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Research Article

Anal Canal Squamous Cell Cancer; Pattern of Recurrence and Survival, 25 Years Experience

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Abstract

Background and objectives: Combined chemo radiation is the standard of care for treatment of squamous cell carcinoma of the anal canal. Our objective was to analyze the treatment results of patients with squamous cell carcinoma of the anal canal treated at our institution.

Methods: We identify patients with confirmed diagnoses of anal canal squamous cell carcinoma treated in our institution (KFSHRC), Riyadh between1994-2017. We retrospectively reviewed their pattern of recurrence and survival rate.

Results: 35 males (70%) and 15 females (30%) were identified. Median age at diagnosis was 58 years. 5(10%) patients underwent initial Abdomino Perineal Resection (APR) while 45 patients (90%) received definitive concurrent chemo radiation (30 using 2D/3DCRT and 15 patients using IMRT). All patients completed their planned treatment course except 4 patients (in 2D/3DCRT arm). IMRT resulted in significant decrease in all toxicity grades in comparison to 2D/3DCRT arm (p value 0.035). After median follow up of 13months, two out of the 5 patients (40%) who underwent initial APR had local recurrence; while after 18 months median follow up 8(19.6%) patients who underwent definitive chemo radiation had local recurrence. The 2 and 5 years Disease Free Survival (DFS) were 79.4% and 53% respectively in IMRT group *vs* 64% and 55% respectively in 2D/3DCRT group (p value 0.79). Regarding Overall survival (OS), the 2 and 5 years OS were 82% and 41% respectively in IMRT *vs* 66% and 44% respectively in the 2D/3DCRT group(p value 0.36). In Univariate analysis, only number of chemotherapy cycles was statistically correlated with DFS and OS with (p value of 0.02 and <0.0001) respectively.

Conclusion: Combined chemo radiation therapy for anal canal squamous cell carcinoma is effective treatment in term of local control and survival. The recurrence and survival pattern of our patients' cohort compare favorably to the international results. Radiation therapy using IMRT resulted in significant decrease of all toxicity grades over 2D/3DCRT, with improvement of the 2 years DFS and OS in comparison to the 2D/3DCRT although it was not statistically significant. In Univariate analysis initial Hb level was not significantly correlated with DFS or OS at 5 years, only number of chemotherapy cycles was statistically correlated with survivals at 5 years.

Introduction

Malignant tumors of the anal canal are considered to be a rare neoplasm represents 0.43% of all malignancies and 2% of the digestive tract malignant tumors [1,2]. Overall, the most common cancer of the anal canal is squamous cell carcinoma (85%), followed by adenocarcinomas (10%). The other rare types such as melanoma, basaloid carcinoma and lymphoma represent less than 5% of all diagnosed tumors of the anal canal [2].

The annual incidence of anal canal cancer has been of 1 in 100,000 people, with higher incidence in females; with about 8600 new cases are diagnosed annually in USA [3]. The survival rate had been changed very little in the last 2 decades. TN stage is the most important prognostic factor for survival, the 5 years survival rate ranged from 45-86% according to stage [4,5].

Some risk factors have been responsible for the development of this neoplasm like Human Papillo Mavirus (HPV) infection, history of sexually transmitted disease and Human Immunodeficiency Virus (HIV) infection [6,7].

Initially, up to the 1980s, surgery in term of Abdominoperineal Resection (APR) with permanent colostomy was the treatment for all anal carcinomas [4,8], with a high recurrence rate and a survival at 5 years of 30-70% [8].

Concomitant chemo radiation therapy was found to be effective treatment with excellent local control, disease-free survival, and quality of life [9]. A systematic review of large six multicenter clinical trials evaluating the results of the combined treatment and revealed the same results of [9,10]. Thus, the standard treatment for non-metastatic squamous cell carcinoma of the anal canal has been the concurrent chemotherapy using 5-FluoroUracil (5FU) and Mitomycin C (MMC) with radiotherapy [8]. This combined modality approach providing a complete regression in 80-90% of patients and 5 years of survival 61-85% [7,11]. APR surgery with permanent colostomy are usually reserved for patients with residual or recurrent disease after a complete treatment of chemo radiotherapy [12], with a local control in 60% of cases and with 5 years survival rate of 30-60% [7].

