Longitudinal cohort analysis of patients with Metastatic Penile Cancer treated in a large quaternary academic centre

Wing K Liu[1*], R.Patel[2*], R.Crawford[3], B.Ayres[3], N.Watkin[3], A.Tree[4], L.Pickering[4], M.Ashfar[1]

Affiliations:

1. Department of Medical Oncology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

2. St George's Medical School, University of London, London, United Kingdom

3. Department of Urology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

4. The Royal Marsden Hospital, London, and The Institute of Cancer Research

Authors:

1) *Wing K Liu MBBS BSc MRCP

   Department of Medical Oncology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom. *Joint first author

2) *Reena Patel MBBS

   St George's Medical School, University of London, London, United Kingdom. *Joint first author

3) Ruairidh Crawford MRCS FRCR

   Department of Urology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

4) Benjamin Ayres BSc(Hons) MBChB(Hons) MRCS FRCS(Urol)

   Department of Urology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

5) Professor Nick Watkin MA MCHir, BMBCh FRCS

Department of Urology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

6) Alison Tree BSc MBBS FRCR MD(res)

The Royal Marsden Hospital, London, and The Institute of Cancer Research

7) Lisa Pickering MBBS BSc MRCP PhD

The Royal Marsden Hospital, London, and The Institute of Cancer Research

8) Mehran Ashfar PhD, MB BS(Lond), MRCP(UK), PGDip(Onc)

Department of Medical Oncology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

Corresponding author:

Mehran Afshar

Consultant Medical Oncologist

St George's University Hospitals NHS Foundation Trust, Blackshaw Road, Tooting, London, SW17 0QT

Mehran.Afshar@stgeorges.nhs.uk

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Abstract

Background:

Metastatic penile squamous carcinoma (mpSCC) has poor outcomes despite the use of platinum-based chemotherapy. There is limited real-world data on the management of these patients and their survival outcomes, particularly those that receive best supportive care.

Methods:

A database of 1720 patients referred to the supra-regional penile multi-disciplinary team (MDT) at St George's Hospital London was prospectively collected from 1st Jan 2006 to 5th May 2020. Patients were treated at St George's Hospital or at other centres with oncology guidance from the St George's MDT. Metastatic disease was defined as the presence of disease outside the pelvis or those in whom curative therapy was not possible. Indication of treatment was to treat symptoms and prolong survival. Clinical benefit rate (CBR), median progression free survival (mPFS) and median overall survival (mOS) was analysed retrospectively.

Results:

101 patients (median age 63 IQR (56-72), 73% ECOG 0/1) were included. 32% (32/101) had previously received adjuvant chemotherapy+/- radiotherapy prior to metastatic recurrence. 58% (59/101) received chemotherapy and 42% (42/101) received best supportive care (BSC). 17% (17/101) received second-line systemic-therapy and 3% (3/101) third-line systemic-therapy. For first-line systemic-therapy, there was a 46% (27/59) CBR with 9% (5/59) complete response, 15% (9/59) partial response and 22% (13/59) stable disease. Patients receiving second-line therapy (n=17) had a 29% (5/17) CBR. mPFS for first- and second-line treatment was 3.2 and 2.2 months respectively. mOS for all patients was 6.2 months. mOS for first line chemotherapy, second-line chemotherapy and

BSC patients was 7.2, 4.5 and 2.0 months respectively. Median follow up for all patients was 6.0 months.

Conclusions:

First-line platinum-based chemotherapy is associated with notable response rates in mpSCC patients. Subsequent therapy can be beneficial but outcomes remain sub-optimal. Agents with better response rates are needed urgently potentially in combination with platinum-based chemotherapy.

Introduction

Penile cancer is a rare disease with an incidence of less than 1/100,000 men in first-world countries.(1) Perhaps due to initial benign symptoms and insufficient awareness, 15-50% men present >1 year from symptom onset, with 25% presenting with advanced disease.(2)

Metastatic penile squamous cell carcinoma (mpSCC) is incurable with a median overall survival (mOS) of less than one year (3). The indication for treatment is symptomatic relief and to prolong survival. The low disease incidence presents a challenge for scientific research, hence international guidance is often guided by retrospective studies with small sample sizes.

mpSCC has limited effective systemic therapy options with notable toxicities. Despite the introduction of taxanes, there is still substantial variability in first-line chemotherapy response rates ranging from 25-100%,(4) with almost all responders progressing. Subsequently, various combination chemotherapy regimens have now shown benefit in the first-line setting, the most common combinations being Cisplatin/ Fluoropyrimidine based.(5) Other regimes include docetaxel/cisplatin/5FU (TPF),(6) and more recently dacomitinib and vinflunine.(7),(8)

With a limited evidence base to guide clinical management and with the aim of expanding our knowledge on the efficacy of chemotherapy, we conducted an analysis of survival outcomes, best response to treatment and chemotherapy toxicities in mpSCC patients with data collected from referrals to the supra-regional penile multi-disciplinary team (MDT) at St George's Hospital London during 2006-2020.

