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Original Article

Epidemiological and prognostic single center study of anal carcinoma

Alaa Mobder Mohammed Alrubai[a], *Manwar Abdulelah Al-Naqqash*[b], *Ahmed Salih Alshewered*[c,*]

[a] *Alamal National Hospital, Baghdad Medical City, Ministry of Health/Environment, Baghdad, Iraq*
[b] *Department of Surgery, University of Baghdad, College of Medicine/Baghdad Radiotherapy and Nuclear Medicine Center/Oncology Teaching Hospital/National Cancer Center, Baghdad Medical City, Baghdad, Iraq*
[c] *Misan Radiation Oncology Center, Misan Health Directorate, Ministry of Health/Environment, Misan, Iraq*

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ABSTRACT

Background: Anorectal carcinoma includes the anal margin, the anal canal, and the lower rectum. The incidences of anal tumors represent 1.4 % of all gastrointestinal tumors.
Patients and methods: Our study is retrospective and was conducted at Baghdad Medical City. Patient's data were collected from the medical records through a predesigned sheet that included the following information: demographic data, medical history, past-history, presenting symptoms, pathological data, and treatment details.
Results: The median age was 49 years. As regard tumor extension, 85.71 % of patients had anal disease, while anorectal cancer was encountered in 14.28 % of cases only. Male to female ratio was 1:3. Most of cases were SCC 78.57 %. Only 11 patients (39.28 %) were diagnosed as Stage I, whereas 12 patients (42.85 %) had Stage II-III disease. Moderate differentiated tumors are the most common. The tumor mass located between 5–10 cm das a distance from anal verge in 12 (42.85 %) of patients. We found 6 (21.42 %) patients with positive virology tests with no specificity detected. APR was the mainstay for treatment of stage I disease. Neoadjuvant treatment followed by TME resection was the treatment found in locally advanced tumors. The mean Overall Survival (OS) for patients received neoadjuvant CRT in the study was 43.5 months, while, the mean OS was 45.73 months in the adjuvant setting. Univariate analysis for OS according to prognostic factors revealed that sites of cancer, grades and histopathology were significant independent prognostic factors for OS in this study. The anal canal tumor was associated with shorter OS (33.25) months in comparison to the anorectal cancer (OS = 47.22 months). Based on tumor grade, well and moderate differentiation have better OS (60.21 months) while, poorly grade was associated with shorter OS (43.07 months). On the concern of SCC, it was associated with shorter OS (37 months) in comparison to higher survival in patients with adenocarcinoma (46.13 months).

* Corresponding author.
E-mail: ahmedsalihdr2008@yahoo.com (A.S. Alshewered).
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Conclusion: Anal canal cancer has poorer prognosis than anorectal. The early-stage has a better OS that needs more effort for early diagnosis and treatment.

Estudo epidemiológico e prognóstico em um único centro de carcinoma anal

Palavras-chave:
Cânceres anorretais
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RESUMO

Antecedentes: O carcinoma anorretal inclui a margem anal, o canal anal e o reto inferior. A incidência de tumores anais representa 1.4 % de todos os tumores gastrointestinais.
Pacientes e métodos: Nosso estudo é retrospectivo e foi realizado no Baghdad Medical City. Os dados do paciente foram coletados dos registros médicos por meio de uma folha pré-projetada que incluía as seguintes informações: dados demográficos, histórico médico, histórico anterior, sintomas de apresentação, dados patológicos e detalhes do tratamento.
Resultados: A idade média foi de 49 anos. Quanto à extensão do tumor; 85,71 % dos pacientes apresentavam doença anal, enquanto o câncer anorretal foi encontrado em 14,28 % dos casos. A proporção homem/mulher foi de 1:3. A maioria dos casos foi de CEC 78,57 %. Apenas 11 pacientes (39,28 %) foram diagnosticados como Estágio I, enquanto 12 pacientes (42,85 %) apresentavam doença em Estágio II–III. Tumores diferenciados moderados são os mais comuns. A massa tumoral localizada entre 5–10 cm das distâncias da margem anal em 12 (42,85 %) dos pacientes. Foram encontrados 6 (21,42 % pacientes com testes virológicos positivos sem especificidade detectada. A TAEG foi a base para o tratamento da doença em Estágio I. O tratamento neoadjuvante seguido pela ressecção do TME foi o tratamento encontrado em tumores localmente avançados. A sobrevida global média OS dos pacientes que receberam TRC neoadjuvante no estudo foi de 43,5 meses, enquanto a OS média foi de 45,73 meses no cenário adjuvante. A análise univariada para OS de acordo com fatores prognósticos revelou que locais de câncer, notas e histopatologia foram fatores prognósticos independentes significativos para OS neste estudo. O tumor do canal anal foi associado a SG mais curtos 33,25 meses em comparação ao câncer anorretal OS = 47,22 meses. Com base no grau do tumor, a diferenciação boa e moderada apresenta melhor OS 60,21 meses, enquanto o grau ruim foi associado a um OS mais curto 43,07 meses. No que diz respeito ao CEC, este foi associado a uma OS mais curta 37 meses em comparação à maior sobrevida em pacientes com adenocarcinoma 46,13 meses.
Conclusão: O câncer de canal anal tem pior prognóstico que o anorretal. O estágio inicial tem um sistema operacional melhor que precisa de mais esforço para diagnóstico e tratamento precoces.

