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Case Report

A case of vulval basosquamous basal cell carcinoma with possible pelvic lymph node metastases

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Background: Basal cell carcinoma (BCC) is the most common cutaneous neoplasm. It is most often a locally invasive tumour and rarely affects the vulva. Distant spread of BCC is rarer still and there are few cases reported of metastatic vulval primary tumours. Basosquamous carcinoma is regarded as a high-risk variant of BCC and its behaviour is unpredictable. Though more aggressive, it tends to grow locally rather than spread to lymph nodes as seen in squamous cell carcinoma (SCC). *Case*: We present a case of a basosquamous BCC arising in the vulva with involvement of the external and common iliac lymph nodes. *Conclusion*: Metastatic BCC has a poor prognosis and there are no definitive guidelines for its investigation or management. We recommend staging with imaging and potentially lymph node dissection in patients with large lesions involving underlying structures or aggressive histology.

Keywords

Vulval cancer; Metastatic basal cell carcinoma; Gynaecology oncology; Staging radiology

1. Introduction

Basal cell carcinoma (BCC) is the most common neoplasm to affect the skin and accounts for almost one third of cancers globally [1, 2]. These tumours arise from the basal layer of the epidermis, mostly due to inappropriate activation of Hedgehog signaling (HH) or loss of the p53 tumour suppressor gene [1]. Both have downstream targets of transcription factors and mutation in either pathway results in uncontrolled proliferation of basal cells. Such mutations are principally caused by ultraviolet radiation and accordingly BCCs are most commonly found in sun-exposed areas such as the head and neck [1]. Other risk factors for BCC include older age, fair complexion, immunocompromise, exposure to ionising radiation, and genetic syndromes such as Xeroderma pigmentosum [1, 3].

Classically, BCCs present as pearly nodules with telangiectasia, a rolled edge and occasionally central ulceration. They are often asymptomatic and therefore present late when they have become large, pruritic or painful lesions [4]. In general, BCCs are slow growing and at most become only locally invasive. Metastasis is rare, with rates reported in the literature ranging from just 0.028 to 5.5 per 100,000 cases [5]. Published cases of BCC with metastases mostly originate in the head and neck region and spread sequentially to local lymph nodes followed by bone, lung and liver [1, 6–8].

BCCs are rarely found to affect the genitalia and only a few hundred cases of vulval BCC have been reported in the current literature [9, 10]. The most common site of occurrence in cases which affect the vulva is in the labia majora and the aetiology of BCC in such a non-sun-exposed area is not clear [4]. The incidence of metastatic vulval BCC is rarer still, with only 10 other cases of metastasis to inguinal lymph nodes reported to date (Table 1, Ref. [6, 7, 11–18]) [6]. Here, we present an exceedingly rare example of an infiltrative vulval BCC with possible spread to the pelvic sidewall lymph nodes. To the best of our knowledge, this is the first case to be reported in which there is possible metastasis to the external and common iliac but not the inguinal group of nodes.

2. Case report

We report a case of an 86-year-old woman who presented with an extensive lesion of the vulva. The lesion had no associated pain or bleeding, however, was noted by the patient to have grown significantly over several months. She had comorbidities of hypertension, pernicious anaemia, chronic kidney disease (CKD), gout and polymyalgia rheumatica which were all medicated. The patient was an ex-smoker and functioning independently.

On initial examination an ulcerated and exophytic mass, 8 × 5 cm in dimensions and just crossing the midline, was found mainly in the right, upper lateral aspect of the vulva. There was no obviously palpable inguinal lymphadenopa-