Methods

A prospective database of patients referred to the supra-regional penile MDT at St George's Hospital London was assimilated. This is currently 1720 patients with co-variables collected from 1st January 2006- 5th May 2020. Patients with metastatic disease were identified from the database using electronic medical records. This was defined as the presence of disease outside the pelvis or those in whom curative therapy for the metastasis was not possible and hence treated with palliative intent. These patients may have presented with metastatic disease, or were initially treated with curative intent and later progressed. Patients had histological evidence of penile or urethral squamous cell carcinoma with radiological evidence of metastatic disease. Patients receiving chemotherapy or best supportive care were included. Descriptive statistics and frequency counts were used to summarise characteristics of the study population.

mOS was defined as time from chemotherapy initiation or decision for BSC to patient death of any cause. Median PFS (mPFS) was defined as time from chemotherapy initiation until disease progression. Progression of disease was assessed by a radiologist at the supra-regional Penile MDT. mPFS and mOS were analysed using the Kaplan-Meier method. Statistical analysis was carried out using SPSS ver.26. Best response to treatment was evaluated according to radiological assessment.

The clinical benefit rate (CBR) to chemotherapy was defined as the percentage of patients who had a complete response (CR), a partial response (PR) or stable disease (SD) as a best response during treatment. Chemotherapy-related toxicities in patients receiving first-line chemotherapy were analysed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, as reported in electronic medical records from St Georges Hospital and other referring sites.

Results

Patient Characteristics

101 mpSCC patients were identified. Patient characteristics are shown in **Table 1**. Eighty-nine percent (90/101) of patients presented with Grade 3 disease and 48% (48/101) patients with pN3 stage disease. Patients commonly presented with metastatic disease to the regional lymph nodes (81%), lungs (63%), soft tissue (18%) and skin (13%). Twenty-eight patients presented with metastatic disease at 1 site: lymph nodes (64%), lung (21%), soft tissue (7%), skin (3%) and adrenal (3%).

Adjuvant and Neoadjuvant Treatments

Ninety-seven percent of patients underwent penile surgery before metastatic recurrence or for local control in the setting of synchronous metastatic disease. Three patients received neoadjuvant treatment: two patients on Cisplatin 5FU Capecitabine and Cisplatin 5FU Docetaxel (TPF) received neoadjuvant chemotherapy only, whilst one patient on Cisplatin Capecitabine received neoadjuvant chemoradiotherapy. Thirty-two patients received adjuvant chemotherapy regimens including: Cisplatin (72%), 5FU Mitomycin C (13%), Cisplatin Capecitabine (6%), Cisplatin 5FU (6%), Cisplatin

Gemcitabine (3%). Of 2 censored patients, one patient discontinued treatment due to renal toxicity and another patient was lost to follow-up.

First-line Chemotherapy or Best Supportive Care at Metastatic Relapse

Fifty-eight percent (59/101) received first-line chemotherapy, whilst 42% (42/101) received BSC. Ninety-three percent (55/59) of patients receiving first-line chemotherapy at metastatic relapse had a performance status of 0/1, in comparison with forty-five percent (19/42) of those for BSC at relapse with a performance status of 0/1 (Table 1). Of those that received first-line chemotherapy, forty-two percent (25/59) presented with T1/2 disease, and fifty-six percent (33/59) with N2/3 disease. Conversely for those receiving BSC, fifty percent (21/42) presented with T3/4 disease, and sixty-nine percent (29/42) presented with N2/3 disease. Eighty percent (47/59) of patients for first-line chemotherapy presented with disease in 1 or 2 metastatic sites, and twenty percent (12/59) with 3 or 4 metastatic sites. However, sixty-seven percent (28/42) of patients for BSC presented with disease in 1 or 2 metastatic sites, and thirty-three percent (14/42) with 3 or 4 metastatic sites.

