follow up data till December 2020 was collected. Primary end point was Disease-free survival (DFS). Secondary end points were Overall Survival (OS), Colostomy-free survival (CFS) Loco regional Failure (LRF) and Toxicities. **Results:** A total of 34 patients were analyzed during a median follow up of 34 months. Twenty five patients (73.5%) were in stage IIIB. Median overall treatment time was 36 days. The estimated two year DFS, OS and CFS were 79.4 %, 93.9 %and 97% respectively. Disease recurrence at any point on follow up occurred in five patients (14.7%). Primary Tumor size of more than or equal to 5 cm and development of grade three anemia during RT was associated with inferior DFS in Univariate analysis. Patients taken less than two cycles of chemotherapy, there was a trend for inferior OS. Acute grade 3 or more dermatological toxicities was 44% and hematological toxicity was 35.3%. Radiotherapy break occurred in 38.2%of patients with a median of 5.5 days (range 2-13). Of the available patients chronic toxicities were reported for 40% and were of grade 2. **Conclusion:** IMRT is associated with favorable toxicity rates and excellent long-term efficacy in Asian population also where patients are presenting in an advanced stage. Reducing the total treatment time by SIB technique may improve the clinical outcome.

KEYWORDS

IMRT, Anal canal Suamous cell Carcinoma, concurrent chemoradiation, SIB Technique, Indian data

INTRODUCTION

The incidence of Anal canal Squamous Cell Carcinoma (ASCC) in the general population has increased over the last 30 years. Traditionally, patients with anal cancer were managed surgically via an Abdominoperineal resection (APR), with an expected 5-year survival of 55% to 71% [1-3]. Based on the seminal work by Nigro et al (1974) Combined chemo radiotherapy with Mitomycin-C (MMC) and 5-fluorouracil (5-FU) has emerged as the preferred method of treatment for anal canal cancer because it can cure many patients while preserving the anal sphincter [4]. The benefit of concurrent chemotherapy with conventional radiation has been confirmed by multiple randomized clinical trials [5-9].

Although oncologic outcomes are favorable, chemo radiation is associated with significant acute toxicity. Radiation Therapy Oncology Group (RTOG) 87-04/Eastern Cooperative Oncology Group (ECOG) 1289 Intergroup randomized trial(1996) reported 23 % Grade 4 to 5 acute toxicities [5] and RTOG-98-11(2008) trial had Grade 3–4 skin toxicity of 48% and Grade 3–4 gastrointestinal toxicity of 35% [8]. Acute toxicities can result in treatment breaks and prolongation of treatment time has been associated with higher colostomy rates in a secondary analyses of RTOG anal cancer trials (2010) [10].

RTOG 0529 (2013) was a multi-institutional prospective study of Intensity Modulated Radiotherapy (IMRT) for anal cancer which reported significant sparing of acute grade 2+ hematologic, and grade 3+ dermatologic and gastrointestinal toxicity [11]. Prospective cohort study by Han et al (2014) has demonstrated that IMRT in comparison with traditional 3-dimensional conformal techniques (3DCRT) results in acute gastrointestinal and hematological toxicity reduction [12]. Using data from National Cancer Data Base (NCDB) Elson, J.K et al (2018) concluded that 'IMRT was associated with significantly reduced overall treatment time and improved survival in comparison with 3DCRT'[13]. IMRT can be delivered by using sequential boost technique or giving different doses to different target volumes at the same time termed as Simultaneously Integrated boost (SIB). The optimal technique of IMRT with or without SIB is still under debate. IMRT has been increasingly used by the radiation oncologist all over the world for the treatment of ASCC although long-term effects are not yet fully characterized.

In our center IMRT has been using for the past few years in treating ASCC patients. In majority of patients dose delivery was by SIB. Clinical audit of these patients were done in this retrospective analysis and is aimed to report the single institution experience from an Asian country utilizing IMRT based Chemo radiation in ASCC with an emphasis on efficacy, toxicity and disease and treatment-related variables associated with outcomes.

MATERIAL AND METHODS

Patient Selection

This retrospective Study was conducted in the department of Radiation Oncology at Regional Cancer Center, Thiruvananthapuram. Institutional review board approval was obtained prior to study. Patients diagnosed with ASCC between January 2014 and December 2018 and receiving curative intent IMRT were identified. All patients of more than 18 years of age with biopsy proven ASCC were included for analysis. Patients with other histology, those receiving adjuvant chemo radiation and patients and with history previous radiation to pelvis were excluded from the study. There were thirty four patients during this period. The demographic data of patients, disease stage,

treatment details, status of disease on follow up, acute and late toxicities documented were collected from the case records. Laboratory parameters were retrospectively collected from the case files and from hospital computer data. Patterns of recurrence, the date of biopsy evidence of residual/recurrent cancer, and date of salvage surgery were also collected and recorded in a structured format. Follow-up information till 31st December 2020 were collected and documented.

