Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients

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Abstract

Background: While treatment of localised anal cancer (AC) is well established, very little evidence is available to inform the management of advanced tumours and the prognosis of these patients remains poor. We have analysed 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.

Material 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 analysed in univariate models.

Results: Sixty-four patients (1997-2014) were included, 16 (25.0%) with inoperable locally advanced and 48 (75.0%) with metastatic tumours. Fifty-one (79.7%) received ≥1 line of chemotherapy and, 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% CI: 18.6-53.2). Paclitaxel-based chemotherapy was used in 15 patients as either 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 (IQR: 2.8-7.6) and 3.2 months (IQR: 2.5-7.1), respectively. 5-year OS in the overall population was 15% (95% CI: 7.0-25.0). Age ≤65 years and liver metastases were predictive of better PFS (HR 0.39, 95% CI: 0.16-0.97, p=0.04) and worse OS (HR 2.25, 95% CI: 1.25-4.03, p=0.01), respectively.

Conclusion: A platinum agent plus a fluoropyrimidine and paclitaxel-based chemotherapy are active regimens for advanced AC. Clinical trials are needed to standardise treatment pathways, investigate the potential of novel therapeutics and improve the poor prognosis of this rare condition.

Implications for practice

Due to the lack of randomised trials, the optimal management of advanced anal cancer is uncertain. Despite the retrospective analysis and the 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. Based on our findings, 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 are estimated to have been diagnosed with anal cancer in 2008 worldwide [1]. Although this tumour accounts for less than 1% of all new cancer diagnoses, incidence rates have progressively increased over the last few decades and more than doubled in some countries including UK and US [2]. This trend is likely to reflect an expansion of behavioural risk factors and predisposing medical conditions such as unsafe sexual practiceshuman immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) (especially after implementation of highly active antiretroviral therapy) and a prior history of vulvar/vaginal or cervical malignancy [3-9]. Epidermoid carcinomas account for the vast majority of anal tumours and an association with human papillomavirus (HPV) infection (especially HPV16 and HPV18) has been consistently reported in ~90% of cases [10-12].

Usually anal cancer presents as a localised or locally-advanced tumour and in this setting chemoradiotherapy is an established treatment allowing sphincter preservation [13-15]. However, approximately 32% and 12% of patients experience isolated loco-regional recurrence and distant metastases, respectively [16]. While 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 the Surveillance, Epidemiology, and End Results Program (SEER) statistics, only 30.7% of patients with stage IV tumours are alive at 5 years [18], this figure confirming that long term survival in this patient population is an unmet need.

Like other rare cancers, randomised clinical trials are lacking and the only available evidence to inform the management of this condition comes from a limited number of small, single-centre, retrospective studies where single-agent or combination chemotherapy regimens have been used 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 as the most reasonable first line treatment choice in fit patients, other cytotoxics including carboplatin, taxanes, doxorubicin and irinotecan or targeted therapies such as the anti-EGFR monoclonal antibody cetuximab are also viewed as potentially active agents. More importantly, participation in clinical trials is strongly encouraged.

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

Material and methods

All patients who were seen in consultation at the Royal Marsden NHS Foundation Trust from 1997 to 2014 following a diagnosis of anal cancer were reviewed. This study included only those patients who had histological confirmation of epidermoid anal carcinoma (i.e., squamocellular, basaloid or cloacogenic histotype), advanced disease (i.e., inoperable locally recurrent or metastatic tumours) and for whom full medical records were available. Demographics, clinico-pathological characteristics at baseline, treatments received before and

after the diagnosis of advanced disease and overall outcome data were retrospectively collected for each patient using the institutional electronic patient record system and 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 tumour response rate (defined as complete or partial response as per RECIST 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 analysed 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, tumour 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 and 95% confidence intervals. A p value <0.05 was considered statistically significant and no multiplicity adjustment was performed.

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. Demographics, clinico-pathological characteristics and previous treatments for non-advanced disease are reported in Table 1. There was a predominance of females (60.9%) and median age was 59.2 years [interquartile range (IQR): 52.1 - 66.4]. The majority of patients (n=49, 76.6%) presented with localised or locally advanced disease while only 15 (23.4%) had distant metastases at diagnosis. Prior radiotherapy to the primary tumour was given to 53 patients (82.8%, in most cases with a curative intent) and 47 of these received concurrent chemotherapy with the most common radiosensitising regime being a combination of either 5-fluorouracil or capecitabine and mitomicin 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 [interquartile range (IQR): 4.1 – 20.9]. Distant metastases were present in 48 patients (75.0%) (extra-pelvic lymphadenopathy and liver metastases accounting for the majority of cases) while only 16 (25.0%) had inoperable locally advanced tumours. 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 actually replaced by raltitrexed to minimise the risk of