The optimal dose of external beam radiation therapy (RT) for the treatment of anal canal cancer is a matter of debate, at least two retrospective studies suggest that 30 Gy of RT with concurrent chemotherapy might be adequate for selected patients with early stage disease [13,14], however, other retrospective reports suggest that RT doses of ≥54 Gy were associated with significantly better overall survival, disease-free survival and local control compared with lower doses [15]. IN United Kingdom (UK), chemo radiation therapy with radiation dose of 50.4Gy/28 fractions without gap and without any boost is considered the standard of care based on a study conducted by James et al who reported excellent complete response rate of 95% [16]. NCCN guidelines recommend a minimum dose of 45 Gy for all patients, a boost dose of 10-14 Gy is added for a total dose of 55-59 Gy. For those patients with T3, T4, or node-positive disease, or T2 tumors with residual disease are 45 Gy [17]. In our institution we usually used a dose of 50-50.4 Gy for T1/T2 disease and 54Gy for T3/T4 disease.

Radiotherapy as well as chemotherapy is known to be more effective in the presence of oxygen than in hypoxic conditions [18-21]. Tumors are thought to be more hypoxic than the surrounding normal tissue. Anemia is present in about 75% of cancer patients, the influence of anemia on the outcome of treatment of many cancer sites was addressed first in cervical cancer patients and later in patients with other tumors such as head and neck squamous cell carcinoma, carcinoma of the lungs, bladder, prostate and anus [22-24].

In this study, we retrospectively analyze the treatment results of our patients' cohort with squamous cell carcinoma of the anal canal to evaluate their pattern of recurrence, survival rate and influence of multi factors including initial HB level on patient outcome.

Patients and Methods

Fifty patients diagnosed with anal canal squamous cell carcinoma in our institution King Faisal Hospital and Research Center (KFSHRC), Riyadh between 1994-2017 were included in this study. All patients had baseline basic labs (CBC, KFT, LFT) and (hepatitis profile and HIV antibody) CT chest abdomen and pelvis, MRI pelvis. PET-CT had been implemented as a routine imaging in our institution for patients with anal canal cancer since 2013), in addition to biopsy of anal canal mass to confirm diagnosis in all patients.

Patients were categorized into 3 categories according to initial Hemoglobin Level (HB) level (category 1 for patients with initial HB less than 10 G/DL, category 2 for patients with HB level between 10-12 G/DL and category 3 for patients with HB more than 12 G/DL). Radiation therapy was given in different dose schedules (50 GY.25 fractions, 50.4 GY/28 fractions or 54 GY/30 fractions), using either 2D/3DCRT (3D conformal radiation therapy or IMRT (intensity modulated radiation therapy. Patients treated with 2D/3DCRT technique had 2 weeks gap after phase 1(initial dose of 30.6Gy/17 fractions) aiming to reduce incidence of acute toxicity. Chemotherapy in form of fluorouracil (5FU) 750 mg/m^2/day (continuous infusion D1-4, D29-33) and mitomycin dose of 12 mg/m^2 (D1, 29). Initial Assessment of response after definitive chemo radiation therapy was done at 8-12 weeks post treatment by local examination. Imaging with MRI pelvis+/PET-CT usually done when indicated. Biopsy usually considered for persistent disease at 12 weeks post treatment.

Statistical Analysis

Descriptive statistics was performed for all available categorical variables. The patients and treatment characteristics were summarized as median (range) values for continuous variables, and frequency (percentage) values for categorical variables. The difference in distributions between the 2 groups (IMRT and 2D/3DCRT) was tested using Pearson's chi-squared test or Fisher exact test. The outcomes studied were local control, DFS and OS. Using Univariate analyses, linear regression model was used to identify independent predictors of control and survival. All statistical tests were two tailed and differences were considered to be statistically significant for a p-value less than 0.05. All statistical analyses were performed using a software package (SPSS version 20, Inc., Chicago, IL, USA).

Results

Fifty patients were included in this review, all patients characteristics listed in Table 1.

Initial APR was performed in 5 patients (10%), while 45 patients (90%) treated with definitive chemo radiation therapy, treatment details are listed in (Table 2).

Based on RTOG-EORTC toxicity criteria, IMRT resulted in significant decrease in all grades of acute toxicity (grade 3 toxicity was 13% *vs* 37.1% for IMRT and 3DCRT respectively with p value of 0.034), detailed toxicity profile listed in (Table 3).

41 patients who completed the full course of chemo radiation therapy were eligible for analysis. Six patients (14.6%) had persistent disease 12 weeks post treatment (2 patients are in IMRT group while 4 patients in the 2D/3DCRT group), (Table 4) showing the detailed response and survival analysis for whole patients group, while (Figures 1 and 2) shows the DFS and OS curves.

Univariate analysis was done for correlation between the DFS and OS at 5 years with multiple factors including (gender, T, N stage, radiation therapy split, initial HB level and number of chemotherapy cycles), only number of chemotherapy cycles was statistically correlated with DFS and OS with (p value of 0.02 and <0.0001) for DFS and OS respectively (Table 5).

