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Gastrointestinal Cancer

# Platinum-Fluoropyrimidine and Paclitaxel-Based Chemotherapy in the Treatment of Advanced Anal Cancer Patients

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Advanced anal cancer • Squamous cell carcinoma • Chemotherapy • InterAACT

## Abstract

***Background.*** Although treatment of localized anal cancer (AC) is well established, very little evidence is available to inform the management of advanced tumors, and the prognosis of these patients remains poor. We have analyzed treatment pathways and outcomes of a single-institution series of advanced AC patients in order to provide insight into the management of this rare condition.

***Materials and Methods.*** Inclusion criteria included epidermoid histology, inoperable locally recurrent or metastatic disease, and availability of full medical records. The primary objective was overall survival (OS). Prognostic factors were analyzed in univariate models.

***Results.*** Sixty-four patients (1997–2014) were included: 16 (25.0%) with inoperable locally advanced and 48 (75.0%) with metastatic tumors. Fifty-one (79.7%) received at least one line of chemotherapy; of these, 37% underwent multimodality treatment. A combination of a platinum agent plus a fluoropyrimidine was the most common first-line regimen (74.5%), with an objective response rate (ORR) of 34.4% (95% confidence interval [CI], 18.6%–53.2%). Paclitaxel-based chemotherapy was used in 15 patients as front-line or salvage treatment, and the overall ORR was 53.3% (95% CI, 26.6%–78.7%). Median progression-free survival (PFS) after first- and second-line chemotherapy was 5.8 (interquartile range [IQR], 2.8–7.6) and 3.2 (IQR, 2.5–7.1) months, respectively. Five-year OS in the overall population was 15% (95% CI, 7.0%–25.0%). Age $\leq$65 years and liver metastases were predictive of better PFS (hazard ratio [HR], 0.39; 95% CI, 0.16–0.97; $p = .04$) and worse OS (HR, 2.25; 95% CI, 1.25–4.03; $p = .01$), respectively.

***Conclusion.*** A platinum agent plus a fluoropyrimidine and paclitaxel-based chemotherapy are active regimens for advanced AC. Clinical trials are needed to standardize treatment pathways, investigate the potential of novel therapeutics, and improve the poor prognosis of this rare condition. ***The Oncologist*** 2017;22:402–408

**Implications for Practice:** Because of the lack of randomized trials, the optimal management of advanced anal cancer is uncertain. Despite its retrospective analysis and relatively small sample size, this is the second largest study ever conducted in this setting, and, as such, it has the potential to serve as a valuable source of information for everyday clinical practice. These findings suggest that chemotherapy with a platinum agent plus a fluoropyrimidine or paclitaxel-containing regimens are reasonable treatment options for patients with inoperable locally recurrent or metastatic anal carcinoma.

## Introduction

Approximately 27,000 individuals worldwide are estimated to have been diagnosed with anal cancer in 2008 [1]. Although this tumor accounts for less than 1% of all new cancer diagnoses, incidence rates have progressively increased over the past few decades and more than doubled in some countries, including the U.K. and U.S. [2]. This trend is likely to reflect an expansion of behavioral risk factors and predisposing medical conditions, such as unsafe sexual practices, HIV/AIDS (especially after implementation of highly active antiretroviral therapy), and a history of vulvar/vaginal or cervical malignancy [3–9]. Epidermoid carcinomas account for most anal tumors, and an association with human papillomavirus (HPV) infection (especially HPV16 and HPV18) has been consistently reported in approximately 90% of cases [10–12].

Usually, anal cancer presents as a localized or locally advanced tumor; in this setting, chemoradiotherapy is an established treatment that allows sphincter preservation [13–15]. However, approximately 32% and 12% of patients experience

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isolated locoregional recurrence and distant metastases, respectively [16]. Although in the former group salvage surgery in the form of abdominoperineal resection (APR) is still a treatment with a potential for cure [17], palliative chemotherapy is the standard approach for inoperable or metastatic disease [10]. According to Surveillance, Epidemiology, and End Results Program statistics, only 30.7% of patients with stage IV tumors are alive at 5 years [18]. This figure confirms that long-term survival in this patient population is an unmet need.