First-line Chemotherapy at metastatic relapse

First-line chemotherapy regimes in our cohort included: Cisplatin Capecitabine (56%), Cisplatin 5FU (9%), Carboplatin Capecitabine (5%), Cisplatin Ifosfamide (3%), TIP (Paclitaxel Ifosfamide Cisplatin) (3%), Cisplatin Docetaxel 5FU (3%), Vinfluine (3%), Cisplatin Gemcitabine (2%), 5FU (2%), Cisplatin Paclitaxel (2%), Cisplatin Methotrexate Bleomycin (2%), Docetaxel (2%), Cisplatin Docetaxel (2%) and ECX (Epirubicin Cisplatin Capecitabine) (2%). 24% (14/59) of patients on first-line chemotherapy received dose-reductions, with 22.0% (13/59) discontinuing treatment due to chemotherapy-related toxicity or rapid disease progression. 12% (12/101) were also treated with metastectomy, of which fifty-eight percent (7/12) were resection of lung metastasis and forty-two percent (5/12) were

cutaneous lesion resections. Of the 12 patients treated with metastectomy, nine patients received first-line chemotherapy, with three progressing before receiving first-line chemotherapy. Three patients went on to receive second-line chemotherapy, two of which then received third-line chemotherapy.

Second-line Chemotherapy

Seventeen patients received second-line chemotherapy, regimes given included: Carboplatin Paclitaxel (41%), Cisplatin Capecitabine (12%), Paclitaxel (12%), Cisplatin Methotrexate (6%), Cisplatin Gemcitabine (6%), Docetaxel (6%), PI3-Kinase inhibitor plus a tyrosine kinase inhibitor (6%), Cetuximab (6%) and Cemiplimab (Anti PD-1) (6%). 2/17 patients on second-line therapy received dose-reductions and 2 patients discontinued treatment.

Third-line Chemotherapy

3 patients received third-line chemotherapy, 2 received Carboplatin Paclitaxel and one received a dual-mTOR inhibitor.

Overall Survival

mOS for all mpSCC patients was 6.2 months (95% CI:5.1-7.2) **(Figure 1a)**. mOS for patients receiving BSC (n=42) and first-line chemotherapy (n=59) was 2.0 months (95% CI:1.1-2.9) and 7.2 months respectively (95% CI:5.9-8.5; p=0.025) **(Figure 1b)**. Median follow up for all patients was 6.0 months. Hazard ratio for death for patients receiving chemotherapy, corrected for age, T-stage and grade, was 0.39 (95% CI:0.26-0.54; p=0.03). mOS patients receiving second-line chemotherapy (n=17) was 4.5 months (95% CI:2.5-6.5; p=0.046) mOS was taken from start of second-line chemotherapy until death. **(Figure 1c)**. mOS for patients on chemotherapy with 1 metastatic site

(n=21) was 11.9 months (95% CI:7.9-15.9), with 7/8 patients who remained alive at time of analysis. mOS for patients with 2 (n=26) and >3 (n=12) metastatic sites was 9.7 months (95% CI:6.6-12.8) and 5.3 months (95% CI:3.6-7.0) respectively **(Figure 2a)**. mOS for synchronous metastases (n=12) compared to metachronous metastases (n=47) was 7.9 months (95% CI:0.0-17.2) and 7.0 months (95% CI:6.0-8.0; p=0.713) **(Figure 2b).**

Best response for metachronous metastases was 9% (4/47) CR, 15% (7/47) PR, 26% (12/47) SD and 51% (24/47) PD. CBR was 49% (23/47) Best response for synchronous metastases was 8% (1/12) CR, 17% (2/12) PR, 8% (1/12) SD and 67% (8/12) PD. CBR was 33% (4/12) (**Table 2**). mOS of patients relapsing after adjuvant chemotherapy <12 months (n=21) and >12 months (n=11) was 5.6 months (95% CI:4.0-7.9) and 9.8 months (95% CI:4.9-14.8; p=0.017) respectively **(Figure 2c).**

Treatment Response and Progression-Free Survival

Best response to first-line chemotherapy was 9% (5/59) CR, 15% (9/59) PR, 22% (13/59) SD and 54% (32/59) PD. CBR was 46% (27/59). Best response to first-line Cisplatin Capecitabine was 9% (3/33) CR, 9% (3/33) CR, 30% (10/33) SD and 52% (17/33) progressive disease. Best response to second-line chemotherapy was 12% (2/17) CR, 0% PR, 18% (3/17) SD and 71% (12/17) PD. CBR was 29% (5/17). mPFS for first-line and second-line chemotherapy were 3.2 months (95% CI:2.0-4.5) and 2.2 months (95% CI:1.9-2.4; p=0.031) respectively **(Figure 2d)**. In total, 7 of 101 patients (7%) had a complete response.