Univariate analysis of DFS and OS at 5 years by (gender, T, N stage, radiation therapy split, initial HB level and number of chemotherapy cycles).

Table 1: Patients characteristics.

Characteristics	No.patients				
	2D/3DCRT(30)	IMRT(15)	P-value	Initial APR(5)	All(50)
Gender					
Male	21	11	0.745	3	35
Female	9	4		2	15
Median age, range (years)	59 (27-80)	57 (32-90)	0.542	55 (40-60)	58 (27-90
Initial T stage					
Tx				3	3
T1	1	2			3
T2	13	8	0.373	1	22
T3	5	2			7
T4	11	3		1	15
Initial N stage					
Nx				1	1
N0	22	2	**0.0053**	1	25
N1	1	3		1	5
N2	5	6		1	12
N3	2	4		1	7
AJCC stage group					
II	15	2	**0.029**	1	18
IIIa	5	3		2	10
IIIb	10	10		2	22
Initial HB at presentation					
Category 1	1	1	0.816		2
Category 2	14	5		2	21
Category 3	15	9		3	27
Immunity status					
Immuno competent	29	12		5	46
Immune compromised	1	3		0	4

Table 2: Treatment modalities used.

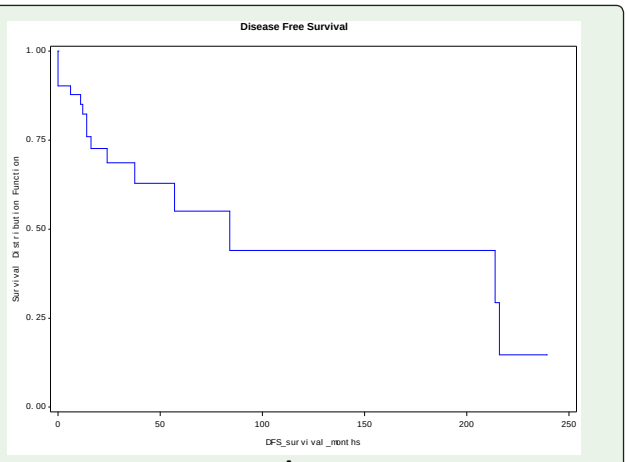
Treatment	No of patients
Initial APR	5
Definitive Radiation therapy	45 (15 IMRT, 30 3DCRT)
Complete the chemo radiationcourse	
Yes	41
No	4 (3DCRT)
Dose of radiation therapy	
50 GY/25 fractions	26
50.4 GY/28 fractions	3
54 GY/30 fractions	12
Chemotherapy	
1 cycle	4 (3DCRT)
2 cycles	41

Table 3: Differences in toxicity grades and pattern between the two radiation therapy groups.

Toxicity	IMRT, NO patients (percentage)	2D/3DCRT, No patients (percentage)
Grades		
Grade 1	5 (33%)	24 (68.6%)
Grade 2	4 (26.7%)	14 (54.3%)
Grade 3	1 (6.7%)	13 (37.1%)
Forms		
Acute		
Diarrhea	3 (20%)	14 (40%)
Vomiting	4 (26.6%)	12 (34.3%)
dermatitis	4 (26.6%)	15 (43%)
myelosuppression	3 (20%)	15 (43%)
chronic		
anal canal stenosis	0	1 (2.8%)

Table 4: response and survival assessment for whole patients group.

	2D/3DCRT (26 cases)	IMRT (15 cases)	P-value	Initial APR (5 cases)
Response at 12 weeks				
CR	22 (84.6%)	13 (86.6%)	0.266	
Persistent disease	4	2		
Median follow up (months)	18	18		13
Recurrence				
NO	15	11		2
Local	7 (27%)	1 (6.7%)	0.35	2 (40 %)
Distant	4	3		1 (20%)
2 years DFS%	64	79.4		
5 years DFS%	55	53	0.79	
2 years OS%	66%	82%		
5 years OS%	44%	41%	0.36	



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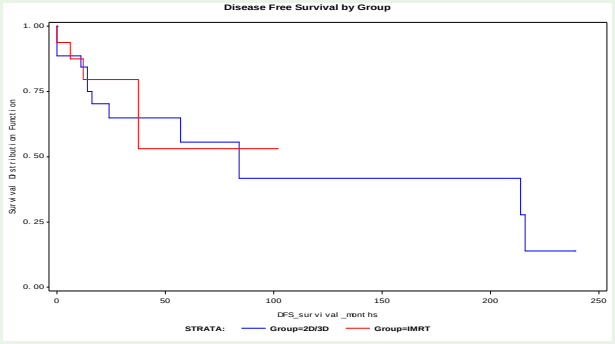

