# Long-Term Survival and Disease-Free Rates in Locoregional Anal Squamous Cell Carcinoma: An Institutional Experience

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**ABSTRACT**

In this study, we aimed that the analysis of demographic characteristics, clinical parameters, treatment modalities, and chemotherapy regimens in patients with anal squamous cell carcinoma (SCC) sheds light on disease management. We scanned the electronic database and patient files for patients with anal SCC who presented to our medical oncology outpatient clinic and treated between January 1, 2002 and June 1, 2022. The study included 44 patients whose information was available. The study included a total of 44 patients. The median age was 59.0 (IQR 49.5-68.0) years. The female to male ratio was approximately 1.93, and 93.6% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. Approximately, half of the patients had a history of recent or past smoking. The tumor location was predominantly (89.4%) anal canal and the tumor stages were 10.6%, 59.6% and 29.8% for stage I, stage II and stage III, respectively. The mean follow-up was 50.0 (IQR 29.3-70.6) months. 3rd- and 5th-year -disease free survival (DFS) rates were 82.8% and 77.9%, respectively. During the last follow-up, 76.9% of patients with anal cancer were alive and 75% of patients were disease-free. There was no statistically significant difference in the survival analysis and DFS times according to age, gender and stage. The clinical and demographic characteristics, treatment modalities, and chemotherapy regimens in patients with anal SCC provide valuable insights into disease management. The diverse tumor staging and widespread use of definitive chemoradiotherapy administered concurrently with mitomycin plus fluorouracil underscore the complexity of treatment decisions for patients with anal SCC.

**Keywords:** Locoregional Anal SCC- Chemoradiotherapy -Long Term Survival-Disease Free Survival-Treatment Outcomes

## INTRODUCTION

Anal canal cancer remains a rare diagnosis, with the majority of cases being squamous cell carcinomas. In 2023, it is estimated that approximately 9,760 new cases of anal cancer—including cancers of the anus, anal canal, and anorectum—will be diagnosed in the United States, accounting for around 2.8% of all digestive system malignancies.[1]

Though it is rare, the incidence of anal cancer has been increasing in the US and other countries.[2-4] This rise has been linked to several risk factors, including female gender, human papillomavirus (HPV) infection, the number of lifetime sexual partners, genital warts, smoking, anal intercourse, and human immunodeficiency virus (HIV) infection.[5] Some projections suggest that anal cancer could surpass cervical cancer as the most common HPV-related cancer among adult women.[6] HIV infection and immunosuppressive treatments may promote the persistence of HPV infection in the anal region, significantly increasing the risk of anal cancer. Studies have shown that individuals living with HIV are 15 to 25 times more likely to develop anal cancer compared to the general population.[7-9]

The proximal region of the anus, anatomically defined as the area where the anal canal transitions into the rectum. It comprises glandular, transitional, and non-keratinized squamous epithelia.[10] This region starts at the anal verge and extends upwards toward the rectal ampulla. Tumors arising from any of these three types of mucosa are considered anal cancers. All carcinomas originating from the mucosal surfaces of the anal canal or perianal skin are staged and treated as anal canal cancer using the TNM (tumor, node, metastasis) staging system.

In this study, we aimed to evaluate treatment responses, the effects of therapy on survival outcomes, and the clinicopathological factors influencing survival in patients with anal squamous cell carcinoma (SCC).

## PATIENTS AND METHODS

We scanned the electronic database and patient files for patients with anal SCC who presented to medical oncology outpatient clinic and treated between January 1, 2002 and June 1, 2022. These data sources included demographic information, clinical parameters, treatment regimens, and follow-up outcomes, all of which were systematically reviewed and recorded in our database for further analysis. A total of 44 local or locally advanced anal squamous cell carcinoma (SCC) patientes with complete data including the availability of key demographic, clinical and treatment-related information were assessed. However, data for 11 additional patients could not be accessed due to missing or incomplete records in the hospital database. On the other hand, 3 patients were diagnosed at metastatic stage at initial diagnosis were excluded. Age, gender, smoking status, semptoms at presentation, staging at presentation, performance at diagnosis, either presence of HIV, HPV, primary treatment and presence or absence of progression were recorded.