Introduction

At 2017, in UA, an estimation of 8200 new patients of anal carcinoma, thus accounting 2.6 % of GIT tumors.[1] About 1/8 of that number have been died. According to SEER data analysis, the incidence of anal SCC increased at a rate of 2.9 % year from 19thcentury to 20th century.[1] It is associated with Human Papilloma Virus (HPV) infection; anal genital warts; history of anal intercourse; STDs; HIV; gynecological malignancies; and others.[1] A strong association between anal tumor and HPV infection especially HPV-16, and HPV-18.[1] The incidence of anal malignancy has been increased in the last 30 years, both in the United States (US) and elsewhere particularly in women.[2] Females are more likely to develop anal cancer than males (ratio of 5:1), this is due to high prevalence of HPV.[2] Homosexuality is increasing the risk of developing anal cancer. Among heterosexual, the number of lifetime sexual partners and the young age at first intercourse are associated with high risk of developing anal cancer.[2] Adenocarcinomas are the most frequent pathological subtype than Squamous Cell Carcinoma (SCC) due to the anorectal region is formed mainly of glandular structure.[2] The high grade of Anal Intraepithelial Neoplasia (AIN) may be a precursor to cancer, and treated this condition may be prevent the development of anal cancer.[1] Many ways of detection of AIN like cytology, HPV virology tests, DRE, anoscopy, and biopsy.[1]

The aims are to study clinico-epidemiological characteristics of the patients with anal carcinoma presented to Oncology Teaching Hospital and National Cancer Center at Baghdad

Medical City from the period of 2014 up to 2019 and this is the primary end point. The Secondary end point is to assess Progression Free Survival (PFS) and Overall Survival (OS) of the patients with different methods of treatment and evaluation of prognostic factors.

Methods

Study design and setting

This study is a retrospective study and was conducted for 5 years includes a review of the total number of available registered cases of patients with lower rectal and anal carcinoma. They were 28 patients presented to Oncology Teaching Hospital and National Cancer Center, Baghdad Medical City during the period from January 2014 to December 2018 inclusive.

Data sources and collection

Patient's data were collected from the medical records through a predesigned sheet. Medical history was collected as well as risk factors as viral infection and sexual behavior then past history to previous operations and/or pelvic irradiation. The presenting symptoms and signs were collected as bleeding per rectum, perianal pain, change in the bowel habit or loss of weight, anal swelling, abscess or fistula and Intestinal Obstruction (IO). Pathological data were obtained as histopathology, primary tumor size and extent. Treatment details including surgery with different surgical modalities, External Beam Radiotherapy (EBRT) and Chemotherapy (CTH) were reported. Treatments outcomes in the form of PFS and OS were calculated for all our patients.

Statistical analysis

Data were revised, coded and analyzed using the computer program, SPSS version "20". Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (fisher exact test) was used to examine the relation between qualitative variables; p-value considered significant when < 0.05. Survival was evaluated using Kaplan–Meier method.

Results

Patient's and tumor characteristics were shown in Table 1. Median age was 49 years, 9 patients (32.14 %) were less than 40 years old, and 19 patients (67.85 %) were $\geq$ 40 years old. Seven patients were male (25 %) while females were 21 patients (75 %). As regard tumor extension, 85.71 % of patients had anal disease, while anorectal cancer was encountered in 14.28 % of cases only. Male to female ratio was 1:3. Most of cases were SCC 78.57 %, whereas 14.28 % were adenocarcinoma. Only 11 patients (39.28 %) were diagnosed as Stage I, whereas 12 patients (42.85 %) had Stage II–III disease, while, 5 patients (17.85 %) had Stage IV disease at the time of diagnosis. Moderate differentiated tumors are the most common among 67.85 % of tumors; poorly differentiated tumors constitute 17.85 % while well differentiated tumors found in 14.28 %. The tumor mass located between 5–10 cm das a distance from anal verge in 12 (42.85 %) of patients. We found 6 (21.42 %) patients with positive virology tests with no specificity detected.