cardiovascular toxicity in a patient who experienced chest pain during previous capecitabine-based chemoradiotherapy). In the vast majority of cases (n=38) 5-fluorouracil or capecitabine was given in combination with either cisplatin or carboplatin while in only 7 patients in combination with mitomicin C plus or minus cisplatin (2 of these had previously received mitomicin C with pelvic radiotherapy). Overall, median duration of first line treatment was 3.2 months (IQR: 2.0 – 4.7) and an objective response was observed in 13/44 assessable patients (29.5%). Thirty-two patients who were treated with a fluoropyrimidine plus either cisplatin or carboplatin were assessable for response to treatment and among these the objective response rate was 34.4% (95% CI: 18.6 – 53.2). Following first line chemotherapy, 16 patients underwent multidisciplinary intervention including (chemo)radiotherapy to the primary tumour (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 both all study patients (IQR: 2.8 – 7.6) and those treated with a fluoropyrimidine plus either cisplatin or carboplatin (IQR: 2.9 – 7.6) (Figure 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 who were re-challenged with the same class of agents used in the first line setting, 42.9%) 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) and an objective response was observed in 6 out of 18 assessable patients (33.3%). Following 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) (Figure 1). Subsequent lines of chemotherapy including investigational drugs within the context of clinical trials were administered in 12 patients (18.8%).

A total of 15 patients (excluding re-challenges) were treated with a paclitaxel-based chemotherapy (i.e., 12 with single agent paclitaxel and 3 with carboplatin plus paclitaxel) at some point during the course of their disease (2 in first line, 8 in second line and 5 in subsequent lines) and the overall response rate was 53.3% (95% CI: 26.6 – 78.7). Similarly, an objective response was observed in 4 out 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 one patient who was subsequently lost to follow-up and as third line treatment in one patient with a *KRAS* exon 2 wild-type tumour who had disease progression as best response.

Patients were followed-up for a median of 71.9 months (IQR 53.5 – 96.0). Median OS was 14.1 months (IQR: 8.0 – 41.4) in the overall study population and 15.4 months (IQR: 10.0 – 45.2) in the group of patients who received at least one line of systemic chemotherapy. Median OS from second line chemotherapy was 14.9 months (IQR: 9.4 – 37.4). The 5-year OS rate in the overall population was 15.0% (95% CI: 7.0-25.0) (Figure 2). When survival estimates were calculated from the date of initial diagnosis, median OS was 2.7 years (95% CI: 1.8 - 3.2) and 5-year OS was 27% (95% CI: 16-39). Among the prognostic factors considered in the univariate analysis, age <65 years was found to be associated with a better PFS (HR 0.39; 95% CI: 0.16 – 0.97, p=0.04) while presence of liver metastases indicated a worse OS (HR 2.25; 95% CI: 1.25 – 4.03, p=0.01) (Table 3).

Discussion

In this retrospective study we have analysed treatment pathways and outcome of a consecutive series of patients who were managed for advanced anal cancer at a UK tertiary cancer centre over a period of approximately two decades.

So far, the decision-making process for advanced anal cancer patients has been based on sub-optimal quality evidence, this 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 tumours have historically hampered the development of randomised 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 and it has therefore the potential to serve as a valuable source of information for clinicians and patients who face uncertainty in the optimal management of this condition. The baseline characteristics of our study population were either consistent with those reported in similar studies or largely expected based on the established clinico-epidemiological features and natural history of anal cancer [32, 34, 35]. Females were predominant over males, the median age was relatively young and approximately 8% of patients had a known history of HIV infection. Although information on the HPV status was not available in our study, it is legitimate to assume that the vast majority of patients had HPV-positive tumours. 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 centres and the recommendation from ESMO and NCCN guidelines [34, 35], a combination regime with a platinum agent plus a fluoropyrimidine was used for the majority of 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 clinico-pathological characteristics of assessable patients and the retrospective evaluation of response to treatment may account for the observed difference.

Over the last 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 et al and Abbas et al who reported promising rates of clinical benefit in small case series of chemotherapy-naïve or previously treated patients [26, 29]. 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 provides further support to 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, options in the therapeutic armamentarium 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, this largely precluding any meaningful analysis or comparison with other series. Assessing the activity of mitomycin in our series is also challenging due to 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 out of 6) seem 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 tumours.