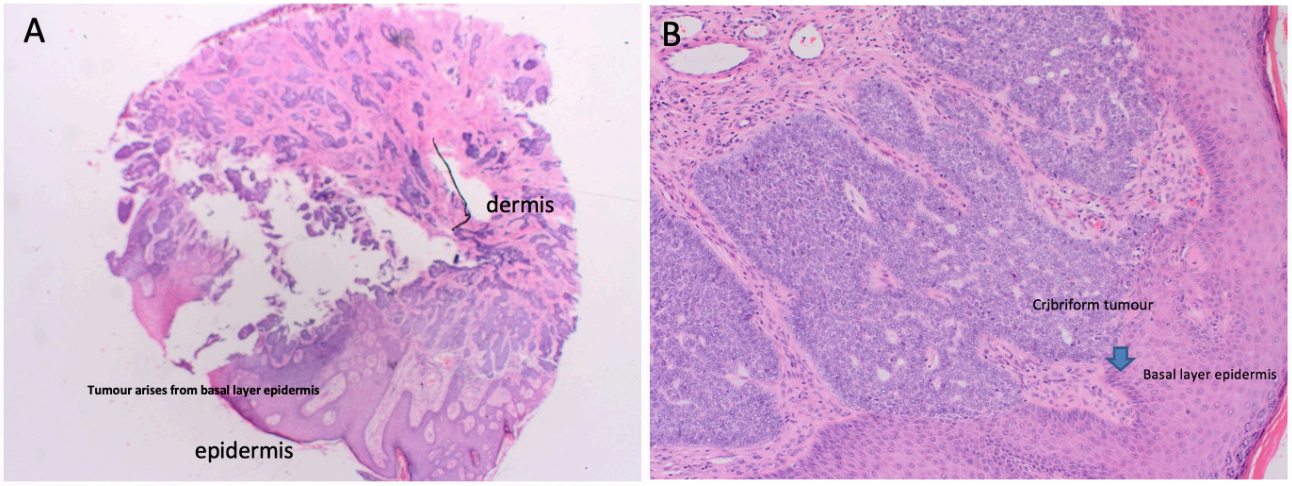

Fig. 1. H&E staining of original vulval mass biopsy. Poorly differentiated cells with coarse chromatin and palisading islands 100× (A). Islands of dark cells from the epidermis invading the dermis 1000× (B).

Table 1. Reported cases of vulval BCC with metastasis to inguinal lymph nodes [6].

Case report	Patient age	Site of metastasis
[11]	41	Left inguinal lymph node
[12]	71	Lymph node in subcutaneous fat
[13]	86	Both inguinal lymph nodes
[14]	74	Left inguinal lymph node
[15]	71	Right inguinal lymph node
[16]	86	Right inguinal lymph node
[7]	79	Right inguinal LN and skin of right thigh
[17]	Not specified	Regional lymph nodes (not specified)
[18]	87	Left inguinal lymph node
[6]	70	Left inguinal lymph node

thy. At vulvoscopy a 6 × 8 cm exophytic, papillary-like lesion was confirmed to be completely replacing the normal skin architecture of the vulva between the clitoris and right thigh. The mass was firm, mobile and bled easily on contact. Three biopsies were taken at the 12, 4 and 6 o'clock positions and histologically showed surface squamous epithelium with severe dysplasia and extensive invasive carcinoma. H&E staining demonstrated sheets of poorly differentiated cells with coarse chromatin, cribriform islands and palisading islands within sclerotic stroma suggestive of an infiltrative BCC (high risk type, Fig. 1A). Islands of dark cells were seen originating from the epidermis and invading the dermis, though with no definite extension into the lymphovascular space (Fig. 1B). BCC was subsequently confirmed with immunohistochemical profiling, as slides of the biopsy stained positive for Ber-EP4 and negative for CD117, CEA and S-100. Ber-EP4 is sensitive marker differentiating basal from squamous cell carcinoma (SCC), whilst CD117 was done to rule out the possibility of adenoid cystic carcinoma given the cribriform morphology of the tumour [19–22].

MRI of the patient's pelvis showed a lobulated intermediate T2 weighted (T2w) signal intensity mass centred on the right labia majora and infiltrating into the upper inner aspect of the thigh (Fig. 2). The mass measured 4 × 4 × 7 cm, showed marked diffusion restriction (Fig. 2C) and did not extend cranially to involve the clitoris, vaginal introitus, external urethral meatus or anal margin. The cervix and both ovaries were unremarkable. There was only mild fluid distension and adhesions within the uterine cavity, with no evidence of endometrial hyperplasia, polyp or a mass lesion. This was reassuring and increased our confidence that a different tumour was not responsible for the pelvic lymphadenopathy noted. The latter consisted of multiple bilateral small volume external iliac and inguinal nodes, as well as two enlarged (>8 mm in short axis dimension) obturator internus nodes (Fig. 3) which on T2w sequences had features increasing the likelihood of underlying metastatic involvement (rounded, of similar signal intensity to the primary tumour and containing small foci of cystic change suggestive of necrosis). Unfortunately, due to their precarious proximity to the iliac vessels, percutaneous biopsy of the suspicious obturator internus lymph nodes was deemed too high risk for the patient even if guided radiologically. There was no retroperitoneal lymphadenopathy and all upper abdominal organs and bones visualised were normal.