Treatment Methods

All patients underwent CT simulation in supine position except three who were planned and treated in prone position. Clinical Target Volume 1 (CTV 1) was the gross tumor with 1.5 cm margin along with coverage of entire anal canal including the internal and external anal sphincters, grossly involved LNs with 0.5cm margin, and elective inclusion of the mesorectal, presacral, bilateral inguinal, internal iliac, and external iliac LNs. CTV2 excluded elective inguinal and external iliac nodes from CTV1.CTV 3(Boost CTV) if planned was gross tumor with 1.5 cm margin. All CTV s were edited from bones and muscles. The planning target volumes (PTVs) consisted of a 1.0 cm expansion from the CTVs.

IMRT with SIB technique was used for 67% of patients. Image guidance typically included daily orthogonal kilo voltage images plus once weekly cone beam CT. Volumetric Arc Therapy (VMAT) was the most commonly used technique of radiation followed by fixed field Intensity Modulated Radiation Therapy .Majority of dose delivery was using Simultaneous Integrated boost (SIB) followed by sequential boost (SeqB), or the combination of this two.

Concurrent chemotherapy was the standard of treatment. All Except three patients received concurrent chemotherapy and the most commonly prescribed chemotherapy regimen was MMC 10 mg/m2 administered on days 1 and 29 and continuous infusion of 5-FU 1000 mg/m2 administered on days 1–4 and days 29–32.

Patient Assessments

During treatment, patients were assessed weekly for acute toxicities and were graded as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and recorded in the radiation charts which were collected and analyzed. All bone marrow toxicities were retrieved from the lab reports and graded. Data on chronic toxicities were collected from case records.

Routine oncologic follow-up included clinical examination with or without diagnostic imaging. First follow up was usually at 6 to 8 weeks post treatment. Patients having residual disease at follow up were closely monitored at monthly intervals and if showing signs of regression was not biopsied. If there was clinical or radiological suspicion of progression biopsy was done depending on the clinical situation. Further follow-up was typically every 3 months for first two years every 6 months until year 5, and annually thereafter.

End Points And Statistical Analysis

Primary end point was Disease-free survival (DFS) which was calculated from the date of diagnosis to the date of local, regional, or distant failure, second primary tumor, or death due to any cause. Secondary end points were Overall Survival (OS), Colostomy-free survival (CFS) Loco regional Failure (LRF) and Toxicities.

OS was calculated from the date of diagnosis to the date of Death due to any cause or last follow up date. CFS was calculated from the date of diagnosis to the date of colostomy.

Local Recurrence (LR) was defined as recurrence or progression at the primary tumor site and Loco Regional Recurrence (LRR) was defined as recurrence or progression within the primary tumor site or non-metastatic regional lymph nodes. Distant metastasis was defined as relapse at non-regional lymph nodes or spread to distant organs. Disease recurrence was confirmed pathologically whenever possible or radio- logically. Acute toxicities were defined as those occurring within 90 days of treatment and late toxicities being defined as those occurring after 90 days.

Continuous variables were expressed as mean and standard deviation and categorical variables as counts and percentage. LRF and toxicities were computed as percentage. DFS, OS, CFS was computed using the Kaplan-Meier method. Statistical significance of survival curves was obtained using Log Rank test. P- value < 0.05 was considered to be statistically significant. Risk for survival was assessed using Cox regression analysis.

RESULTS

Patient And Tumor Characteristics

A total of thirty four patients were analyzed. Patient demographics, tumor characteristics are shown in Table 1. The median age was 60 years, and the majority of patients (64.7%) were male. One patient was retrovirus positive and status was unknown for sixteen patients. Three patients had Baseloid variant of Squamous Cell Carcinoma (SCC) and all others were having SCC with four patients having poorly differentiated grade. As per AJCC 7TH staging sixteen patients (47.1%) had T4 stage and most common N stage was N3 (35.3%). Twenty five patients (73.5%) were in stage IIIB and all other stages had three patients each. Median tumor size was 4 cm (range 2-10).

Treatment

Median radiation dose to the primary was 50.4Gy (range, 50-60 Gy) and to the nodes was 45Gy (range, 30.6-46Gy). Treatment details are given in Table 2. Most commonly used radiotherapy (RT) schedule was 50 Gy in 25 fractions to the primary and 45 Gy in 25 fractions for the nodes as SIB. Median overall treatment time was 36 days (range 31-50).

Concurrent chemotherapy was used for thirty one patients (91.2%) and consisted of Mitomycin and 5 FU for 26 patients (76.4%), Capcitabine and Mitomycin in two patients (5.9%), Cisplatin and 5FU in one patient and Capecitabine alone for two patients(5.9%).Of the Patients on infusion chemotherapy Twenty two patients (81.5 %) had two courses of chemotherapy. Chemotherapy was deferred in three; two due to old age and one due to chronic renal failure.

Treatment Response And Outcome

Median follow up was 34 months (range 3-82).Twenty patients (58.8%) achieved complete response at six months and median time to response was four months (2-12 range). Disease recurrence at any point on follow up occurred in five patients (14.7%). Out of the five recurrences, two had local recurrence alone, one had progressive disease at primary site, one had metastatic relapse and one had both regional and metastatic relapse. Median time for recurrence was 18 months.