As with other rare cancers, randomized clinical trials are lacking, and the only available evidence to inform the management of this condition comes from a limited number of small, single-center, retrospective studies that used single-agent or combination chemotherapy regimens in heterogeneous patient populations [19–33]. This uncertainty is reflected by the lack of strong recommendations from most international guidelines [34, 35]. Although doublet chemotherapy with cisplatin plus infusional fluorouracil is generally considered the most reasonable first-line treatment choice in fit patients, other cytotoxic agents (including carboplatin, taxanes, doxorubicin, and irinotecan) or targeted therapies (such as the anti-epidermal growth factor receptor [EGFR] monoclonal antibody cetuximab) are also viewed as potentially active agents. More important, participation in clinical trials is strongly encouraged.

In this context, auditing and sharing institutional experiences with the international scientific community may consolidate or challenge current practice and possibly convert anecdotal data into more robust, consensus-creating information to compensate for the lack of high-quality, prospective evidence. Therefore, we have analyzed treatment patterns and overall outcome of advanced anal cancer patients who were treated at our institution over a period of approximately 17 years.

## Materials and Methods

All patients who were seen in consultation at the Royal Marsden NHS Foundation Trust from 1997 to 2014 after a diagnosis of anal cancer were reviewed. This study included only patients who had histological confirmation of epidermoid anal carcinoma (i.e., squamocellular, basaloid, or cloacogenic histotype) and advanced disease (i.e., inoperable locally recurrent or metastatic tumors) and for whom full medical records were available. Demographic characteristics, clinicopathological characteristics at baseline, treatments received before and after the diagnosis of advanced disease, and overall outcome data were retrospectively collected for each patient by using the institutional electronic patient record system and were entered into a database.

The primary objective of the study was overall survival (OS). This was defined as time from date of diagnosis of advanced disease to date of death from any cause. Alive patients were censored at date of last follow-up. Secondary objectives included objective tumor response rate (defined as complete or partial response as per Response Evaluation Criteria In Solid Tumors criteria, version 1.1) and progression-free survival (PFS) (defined as time from start of treatment to date of progression or death from any cause) for first- and second-line chemotherapy. For the analysis of PFS, patients with no events were censored to date of subsequent line of chemotherapy. Both OS and PFS were analyzed by using the Kaplan-Meier method. In exploratory analyses, all outcome measures were also assessed by type of chemotherapy regimen.

The prognostic value of selected factors, including gender, age, tumor grading, time to development of advanced disease, number of metastatic sites, presence of liver metastases, and response to first-line chemotherapy, was tested in a univariate model. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). A $p$ value $<.05$ was considered to represent a statistically significant difference, and no multiplicity adjustment was performed. Stata software was used to perform statistical analyses (StataCorp, College Station, TX; http://www.stata.com/)

The study was approved by the Research & Development Department at the Royal Marsden NHS Foundation Trust. Given that this was a retrospective analysis of clinical data, consent from patients included in the study was not required.

## Results

Sixty-four patients met the eligibility criteria and were included in the study. Demographic characteristics, clinicopathological characteristics, and previous treatments for nonadvanced disease are reported in Table 1. There was a predominance of women (60.9%), and the median age was 59.2 years (interquartile range [IQR], 52.1–66.4). Most patients ($n = 49$, 76.6%) presented with localized or locally advanced disease, whereas only 15 (23.4%) had distant metastases at diagnosis. Prior radiotherapy to the primary tumor was given to 53 patients (82.8%, in most cases with a curative intent), and 47 of these received concurrent chemotherapy; the most common radiosensitizing regimen was a combination of either 5-fluorouracil or capecitabine and mitomycin C. Eleven patients (17.2%) underwent prior salvage surgery, including APR ($n = 10$) and lung metastasectomy ($n = 1$).