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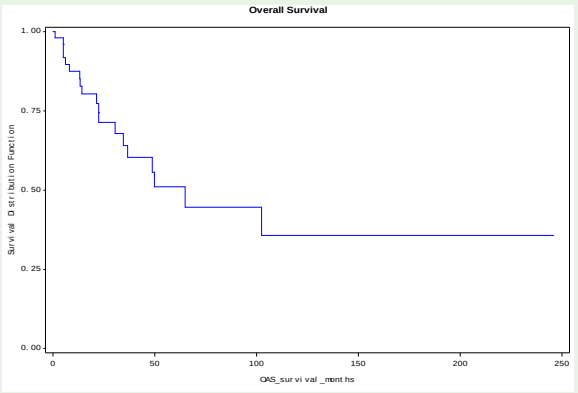
Figure 1: Showing DFS (**A** for whole patients group and by radiation treatment group).



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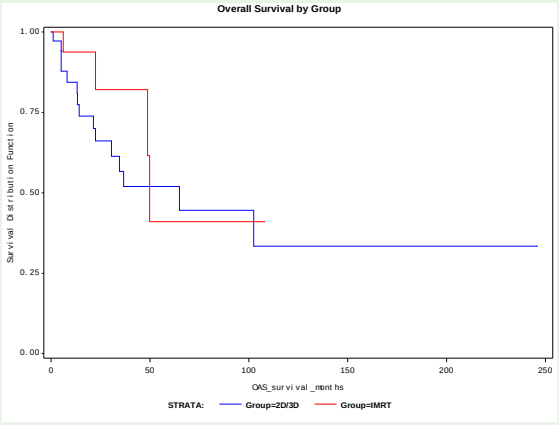

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Figure 2: Showing OS (**A** for whole patients group and by radiation treatment group).

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Table 5: Univariate analysis of DFS and OS at 5 years by (gender, T, N stage), radiation therapy split, initial HB level and number of chemotherapy cycle.

Parameter	Correlated factors	P value
DFS	Sex	0.219
	T stage	0.372
	N stage	0.274
	Initial HB at presentation	0.395
	Radiation therapy split	0.528
	Number of chemotherapy cycles	***0.02***
OS	Sex	0.223
	T stage	0.147
	N stage	0.171
	Initial HB at presentation	0.328
	Radiation therapy split	0.925
	Number of chemotherapy cycles	***0.001***

Discussion

Definitive chemo radiation therapy is the current standard of care and provided excellent results in term of sphincter preservation, loco-regional control and overall survival in expense of relevant acute dermatological, genitourinary and gastrointestinal toxicities. Earlier in the clinical trials, people used the 2D technique in which the bony land mark was used to guide for radiation field using X ray images, then eventually radiation techniques improved with using CT based, 3DCRT with better delineation of both target and risk structures with improving treatment accuracy, despite the better treatment tolerability with less toxicity of 3DCRT over 2D technique , the incidence of grade ≥3 gastrointestinal (GI) and skin toxicity reported in Radiation Therapy Oncology Group (RTOG) 98-11study were 34% and 48%, respectively [25]. Intensity Modulated Radiation Therapy (IMRT) based on the delivery of non-uniform photon beams from different entry portals to generate a highly uniform target irradiation with the maximization of the sparing of the surrounding healthy tissues, with a great ability to reduce acute and chronic treatment-related toxicity. The use of IMRT in treatment of anal canal cancer resulted in lower rates of acute and late grade > 3 toxicity while maintaining at least similar outcomes in terms of local control and survival as reported in several studies [26-32].

Regarding our data we had total 50patients , median age at diagnosis was 58(95%CI 52.7-61.1), 35(70%) patients were males while 15(30%) patients were females in comparison to worldwide incidence where the average age at diagnosis is 60 years , while the disease was more common in females.

Five out of 50 patients (10%) underwent initial APR, although it is not the standard of care in our hospital since 1990s, but all these patients were treated with surgery outside our hospital and then referred to us for further treatment. After median follow up time of 13 months, local control rate was 60% , with median DFS and OS of 12.8 and 22.2 months, these results were comparable to the reported poor results for Initial APR with local recurrence rates as high as 50% and 5-year survivals rates of only 33% to 60% [4,33,34].