Following MRI, a CT of the chest, abdomen and pelvis to look for extra-pelvic disease showed an indeterminate 9 mm nodule in the lower lobe of the left lung (not shown), with no enlargement of the hilar or mediastinal lymph nodes. The patient had no pleural or pericardial effusion and there was no significant retroperitoneal lymphadenopathy, liver lesions, bowel masses, ascites or bony pathology on this scan.

Staging of this patient's disease was imperative to guiding whether radical surgery could be considered as curative treatment. Since histological analysis of the inguinal and iliac lymph nodes was not possible, the patient underwent

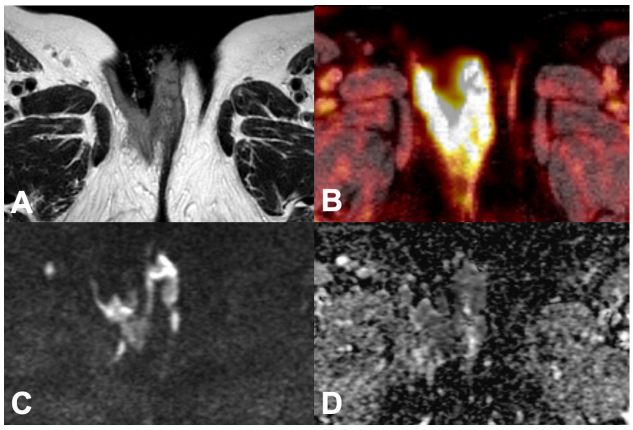

Fig. 2. Axial T2 (A), FDG-PET/CT (B), DWI (C) and ADC map (D) shows an intermediate, T2w signal intensity mass centred on the right labia majora extending into the upper inner aspect of the thigh. The mass is high signal on the diffusion weighted imaging and low signal on the ADC map in keeping with tumour. It is markedly avid on FDG-PET/CT (SUV max 16.6).

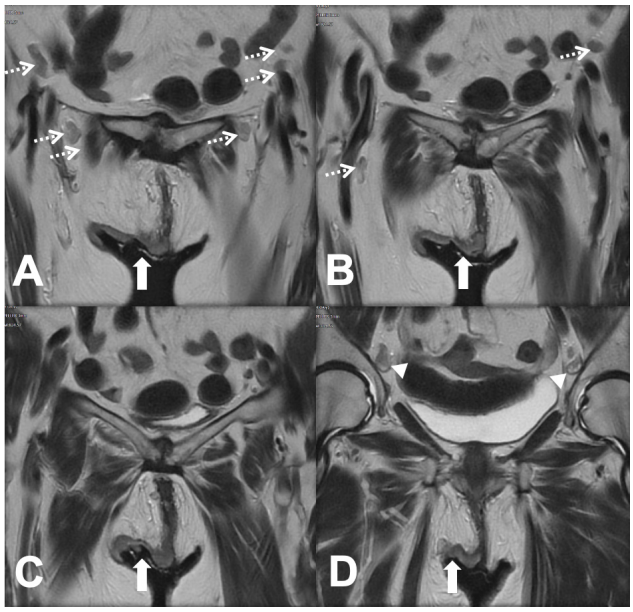

Fig. 3. Coronal images of the vulva in the same plane from most anterior (A) to posterior (D) showing the infiltrating intermediate T2w signal intensity mass between the midline labia majora and right medial upper inner thigh (solid arrows). There are multiple bilateral predominantly small volume inguinal and external iliac lymph nodes (dashed arrows). Of note are two enlarged obturator internus lymph nodes (>8 mm) in the pelvic sidewall (triangle, D) which show small foci of hyperintense T2w signal intensity. These are cystic changes in keeping with necrosis, suspicious of metastasis.