Sub-analysis of urethral tumours

10 patients had metastatic urethral SCC of which five were still alive at point of analysis. Duration of follow-up (from metastatic recurrence) was 14.6m (95% CI:6.7-22.5). All patients were PS 0/1. 50%

(5/10) received adjuvant chemo-radiotherapy and 10% (1/10) neo-adjuvant radiotherapy. 8 had lymph node metastasis and 4 lung. All patients received platinum-based chemotherapy first-line. Best response for 1st-line chemotherapy was 40% (4/10) CR, 30% (3/10) PR, 10% (1/10) SD and 20% (2/10) PD. 6 patients subsequently had second-line chemotherapy with 33% (2/6) patients obtaining CR and 67% (4/6) patients PD. Of these 6 patients, 2 has subsequent chemotherapy with one obtaining PR and one PD. mOS was not reached.

Toxicity and Treatment Modifications

Overall, treatment was well tolerated. **Table 3** shows a comparison of Grade 3 toxicities amongst different regimes of first-line chemotherapy. Twenty-three percent (23/101) of patients experienced Grade 3 toxicities during their treatment. Thirty-two percent of patients (19/59) on first-line treatment and twenty-nine percent of patients (5/17) on second-line treatment experienced grade three toxicities. Five percent of patients experienced neutropenia (5/101) and five percent acute kidney injury (5/101) as the most common grade three toxicities. Nausea and fatigue were the most frequent grade 1/2 adverse effects occurring in fifteen percent (15/101) and thirteen percent (13/101) of patients respectively. Dose reductions occurred in fifteen percent (15/101) of patients. Sixteen percent (16/101) of patients discontinued treatment. No deaths due to treatment toxicity occurred.

Discussion

We present a real-world analysis of treatment outcomes in 101 mpSCC patients. Ninety percent of patients presented with grade 3/4 disease, suggesting that low grade penile cancers are less likely to recur. Forty-eight percent of mpSCC patients were N3 compared to 14% with N2 disease, demonstrating the aggressiveness of penile cancers with high nodal burden at initial presentation.

Common sites of metastasis were lymph node and lung. 13% patients had skin metastasis, with only case reports described in literature. (9) Most patients received some form of penile surgery prior or during metastatic recurrence, with those relapsing after 12 months achieving better outcomes than those relapsing earlier. Our data shows a statistically significant difference between BSC and first-line chemotherapy outcomes, supporting the use of chemotherapy in fit mpSCC patients. This is in keeping with clinical trial data from initial platinum based chemotherapy trials. (3) It should be noted the BSC cohort may be under-represented as mpSCC patients who progress rapidly with aggressive disease may not be referred to MDT.

Patients in our cohort received predominately platinum-based therapies in the first-line setting and taxane-based treatment second-line. Our data showed some clinical benefit for second-line therapy in patients who maintain a good PS after progressing on first-line therapy. Only three patients received third-line chemotherapy, one receiving immunotherapy.

A sub-analysis of metachronous and synchronous mpSCC, did not show a statistically significant difference in mOS. This is possibly due to the disbalanced numbers of metachronous and synchronous mpSCC patients, as synchronous mpSCC is rarer.

To our knowledge, this is the largest study of its type analysing mpSCC. The paucity of data on chemotherapy in penile cancer is explained by the disease’s low incidence and aggressive nature, as well as a limited number of centres’ ability to evaluate a sufficient number of patient outcomes due to the wide distribution of treating institutions. Studies which aim to account for this by converging data from multiple institutions from different nations run the risk of numerous biases and confounders as a result of a mixed cohort. The overall management decisions were overseen at our single supra-

regional centre MDT, with chemotherapy for some penile cancer patients delivered in local hospitals. Centralisation of penile cancer care has allowed uniformity in management and comparison of outcomes across a few centres. A strength of our study was that all patients in our cohort were treated according to one set of supra-regional guidelines and decisions made by a single group of clinicians. For rare tumours this is an important method to obtain clinically meaningful data but requires improved networking, cooperation and common guidelines for treatment and reporting.

As an analysis of chemotherapeutic strategies in mpSCC our study offers valuable insight into a wide variety of real-world treatment outcomes, considering that existing evidence predominately consists of early phase/small clinical studies or case reports. A strength of this study is its analysis of outcomes in mpSCC patients receiving BSC after metastatic relapse, which is often missing in similar studies. Furthermore, our data expands on the limited literature existing on second-line and third-line treatments in penile cancer. Our database was created prospectively however the data obtained from it is retrospective. Although the retrospective nature of this study may be a limitation, prospective clinical trials are incredibly difficult to conduct with the disease's very low incidence and aggressive nature.

pN2-3 disease is known to have much worse prognosis with 5-year survival <30% when compared to approximately 90% in pN0 disease (10) This also reflects the survival data in our own cohort suggesting that nodal involvement is a risk factor of development of distant metastatic disease and hence poorer prognosis.