In this study, we retrospectively evaluated overall survival (OS) and disease-free survival (DFS) according to the treatment regimens and responses of the patients.

### *Treatment Regimens*

The patients received concurrent chemotherapy (CT) and radiotherapy (RT). Twenty patients were treated with mitomycin+5-fluorouracil (5 FU) concurrently with radiation (FU 1000 mg/m$^2$/day continuous infusion on days 1-4 and 29-32, mitomycin 10 mg/m$^2$ ıntravenous (IV) bolus on days 1 and 29). Nine patients received cisplatin+ 5-FU+ RT (cisplatin 75 mg/m$^2$ on day 1, 5-FU 1000 mg/m$^2$/day on days 1-4, and the regimen was repeated every 4 weeks concurrently with RT). Six patients received mitomycin+capecitabine+RT (capecitabine 825 mg/m$^2$ twice daily on days 1-5 throughout the oral radiotherapy, and mitomycin 10 mg/m$^2$ on days 1 and 29).

### Statical Analysis

The DFS was calculated from the date of complete response after treatment until the date of disease recurrence or last follow-up, as applicable. We have standardized the definition of OS as starting from the date of diagnosis until the date of death from any cause or the last follow-up for surviving patients. Data were presented as median (25th-75th interquartile range). Categorical variables were reported as frequencies and group percentages. DFS and OS values were estimated using the Kaplan–Meier method. P value less than 0.05 was considered statistically significant.

The study was approved by Marmara University Ethics Committee (approval date and number: 22.04.2024 / 540).

## RESULTS

### *Study Population*

The study included a total of 44 patients. The median age of study patients was 59.0 (IQR: 49.5-68.0) years. 65.9% of all patients were female and the female to male ratio was approximately 1.93. 93.6% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1. Approximately, half of the patients had a history of recent or past smoking. The tumor location was predominantly (89.4%) anal canal. The tumor stages were 10.6%, 59.6% and 29.8% for stage I, stage II and stage III at diagnosis.

Half of the patients (50%) had grade 2 tumors (Table 1).

**Table 1.** Demographic and clinical characteristics of the study population

| Variables | n (%) |
|---|---|
| Age, year | 58.5 |
| Median (Interquartile range) | (49.0-68.0) |
| Gender | |
| Female | 29 (65.9) |
| Male | 15 (34.1) |
| ECOG-perfomance score, n (%) | |
| 0-1 | 41 (93.2) |
| 2 and above | 3 (6.8) |
| HPV serology, positive/negative | 2/12 |
| HIV serology, positive/negative | 2/31 |
| Smoking | 22 (50.0) |
| Alcohol | 5 (11.4) |
| Primary location | |
| Perianal | 4 (9.1) |
| Anal canal | 40 (90.9) |
| Grade | |
| Grade 1 | 6 (13.6) |
| Grade 2 | 22 (50.0) |
| Grade 3 | 8 (18.2) |
| Unknown | 8 (18.2) |
| T stage | |
| T1 | 6 (13.6) |
| T2 | 27 (61.4) |
| T3 | 10 (22.7) |
| T4 | 1 (2.3) |
| N stage | |
| N1a | 14 (31.8) |
| N1b | 4 (9.1) |
| N1c | 2 (4.5) |
| TNM (AJCC 9th) | |
| Stage I | 5 (11.4) |
| Stage IIa/b | 13 (29.5) / 15 (34.1) |
| Stage III a/b/c | 9 (20.5)/1 (2.3)/1 (2.3) |
| CT regimen | |
| Mitomycin plus fluoroupyrimidine | 25 (56.8) |
| Platin plus fluoroupyrimidine | 10 (22.7) |

