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COMMENTARY

Small-Cell Carcinoma of the Prostate – Challenges of Diagnosis and Treatment: A Next of Kin and Physician Perspective Piece

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ABSTRACT

This article was co-authored by a patient's relative describing their experiences of receiving a diagnosis and subsequent clinical management of a rare form of prostate cancer, neuroendocrine prostate cancer (NEPC). The difficulty of receiving this diagnosis, particularly as this was terminal with no options for systemic treatment, and experiences throughout this process are detailed. The relative's questions regarding the care of her partner, NEPC and clinical management are answered. The treating physician's perspective regarding clinical management is enclosed. Prostate cancer remains one of the most common cancer diagnoses, with small-cell carcinoma (SCC) of the prostate representing 0.5–2% of these. Prostatic SCC frequently develops in patients previously treated for prostate adenocarcinoma, more rarely arising de novo. Diagnosis and management present clinical challenges owing to its rarity, frequently aggressive disease course, lack of specific diagnostic and monitoring biomarkers, and treatment limitations. Current pathophysiological understanding of prostatic SCC, genomics and contemporary and evolving treatment options in addition to current guidelines are discussed. Written principally from the patient's relatives and physician experience with discussion of current evidence, diagnostic and treatment options, we hope this piece is informative for both patients and healthcare professionals alike.

Keywords: Small-cell carcinoma; Prostate cancer; Treatment; Physician perspective

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Key Summary Points
Small-cell carcinoma is a rare and aggressive variant of prostate cancer.
It represents between 0.5–2% of prostate cancer diagnoses.
This multi-perspective piece is co-authored by the next-of-kin of a patient with this diagnosis, his treating physician, and other oncologists in genitourinary oncology.
It provides a reflection of how the disease presents itself, the diagnostic challenges, and the difficulties and limitations associated with treating the cancer.
We also provide a comprehensive literature review of the current systemic treatment options and associated guidelines, as well as evolving treatment options in this rare disease.

THE NEXT OF KIN'S PERSPECTIVE

An Introduction to Phil and Trish

My husband of over 45 years, Philip Abbott, was the patient who will be discussed in this piece. He had an extremely rare and aggressive strain of prostate cancer. He was a computer consultant, and we had run our own successful business in the Yorkshire Dales for 11 years, when we decided to "escape to the country" back in 2000, having lived most of our married life in Dartford, an industrial town in Kent.

We decided to retire to Norfolk, a county we both loved, in 2011, and although very happy to be out of the world of IT, Phil did not want to fully retire. He became a bus driver for a centre for the disabled on a part-time basis and enjoyed not sitting behind a computer screen for hours every day, and it also gave him the exercise he needed to remain healthy (or so we thought).

Early Signs

In late 2014 he was becoming increasingly breathless and had a niggling ache in his chest. Having been diagnosed years back with a hiatus hernia, he just thought it was this playing up, but this was not so. In February 2015, after a bad scare and an overnight stay in our local hospital, Phil was found to have quite a significant blockage in his left ventricular coronary artery. He was successfully fitted with a stent and recovery was swift and amazingly uneventful.

All was well, and we decided to change our eating habits and lose some weight. Phil lost 2 and a half stone by cutting down on carbohydrates, which made him feel healthier than he had in quite some years.

At the end of January 2018, and with no other symptoms, Phil discovered a small amount of blood in his urine when he went to the bathroom. Although he felt well, we made him an appointment with our general practitioner (GP) to see if he had a kidney infection. Our GP arranged for a blood test to be done and performed a digital rectal examination of the prostate. This was found to be enlarged and a bit lumpy instead of being round and smooth. To be on the safe side, he referred Phil to a urologist.

I will add that when my husband was 65 years old in 2016, he went for his WellMan appointment with his GP and asked for a prostate specific antigen (PSA) test to be included with the other blood test. He was concerned, as although he showed no symptoms, he had lost two friends from prostate cancer just the year before. He was talked out of it by the GP, who said that it alone was not a very reliable test as an indicator and that it may give him false positive or negative results, so it was never done.