One of the patient with local recurrence had salvage surgery as Abdominal Perineal Resection (APR); but developed metastatic relapse later. One patient with progressive disease general condition was not fit for salvage surgery and he was lost to follow up. The third patient who had local progression after 15 months of treatment had associated liver cirrhosis and hence salvage could not be planned. One patient having metastatic recurrence in lung had palliative chemotherapy. One patient with inguinal node and Para aortic nodal recurrence (PALN) was treated with palliative RT to PALN and was given palliative chemotherapy.

Two patients had Colostomy; one as salvage for recurrence and the other patient had pretreatment colostomy which could not be reverted back as there was anal canal stenosis eventhogh he had complete radiological response to treatment .Two patients did not report for follow up after treatment and one patient died of treatment complication during RT.

The estimated two year DFS, OS and CFS were 79.4 %, 93.9 % and 97% respectively .Kaplan-Meier estimates of DFS, OS, and CFS are demonstrated in Fig. 1. Univariate associates with DFS, OS are shown in Table 3. When various demographic features, tumor characteristics, treatment factors and toxicities were analyzed for the clinical outcome, Primary Tumour size of more than or equal to 5 cm (HR= 4.96 95% CI =0.99-24.76; P=0.051) and development of grade three anaemia during RT (HR=7.81 95% CI 1.47-41.38;P value 0.016) was associated with inferior DFS in univariate analysis. In Kaplan Meir estimate AJCC stage III was also shown to have lower DFS (63% VS 100%) but the risk was not seen in regression analysis (figure 2). Patients taken less than two cycles of chemotherapy, there was a trend for inferior OS (HR=0.16 CI=0.02-1.12;P value 0.064). CFS was not significantly associated with any of the parameters.

After the median period of 34 months, of the evaluable patients, eighteen patients (52.9%) were alive and disease free. Five patients

(14.7%) died at last follow up, one due to acute toxicity and all others due to medical problems during follow up period.

Table 1. Patient And Tumor Characteristics(n-34)

Variable	Number(Percentage)
Sex	
Male	22 (64.7)
Female	12 (35.3)
Age	
Median	60
Range	36-92
ECOG PS	
1	29(85.3)
2	05 (14.7)
Socioeconomic status	
Low	17(50)
Middle	10(29.4)
High	7(20.6)
Smoking status	
Nonsmokers	17(50)
Smokers	17(50)
Comorbidities	
Yes	14(41.2)
No	20(58.8)
HIV status	
Positive	1(2.9)
Negative	17(50)
Unknown	16(47.1)
Tumour histology	
Squamous	31(91.2)
Baseloid	03(8.8)
Tumour differentiation	
Well differentiated	30(88.2)
Poorly differentiated	04(11.8)
T stage	
1	4(11.8)
2	9(26.5)
3	5(14.7)
4	16(47.1)
N stage (AJCC 7TH)	
0	9(26.5)
1	7(2.6)
2	6(17.6)
3	12(35.3)
Composite stage(AJCC 7)	
1	3(8.8)
2	3(8.8)
3A	3(8.8)
3B	25(73.5)
Cross sectional imaging	
CT	17(50)
MRI	17(50)
Tumour location	
Anal canal	23(67.6)
Extending above dentate line	3(8.8)
Extending to perianal skin	4(11.8)
Others	4(11.8)
Primary Tumour size (CM)	
More than or equal to 5 cm	13 (38.2)
Less than 5 cm	16(47.1)
Unknown	5(14.7)

Table 2. Treatment Details (n 34)

Variable	Number (%)
RT Technique and dose delivery	
VMAT-SIB	19(55.9)
VMAT-SeqB	7(20.6)
IMRT-SIB	2(5.9)
IMRT-SeqB	3(8.8)
VMAT SIB followed by SeqB	3(8.8)
Primary tumour dose (Gy)	
More than 54	13(38.2)
Less than 54	21(61.8)
RT dose to elective lymph nodes(Gy)	
45 or more	28(82.4)
Less than 45	6(17.6)
Delay of treatment Start	
More than 6 weeks of diagnosis	16 (47.1)
Less than six weeks of diagnosis	18 (52.9)
RT dose schedules to primary (Gy/Fraction)	
50/25	16(47.1)
50.4/28	4(11.8)
54/25	2(5.9)
54/27	1(2.9)
54/30	3(8.8)
55.8/26	1(2.9)
56/28	1(2.9)
59.4/33	4(11.8)
59/32	1(2.9)
60/30	1(2.9)
Elective nodal RT schedules (Gy/Fraction)	
45/25	24 (70.4)
36/20	1 (2.9)
39.6/22	2 (5.9)
45/30	3 (8.8)
30.6/17	3 (8.8)
46/23	1(2.9)
RT Break	
Present	13(38.2)
Absent	21(61.8)
Chemotherapy Shedule	
Inj 5 FU + Inj Mitomycin X 2cycles	22(64.7)
Inj 5 FU + Inj Mitomycin x 1 cycle	4(11.7)
Inj Mitomycin+T.Capcitabine	2(5.9)
Inj Cisplatin+ Inj 5FU (one cycle)	1(2.9)
T Capcitabine alone	2(5.9)
Not taken	3(8.8)