**Table 2.** Treatment modalities

| Primary treatment modality | n (%) |
|---|---|
| Definitive CRT | 37 (84) |
| Stage I | 3 (8.3) |
| Stage II | 25 (67.5) |
| Stage III | 9 (25.0) |
| Surgery alone | 2 (4.5) |
| Stage I | 1 (50.0) |
| Stage III | 1 (50.0) |
| Surgery followed by RT | 2 (4.5) |
| Stage I | 1 (50.0) |
| Stage II | 1 (50.0) |
| Surgery followed by CRT | 2 (4.5) |
| Stage II | 1 (50.0) |
| Stage III | 1 (50.0) |
| RT alone | 1 (2.3) |
| Stage II | 1 (100) |
| Chemotherapy regimens, n (%) | |
| CRT | |
| Mitomycin – capecitabine | 6 (13.6) |
| Mitomycin – fluorouracil | 19 (43.1) |
| Cisplatin – fluorouracil | 9 (20.4) |
| Cisplatin - capecitabine | 1 (2.3) |
| Capecitabine alone | 2 (4.5) |
| Fluorouracil alone | 1 (2.3) |

### *Treatment Modalities*

When we analyzed the treatment modalities of the study patients, approximately 81.8% of all curative treatment modalities included CT. Only 2 patients (4.5%) underwent resection and RT and 2 patients (4.5%) underwent resection and chemoradiotherapy. Of these modalities, about 56.8% of concurrent chemotherapy regimen included mitomycin+capecitabine or 5-fluorouracil combinations and about 22.7% included platinum+fluoropyrimidine regimen (Table 2).

### *Survival Analyses*

The mean follow-up was 50.0 (IQR: 29.3-70.6) months. 3rd- and 5th-year -DFS rates were 82.8% and 77.9%, respectively (Figure 1). During the last follow-up, 76.9% of patients with anal cancer were alive and 75% of patients were disease-free. There was no statistically significant difference in the survival analysis and disease-free survival times according to age, gender, smoking exposure, CT regimen and stage (Table 3). Gender, smoking status, T stage and lymph node status were not significantly associated with overall OS. Survival analysis showed no statistically significant difference between platinum+fluoropyrimidine and mitomycin+fluoropyrimidine regimens. The 5-year survival percentages of patients receiving mitomycin plus fluoropyrimidine and platinum plus fluoropyrimidine were 75.8% and 74.6% (Table 4).

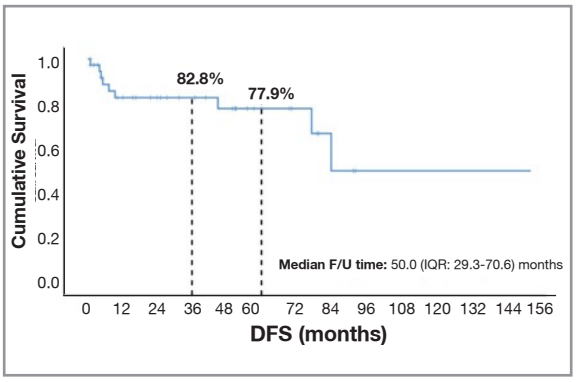


**Figure 1.** Disease-free survival analysis

## DISCUSSION

When we investigated demographic characteristics, clinical parameters, treatment modalities and chemotherapy regimens affecting survival in patients with non metastatic anal SCC, we found that there was no relationship between TNM stage, CT regimen, gender, age, and smoking with OS in univariate analysis. The study population demonstrated a wide age range with favorable functional status based on ECOG scores. The two chemotherapy regimens evaluated in this study were mitomycin plus fluoropyrimidine and platinum plus fluoropyrimidine. No significant difference was observed between the two regimens. Furthermore, no significant correlation with DFS or OS was found in univariate analysis