Multi-modal therapy is preferred in patients with advanced lymph node involvement. Neoadjuvant chemotherapy followed by surgical node dissection is recommended in stage N3 disease, with many

studies reporting promising response rates and higher proportions of long-term survivors across different regimens.(11),(12),(13) Our present study noted only a few patients receiving neoadjuvant chemotherapy before relapse hence conclusions regarding their use were not drawn.

Current European Association of Urology guidelines recommend adjuvant chemotherapy for stage N2/N3 disease based on several small case series, (4),(14),(15) however little evidence exists on which regimen is best in this setting.(16) We also analysed mpSCC patients who were stratified from start of adjuvant chemotherapy to metastatic recurrence or decision to start systemic treatment into two groups; patients relapsing before 12 months and those after 12 months. With most patients undergoing penile surgery our data showed a statistically significant difference between mOS of patients relapsing before and after 12 months of adjuvant chemotherapy. Our cohort only showed patients who were metastatic and recurred hence we cannot comment on the efficacy of adjuvant chemotherapy in mpSCC patients. However, time to recurrence could potentially be a useful prognostic marker in assessing the potential effectiveness of systemic therapy in patients.

In our series, most patients received platinum-based first-line treatment and taxane-based second-line treatment, reflecting little change of therapeutic choice over the past 20 years.(17) First-line platinum-based chemotherapy response rates were in keeping with other retrospective studies.(18),(19)

In our study there was a wide range of first line treatment options used which reflects the long period of time (14 years) our study was conducted over during which new data on treatments became available. Also, there are individual differences between mpSCC patients and a proportion of these patients also entered clinical trials.

Responses were not durable and most patients eventually progressed. Of the 5 patients who achieved a CR all eventually progressed. Several studies of mpSCC patients have reported that cisplatin-based therapies had better outcomes than non-cisplatin-based regimens.(20),(21) Minimal benefit has been observed with gemcitabine–cisplatin.(22),(23) Treatment in our series was generally well tolerated with toxicities in keeping with previous data on platinum-based chemotherapy.(17) There were no treatment related deaths.

Patients with systemic disease often progress quickly on first-line regimes, hence there are few studies on the efficacy of second-line therapies. In a phase II trial of 25 patients treated with paclitaxel monotherapy following progression on a previous chemotherapy agent, mPFS and mOS were 11 weeks and 23 weeks respectively.(24) With a wide array of second-line agents used in our analysis, these poor survival outcomes were comparable to ours. New epidermal growth factor receptor (EGFR) targeted therapies such as cetuximab and panitumumab have reported notable responses rates in several case series. (25,26) However, in our cohort, only one patient received an EGFR inhibitor.

An exploratory sub-analysis of metastatic urethral SCC patients showed impressive response rates when compared to mpSCC patients. Potentially these patients do better on chemotherapy and biologically may have a different tumour prognosis when compared to conventional mpSCC patients.(27)

In our study further work could be done looking at neoadjuvant chemotherapy and potential optimal regimes e.g. paclitaxel, ifosfamide and cisplatin as defined in the TIP trial(13). Better outcomes for

mpSCC patients positive for the Human papilloma virus have also been reported(28) and further work on biomarkers may help identify patients most likely to respond to chemotherapy. Since long-term outcomes are poor, appropriate chemotherapy selection is paramount in obtaining optimal response and minimal toxicity. In our cohort platinum/fluoropyrimidine doublet regimens were found to be active and well tolerated.

Conclusion

First-line platinum-based chemotherapy is associated with notable response and clinical benefit rates in metastatic penile cancer patients. Subsequent therapy after progression on first-line chemotherapy can be beneficial in a subset of patients particularly those with one metastatic site and good performance status but survival outcomes remain sub-optimal. Agents with better response rates are urgently needed possibly in combination with platinum-based chemotherapy to improve outcomes.