Median time from the histological evidence of anal carcinoma to the diagnosis of advanced disease was 9.1 months (IQR, 4.1–20.9 months). Distant metastases were present in 48 patients (75.0%) (extrapelvic lymphadenopathy and liver metastases accounting for most cases), whereas only 16 (25.0%) had inoperable locally advanced tumors. Only 51 patients (79.7%) were treated with systemic chemotherapy (median number of chemotherapy lines, 1; range, 0–5). Of the 13 patients who did not receive chemotherapy, 5 were lost to follow-up, 5 had poor performance status, 2 died before treatment, and 1 was treated with only bisphosphonates and radiotherapy.

Type of chemotherapy used in the study population is reported in Table 2. A fluoropyrimidine-containing combination regimen was prescribed as first-line treatment in 94.1% of patients ($n = 48$) (fluoropyrimidine was replaced by raltitrexed to minimize the risk for cardiovascular toxicity in a patient who experienced chest pain during previous capecitabine-based chemoradiotherapy). In most cases ($n = 38$), 5-fluorouracil or capecitabine was given in combination with cisplatin or carboplatin; only 7 patients received 5-fluorouracil or capecitabine in combination with mitomycin C plus or minus cisplatin (2 of these had previously received mitomycin C with pelvic radiotherapy). Overall, median duration of first-line treatment was 3.2 months (IQR, 2.0–4.7 months), and an objective response was observed in 13 of 44 assessable patients (29.5%). Thirty-two patients who were treated with a fluoropyrimidine plus either cisplatin or carboplatin were assessable for response to


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**Table 1.** Patient characteristics

| Characteristic | Value |
|---|---|
| Gender | |
| Female | 39 (60.9) |
| Male | 25 (39.1) |
| Median age (range), yr | 59.2 (35.4–85.2) |
| HIV infection | |
| No known history | 59 (92.2) |
| Yes | 5 (7.8) |
| Histology | |
| Squamous cell carcinoma | 58 (90.6) |
| Squamous cell carcinoma: basaloid | 5 (7.8) |
| Squamous cell carcinoma: epidermoid | 1 (1.6) |
| Tumor grade | |
| Moderately differentiated | 30 (46.9) |
| Poorly differentiated | 25 (39.1) |
| Unknown | 9 (14.0) |
| Stage (TNM) at diagnosis | |
| I, II, III | 49 (76.6) |
| IV | 15 (23.4) |
| Prior radiotherapy to the primary tumor | |
| No | 11 (17.2) |
| Yes | 53 (82.8) |
| Curative | 44 (83.0) |
| Palliative | 7 (13.2) |
| After resection of primary tumor | 2 (3.8) |
| Prior radiosensitizing chemotherapy | |
| No | 6 (11.3) |
| Yes | 47 (88.7) |
| Fluoropyrimidine + MMC | 36 (76.6) |
| Fluoropyrimidine alone | 4 (8.5) |
| Fluoropyrimidine + cisplatin | 5 (10.6) |
| Other | 2 (.3) |
| Prior salvage APR | |
| No | 54 (84.4) |
| Yes | 10 (15.6) |
| Time to advanced disease | |
| Median (range), months | 9.3 (0–130.5) |
| ≤12 months | 38 (59.4) |
| >12 months | 26 (40.6) |
| Extent of disease before first-line chemotherapy | |
| Locally advanced | 16 (25.0) |
| Metastatic | 48 (75.0) |
| No. of sites of disease | |
| 1 | 43 (67.2) |
| >2 | 21 (32.8) |
| Sites of disease | |
| Extrapelvic nodes | 22 (34.4) |
| Liver | 21 (32.8) |
| Pelvis | 16 (25.0) |
| Lung | 11 (17.2) |
| Bone | 8 (12.5) |
| Other | 7 (10.9) |

Unless otherwise noted, values are the number (percentage) of patients.
Abbreviations: APR, abdominoperineal resection; MMC, mitomycin C.