Historically, the standard treatment for invasive anal SCC has been surgical resection with very high morbidity requiring a permanent colostomy. In 1974, Nigro et al. observed complete response in some patients treated with preoperative 5-FU-based mitomycin or porphiromycin in combination with RT, suggesting that it may be possible to treat anal carcinoma without permanent colostomy and surgery.[11] A study conducted by EORTC in 1997 was one of the early randomized phase III trials investigating the combination of RT concurrent 5-FU and mitomycin compared to RT alone in patients with locally advanced anal SCC. The study included 110 patients. The results confirmed the role of multimodality treatment with chemoradiotherapy (CRT) in achieving significantly improved complete response (CR) rates, lower locoregional recurrence rates, higher locoregional control and longer colostomy-free period.[12] Although survival with surgery is good[13], the need for colostomy severely impairs patients' quality of life. Surgery is considered a salvage treatment for those with re-

**Table 3.** Univariable analysis related to DFS

| | DFS | | |
|---|---|---|---|
| | **HR** | **P value** | **5th -year (%)** |
| Age | | | |
| ≤ 58 years | 0.69 (0.18-2.60) | 0.10 | 79.2 |
| 58 years and above | Ref | | 75.0 |
| Gender | | | |
| Female | 0.74 (0.18-2.99) | 0.67 | 82.8 |
| Male | Ref | | 61.9 |
| Smoking | | | |
| No | 0.43 (0.10-1.82) | 0.24 | 83.6 |
| Yes | Ref | | 70.2 |
| T stage | | | |
| T1-T2 | 0.82 (0.16-4.12) | 0.81 | 78.1 |
| T3-T4 | Ref | | 78.8 |
| N stage | | | |
| N0 | 0.78 (0.19-3.16) | 0.73 | 74.1 |
| N1 | Ref | | 82.2 |
| TNM, stage | | | |
| Stage I-II | 0.82 (0.16-4.12) | 0.81 | 78.1 |
| Stage III | Ref | | 78.8 |
| CT regimen | | | |
| Mitomycin plus fluoropyrimidine | 1.04 (0.20-5.19) | 0.95 | 74.2 |
| Platinum plus fluoropyrimidine | Ref | | 77.1 |

**Table 4.** Univariable analysis related to OS

| | OS | | |
|---|---|---|---|
| | **HR** | **P value** | **5th -year (%)** |
| Age | | | |
| ≤ 58 years | 0.59 (0.16-2.11) | 0.42 | 80.9 |
| 58 years and above | Ref | | 73.8 |
| Gender | | | |
| Female | 0.61 (0.17-2.22) | 0.45 | 80.7 |
| Male | Ref | | 72.2 |
| Smoking | | | |
| No | 0.54 (0.14-2.07) | 0.37 | 82.5 |
| Yes | Ref | | 72.8 |
| T stage | | | |
| T1-T2 | 1.03 (0.21-5.03) | 0.96 | 78.6 |
| T3-T4 | Ref | | 80.8 |
| N stage | | | |
| N0 | 0.90 (0.23-3.42) | 0.87 | 71.9 |
| N1 | Ref | | 83.5 |
| TNM, stage | | | |
| Stage I-II | 1.03 (0.21-5.03) | 0.96 | 78.6 |
| Stage III | Ref | | 80.8 |
| CT regimen | | | |
| Mitomycin plus fluoropyrimidine | 0.87 (0.17-4.37) | 0.87 | 75.8 |
| Platinum plus fluoropyrimidine | Ref | | 74.6 |

currence or residual disease after initial CRT. In our study, the majority of our patients were treated with CRT and the treatment responses were very good in accordance with the literature.

In an intergroup phase III study, colostomy was significantly lower (9% vs. 22%) and 4-year DFS was significantly higher (73% vs. 51%) in patients receiving CRT with the combination of 5-FU and mitomycin. In our study, patients who received mitomycin and 5-FU+ RT had a good 5-year DFS and OS. These results support the important role of mitomycin plus pyrimidine combination and concurrent RT in the treatment of anal carcinoma.[14]

There are data showing that the use of daily oral capecitabine in combination with IV mitomycin as an alternative to 5-FU is well tolerated with minimal toxicity 15, 16. A phase 2 study of 31 patients showed that 77% of patients achieved a complete response 4 weeks after completion of treatment.[15] In our study, 6 patients were given capecitabine instead of 5-FU due to intravenous access problems, and no statistically significant difference in disease control was observed. Although the result is not strong enough due to the small number of patients, we believe that the combination of capecitabine and mitomycin is an acceptable alternative to infusional FU+mitomycin.