The Diagnosis Journey and Early Treatment

In early February 2018, Phil attended the Urology department at the Norfolk and Norwich University Hospital (NNUH), where an ultrasound and a flexible cystoscopy were

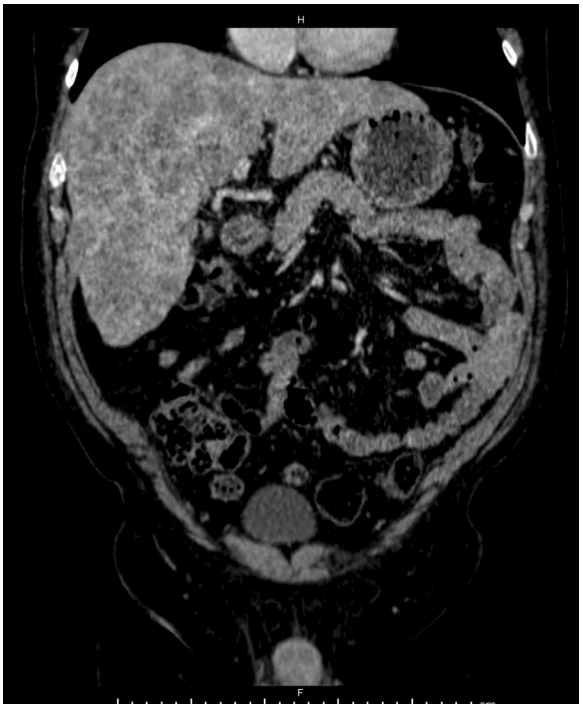

Fig. 1 CT scan of the thorax and abdomen

performed. The cystoscopy results confirmed a grossly abnormal prostate with a papillary lesion sitting on the median lobe of the prostate which projected into the bladder. The bladder itself was normal. More worrying though was the ultrasound result, which showed some incidental lesions on the liver. We were really becoming quite worried at that point and thought the worst.

Computed tomography (CT) scans of the thorax and abdomen (Fig. 1) were arranged, and in late February 2018 Phil had a transrectal ultrasound scan and biopsy of the prostate. By the beginning of March, Phil had started to feel noticeably unwell, consumed by fatigue as well as dizziness, night sweats, a racing heart and aches in his body. So back to the GP we went, where she immediately contacted the medical registrar at the NNUH. With just yeses and noes and furtive looks from our GP, we began to expect the worst. They informed us to go straight to the walk-in department at NNUH.

Here we saw an oncology consultant Dr Jenny Nobes, who confirmed our worst nightmare when she diagnosed Phil with having Gleason 10 prostate cancer with a PSA of 9.5. She also suspected that he had widespread liver metastases, which could possibly be another primary cancer. What luck!

Although his prostate cancer was not curable, it could be managed quite well with medication and possibly chemotherapy, depending on a liver biopsy. The body scans had come back clear, with no spread to the lymph nodes or pelvic area.

Phil was started straight away with bicalutamide to take for 4 weeks and an injection of leuprorelin was arranged for 2 weeks later, which would need to be continued indefinitely. Dr Nobes also arranged for an urgent liver biopsy and prescribed dexemethasone to manage his liver symptoms.

On the 20 March, an ultrasound-guided biopsy of the liver was performed under general anaesthetic. A nuclear bone scan followed a few weeks later to see whether Phil's cancer had spread into any bones. We waited 6 weeks for an appointment for the results, thinking that, had it been really bad, then the consultant would have been in touch straight away.

Advancement: Rare Small-Cell Prostate Cancer

An appointment with the oncologist came on the 24 April 2018 – a day we will never forget, as it was here that we were delivered the shocking blow. Phil had an extremely rare and aggressive small-cell prostate cancer that had spread to the liver. The bone scan was clear, but nonetheless, the diagnosis was terminal. We were numb with shock and just looked at each other. We asked about chemotherapy, and Dr Nobes said that there was nothing that could be offered; in fact, chemotherapy in this case could prove fatal – another blow.