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Table 1. Patient characteristics at time of metastatic relapse

	Best supportive care alone (n=42)	First-line chemotherapy received (n=59)	All patients (n=101)
Median age at diagnosis of primary tumour, years (IQR)	64 (59-75)	61 (53-69)	63 (56-72)
¶ECOG performance status, n (%)			
0	4 (9.5%)	24 (40.7%)	28 (27.7 %)
1	15 (35.7%)	31 (52.5%)	46 (45.5%)
2	16 (38.1%)	3 (5.1%)	19 (18.8%)
3	7 (16.7%)	1 (1.7%)	8 (7.9%)

Treatment before metastatic disease, n (%)			
Surgery	41 (97.6%)	57 (96.6%)	98 (97.0%)
No surgery	1 (2.4%)	2 (3.4%)	3 (3.0%)
Lymph Node dissection	15 (35.7%)	17 (28.8%)	32 (31.7%)
Neo-adjuvant treatment			3 (3.0%)
– Neo-adjuvant chemotherapy only	2 (4.8%)	0 (0.0%)	2 (2.0%)
– Neo-adjuvant chemoradiotherapy	0 (0.0%)	1 (1.7%)	1 (1.0%)
Adjuvant treatment			40 (39.6%)
– Adjuvant chemoradiotherapy	12 (28.6%)	20 (33.9%)	32 (31.7%)
– Adjuvant radiotherapy only	4 (9.5%)	4 (6.8%)	8 (7.9%)
Grade at diagnosis, n (%)			
1	0 (0.0%)	1 (1.7%)	1 (1.0%)
2	6 (14.3%)	2 (3.4%)	8 (7.9%)
3	36 (85.7%)	54 (91.5%)	90 (89.1%)
4	0 (0.0%)	1 (1.7%)	1 (1.0%)
Not available	0 (0.0%)	1 (1.7%)	1 (1.0%)
†Pathological T stage at diagnosis, n (%)			
T1	4 (9.5%)	5 (8.5%)	9 (8.9%)
T1b	0 (0.0%)	4 (6.8%)	4 (4.0%)
T2	6 (14.3%)	8 (13.5%)	14 (13.9%)
T2a	7 (16.7%)	12 (20.3%)	19 (18.8%)
T2b	4 (9.5%)	5 (8.5%)	9 (8.9%)
T3	8 (19.0%)	11 (18.6%)	19 (18.8%)
T3a	10 (23.8%)	5 (8.5%)	15 (14.9%)
T3b	1 (2.4%)	3 (5.1%)	4 (4.0%)
T4	2 (4.8%)	5 (8.5%)	7 (6.9%)
Not available	0 (0.0%)	1 (1.7%)	1 (1.0%)
Pathological N stage at diagnosis, n (%)			
N0	6 (14.3%)	12 (20.3%)	18 (17.8%)
N1	7 (16.7%)	14 (23.7%)	21 (20.8%)
N2	5 (11.9%)	9 (15.3%)	14 (13.9%)
N3	24 (57.1%)	24 (40.7%)	48 (47.5%)
Metastatic site at time of diagnosis, n (%)			
Lymph node	34 (81.0%)	48 (81.2%)	82 (81.2%)
Lung	28 (66.7%)	36 (61.0%)	64 (63.4%)
Soft tissue	9 (21.4%)	9 (15.3%)	18 (17.8%)
Skin	5 (11.9%)	8 (13.6%)	13 (12.9%)
Bone	6 (14.3%)	4 (6.8%)	10 (9.9%)
Liver	4 (9.5%)	3 (5.1%)	7 (6.9%)
Adrenal	3 (7.1%)	1 (1.7%)	4 (4.0%)
Other	1 (2.4%)	5 (8.5%)	6 (5.9%)
Number of metastatic sites, n (%)			
1	7 (16.7%)	21 (35.6%)	28 (27.7%)
2	21 (50.0%)	26 (44.1%)	47 (46.5%)
3	12 (28.6%)	9 (15.3%)	21 (20.8%)

4	2 (4.8%)	3 (5.1%)	5 (5.0%)
*Histology, n (%)			
KS	38 (90.5%)	42 (71.2%)	80 (79.2%)
SCB	1 (2.4%)	6 (10.2%)	7 (6.9%)
SA	2 (4.8%)	1 (1.7%)	3 (3.0%)
MS	0 (0.0%)	1 (1.7%)	1 (1.0%)
Urethral	1 (2.4%)	9 (15.3%)	10 (9.9%)
Median age at diagnosis of metastatic recurrence, years (IQR)	65 (60-77)	61 (53-69)	63 (57-72)

Legend:
¶ ECOG- Eastern Cooperative Oncology Group
†Tumour staging for all patients was determined using cross-sectional imaging at MDT.
*Histology: KS-Keratinizing squamous cell, SCB- Squamous cell/ basaloid, MS-Mixed squamous/verrucous, SA- sarcomatoid
Percentages may not total 100 because of rounding.