**Table 2.** Chemotherapy regimens used in the first- and second-line settings.

| Regimen | Patients, *n* (%) |
|---|---|
| First-line chemotherapy (*n*=51) | |
| Cisplatin/carboplatin + fluoropyrimidine (or raltitrexed) | 38 (74.5) |
| Carboplatin + capecitabine | 22 (43.1) |
| Cisplatin + capecitabine | 8 (15.7) |
| Cisplatin + 5-fluorouracil | 6 (11.8) |
| Carboplatin + 5-fluorouracil | 1 (2.0) |
| Carboplatin + raltitrexed | 1 (2.0) |
| MMC + fluoropyrimidine ± platinum agent | 7 (13.7) |
| MMC + capecitabine | 3 (5.9) |
| MMC + 5-fluorouracil + cisplatin | 3 (5.9) |
| MMC + 5-fluorouracil | 1 (2.0) |
| Other | 6 (11.8) |
| Second-line chemotherapy (*n*=21) | |
| Cisplatin/carboplatin ± fluoropyrimidine | 9 (42.9) |
| Carboplatin + capecitabine | 6 (28.6) |
| Cisplatin + capecitabine | 1 (4.8) |
| Cisplatin + 5-fluorouracil | 1 (4.8) |
| Cisplatin | 1 (4.8) |
| Paclitaxel ± carboplatin | 8 (38.1) |
| Paclitaxel | 7 (33.3) |
| Carboplatin + paclitaxel | 1 (4.8) |
| Other | 4 (23.8) |

Abbreviation: MMC, mitomycin C.

treatment; among these the objective response rate was 34.4% (95% CI, 18.6%–53.2%). After first-line chemotherapy, 16 patients underwent multidisciplinary intervention, including (chemo)radiotherapy to the primary tumor ($n = 5$), APR/pelvic exenteration ($n = 6$), inguinal node dissection ($n = 2$), hepatectomy ($n = 1$), and radiofrequency ablation ($n = 2$ [1 liver and 1 lung]). Median PFS was 5.8 months for all study patients (IQR, 2.8–7.6 months) and for those treated with a fluoropyrimidine plus either cisplatin or carboplatin (IQR, 2.9–7.6 months) (Fig. 1).

Second-line systemic treatment was administered in 21 patients (32.8%). In most cases this consisted of a platinum agent plus or minus a fluoropyrimidine ($n = 9$, including 7 patients [42.9%] who were rechallenged with the same class of agents used in the first-line setting) or a paclitaxel-based regimen ($n = 8$, 38.1%). Overall, median duration of second-line treatment was 2.6 months (IQR, 2.1–5.1) months, and an objective response was observed in 6 of 18 assessable patients (33.3%). After second-line chemotherapy, 2 patients underwent multidisciplinary intervention, including APR ($n = 1$) and lung metastasectomy plus radiofrequency ablation to lung ($n = 1$). Median PFS was 3.2 months (IQR, 2.5–7.1 months) (Fig. 1). Subsequent lines of chemotherapy, including investigational drugs within the context of clinical trials, were administered in 12 patients (18.8%).

Fifteen patients (excluding rechallenges) were treated with a paclitaxel-based chemotherapy (i.e., 12 with single-agent paclitaxel and 3 with carboplatin plus paclitaxel) at some point

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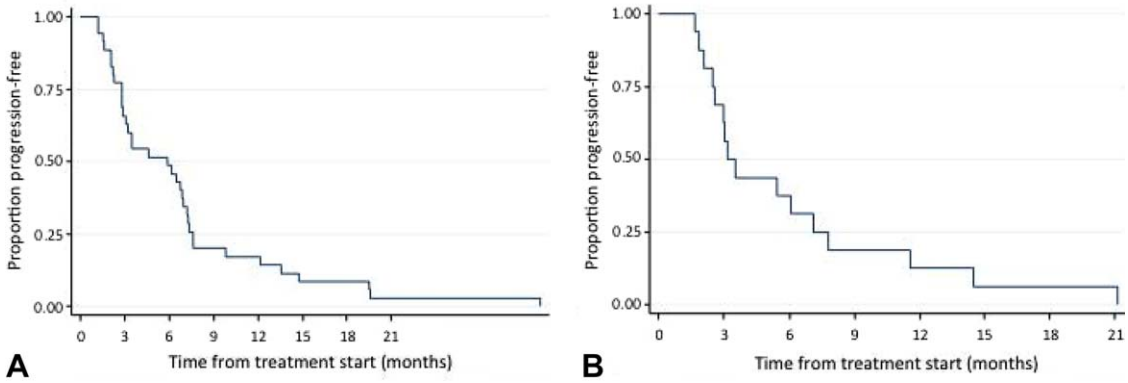