She said that in her 8 years as a consultant, she had only ever seen one case as rare as ours. Although she gave us the news with the utmost care and with great sensitivity, we were totally devastated. The palliative care team would be in touch, and she advised us to make any plans to visit anyone we needed to, sooner rather than later. After we could think again, I asked for a

prognosis, to which the reply was "a few weeks". I was in shock, so asked whether she instead meant a few months, and she again said, "no, a few weeks". I wanted some plain speaking here; I needed to know just how much time we had left. The poor consultant was very uncomfortable saying this, but I had to know! Eventually, the answer came: "It could be as little as 6–8 weeks".

We were understandably knocked down by this terrible news and were faced with the gut-wrenching task of telling our children and Phil's family and friends. Our son, who lives in America, had been to visit in April after the first initial diagnosis and made swift arrangements to visit us in early June, thinking he could spend some more precious time with his dad. Our daughter and son-in-law, who live about 5 hours away visited soon after our tearful phone conversation and continued to support us as much as they could.

Phil's work colleagues took him out and visited him at home, and friends who lived further afield came over to see us. Everyone was so saddened and could not believe the news.

The palliative care team sorted out everything needed to make him comfortable and helped with the forms for financial support. The worst form for me that he had to fill in was a do-not-attempt-cardiopulmonary-resuscitation form, which really hit the situation home and left me sobbing.

Phil really wanted to stay at home, but it soon became apparent that we could not manage physically as he became increasingly poorly. He ultimately changed his mind and asked to go into the local hospice when the time came. Sadly, the waiting list was quite long, and he did not have the luxury of time.

End of Life

Continuing to decline quite rapidly, Phil suffered from restless leg syndrome, for which he was prescribed ropinirole. His sleep was disturbed, and even lorazepam and oral morphine had little effect. I spent many a night with him on the edge of the bed unable to sleep and not knowing how to help him.

He contracted a painful skin infection on his thigh and lower back over the late-May bank holiday, and he was admitted by ambulance to our local James Paget Hospital Accident and Emergency (A&E), where he was put on intravenous antibiotics. By this stage, he was too weak and ill to fight, and although the antibiotics did clear up the infection well, he never really recovered from it. He was extremely uncomfortable for that last week because the location of the infection rash meant it was constantly agitated and left him wet and sore. Additionally, with his liver giving up, he also became heavy and bloated around his lower body and could not move without help. After 5 days in an A&E overflow ward, he was transferred to a side room in a ward more dedicated to cancer.

Our son got over to see his dad on 2 June 2018, and they had some quality hours together. My son and my daughter stayed with me, fed me and ferried me to and from to the hospital. I am not sure I would have coped on my own without them.

Farewell

My dear brave husband died on 4 June 2018 on his 67th birthday. He had one set goal – of reaching his birthday – which we were all so happy he achieved. This was exactly 6 weeks after being given the final diagnosis. He was taken too soon, and my heart was ripped out in the process.

Phil was always philosophical about the diagnosis. He accepted that there was nothing that could be done and said things such as "none of us will be getting out of this alive" and "it is what it is". He kept his sense of humour even when he knew there was no hope. He also had so much praise for the National Health Service (NHS) staff and the ambulance service and was always grateful for the care he received, but I admittedly felt let down by the palliative care team.

I miss him terribly, but if my story can help those who read it and can encourage more research into rare prostate cancers so that

maybe others in the future can get the help they need, then all was not lost.

I am grateful for the 6 weeks we had left together so that we could start to make plans that would help me after he passed, and so that we could say the things to each other and to others that needed to be said. Some wives kiss their husbands goodbye when they leave the house, only for them to never return again when fate deals them a blow. So at least we had those 6 weeks. They may have been the hardest and saddest weeks of our lives, but it is a time I will always cherish.

Questions from the Next of Kin

It has been 5 years since Phil was first diagnosed with prostate cancer. I have reflected on this case and created a list of questions which I hope physicians treating this cancer will be able to address. I hope that these questions will be useful for patients and their close ones in better understanding this rare subtype of prostate cancer, and maybe even help guide further research in the area:

1. Why do these rare cancers mostly have a low PSA reading?

Answer: Small-cell carcinoma (SCC) of the prostate is composed of neuro-endocrine (NE) tumour cells, which are not associated with PSA production [1]. *PSA levels therefore tend to remain disproportionately low and thus are not a reliable indicator of disease burden* [1].