Table 1 – Patient's and tumor characteristics.

Characteristics	N° (%)
Age in years	
Median (minimum–maximum)	49 (25–75)
Age < 40years	9 (32.14)
Age ≥ 40 years	19 (67.85)
Sex	
Male	7 (25)
Female	21 (75)
Site of primary tumor	
Anal	24 (85.71)
Anorectal	4 (14.28)
Histopathological types	
Squamous cell carcinoma	22 (78.57)
Adenocarcinomas	4 (14.28)
Undifferentiated	2 (7.14)
Clinical stage	
Stage I	11 (39.28)
Stage II–III	12 (42.85)
Stage IV	5 (17.85)
Grade	
Well differentiation	4 (14.28)
Moderate differentiation	19 (67.85)
Poorly differentiation	5 (17.85)
Distance from anal verge	
<5 cm	9 (32.14)
5–10 cm	12 (42.85)
>10 cm	7 (25)
Virology	
Positive	6 (21.42)
Negative	22 (78.57)

Table 2 – Treatment algorithm of 28 patients who received treatment.

Treatment analysis	N° (%)
Stage I	11
APR without adjuvant treatment	4 (14.28)
APR with adjuvant treatment	7 (25 %)
Stage II–III	12
Neoadjuvant treatment followed by TME	7 (25 %)
APR followed by adjuvant CRT	5 (17.85 %)
Stage IV	5
Palliative chemotherapy	2 (7.14 %)
Palliative radiotherapy	2 (7.14 %)
Palliative surgery	1 (3.57 %)

Management details are described in Table 2. APR was the mainstay for treatment of Stage I disease. It is associated with or without adjuvant CRT with a percent from total number of Stage I (11 patients) as 14.28 %, 25 % respectively. Neoadjuvant treatment followed by TME resection was the treatment found in locally advanced tumors Stage II–III (25 %), despite, primary APR followed by adjuvant CRT was managed 17.85 % of patients. Palliative chemotherapy was the prevalent among metastatic disease 7.14 % with palliative radiotherapy 7.14 % whereas palliative surgery performed in 3.57 % of patients.

The mean Overall Survival (OS) for patients received neoadjuvant CRT in the study was 43.5 months, while, the mean