Toxicity

Acute toxicities are summarized in Table 4. The most common acute toxicity was dermatologic toxicity followed by hematological toxicity. One patient had grade 5 hematological toxicity and died of toxicity after seven days of starting treatment. Grade 4 dermatologic toxicity and hematological toxicity were there for two and four patients respectively. Gastrointestinal toxicity (GI) was uncommon; but two patients had grade 3 hyponatremia. Two patients RT was terminated prematurely four days before completion of treatment, one due to persistent bone marrow suppression and other due to grade 4 dermatological toxicity. Eight patients (23.5%) were admitted during treatment due to toxicity and the most common reason for admission was grade 3-4 hematological toxicity. Radiotherapy break occurred in twelve patients (38. 2%) and the median was 5.5 days (range 2-13) and the most common reason for RT break was dermatological toxicity.

Chronic toxicities were available for 30 patients (88.2%) and of them 12 patients (40%) had documented chronic toxicity and none had grade 3.The most common was chronic GI toxicity occurring in six patients (20%) presenting as decreased anal tone which was of grade 2. Three patents (10%) had lymphedema of grade 2 and another three (10%) had late grade one skin toxicity as telangiectasia.

Table 3: Univariate Associates Of DFS And OS

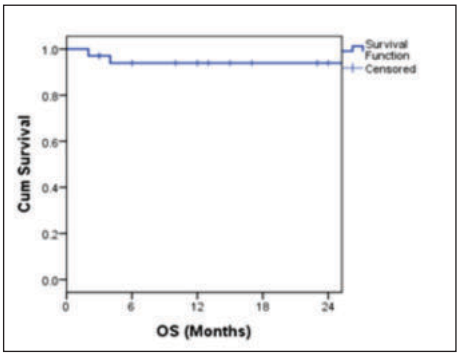
	DFS		OS	
	HR(95% CI)	p value	HR(95%CI)	p valu
Current smoking	2.59(0.67-10.10)	0.170	1.73(0.29-10.37)	0.551
Primary Tumour size of >/= 5Cm	4.96(0.99-24.76)	0.051	4.44(0.46-42.83)	0.198
Presence of N3 nodal staging	1.23(0.20-7.34)	0.824	1.45(0.13-16.08)	0.760
Treated with SIB technique	1.50(0.31-7.16)	0.611	0.41(0.07-2.48)	0.329
RT dose less than 54 Gy to Primary	0.42(0.11-1.50)	0.183	0.45(0.07-2.67)	0.376
Delay of treatment >than 6 weeks of diagnosis	0.70(0.19-2.49)	0.584	1.54(0.26-9.31	0.638
RT period >39 days	1.79(0.50-6.40)	0.371	0.77(0.08-7.01)	0.818
Presence of RT break	3.10(0.321-30.01)	0.328	1.56(0.25-9.54)	0.633
Less than 2 cycles of Chemo	0.52(0.11-2.53)	0.419	0.155(0.02-1.12)	0.064

Presence of Grade 3 Hematological toxicity	2.87(0.80-10.30)	0.105	0.47(0.05-4.26)	0.505
Presence of Grade 3 skin toxicity	1.56(0.44-5.53)	0.493	1.76(0.29-10.58)	0.537
Presence of Grade 3 Anaemia	7.80(1.47-41.38)	0.016	****	

**** biased data

Table 4 : Acute Toxicities Of Patients

Type of toxicity	Grade 1-2		Grade 3+	
	N	%	N	%
Dermatological	7	20.5	15	44.1
Any form of hematological	6	17.6	12	35.3
Electrolyte imbalance	-	-	2	5.8
Gastrointestinal	1	2.9	-	-
Anaemia	6	17.6	4	11.7
Leukopenia	6	17.6	8	23.2
Thrombocytopenia	6	17.6	5	14.7



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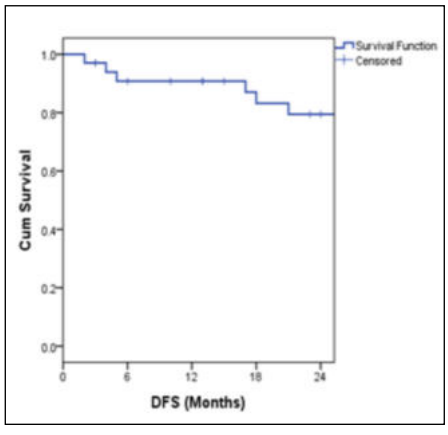