**Figure 1.** Progression-free survival after first-line (A) and second-line (B) chemotherapy in the chemotherapy-treated population.

during the course of their disease (2 in first line, 8 in second line, and 5 in subsequent lines); the overall response rate was 53.3% (95% CI, 26.6%–78.7%). Similarly, an objective response was observed in 4 of 6 patients (all treated in the first-line setting) who received a combination with a fluoropyrimidine plus mitomycin C. Irinotecan plus cetuximab was used as second-line treatment in 1 patient who was subsequently lost to follow-up and as third-line treatment in 1 patient with a *KRAS* exon 2 wild-type tumor who had disease progression as best response.

Patients were followed up for a median of 71.9 months (IQR, 53.5–96.0 months). Median OS was 14.1 months (IQR, 8.0–41.4 months) in the overall study population and 15.4 months (IQR, 10.0–45.2 months) in the patients who received at least 1 line of systemic chemotherapy. Median OS from second-line chemotherapy was 14.9 months (IQR, 9.4–37.4 months). The 5-year OS rate in the overall population was 15.0% (95% CI, 7.0–25.0 months) (Fig. 2). When survival estimates were calculated from the date of initial diagnosis, median OS was 2.7 years (95% CI, 1.8–3.2 years) and 5-year OS was 27% (95% CI, 16%–39%). Among the prognostic factors considered in the univariate analysis, age $<$65 years was associated with a better PFS (HR, 0.39; 95% CI, 0.16–0.97; $p = .04$), while presence of liver metastases indicated a worse OS (HR, 2.25; 95% CI, 1.25–4.03; $p = .01$) (Table 3).

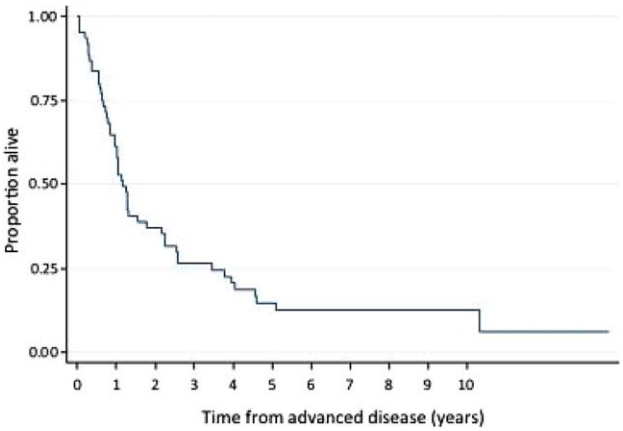


**Figure 2.** Overall survival from advanced disease in the overall population.

## Discussion

In this retrospective study, we analyzed treatment pathways and outcomes in a consecutive series of patients who were managed for advanced anal cancer at a UK tertiary cancer center during a period of approximately two decades.

So far, the decision-making process for advanced anal cancer patients has been based on evidence of suboptimal quality, largely consisting of anecdotal case reports; case series; phase I studies; or small, single-arm phase II studies [19–33]. The relatively low incidence of this condition, the common pattern of clinical presentation at diagnosis, and the high success rate of definitive chemoradiotherapy for early-stage tumors have historically hampered the development of randomized clinical trials. Therefore, no consensus has been reached, and the optimal management of patients with advanced anal cancer is still a matter of controversy.