2. Could these rare cancers be present in the body long before any symptoms are felt or an advanced stage of diagnosis confirmed?

Answer: SCC of the prostate remains a rare prostate cancer subtype representing 0.5–2% of patients [2, 3]. *It tends to follow an aggressive and rapid disease course with early metastatic spread* [2, 3]. *Common presenting symptoms include lower urinary tract symptoms such as hesitancy and dysuria or may relate to site of metastatic spread, for example, bone pain or respiratory symptoms* [4]. *Further research may inform reliable biomarkers to aid early diagnosis of prostatic SCC; however, given the disposition to rapid disease spread, patients unfortunately often present in the advanced stages of disease* [1, 5, 6].

3. How are rare cancers such as these picked up, apart from the commonly used PSA? Of note, Phil had a full set of annual blood tests in late 2017, and all were normal as far as we knew.

Answer: PSA may aid diagnosis and monitoring of the more commonly diagnosed adenocarcinoma subtype of prostate cancer [7]. *SCC of the prostate and prostate adenocarcinoma often present with similar clinical symptoms* [4]. *Although radiological evidence of osteolytic bone metastasis, compared with osteoblastic bone metastasis seen in prostate adenocarcinoma, may raise suspicion of prostatic SCC, diagnosis primarily relies on biopsy of suspected lesions and further histological classification* [4, 5]. *Potential diagnostic and monitorable biomarkers for prostate SCC have been identified but require further research to allow standard clinical implementation* [1, 6].

4. Why were we only offered hormone therapy and steroids as a palliative treatment plan, having been told that chemotherapy could be fatal and so not an option?

Answer: Chemotherapy prescribing should carefully balance potential risks and benefits and aim to minimise patient morbidity and mortality [8]. *Patients with evidence of organ dysfunction, such as deranged liver function tests and a deteriorating performance status as in the present case, are at higher risks of chemotherapy-related complications which can be life-threatening. Where the potential risks are judged too great, palliative input with prioritisation of symptom management is often more appropriate to maximise quality of life* [8].

5. Will men ever be offered a screening programme to pick up these rare and aggressive forms of prostate cancer, before it becomes an advanced stage and incurable?

Answer: Despite its prevalence, screening programmes for prostate cancer remain contentious owing to a lack of evidence that modalities such as PSA measurements precipitate a significant mortality reduction [7]. *Furthermore, there are concerns that screening may contribute additional risk and even harm to patients, such as unnecessary and invasive investigations and treatment* [7]. *Recent evidence following 15 year follow-up of the Prostate Testing for Cancer and Treatment (ProtecT) trial has, for example, demonstrated a low mortality regardless of patients with localised prostate cancer being assigned to active monitoring, prostatectomy*

or radiotherapy treatment [9]. *Biomarkers such as chromogranin A, neuron-specific enolase or carcinoembryonic antigen have been identified as potential diagnostic and monitoring parameters for prostate SCC; however, these require further analysis and definition prior to implementation* [1, 6]. *Further clarification regarding the efficacy and modality of prostate cancer screening is therefore needed, particularly when considering histological subtypes.*

THE PHYSICIAN'S PERSPECTIVE

Small-Cell Prostate Carcinoma: A Case Discussion

In February 2018 a previously fit 66-year-old gentleman presented to his GP with visible haematuria. His PSA was elevated at 9.5 ng/ml. He was referred to the one-stop haematuria urology clinic and was found to have a grossly abnormal prostate at flexible cystoscopy, with a clinically malignant, hard nodule on digital rectal examination of the prostate.

On 7 February 2018 he underwent an ultrasound scan of the urinary tract. This noted normal size, shape and echotexture of both kidneys and no ultrasound evidence of large calculi, solid mass or pelvicalyceal dilatation. The bladder was underfilled, but no gross abnormality was demonstrated. On scanning the right kidney, an incidental note was made of a heterogeneous liver with the appearance of multiple hyperechoic lesions within. A CT scan was recommended for further evaluation.