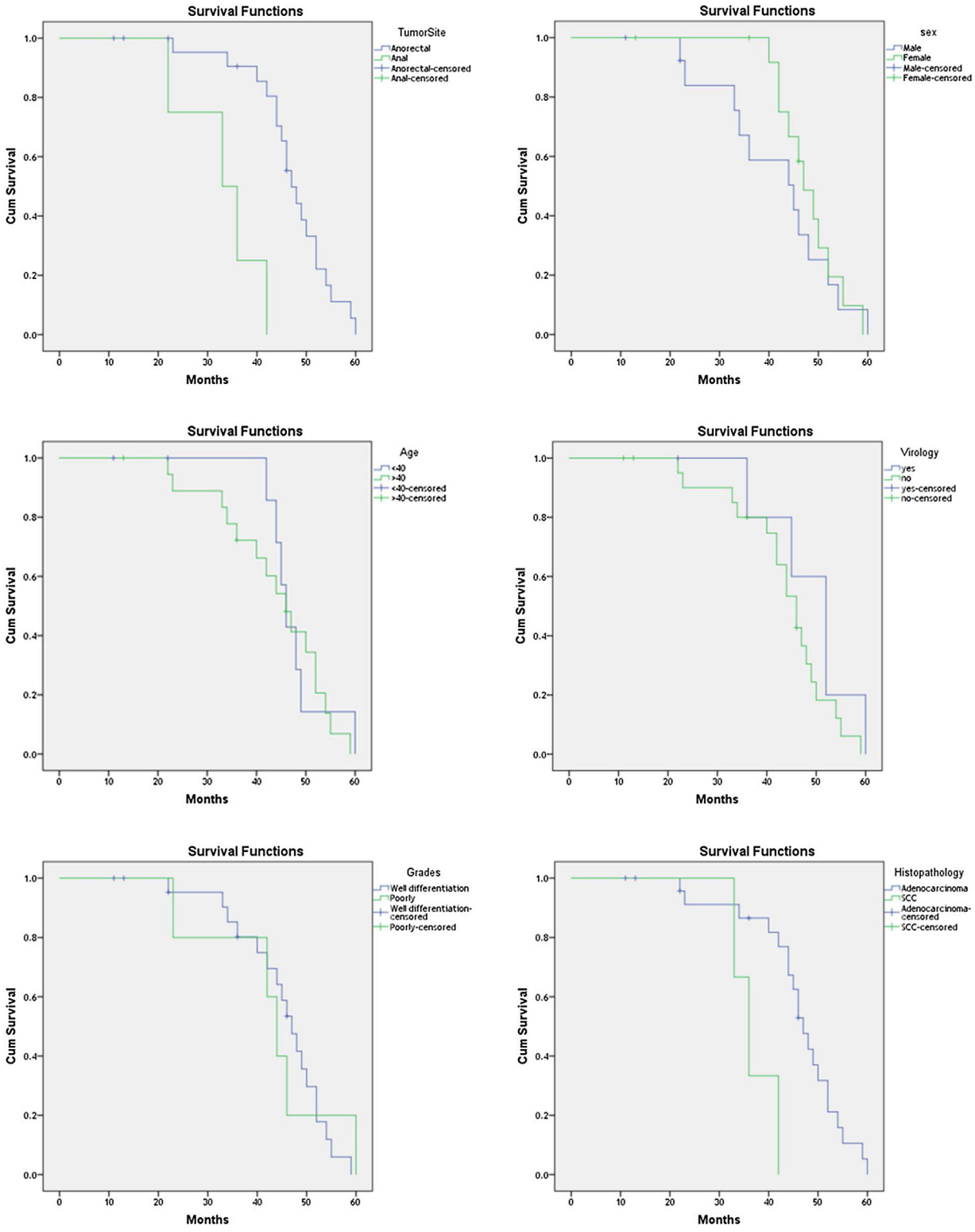

Fig. 1 – Overall survival (OS) curves according to prognostic factors.

OS was 45.73 months in the adjuvant setting. Univariate analysis for OS according to prognostic factors as shown in Table 3 revealed that sites of cancer, grades and histopathology were significant independent prognostic factors for OS in this study. The anal canal tumor was associated with shorter OS (33.25) months in comparison to the anorectal cancer (OS = 47.22 months) and this was highly statistically significant ($p < 0.000$). Based on tumor grade, well and moderate differentiation have better OS (60.21 months) while, poorly grade was associated with shorter OS (43.07 months) and this was