Cisplatin is the backbone of chemotherapy for many solid cancers and is a highly effective option in squamous cell carcinoma. There are some studies in which cisplatin was used instead of mitomycin in the treatment of anal SCC. Concurrent CRT followed by cisplatin and FU induction chemotherapy was directly compared with the standard treatment regimen. A total of 682 patients were included in the study. In this analysis, 5-year DFS (68% vs 58%) and OS (78% vs 65%) 17 favored mitomycin. However, these results should be interpreted with caution, as patients in the cisplatin arm received induction therapy with 5-FU and cisplatin before CRT, whereas those in the mitomycin arm did not. The ACT II study was a phase 3 study comparing the use of mitomycin and cisplatin. The study enrolled 940 HIV-uninfected patients with anal SCC 18. Treatment consisted of RT and infusional FU in both arms, and mitomycin in one arm and cisplatin in the other. In the study analysis, the 3-year colostomy-free survival rate was similar in both arms

(72% to 75% in all arms). At a median follow-up of 5.1 years, 3-year PFS and OS were similar between cisplatin and mitomycin. Our study included 9 patients who received cisplatin+FU+RT. No statistically significant difference was observed in DFS and OS between the mitomycin and cisplatin arms, and the results were consistent with the literature. All these data together suggest that FU+mitomycin remains the standard of care, but FU and cisplatin may also be a reasonable and alternative option.

Randomized trials demonstrated superiority of CRT in DFS, local recurrence and colostomy-free survival over RT alone. Several retrospective series report favourable outcomes with RT alone only in those with T1-2N0M0 disease.[19-21] In our study, only 2 patients received radiotherapy, which was statistically insignificant for comparative analysis.

In anal SCC, the main prognostic factors we know are tumor size and lymph node status.[22] In the EORTC study, local disease control and OS were better in node-negative patients than in node-positive patients.[12] In our study, no significant difference was observed between DFS and OS according to tumor size and lymph node involvement. This may be explained by the small number of patients.

This study has several important limitations. First, the smaller study groups were subject to certain limitations. In addition, the lack of randomization resulting from the small number of subjects in retrospective studies makes it difficult to establish causal relationships between variables. Second, we did not have colostomy-free time data in our cohort. Third, we did not have information on HIV and HPV infection status for most of our patients. Our information on this issue was limited because these tests were not performed on patients presenting in previous years. Despite these limitations, our study one of the few long-term analyses of patients with anal squamous cell carcinoma, providing a unique institutional perspective on survival and disease-free rates in a real-world clinical setting. While most studies in the literature focus on short-term outcomes, our analysis offers a more comprehensive view of the long-term efficacy of treatment regimens, including the use of concurrent chemoradiotherapy.

Additionally, the study provides valuable data on the role of alternative chemotherapy regimens, such as the use of capecitabine in place of 5-FU for patients with intravenous access challenges, and its comparable effectiveness in disease control. These findings have the potential to inform clinical decision-making, particularly in tailoring treatment options for patients with similar clinical constraints.

In conclusion, the clinical and demographic characteristics, treatment modalities, and chemotherapy regimens in patients with anal SCC provide valuable insights into disease management. The diverse tumor staging and widespread use of definitive RT administered concurrently with mitomycin plus fluorouracil underscore the complexity of treatment decisions for patients with anal SCC. Although no significant differences were observed between the two chemotherapy regimens assessed, further research with larger cohorts and multivariate analyses is necessary to optimize personalized treatment approaches, aiming to improve patient management and survival rates in anal SCC.

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