Forty-five patients underwent definitive Chemo Radiation Therapy (CRT), 30 patients in the 2D/3DCRT arm while 15 patients in the IMRT arm. IMRT resulted in better local control rate (93.3% for IMRT *vs* 73% in 3DCRT). 2 years DFS (79.4% in IMRT *vs* 64% in 2D/3DCRT group and 2 years OS (82% in IMRT *vs* 66% in 3DCRT group), in spite of the more advanced stage (stage III and N+ disease in IMRT group rather than those patients in 3DCRT). The non-statistically significant difference between the two groups could be due to the small sample size, these results were comparable to a study conducted by Bazan et al. [31], where the 3-years OS, Loco Regional Control (LRC), and Progression-Free Survival (PFS) were 87.8%, 91.9%, and 84.2%, respectively, for the IMRT groups and 51.8%, 56.7%, and 56.7% respectively in the 3DCRT group.

In spite of better 2 year DFS and OS in the IMRT than the 3DCRT group in our study , the 5 years DFS and OS were comparable between the 2 groups, this may be due to that most of the recurrences local and distant were occurring in the first 2 years post treatment in 2D/3DCRT , moreover most of the treated patients in IMRT group treated in the period between 2015 and 2017 with shorter follow up time and eventually shorter survival than those patients treated in 2D/3DCRT group treated in the period between 1993 and 2008.

In Univariate analysis for DFS and OS at 5 years, only number of chemotherapy cycles was statistically correlate with survival. Radiation therapy split with a planned gap after phase 1was not significantly correlated with either DFS or OS. In comparison to the results from the study conducted by Bazan et al. [31], where treatment duration was independent prognostic factor for OS, also the initial HB level was not significantly correlate with either DFS or OS in our study, however another study conducted by Oblak et al. [35], concluded that pre-treatment Hb> 120 g/L was an independent prognostic factor for OS of patients with anal canal cancer. The difference between our results and these studies may be due to the small patients' number enrolled in our study.

IMRT treatment course was completed in all patients with only two breaks (with average overall treatment time of 44 days), while 4 out of 30 patients (13.3%) in 2D/3DCRT did not complete their treatment course due to severe toxicity (with average over all treatment time of 54 days). IMRT resulted in significant decrease in the rate of acute toxicity (all grades) than 2D/3DCRT. In reviewing acute toxicity grades in IMRT group , the incidence of grade 3 toxicity is limited only for hematological toxicity in 6.7% with no reported gastrointestinal or dermatologic toxicity, in comparison to the RTOG 05-29 phase II study [29], the incidence of ≥ grade 3 hematologic toxicity is 51%, dermatologic toxicity is 10% and gastrointestinal toxicity in 7%, another study conducted by salama et al. [27], the incidence of ≥ grade 3 gastrointestinal toxicity is 15.1% , dermatological toxicity is 37.7% while hematological toxicity is 30%. The difference in toxicity rate between our patients cohort in IMRT arm and these studies may be related to the more strict dose constrains applied in our cases(small bowel V45Gy< 20 cc and maximum point dose of 50 Gy, and for the bone marrow V40 Gy<35% and mean dose < 20 GY).

6 out of 41 patients (14.6%) had persistent disease post full course Chemo RadioTherapy (CRT), 2 patients in IMRT and 4 patients in 2D/3DCRT group, the results was comparable to results of RTOG 05-29 study. [29], where seven patients (14%) had clinical disease

persistence and one had clinical progression. Local failure occurred in 8/41 patients (19.5%) in our patient cohort (1 in IMRT and 7 patients in 2D/3DCRT group) , in comparison to a study previously conducted in our department by El Haddad et al. [36], where the whole 33 patients of anal canal cancer underwent chemo radiation therapy course using mainly the 2D and to lesser extent 3DCRT, the local failure rate was approximately 30% and five-year PFS was 50.86%, the improvement noticed in the current study than the previous one comes mainly from the IMRT arm where the local failure rate is 1/15(6,7%), while in the 2D/3DCRT was 26.9%. These results was comparable to the previous date from many trials with reported failure rate of CRT in 20-30% of patients, resulting in persistent or local recurrent disease in 10-15% of cases [4,37,38].

Conclusion

Combined chemo radiation therapy for anal canal squamous cell carcinoma is effective treatment in term of local control and survival .The recurrence and survival pattern of our patients cohort compare favorably to the international results. Radiation therapy using IMRT resulted in significant decrease of all toxicity grades over 2D/3DCRT, with improvement of the 2 years DFS and OS in comparison to the 2D/3DCRT although it was not statistically significant. In Univariate analysis initial Hb level was not significantly correlated with DFS or OS at 5 years, only number of chemotherapy cycles was statistically correlated with survivals at 5 years.

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