CT Report 17 February 2018: The prostate was noted to look unremarkable on CT. There was a borderline enlarged 8 mm right obturator node, but no other pelvic and no para-aortic lymphadenopathy. The liver parenchyma was virtually replaced by innumerable metastases. A 9 mm bland cyst in the uncinate process of the pancreas is not overtly suspicious and is probably an intraductal papillary mucinous neoplasm. His CT chest was clear, and there were no other suspicious lesions suggestive of another primary tumour. The report concluded that there was widespread hepatic metastatic disease which was unlikely to be secondary to a prostatic primary because of the unremarkable appearances.

The patient underwent a transrectal ultrasound-guided prostate biopsy on 27 February 2018. All 10 cores of prostatic tissue showed extensive infiltration by Gleason 5 + 5 = 10, Grade group 5 adenocarcinoma. Perineural invasion was present, but lymphovascular invasion was not recognised. Some parts of the tumour showed possible neuroendocrine features. Further immunohistochemical staining was conducted and concluded that much of the carcinoma in this biopsy was immunoreactive for CD56 and synaptophysin, in keeping with neuroendocrine differentiation. The appearances were those of small-cell carcinoma. Some areas (a minority) showed more conventional high-grade prostatic adenocarcinoma (Fig. 2).

The patient was reviewed on 6 March in the oncology clinic, which requested ultrasound (US)-guided liver biopsy to confirm the origin of his liver metastases, as discussed with the radiology team. On 20 March 2018 he underwent a US-guided liver biopsy. Two cores of tissue, with a total length of 2.8 cm, were taken. The microscopic description was that the liver cores were widely infiltrated by small-cell carcinoma, with identical features to the neuroendocrine carcinoma seen in the prostate biopsies (Fig. 3).

Unfortunately, his liver function tests were grossly deranged by this stage, meaning that chemotherapy was contraindicated. Clinically he had also deteriorated in terms of performance status and was jaundiced and extremely fatigued. He was commenced on oral corticosteroids for symptom control of liver capsule pain and referred back to the GP and community palliative care team for end-of-life care at home.

SMALL-CELL CARCINOMA OF THE PROSTATE COMMENTARY

Challenges in the Treatment of Small-Cell Carcinoma of the Prostate

Prostate cancer remains one of the most common cancer diagnoses and, although recognised as the second leading cause of male-cancer-