Although our analysis focused on the efficacy of treatments, safety is an important consideration when 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 a number of biases and may not provide a reliable estimate of the overall burden of treatment-related morbidities. Moreover, safety profile of the chemotherapy regimens that were used in our patient population is well known these being routinely prescribed in several tumour 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 loco-regional procedures including surgical resection of the primary tumour or metastases, chemoradiotherapy to the primary tumour 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 found to be 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 clinico-pathological factors that could be used for treatment selection in routine practice or patient stratification in clinical trials.

Long-term outcome of our patient population was 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 standardise treatment pathways and investigate novel therapeutics. The International Rare Cancer Initiative (IRCI) 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 characterisation of anal cancer have been increasingly reported and revealed genetic alterations

and aberrant signaling pathways which can be possibly investigated as valuable therapeutic targets [38, 39]. Finally, preliminary evidence has been reported suggesting 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 versus 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 provide further support to the decision to use a paclitaxel-based regimen in the comparator arm of the InterAACT trial. A number of 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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Disclosure of Potential Conflicts of Interest

David Cunningham received research funding from: Roche, Amgen, Celgene, Sanofi, Merck Serono, Novartis, AstraZeneca, Bayer, Merrimack and MedImmune. Ian Chau has had

advisory roles with Merck Serono, Roche, Sanofi Oncology, Bristol Myers Squibb, Eli-Lilly, Novartis, Gilead Science. He has received research funding from Merck-Serono, Novartis, Roche and Sanofi Oncology, and honoraria from Roche, Sanofi-Oncology, Eli-Lilly, Taiho. All other authors have no conflicts of interest to disclose.

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BEST PRACTICE	CURRENT PRACTICE	RESULTING GAPS	LEARNING OBJECTIVES
Conducting international multicentre clinical trials is paramount to optimise and standardise treatment for rare cancers. No randomised clinical trials have ever been conducted in the setting of advanced anal cancer.	There is currently no consensus on the optimal management of advanced anal cancer. Systemic chemotherapy in the form of combination regimens is the most common treatment approach. Variability across international institutions exists and a universally accepted treatment pathway cannot be identified.	Significant uncertainty regarding treatment of advanced anal cancer remains and decisions in everyday clinical practice are largely empirical. No significant progress has been made over the last few decades in the management of advanced anal cancer and the prognosis of patients with advanced anal cancer remains poor.	To consider the lack of high-quality evidence for the management of advanced anal cancer
			To obtain useful information on treatment pathways and outcomes for patients with advanced anal cancer treated in a large tertiary cancer centre
			To consider the importance of conducting prospective randomised clinical trials in advanced anal cancer and other rare tumour types