Table 2. Response to Treatment According to Radiological Assessment

	1st line chemotherapy (n=59)	2nd line chemotherapy (n=17)	3rd line chemotherapy (n=3)	¶Metachronous Disease (n=47)	Synchronous Disease (n=12)
¶ Responses, n (%)					
Complete response	5 (8.5%)	2 (11.8%)	0 (0.0%)	4 (8.5%)	1 (8.3%)
Partial response	9 (15.3%)	0 (0.0%)	1 (33.3%)	7 (14.9%)	2 (16.7%)
Stable disease	13 (22.0%)	3 (17.6%)	0 (0.0%)	12 (25.5%)	1 (8.3%)
Progressive Disease	32 (54.2%)	12 (70.6%)	2 (66.7%)	24 (51.1%)	8 (66.7%)
Clinical Benefit Rate	27 (45.8%)	5 (29.4%)	1(33.3%)	23 (48.9%)	4 (33.3%)

Median (IQR) number of cycles	3 (2-6)	2 (1-3)	3 (3-7)	3 (3-6)	3 (2-6)
Median (IQR) *PFS, months	3.2 (2.1-5.2)	2.2 (0.9-4.3)	6.2 (4.5-7.8)	3.3 (2.3-5.2)	2.8 (1.3-5.1)
Dose reductions Treatment stopped early	14 (23.7%) 13 (22.0%)	2 (11.8%) 2 (11.8%)	0 (0.0%) 1 (33.3%)		

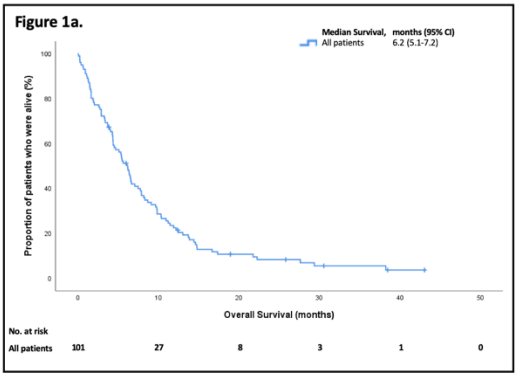
¶ Responses were defined as per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Percentages may not total 100 because of rounding.
*Median PFS (mPFS) was defined as time from chemotherapy initiation until disease progression. This was calculated with the use of the Kaplan-Meier method.
¶ Best response to treatment with first-line systemic therapy for patients with metachronous or synchronous disease was assessed

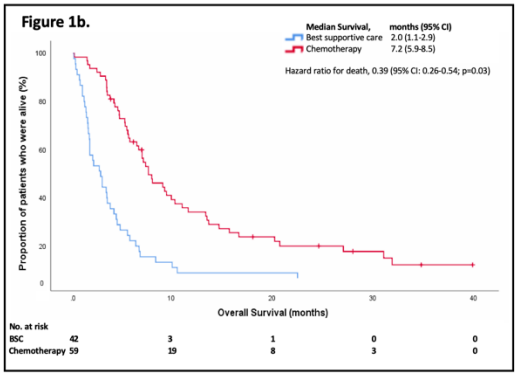
Table 3. Grade 3/4 chemotherapy-related toxicities in patients receiving first-line chemotherapy (n=59)

Grade 3/4 Toxicity	*Cis-Cap (n=33)	TPF (n=3)	TIP (n=2)	CMB (n=2)	Cis-Ifo (n=2)	Cis-Doc (n=1)	Cis-Meth (n=1)	ECX (n=1)	Total (All regimes)
Fatigue	2								2
Neutropenia	2		1				1	1	5
Anaemia	1					1			2
Thrombocytopenia	1								1

Alopecia		1							1
Oral mucositis	1								1
Diarrhoea	1				1				2
Hearing loss/tinnitus	1								1
Pneumonia	2								2
Arrhythmias			1						1
Urosepsis	3					1			4
Stomatitis				1					1
Renal Failure	3					1		1	5
Encephalopathy					1				1
Palmer Plantar Erythrodysesthesia	1								1

Shown are all Grade 3/4 adverse events that occurred while patients were receiving first line chemotherapy. Adverse Events were defined as per the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).
*Chemotherapy regimes were defined as Cis-Cap (Cisplatin Capecitabine), TPF (Cisplatin Docetaxel 5FU), TIP (Paclitaxel, Ifosfamide Cisplatin), CMB (Cisplatin Methotrexate Bleomycin), Cis-Doc (Cisplatin Docetaxel), Cis-Meth (Cisplatin Methotrexate), ECX (Epirubicin Cisplatin Capecitabine). No deaths due to treatment toxicity were recorded.