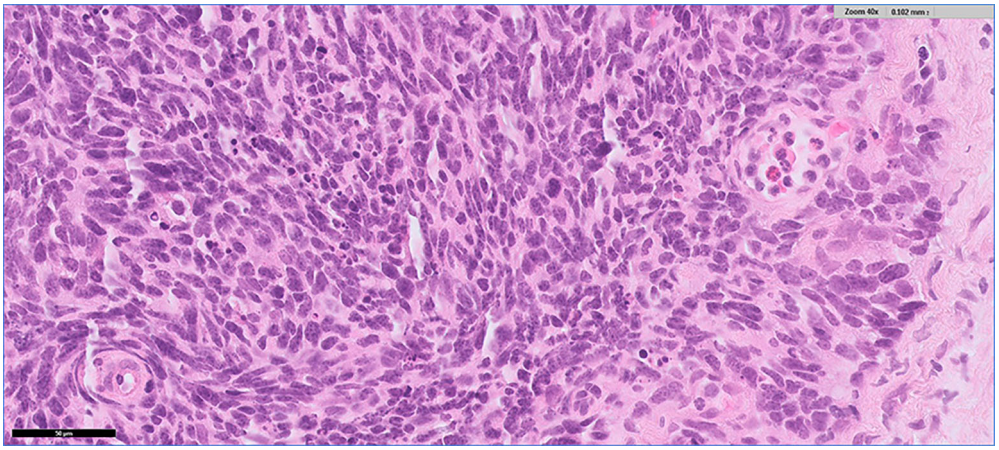

Fig. 2 Prostate with small-cell carcinoma

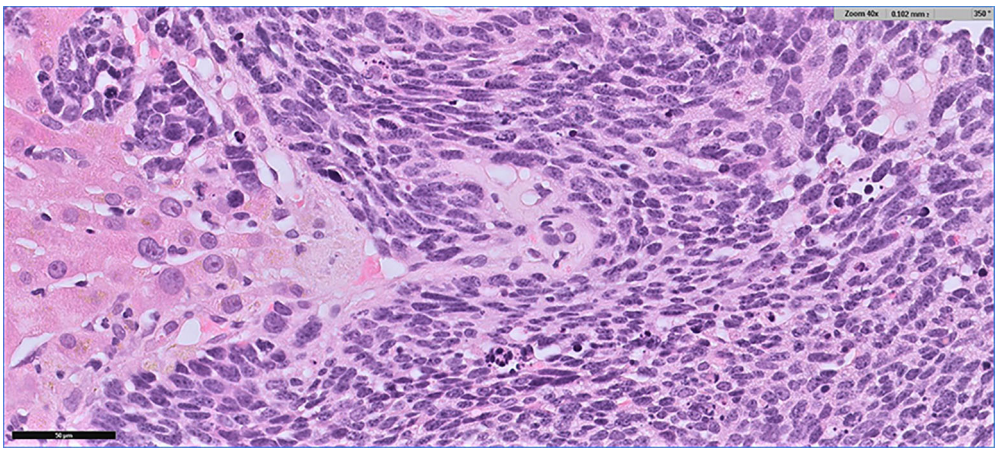

Fig. 3 Liver metastases with small-cell carcinoma

associated mortality worldwide, often follows an indolent clinical course [2]. SCC of the prostate, composed of NE tumour cells, represents 0.5–2% of prostate cancer diagnoses [10, 11]. NE cells may rarely arise de novo but are more commonly diagnosed in patients with previously diagnosed prostatic adenocarcinomas, many of whom have received hormone treatment and developed disease resistant to targeted androgen receptor therapies [3, 10, 12]. Contradictory to the more commonly diagnosed adenocarcinoma subtype, neuroendocrine prostate cancers (NEPC) display an aggressive disease course [2, 3]. They are additionally associated with frequent and early visceral and bony metastatic spread, recognised paraneoplastic associations including hypercalcaemia and syndrome of inappropriate antidiuretic hormone, and a median survival of less than 2 years from time of diagnosis [2, 3]. Due to its affiliation with rapid disease progression and comparatively low PSA levels in respect to cancer burden, patients often present with advanced disease [5]. Prostatic SCC's additionally display a short or no response to androgen deprivation therapy (ADT) due to a cellular lack of androgen receptor expression, and owing to their rarity, standardised and optimal treatments, particularly second-line regimens, remain in their infancy [1, 5].

While most NE tumours develop after patients have received prior therapies for

metastatic castration-resistant prostate cancer (mCRPC), they can arise de novo, as with the patient discussed in this perspective piece. NEPC share common genomic aberrations to prostate adenocarcinoma, for example, TMPRSS2-ERG fusion supporting their common cellular origin [13]. However, they are enriched with acquired alterations including RB1 loss and TP53 alterations which more closely mimic the make-up of small-cell lung cancer [14, 15]. It is perhaps not a coincidence that RB1 loss, as with other tumour suppressor proteins such as TP53 and PTEN in CRPC, has been associated with aggressive disease and poor prognosis [16]. Whole genome and transcriptome analysis has additionally demonstrated reduced expression of androgen receptor (AR) and its downstream targets in patients previously receiving ADT, indicating the potential role of selective pressures in the emergence of NEPC in these patients [17]. Characterisation of genomic aberrations may help identify novel therapeutic targets. A diagnosis of prostatic SCC typically requires imaging, with a low threshold for brain imaging owing to a propensity for intracranial metastatic spread, and histological analysis of suspected malignant lesions [5]. Whereas androgen-receptor-positive tumours generate receptor-dependent products, including PSA, prostatic SCC PSA levels tend to remain disproportionally low, as NE cells do not produce PSA [1]. Biomarkers including chromogranin A, neuron-specific enolase or carcinoembryonic antigen may instead be suitable for diagnostic and monitoring purposes [1, 18]. Owing to the disposition for SCC of the prostate to rapidly progress, patients may present in the terminal phase of their disease course with systemic treatment options not being appropriate [2, 3]. Despite presenting in the terminal phase, diagnostic investigations including histological analysis may still be considered to help clinician and patient understanding of their disease.