PET/CT pre-operatively for the purposes of staging and diagnostic clarification. This confirmed a markedly FDG-avid vulval mass (Fig. 2B) and multiple bilateral pelvic sidewall lymph nodes measuring up to 10 mm in short-axis diameter (Fig. 4). The enlarged nodes demonstrated low-grade uptake and were indeterminate in nature, with potential of being either metastatic or reactive. The pulmonary nodule initially noted on CT did not appear to be suspicious and there remained no pleural or pericardial effusion. The liver, pancreas, spleen, kidneys and adrenal glands appeared normal and there was no increased uptake in any bones.

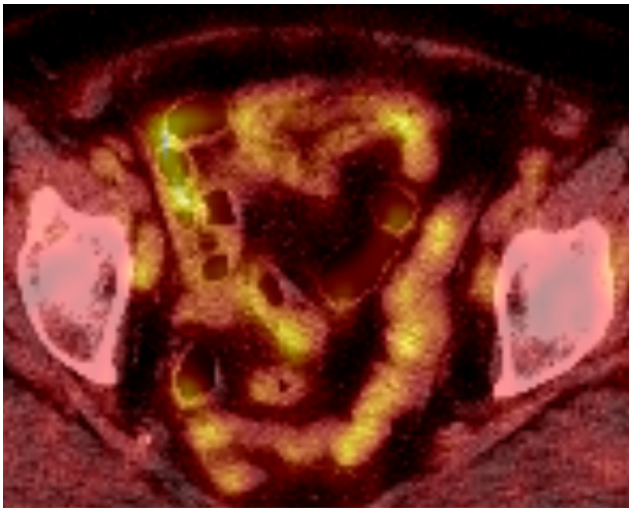

Fig. 4. Axial image of the two enlarged obturator internus lymph nodes with necrosis (arrows) demonstrated in Fig. 3 showing low-grade uptake on FDG-PET/CT.

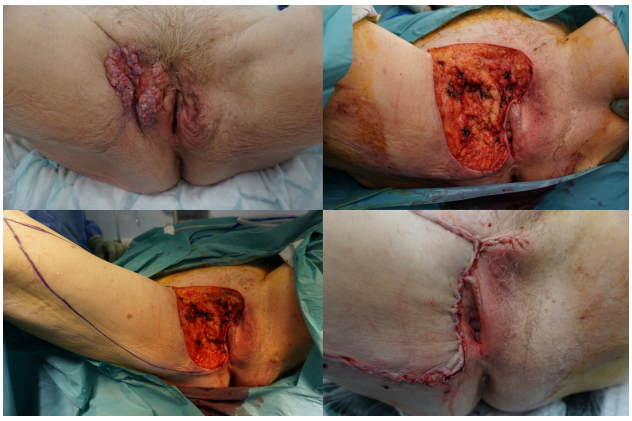

Fig. 5. Intra-operative photographs demonstrating complete tumour excision and reconstruction of the vulval defect using V-Y advancement flap from the right thigh.

Owing to the patient's age and comorbidities, she was offered radical surgery without lymph node dissection. Though it would not address the distant spread of disease, this was considered to be the avenue of least morbidity. The patient was in agreement and successfully underwent complete local excision of the lesion, followed by V-Y advancement reconstruction of the vulva using a flap harvested from the medial right thigh (Fig. 5). The resected specimen encompassed