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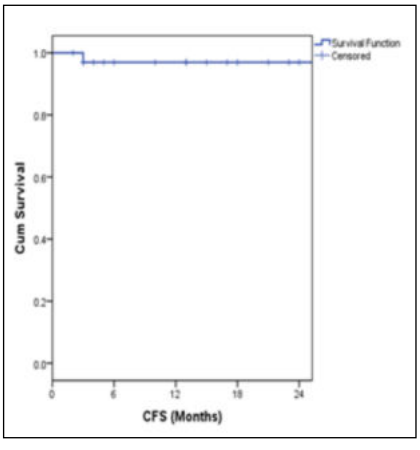

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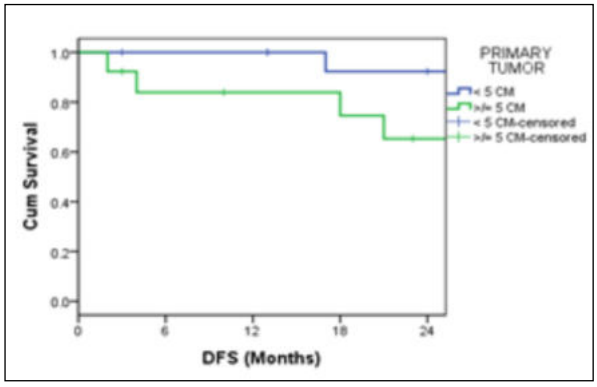
Figure 1 Kaplan Meier Estimates Of (A) OS (B) DFS AND (C) CFS



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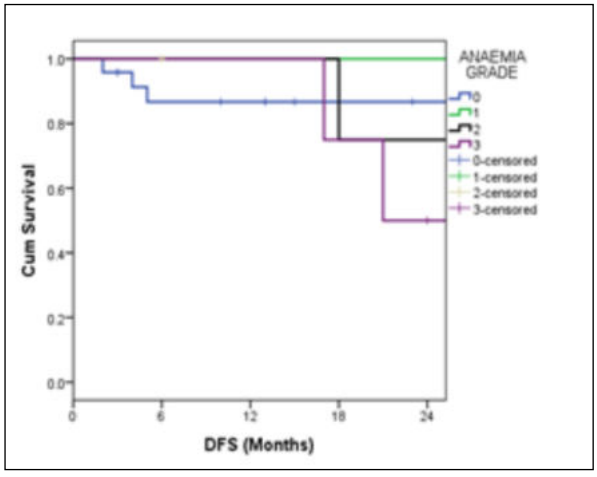

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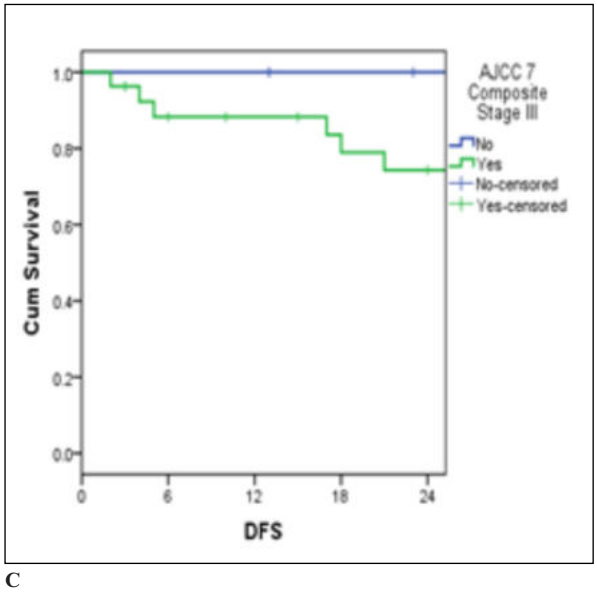

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Figure 2: Kaplan Meier Curves of DFS With (A) Tumour Size (B) Deveolpment Of Anemia And (C) Stage

DISCUSSION

The effectiveness of Concurrent chemo radiation as a radical treatment was established by numerous nonrandomized studies and confirmed in randomized trials [5-9] but undoubtedly, combined CRT approaches are quite toxic owing to the inclusion of normal tissues like the small bowel, bladder, genitalia and pelvic bone marrow. Long-Term Outcomes of NRG Oncology/RTOG 0529 showed: 'Chemo radiation using DP-IMRT for anal canal cancer provided reduced acute morbidity with comparable long-term efficacy and late effects as compared to non-conformal radiation delivery' [14]. IMRT is the most common method of radiation technique in the treatment of ASCC worldwide.

We report five year single institution experience of IMRT in treating ASCC from a tertiary cancer care center in India. Concurrent chemo RT was used in 91.2 %of patients. Our treatment outcomes are favorable with two year DFS, OS, CFS reported as 79.4 %, 93.9 % and 97% respectively at a median follow up of 34 months. RTOG 0529 on their long term efficacy data (2017) had five year DFS, OS and CFS as 68%, 76% and 74% respectively [14]. Various IMRT studies including the RTOG 0529 with the comparison of stage grouping, outcome, toxicities are given in Table 5. We had a favorable DFS, OS at 2 year comparable to them and had a higher CFS than any other reported studies [12, 15-27](Table 5).