Systemic Treatment Options

The importance of accurate and rapid differentiation of SCC of the prostate from further histological subtypes is highlighted by contrasting treatment approaches. Prostatic SCC tends to initially respond to both chemotherapy and radiotherapy, although durable responses are less common [5]. For non-metastatic disease, adjuvant platinum-based chemotherapy following prostatectomy may be indicated [5]. Treatment of metastatic disease typically includes coupled platinum- and taxane-based chemotherapy agents [1, 5, 19]. Combination platinum chemotherapy and etoposide is considered for small-cell lung cancers and many neuroendocrine tumours. However, the combination of carboplatin and etoposide in NEPC has been studied in the Phase II GETUG-01 trial, demonstrating poor response rates and high toxicity in the form of myelosuppression [20]. The combination of carboplatin and cabazitaxel is now supported by the National Comprehensive Cancer Network (NCCN) guidelines for patients with an aggressive variant or unfavourable genomics (loss of function involving at least two of PTEN, TP53 and Rb1). This recommendation is based on a few studies: in a phase II study, 113 men meeting aggressive variant prostate cancer (AVPC) clinical criteria were treated with carboplatin plus docetaxel followed by cisplatin plus etoposide at progression [16]. Median progression-free survival with carboplatin plus docetaxel was 5.1 months with overall survival of 16.0 months [13]. In a further phase II study, 160 men with metastatic CRPC with aggressive variant features were randomised to receive cabazitaxel or cabazitaxel plus carboplatin. There was a substantial improvement in PFS in the combination therapy in patients who had features of the aggressive variant as opposed to those without these features (hazard ratio 0.58 versus 0.74). The combination of cabazitaxel with carboplatin may have scientific basis in NEPC, given the activity of cabazitaxel in CRPC and mixed tumour histologies [3]. While combination chemotherapy offers some degree of disease control and response, this is contingent on the patient having satisfactory liver and renal function for metabolism. The patient discussed in this article had significant liver dysfunction

secondary to metastatic deposits, greatly limiting the delivery of effective chemotherapy and increasing the risk of toxicity. Taxane-based agents such as docetaxel and cabazitaxel are extensively metabolised in the liver, and therefore severe hepatic impairment will limit the ability for this regimen to be safely delivered.

Evolving Treatment Options

There are evolving treatment options in NEPC, but the developments have not kept pace with some more common cancers, perhaps due to the relative rarity of this subtype of cancer. Immunotherapy and novel and targeted treatments improve outcomes and are awaiting further characterisation through trial participation [6, 21]. Prostatic SCCs in the castrate-resistant setting may arise due to lineage plasticity and can present mixed phenotypes displaying both NE and adenocarcinoma tumour cells [1]. Dominant histology can therefore establish treatment in these patients whilst defining epigenetic and genomic determinants of lineage plasticity and identifying corresponding depictive and predictive biomarkers could advance diagnosis, treatment and prognosis [1]. ADT may be considered given the prevalence of concomitant cellular adenocarcinoma components [5]. In patients presenting with advanced prostatic SCC, an emphasis on symptomatic management may be appropriate. Given distinct treatment options, inclination towards rapid disease progression and prevalence of prostatic SCC in patients previously treated for adenocarcinoma of the prostate, a high index of suspicion is essential towards achieving early diagnosis and initiating appropriate clinical management. Due to its rarity, disproportionally low PSA levels and lack of clinical evidence, the diagnosis and treatment of SCC of the prostate remains a challenge. Further research identifying the efficacy of novel and targeted treatments, specific clinical features and biomarkers, particularly in patients developing prostatic SCC in advanced disease, may improve clinical outcomes.

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Data Availability. Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

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