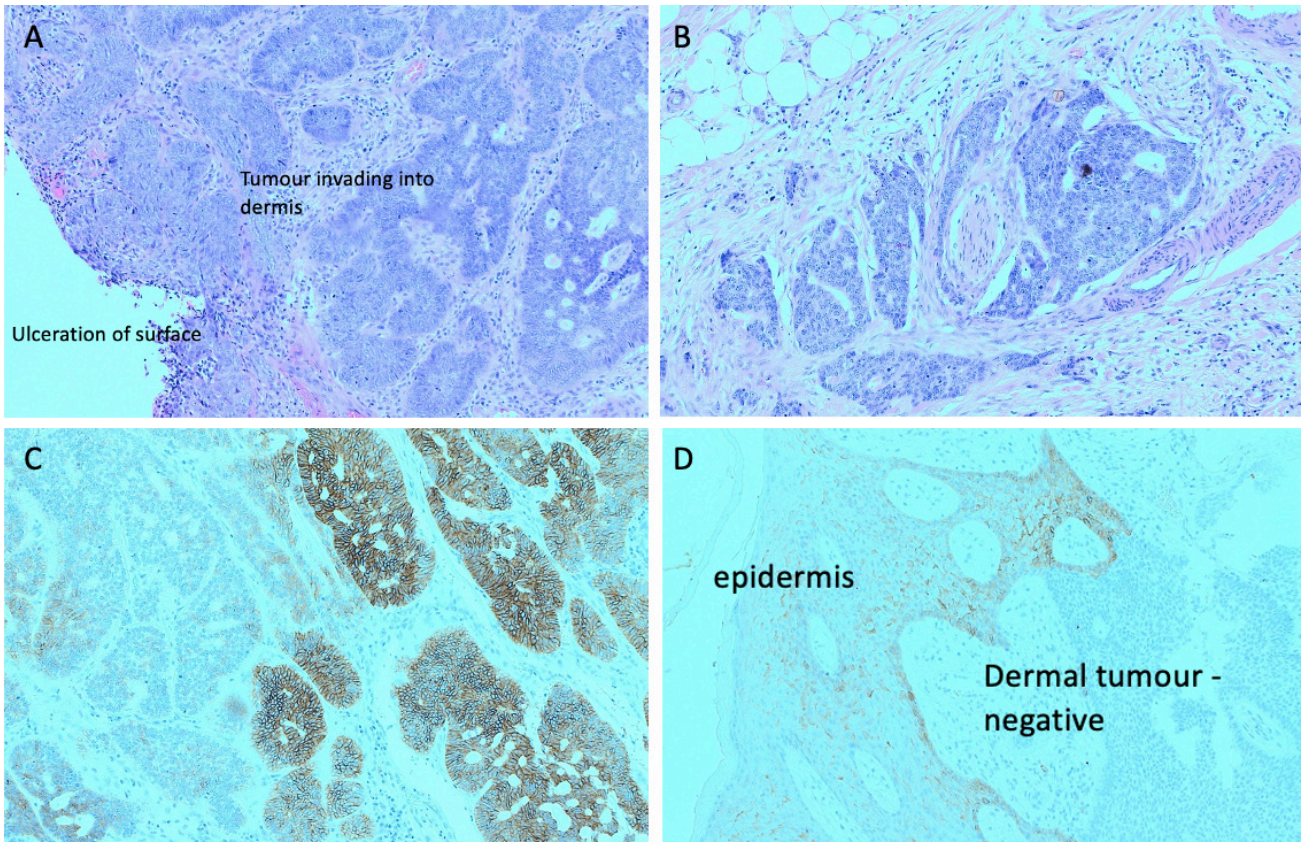

Fig. 6. Staining of resected specimen. Pallisading islands of dark basaloid cells arising from basal layer of epidermis, cribriform and solid areas 100× (A). Lower border of the tumour shows infiltrative growth with focal neural invasion 100× (B). There is strongly positive Ber-EP4 staining 100× (C) and negative EMA staining throughout 100× (D).

an ulcerated, infiltrative tumour of diameter 7 cm and depth 1.5 cm. Histologically it had the appearances of a BCC, with palisaded islands of dark basaloid cells arising from the basal layer of the epidermis (Fig. 6A). This larger sample of tumour to examine revealed pinker areas which did not stain positive for Ber-EP4. These were squamoid in nature, like islands within the BCC and a feature not seen on the original biopsy. Though parts of the tumour were strongly positive for Ber-EP4 (Fig. 6C) and negative for CD117, BCCs classically show diffuse positivity for Ber-EP4. The epidermis of the specimen stained positive for EMA and was negative for this throughout the remaining tumour (Fig. 6D), consistent with a BCC over SCC [20]. Whilst the lower border of the tumour showed focal neural invasion, a marginal clearance of 7 mm showed only fibrofatty tissue with no lymphovascular involvement (Fig. 6B). Overall, it was concluded that these features were in keeping with a basosquamous carcinoma, an aggressive subtype of BCC showing squamous differentiation [23].