Compared to the other IMRT studies our study had 82.5% of patients in the stage III of AJCC C 7TH (Table 5). The subset analysis of the RTOG 9811 trial (2015) reported the effect of tumor stage and LN status on oncologic outcomes with relatively poor disease-free survival for patients with T4N0, T3N+, and T4N+ disease which was 50%, 38%, and 31% respectively [28]. But our DFS, loco regional tumour control and CFS were good even with this advanced stage group. Majority of the patients (70.5%) were treated with SIB technique in this study and this has reduced the overall treatment time and may be the reason for the better loco regional control and CFS. Median overall treatment time was 36 days (range 31-50) in this study compared to 43 days for RTOG 0529 (range 32-59) and 49 days (range 4-100) for the RTOG 9811[11, 9]. A large 16-year single institution experience utilizing IMRT for patients with ASCC by K.R.Jethwa et al (2021) showed that Overall treatment duration greater than 39 days was associated with an increased risk of LRR (Hazard Ratio [HR]: 5.2, 95% CI: 1.4–19.5,p = 0.015) [27]. A Pooled Data Analysis of Radiation Therapy Oncology Group Trials 87-04 and 98-11 by Ben-Josef et al (2010) shown that total treatment time duration of more than 53 days was associated with an increased risk of LRR and colostomy and may have a detrimental effect on local control and CFS in anal cancer [10]. R. Glynne-Jones et al (2020) in a post hoc analysis from the randomized phase III ACT II trial showed prolonging the overall treatment duration greater than 42 days was associated with worse Progression Free Survival and OS[29]. Thus reducing the overall treatment time in this study by the usage of SIB technique in dose delivery might have resulted in the superior CFS and favorable DFS even after the majority of patients being in the stage III.

Advanced primary tumor (size more than 5 cm) was associated with inferior DFS in our study (HR= 4.96 95% CI =0.99-24.76; P=0.051). This association was reported in two other studies [14, 21]. Long-Term Outcomes of NRG Oncology/RTOG 0529 by L.A. Kachnic et all (2017) showed that 'tumor size of more than 4 cm was associated with increased loco regional failure (HR = 3.78, 95% CI = 0.78-18.40; P = 0.099) and poorer OS (HR = 2.41, 95% CI = 0.87-6.65; P = 0.089)' [14]. D. Mitra et al (2017) on their study showed advanced T-stage was associated with significance for the outcome of Event Free Survival (hazard ratio 4.9; 95% confidence interval1.75-13.89; P = .003) [21].

Development of grade 3 anemia during treatment was associated with inferior DFS in this study ((HR=7.805 95% CI =1.47-41.38; P value 0.016). Pretreatment mean Hemoglobin (Hb) value was 12.2Gm / DL (range 6-17) in our study but during treatment development of anemia of any grade was reported in 29.4 % of patients (14.7% grade 2 and 11.8% grade 3). GB Roldan et al (2010) in their retrospective study showed ' a pretreatment Hb level of <130 g/L was associated with worse progression-free and overall survival (both P < .0001) and Hb on-treatment value of <121 g/L was associated with PFS and OS (P < .0001 and P = .019, respectively) when stratified by gender' [30]. Irena Oblak et al (2016) evaluated the influence of anaemia on radio chemotherapy treatment outcome in patients with squamous cell carcinoma of the anal canal. Patients with mean on-treatment Hb > 120 g/L had statistically significant better LRC and OS than patients with Hb ≤ 120 g/L in this study where patients were treated with both 3D Conformal and IMRT [31]. None of the other IMRT studies has shown any association with development of anaemia during treatment and clinical outcome in ASCC patients.

The number of chemotherapy cycles taken concurrently with radiation was seen associated with OS in this study, with patients having less than two cycles of chemotherapy showing a trend for inferior outcome (HR=0.16 CI=0.02-1.12;P value 0.064). In our study 81.5 % of patients had two cycles of chemotherapy in the 5 FU +MMC group. One patient receiving Cisplatin +5 FU had only one course of chemo due to grade 4 hyponatremia after the first cycle resulting in poor performance status. The reason for skipping the second dose in all other patients was persistence of hematological toxicity. The percentage of patients receiving the full course of chemotherapy in various studies is given in table 6 . In the landmark trials of ASCC [UKCCR, RTOG98-11, ACT II] it varied from 75 to 95% [6-9] while in the IMRT series it varied from 74% to 91.4% [Table6]. In none of these studies there has seen any association between the number of cycles of chemotherapy and overall survival.