Despite the relatively small sample size, this is the second largest study ever published on this topic. It therefore has the potential to serve as a valuable source of information for clinicians and patients who face uncertainty about the optimal management of this condition. The baseline characteristics of our study population were consistent with those reported in similar studies or largely expected on the basis of the established clinicoepidemiological features and natural history of anal cancer [32, 34, 35]. Female patients were predominant over male patients, the median age was relatively young, and approximately 8% of patients had a known history of HIV infection. Although information on HPV status was not available in our study, it is legitimate to assume that most patients had HPV-positive tumors. Expectedly, in most cases previous chemoradiotherapy plus or minus subsequent salvage APR was administered with a curative intent for the management of early-stage disease.

In keeping with common practice in most international centers and the recommendation from the European Society for Medical Oncology and National Comprehensive Cancer Network guidelines [34, 35], a combination regimen with a platinum agent plus a fluoropyrimidine was used for most chemotherapy-naïve patients, with an overall objective response rate of 34.4% and a median PFS of 5.8 months. Although these figures confirm the activity of this doublet chemotherapy, they appear somehow lower than those previously reported for the combination of cisplatin plus infusional fluorouracil in previous series [22, 32]. However, substantial heterogeneity across studies, especially in terms of number and clinicopathological characteristics of assessable patients


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**Table 3.** Univariate analysis of prognostic factors for progression-free survival and overall survival

| | PFS | | OS | |
|---|---|---|---|---|
| **Variable** | **HR (95% I)** | ***p* value** | **HR (95% CI)** | ***p* value** |
| Gender | | | | |
| Female | — | — | — | — |
| Male | 1.66 (0.81–3.41) | .17 | 1.41 (0.80–2.48) | .23 |
| Age | | | | |
| <65 yr | — | — | — | — |
| ≥65 yr | 0.39 (0.16–0.97) | .04 | 1.05 (0.57–1.93) | .87 |
| Tumor grade | | | | |
| Moderate | — | — | — | — |
| Poor | 1.09 (0.52–2.29) | .81 | 0.85 (0.47–1.51) | .57 |
| Liver metastases | | | | |
| No | — | — | — | — |
| Yes | 1.07 (0.49–2.33) | .87 | 2.25 (1.25–4.03) | .01 |
| No. of sites of disease | | | | |
| 0–1 | — | — | — | — |
| ≥1 | 0.97 (0.42–2.24) | .94 | 1.66 (0.89–3.10) | .11 |
| Time to advanced disease | | | | |
| < 12 months | — | — | — | — |
| ≥ 12 months | 0.49 (0.23–1.04) | .06 | 1.24 (0.71–2.16) | .46 |
| Response to first-line chemotherapy | | | | |
| No | — | — | — | — |
| Yes | 0.62 (0.28–1.39) | .25 | 0.61 (0.29–1.28) | .19 |

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

and the retrospective evaluation of response to treatment, may account for the observed difference.

Over the past few years, evidence has emerged suggesting that paclitaxel-based chemotherapy may also be a valuable treatment option for patients with advanced anal cancer. The use of single-agent paclitaxel in this setting was first described by Alcindor [26] and Abbas et al. [29], who reported promising rates of clinical benefit in small case series of chemotherapy-naïve or previously treated patients. Subsequently, partial response rates ranging from 33% to 69% were observed in untreated patients with the combination of carboplatin plus paclitaxel [31, 32]. Also, in a small phase I study, intra-arterial administration of nab-paclitaxel led to partial response in 58% of cases [24]. Our study further supports the contention that paclitaxel, either as a single agent or in combination with a platinum agent, should be considered as one of the most effective currently available therapies for advanced anal cancer. Indeed, we observed an overall response rate of 53.3% that is particularly interesting, especially if we consider that in most cases our patients received this agent as monotherapy in the refractory setting.

Additional therapeutic approaches, including triplet chemotherapy and anti-EGFR monoclonal antibodies, have been reported as potentially effective in this setting [23, 25, 27, 28, 30, 33]. In our study, such treatments were used in only 4 and 2 patients, respectively, thereby largely precluding any meaningful analysis or comparison with other series. Assessing the activity of mitomycin in our series is also challenging for the same reasons. However, the proportion of objective responses observed in the group of patients treated with a combination of mitomycin and a fluoropyrimidine (4 of 6) seems to suggest that, in addition to the established role in the early-stage setting, a mitomycin-based treatment may also be considered as a valid therapeutic option for the management of patients with advanced tumors.