The patient made a good recovery, complicated only by superficial infection in parts of the wound. She underwent post-operative imaging with repeat MRI and PET/CT (Fig. 7) 8 months following her initial scans. MRI revealed increased conspicuity of the bilateral obturator lymph nodes and interval development of a cluster of enlarged (>8 mm in short-axis diameter) right external and common iliac lymph nodes. These had low-grade uptake on the repeat PET/CT and were considered highly suspicious for pelvic metastases given the right sided position of the original tumour. This, together with post-operative histological demonstration of an aggressive variant of BCC, large size and perineural invasion of the lesion, albeit focal, made a compelling case for Post-Operative Radiotherapy (PORT) to the site in the vulva. A pragmatic PORT dose in this setting of 50 Gy in 20 daily fractions using Volumetric Modulated Arc Therapy (VMAT) was delivered. A considered decision was made not to treat the pelvis concurrently, given the resultant large treatment volume in the context of the patient's age and borderline post-operative WHO performance status of 2. The pelvic nodes will, however, be kept on imaging surveillance with expected need for pelvic nodal radiotherapy at a later point.

3. Discussion

This is a case of a profound vulval lesion which was confirmed histologically to be a basosquamous BCC. We found this extremely surprising, as BCC is both a rare tumour at this site and the diagnosis was not in keeping with the short history of the patient's presenting symptoms [9, 10]. We

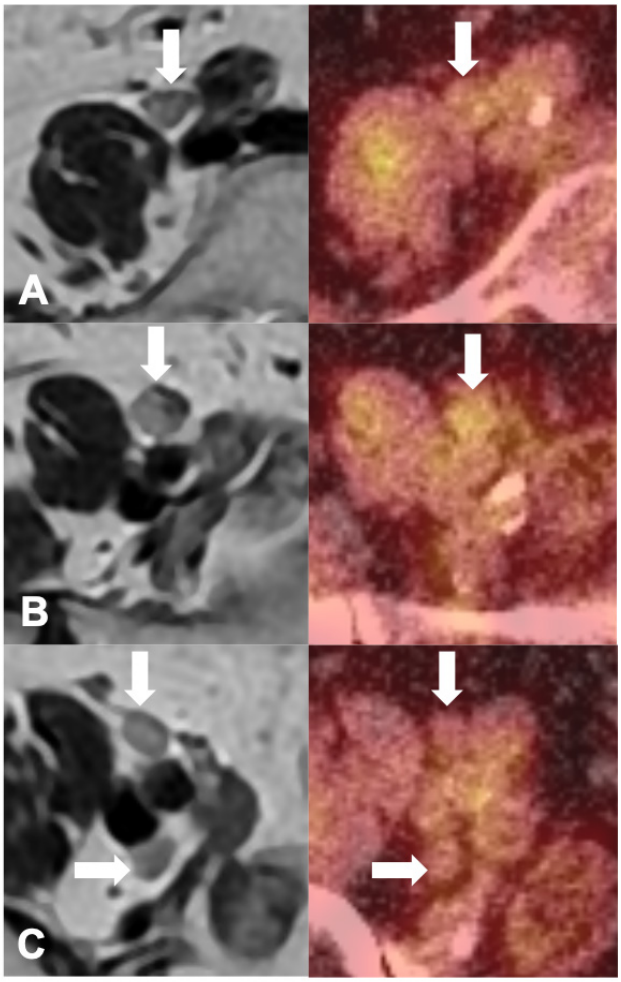

Fig. 7. Post-operative repeat axial T2w and equivalent slice on FDG-PET/CT 8 months following initial presentation. There is development of multiple enlarged right sided common (1.2 × 0.8 cm in A) and external iliac (1.6 × 0.9 cm in B, 1.1 × 0.7 cm and 1 × 0.6 cm in C) lymph nodes (arrows) with low-grade uptake on the PET/CT.

were further surprised by the presence of suspicious pelvic lymph nodes, as metastatic spread from a BCC has been reported in only 10 other cases in the literature [6]. Consistent with the tumour's histology, however, it is large primary lesions, aggressive subtypes such as basosquamous and those with perineural invasion which have been associated with metastasis and recurrence [15, 24]. The patient's preoperative MRI demonstrated bilateral necrotic obturator internus lymph nodes and these showed low grade uptake on subsequent PET/CT. With no evidence of another tumour in the pelvis to account for this, we managed the case as a vulval primary of stage 4b [25]. Though lymph node biopsy would have been required to confirm lymphatic spread of the BCC histologically, the risks of this procedure were deemed to outweigh the benefits as it was unlikely to change the patient's management.