Regarding acute toxicities we had more percentage of patients with grade 3 or more dermatological toxicities compared to RTOG 0529 (44% vs. 23%) [11], but was definitely less than the 3DCRT studies - ACT II and RTOG 98-11 (48% and 49% respectively) [8, 9]. The prospective IMRT studies by Han et al (2014) and Vendrely et al (2015) had similar dermatological toxicity [12, 16]. Grade 3 hematological toxicity was less in our study compared to RTOG0529 (35.3% VS 57.6%) [11]but one patient had grade 5 hematological toxicity which was reported early during the course of treatment (post chemo day 5) and he died of toxicity one week after starting treatment. This patient might have had DPD deficiency which was not routinely done at that time. Acute Gastro Intestinal (GI) toxicities were less, with none of them having grade 3 GI toxicity. One of the advantages of IMRT is reduction of acute grade 3 GI toxicities which was not reported in this study compared to, 21% RTOG0529 and 36 % in RTOG 9811. Being a retrospective study may be under reporting of GI toxicities might have resulted in reduced percentage.

When analyzing the acute dermatological toxicity since this is a retrospective data there is lack of clarity regarding the documentation of grade of toxicity. There may be an overestimation of dermatological toxicity. Treatment interruption is a sign of acute toxicity especially grade 3+ dermatological toxicity. Although grade 3 + dermatological toxicities were higher in this study, percentage of patients needing treatment break was less than the RTOG 0529(38.2% Vs 49%) [11]. The median days/ range of RT break in our study was comparable with the studies by Han et al (2014), Vendrely et al(2015), K. Joseph et al (2015), Arcadipane et al (2017) and Foster et al(2018) [12,16,17,22 ,24] .The prospective studies of IMRT other than the RTOG 0529 were that by Han et al (2014), Vendrely et al(2015) and K.Joseph et al(2015)[12,16,17] and in all these studies the percentage of patients with grade3+ dermatological toxicity and treatment break were well correlated due to the prospective nature of the studies.

Among evaluable patients chronic toxicities were reported for 40% and were of grade 2 only in our study. The most common was chronic GI toxicities. This is comparable to the various IMRT series[17,21,24,27] .Worst overall late effects in RTOG 0529 [2017] was '18% grade 1, 55% grade 2, 16% grade 3, 0% grade 4, 2% grade 5 (sinus bradycardia)'[17]. K.R.Jethwa et al(2021) reported late grade 3+ Adverse Events as GI (3%), Genito Urinary (GU) (2%), and pain (1%)[27]. Foster et al (2018) reported late GI and GU toxicity for 62% of patients, of which grade 2 GI was 25%, grade 3 GI was 3% and late grade 2 GU was 9% [24]. In the Study by D. Mitra et al (2017) 15% of patients developed a grade 2 +late toxicity, including 12% of patients developing radiation proctitis and the most common late toxicity was grade one diarrhea observing in 37% of patients. Grade 3 toxicity was reported only in 3% of patients [21].

To our knowledge this is the largest clinical data on IMRT for ASCC, with majority of patient's dose delivery by SIB technique, from Indian population with detailing of toxicities with analysis of factors affecting outcome. Data from another South Indian institute by Singh, K.et al (2021) shows 75% of patients disease free after a Median follow up time of 7.5 months and grade III skin toxicity of 35 % (CTCAE version5) [34]. Compared to western data, percentage of patients presenting in advanced stage of the disease are more in our study. The results are encouraging and provide continued support for the use of IMRT in ASCC. This study has some limitations. First of all this is a retrospective study and hence limited by underestimation of some acute toxicity like GI and GU toxicities and overestimation of dermatological toxicity .Chronic toxicities may be underestimated due to the retrospective nature of data collection .Assessments of clinical outcome were limited by smaller number of patients and relatively less number of events and a proportion of patients having lost to follow up. Patient reported toxicities and quality of life data are not available. The percentage of patients having lost follow up was higher which might have resulted in overestimation of outcomes. Retrovirus status was unknown for 47.1% of patients.

CONCLUSION

This data from the Asian subgroup of patients and its comparison to other IMRT series from the western world clearly shows that IMRT is associated with favorable toxicities and good local control in Indian population also and it can be used as the preferred technique for treating ASCC. Correction of Anemia during treatment should be given importance. Careful RT planning to reduce the Bone Marrow involved in RT portals may help in reducing the hematological toxicity further and thus more percentage of patients receiving the full course of chemotherapy. Reducing the total treatment time by SIB technique may improve the clinical outcome.