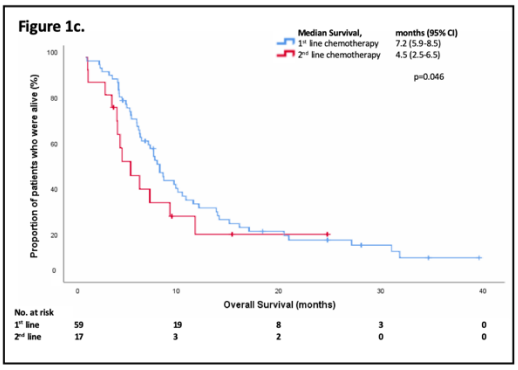
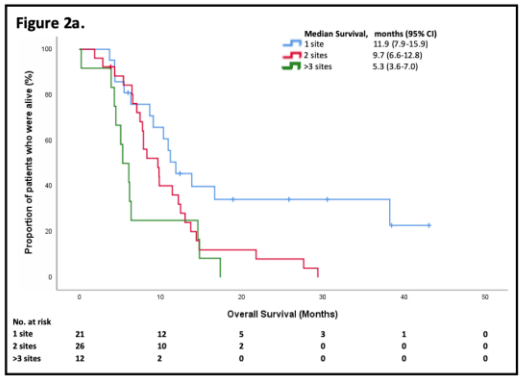
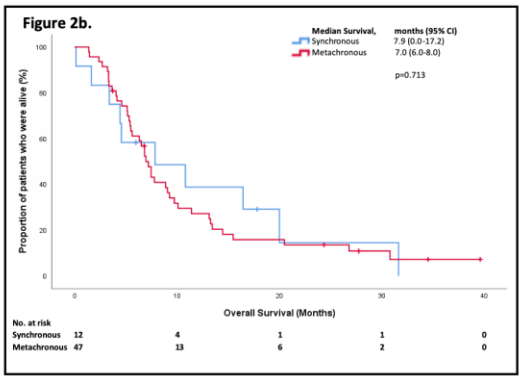
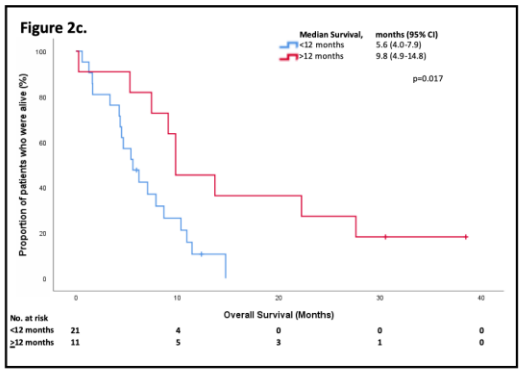


Figure 1a. Kaplan Meier of median overall survival in all metastatic patients (n=101)
Figure 1b. Kaplan Meier of median overall survival between patients who received best supportive care (BSC) (n=42) vs. chemotherapy (n=59) Hazard ratio for death for patients receiving chemotherapy, was corrected for age, T-stage and grade.
Figure 1c. Kaplan Meier of median overall survival between patients who received 1st line chemotherapy (n=59) vs. 2nd line (n=17)
*Median Overall Survival was defined as time from chemotherapy initiation or decision for best supportive care to patient death of any cause.







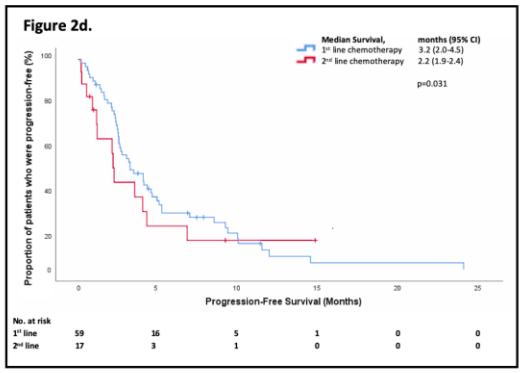


Figure 2a. Kaplan Meier of median overall survival of patients who received chemotherapy (n=59) according to number of metastatic sites
Figure 2b. Kaplan Meier of median overall survival of patients receiving chemotherapy according to metachronous (n=47) vs. synchronous (n=12) metastases
Figure 2c. Kaplan Meier of median overall survival of patients receiving adjuvant chemotherapy stratified from start of adjuvant chemotherapy to recurrence
*Median Overall Survival was defined as time from chemotherapy initiation or decision for best supportive care to patient death of any cause. 2 patients were censored, one patient did not complete treatment due to renal toxicity and another patient relocated abroad and was lost to follow-up.
Figure 2d. Kaplan Meier of median progression-free survival between patients who received 1st line chemotherapy (n=59) vs. 2nd line chemotherapy (n=17)
*Median Progression Free Survival was defined as time from chemotherapy initiation until disease progression.