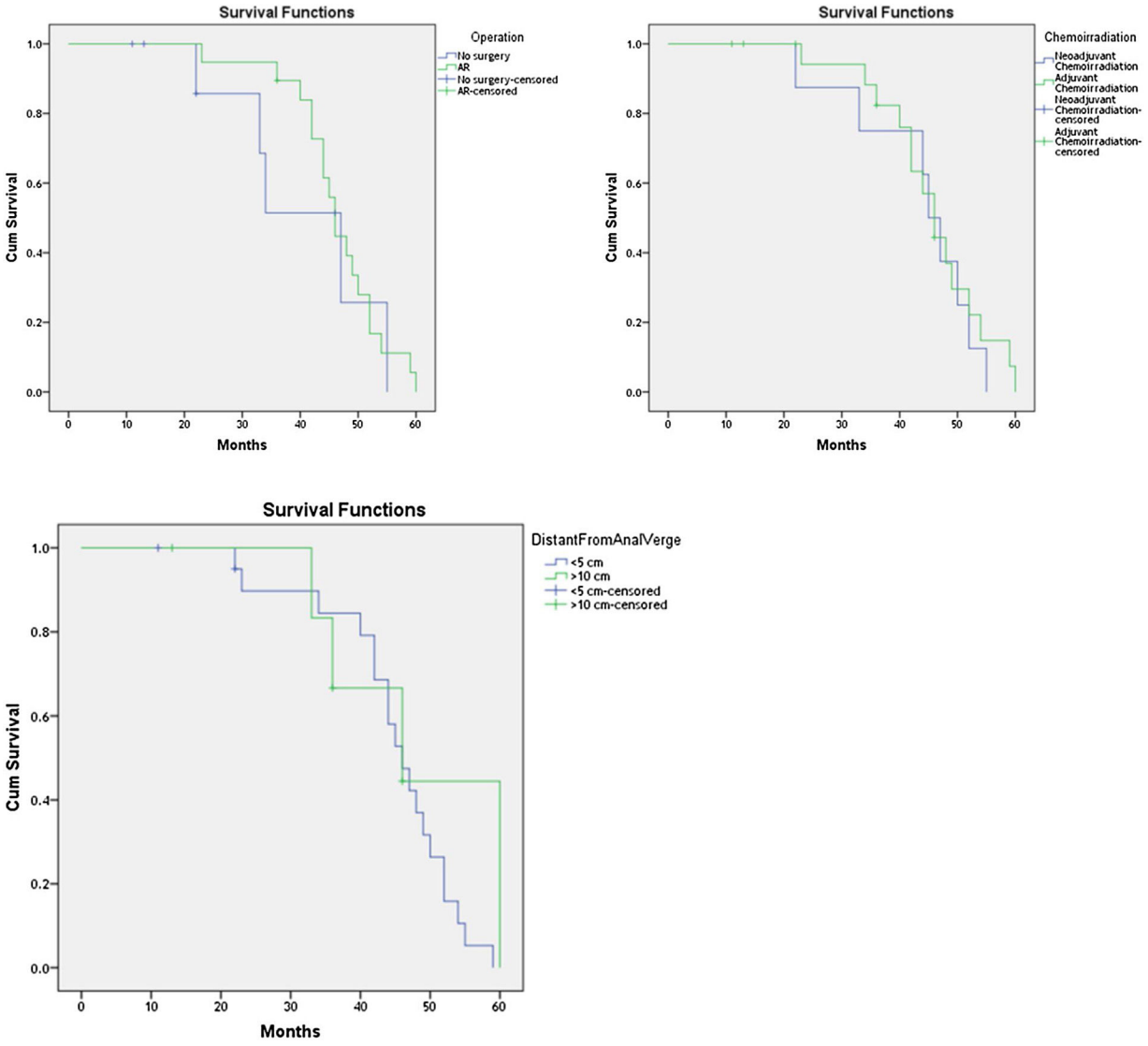

Fig. 1 – *(Continued)*

highly statistically significant (p = 0.01). On the concern of SCC, it was associated with shorter OS (37 months) in comparison to higher survival in patients with adenocarcinoma (46.13 months) and this was significantly high (p = 0.004). Age, sex, distance from anal verge, virology study, and type of surgery were not affected the survival of anal cancer, showed in Fig. 1.

Discussion

Regarding that in Iraq, the incidence is increasing annually, and the chance of being diagnosed has risen in recent years, this may be attributed to increased awareness of symptoms like BPR, and constipation, and early detection of small lesion secondary to more widespread use of colonoscopy and fine needle aspiration of any suspicious lesion in treatment centers. Globally, the new cases of anus tumor at 2018 were 48,541 0.3 %, and patients die from anal cancer found to be 19,129 0.2 %) at same year.[3] In Iraq, ICR reporting the incidence rate of anal cancer at 2015 was 0.09.[4] Recent studies conducted by Alshewered and Al-Naqqash and Alhilfi et al. in Iraq dealing with colon and rectal cancers but not mention of anal cancer as a part of their studies.[5,6]

The majority of patients were above the age of 40 years old at presentation. The median age were 49 years, however it was still younger than the median age of 64 years in the US as published by SEER cancer statistics.[7] This variation may be attributed to different geographic risk factors as diet variations, smoking, obesity, genetic factors and availability of colonoscopy in treatment centers. Gender is associated with varying incidence of anorectal cancer, since M:F ratio was 1:3, and it is differ with Jemal and his colleagues,[7–9] and opposite to research studying the difference according to gender, which was 1.9:1.[7]

Most of the patients had SCC; this similar to Franklin et al. report at 2016. They reported that anal SCC predominate than adenocarcinoma and lower anorectal tumor respectively.[9,10] This may be related to increased incidence of HPV infection of ano-genital tumors in US, and high percent of homosexuality.[11]

Table 3 – Survival of patients according to prognostic factors.