Table 5 Comparison Of Various IMRT Series With Present Study

STUDY [REF]	NATURE/YEAR OF PUBLICATION	NUMBER OF PATIENTS/ STUDY	STAGE DISTRIBUTION (%)		DOSE TO PRIMARY-RANGE (GY/#)	DOSE TO LUMPH NODES(GY/#) RANGE	DFS[yr] (%)	OS[yr] (%)	CFS[yr] (%)	ACUTE TOXICITY GRADE >OR = 3(%)		TREATMENT BREAK	
Current study	Retrospective/	34/5	Stage I-II	Stage III	50/25-60/30	30.6/17-45/25	79.4[2]	93.9[2]	97[2]	Dermatological	Hematological	DAYS-median (range)	% of patients
			17.6	82.4						44	35.3	5.5(2-13)	38.2
RTOG 0529 [1,17]	Prospective phase2 /2012	63-52 evaluable / NA	54	46	50.4/28-54/30	42/28-54/30	68[5] 60[8]	76[5] 68[8]	74[5] 66[8]	23	57.6	0(0-12)	49
Han et al[12]	Prospective cohort/2014	58/ 2.4	66	26	45/25-63/35	27/15-36/20	77[2]	90[2]	84[2]	46	38	8(1-15)	45
Janssen et al[15]	Retrospective/2014	25/ 5.5	NA[x]	NA[x]	54/30-59/32	38-45/25	92[2 y]	88[2]	92[2]	24	16	1(1-4)	40
Vendrely et al[16]	Prospective/ 2015	64/5	NA[z]	NA[z]	59.4/33	45/25	68.7[1]	85.6[2]	75.5[1]	46.9	17.2	5.9[a](0-23)	46.8
K.Joseph et al[17]	Prospective phase II/2015	57/ NA	48	52	54/30	45/30	80[3]	91[3]	77[3]	11	45.7	6-14[b]	14.03[b]
P.Franco et al[18]	Retrospective/2015	54/7	54	46	50.4/28-60/30	42/28-54/30	65.5[4]	77.7[4]	68.9[4]	13	13[c]	3.9[a]	17
Call et al[19]	Retrospective /2016	152/NA	NA	NA	51.25/28 (median)	Varied with centers	Local control - 87[3]	87[3]	92[3]	20	41	NA	NA
Nathalie B et al[20]	Retrospective/2016	106/7	36.8	54.7	59.4/33	49.5/33	79[4] (LRC)	77[4]	77[4]	67 (CRT)	8 (CRT)	NA	5.7
D. Mitra et al[21]	Retrospective/2017	99/11	52	47	50.4/28-54/30	42/28-54/30	75.5[4](EFS)	85.8[4]	NA	13	63	3(NA)	34.3
Arcadipane et al[22]	Retrospective/2017	87/9	62.1	37.9	50.4/28-54/30	42/28-54/30	71[3]	79[3]	64[3]	16	26	NA (1-9)	13.8
Franco et al[23]	Retrospective comparative study /2018	190/9	53.1	46.9	50.4/28-59.4Gy/30	36/20-45/30		87.5[2] (SIB); 85.4[2] (SeqB)	78.1[2] (SIB) 73.5[2](SeqB)	NA	26(SIB) 22(SeqB)	NA	NA
Foster et al[24]	Retrospective/2018	52/17	NA[m]	NA[m]	54(median 45-59.4)	30.6/17-45/15	FFLRF- 94[3] FFDM-85[3]	90[3]	91[3]	42.3	62.5[d]	NA(1-10)	61.5
Bryant et al[25]	Retrospective /2018	376/16	60	40	53.5(mean)	NA	NA	74[5]	10[5] (colostomy rate)	NA	47	NA	43
Shakir et al[26]	Retrospective/2020	385/5	42	57.4	50.4-53.2 in 1.8Gy/#	40-53.2 in 1.8 Gy/#	75.6[3]	85.6[3]	69[3]	NA	NA	NA	3.1
K.R.Jethwa et al[27]	Retrospective /2021	127/16	28	60	50.4 Gy–54.0 Gy/ 25–30	42.0 Gy–56.25 Gy/ 25–30	78[4]-(PFS)	81[4]	77[4]	16	32	NA	NA

***x**-composite staging not available; majority early stage -60% T1 $ T2, 0nly 24 % N2 or N3; **y**- 2-year-local control and distant metastases-free survival **; z-** 67.2 % of these tumours were T3 or T4 tumours and sixty-one percent of the patients had lymph node involvement;*

***a**-mean; **b**-Exact figure not given; calculated from the supplementary data; **c**-Neutropenia; **m**-composite stage NA - T2/T3 (79%), N0 (62%); d-leucopenia*

NA –Not Available ; **LRC** -Locoregional control; **CRT**- Concurrent ChemoRT; **EFS**-Event Free Survival;**FFLRF**-freedom from loco regional failure: **FFDM** - freedom from distant metastasis

Table 6: Data Of Patients Receiving The Full Course Of Chemotherapy In Various Studies

STUDY (YEAR)	RT TECHNIQUE (3DCRT/IMRT)	%OF PATIENTS RECEIVING FULL CYCLE OF CHEMO (5FU +MMC)
UKCCR (1996)[6]	3DCRT	74
RTOG 98-11 trial (2008)[8]	3DCRT(MITOMYCIN GP)	95
ACT II (2013) [9]	3DCRT	75
J.A. Call et al (2012) [32]	IMRT	91
Han et al (2014) [12]	IMRT	73.4
Janssen et al (2014) [15]	IMRT	80
P.Franco et al (2015) [18]	IMRT	74[a]
K.Joseph (2015) [17]	IMRT	91.4
D. Mitra et al (2017) [21]	IMRT	92
C M. Jones et al(2018 [33]	IMRT	90
Franco et al (2018) [23]	IMRT	83.7
A K. Bryant et al(2018) [25]	IMRT CONVENTIONAL RT	81 57
K.R.Jethwa et al (2021) [27]	IMRT	85

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