It is worth mentioning at this point that reports of the diagnostic performance of FDG-PET/CT in evaluating nodal metastases of vulvar carcinoma vary widely. Several studies based on squamous cell carcinoma, for example, have found the sensitivity of PET/CT for this to be as low as 50% [26–28]. Thus, a normal scan result does not necessarily confirm the groin to be pathologically negative as such findings could be explained by the presence of either necrosis that is metabolically inactive or micrometastases (<5 mm) which are beyond the spatial resolution of PET/CT [29]. In our case, the necrotic areas noted in the bilateral obturator internus nodes may therefore account for the only low-grade uptake on the patient's PET/CT. In contrast, concerning the false positive rate of PET/CT in detecting nodal metastases, the groups Crivellaro *et al.* [26] and Lin *et al.* [30] found specificity and positive predictive values of 67%, 58% and 91%, 85% respectively. This is largely due to the presentation of vulvar cancers as ulcerative lesions with concomitant inflammation and enlarged, reactive nodes. The development of further lymph nodes in the external and common iliac locations on our patient's MRI four months following surgery, however, reduced the likelihood of their simply being reactive in nature and reinforced our initial suspicion of stage 4b disease at presentation. Since there was no obvious involvement of the inguinal nodes, we believe this may also be the first example of such a pattern of lymphatic spread to the pelvic nodes in the absence of inguinal lymphadenopathy in the first instance.

Much deliberation was given to the management of this patient. The primary lesion was surgically excised, which was considered more amenable to her age and comorbidities compared to the prolonged radiotherapy that would have been needed to deliver local control for a BCC of such a large area. In addition, responses to primary radiotherapy are often delayed by many months with a long period of non-healing in the treated area. In most circumstances, owing to its low propensity for metastasis, surgical excision alone of BCC is associated with excellent outcomes [31]. There are at present, however, no guidelines for the recommended management of metastatic BCC. This has a poor prognosis reported to be between 8 months to 3.5 years and little is published regarding the outcomes of lymph node only metastasis [32]. In this case, pathology directed PORT to reduce chances of local recurrence was regarded as priority and deferment of treating the low volume nodal disease in the pelvis for initial surveillance was adopted to limit morbidity. Studies of various systemic treatments have had poor outcomes and the benefit of neoadjuvant or PORT remains limited to a few cases published in the literature [8, 15]. Recently, the development of specific inhibitors of the HH pathway such as Vismodegib have shown some promising results and others are currently under trial [33, 34].

Although vulval BCC and metastatic cases are rare, such tumours are associated with high morbidity and mortality. In light of this, we advise that lymphatic spread should be investigated in certain patients with imaging and potentially regional lymph node sampling. This has previously been recommended for patients with large lesions (>20 mm) which

affect underlying structures and have an invasive histological subtype, as these BCC carry higher risks of both metastasis and recurrence [6, 13, 35]. Further evidence, however, is required to inform the staging and post-operative surveillance of such cases.

4. Conclusions

Vulval BCC is a rare entity and metastasis of this tumour is rarer still. To date, there are few cases published of vulval BCC with metastasis to regional lymph nodes. Here we report an example of a large, basosquamous BCC with pelvic sidewall lymph nodes suspicious for metastasis on imaging. In general, patients with BCC are not subject to imaging as part of staging investigations and this report emphasises caution and recognition of exceptions to this approach. Metastatic BCCs carry poor prognosis and we recommend imaging and potentially histological staging in amenable patients with certain risk factors to guide their management.

Author contributions

The project was conceived by SHL. The manuscript was written by NJH, with revision and intellectual input from KR, MM, SM, MS, KSM and SHL. Radiology images included were produced and annotated by SM and SHL. Pathology slides and images were produced and annotated by MS. Details regarding Post-Operative Radiotherapy were provided by KSM. Consent from the patient and intra-operative photographs were obtained by KMN. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Informed, written consent for publication of the personal details and photographs contained in this report was granted by the patient subject.

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Conflict of interest

The authors declare no conflict of interest.

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