Items	Overall survival	
	Median (CI) in months	*p*-Value
Age groups		
< 40 years old	47.71 (43.3–52)	0.681
≥ 40 years old	43.95 (38.8–49)	
Sex		
Male	41.55 (34.8–48.2)	0.475
Female	48.16 (44.7–51.5)	
Site		
Anorectal	47.22 (43.5–50.9)	<0.000
Anal canal	33.25 (25–41.46)	
Grade		
Good differentiated	60.21 (51.1–70.9)	0.01
Poorly differentiated	43.07 (31.4–54.5)	
Histopathological types		
Squamous cell carcinoma	37 (31.8–42.1)	0.004
Adenocarcinomas	46.13 (42–50.2)	
Distance from anal verge		
<5 cm	44.69 (40.3–49)	0.372
>10 cm	48.38 (37.6–59.1)	
Virology		
Positive	49.02 (41.1–56.8)	0.215
Negative	43.88 (39.5–48.2)	
Type of surgery		
Sphincter preserving	46.33 (42.4–50.1)	0.592
Non sphincter preserving	40.85 (30.7–50.9)	
CRT		
Neoadjuvant	43.5 (35.9–51)	0.619
Adjuvant	45.73 (41–50.3)	

Regional and locally advanced stages were the predominant among our patients, but this is different than SEER data base at US that reported that the localized group (47 %), regional (36.5 %), metastatic (16.5 %). This may be due to different sample size, and early diagnosis and treatment due to screening programs and health education and awareness in the US and other developed countries.[2,12] Localized resection for early stage rectal cancer wasn't reported for clinically stage I patients and this is differ than US were localized resection has been increased to be 20 % of T1–2 rectal cancer to preserve anal function as published at Huntsman Cancer Hospital at the University of Utah Salt Lake City.[12] This may be due to lack of good preoperative assessment of the patients and overestimation of the surgeons. Abdominal Perineal Resection (APR) was the primary treatment for locally advanced Stage II and stage III followed by adjuvant CRT. This is different than Park et al. that shows all locally advanced rectal cancer patients undergo for neoadjuvant chemoradiotherapy for tumor downstaging and good anal sphincter preservation.[2,12]

Neoadjuvant treatment is limited at our locality due to low resources for radiotherapy and prolonged waiting list. As a result there was no any significant difference in OS among patients weather received neoadjuvant or adjuvant CRT.

We analyze the prognostic factors affecting survival, we found that young patients less than 40 years had good OS and slightly increased than OS of patients aged more than 40 years; this is differ to the results of Gado and his colleagues at 2014, who found that the progression of patients less than 40 years was worse and carry a bad prognosis.[12,13] This required more evaluation at level of tumor biology and early detection of cancer among this age group. There is no significant difference of OS according to gender and this is different than the results of Tsai et al., which showing there were significant differences between both sex.[14] This may be due to large sample size and significant difference between gene mutations among male and female. So, this is another recommendation for more evaluation at our nationality. Regarding the pathological site, anal canal tumor has the worst prognosis in comparison to the counterpart histological anorectal. This is in line with the results of 57.369 cases with median OS was significantly lower for anal (33 months), compared with anorectal (33 months).[15] The adenocarcinoma histopathology has better OS than those diagnosed with SCC.

As regard clinical stage of the tumor, localized disease, and low grade have better OS (63 months) compared with regional disease and high grade. This is close to the results reported by SEER CRC statistics 2014.[2] But lower than FLORIDA study that show survival for Stage I, II, III (87 %, 72 % and 59 % respectively).[16,17] This may be due to early diagnosis and availability of facilities and multidisciplinary team approaches for best management and high prevalence of target therapy. There is no significant difference in survival among patients underwent sphincter and non-sphincter preserving surgery, and this in the same track with the result of Puthawala et al.[18] The independent treatment-related predictors of decreased mortality were clinical staging, LV/PNI after surgery and this more or less near to the results of McKenna et al.[19] The prognosis of anal tumor is connected to the tumor size, and the presence of LN extension.[1] NCCN 2019 reported in his guideline the data of RTOG 98–11 trial that showed male sex, positive LN and tumor size more than 5 cm were independently prognostic factors for worse OS.[1] Recently many studies found that HPV is prognostic for improvement of OS in case with anal carcinoma, which of limited entity in our country.[1]

Conclusions

Anorectal carcinoma includes tumors of lower rectum, anal canal and anal margin. This study shows SCC predominance. Anal adenocarcinoma is often conflicted with either its common anatomic join in anal SCC or its histological correlate in rectal adenocarcinoma. Neoadjuvant treatment followed by resection was not different in survival era of treatment among locally advanced tumors. The most significant prognostic factor affecting OS and PFS was tumor site, tumor grades, and histopathology of disease. Anal SCC has the worse prognosis than other histological counterpart.

Conflicts of interest

The authors declare no conflicts of interest.

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