Figures

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

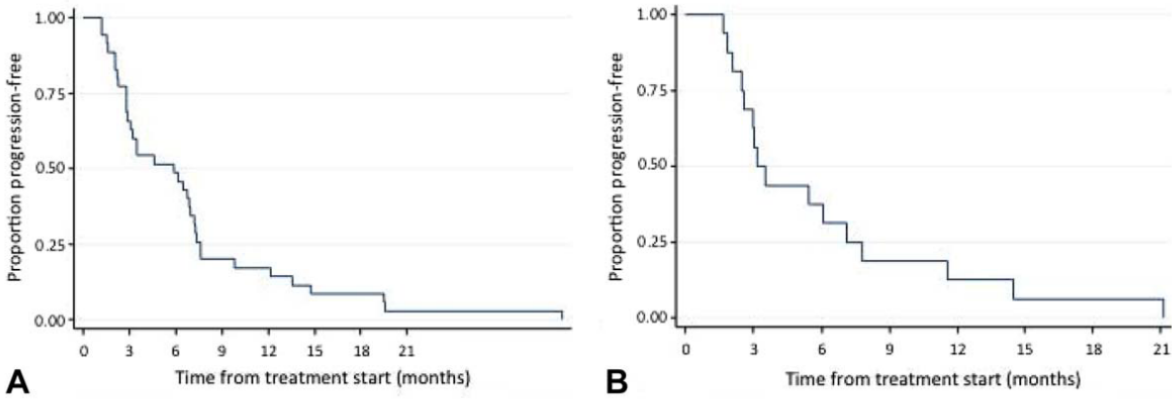

Figure 2. Overall survival from advanced disease in the overall population

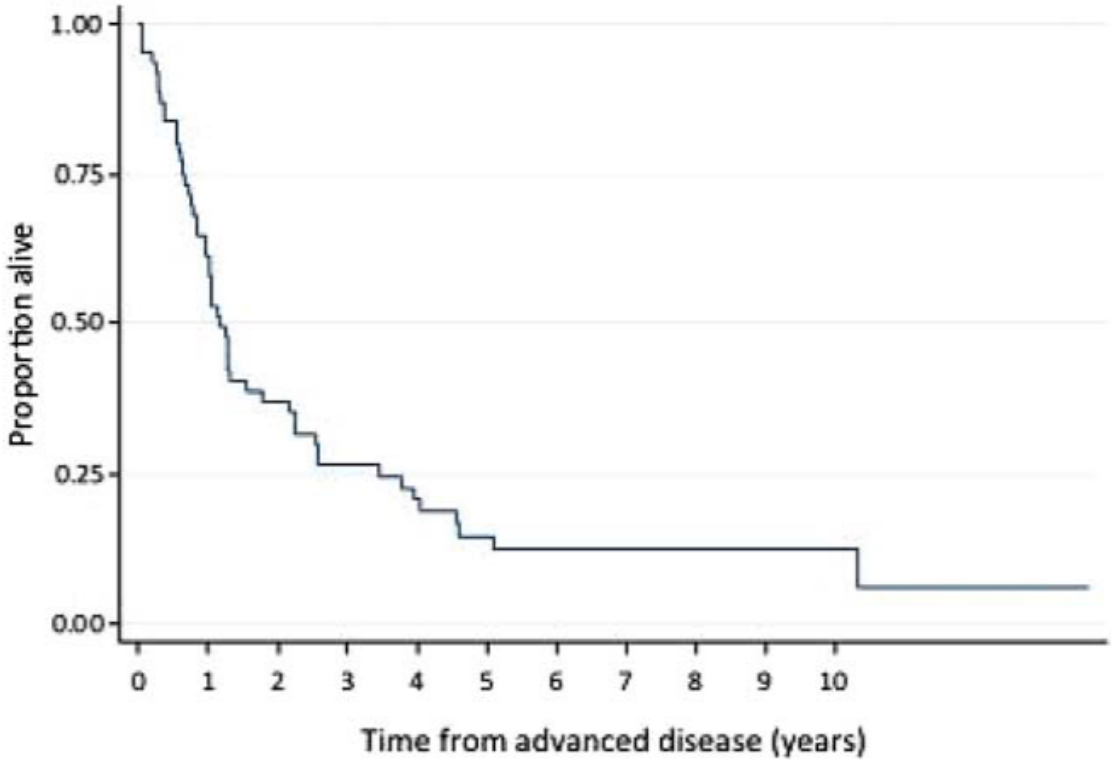

Table 1. Patient characteristics

	N	%
Gender		
Female	39	60.9
Male	25	39.1
Age		
Median (range)	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
Tumour 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 tumour		
No	11	17.2
Yes	53	82.8
(Curative)	(44)	(83.0)
(Palliative)	(7)	(13.2)
(After resection of primary tumour)	(2)	(3.8)
Prior radiosensitising 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)	(4.3)
Prior salvage APR		
No	54	84.4
Yes	10	15.6
Time to advanced disease – months		
Median (range)	9.3 (0 – 130.5)	
≤ 12 months	38	59.4
> 12 months	26	40.6
Extent of disease before 1st line chemotherapy		
Locally advanced	16	25.0
Metastatic	48	75.0
Number 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

Abbreviations: MMC: mitomycin C; APR: abdominoperineal resection.

Table 2. Chemotherapy regimens used in the first and second line setting

	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

Abbreviations: MMC: mitomycin C.

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

Variable		PFS		OS	
		HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
Gender	Female	-	-	-	-
	Male	1.66 (0.81-3.41)	0.17	1.41 (0.80-2.48)	0.23
Age	<65	-	-	-	-
	≥65	0.39 (0.16-0.97)	0.04	1.05 (0.57-1.93)	0.87
Tumour grade	Moderate	-	-	-	-
	Poor	1.09 (0.52-2.29)	0.81	0.85 (0.47-1.51)	0.57
Liver metastases	No	-	-	-	-
	Yes	1.07 (0.49-2.33)	0.87	2.25 (1.25-4.03)	0.01
N of sites of disease	0-1	-	-	-	-
	1+	0.97 (0.42-2.24)	0.94	1.66 (0.89-3.10)	0.11
Time to advanced disease	< 12m	-	-	-	-
	≥ 12m	0.49 (0.23-1.04)	0.06	1.24 (0.71-2.16)	0.46
Response to 1st line chemotherapy	No	-	-	-	-
	Yes	0.62 (0.28-1.39)	0.25	0.61 (0.29-1.28)	0.19

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