Although our analysis focused on the efficacy of treatments, safety is an important consideration in making decision for patients with advanced anal cancer. We did not report toxicity data, and this is certainly a limitation of our study. However, retrospective collection of patient-reported adverse events is subject to several biases and may not provide a reliable estimate of the overall burden of treatment-related morbidities. Moreover, the safety profile of the chemotherapy regimens used in our patient population is well known because these regimens are routinely prescribed for several tumor types.

We confirmed that a multidisciplinary approach might play an important role in the management of advanced anal cancer. In our series, 37% of patients who received at least one line of chemotherapy were also deemed suitable candidates for locoregional procedures, including surgical resection of the primary tumor or metastases, chemoradiotherapy to the primary tumor, and radiofrequency ablation of metastatic lesions. Multidisciplinary management of advanced anal cancer has been considered by Eng et al. as an effective strategy with the potential to improve the outcome of selected anal cancer patients [32]. Although evaluation of the true effect of a multimodality treatment approach in this setting is hampered by inherent selection biases, we share the opinion that consideration should be given, whenever feasible, to adopt any additional therapeutic strategy that can possibly consolidate the effect of previous systemic treatments.

In our series, age and liver metastases were prognostic factors. However, we recommend caution when interpreting these findings. Our univariate analysis of predictive factors for PFS and OS should be considered as exploratory given the small sample size and the significant patient heterogeneity, especially in terms of baseline characteristics and treatments. Larger series are certainly needed to identify and validate clinicopathological factors that could be used for treatment selection in routine practice or patient stratification in clinical trials.

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Long-term outcomes of our patient population were in line with previously reported data [31, 35]. Median overall survival was 14 months, and only 13% of patients were alive 5 years after the diagnosis of advanced disease. These disappointing figures suggest that long-term disease control is still an unmet need in this setting and there is significant scope for improvement. In this regard, there has recently been increased awareness within the scientific community of the need to standardize treatment pathways and investigate novel therapeutics. The International Rare Cancer Initiative group has recently promoted the development of the first INTERnational Advanced Anal Cancer Trial (InterAACT), a global, randomised phase II study that is comparing efficacy and safety of cisplatin plus fluorouracil versus carboplatin plus paclitaxel for the first-line treatment of patients with inoperable locally recurrent or metastatic anal carcinoma (NCT02051868) [37]. Moreover, studies aiming to provide a molecular characterization of anal cancer have been increasingly reported and have revealed genetic alterations and aberrant signaling pathways that might be investigated as valuable therapeutic targets [38, 39]. Finally, preliminary evidence suggests that immunotherapy may be an effective strategy for the management of this disease [40, 41].

## Conclusion

The purpose of this study was to provide insight into the management of advanced anal cancer. Although the study was neither designed nor powered to determine any superiority of one chemotherapy regimen over the other, our results confirm that a combination of a platinum agent plus a fluoropyrimidine is a reasonable first-line treatment choice in these patients and further support the decision to use a paclitaxel-based regimen in the comparator arm of the InterAACT trial. Several limitations and biases are inherent to small, single-institution studies that are solely based on retrospective patient data collection. Hence, such studies are regarded as suboptimal by international guidelines that rank levels of evidence. Nevertheless, in the absence of better-quality studies, they still provide important evidence to guide the management of patients with this rare condition, establish an international consensus and collaborative database, and inform the design of future clinical trials.

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## Author Contributions

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## Disclosures

**David Cunningham**: Amgen, AstraZeneca, Bayer, Celgene, Merrimack, MedImmune, Merck Serono, Sanofi (RF); **Sheela Rao**: Amgen, Celgene, Eli Lilly, Roche, Baxalta, Merck Serono (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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